Classification of Histopathological Images of Penile Cancer using DenseNet and Transfer Learning

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Abstract: Penile cancer is a rare tumor that accounts for 2% of cancer cases in men in Brazil. Histopathological analyzes are commonly used in its diagnosis, making it possible to assess the degree of the disease, its evolution, and its nature. About a decade ago, scientific works in the field of deep learning were developed to help pathologists make decisions quickly and reliably, opening up possibilities for new contributions to improve such a complex and time-consuming activity for these professionals. In this work, we present the development of a method that uses a DenseNet to diagnose penile cancer in histopathological images, and the construction of a dataset (via the Legal Amazon Penis Cancer Project) used to validate this method. In the experiments performed, an F1-Score of up to 97.39% and a sensitivity of up to 98.33% were achieved in this binary classification problem (normal or squamous cell carcinoma).

1 INTRODUCTION

Cancer is related to disordered cell growth. Depending on the degree of malignancy, it can invade adjacent tissues or organs, leading the patient to death if there is no adequate early treatment. Penile cancer is a rare tumor and represents 0.4% to 0.6% of all cancers in Europe and North America but is considerably more common in developing countries in Latin America, Africa, and Asia (Douglawi and Masterson, 2017). According (INCA, 2021), this disease has a higher incidence in men aged 50 years and over in Brazil, being more common in the North and Northeast regions of the country and corresponding to 2% of cancer cases in men. A report from the state of Maranhão, Brazil, indicates an age-standardized incidence rate of 6.15 per 100,000 (Coelho et al., 2018), which is very worrying. This type of tumor is linked to some factors, such as lack of hygiene, human papillomavirus (HPV) infection, the presence of phimosis, and risky sexual behavior (Vieira et al., 2020).

According to (ACS, 2021), and (Thomas et al., 2021), one of the exams that can be indicated for the diagnosis of this disease is the histopathological analysis of tissues collected through biopsy, which consists of the microscopic evaluation of very fine tissues extracted from the region of interest. Before being taken for analysis, these tissues are stained using Eosin and Hematoxylin, then placed on glass slides (Neto, 2012). The pathologist verifies the structure of tissue cells understanding the evolution, subtype, and extent of the disease, making it possible to make safer decisions about the type of treatment or surgery to be prescribed. However, according to (Melo et al., 2020), this activity tends to be very complex and time-

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consuming because the process is detailed and has a subjective conclusion, depending a lot on the professional's expertise. Because of this, software-based solutions can help these professionals, bringing more reliability, enabling a faster diagnosis, and the sooner the disease is detected and together with adequate treatment, the greater the probability of cure.

With the evolution of machine learning techniques and image processing applied to medical images, several related scientific research based on diagnosis using histopathological images has been developed (Srinidhi et al., 2021), such as for breast cancer (Cruz-Roa et al., 2014) , prostate (Linkon et al., 2021), liver (Kiani et al., 2020), colon (Sarwinda et al., 2021) and lung (Wei et al., 2019). Thus, deep learning architectures, specifically convolutional neural networks (CNNs), ended up becoming quite popular for this type of problem. This popularity was due to its performance, in certain cases, superior to traditional methods of feature extraction and classifiers not based on neural networks; this can be seen in the results obtained in (Spanhol et al., 2016a), for example. However, concerning cancer diagnosis based on images at cellular levels of the penile tissue, the lack of a dataset that can support the researchers' experiments becomes an impediment to the development of specialized methods.

In order to fill this gap, this article proposes an automated penile cancer diagnosis method that analyzes the histopathological images and determines whether there is cancer or not. This method is based on transfer learning that uses a pre-trained DenseNet-201 type convolutional network for the ImageNet challenge with an image preprocessing step using an algorithm known as CLAHE (Contrast Limited Adaptive Histogram Equalization). In addition, the developed method was validated in a dataset built through the Legal Amazon Penis Cancer Project, comprising 194 histopathological images classified as normal or cancer (squamous cell carcinoma).

Our contributions are listed below: (a) the proposition of a new method for automated diagnosis of penile cancer based on deep learning using microscope images; (b) the construction of a new dataset of penile cancer histopathological images that served to validate the developed method; and (c) analysis and comparison of the proposed method with another one built by the same author based on deep features and traditional classifiers.

This paper's remainder is organized as follows: Section II presents the related works that served as the basis for the research that resulted in this paper, Section III explains how the histopathological images of penile cancer were acquired and details about the proposed method based on deep learning, Section IV, which presents an analysis of the results obtained through the method and other experiments carried out; and, finally, Section V, which concludes the work with some final considerations.

2 RELATED WORKS

Computer recognition of medical images, specifically cancer histopathological images, is a widely explored research topic, with many works available to obtain theoretical foundations that served as the basis for the entire development of a methodology and experiments.

In (Filipczuk et al., 2013), the Hough Transform was used to detect cell nuclei in histopathological images, and these had their characteristics extracted and used as input for an SVM (Support Vector Machine) classifier. In work described in (Spanhol et al., 2016b), feature extraction techniques such as Local Binary Patterns, Gray-Level Co-Occurrence Matrices, and Local Phase Quantization were used in several experiments with traditional classifiers in a dataset consisting of 7,909 breast cancer images.

Over time, traditional feature extraction techniques were replaced by techniques based on deep learning for this type of problem, with better results. In (Sharma et al., 2017), a CNN architecture was constructed and applied for cancer classification and necrosis detection using a gastric cancer histopathological image dataset. This work showed superior performance compared to the Random Forest classifier.

The use of preprocessing techniques is essential to improve image classification task performance. A work developed by (Sarwinda et al., 2021) demonstrated the use of the CLAHE algorithm together with the ResNet-18 and ResNet-50 neural networks for a binary classification problem (malignant or benign). In this case, a database of large intestine tissue images had its samples converted to grayscale and preprocessed using the CLAHE algorithm, substantially improving the classification results.

The transfer of learning technique in the classification of histopathological images has become very promising and popular, especially in cases where experiments are restricted to less powerful computers and datasets with few samples. This procedure consists of using pre-trained networks in a given domain in a similar or different one. The application of this technique can be seen in (Spanhol et al., 2017), (Boumaraf et al., 2021) and (Choudhary et al., 2021), and in this last work cited, the pre-trained network had its less important weights removed, improving the overall result of the model. In addition, data augmentation can be used to circumvent the sample quantity limitation, the class imbalance, and the overfitting problem, which can considerably affect the performance of deep learning techniques, as they perform better on image bases with thousands or millions of samples, such as ImageNet (Russakovsky et al., 2015). This technique causes the images to undergo some kind of transformation, thus producing new samples, works such as those reported in (Rakhlin et al., 2018) and (Tellez et al., 2019) showed very promising results when using it.

Finally, these works are a sample of the growing diversity of software-based studies with the purpose of automating the activity of analyzing histopathological images that represent state of the art in this field of research, being the foundation for the application of a specialized diagnostic method in a type of cancer image not explored in the literature.

3 MATERIALS AND METHOD

This section details the construction process of the dataset of penile cancer histopathological images used and the proposed method (Figure 1) that has its following steps: image acquisition; image preprocessing using the CLAHE (Contrast Limited Adaptive Histogram Equalization) algorithm; transfer learning and classification using an ImageNet pre-trained model based on the DenseNet convolutional network architecture; evaluation of the results on the subset of test image.

3.1 Histopathological Images Dataset Construction

The dataset of images provided by the Legal Amazon Penis Cancer Project, which served to validate the proposed method, consists of 194 RGB images with a resolution of 2048x1536 pixels. These files were grouped by magnification and pathological classification according to Table 1.

Table 1: Distribution of images according to magnification and pathological classification.

Category/Magnification	40X	100X
Normal	40	40
Cancer (squamous cell carcinoma)	57	57
Total	**97**	**97**

The image capture process was carried out in 2021 using penile tissue samples representing tumors and adjacent non-tumor areas, stained with hematoxylin and eosin stored at the Maranhão Tumour and DNA Biobank. Two graduate students photographed the samples using a high-definition camera (Leica ICC50 HD) coupled to a brightfield microscope (Leica DM500). With the aid of specific software (Leica Aperio ImageScope), the images were analyzed and classified by two pathologists as penile cancer or non-tumor tissue, according to the international classification of penile tumors (Epstein et al., 2020). Some examples of these images are shown in Figure 2.

3.2 Preprocessing

Before training or testing the model based on convolutional neural networks, we verified that the images had differences in light distribution. To minimize the effect, we propose a preprocessing via CLAHE (Contrast Limited Adaptive Histogram Equalization) algorithm presented in (Zuiderveld, 1994).

According to (Kumar and Shaik, 2015) CLAHE is an evolution of Adaptive Histogram Equalization (AHE) and its most basic precursor, Histogram Equalization (HE). Created for medical images, this algorithm is easy to implement and has good results when applied to microscopic images that are most often affected by low lighting effects at the time of acquisition (Kumar and Shaik, 2015). The main difference compared to its predecessors is in the way the histogram equalization is applied, not being on the whole image at once but on regions of adjustable size. The image is divided into blocks that are adaptively equalized, then combined and treated to avoid edge effects using bilinear interpolation.

In this work, initially, the images are resized to 224x224 pixels and converted from RGB to YUV. This transformation is necessary because all channels in RGB space carry color information. Therefore, undesirable effects on image colors would be noticeable after the equalization of these channels. Thus, the CLAHE algorithm was applied to the Y channel of the YUV color space (Villán, 2019). This channel represents the intensity information that needs to be improved. After this operation, the equalized images were converted to RGB. An example of this technique can be seen in Figure 3, where it is possible to see how evident the cellular structures of the tissue are after the operation.

3.3 Transfer Learning with Convolutional Networks

Convolutional Neural Networks are special architectures inspired by the biological mechanisms of vi-

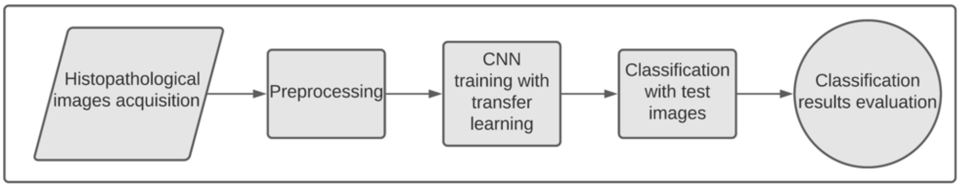

Figure 1: Proposed method.

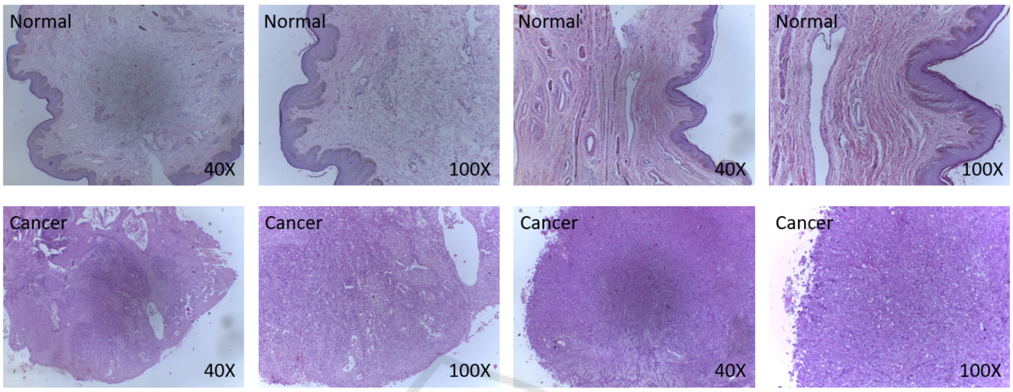

Figure 2: Examples of histopathological images of penile cancer by category and magnification.

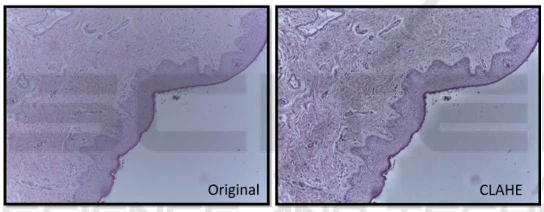

Figure 3: This example demonstrates the application of the CLAHE enhancement algorithm on a histopathological image of penile cancer.

sion of living beings, being used in classification, segmentation and object recognition tasks, for example. What makes them different from other neural network-based architectures are convolution operations in some of their layers. Still, in a complementary way, their structure is usually composed of other layers, such as pooling and fully connected layers. The first publication of this type of neural network was made by (Lecun et al., 1998). Still, they only became popular through the work of (Krizhevsky et al., 2012) for the 2012 ImageNet challenge as commented on in (Zhang et al., 2021), after that, many other new architectures emerged, being widely applied in the context of medical image analysis.

The complete training of a CNN started with random weights depends on an extremely large amount of images and many computational resources to process them. The quantity of samples tends to be a problem in the case of medical images, as there is an entire technical procedure to acquire this data in a correct and controlled manner to produce quality artifacts. Furthermore, there is another factor which is the availability of patients in a particular medical condition (Morid et al., 2021). To get around this problem, the use of transfer learning technique is the most indicated, in this approach the weights learned by a neural network in a given problem domain can be reused in another different domain, but as the classification layer is specific for the original problem, it is necessary to change the last layer to adapt this CNN architecture to a new problem. According to (Tajbakhsh et al., 2016), the initial layers of convolutional networks learn low-level characteristics that are generally applicable to most computer vision tasks. In contrast, those from deeper layers learn high-level characteristics specific to the problem domain by which they are being applied. Based on these statements, an auxiliary technique can be used together with transfer learning to improve training results, called fine-tuning, which consists of training the aggregated layers and those from the pre-trained CNN.

DenseNets were presented in (Huang et al., 2017), their main objectives are: to reduce the so-called vanishing gradient effect that often occurs in deep neural networks, in addition to strengthening the propagation of features and significantly reducing the number of parameters to be learned. The main characteristic of this type of CNN is how data is sent between the layers, each of which has connections with the other layers later, something very similar to ResNets. A DenseNet network is composed of several dense blocks that are separated by a transition layer that aims to reduce the size of the generated feature maps that will be sent to the next layers. There are several versions of DenseNets from the original work (Huang et al., 2017), numbered by the number of layers; in this case, the architecture used in this work has exactly 201 layers by default.

The proposed method uses a pre-trained model through the DenseNet-201 architecture in the ImageNet image base available in the Keras library written in Python. The use of this CNN type is justified because it had a superior performance in experiments performed concerning other architectures such as Xception and InceptionResnetV2, for example. This model was then trained using an Nvidia Geforce 3060 RTX in the penile cancer histopathological image dataset for both types of magnification in accordance with the transfer-learning technique. The classification layers were removed. The other layers of the network remained frozen. Three additional layers were added: an average pooling layer, a dense layer that uses the Relu activation function with 256 neurons, and an output layer that uses the Softmax algorithm. Furthermore, a dropout with an empirically defined probability of 0.35 has been added between the last two layers. Figure 4 shows the entire CNN architecture with the dense blocks, its connections between the transition layers, and the layers added by the author that are suitable for this binary classification problem.

Each training was performed in 35 epochs using the Adam optimizer configured with a learning rate of 0.0001. The batch size was adjusted to 32, and some experiments used data augmentation (horizontal and vertical flip and random rotation up to 90º). After each training, the resulting model was fine-tuned to improve the results. All layers of this network were unfrozen, and the model was retrained with eight epochs using a learning rate equal to 0.00001.

4 RESULTS AND DISCUSSION

After preprocessing the color images, the model was trained using k-fold cross-validation to assess the generalizability of the model. Each experiment was configured for five folds in a stratified way, and for each of the five rounds, a different fold of images is selected for testing; the others are used to compose the training and validation partitions, respectively 80% and 20% also in a stratified way. Table 2 presents the experiments performed that demonstrate the influence of preprocessing and data augmentation on the results. In order to evaluate the proposed method, the following metrics were used: accuracy, sensitivity, specificity, precision, and F1-Score, with the latter indicator being the criterion used to indicate the best model.

Table 2: List of experiments performed to demonstrate the contribution of preprocessing with CLAHE and data augmentation to method results.

Experiments			
No.	**Mag**	**Preprocessing**	**Augmentation**
1	40X	Raw	No
2	100X	Raw	No
3	40X	CLAHE	No
4	100X	CLAHE	No
5	40X	Raw	Yes
6	100X	Raw	Yes
7	40X	CLAHE	Yes
8	100X	CLAHE	Yes

As shown in Table 3, the application of the CLAHE contributed to the method obtaining a good result for the 40X magnification based on the F1-Score metric, which is the harmonic mean between precision and recall; therefore, for experiment 3, the result was 97.39%(+/-2.13). For the 100X magnification, it is verified that the data augmentation contributed together with the CLAHE algorithm in experiment 8, which obtained 97.31 (+/-3.62) of F1-Score.

In addition to good F1-Scores, these trained models had significant results regarding recall. This metric reports the proportion of images that have cancer and that were rated positively. Therefore, experiment 3, carried out on images of 40X magnification, had the result 98.33%(+/-3.33), being more stable with a smaller standard deviation than other experiments; for the 100X magnification, experiment 8 resulted in 98.18%(+/-3.64).

In addition to the experiments carried out to verify the performance of the method proposed in this dataset of histopathological images, the author experimented with another similar method based on the deep features technique. DenseNet was used to extract features from the resized images (224x244 pixels) that were highlighted by the CLAHE algorithm. Then the resulting feature vectors served as input to a classifier in the training and testing steps. To find a good model among several classifiers (Decision Tree, Random Forest, and K-Nearest Neighbors), we used the GridSearch algorithm with stratified 5x5 folds nested cross-validation. The results by magnification and classifier can be seen in table 4. The results, in this case, were very promising, especially for the selected model trained in the KNN classifier for 40X magnification, which had its indicators slightly higher than the others, obtaining an F1-Score

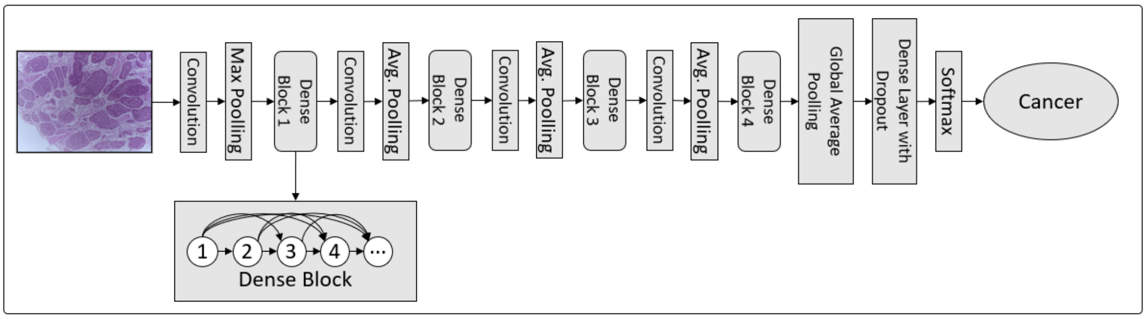

Figure 4: DenseNet-201 architecture along with the layers added by the author: shortcut connections are pertinent to each dense block, and the operations between blocks are the transition layers; finally, additional layers were included in order to improve and adapt the network to the binary classification problem.

Table 3: Results of the proposed experiments.

Experiment No.	Accuracy(%)	Recall(%)	Especificity(%)	Precision(%)	F1-Score(%)
1	92.74(+/-4.26)	96.52(+/-4.27)	87.50(+/-7.91)	91.79(+/-5.28)	93.98(+/-3.52)
2	92.89(+/-5.06)	100.00(+/-0.00)	82.50(+/-12.75)	89.81(+/-6.69)	94.50(+/-3.72)
3	**96.89(+/-2.54)**	**98.33(+/-3.33)**	**95.00(+/-6.12)**	**96.67(+/-4.08)**	**97.39(+/-2.13)**
4	94.89(+/-3.16)	100.00(+/-0.00)	87.50(+/-7.91)	92.27(+/-4.55)	95.92(+/-2.44)
5	91.68(+/-6.37)	92.88(+/-6.77)	90.00(+/-9.35)	93.16(+/-6.71)	92.87(+/-5.53)
6	93.89(+/-3.72)	98.33(+/-3.33)	87.50(+/-7.91)	92.14(+/-4.56)	95.06(+/-2.97)
7	92.74(+/-4.26)	94.55(+/-7.27)	90.00(+/-5.00)	93.26(+/-3.48)	93.72(+/-4.01)
8	**96.84(+/-4.21)**	**98.18(+/-3.64)**	**95.00(+/-6.12)**	**96.52(+/-4.27)**	**97.31(+/-3.62)**

of 95.47%(+/-5.23). For the 100X magnification, the model trained by the RF classifier obtained an F1-Score of 95.71%(+/-2.89). Despite these results, the proposed method did better according to the comparison presented in table 5.

Complementary, some experiments were carried out on the test images to verify which regions the convolutional neural network took into account to make a given classification decision. This verification was performed based on the results of the Gradient-weighted Class Activation Mapping algorithm, known as Grad-CAM (Selvaraju et al., 2019), which is based on the gradient data of the last convolutional layer of a CNN. This approach allowed a heat map type image superimposed on each image classified by the DenseNet network. Examples of these experiments can be seen in Figure 5 for the 40X magnification images and in Figure 6 for the 100X magnification images. In this case, we conclude that the neural network considered the tissue edge regions in all cases as the most important for classification.

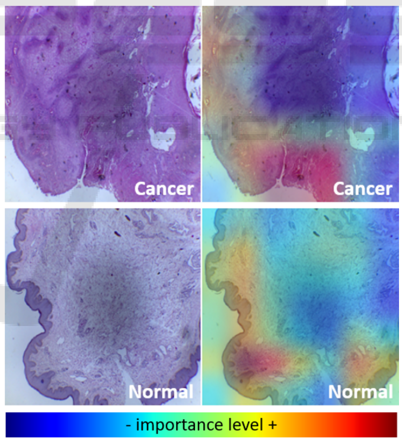

Figure 5: Grad-CAM algorithm result when overlaying the heat maps with the evaluated 40X magnification images.

5 CONCLUSION

In this work, a specialized method based on deep learning and image enhancement for the problem of binary classification of penile cancer histopathological images was presented. As discussed above, it achieved promising results with an F1-Score of up to 97.39%(+/-2.13) on an imaging database used for the first time in experiments to automate image-based medical diagnoses.

As future work, we suggest to use techniques that can better take advantage of the characteristics of high-resolution images, such as patch extraction methods and the use of weakly supervised learning through multiple instance learning techniques, for example. We pretend, furthermore, to update the dataset

Table 4: Additional results for ablation experiments based on deep features and on the use of GridSearch for the selection of models. The classifiers were represented by the following abbreviations: DT = Decision Tree; RF = Randon Forest; and KNN = K-Nearest Neighbors.

Mag.	Classifier	Accuracy(%)	Recall(%)	Especificity(%)	Precision(%)	F1-Score(%)
40X	DT	87.68(+/-3.99)	91.36(+/-9.14)	82.50(+/-15.00)	89.59(+/-8.63)	89.69(+/-3.42)
40X	RF	93.84(+/-1.92)	98.33(+/-3.33)	87.50(+/-7.91)	92.14(+/-4.56)	94.98(+/-1.34)
40X	**KNN**	**94.84(+/-5.77)**	**94.70(+/-7.20)**	**95.00(+/-6.12)**	**96.46(+/-4.39)**	**95.47(+/-5.23)**
100X	DT	78.47(+/-5.48)	82.73(+/-8.87)	72.50(+/-9.35)	81.44(+/-4.89)	81.75(+/-5.10)
100X	**RF**	**94.84(+/-3.33)**	**98.18(+/-3.64)**	**90.00(+/-5.00)**	**93.44(+/-3.32)**	**95.71(+/-2.89)**
100X	KNN	91.84(+/-8.27)	94.70(+/-7.20)	87.50(+/-13.69)	92.18(+/-7.90)	93.27(+/-6.78)

Table 5: Comparison between the proposed method (line 1 and 2) and another one created by the same author based on deep features (line 3 and 4).

Mag.	Feat. Ext.	Classifier	F1-Score(%)
40X	**DenseNet**	**DenseNet**	**97.39(+/-2.13)**
100X	**DenseNet**	**DenseNet**	**97.31(+/-3.62)**
40X	DenseNet	KNN	95.47(+/-5.23)
100X	DenseNet	RF	95.71(+/-2.89)

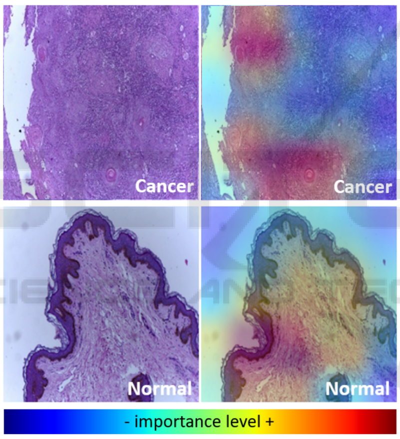

Figure 6: Grad-CAM algorithm result when overlaying the heat maps with the evaluated 100X magnification images.

with new images and information that will make it possible to evolve the method presented in order to classify images with cancer by the presence of HPV and histological grade.

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