Informatics in Medicine Unlocked 8 (2017) 74–79

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: www.elsevier.com/locate/imu

Detection of breast cancer on digital histopathology images: Present status and future possibilities

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ARTICLE INFO

Keywords:
Breast cancer
Biopsy
Histopathological image analysis
Image segmentation
Image classification
Feature extraction

ABSTRACT

Breast cancer is a very common type of cancer in women around the world and more so in India. It affects not only women but also men. In India, we have a very disturbing trend of increase in cancer patients especially in urban areas. Out of 100 cancer patients, 25–32 patients are affected with breast cancer. The modern medical science has several advanced methodologies and techniques for the identification of breast cancer. Digital pathology is one of the emerging trends in modern medicine. Pathological studies are getting more prominence in detection of various types of cancers. This article reviews and summarizes the applications of digital image processing techniques on histopathological images for the detection of breast cancer and discusses its future possibilities.

1. Introduction

Cancer has become a major threat to individuals all around the world. In India, the rate of death due to cancer is huge and surpassing 8 lakhs reported cases by the year 2000 according to Indian populace registration information [1]. It is the second largest chronic infection in India in charge of greatest mortality with around 0.3 million passing for every year. The increase in the number of cancer patients every year from 2005 is shown in Fig. 1 [1]. The increasing trend of cancer patients in the last few decades enables us to predict the count of patients by the end of 2020 in India.

Breast cancer topped the list for females and mouth cancer for males [19]. Breast cancer became a chronic disease affecting worldwide women population. Even though the most of elemental causes and other features are common around the world, every region has its own specific causes for cancer. In India around 1.5 lakh new cases with breast cancer (over 10% of all cancers) have been registered in 2016 [31]. It's not the first time medical researchers are targeting breast cancer. Due to lack of advancement in medical field, this disease is growing as one of the most chronic diseases of the era. Recent trends in image processing shows what an engineer can do in the medical field. Medical image processing became highly acceptable mechanism now days. The vast development in information technology makes this mechanism reliable and efficient. Medical image processing is not only used in cancer detection but also for diagnosis of other diseases [37]. The procedure that takes out a piece of the mass or a sample from human body for testing is called a biopsy. The tissue sample is called the biopsy sample or specimen. The testing process is referred to as pathology. The process of histopathology defined as the detailed analysis of a biopsy sample by a pathologist. First the sample has been processed and then sectioned onto glass slides. On the other hand, histopathology is the examination of biopsy sample taken by either intrusive or minimal intrusive methods by a pathologist under an instrument like microscope for studying the growth of cancer, tumour etc.

Different structures of the tissue are coloured with different stains for the sake of conceptualizing under the microscope. Then, a detailed study on these tissues has been done by a pathologist for the detection of lesions or tumours [15]. Scientists in have been familiar with the significance of quantitative examination of histopathological images. Quantitative examination can be used to support pathologists' decision about the closeness or the nonappearance of a disease, besides to help in infection development evaluation. Additionally, quantitative depiction is key, not only for clinical use (e.g., to expand the demonstrative unwavering quality), additionally for exploration applications (e.g., drug revelation [35]) and organic systems of ailment [13]. As an outcome, the utilization of PC supported analysis in pathology can considerably upgrade the productivity and precision of pathologist's choices, and generally speaking advantage the patient.

On account of new advancement in image processing techniques several methods have been suggested for accurate detection of breast cancer. Among the different studies, robotized segmentation and classification of nuclei/cell is a repeating task, especially troublesome on histopathology images. The segmentation of nuclei (histological

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http://dx.doi.org/10.1016/j.imu.2016.11.001
Received 6 October 2016; Accepted 5 November 2016
Available online 11 November 2016

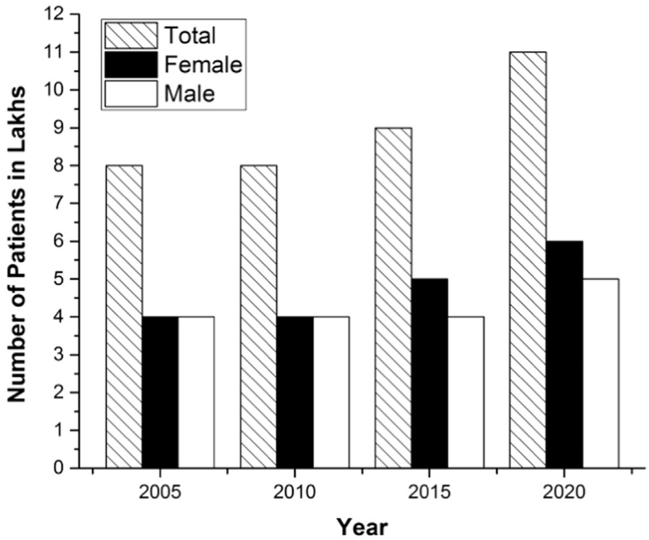


Fig. 1. Total cancer prevalence in India year wise (predicted case for the year 2020).

structures) on histopathological images is more troublesome since the greater parts of the cells are frequently part of unpredictable and sporadic visual angles [15]. This article reviews some of the most accepted computer aided techniques for the analysis of breast cancer from a histopathology image.

The article composed in seven sections. Section 2 presents the types of dyeing and distinctive image modalities in histopathology. Section 3 highlights various methods used for histopathology image analysis. Different parameters used for performance assessment of a classifier explained in Section 4. Section 5 discusses and compares different algorithms used for nuclei detection, segmentation and classification. Section 6 describes conclusion along with future possibilities explained in Section 7.

2. Staining of histology slides

Histology is the anatomical study of tissues and histology slide preparation involves steps viz: fixing, processing, embedding, sectioning and staining. The type of stain is selected according to the tissue that going to process. The tissue is dyed with one or more stains for clear visualization under the microscope [2].

The most normally utilized recoloring frameworks are Haemotoxylin and Eosin (H & E) staining and Immunohistochemistry (IHC) staining. Eosin is a negatively charged acidic color. It stains basic (or acidophilic) structures red or pink. This is likewise some of the time termed 'eosinophilic'. Along these lines the cytoplasm, stroma, etc. are stained pink by H & E staining. Haematoxylin is a basic colour utilized to dye acidic (or basophilic) structures a purplish blue. Hence the nucleus is stained purple [32]. Immunohistochemistry (IHC) is another technique using for staining. According to the presence and absence of some particular proteins (antigens or antibodies) in the tissue, we can predict stage of cancer. Fig. 2 shows examples of H & E and IHC stained images. H & E image is adapted from UCSB dataset of a benign case (stage 0) [11]. IHC stained image of invasive breast carcinoma (stage 2) shown in Fig. 2 is adapted from Jennifer et al. [18]. The quality of IHC is the natural visual yield that uncovers the presence and limitation of the particular protein with regards to various types of cells, organic states, and/or sub cellular localization inside complex tissues [9].

3. Histopathology image analysis

Histopathology refers to the tiny examination of a biopsy sample that is artificially taking outside and separated onto microscopic slides to study cancer growth, genetic progression furthermore, cell morphology for tumour finding and anticipation. The word histopathology came from Greek words: 'Histos' which means tissue, pathos which means disease and logos which means study [25]. The fundamental utilization of histopathology is in clinical medicine where it commonly includes the examination of a biopsy (i.e. a surgically expelled test or example taken from a patient for the motivations behind point by point study) by an expert doctor called a pathologist. With the late appearance of whole slide computerized scanners, tissue histopathology slides can now be digitized and put away in computerized image i.e. in a digital form.

Histological images can be obtained by using a Charge Coupled Device (CCD) camera with microscope in which an automated computerized technique can be performed [37]. The main objective of most of the digitized techniques is to get quantitative data from images. These quantitative data include size of the cell, abnormalities in the tissue and disproportionate number of cells. The main steps involved in digital image analysis: Preprocessing, segmentation, feature extraction and classification. There are many algorithms which are computer aided, available for histopathology image analysis of breast cancer. Some of the important algorithms used for histopathology image analysis are summarized in Table 1.

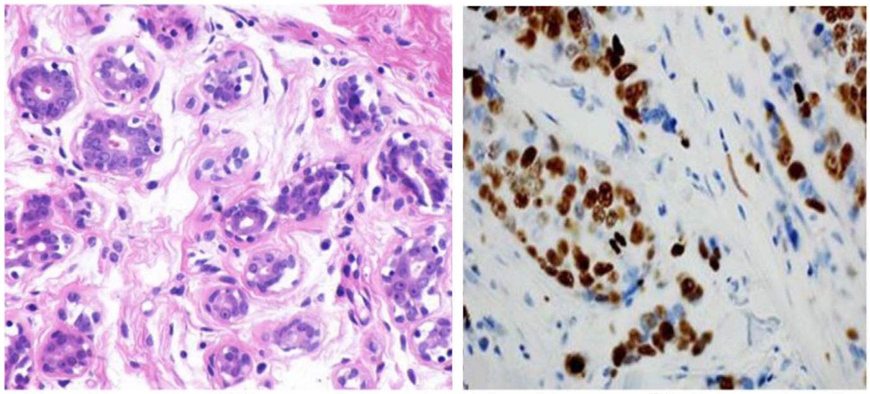
3.1. Preprocessing of histopathology image

For an automated detection using image processing techniques, preprocessing is the first step. Image preprocessing generally involves undesirable noise expulsion and corresponding enhancement in the image. Preprocessing can be achieved through different morphological operations like dilation and erosion, low pass filtering (median and averaging) thresholding etc. [17]. Region of interest (ROI) can be obtained in preprocessing stage which will reduces the processing time. Different preprocessing steps are illuminant normalization, color normalization, noise expulsion with smoothening and ROI detection. Illuminant normalization is a technique that clarifies the illuminant variations in the image due to a non standard imaging source. Color normalization is the method for addressing the problem of color variations in the image due to staining. Li and Plataniotis [23] suggested a method, complete normalization scheme, which is suitable for both color and illuminant normalization. Other methods are white shading correction, histogram normalization etc. Noise reduction is accomplished by using thresholding technique after which follows filtering and background correction.

3.2. Detection and segmentation of nuclei

Lymphocyte and epithelial cells are the most important types of nuclei. Nuclei structure may look dissimilar as per various components for example, type of nuclei, severity of disease, and nuclei life cycle. By analyzing histopathological images, an overall idea regarding cell structure, depth of cancer growth etc can be obtain. Information like size and shape of tumour and other cytological data can be avail through the analysis procedure. Thus prediction of breast cancer development is possible. To examine the region of interest histopathology images firstly ought to be segmented. Segmentation is the process of separating region of interest from the background and is a troublesome task in microscopic images [5]. Usually segmentation can be used to detect nuclei, stroma and background [12].

Nuclei detection and classification on histopathology images is difficult because of its complex structure. Basic segmentation techniques like Hidden Markov Model (HMM), Active Contour Model (ACM), watershed algorithm and extended forms of then can be utilized for detection. Fuzzy logic (I and II types), region growing using seeds etc are other new methodologies with same purpose. Some of the important techniques that have been used for nuclei detection and segmentation are discussed below.



(a) (b)

Fig. 2. (a) H & E (Haemotoxylin & Eosin) stained image of a benign case (stage 0) from UCSB dataset (Adapted from Gelasca et al. [11]), (b) IHC (Immunohistochemistry) stained image of invasive breast carcinoma (stage 2) (Adapted from Jennifer et al. [18]). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.).

Table 1
Summary of different algorithms used in literature for histopathology image analysis.

Authors who proposed the algorithm	Algorithm for analysis	Accuracy result	Difficulties with this method
Basavanhally et al. [4]	Active Contour model based on Color Gradient with Hierarchical Normalized cut	89% segmentation accuracy	False positive rate is little high
Dundar et al. [8]	Gaussian Mixture Model based spatial information and Expectation Maximization (EM) Algorithm	Overall accuracy of 87.9%	Requires parameter optimization
Tosun and Gunduz-Demir [33]	Graph Run length matrices	99% accuracy for segmentation	High computational complexity
Veta et al. [34]	Marker-controlled watershed algorithm and Fast radial symmetry transform	Accuracy of 81.2%	Not suitable for specimens containing larger numbers of nuclei with excessive overlapping and touching of cells
Jain et al. [17]	Active Contour Model (Both region based and boundary based) with General Classifier Neural Network (GCNN)	83.47% accuracy	ACM fails in images containing high noise and excessive overlapping nuclei
Karsnas [20]	Intuitive Segmentation using vectorial data	Not mentioned	The region keep growing without spatial constraints

3.2.1. Segmentation using marker-controlled watershed algorithm

Veta et al. [34] proposed a procedure for the segmentation of H & E stained images. The procedure incorporates colouring de convolution to exclude unwanted or border areas from the image during pre-processing stage. Markers are required for the marker controlled watershed algorithm. These markers are the cell/nuclei positions obtained by using fast radial transform. In a pre-processed image with the morphological operations having a scale value, n done, watershed segmentation has to perform. This segmentation uses two markers which focus on two particular sorts of nuclei. One marker utilizes Fast Radial Symmetry Transform markers and the other one utilizing regional minima markers. Radii R can be obtain by processing Fast Radial Symmetry Transform, S. This arrangement of radii mirrors the measure of the nuclei that are reproduced well in the pre-processed image. The nuclei markers are extracted from the minima of S using a default parameter h=0.4. The h-minima transform of FRST, S is defined by (Eq. (1)):

$$S_h = \rho_S^E(S + h) \tag{1}$$

where ρ as grayscale factor and E is erosion operator. The background also needs to be marked for a successful segmentation. To accomplish this, we need foreground area marker. Then this marker compared to the maximum value inside the set R. The skeleton image of the background map is utilized as a marker for background segmentation. The regions which are not likely to speak about nuclei are expelled in the post processing stage. Fig. 3 shows the segmentation result using marker controlled watershed segmentation. The achievement rate of watershed algorithm is nearly 81.2%.

3.2.2. Segmentation using active contour model (ACM)

Jain et al. [17] gives an idea of using Active contour model. Active contour model based on two functions: region based and boundary based. Thresholding technique is the basic method used in region based ACM. But it is not perfect for separating overlapping cells. In this context, watershed Algorithm can be used to find out the edges between overlapping cells. ACM has its own importance particularly when sporadic shapes, for example, malignant cells are available inside an image. In this technique they started with some predefined contours, characterized by a suitable function. These contours are defined in both regions which are inside and outside the contour. These contours are growing from a predefined level set function. The specifications of this level set function can be changed to obtain required optimization. Chan and Vese [7] used a technique that is suitable to the histopathology image segmentation. Unlike Active Contour Model, this technique does not depend on boundary location. In Chan-Vese model an energy fitting operation is used with the accompanying four parameters:- Difference in gray scale/RGB inside the given contour, difference in gray scale/RGB outside the given contour, length of the contour, area of the region inside the contour. Fig. 4 shows the segmented output using ACM.

Initialize the contour (using Eq. (2)):

$$\varphi(x, y) = \sin\left(\frac{\pi x}{10}\right).\ \sin\left(\frac{\pi y}{10}\right) \tag{2}$$

where x and y are x co-ordinate and y co-ordinate.

Steps of ACM segmentation algorithm [7]:

1. Initialization of ϕ
2. Do step 1 for several iterations.
3. Computation of c_1 and c_2 for the present ϕ.
4. Update ϕ using new values.

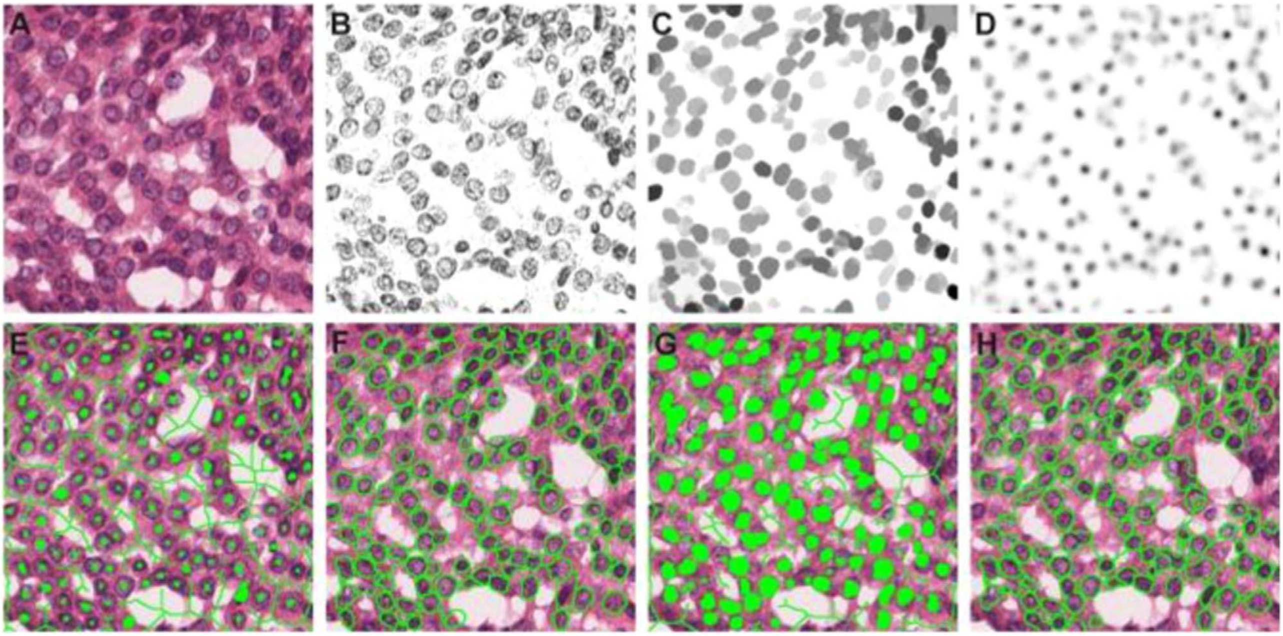


Fig. 3. Marker imposition and watershed segmentation for nuclei segmentation. a) Original image, b) Hematoxylin channel, c) Pre-processed image (hematoxylin channel processed with series of morphological operations), d) Fast radial symmetry transforms (FRST), e) FRST foreground and background markers, f) Watershed segmentation with FRST markers, g) Regional minima foreground and background markers, h) Watershed segmentation with regional minima markers (Adapted from Veta et al. [34]).

5. Compute difference between ϕ_n and ϕ_{n-1}

3.2.3. Intuitive segmentation using vectorial data

Region growing strategies are usually utilized for image segmentation. These methods assume all pixels which are nearer to each other having same properties. The two endpoints in a path have high likelihood of having position in the same region or belong to same object. Region growing techniques are regularly utilized for intuitive methods for segmentation because of their high efficiency in computation. Be that as it may, today images speaking to vectorial information, e.g., colour and textural components are natural. Joining multimodular information with this segmentation technique could possibly expand the execution because more data is accessible which in turn help the region developing criteria.

In an image contains vectorial information, pixel to pixel separation can be found out by using the vectorial least barrier distance. For example, values speaking to various colour intensities or different features. This technique requires no training [20].

3.3. Feature extraction and classification

Visual information of an image can be obtained by feature extraction. Features obtained from the segmented nuclei are the input for classification. The most widely used classifiers are Artificial Neural Network (ANN). These networks will learn the features of cancer cells during training phase and classifies the cancer nuclei into various classes during the testing phase. Irshad et al. [15] trained the classifier using features that belongs to four categories viz: cytological, intensity, morphological and texture features. The size and shape of nucleoli are obtained from cytological information. Morphological features are useful to get shape and margin (smooth or irregular) of lesions. Texture features are related to the pattern distribution of nuclei inside the tissue [26].

Jain et al. [17] recently used eight morphological features of each cell and used for classification. A 2-D array format is used to store these features. In this array cells are represented using columns and features are represented using rows. The features extracted are area, perimeter, mean, median and standard deviation in both x and y directions. Later a General Classifier Neural Network (GCNN) is used for classifying cells into cancerous and non cancerous.

Niwas et al. [28] proposed complex wavelets for the extraction of feature set describing the chromatin structure of cancer cell. These features are going to train the classifier which is based on k-nearest neighbour algorithm. Thus classification to benign (normal) or malig-

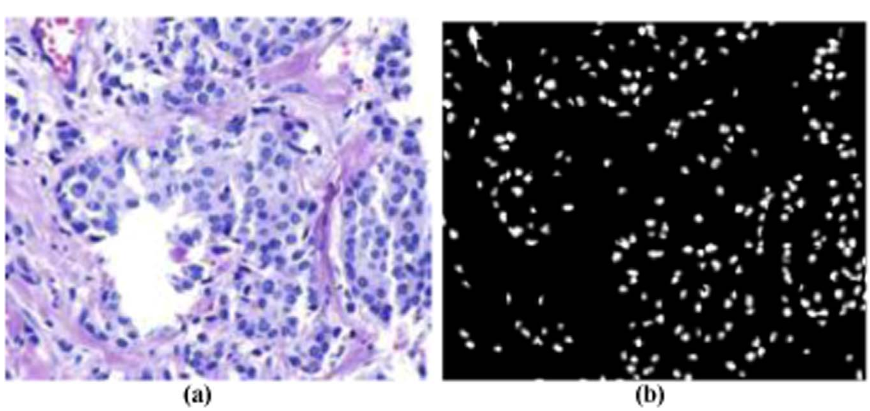


Fig. 4. (a) Input image for Active Contour Model, (b) Segmented output using Active Contour Model (Adapted from Jain et al. [17]).

Table 2
Features extracted using the methods Histogram features, Co-occurrence matrix features and Intensity based features.

Methods	Features
Histogram features	Smoothness, Mean, Skewness Uniformity, Entropy
Co-occurrence matrix features	Contrast, Energy, Sum of square of variance
Intensity based features	Median, Mode, Variance, Standard deviation

nant (abnormal) tissue is obtained. They achieved a 93.33% successful classification rate.

Nie et al. [27] proposed different techniques based on histogram, intensity and Gray level Co-occurrence matrix (GLCM) for feature extraction. Histogram is a measure of number of pixels contained by various intensity levels. There are 256 intensity values for an 8-bit gray scale image. Histogram is plotted for an image and then four first order statistic features are derived. GLCM method is used to obtain texture features. Using this method, second order statistic features are obtained. GLCM is a 2-D array which explains the specific position of a pixel with respect to neighbouring pixels. Intensity is one of the basic features of an image and depends only on spatial domain. Classification is based on an artificial neural network having sigmoid function. All these features are used to train the classifier. Table 2 shows the features extracted using the above said methods.

4. Parameters for performance assessment of a classifier

There are different parameters for measuring the performance of various methods of classification. Classification accuracy (ϕ), Matthew's Correlation Coefficients (ρ), Specificity (τ) and sensitivity (λ) are some among them. All the parameters can be calculated from confusion matrix, describing real and predicted outcomes of the proposed technique [14, 22], which is shown in Table 3.

4.1. Classification accuracy (ϕ)

Accuracy determines how accurate the classifier in predicting the classes. Simply, it is a measure of effectiveness of the classifier (Eq. (3)).

$$\varphi = \frac{(\alpha + \omega)}{(\alpha + \mu + \omega + \beta)} \tag{3}$$

where α – is the number of true predictions that an occurrence is true.

μ – is the number of false predictions that an occurrence is true.
ω – is the number of true predictions that an occurrence is false.
β – is the number of false predictions that an occurrence is false.

4.2. Matthew's correlation coefficient (ρ)

Matthew's correlation coefficient is introduced by Matthews (1975), a famous biochemist. It is a measure of quality of two – classes (binary) classification. It can be directly calculated from confusion matrix using the formula given in Eq. (4):

Table 3
Contingency Table (Confusion Matrix).

Real Value	Predicted Outcome	
	Yes	No
Yes	α	Β
No	μ	Ω

$$\rho = \frac{(\alpha \times \omega) - (\mu \times \beta)}{(\alpha + \mu)(\alpha + \beta)(\omega + \beta)(\omega + \mu)} \tag{4}$$

4.3. Specificity (τ)

Specificity is also defined as rate of ω. It is a measure of percentage of predicted classes that are correct (Eq. (5)).

$$\tau = \frac{\alpha}{(\alpha + \mu)} \tag{5}$$

4.4. Sensitivity (λ)

Sensitivity is also defined as rate of α. It is a measure of percentage of correct classes that are predicted (Eq. (6)).

$$\lambda = \frac{\alpha}{(\alpha + \beta)} \tag{6}$$

5. Discussion

Many digital image analysis techniques were proposed by researchers for histopathology images recently. But one problem is that these breast cancer analyses are carried out on a small dataset due to the unavailability of public dataset containing large quantity of images. To mitigate this, Spanhol et al. [30] approximately 7900 images from 82 patients. They trained classifiers using texture descriptors and came up with an accuracy rate of 85%.

But most of the scientists are not convinced with the existing feature extraction methods [21]. The convolutional neural network (CNN) architectures are widely accepted for texture image analysis. They can be used for both high resolution and low resolution texture images. CNN has high performance compared to other conventional architectures [36]. Other deep learning techniques that got wide acceptance are fuzzy c-means clustering and method of DFDL (Discriminative Feature-oriented Dictionary Learning). Fuzzy c-means algorithm is a powerful method for pattern recognition including segmentation [16].

Histopathology image processing and analysis has more difficult issues compared to radiological image processing and analysis. Histopathology images have exceptionally muddled structure compared to other images [29]. The study on various parts of histopathological image investigation prompts exceptionally encouraging results. In any case, the comparison of various techniques applied to histology images is troublesome since every method utilizes distinctive image dataset and gives diverse measurements to obtain results [6].

Not only that, even the images at various magnification levels are utilizing according to the purpose of study. Likewise the nuclei structure and cell information are diverse for various images; subsequently the technique connected to one image may not take a shot at another. A comparative study has been made for different algorithms and summarized in Table 1.

6. Conclusion

This article discusses the necessary options, inspiration, results from the early developments and future possibilities of Computer Aided Diagnosis (CAD) systems. Histopathological examination of biopsy sample is critical in all aspects, ranging from cancer detection to treatment planning. This article reviews different techniques used for histopathology image analysis with a focus on breast cancer detection and classification. This review aims at complementing the effort of pathologists, in examining and analyzing biopsy samples, by computer aided techniques. This study is an endeavor to point out recent development in breast cancer detection and classification and gives an outlook on efficiency, authenticity and accuracy of different techniques. Digital mammography was once extensively used for early detection of cancer. Due to its adverse effects on human body, biopsy and magnetic resonance imaging (MRI) are proposed. Among them the most accurate imaging method is biopsy.

7. Future possibilities

The field of digital image analysis of breast cancer detection is very vast. According to wide variety of image modalities and disease characteristics, study in this area is still unlocked and distinctive challenges are there to explore according to specific applications. Multimodal fusion is one such task that can be taken into account from a research point of view [10]. The images taken from consecutive data or from different image modalities like computer tomography, Magnetic Resonance Imaging (MRI), ultrasound can be combined to make a strong aid for cancer diagnosis, development and treatment [3]. As multimodal data usage increases, the need for a tool that can envisage the data becomes important.

Spectral imaging is one important challenge in histopathology. Spectral imaging can achieve images at different wavelengths instead of ordinary RGB (3-channel) input image [20]. This can potentially provide additional significant information to assist in cancer detection. The use of a digitized breast cancer system in histopathology images for clinical purposes will be a milestone in the medical history. Recent advancement in the field of digital imaging along with new powerful analytic tools will improve the destiny of digital pathology.

Recently patients in Europe are offered with digital breast cancer detection system by Philips. Philip's digital pathology along with a set of algorithms, Visopharm algorithms, helps pathologists for more objective diagnosis. Thus high resolution and high quality images with advanced analytic algorithms will enhance the performance of breast cancer detection [24]. The existing manual biomarker assessment is highly susceptible for subjective variations from one pathologist to another. Many researchers reported that digital image analysis along with pathologist's observation will lead to a more accurate detection of cancer.

References

[1] Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. J Cancer Ther 2011;8(1):56–70.
[2] American Cancer Society. Testing biopsy and cytology specimens for cancer. (Last Revised 07.30.15).
[3] Anshad PYM, Kumar SS. Recent methods for the detection of tumor using computer aided diagnosis — a review. In: Proceedings of the International conference on control, instrumentation, communication and computational technologies (ICCICCT), Thuckalay, India; 2014.
[4] Basavanhally A, Yu E, Xu J, Ganesan S, Feldman M, Tomaszewski J, Madabhushi A. Incorporating domain knowledge for tubule detection in breast histopathology using O'Callaghan neighborhoods. Proc SPIE 2011;7963:796310–25.
[5] Belsare AD, Mushrif MM. Histopathological image analysis using image processing techniques: An overview. Signal Image Proc Int J 2012;3(4):23–36.
[6] Bowman TC, El-Shenawce M, Campbell LK. Terahertz imaging of excised breast tumor tissue on paraffin sections. IEEE Trans. Antennas Propag 2015;63(5):2088–97.
[7] Chan T, Vese L. Active contours without edges. IEEE Trans Image Proc 2001;10(2):266–77.
[8] Dundar M, Badve S, Bilgin G, Raykar VC, Jain RK, Sertel O, et al. Computerized classification of intraductal breast lesions using histopathological images. IEEE Trans Biomed Eng 2011;58(7):1977–84.
[9] Fan L, Jeffrey P. Handbook of practical immunohistochemistry: frequently asked questions, 2nd ed.. New York: Springer; 2015.
[10] FEZA El-Gamal, Elmogy M, Atwan A. Current trends in medical image registration and fusion. Egypt Inform J 2016;17(1):99–124.
[11] Gelasca ED et al., Evaluation and benchmark for biological image segmentation. In: Proceedings of the international conference on image processing; 12-15 October-2008, San Diego, USA.
[12] Gonzalez RC, Woods RE. Digital Image Processing, 3rd ed.. Upper Saddle River, NJ, USA: Prentice-Hall, Inc.; 2008.
[13] Gurcan MN, Boucheron LE, Can A, Madabhushi A, Rajpoot NM, Yener B. Histopathological image analysis: a review. IEEE Rev Biomed Eng 2009;2:147–71.
[14] Hamilton R, Xu P, Asgari S, Kasprowicz M, Vespa P, Bergsneider M, Hu X. Forecasting intracranial pressure elevation using pulse waveform morphology, paper presented in the 38th annual international conference of the IEEE Engineering in Medicine and Biology Society; 3-6 September-2009. Florida, USA
[15] Irshad H, Veillard A, Roux L, Racoceanu D. Methods for nuclei detection, segmentation and classification in digital histopathology: a review—current status and future potential. IEEE Rev Biomed Eng 2014;7:97–114.
[16] Jagannath M, Adalarasu K. Diagnosis of diabetic retinopathy from fundus image using fuzzy c-means clustering algorithm. J Inst Integr Omics Appl Biotechnol 2015;6(4):3–9.
[17] Jain A, Atey S, Vinayak S, Srivastava V. Cancerous cell detection using histo-pathological image analysis. Int J Innov Res Comput Commun Engng 2014;2(12):7419–26.
[18] Jennifer S, Woo MD, Neda A, Moatamed MD, Peggy S, Sullivan MD, David Y, Lu MD, Rena Callahan MD, Sophia Apple MD. Comparison of phosphohistone H3 immunohistochemical staining, Ki-67, and H & E mitotic count in invasive breast carcinoma. Journal of Brain and Spinal Cancer 2015;1(1):1–11.
[19] Jyothi D. Breast, mouth cancer top new cases in Indian women and men, respectively; 2015 ⟨http://www.thehindubusinessline.com/news/breast-mouth-cancer-top-new-cases-in-indian-women-and-men-respectively/article7259256.ece⟩ (accessed 03.10.16).
[20] Karsnas A. Image analysis methods and tools for digital histopathology applications relevant to breast cancer diagnosis. Digit Compr Summ Upps Diss Fac Sci Technol 2014:1128.
[21] LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015;521:436–44.
[22] Lewis HG, Brown M. A generalized confusion matrix for assessing area estimates from remotely sensed data. Int J Remote Sensing 2001;12:3223–35.
[23] Li X, Plataniotis K. A complete color normalization approach to histopathology images using color cues computed from saturation-weighted statistics. IEEE Trans Biomed Eng 2015;62(7):1862–73.
[24] Lowe A, Grunkin M, Kristenson M et al. Visiopharm digital pathology blog, philips teams up with Visiopharm to boost breast cancer diagnosis objectivity through computational pathology; 2016 ⟨http://www.visiopharm.com/blog/category/image-analysis/⟩ (accessed on 07.11.16)
[25] Mohan H. Textbook of Pathology, 7th ed.. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd.; 2014.
[26] Montironi R, Braccischi A, Scarpelli M, Matera G, Alberti R. Value of quantitative nucleolar features in the preoperative cytological diagnosis of follicular neoplasias of the thyroid. J Clin Pathol 1991;44(6):509–14.
[27] Nie K, Chen J-H, Yu HJ, Chu Y, Nalcioglu O, Su M-Y. Quantitative analysis of lesion morphology and texture features for diagnostic prediction in breast MRI. Acad radiol 2008;15(12):1513–25.
[28] Niwas SI, Palanisamy P Sujathan K. Wavelet based feature extraction method for breast cancer cytology images. In: Proceedings of the IEEE symposium on industrial electronics & applications; 3-5 October 2010.
[29] Sazzad T, Armstrong L, Tripathy A. An Automated approach to detect human ovarian tissues using type P63 counter stained histopathology digitized color images. In: Proceedinghs of the IEEE-EMBS International conference on Biomedical and Health Informatics (BHI); 2016 pp. 25-28
[30] Spanhol F, Oliveira LS, Petitjean C, Heutte L. A dataset for breast cancer histopathological image classification. IEEE Trans Biomed Eng 2016;63(7):1455–62.
[31] Sushmi D. Cancer cases in India likely to soar 25% by 2020: ICMR; 2016 ⟨http://timesofindia.indiatimes.com/india/Cancer-cases-in-India-likely-to-soar-25-by-2020-CMR/articleshow/52334632.cm8s⟩ (accessed by 03.10.16)
[32] Ter Haar Romeny B. Front-end vision and multi-scale image analysis: multi-scale computer vision theory and applications, written in Mathematica, Netherlands; 2008.
[38] A.B. Tosun and C. Gunduz-Demir, C. Graph run-length matrices for histopathological image segmentation, *IEEE Transactions on Medical Imaging* **30** (3), 2011, 732-566
[34] Veta M, van Diest PJ, Kornegoor R, Huisman A, Viergever MA, Pluim JPW. Automatic nuclei segmentation in H & E stained breast cancer histopathology images. PloS ONE 2013;8(7):e70221.
[35] Zhou X, Wong S. Informatics challenges of high-throughput microscopy. IEEE Signal Proc Mag 2006;23(3):63–72.
[36] Xing F, Xie Y, Yang L. An automatic learning-based framework for robust nucleus segmentation. IEEE Trans Biomed Imaging 2015;35(2):550–66.
[37] Yasmin M, Sharif M, Mohsin S. Survey paper on diagnosis of breast cancer using image processing techniques. Res J Recent Sci 2013;2(10):88–98.