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EVALUATION OF BREAST CANCER

Engineering

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ABSTRACT

Immunohistochemistry (IHC) markers Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor2 (HER2)) are few of the valuable markers in detecting and estimating the extent of breast cancer. This paper presents an innovative approach of classifying and correlating the makers on single patient, known as three marker method. IHC- ER/PR marker score is evaluated based on number of cells using modified watershed algorithm, which give accurate results over traditional watershed algorithm. Similarly, the score of IHC-HER2 marker is evaluated using intensity, density and color of cell membrane for which Stain Measure Algorithm is developed. The evaluation of markers is obtained through development of algorithms in MATLAB simulation software. The statistical result analysis is done and validated with doctors score. This systems helps in assisting the pathologists to provide reliable, repeatable and timely evalution over traditonal approach and will definetly pentetrate to the affected, downtrodden and economically weaker sections.Deep learning has the potential to achieve good level of accuracy in the prognosis of breast cancer detection,

KEYWORDS

Breast Cancer, marker, Cell Count, Cell membrane staining, Classification and Correlation.

I. INTRODUCTION

Breast cancer is a leading cause of death among women in world. In IHC receptors, a visible cell change is seen under microscope, when pathologists combine external antibodies with these receptors [1]. The Estrogen receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor2 (HER2) are the most reliable IHC markers, which are evaluated and estimated manually under a simple microscope.

To minimize the human error, an alternate approach is developed so as to automate the evaluation, estimation and analyze the severity of breast cancer patients. The benefits of such automation aids pathologists by decreasing time, avoid routine scans such that they can focus on more complicated issues. The implementation of these algorithms shall be user friendly to the doctors/pathologists as they can collect the digital images and process them for future use, this shall yield accurate therapeutic decisions and minimize the overall treatment cost.

II. REVIEW OF LITERATURE

An extensive survey of literature, in the context of breast cancer is undertaken and the researchers have developed different methodologies and algorithms.

In [5], authors proposed a method to overcome the segmentation error for IHC-ER marker by developing marker controlled watershed algorithm.

In [6], the authors achieved a fairly high accuracy of 80% by marker controlled watershed algorithm. However, the extraction process of IHC markers became difficult due to merging of different objects [7].

In [8], authors proposed an algorithm based on "constrained region labeling" for marker extraction but it involved more complexity.

IHC - HER2 marker, [9] evaluating criteria such as intensity and uniformity of staining and estimating the percentage of stained cells is a subjective process. A recent study on the evaluation of HER2 by five observers reported complete agreement in 48% of HER2 cases (22 out of 46).

In [10] the paper presents an automated method about the quantitative assessment of HER2 expression of IHC stained images. The proposed system efficiently extracts nuclei of interest including positive stained nuclei and negative stained nuclei.

III. IMAGE PROCESSING IMPLEMENTATION FOR ER AND PR MARKERS

A. Eliminating over-segmentation errors

The traditional watershed algorithm was unable to count the accurate number of cells due to intensity variation in the cell. So, a modified watershed algorithm was developed to eliminate the estimation of over segmentation error by introducing the concept of thresholding (equation 1), where if the cell centroid distance between two cells is less than the threshold value, new cell centroid is calculated by averaging the cell centroids in consideration (refer Figure 1).

$$d_j = \sqrt{\left(x_j^2 - x_{j+1}^2\right) + \left(y_j^2 - y_{j+1}^2\right)} \ldots for\ j = 1 \ldots \ldots n, \quad (1)$$

where 'j' signifies the present segment of the cells and 'n' denotes the total number of segmented cells.

Figure 1: Conceptual image to eliminate over-segmentation error

An iterative process was performed using equation (1) until all segments were considered. A conceptual image to eliminate the over segmentation error is shown in Figure 1.

IV. IHC - HER2 MARKER

IHC - HER2 over expression and amplification are documented as one of the significant marker in breast cancer and specific therapies, such as Lapatinib and Trastuzumab, approved by Food and Drug Administration (FDA.

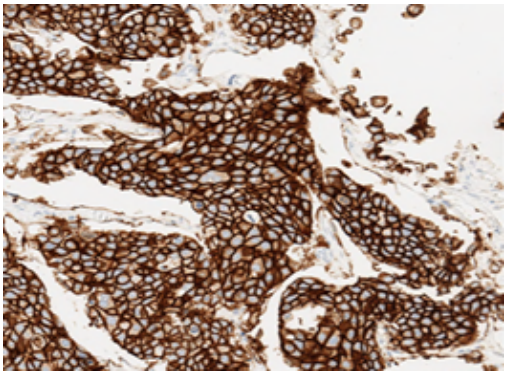

Figure 2: Typical HER2 sample with 3+ staining of cell membrane

V. Image Processing Implementation For Ihc - Her2 Marker

IHC - HER2 marker evaluation is done by estimating the membrane stained region based on intensity, color and density of cell membrane. Thus, the evaluation of HER2 images is classified into four categories of {0, 1+, 2+, 3+}.

This fact is evident from Table II. The time taken is proportional to the number of cells recognized in the image as well as to the size of the image: in a larger image, a higher number of pixels have to be analyzed in the region growing process. A fixed size of image is preferred. The sizes of the image used are fixed and equal to 1024 x 1024 pixels. For the HER2 image, number of pixels in stained region is 424062. The area of the image is 1048576 pixels. The ratio of the two is 0.4044 or 40.44 percent.

Table II: Statistical Analysis for IHC – HER2 marker

Dr.	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
AJ	100	50	69.56	100	75.86
KD	100	64.28	76.19	100	83.33
MAK	100	69.23	80.95	100	86.67

VI. Classification And Correlation Of IHC Markers

The results obtained by the Cell Count algorithm for IHC ER/PR markers in estimating the severity of the breast cancer score is based on the cell count. The Stain Measure Algorithm for IHC - HER2 marker estimates the extent of cancer based on the breast tissue sample, its statistical analysis is shown in Table III.

IHC markers ER, PR and HER2 are evaluated individually. The correlation of ER, PR and HER2 for one patient is a predictive and prognosis evaluation of the breast cancer patient. The correlation of ER, PR and HER2 identifies a three-marker method.

Table III: Statistical Analysis of IHC- ER, PR and HER2 markers

Markers	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
ER	83.33	100.00	77.78	71.42	88.23
PR	75.00	60.00	81.81	50.00	70.58
HER2	83.33	40.00	76.92	50.00	70.58

Classification: The correlation of the IHC markers ER, PR and HER2 and its prognosis classified by three marker methods. In addition to this, correlation of the IHC markers such as ER, PR, and HER2 is also evaluated for 17 - single breast cancer patient.

The accuracy is calculated as shown in Table IV based on the results of IHC markers on single patient along with the comparison of classification algorithm and Doctors score.

Table IV: Correlation of IHC – ER, PR, HER2 on Single Patient

Subtype	ER/ PR	HER2	EGFR-Ck5/6	Algorithm	Dr. AJ	Accuracy %
Luminal A	+	-	- Or +	04	04	100
Luminal B	+	+	- Or +	10	09	90.00
HER2	-	+	- Or +	02	03	66.66
Unclassified	-	-	-	01	01	100

VII. CONCLUSION

The count of IHC-ER/PR markers was better when implemented by modified watershed algorithm over manual analysis by the pathologist giving higher accuracy. The statistical analysis Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Accuracy are calculated for 17 images of IHC- ER, PR and HER2. Based on the correlation of these IHC markers, classification was evaluated on 17 images of a single patient. The accuracy of algorithm used to evaluate the three-marker method was closely concurrent with the Doctors evaluation for breast cancer patients.

Future Scope

A deep learning framework for semantic segmentation and classification of cell membrane and nucleus of HER2 marker in breast cancer evaluation. Digital imaging technology is a pixel based technology, which decreases the Inter observer variability and false positivity by improving detection, segmentation accuracy and other factors. Thus HER2 marker prognosis can be more reliable and feasible using deep learning framework. The performance can be improved as the training set data is increased. Eventually its treatment can be improved long term outcomes and it can reduce risk due to unnecessary treatment. CNN, ANN are the most popular deep learning models for processing multi-dimensional array data such as color images in breast cancer detection [11]. The only requirement to improve the performance is to have more number of images for the prognosis of breast cancer patients.

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