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Classification of Breast Cancer Histopathological Images Using Semi-Supervised GANs

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Abstract: Breast cancer is diagnosed more frequently than skin cancer in women in the United States. Most breast cancer cases are diagnosed in women, while children and men are less likely to develop the disease. Various tissues in the breast grow uncontrollably, resulting in breast cancer. Different treatments analyze microscopic histopathology images for diagnosis that help accurately detect cancer cells. Deep learning is one of the evolving techniques to classify images where accuracy depends on the volume and quality of labeled images. This study used various pre-trained models to train the histopathological images and analyze these models to create a new CNN. Deep neural networks are trained in a generative adversarial fashion in a semi-supervised environment by extracting low-level features that improve classification accuracy. This paper proposes an eloquent approach to classifying histopathological images accurately using Semi-Supervised GANs with a classification accuracy greater than 93%.

1 Introduction

Breast cancer is the second most prevalent cause of cancer death in women. However, breast cancer is often treatable when diagnosed in the initial stages. Early detection and the proper treatment help reduce the mortality rate. The initial stages of cancer, where there are no cancerous cells in the tumor, are benign, and if the cancer is not treated, it grows over time to contain cancerous cells and becomes malignant.

Breast cancer affects females significantly but has traces of evidence affecting men and children at a lower percentage compared to females. Based on a recent study, around 1% of breast cancers are reported in men in the US. According to the National Breast Cancer Institute, around 2000 new cases are diagnosed yearly for men with breast cancer, and around 400 deaths occur as a result. Breast cancer is treated the same way for men and women, but it is detected earlier in females. [21][22].

Breast cancer in children is rare; even if diagnosed, the tumor cells are not cancerous and require constant monitoring. If cancer develops in children, it is treated by radiation and therapy to remove the tumor cells [23].

Pathologists play a significant role in cancer diagnosis. They are the ones who operate behind the scenes and confirm the detection of tumor cells using histopathological slides under a 20× or 40× light microscope. They provide treatment recommendations to doctors. Pathologists often conduct additional tests to determine

whether the cancer is benign or malignant, which is crucial in diagnosis. A manual examination is tedious and time-consuming and often leads to variation in results. According to one of the research studies in Medscape's annual survey, the number of US pathologists decreased by 18% between 2007 and 2017. The major concerning factor in this field is the shortage of experienced pathologists and the increasing number of females affected. Research shows that women diagnosed with breast cancer at the earlier stages are six times likelier to live past five years than those diagnosed at a later stage [20]. When the pathologists delay the initial diagnosis, it leads to a delay in treatment and a reduction in survival rates. The unavailability of labeled datasets has also created another big challenge for pathologists to classify cancer as benign or malignant. Researching the small datasets creates data imbalance and results in an inefficient performance of the model.

Researchers and clinicians have been interested in deep learning techniques in the past few years to help with automated analysis and classification of cancer from digital pathology images. Convolutional Neural Network models have helped improve the classification of histopathological images with much better performance and improved accuracy. Different researchers have performed image classification techniques and continue to help detect breast cancer at an earlier stage. Saha et al. [11] 's research detected mitoses from histopathological images with a precision rate and recall rate of 92% and 88%, respectively. Han et al. [12] automated image classification used a hierarchical deep learning model method with an accuracy rate of 93%. Zheng et al. [13] proposed an automated image classification method to classify images as benign or malignant using the CNN model with a precision of 96%. Jia et al. [14] researched to develop a framework that helps segment cancer areas in histopathological images using a fully connected network algorithm. Xu et al. [15] proposed a model that segments and labels histopathology pictures using transfer learning. Shi et al. [16] developed a deep hashing method for retrieving and classifying histopathological images.

This paper uses an automated framework for image classification technique to diagnose a tumor with cancerous cells as benign or malignant. The focus is on Semi-Supervised GANs to generate synthetic data for classifying labeled and unlabeled data. Automated image classification and machine learning techniques have been used to classify a cancer type with a better classification accuracy of 93% and higher. Furthermore, the computerized process can mimic the human mind to a certain extent and would be able to classify based on the statistical features.

2 Literature Review

2.1 Breast Cancer

Cancer is one of the leading causes of death, among other cancers and diseases. In 2008, 8 million deaths were recorded due to cancer, estimated to reach 11 million by 2030 [17]. Globally, breast cancer is the most common cause of death among women, and its severity varies across countries based on factors such as lifestyle, demographics, and hormone factors. However, breast cancer in men and children cannot be ruled out entirely as the % of infected is less than in women.

1 in 8 women has a chance of developing breast cancer in America [18], which also depends on factors such as race and ethnicity**.** In addition, breast cancer cases are higher in North America than in Africa and Asia [19]. However, owing to recent research on various diagnostic methods and therapeutic processes, the survival rate of breast cancer is improving [20].

Breast cancer starts in breast cells in lobules. It is classified as benign and malignant. Benign means non-cancer, whereas malignant cells are cancerous cells that can spread to other body parts [8].

In noncancerous tissues, cell growth and spread can be regulated. Cancer cells continuously divide, fill the blood with their kind, and destroy healthy cells. Benign cancer cell growth does not pose such a threat as it can form anywhere in the body, grows more slowly, does not spread to other parts quickly, and does not always require treatment.

Benign breast cancer tumors are surgically removed or treated for health or cosmetic reasons. However, benign and malignant tumors require a different treatment based on cell structure [8].

2.2 Diagnosing Breast Cancers

Mammogram, ultrasound, MRI, and biopsy are some standard diagnosis methods to identify breast cancer at the preliminary stages. These tests were decided based on the severity of symptoms. The ability of ultrasounds and mammograms to detect breast cancer depends on the tumor's size and the radiologist's skill. Breast cancer treatment depends on the cancer classification and its stage. The classifications are based on the kind of breast tissue where cancer originated and how far cancer has spread. Conventional medical therapy for breast cancer may include chemotherapy, surgery, or hormonal drugs based on the severity of symptoms and stage of cancer [9].

Histopathology is the diagnosis and study of disease of tissues that is done by examining tissues under a microscope. Histopathological images are a significant resource to determine the state of biological structure to support a diagnosis of a disease like cancer or to study the structure of cells and tissues [1]. In addition, it allows distinguishing between distinct levels of cancers (benign or malignant) from tissue evaluation. Pathologists now understand the importance of image recognition and adopt the latest methods in recent diagnosis methods.

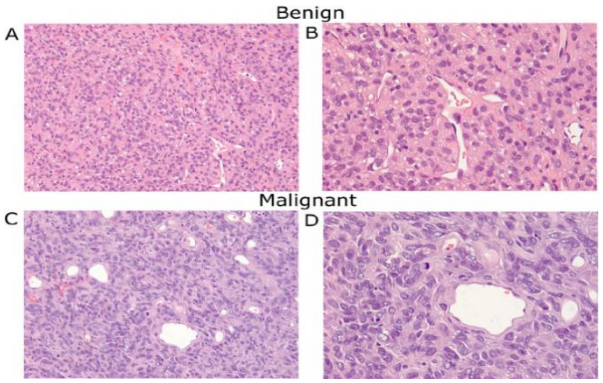

Fig. 1. Breast cancer histopathological images

In the past, researchers implemented various deep learning models and different architectures of CNN like Inception Networks, Residual Networks, and Deep Belief networks with limited labeled images [19] [20] [21]. However, model creation with histopathological images requires extensive, labeled data for better classification accuracy. Obtaining histopathological slide data from pathologists creates a barrier in implementing a deep learning neural network model for cancer classification.

This paper explores possible candidate models or architectures through literature research and expert guidance to create the best classification model that could help health care teams correctly identify breast cancer. Three potential machine learning options emerge: build a Convolutional Neural Network (CNN), transfer learning techniques, and Semi-Supervised Generative Adversarial Networks to generate synthetic images and classify [3].

2.3 Convolutional Neural Networks

Deep learning is key for any applications involving computer vision and speech recognition. In general, CNN was widely implemented in computer vision tasks, and its high performance and ease of use are the main factors driving its popularity [13].

Simple Convolutional Neural Network consists of a convolutional base (feature extraction) and a classifier (image classifier) deep learning model, as shown in Figure 2, can learn features automatically; usually convolutional base refers to general features, and the classifier's part refers to specialized features [7].

The architecture of CNN is like a multilayer perceptron designed to reduce processing conditions. An input layer, a hidden layer with several pooling layers, and fully connected layers in a CNN architecture. One of the issues with traditional neural networks is not covering the entire visual field. To avoid incremental image processing problems, the neurons in hidden layers are arranged in such a way as to cover the entire visual area [18].

Typically, images are either gray colored (one channel) or multiple colors or channels (For example, Red-Green-Blue channels). Traditional CNN architecture can be modified to process images with multiple channels. This results in a model architecture far superior and simpler to train for image processing with multiple channels and removes limitations related to multiple channel processing.

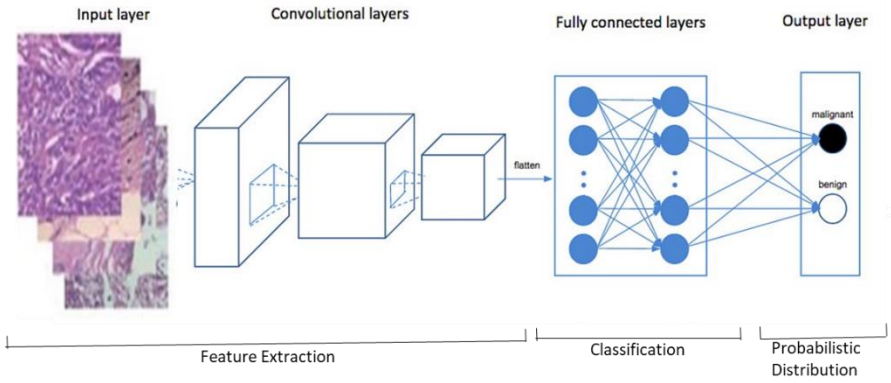

Fig. 2. Conventional CNN architecture

2.4 Transfer Learning

Transfer learning technique is an optimization technique where a previously trained model can be reused on a new problem. This technique focuses on transferring knowledge gained during the training of a machine learning model to a different but similar problem. One of the primary purposes of this technique is to solve the issue of limited labeled data in the target domain like the medical domain [10]. Transfer learning in deep learning can be applied by reusing the pre-trained model architecture and model parameters. There are numerous applications of transfer learning techniques in Convolutional Neural networks (CNN). This reduces the effort to build a neural network model from scratch, reducing computational time. This paper explores some pre-trained models that have been trained on millions of images of various categories (ImageNet dataset).

2.5 General Adversarial Networks (GANs)

This is a neural network used for unsupervised machine learning. Developed by Ian Goodfellow in 2014, GANs can be simplified into two parts, the generator and the discriminator [6]. The main idea is that the generator creates fake data, and the discriminator validates it to see if it is real or fake. Since GANs are typically used in synthetic data, they can be applied to improve classification. The basic GAN (General Adversarial Networks) architecture is shown below in Figure 3.

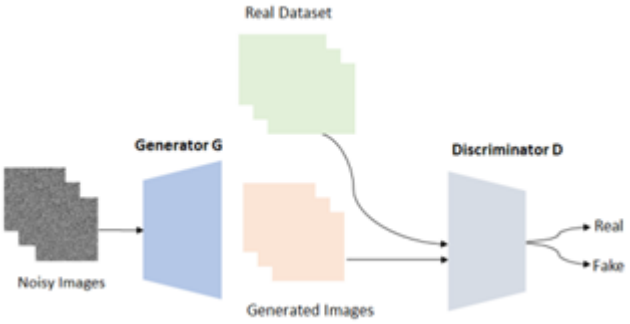

Fig. 3. Conventional GAN architecture

In a paper published by Shengyu Zhao etc. [19], Differentiable Augmentation (DiffAugment) is proposed to enhance traditional GAN further. This simple method applies various differentiable augmentation techniques to real and fake data to improve the performance of the GAN model. The DiffAugment method uses differentiable augmentation for the generated samples to stabilize the GAN's training and provide better convergence. These experiments were conducted over various GAN architectures with loss functions that demonstrated consistent improvements for both unconditional and class-conditional generation of new data.

GAN is a relatively new deep learning methodology with multiple loss functions to train discriminative or generative models. But it remains unclear how these loss functions perform against one another in an adversarial training of generator and discriminator. These adversarial loss functions are explained clearly by decoupling the effects of both generator and discriminator functions by Yi-Hsuan Yang etc., in May 2020 [20]. Furthermore, other adversarial losses are compared with a simple comparative framework and dubbed DANTest.

2.6 Semi-Supervised GANs

The Semi-Supervised GAN model is shown in Figure 4. This model uses labeled and unlabeled data to train the model in an adversarial manner. Semi-Supervised GANs are composed of discriminator and generator models. The discriminator model involves layering unsupervised and supervised models and sharing parameters [4].

The discriminator model works the same as traditional GAN in the unsupervised mode. The classifier model learns the data distribution of the unlabeled samples and classifies unlabeled samples as real, or samples generated by a generator. Whereas, in the supervised mode, the discriminator model categorizes the samples into different class labels using the extracted features utilizing the information gained from the limited set of labeled samples [5].

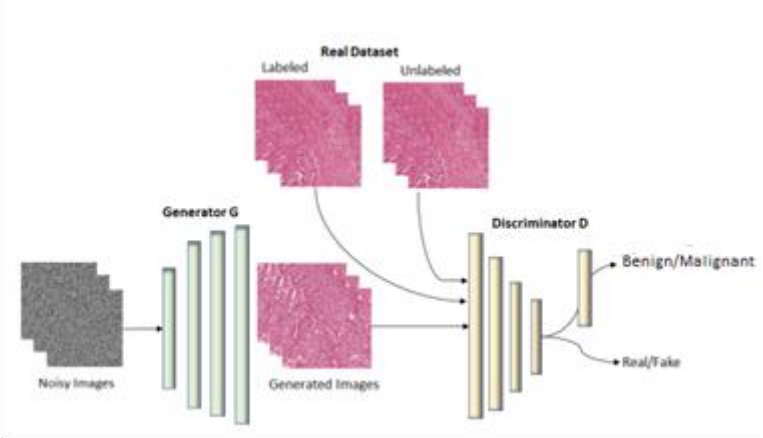

Fig. 4. Semi-Supervised GAN architecture

To differentiate histopathological images as benign or malignant, Semi-Supervised GAN uses the limited labeled samples and the large unlabeled images generated by a generator by following a Semi-Supervised learning framework.

3 Methods

This section presents an overview of data, methods, exploratory data analysis, and metrics used to classify histopathological images into benign or malignant.

3.1 Data

The dataset used in this research consists of 7,842 microscopic histopathological images. The image represents tumor tissue samples from 82 patients measured at four magnification levels (40X, 100X, 200X, and 400X). A total of 5,362 malignant and 2,480 benign samples are included in this dataset. The samples have 3 RGB channels and 460x700 pixel sizes.

Samples of histopathological images in the dataset were obtained through partial mastectomy or excisional biopsy. The larger tissue is removed during this procedure, and the procedure is performed in a hospital. The study used 80 percent of the images for training and 20 percent for independent testing. Split the data into 8:2 image ratios for training and testing each type of image.

3.2 Methods

3.2.1 Convolutional Neural Networks (CNN)

Convolutional Neural Networks are deep learning algorithms that can take an image and assign weights and biases to various features in it, then be able to differentiate them based on their importance. As part of the modeling process, a Convolutional Neural Network with different layers will be built to classify histopathological images.

CNN Model Architecture: Key features of Inception, ResNet, and AlexNet network structures were used to build Convolutional Neural Network. AlexNet is used as a basic architecture that contains four convolution layers and two pooling layers. The convolution layers consist of 96, 256, and 384 filters with a filter size of 3x3, respectively. The ReLU activation function is applied with each convolutional layer, and after the second and fourth convolutional layer, the max-pooling layer is applied. After the basic AlexNet structure, the inception block was used. Inception block maximizes the size of the features gradually, preserving the depth of CNN without increasing the memory requirements. Using Inception blocks, data can be normalized, and large convolutional layers are decomposed into parallel layers. Convolution kernels are limited to 1x1, 3x3, and 5x5. To prevent deep learning networks from degrading, it was decided to use the ResNet block. The ResNet block enables deep networks to train faster and provide faster convergence.

3.2.2 Pre-trained models

Various pre-trained models are used on histopathological images to extract complete details for the classification of breast cancer. These pre-trained models were trained on the ImageNet dataset.

- Visual Geometry Group (VGG)

- MobileNet
- Inception-v3
- ResNet50
- EfficientNet

This research will initially use the above pre-trained models to train the histopathological image dataset. Then the model will be fine-tuned according to features extracted from the dataset.

3.2.3 Semi-Supervised GANs

Create a Semi-Supervised GAN with a generator, a supervised discriminator, and an unsupervised discriminator that are trained simultaneously for classification. Any pre-trained model is used in Supervised discriminator.

Semi-Supervised GAN Architecture: Generator network consists of reshaping a random vector z to have a 4D shape followed by two transpose convolutions composed of 128 and 256 filters of size 4x4, respectively, with leaky RELU non-linear activations to increase spatial dimensions of input random noise vector and decreasing the number of channels. The Hyperbolic Tangent Function transforms the 224x224x3 RGB tensor the network produces into values between -1 and 1.

The Discriminator network consists of three convolutions comprising 128 filters of size 3x3 followed by leaky RELUs activation functions. Finally, a fully connected layer and a dropout.

3.3 Exploratory data analysis (EDA)

The dataset consists of histopathological images for which EDA is not straightforward like other medical images and regular datasets. The images available are classified as benign and malignant, and internally they are categorized into four sub-categories under benign and four sub-categories under malignant categories based on image magnification 40X', '100X', '200X', '400X'.

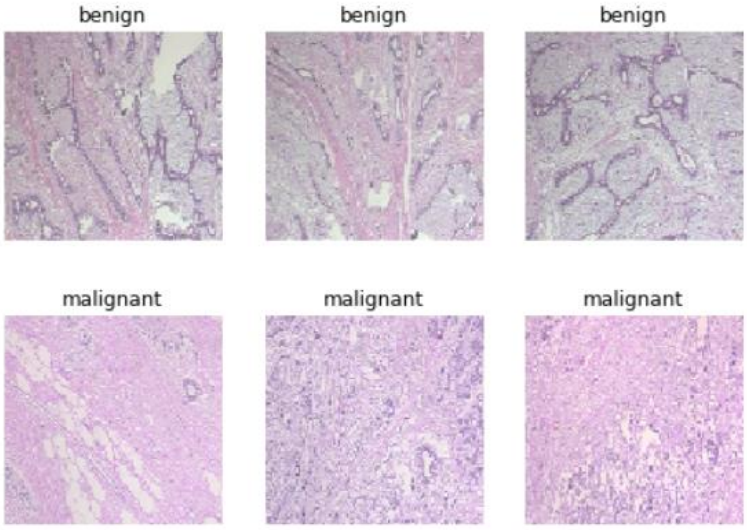

Fig. 5. Sample 40X images from the data set

The first step is to analyze the images and identify class imbalance by finding the number of images assigned to each category and subtype of the tumors for the different image magnification types available.

The distribution of images for four magnification levels for both main tumor categories and each sub-category is provided in Table 1. It is learned that the number of images in 100X magnification is 2059 (highest), and 400X magnification is 1812 (lowest). The count of images in each magnification is not equally distributed. It is observed that the number of malignant images is more than the benign images, which indicates data imbalance that should be considered during the modeling process.

Table 1. Image distribution among the main category and sub-category

			Image magnification			
Main Category	**Sub-Category**	**HxW**	**40 X**	**100 X**	**200 X**	**400 X**
Benign	Adenosis	460x700	114	113	111	106
	Fibroadenoma	460x700	253	260	264	237
	Phyllodes	460x700	109	121	108	115
	Tubular Adenoma	460x700	149	150	140	130
	Total		625	644	623	588
Malignant	Carcinoma	460x700	850	881	873	780
	Lobular Carcinoma	460x700	156	170	163	137
	Mucinous Carcinoma	460x700	205	222	196	169

	Papillary Carcinoma	456x700	21	21	19	13
		460x700	124	121	116	125
	Total		1356	1415	1367	1224
Total Images			**1981**	**2059**	**1990**	**1812**

The distribution of benign images is 35%, and malignant is 65% on average compared to the overall images available for the research, as shown in Figure 6.

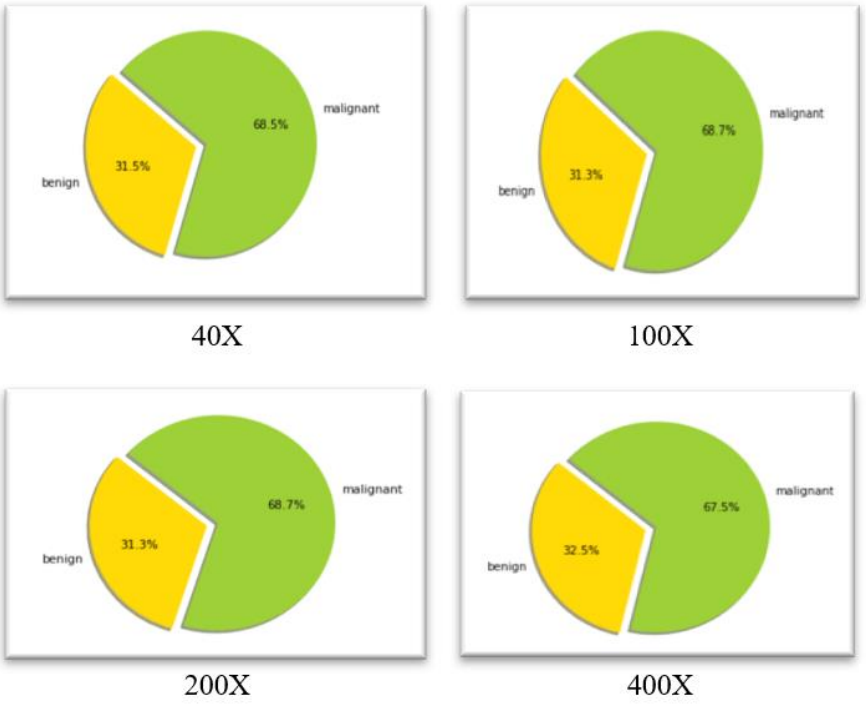

Fig. 6. Percentage of Image distribution among benign and malignant

The next step is to analyze the size of each image, and it is learned that all images have the same width and height of 460x700, but malignant images of sub-category papillary carcinoma have 75 images of size 456x700 size. This cannot be considered the outlier as the intent is to resize all the images to 224x224 or 299x299 based on the pre-trained models used for the research to identify the accuracy of the impacted models on the different magnification of images.

3.4 Evaluation metrics

Metrics such as accuracy, precision, and recall are used to compare the results of various classification models. The precision for classification models represents the ratio of the images that the model correctly identifies as malignant out of all the malignant images. The recall (also called sensitivity) represents the model's ability to correctly identify true positives. Accuracy means how well the model classifies both benign and malignant images correctly. AUC (Area under the curve; Receiver Operating Characteristic) could also be an effective metric under this principle as it measures the ability of the model to predict a higher score for positive examples.

4 Results

4.1 Transfer Learning Models

Several pre-trained models from the TensorFlow library were used to train histopathological images, including VGG, ResNet, Inception_v3, MobileNet, and EfficientNet. In these models, all convolution layers have been frozen except for the last fully connected layer (FC), which has been replaced with a dense layer with sigmoid activation functions. The loss and accuracy curves for training and validation sets of the VGG model are shown in Figure 7 below, which was trained for 50 epochs.

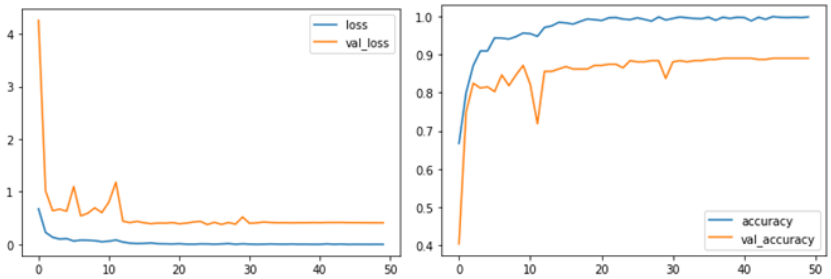

Fig 7. VGG model Loss (left) and Accuracy (right) curves of training and validation sets

VGG model confusion matrix of the test set shows the high classification accuracy rates of benign and malignant tumors at 82.08% and 89.43%, respectively. Malignant tumors were misclassified as benign in 10.56% of cases, while benign tumors were misclassified as malignant in 17.9 % of cases.

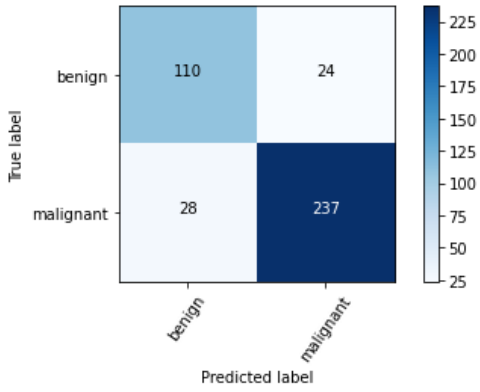

Fig 8. VGG model confusion matrix

VGG model performance is also assessed based on receiver operating characteristic curve (ROC) and area under the curve (AUC) values. AUC depicts the

summary measure of accuracy across all classification thresholds, which is 85.8% for the VGG model, as shown in figure 9.

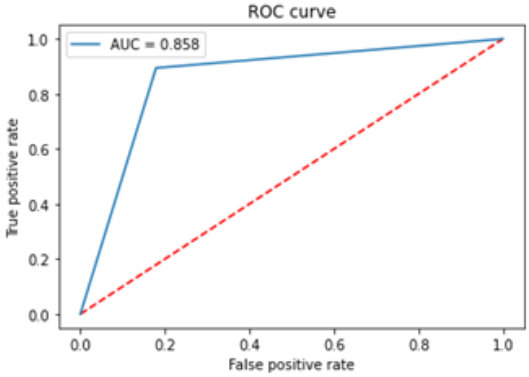

Fig 9. ROC curve for VGG model

Training, test accuracies, and other performance metrics of other pre-trained models are summarized in Table 2. Amongst the five models that were trained, the best performance results are with the VGG16 model, whereas EfficientNet exhibits the lowest performance results.

Table 2. Performance metrics of various pre-trained models

Model	Train Accuracy	Test Accuracy	Precision	Recall	F1-score
VGG16	99%	87%	86%	86%	86%
InceptionV3	99.29%	86%	84%	85%	84%
ResNet	99.99%	87%	86%	84%	85%
MobileNet	85%	73%	70%	70%	70%
EfficientNet	70%	63%	60%	61%	60%

4.2 CNN Model

Using Adam optimizer and a learning rate of 0.00002, the CNN model was trained for 200 epochs. The loss and accuracy curves for training and validation sets of the model are shown in Figure 10.

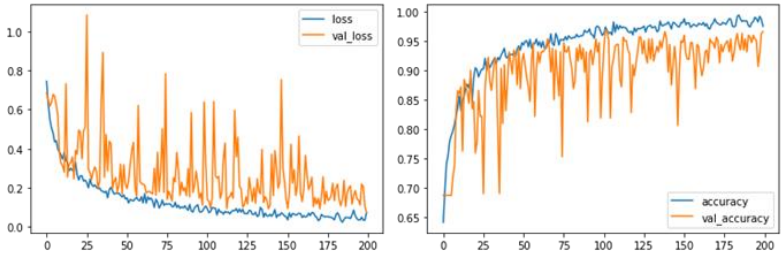

Fig 10. CNN model Loss (left) and Accuracy (right) curves of training and Validation sets

The CNN model confusion matrix of the test set is shown in Figure 11, which shows accuracy rates of 96% and 97.81% for benign and malignant tumors, respectively, with an F1 score of 97%. The misclassification rate is low compared to transfer learning models at 4% and 2.18%.

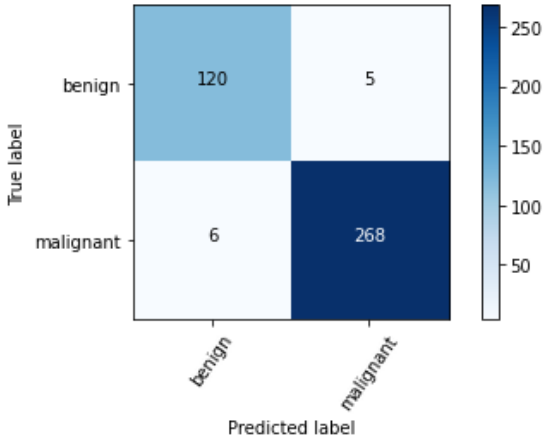

Fig 11. CNN model confusion matrix

The receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC) for the CNN model is shown in Figure 12. The AUC is 96.7%.

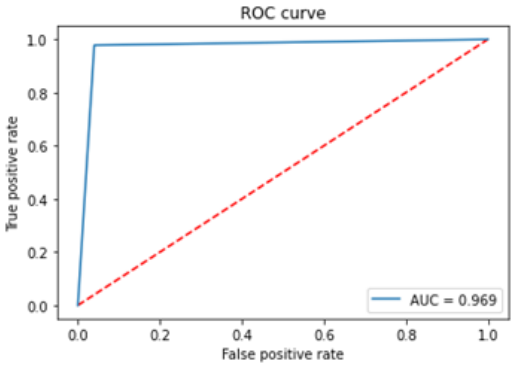

Fig 12. ROC curve for CNN model

4.3 Semi-Supervised GAN

Supervised and unsupervised discriminator models are stacked to extract the data distribution of real images. In an adversarial manner, generator and discriminator models were trained for 100 epochs with a batch size of 16. The accuracy curve for training sets of the supervised discriminator model is shown in Figure 13 below.

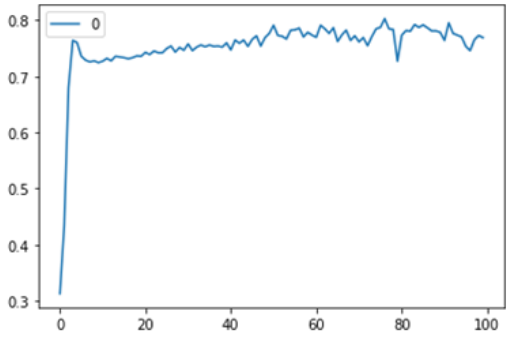

Fig 13. Semi-Supervised GAN Accuracy curve of the training set

The loss curve for training sets of the stacked discriminator and generator model is shown in Figure 14 below.

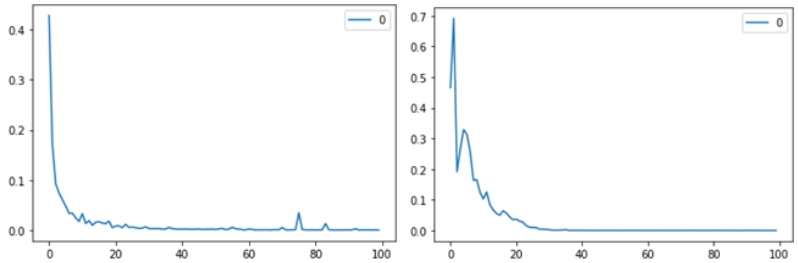

Fig 14. Semi-Supervised GAN discriminator (left) and generator (right) loss curves of the training set

The semi-Supervised GAN model confusion matrix of the test set is shown in Figure 15, which shows overall accuracy of 85%.

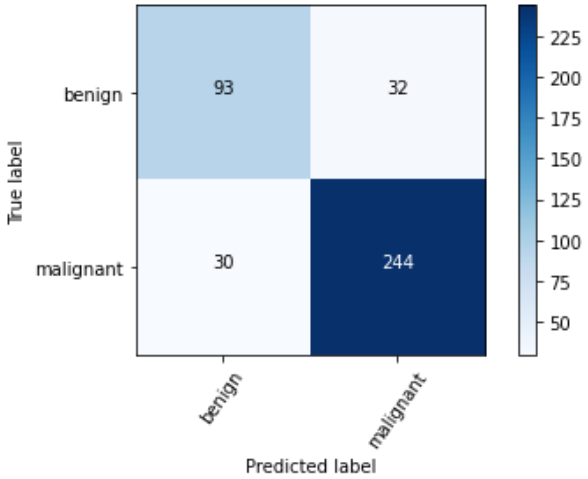

Fig 14. Semi-Supervised GAN model confusion matrix

5 Discussion

This paper aimed to check how Semi-Supervised GANs help to generate synthetic data to build models with better classification accuracy. At the same time, transfer learning models such as ResNet, Inception_v3, MobileNet, and EfficientNet were implemented on histopathological images, and accuracy is compared among them. The results from this paper can be used to replace the existing modeling techniques used to classify the histopathological image. In this research, three different approaches are considered. The first approach is to develop a deep Convolution Neural Network (CNN) with many layers to extract maximum information using limited labeled histopathological images. The second approach is to use the state of art pre-trained models like Alexnet, VGG16/VGG19, Inception, and ResNet. These pre-trained models were trained on millions of ImageNet images of 1000 categories that can help extract the maximum features. The final approach will use Semi-Supervised GANs where a generator model generates synthetic data, and discriminator models operate in two modes, supervised and unsupervised models. The discriminator model in the supervised model is trained to predict the class of images, while the discriminator model in the unsupervised model is trained to determine if the images are real or generated. But generating synthetic images using Semi-Supervised GANs is unique and remarkably interesting to see the generated data.

The two main challenges while training the model are vanishing gradient and the amount of computing time to train the model. Vanishing gradient problems are observed during the initial training epochs and are corrected by choosing the correct learning rate.

Out of the implemented models, the CNN model gave the best accuracy of 97.24% compared to other transfer learning models and Semi-Supervised GAN models. On the other hand, transfer learning models such as VGGNet, Inception, and AlexNet showed an accuracy greater than 87%. Still, MobileNet and EfficientNet performed with poor accuracy, which might be due to the images they trained on.

A Semi-Supervised GANs model can train on a smaller set of labeled data but still generalizes satisfactorily on an unseen test set. In contrast, the other algorithms that form the supervised learning techniques need more labeled data to be trained before they can accurately classify unseen test samples. In this study, the training process of the supervised discriminator model utilized only 20% of the labeled samples. The supervised discriminator model achieved over 85% average validation accuracy within just ten epochs and maintained accuracy throughout training.

Ethical Concerns

The dataset used for this research/study is a publicly available dataset from P&D Lab that does not have a patient or any Protected Health Information/Personally Identifiable Information (PHI/PII). This does not require any ethics approval or informed consent. Since the core goal of this research is to improve the accuracy of the different classification models, there does not seem to be any negative impact on ethics.

However, in the real-world scenario, a pathologist must abide by pathology ethics as they are involved in tissue research, professionalism, and patient confidentiality. The

results from the study should be used as a reference by pathologists and not as a replacement for any current diagnosis because of the chances of false negatives and false positives, which can be harmful to the patient.

The consent for biopsy needed to be discussed with patients where pathologists are required, although there is minimal contact to lay their professional relationship.

6 Conclusion and Future Work

The lack of extensive and labeled data significantly impacts the performance of breast cancer classification. The research conducted in this paper is Semi-Supervised GANs with a supervised discriminator model stacked over an unsupervised discriminator. This was used to generate synthetic histopathological image data and classification accuracies between 82% to 85% obtained. Obtaining this accuracy by providing limited labeled data to the model is interesting compared to other transfer learning models.

However, there are still improvements to tune the model to cut down the training time and improve classification accuracy. This research uses publicly available breast cancer histopathological data to train the Semi-Supervised GAN model. This should also be extended to use on various medical images such as CT scans, Xray, etc., and to study various kinds of cancer (skin, intestine, blood, reproductive organs) where histopathological images are used.

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