KMIT-Pathology: Digital Pathology AI Platform for Cancer Biomarkers Identification on Whole Slide Images

Digital Pathology AI Platform for Cancer Biomarker Identification

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***Abstract*—Analysis and identification of cancer imaging bio markers on biopsy tissues are done through optical microscope. Digital tissue scanners and Deep learning models automate this task and produce unbiased diagnostics. The digital tissue scanner is called as virtual microscopy which digitize the glass slide tissues and the digitized images are called as Whole Slide Images (WSI). They are multi-layered (level) images having high resolution, huge in size and stored as a pyramidal tiff file. As normal web browsers are unable to handle WSI, a special web imaging platform is needed to obtain, store, visualize and process WSI. This platform must provide basic facilities for uploading, viewing and annotating WSI which are the inputs to the deep learning models. The integration of deep learning models with the platform and the WSI database provides a complete solution to cancer diagnostics and detection. This paper proposes two AI deep learning models for the diagnostics and the detection of cancer imaging bio markers on breast cancer and prostate cancer WSI. Efficientnet deep learning model is used to detect ISUP (International Society of Urologic Pathologists) grading for prostate cancer which is trained and tested by 5000 prostate WSI and produces 80% accuracy with 0.6898 quadratic weighted kappa (QWK) score. R2Unet model is used to identify tubule structures for breast cancer which is a morphological component to grade breast cancer. The model is trained and tested by 17432 WSI tiles and generates f1 metric accuracy as 0.9961 with mean_io_u 0.8612. The paper also shows the complete execution of these two Deep learning models (from uploading WSI to visualize the AI detected results) on the newly developed WSI imaging web platform.**

Keywords—AI for cancer prediction and diagnostics; deep learning for WSI analysis; tubule prediction on breast cancer; ISUP grading for prostate cancer; WSI imaging platform

I. INTRODUCTION

Optical microscope is the fundamental device for analysing, diagnosing and identifying disease bio markers on the tissue slides. It helps to identify morphological and cell artifacts of the disease. The heavy workload and continuous diagnosis through naked eye on microscope by pathologist may lead to a biased analysis for the disease. Digital scanners remove all these limitations and introduce a new research field called Digital pathology. Digital scanners capture high resolution images of the glass slide tissues and produce Whole Slide Images (WSI) by scanning the conventional glass tissue slides which are the most usable imaging modality by the pathologists worldwide. WSI system, also called as virtual microscopy, consists of two parts namely a scanner (hardware) and a virtual slide viewer (software). Scanner scans the conventional glass slide into digital image (file) and virtual slide viewer helps to view and analyse these digital images.

The digital WSI files are larger than any other healthcare digital images such as radiology images. These files are multi gigabyte in size (about 1600 megapixels) and requires a storage space about 4.6 GB [1]. They are stored in various types of image formats used by whole-slide imaging equipment sellers, out of which the common ones are TIFF, OME-TIFF, JPEG, NDPI or SVS. All these vendor specific formats are handled in the WSI platform by Open Slide [2] and Bio-Formats which are C and java-based software tools developed by Carnegie Mellon University and OME Consortium [3] respectively. The main processes related to WSI are obtaining, storing, visualizing and processing the digitized WSI. As these files are constructed as a multi-layered pyramid structure which provides a microscopy visual effect to the users to view and navigate (pan and zoom) slides on the computer screen.

Deep learning is used to improve diagnostic accuracy in digital pathology. Various pathologists from different locations can collaborate on the web based WSI platform. The whole slide images can be visualized in the web browser and the pathologists can annotate (mark) the affected (cancer) region on the WSI with the help of annotation tools. These annotations can then be used as inputs for training deep learning models to detect and analyse the cancer regions.

Currently, there are a lot of WSI viewers available in the market. A few examples are Digital slide Archive (DSA) which has an inbuilt WSI viewer [4], Orbit image analysis which is a WSI viewer/analysis tool [5], Orthanc WSI is a web viewer [6], OpenSeadragon AJAX image viewer [7] is a web image viewer for reading and viewing WSI, SlideRunner is an open-source cell annotations and visualization tool [8] and QUPATH is a desktop application for WSI data analysis [9].

This paper proposes two AI deep learning models for Tubule structure detection in Breast Cancer and ISUP Grading detection in Prostate Cancer using a newly developed web imaging platform called as KMIT-Pathology. It also describes the important features of the WSI imaging platform such as obtaining/storing WSI, WSI/Tiles retrieval, annotations, visualizations, images analysis and AI predictions.

This paper is organized as follows; Section II discusses the related works. Section III describes the proposed web platform and deep learning models for cancer diagnostics and detection. Section IV presents the Results. Section V gives the Conclusion, Limitations and Further enhancement of cancer detection, deep learning models and the web-based imaging platform for WSI.

II. RELATED WORKS

The authors Tiago Marques Godinho [10] proposed an architecture to integrate digital pathology workflows with a universal Picture Archive and Communications Systems (PACS) using solely DICOM standard data formats and communications. They suggested that storing a WSI using tiled organization shown in Fig. 1 (Middle) is an efficient way than storing it in a single frame organization shown in Fig. 1 (Left). In single frame organization the entire image pixels are stored sequential array where as in tiled organization the entire image is stored as a series of rectangular regions which makes easy to directly access any 2D sub regions of the image.

Image pyramid organization shown in Fig. 1 (Right) helps to perform panning and zooming vision of WSI. Pyramid organization contains various zoom level tiled images of same WSI at various layers of the pyramid. The top layer of the pyramid contains the lowest resolution of the WSI called thumb nail whereas the bottom layer contains highest resolution tiled images of WSI. This structure felicitates the zooming/panning visualization of WSI. Pyramid organization is the accepted visualization standard for WSI by DICOM [11].

David A Gutman et al. [4] developed an open-source web-based platform called Digital Slide Archive (DSA) for digital pathology. DSA allows users to manage large collections of pathology images. DSA has an image viewer which can be used to view the pathology images. DSA represents the WSI (whole slide image) data in a pyramid structure that contains several images at different resolutions. Partitioning of WSI into tiles is done by the DSA for efficient image analysis and visualization which makes DSA scalable. They also discussed several image analysis algorithms and pipelines for WSI images.

OpenSeadragon (OSD) a JavaScript based open-source web viewer uses deep zoom images (DZI) developed by Microsoft to save pyramidal file for WSI. This helps OSD to extract/display querying image tiles rather than downloading the entire WSI. OSD provides efficient zoom and navigation on WSI through DZI file format and the different file formats of the various vendors are handled by open slide, a C based library developed by Carnegie Mellon University.

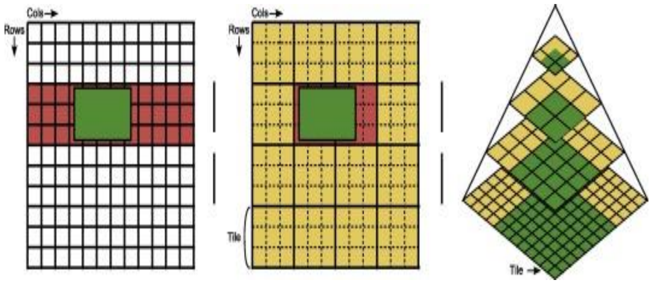


Fig. 1. Storage Structure of WSI (Single Frame Structure, Tiled Structure and Pyramidal Structure of WSI).

Slide Runner [8] is a python based open source WSI tool for massive cell annotation and visualization developed at Pattern Recognition Lab, Fried rich-Alexander-Universität Endanger-Nürnberg and the Institute of Veterinary Pathology, Freie University Berlin. It can perform various cell annotations such as centre of the cell, boundary of the cell, single cell annotation and multi cell annotations by a single click. It uses open slide to manage vendor formats of WSI and provide plugins for various image processing operations such as threshold, segmentation and normalization.

QuPath is a java-based desktop software for WSI imaging analysis. It provides annotation, segmentation and classification for individual nuclei or cells. It performs cellular map and morphological feature extraction of the entire tissue section. It uses ImageJ and open CV libraries for image processing operations. Users can create their custom workflow by using scripting functionalities and add their extensions along with the existing QuPath tools. Neofytos Dimitriou et al. [12] discuss the various deep neural networks training models for WSI and emphasize the different methodologies involved in these network models. They also discuss various image formats of WSI and the lack of a universal image format. They give the insights for better performance of deep learning training by using patches of WSI than the entire WSI.

Famke Aeffner et al. [13] gives a brief introduction for modern digital pathology concepts which includes digitization of glass slides, software tools and the complement between computational image analysis and GUI for displaying the WSI. They also discuss in detail about the importance of a pathologist's role in image analysis and emerging role of AI in digital pathology. The authors, Laura Barisoni et al. [14] describe the evolution of digital pathology and computational image analysis which brings a lot of new changes in the pathology ecosystem. They also talk about the use of computer vision and AI techniques in the conversion of digital pathology images into mine able data, extraction of image information, developing techniques to diagnostic diseases and help to accurately identify patients at risk.

Breast cancer is the most leading cancer in the world. Histological grading is used to evaluate the behaviour and prognosis of breast cancer on H&E images. It quantifies the tumour architecture and the cytology deviation of the breast cancer tissue against the normal. Nottingham Grading system is a globally accepted breast cancer grading system in which Tubule identification is one of the morphological components to grade breast cancer classification [15]. The authors, Xiao

Jian Tan et al. [16] used independent data set and support vector machine to classify tubule and non-tubule. They used three parameters spatial angle, distribution and harmonic mean to measure the amount of tubule and non-tubule formation and they got the classification accuracy as 98%.

Ajay Basavanhally et al. [17] used O'Callaghan neighbourhood method to identify tubule on H&E breast tissue. They involved not only low-level attributes for training but also include the spatial distances of lumen, cytoplasm and nuclei to detect tubule. They used colour convolution method to detect nuclei. Colour gradient based active contour model and hierarchical neighbourhood algorithm are used to detect lumen areas in tubule which produced 80% classification accuracy.

Prostate cancer is the deadliest cancer affects and destroys the stroma and normal arrangements of prostate glands. International Society of Urologic Pathologists (ISUP) grades the morphological /cytological patterns of the cells in prostate cancer tissues. Gleason Scoring System (GSS) is a part of ISUP grading which helps ISUP to find major and minor patterns of the cells. These major and minor patterns decide the value of ISUP which ultimately decides the grade of the prostate cancer. Yuchen Li et al. [18] combined different neural networks such as multi scale parallel branch convolution neural network (MP B-CNN) and DeepLabv architecture to identify Gleason grading and pattern segmentation for prostate cancer. The system used 1211 WSI for training and testing and produce mean IOU as 77.29 with quadratic weighted kappa (QWK) as 0.77.

III. PROCEDURE AND APPROACH

The WSI imaging platforms QuPath, Slide Runner and Digital Slide Archive (DSA) provide facilities for Data Annotations, Images uploading, retrieval and visualizations. QuPath is a desktop-oriented platform. All these platforms provide tools to perform WSI image processing techniques. There exists a gap in digital pathology which handles WSI images and require a web-based platform. This platform should perform an end-to-end operation such as images uploading, retrieval, annotations, visualizations with AI predictions.

The proposed KMIT-Pathology platform is designed to fill-in this identified gap by performing above listed end-to-end operations. This section describes the various features of KMIT-Pathology platform such as Description of pyramidal data structure of WSI, Annotations and visualization of WSI. This section also discusses about the deep learning models to identify tubule on breast cancer and to find ISUP grading for prostate cancer.

A. *WSI Visualization and Annotations*

KMIT-Pathology uses pyramidal structure files of WSI which are stored as .tiff and .SVS formats. Pyramidal images are stored with different levels of resolutions. The base level is having full resolution and as it goes up the resolution of levels decreases [19]. The thumbnail (the top most level) is a very low-resolution version of the image. Fig. 2 represents pyramidal image having various levels with different resolutions. SVS files are the digital slide images produced by Aperio digital pathology slide scanner [20]. SVS image format is essentially based upon the Tiled TIFF format, it also stores the tiles in pyramidal form. It has all the essential features of TIFF format with few additional features such as storing the thumbnail image and new non-standard compression tags (33003 and 33005) [21].

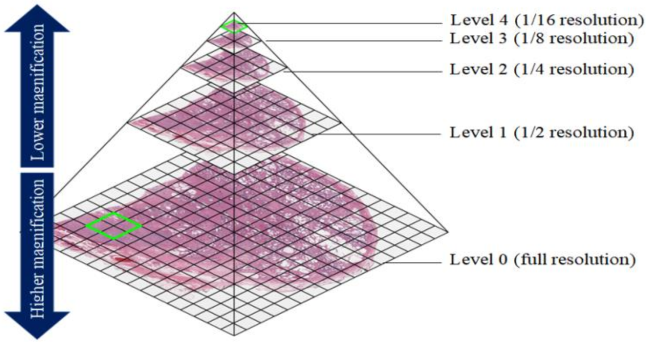


Fig. 2. Pyramidal Image with different Levels of Resolution.

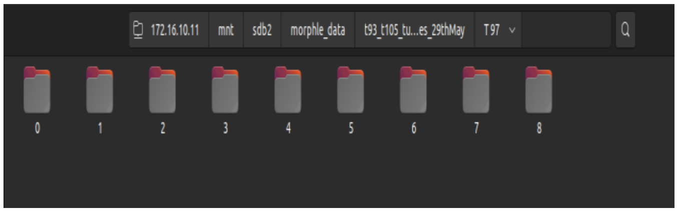
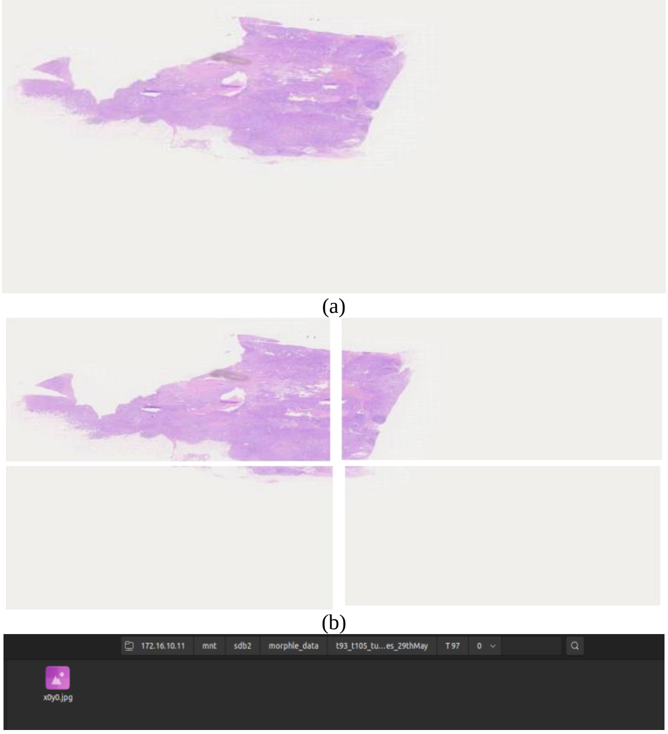


Fig. 3. Pyramidal Tiff (Level Wise Folders) of WSI.

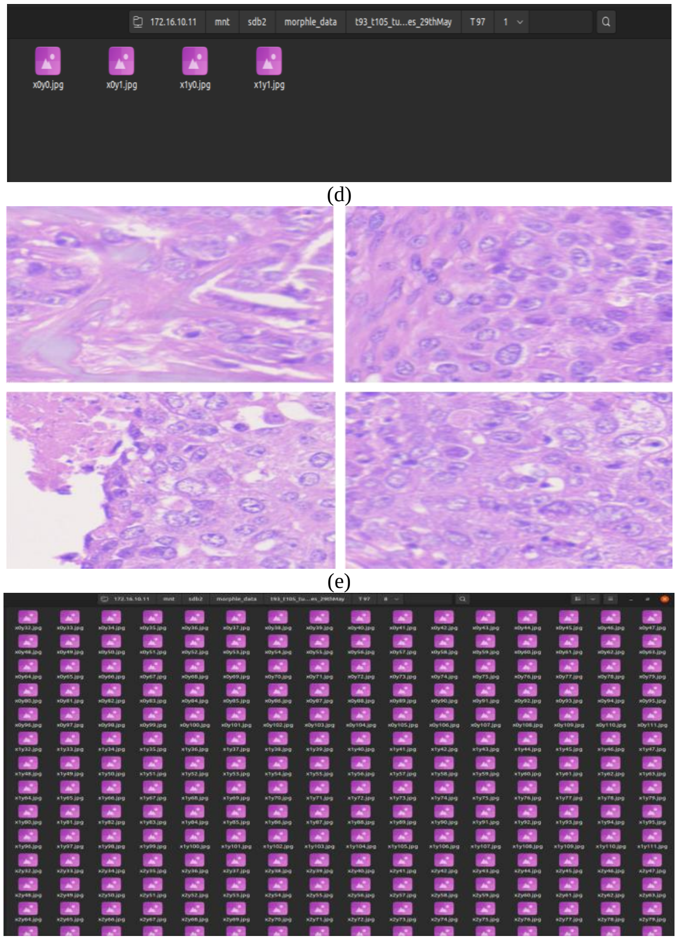
Morphle continum 240 scanner generates pyramidal TIFF files as a list of sequential folders (level wise resolution) with each folder containing a number of tiles belonging to the resolution of the respective levels as shown in Fig. 3.



(a)

(b)

(c)


(d)

(e)

(f)

Fig. 4. (a) Level 0 Resolution Image, Level 0 Low Resolution Image is shown in Fig. 4 (a), Fig 4(b). Level 1 Resolution Image, Level 1 Low Resolution Images are Shown in Fig. 4 (b), Fig 4 (c). Level 0 Images Folder, Level 0 Low Resolution Images Folder is Shown in Fig. 4(c), Fig 4 (d). Level 1 Images Folder, Level 1 Low Resolution Images Folders are Shown in Fig. 4(d), Fig 4 (e). Level 8 High Resolution Images, Level 8 High Resolution Images are Shown in Fig. 4(e), Fig 4 (f). Level 8 Images Folders, Level 8 High Resolution Images' Folders are Shown in Fig. 4 (f).

KMIT-Pathology uses zero to eight folders to view various zoom levels from 0x to 80x. Level zero (Folder 0) is the thumbnail of WSI and level eight contains high resolution tiles of WSI. Each level contains twice the number of tiles than the previous level. Level zero consists of one image, level one contains four images and level eight consists of thousands of tiled images which are shown in Fig. 4(a) to Fig. 4(f). OpenSlide is used for zooming and panning operations (for visualization) on tiles which are present in various levels of WSI as shown in Fig. 4(a) to Fig. 4(f). Visualization of a WSI (at Zoom level 1) on KMIT-Pathology platform is shown in Fig. 5.

Annotations on WSI done by pathologist shows the diseased region (ground truth) and deep learning models learns the features of the diseased regions from ground truth and identifying (or predicting) the diseased region on any new image, if it exists. Even though WSI can be visualized at various zoom levels (resolution), the annotations performed at any level will be reflected only at the base level (high resolution level). So, KMIT-Pathology provides facilities to annotate on base level tiles as well as on whole WSI. For example, as mitosis annotations (Fig 6(a)) requires base level annotations whereas tubule annotations (Fig. 6(b)) depend on structures which can be performed on whole WSI at any level.

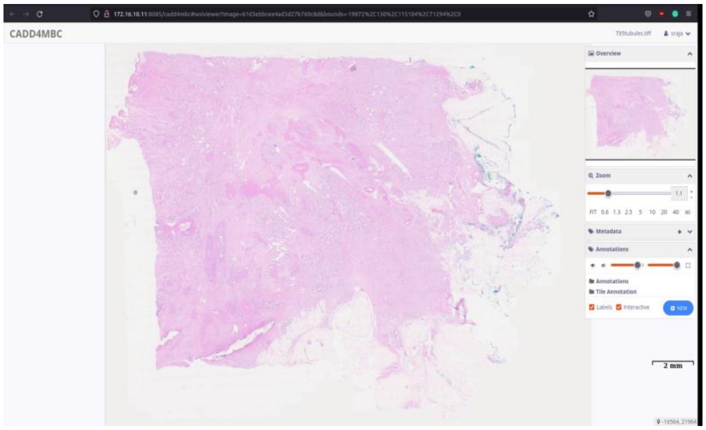
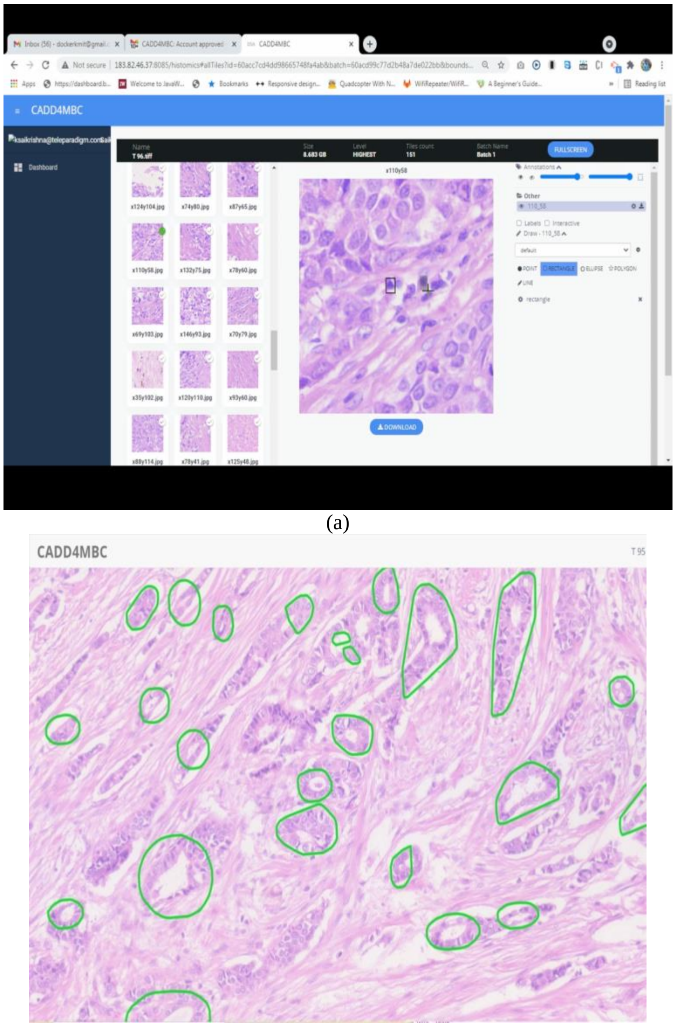


Fig. 5. Visualization of a WSI.



(a)

(b)

Fig. 6. (a). Annotations on WSI-Tiles by KMIT-Patholog, (b). Annotations on whole WSI by KMIT-Pathology.

KMIT-Pathology provides drawing tools needed for annotations and having a provision to download the .json files of the annotations which are later used by deep learning models for prediction.

B. Deep Learning Models

KMIT-Pathology performs WSI image analysis, primarily for Cancer detection and diagnostics. This section discusses about two deep learning models to identify tubule on Breast Cancer WSI images and ISUP grading for Prostate cancer using WSI images.

1) Tubules identification on breast cancer WSI using KMIT-Pathology platform: Histological grading is used to evaluate the behaviour and prognosis of breast cancer on H&E images. Histological grading provides the degree of differentiation in the morphological assessment of breast cancer. Nottingham grading system (NGS) was globally accepted as a histological guide for breast cancer grading classification. Identification of tubule is one of the major components in NGS system [22]. Tubules are a special type of Breast Carcinoma which are composed of tubular structures. They have an open lumina, lined by a single layer of epithelial cells. 2 - 6 % of malignant tumours are Tubular [23]. They define the aggressiveness of cancer and become disorganized as they progress. In Benign cases, the tubules that are almost round and mostly identical, but in malignant cases they are highly random and identifying boundaries is difficult for experts as well.

Deep learning model R2Unet is used for training and testing to identify tubule on breast WSI. There are around 50 breast cancer WSI of size varies from 8 GB to 12 GB are collected and annotated by three pathologists on WSI using KMIT-Pathology web platform. The annotations are cropped from WSI and the mask are created to run deep learning models.

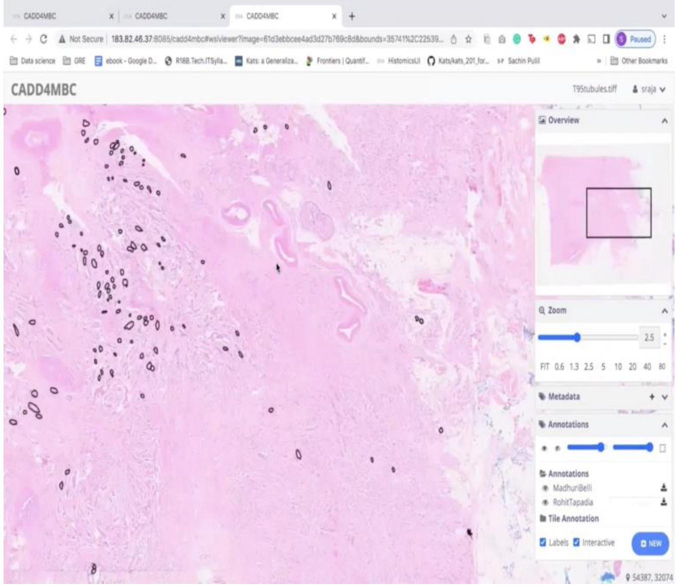


Fig. 7. Tubule Identification on Breast Cancer WSI using R2Unet.

The model uses 140000 tiles of size 256*256 of magnification 40x for training and testing and the model got accuracy of F1 score 0.9295. The tubule identification on breast cancer WSI is shown in Fig. 7.

2) ISUP grade prediction for prostate cancer using KMIT-Pathology: Prostate cancer is the second largest cancer which causes more death in men worldwide. Lack of expert pathologist delays the diagnosis and creates human biased decisions in analysis and the diagnosis of the cancer. AI driven computer aided diagnosis (CAD) system automatically predict ISUP grading for prostate cancer and also helps the pathologist for early prediction and diagnosis.AI driven KMIT-ISUP grade prediction model for prostate cancer [24] uses EfficientNet to predict Gleason scores. ISUP grade depends on the Gleason Scoring (GS) system. GS system defines the structural growth pattern of cancer cells in the tissue. ISUP grading is calculated with respect to the combined score of GS majority and minority scores.

KMIT-ISUP grade identification deep learning model predicts GS score and the respective ISUP grade. KMIT-ISUP model uses Prostate Cancer Grade Assessment (PANDA) challenge dataset provided by Radboud University Medical Center and Karolinska Institute [PANDA Challenge, 21]. The model uses 5000 WSI and the respective semantic masks for various Gleason scores.

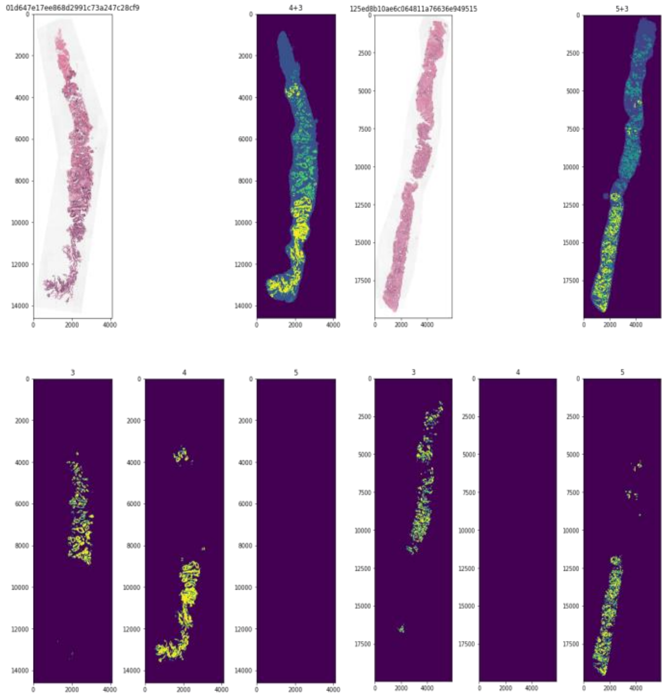


Fig. 8. Sample Prostate WSIs and the Masks with Gleason Score Labels.

Fig. 9. Prostate WSI with Gleason Score Identification.

The WSI images and the masks are divided into 92783 patches of size 224x224 for training and testing and the model produces 80% of accuracy for ISUP grading prediction. Sample prostate WSIs and the semantic masks for ISUP 3 (4+3) and ISUP 4 (5+3) are shown in Fig. 8. The majority and the minority Gleason score (GS) for ISUP grade 3 is GS 4 and GS 3 whereas for ISUP grade 4 the majority and the minority Gleason scores (GS) are GS5 and GS3. The mask for GS3, GS4 and GS5 are generated using the mask of whole WSI which are also shown in Fig 8. Deep learning predictions for Gleason scores of prostate WSI patches and the color representation for the various GS are shown in Fig. 9. Gleason scores of the patches of WSI are sorted and the two topmost scores (majority and minority patterns) are considered to calculate ISUP grade of the WSI.

IV. RESULTS

KMIT-Pathology imaging platform is an End-to-End digitized pathology imaging platform having various necessary features like WSI data storage in Pyramidal structure with respective folders structures, Pathology Annotations tools for both complete WSI image and for Image-tiles, visualization of AI-Predictions. The deep learning models for Breast Cancer and Prostate Cancer, which are detailed in this publication are developed using KMIT-Pathology platform. Thus, proposed KMIT-Pathology imaging platform has been effectively showcased by using its various features like WSI Images storage and retrieval, Images Annotations, AI-Predictions visualizations etc.

This paper also discusses about the implementation of two AI deep learning models viz. 1) to identify Tubule on Breast Cancer WSI 2) ISUP grading on Prostate cancer by using KMIT-Pathology platform. Tubule deep learning model R2Unet uses 140000 tiles of size 256*256 of magnification 40x for training and testing to identify tubule and the model got accuracy of F1 score 0.9295. The deep learning model EfficientNet is used to predict Gleason scores of the prostate cancer which uses 92783 tiles of size 224x224 for training and testing and the model produces 80% of accuracy for ISUP grading prediction.

Both the deep learning model used KMIT-Pathology for Image/WSI uploading, retrieval, storage, image annotations, AI based cancer bio-markers identification and visualizations of the AI results.

The other imaging platforms like QuPath, OpenSeaDragon Slide Runner and Digital Slide Archive (DSA) provide facilities for Data Storage, Annotations and Visualization. Whereas, KMIT-Pathology includes all the above-mentioned features, along with AI-Deep Learning Models to identify Cancer Biomarkers on WSI images.

V. CONCLUSION AND THE FUTURE ENHANCEMENT

The invention of digital scanners gives a new era to pathology labs and opens a new research area called Digital pathology. Digital scanners capture high resolution images of the glass slide tissues. These virtual microscopy images need to be stored, visualized, analyzed and produce AI driven predictions. Various people located in different places like lab technicians, pathologists and AI engineers are needed to collaborate to perform these operations. So, they need a common web platform to interact with each other. KMIT-Pathology is a web-based platform for WSI image analysis. This platform provides facilities to perform upload, annotate and visualize WSI images. The integration of AI models with the web-based platform helps to identify cancer imaging biomarkers.

This paper also demonstrates the usage of KMIT-Pathology platform for End-to-End Cancer Bio-markers identification for Breast Cancer and Prostate Cancer WSI images.

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