ARTIFICIAL INTELLIGENCE-BASED SOLUTION TO PATHOLOGICAL DILEMMAS: MELANOCYTIC LESIONS

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Abstract

Artificial intelligence is a rising star in pathology. Applying artificial intelligence methods to pathology is a gleam of hope to reduce the workload of pathologists. Diagnosis in melanocytic lesions can be challenging. There are lesions that cannot be clearly addressed, not only for general pathologists, but even for dermatopathologists. Can artificial intelligence help us with this dilemmas? To find an answer we aimed to measure the contribution of artificial intelligence to the differential diagnosis of melanocytic lesions. We used machine learning in the first part and deep learning in the second part in order to measure artificial intelligence's contribution to the discrimination of melanocytic lesions. It has been observed that both methods can provide diagnostic support with high accuracy rates. Our study shows that we can get the support of artificial intelligence in the field of pathology. However, there are still issues to be discussed and resolved regarding the place of artificial intelligence in pathology.

Key Words

Artificial intelligence, Deep learning, Machine learning, Melanocytic lesions, Pathological dilemmas

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1. Introduction

Artificial intelligence (AI) can be defined as the intelligence of computers that uses an algorithmic mathematical approach. It uses the ability to the inference of probabilities to solve problems. Machine learning is a part of AI and includes different methods (decision tree, K-nearest neighbor algorithm, support vector machine, etc.). These methods learn from experience, making the algorithm learn from the training data and applying it to new data to make decisions. It can be either supervised or unsupervised. Deep learning is a network simulating the human brain that analyzes inputs and gives outputs. Perceptrons, nodes transferring data to the next layers, work as neurons and create three main layers of the network: input, hidden, and output. Convolutional neural network (CNN), recurrent neural network (RNN), long short-term memory, and U-net are the most often utilized deep learning methods (1). In pathology, AI must identify patterns, extract features, and classify them. Thus, it can make inferences from new data. CNN is the most applied network in pathology in distinguishing benign versus malignant tumors, histopathologic grading, subtype determination, etc. (2,3,4).

Malignant melanoma is the most common cause of death from skin cancers. The diagnosis is made upon histopathological criteria whether an excised nevoid lesion is benign (ordinary nevus-ON), malignant (malignant melanoma-MM) or gray zone lesion (dysplastic nevus-DN). Disagreement between two pathologists may occur in the relative evaluations made with human perception at the stages of diagnosis (5). In our paper, melanocytic lesions are introduced to machine learning and deep learning algorithms using previously applied AI models. Their guidance as an auxiliary method in differential diagnosis is evaluated.

2. Material and Methods

The study was performed according to the tenets of the Helsinki Declaration and according to approval by the local Ethics Committee of the Duzce University Medical School (prot. 2019/265 of 16 December, 2019).

This project consists of two steps. In the first step, machine learning algorithms are trained to categorize melanocytic lesions (MM-ON) according to their clinicodemographic features. In the second part, CNN is trained with the images of the lesions (MM-DN-ON) to distiguish them.

2.1 Part 1: Machine Learning

The Pathology Department database of Düzce University Medical School was searched for melanocytic lesions. The dataset for machine learning includes 51 MM and 54 ON cases, with almost equal numbers of examples in each category. The clinicodemographic features, including age, gender, localization, and diameter of the lesion have been documented as an excel file.

In this part, a classification system (machine learning-based clinical support decision system-CDSS) has been developed to teach clinicodemographic features to AI and is used in lesion classification (MM/ON). Four machine learning methods consisting of KNN, SVM, Logistic Regression, and Decision Tree were trained in two different developmental environments: Python (Python 3.7 version) and MATLAB (Matlab Classification Learner tool). The patients' age, and gender as well as the localization and diameter of the lesion are tought to machine learning algorithms. 80% of the data set was used for training and 20% for testing.

2.2 Part 2: Deep Learning

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The archive of Düzce University Department of Pathology was searched for melanocytic lesions. 51 MM, 36 DN, 105 ON cases were evaluated; Cases with inaccessible slides, whose paint was faded and/or where a proper preparation could not be obtained in new sections were excluded from the study. Available slides with optimal sectioning and staining quality were selected. Additional 12 DN cases were added to the study from the archive of Ankara University Department of Pathology. Finally, a total of 147 melanocytic lesions consisting of 36 MM, 38 DN, 73 ON were included. Haematoxylin and Eosin-stained slides were reviewed by two authors (MG, SB) to confirm the diagnosis. The most appropriate slides (with no artifacts) were scanned by PANNORAMIC® Flash DESK DX scanner to obtain whole slide images (original size:1392 × 1040 pixels). Since the CPU was not capable of processing the whole image, the images were split into representative sections (512x512 pixels; 2x magnification). Due to the small number of cases, data augmentation (rotation, flip, etc.) was performed to train the artificial neural network efficiently. As a result of data augmentation, 3900 images were obtained, including an equal number of MM, DN, and ON. The implementation of this study was carried out using Keras's deep learning library on the Tensorflow infrastructure. CNN architecture including "cyclical Conv2D-BatchNormalization-MaxPooling-Dropout" and flatten-dense parts was applied. 80% of the data set was used for training and 20% for testing. In the training phase of the developed CNN architecture, hyper-parameters (optimization algorithms, number of training rounds, number of simultaneously processed images) have been tested by changing them until the highest performance (accuracy, sensitivity, etc.) is obtained, and the obtained results are measured. Using only x2 magnifications from the pictures is a limitation of our study.
Figure 1 shows a schematic representation of the image processing and CNN networks` algorithms.

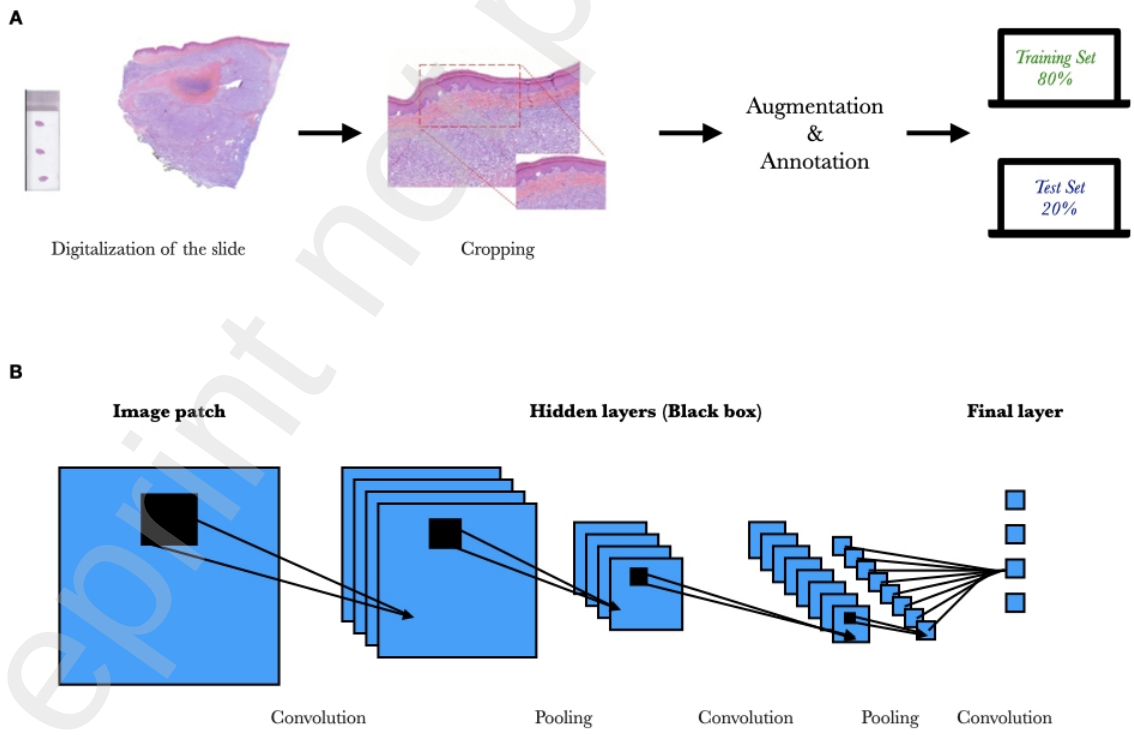


Fig. 1 Schematic representation of image processing (A) and CNN algorithm (B).

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3. Results

In this study, clinicodemographic features were taught to the machine learning and histopathological features were taught to neural networks in order to differentiate melanocytic lesions with artificial intelligence.

3.1 Part 1: Machine Learning

A CDSS estimates case-specific diagnosis by storing data on the patient's disease. Figure 2 demonstrates the accuracy rates of the algorithms trained in this study. The highest classification success was obtained with the KNN classifier in the Python program, with 93.3%. The success of the classification shows that CDDS can assist the pathologist as well as the dermatologist in the diagnosis of melanoma with high accuracy.

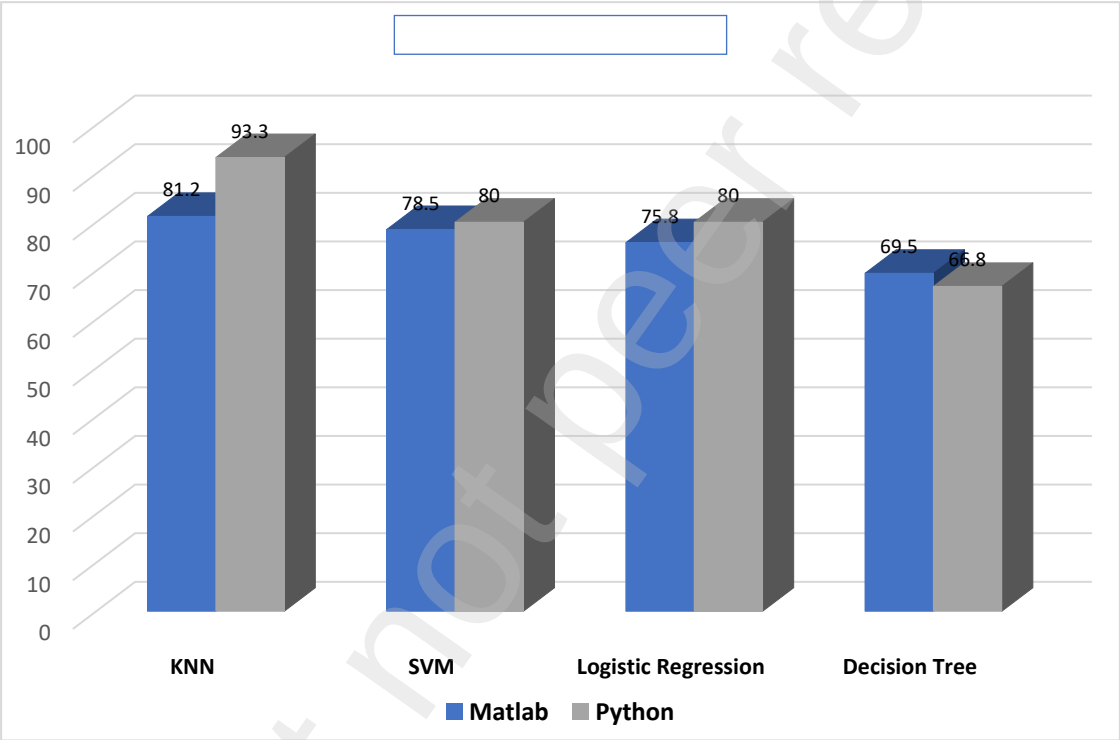


Fig. 2 The graphical presentation of the comparative accuracy scores of Machine Learning Algorithms in this study (%)

3.2 Part 2: Deep Learning

The time taken during the training and testing of the deep learning architecture developed in this study is calculated in seconds. The duration of training of the architecture, which was designed using the filter size 3x3, the number of filters 32, the scrolling step 1, the number of images processed at the same time 60, the optimization algorithm RMSProp, the number of training rounds 60 and the number of convolution layers 3, took 8 hours and 13 minutes. The accuracy value of the model, which is used to measure the success of the model and is required to converge to 1, was 0.8675, the F1 score was 0.8298, the sensitivity value was 0.8383, and the recall value was 0.8762.

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4. Discussion

In addition to many other sectors, artificial intelligence has begun to be employed in the medical field, especially in the last ten years. It has a wide variety of application possibility in pathology, since diagnostic methods necessitate the usage of tissue images. In our investigation, both machine learning and CNN were trained, and both offered highly accurate differentiation in melanocytic lesions. In the future, by training machine learning and artificial neural networks with larger data sets, a cascading support system can be created for the diagnostic process of melanocytic lesions in pathology. This method can provide a more reliable use of AI.

Radiologists applied a multistage AI assessment and termed it "radiomics" (1). Pathological evaluation is multidirectional and involves numerous steps before reaching a diagnosis. It is suitable for applying a similar approach as radiomics. AI could be employed to gradually reduce differential diagnoses until the proper diagnosis is reached. First, the algorithm will know the organ region. Then, by introducing the clinicodemographic variables and biopsy location, it will guide AI into certain diagnostic categories. After AI has made a judgment about the lesion, the algorithm will be provided with the macroscopic features (which can be photographs or text). Then, it will search for similar images of the H&E slides to arrive at a diagnosis. Immunohistochemistry results will be used to support the diagnosis. Finally, AI will determine prognostic and therapeutic parameters. If necessary, molecular pathology steps will be defined among them. The data obtained as a result of all these steps will not only guide pathologists but also help reduce their workload. It will also give an objective perspective on subjective evaluations. To get an effective AI algorithm, we need a huge library of digital slides and an enormous amount of data.

Hekler et al. trained the CNN network to differentiate melanocytic lesions (nevus/melanoma). Although a limited area of lesions (1 area per x10 magnified lesion) was taught to CNN, the discordance rate was approximately 20% for both at melanomas and nevi (5). In the continuation of their work, they compared pathologists with AI and found that it outperformed pathologists with an accuracy rate of 68% (6). The literature and our study's high accuracy rate (86,7%) support the utilization of artificial intelligence in the pathological diagnosis of melanocytic lesions. In addition, in the study of Hekler et al. (x10) and ours (x2), only a certain fraction of the images were represented at a certain magnification. Even in this state, AI was able to diagnose with high accuracy rates. Cropping the images did lower the training time of AI in Hart et al.'s study (7). The pathologist brain reaches the diagnosis with a deductive method. However, training AI with coded fields and cropped images seems for now to create a more efficient and robust assistant.What is more to overcome the obstacles of binary systems and create more reliable diagnostic tools, AI needs to be taught to distinguish and diagnose more distracting categories of lesions (8).

It is unclear where the CNN focuses and how it reaches a decision while processing the image due to its hidden layers (known as the black box). The existence of this black box prevents us from truly comprehending the underlying mechanics that AI uses to reach a decision. The learning phase of CNN is unsupervised, thus increasing the risk of algorithmic bias. This is a barrier to the widespread application of AI in pathology. The grand challenge to classify breast lesions into four categories (BACH) has highlighted this issue with an example. Because they had previously been educated with similar images, the CNN algorithms they constructed categorized fat necrosis as malignant and benign lesions as in-situ carcinoma. Pathologists who closely examine the images noticed that AI has concentrated on the general architecture of the images rather than on nuclear details (9). A different set of CNN models may be deployed to overcome this barrier.

The pathological diagnostic process is a complicated one that involves examining a wide range of information to arrive at a diagnosis. It is challenging to incorporate AI directly into diagnostic processes with the purpose of creating annotations. The pathologist determines if the

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lesion is MM/DN/ON based on several histological parameters. Histopathological diagnostic criteria of MM are asymmetry, the pagetoid spread of melanocytes, lack of maturation, nuclear atypia, mitosis, etc. The presence of mitosis is the most definable and reliable indicator. Mitosis is not expected in ON, especially in the deep dermis. Furthermore, nevoid melanoma is an insidious lesion that can be easily overlooked especially by general pathologists. Detection of mitosis in a banal melanocytic lesion raises suspicion of nevoid melanoma. Region-based CNN (R-CNN) allows annotations and discriminates regions from the images as an output. As an approach R-CNN can be applied to increase the reliability of AI in pathology. Labeling mitosis in MM and feding it to R-CNN may be a method to improve accuracy. Deep learning methods can be combined with machine learning methods to broaden their usefulness. For example, before labeling the mitosis, a "Conditional Random Field (CRF)" might be used to emphasize the tumor region (Region of interest-ROI). Zormpas-Petridis et al. used this method to assess the effect of the tumor microenvironment on MM prognosis and survival analysis (10). ROI extraction was also used to discriminate the tumor area by Ianni et al in which they classified H&E stained WSI into four diagnostic category (11). So, R-CNN can be used to search for mitosis in the ROI and give labeled image results to the pathologist.

Following the AI's diagnosis of MM, pathologists must specify the histopathological prognostic parameters. The primary histopathologic prognostic indicators of MM include Breslow thickness, neurotropism, mitosis, lymphocytic response, and ulceration. CNN may learn to define these parameters and quantify the precise value of the parameters by highlighting and annotating the ROI. This will assist to save reporting time and get an objective assessment also for quality assurance approach. It will reduce the workload for pathologists and may also be a solution for the shortage of trained dermatopathologists.

An interesting approach is defined by Kulkarni et al. They introduced melanoma images to CNN to identify a prognostic tool and quantified its impact on disease-related survival. CNN essentially used the proportion of immune system cells and found a correlation with disease-related survival (12). This next-step approach can be added to pathology reports and may have a transformative impact on clinical decisions and patient care.

Diagnosis of melanocytic lesions can be challenging and a lack of agreement is seen even among expert dermatopathologists (13). Considering the rare variants (14) and the diversity of subtypes (15), the differentiation of melanocytic lesions becomes more difficult. For example, it is difficult to differentiate a cellular blue nevus from a malignant blue nevus or a desmoplastic melanoma. In addition, it may be difficult to distinguish malignant peripheral nerve sheath tumors from spindle cell melanoma. Although they have different tumorigenesis, as shown in our previous study (16), they can be morphologically similar. Pathologists assess the lesion as a whole first and then formulate an algorithm by focusing on the relevant regions of interest. Since, the WSI data size is very large, the training of AI is done by dividing the images into small pieces. At this point, we can use immunohistochemistry to teach the lesion to AI, just like we use it in our daily practice. The model of immunohistochemically stained slides with dual staining of SOX 10 and keratin (to highlight the association of epidermis and lesion) can also be taught to AI. So, AI can recognize the immunohistochemically labeled cell distribution pattern. Here, the immunohistochemistry will act as a filter, the AI will recognize the cells of interest much more easily, and the segmentation of the image will be done more reliably at low magnification. This will reduce the demand for high software capacity and make the diagnostic challenge for AI easier. The cloud systems and CPU-GPU are continuously developing. However, they are still unable to handle pathological slides with high resolution. Therefore, we require a strategy that is both useful and does not require a significant amount of computational resources.

4.1 Applicability; Problems and solutions

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Pathology slide digitalization necessitates a massive computational space. Every slide constitutes a storage space measured in gigabytes. Petabytes of data will be generated by scanning every slide at every institution. The overload of images, as well as the fees necessary to retain them, will stymie the advancement of digital pathology.At this point, a question that comes to mind is 'Does artificial intelligence need such high quality images?'. Jiang et al. showed that AI can make diagnoses from microscopic images taken with smartphones (17) which can be a solution and also an answer to the question.

Separating cases into appropriate diagnostic classes is also a workload. Multi-institutional collaborations are needed to form reliable, cost-effective libraries of entities in addition to the novel-technology of ‘cytoscanner’ devices and slide-preparation techniques to increase efficiency of the process (18). Multi-institutional collaborations will also boost data heterogeneity, which will improve AI's ability to form inferences.

Another issue is that not every institution has the capability of scanning their slides in order to use AI. However social media has revolutionized our capabilities of sharing images worldwide by providing an easily accessible, dynamic, fast-paced, and limitless platform. Sharing images is also within the scope of telepathology, which aims to provide an easy approach for diagnosis (rapid-on-site evaluation, intraoperative diagnosis, consultation, ancillary tests, etc.), teaching, testing, archiving, and quality assessment (19). Schaumberg et al. even developed a tool in which the images on social media were the main source of image data. The tool (pathobot) helped pathologists to find the entities similar to their cases and predict the disease (20). Pathobot also made it possible to use the application with the mobile cameras we use in our daily life. The existence of an accessible AI application that will guide pathologists in the future is not impossible. The availability of this technology can also contribute to resident training in pathology. Building a common educational platform and providing assessment systems around the world may be possible with the support of AI and digital pathology.

Validation is critical for the use of AI in pathology since the results will emerge as a "definitive diagnosis" that will guide the treatment. Therefore, validation is essential to have a reliable algorithm. Experienced pathologists should be included as a descriptive team and the most appropriate AI method should be applied to obtain optimal and reliable validation. In addition to the technical validation, how could the scientific thinking be taught to AI? Surely, the collective scientific knowledge of mankind is the greatest miracle of the world. According to Karl Popper's philosophy of science, a theory should not only be ‘verified’ but should also be ‘tested’ and even be ‘objectified’ to be considered as scientific (21).

Humanity and the advance of science throughout human history may be likened to a baby crawling in a huge labyrinth through a range of obstacles; including verifiability, testability, and objective evaluation. Once this labyrinth has been enlightened; road maps, flowcharts, and algorithms are created. Today's promising AI studies might also need to remain within the bounds of scientific and critical thinking required by falsifiability. Scientists must continue their unrestricted and also skeptical research to find the new route for AI in the ‘Labyrinth’. Skepticism has been the process of applying reason and critical thinking to determine validity (22).

Another subject that must be addressed is ethics. Ethics should not be an issue, and AI should not be included in the scope of ethics because the images include no information about the patient's identity and vanish when the algorithm is formed. This issue needs to be clarified according to make studies with free minds. Also, the responsibility of using the diagnosis of AI is an issue that needs to be clarified, as addressed and discussed in the article by Timothy Craig Allen (23).

5. Conclusion

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Artificial intelligence could aid in resolving the diagnostic quandary of challenging melanocytic lesions. It will also help to save reporting time and achieve an objective assessment. So, it will reduce the workload for pathologists and may be a solution for the shortage of trained dermatopathologists. As previously noted, AI is very applicable to pathological assessments. However, it needs to be much more developed to join the collaboration with pathologists. Both machine learning and deep learning algorithms have enormous potential. A pathological diagnostic procedure is a complex evaluation in which the lesion is assessed initially with its surrounding environmental structures. The pathologist then focuses on the area with the potential abnormality and makes an interpretation. These experience-based diagnostic approaches have a 'multi-tasked' processor: the brain. To apply 'artificial' intelligence to pathological diagnostic processes in a reliable and practical manner, pathologists must first be familiar with the fundamentals of AI and join forces to do good deeds for a greater patient care.

Conflict of interest statement

Declarations of interest: none

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