

PROSTATE CANCER GRADING – A REVIEW ON HISTOPATHOLOGY IMAGES

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ABSTRACT

The prostate cancer is the second leading cancer among men. The incident rates of prostate cancer are increasing in, all over the world. The histopathology based grading system, is mainly used in prostate cancer diagnosis, in which the pathologist assigns a Gleason grade, based on the architecture of the tissue. It is important in risk assessment and treatment planning for the patients. Cancer affects the epithelial cell of prostate tissue. Several computer aided methods are proposed in the literature, using various handcrafted image features and machine learning algorithms, for the classification of grades. In this paper, we review various automated methods which are used in the prostate cancer grading. In the Deep Learning models the image features where automatically extracted from the images but in conventional machine learning approaches, the features are manually selected. The deep learning papers in the histopathology of prostate cancer are limited since the development of deep learning models have started in recent past. The conventional machine learning models perform with high accuracy in small datasets while the deep learning models perform with high accuracy in adequate datasets. For automating the cancer grading deep learning models using Convolutional Neural Networks (CNN) are performing well while compared with the conventional machine learning models.

KEYWORDS: Prostate, Gleason grade, Image processing, Machine learning, Deep learning, CNN.

I. INTRODUCTION :

Prostate cancer forms in the glandular cells (adenocarcinomas) of the prostate glands in males. It is a slow growing cancer. The prostate tissue consists of glandular structures, tubules surrounded by stroma and a basement layer. The glands consist of epithelial cells surrounded by lumen. A normal gland is formed by single layer of luminal cells, surrounded by basal cell which is a type of epithelial cell. If a cell got affected by the cancer then we can observe the loss of basal cells and changes in gland architecture [1]

In the Indian cities like Thiruvananthapuram, Delhi, Pune and Kolkata prostate was the second leading site of cancer among males and the third leading site of cancer in the cities like Bangalore and Mumbai. The prostate cancer is in the top ten leading sites of cancers in the rest of Population Based Cancer Registries (PBCRs). The prevalence of prostate cancer in India was far lower as compared with western countries. More cases of prostate cancer are reported due to the increased migration of rural population, changing life styles of people, increased awareness and easy access to medical facilities. According to the cancer projection data, the number of cases will be doubled by 2020 [2].

The prostate cancer is usually considered as the old age cancer but the 10% of new diagnosis in the USA occur in men aged ≤ 55 . The main cause of the men with early-onset prostate cancer is genetic components. The men with early onset prostate cancer poses some unique challenges, includes long-term effects of treatment related morbidities and long term risk of disease progression leading to death [3][4]. The prostate cancer is considered serious because of its invasion into other organs.

The histopathology forms the definitive diagnosis of prostate cancer. The cancer tissue is assigned a grade between 1 and 5 based on the Gleason grading system. Dr Donald Gleason introduced a grading system based on the architecture features of glands on 1966 [5]. The Gleason grading undergoes various evolutions and will evolve further. Dr Gleason himself made several updates to the system [6][7]. The International Society of Urological Pathology (ISUP) introduced significant improvements in 2005 [8] and in 2014 [9] and it continues to be updated

by the consensus of International Society for Urological Pathology (ISUP).

Every year, millions of biopsies are produced and it requires a high-throughput pathology services, but most Gleason scores are assigned manually through pathologist review, which is a time consuming process. The personal skill and experience of the pathologist will determine the diagnostic accuracy. The Gleason grading usually suffers from inter – and intra-observer variations [10] - [12] and the pathologist usually find it difficult to differentiating grade 3 and grade 4 due to the minute variations within the gland architecture. These issues with the current prostate grading system question the accuracy and reliability of the pathology service. Several digital pathology systems have been proposed to improve the current practice of the pathology using various machine learning frameworks.

The biopsied tissue of prostate mainly contains epithelial and stroma tissues. The hematoxylin and eosin (H&E) stains are mainly used for prostate biopsy in which the epithelial are hematoxylin stained. The epithelial tissues, mainly contains the cancerous cells.

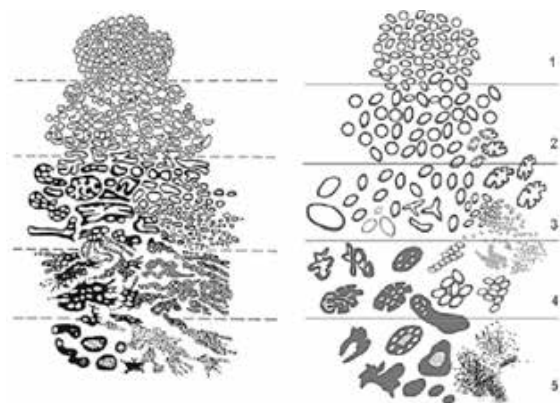


Figure 1. Histologic pattern by Gleason and ISUP updation in 2015 [9]

In this paper, we compared the performance of various machine learning methods and deep learning methods in histopathology images, the network architectures in the deep learning models and the algorithms

in the machine learning models were discussed.

II. METHODS :

DEEP LEARNING

The increase in the image data and the improvement in the hardware capabilities give rise to various deep learning algorithms in the medical field. The deep learning methods can be used as a tool for increasing the accuracy and efficiency of histopathology images [14].

The accuracy and performance of the system depend upon the number of images employed to the process but in some cases the amount of image data will be limited in those cases the data augmentation techniques will be used.

The color deconvolution [13] methods usually applied to separate the stains. Jin Tae kwak and Stephen M. Hewitt [15], in their work based on

the architecture of the nucleus in tissue microarray dataset of prostate, Color deconvolution method was employed to separate the stains and in the hematoxylin stain and Otsu's thresholding was done followed by the Euclidian distance transform and watershed algorithm. Ida Arvidsson et al.[17] in their method for generalization of prostate cancer classification for multiple sites digital stain separation and normalization were applied to remove variations in hue and intensity of the stains between different sites.

The network architectures were used in the preprocessing steps for downsampling, feature extracting and segmenting the images .The Autoencoders were trained for efficient down sampling of the images [17]. Hanna kallen et al.(2016) used the pretrained network OverFeat [19] for the feature extraction. Wenyuan Li et al. [16] used ResNet to extract the feature maps. The image processing techniques were usually employed to minimize the complexity in the images.

Table 1. Comparison table for different Neural Networks

Author	Dataset	Network	Accuracy
Jin Tae kwak and Stephen M. Hewitt[15]	4 Tissue Microarray datasets (TMA)	6 layer CNN	AUC : 0.974
Wenyuan Li et al. (2018) [16]	513 WholeSlideImages (WSI)	Path R-CNN	AUC :0.998(epithelial detection) mIOU: 79.56% (Gleason grading)
Ida Arvidsson et al.(2018) [17]	3 WSI datasets	Autoencoder 2 CNN for 20x and 5x magnification	95%(benign vs. malignant) 81%(Gleason grades)
Hanna kallen et al.(2016)[18]	213 WholeSlideImages	OverFeat	89.2 %
Anna Gummeson et al.(2017) [20]	213 cropped Gleason grade images	CNN	92.7%
Jiayan Li et al [21] (stroma, benign glands, prostate cancer)	224 Whole Slide Images	U-Net Multi-scale U-Net Pixel-wise CNN	Mean Jaccard index:75.0% Mean Jaccard index:75.5% Mean Jaccard index:65.0%
Jiayan Li et al [21] (stroma, Gleason 3, Gleason 4 and benign glands)	224 Whole Slide Images	U-Net Multi-scale U-Net Pixel-wise CNN	Mean Jaccard index:64.4% Mean Jaccard index:65.8% Mean Jaccard index:45.0%
Nathan Ing et al [22] (Tile 10x)	513 Whole Slide Images	FCN-8s SegNet-Full SegNet-Basic U-Net	0.873 0.822 0.762 0.885

MACHINE LEARNING

For the automatic detection of cancer various machine learning algorithms have employed. The image features are extracted using feature extraction methods and pass them to the classifier for training. The machine learning algorithms were giving state of art performance over the last decade. The machine learning algorithms gave the researchers the insight for developing complex computer aided methods. MKhalid Khan Niazi et al. [23] developed a method in which a set of visually meaningful features was used to differentiate between low and high grade prostate cancer, because the most of the proposed method lacks interpretability. The visually meaningful features, luminal features and the architecture features, were used to create two subspaces in which one is for high grade and other is for low grade. The grade associated with a subspace, which results in minimum reconstruction error in terms of Euclidean distance is considered as the prediction for the test image.

Kien Nguyen et al. [24] proposed a method for prostate grading using gland segmentation and structural features. They preferred Lab color space over RGB, because it was designed to approximate the human color perception in human visual system. They classify points in Lab color space into five classes i.e., stroma, nuclei, cytoplasm, lumen and mucin followed by voronoi tessellation. Once all the pixels had been classified, they identify nuclei and lumina, the two most important components of the gland. In order to construct a gland boundary they had taken two steps. In the first step, nucleus objects were enlarged by combining them with cytoplasm pixels. In the second step, they group enlarged nuclei which intersect each other to construct gland boundary segments. To segment the complete gland units they had implemented an algorithm for unifying lumen objects with gland boundary segments to form complete gland units. The non-tissue areas were discriminated from lumen objects by their contacts with the image boundary. The algorithm was based on an expansion procedure of lumen objects and they had extracted 15 features from each gland region.

Kien Nguyen et al [25] proposed a method for Prostate cancer using graph cut and the spatial

arrangement of the nuclei. This method was implemented to overcome the limitations in the [24] to improve the performance of grade 3 versus grade 4 classification problem. They proposed a nuclei-based approach that utilizes graph theory techniques to segment glands and compute a gland-score to estimate how similar a segmented region is to a gland and they a fusion method was created by combining the nuclei-based method with the lumen-based method to improve the performance of grade 3 versus grade 4 classification problem. In order to segment glands, they have build a graph of nuclei and lumina in the image, and use the normalized cut method to partition the graph into different components, each corresponding to a gland.

Clara Mosquera Lopez and Sos Agaian [26] introduced a new method to classify histopathology images belonging to Gleason patterns 3, 4, and 5 by using a combination of wavelet and fractal features. They had used Haar wavelet transform and a modified algorithm for color fractal dimension calculation to extract valuable features from each image. Fractal feature was included to improve the classification accuracy between grade 3 and grade 4.

Scott Doyle et al [27] presented a boosted Bayesian multiresolution (BBMR) system to identify regions of prostate cancer on digital biopsy slides. This method was introduced as a preceding step to a Gleason grading algorithm. In the first step, their algorithm decomposed the whole-slide image into an image pyramid comprising of multiple resolution levels and they convert the images from the original RGB color space to the HSI space. The features they have used for feature extraction were first-order Statistics, co-occurrence features and gabor features. For the classification they first construct a set of weak Bayesian classifiers, one for each of the extracted features. Once the weak classifiers have been constructed, they were combined to create a single strong classifier via the AdaBoost ensemble method and multiresolution algorithm is applied to it.

Lena Gorelick et al [28] described and evaluated a system for automatic prostate cancer detection and grading on hematoxylin & eosin-stained tissue images. The proposed system used

two stages of AdaBoost-based classification in which the first stage was provided with high-level tissue component labeling of a superpixel image partitioning. The second used the tissue component labeling to provide a classification of cancer versus noncancer and low-grade versus high-grade cancer. They had used tissue component histograms as feature vectors for cancer detection and classification using boosted decision trees.

Ali Tabesh et al [29] presented a study of image features for cancer diagnosis and Gleason grading of the histological images of prostate. They had used all three types of potentially useful visual cues, namely, color, texture, and morphometric features at the image (global) and histological object levels. The preprocessing includes background removal where regions corresponding to the tissue background were identified and removed from the analysis and matching of the image histogram to that of a reference image. The features from the different visual cues were fed into a supervised learning framework and the performance of the Gaussian, k-nearest neighbor and SVM classifier together with sequential forward feature selection algorithm were compared and evaluated.

Kourosh Jafari-Khouzani and Hamid Soltanian-Zadeh [30] proposed a Multiwavelet Grading of Pathological Images of Prostate. The texture analysis tools like wavelet transform perform well in Gleason grading, because it was mainly based on texture properties of the image. The multiwavelet transform had more than one scaling function so that they had taken the multiwavelets and the energy and entropy features of multiwavelet coefficients of the image were calculated. They select most discriminative features by simulated annealing. Mikhail Teverovskiy et al [31] using advanced image processing techniques, Aureon Biosciences Corporation has developed a proprietary image analysis system (MAGIC™). MAGIC™ was a tissue image analysis system that uses advanced image processing algorithms in order to segment and measure properties of the histopathological objects. In MAGIC™ images were first segmented into small groups of contiguous pixels known as objects. The different components of MAGIC™ were background extraction, coarse segmentation,

white space classification and Nuclei De-fusion and classification. The background extraction stage segments the TMA tissue core from the background using intensity threshold and convex hull. In the Coarse Segmentation the foreground (TMA core) were then re-segmented into rough regions corresponding to nuclei and white spaces. In the stage of coarse segmentation, the white space regions may correspond to both lumen (pathological object) and artifacts (broken tissue areas) in the image. The smaller white space objects (area less than 100 pixels) are usually artifacts. In the stage of coarse segmentation, the nuclei area is often obtained as contiguous fused regions that encompass several real nuclei. These fused nuclei areas needed to be de-fused in order to obtain individual nuclei. The classifier used are Bayesian and k nearest neighbor classifier. Po-Whei Huang and Cheng-Hsiung Lee [32] proposed two feature extraction methods based on fractal dimension to analyze variations of intensity and texture complexity in regions of interest. In order to estimate the fractal dimension, the differential box counting (DBC) was used and to analyze the texture complexity in pathological images for different Gleason grades, an entropy-based method for estimating the fractal dimension of an image was used. They combine the features from the two methods and classified images into an appropriate grade by using Bayesian, k-NN, and support vector machine (SVM) classifiers.

Hong-Jun Yoon et al [33] presented their study on application of cardinal multiridgelet transform (CMRT) to prostate cancer images to extract texture features in the transform domain. CMRT will provide cardinality, approximate translation invariance and rotation invariance simultaneously. The cardinal multiridgelet transform has the excellent directional selectivity to quantitatively represent the glandular architecture effectively and reproducibly so they explore the application of the developed cardinal multiridgelet transform to extract tissue texture features for use in a Gaussian-kernel support vector machine to classify the Gleason grading.

Table 2. Comparison of different machine learning approaches

Author	Dataset	Features	Classification	Accuracy
M Khalid Khan Niazi et al. [23]	25 Whole Slide Images	luminal features architecture features	Euclidean distance	93.0%(training) 97.6% (testing)
Kien Nguyen et al. [24]	26 digitized tissue specimens	Gland boundary	Adaboost SVM Nearest Neighbor Naïve Bayes Decision tree Feed forward neural network	75.3 87.8 80.3 81.5 79.0 87.8
Kien Nguyen et al [25]	317 tissue images	the normalized cut method to partition the graph into different components, each corresponding to a gland	SVM	88%
Clara Mosquera Lopez and Sos Aгаian [26]	106 tissue images	wavelet and fractal features	SVM	97%
Scott Doyle et al [27]	100 whole slide images	First-order, co-occurrence and gabor features	Boosted Bayesian classifier	AUC: 0.84,0.83 and 0.74 for the lowest, medium and highest image resolution
Lena Gorelick et al [28]	991 whole slide images	tissue component histograms	boosted decision trees	90% and 85% for cancer versus noncancerous and high-grade versus low-grade classification tasks
Ali Tabesh et al [29]	367 TMA	Color, Texture, and Morphometric Features	Gaussian,K-NN and SVM classifiers together with the sequential forward search (SFS) algorithm	five-fold cross-validation accuracy of 96.7%. Gleason grading – 81%
Kouros Jafari-Khouzani and Hamid Soltanian-Zadeh [30]	100 prostate tissue sample images	Entropy and energy of the multiwavelet coefficients	K-NN	97%
Po-Wei Huang and Cheng-Hsiung Lee [32]	205 pathological prostate images	fractal dimension to analyze variations of intensity and texture complexity in regions of interest	Bayesian k-NN SVM	91.2% 93.7% 93.7%
Hong-Jun Yoon et al [33]	32 TMA	cardinal multiridgelet transform	SVM	0.9651

III. OBSERVATION AND DISCUSSION :

Several methods based on machine learning and deep learning algorithms are developed for the automatic classification of prostate grades. The deep learning methods are superior to the handcrafted features using machine learning methods. In the machine learning methods, we are extracting some specific features from the tissue but in the deep learning methods we are extracting almost all features of the image. In a single slide, different grades are present, so different semantic segmentation techniques are adopted to segment the patches from the image.

The prostate datasets consist in the form of whole slide image and tissue microarrays. The whole slide images are mainly used in the most researches. The datasets in which the researchers are working on may have observer variations which may led into some uncertainties in the classification. The datasets have to be collected from different pathologist across the globe in order to tackle the inter and intra observer variations. Even though many work has done in histological image analysis of prostate cancer, a very few addressed the problem of differentiating grades.

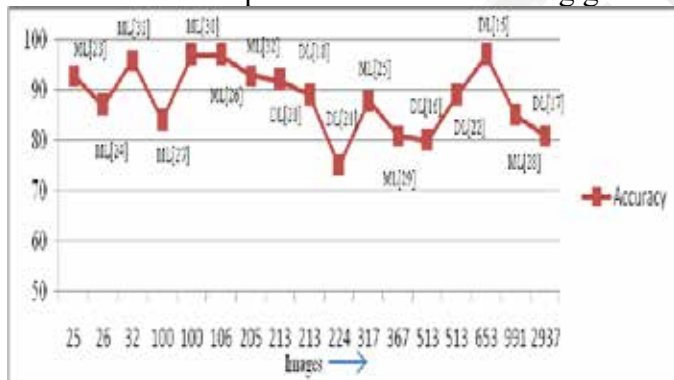


Figure2. Comparison of number of images with accuracy in Deep Learning (DL) & Machine Learning (ML) techniques

In Figure 2, Machine learning techniques are providing better accuracy with less number of images but deep learning techniques need more images. The deep learning techniques are showing low accuracy in some of the models, due to the limited number of datasets. The algorithms that work on a certain datasets may not give good accuracy in the other datasets due to variations in staining. Even though there are several methods have been proposed using machine

learning and deep learning models there is still difficulty in differentiating grades. The researches in the Gleason grading scheme is still going on. Since the deep learning models have been extracting all the features from the images, it may help in the future also.

IV. CONCLUSION :

The machine learning approaches have contributed significant advancement in the automation of prostate cancer grading over the last decade. The deep learning models outperform the conventional machine learning models. The approaches we discussed, shows that there is a more room for improvement. The difficulties in distinguishing grades are still a bizarre for the researchers. Since the grading of prostate have based on the architectural features of the tissue, a basic understanding of the architecture is necessary. The construction of an annotated big dataset, with the biopsied images across the globe, will help the researchers to improve their work and it will attract more in this area. The automated methods will help to reduce the inter- and intra- observer variance, it assists the pathologist in decision making, and it helps the patients to have a proper treatment.

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