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Image Processing in Breast Carcinoma Histopathological Image: A Review

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ABSTRACT

Breast carcinoma grading of histopathological images is the standard clinical practice for the prognosis and diagnosis of breast carcinoma development. The grading provides semi-quantitative assessment for mitotic activity, tubules formation and nucleus pleomorphism. Semi-quantitative scores obtained from the manual grading are inconsistent and may lead to inter- and intra- raters variability. Fortunately, the recent advances in image processing have significantly increased the possibility of fully quantifying the breast carcinoma features, reducing workload of pathologist and providing reproducible and high accuracy results. This paper is meant as an introduction for non-experts. It starts with an overview of the breast carcinoma, breast carcinoma grading systems and followed by a discussion on different image processing techniques applied to measure tubules formation, nucleus pleomorphism and mitotic activity as well as a discussion on complete system for the breast carcinoma measurement.

Keywords: Biomedical Engineering, Image Processing, Breast Carcinoma, Nottingham Grading System, Quantitative Measurement.

1. INTRODUCTION

Breast carcinoma represents a huge global health problem among women in both developed and developing countries. It is estimated that over 508,000 women worldwide died in 2011 due to breast carcinoma [1]. The WHO statistics showed that 50% of breast carcinoma cases and 58% of the deaths occurred in the developing countries such as Malaysia, Indonesia and Thailand [1]. The incidence rates of breast carcinoma vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In developing countries, the incidence rates are below 40 per 100,000 cases [1]. African countries found to be the lowest incidence rates across the globe. The survival rates of breast carcinoma vary greatly worldwide, ranging from more than 80% in Sweden, Japan and North America to around 60% in the middle-income countries and below 40% in the low-income countries [1].

A recent study found that Malaysian women are prone to a high risk in developing breast carcinoma during their lifetime: 1 in 28 women [2]. The incidence rates are higher in the urban areas: 1 in 22 women, as compared to the rural areas: 1 in 60 women [2]. Some states in Malaysia were reported to have higher breast carcinoma incidences. Penang, Kuala Lumpur and Johor are the top three states with Age-standardised rate (ASR): 50.0, 42.2 and 39.8 incidences per 100,000 people, respectively. Breast carcinoma has been found to be the top cancer that commonly develops in women during their lifetime: 32.1%. The incidence cases of breast carcinoma in Malaysia have increased since 2007. There were 3579 positive cases reported in

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2007 and 3766 positive cases reported in 2011. The average age of the high risk group in Malaysia is 53 to 57 years [2]. Genetic mutation, particular in BRCA1, BRCA2 and p53, lack of breastfeeding, higher levels of endogenous estrogens, certain dietary patterns, obesity and late menopause are the risk factors of breast carcinoma.

Breast carcinoma has a significant burden in term of morbidity, mortality and health care cost worldwide in developed and developing countries [1]. This has initiated the global interest in breast carcinoma studies as well as the public interest in breast carcinoma assessments and treatments. Precise and accurate evaluation in breast carcinoma grading is crucial to provide a better and more efficient treatment planning.

Breast carcinoma is a complex, heterogeneous and fatal disease [3]. It is a malignant tumour and starts from cells of the breast. Breast carcinoma can either begin in the cells lining of lobules or ducts and for rare type the cancer begins in the stromal tissues [3]. There are different types of breast carcinoma. The most common type of breast carcinoma is Invasive Ductal Carcinoma (IDC) [4]. Cancer cells that start inside the milk ducts is known as Ductal Carcinoma In Situ (DCIS). The new WHO classification listed DCIS as precursor lesions of the breast [4].

Breast carcinoma can be cured if immediate and precise treatments are delivered to the patients [5]. Abnormalities found during the clinical breast examinations (such as mammograms, breast MRI or breast ultrasound) require a definite diagnosis using a biopsy test [5] .There are three main types of biopsies; surgical biopsy, fine needles aspiration biopsy and core biopsy [5]. The tissues obtained from this biopsy procedure are examined under a microscope by a pathologist. The pathologist grades the breast carcinoma by referring to a grading system. The grading results are used to evaluate tumour characteristics and for patient prognosis and theragnosis [6-8]. The breast tissues examined under a microscope can be captured using a camera or scanner and kept in form of images. A number of studies have used the captured images to fully quantify cancer features by utilising image processing techniques [9-11].

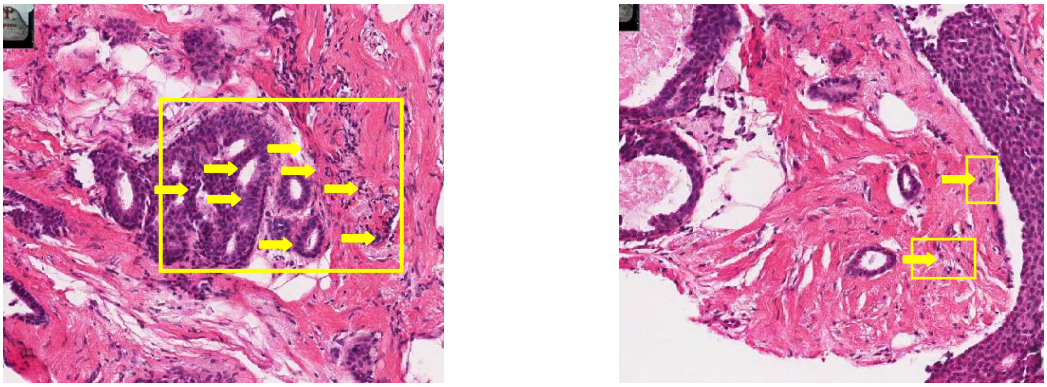
This paper is meant as an introduction for non-experts. It starts with a review on the established methods in the assessment of breast carcinoma overall grade based on Nottingham Histopathological Grading (NHG) system. In the NHG system, three criteria are used to assess the overall grading: percentage of tubule formation, nucleus pleomorphism, and mitotic count. These criteria are discussed in detail in Section 2.0. Reviews on established methods based on the three criteria are discussed in Section 3.0. Discussion on the established methods is presented in Section 4.0.

2. GRADING OF BREAST CARCINOMA

Histological grading is typically referred to the growth pattern, degree of differentiation and is used to describe the resemble of the normal breast epithelial cells [11]. There are several grading systems have been introduced to grade breast carcinoma. Examples of the breast carcinoma grading system are the original Scarff-Bloom-Richardson (SBR) system [11, 12] and the Black method [12, 13]. The SBR system provides score (ie., ranging from 1 to 3) for each of the following criteria: nuclear features, tubule formation and mitotic rate. A total score is obtained by summing scores in each criterion (3-9). This total score provides grade for the breast carcinoma. Grades 1, 2 and 3 have the following respectively total scores: 3 to 5, 6 to 7 and 8 to 9. The Black Method [13] only provides score for nucleus features. Tubule formation and mitotic rate are not considered in the Black Method system.
Recently, the Elston-Ellis modification of the SBR grading system or Nottingham Histological Grading (NHG) system is becoming the most commonly used grading system worldwide [12, 14, 15]. The NHG system is accepted as the gold standard for grading of breast carcinoma [16, 17]. The NHG system is recommended by World Health Organization (WHO), the European Union

(EU), the Royal College of Pathologists (UK RCPath) and the American Joint Committee on Cancer (AJCC) [15, 18]. The NHG system provides more objective criteria for each of the elements in SBR system and provides a more systematic way to determine mitotic rate [15]. The NHG system has been proven to be more reproducible among pathologists [19-30]. This may directly influence the types of treatment that could be delivered to the patients. The NHG system uses the same criteria as in SBR system to grade the breast carcinoma (ie., tubule formation, nuclear pleomorphism and mitotic count).

Tubule formation can be described by how well the tumour cells differentiate [14]. Well differentiated tumour cells tend to have the similar structure as the normal cells. The tumour cells form tubule and this tubule creates a lumen (Figure 1). Poor differentiated tumour cells do not have a lumen as the tumour cells tend to invade into the lumen area, resulting in lumen degeneration [9]. Tubule formation is measured in percentage ratio against the overall cell structures. The tubule formation scoring system is shown in Table 1.



(a) **(b)**

Figure 1. Histopathological images with tubules and lumens. The tubules are highlighted with yellow squares while lumens are pointed by the yellow arrows.

Table 1 Scoring system of tubule formation [14].

Score	Percentage of tumour area forming tubular structures
1	>75%
2	10% to 75%
3	<10%

Nuclear pleomorphism refers to the variation of tumour cells that occurred in shape, size as well as the staining of cells and nuclei [14] as shown in Figure 2. The degree of variation has been used to describe the severity of the tumour cells. The scoring of nuclear pleomorphism is defined in Table 2.

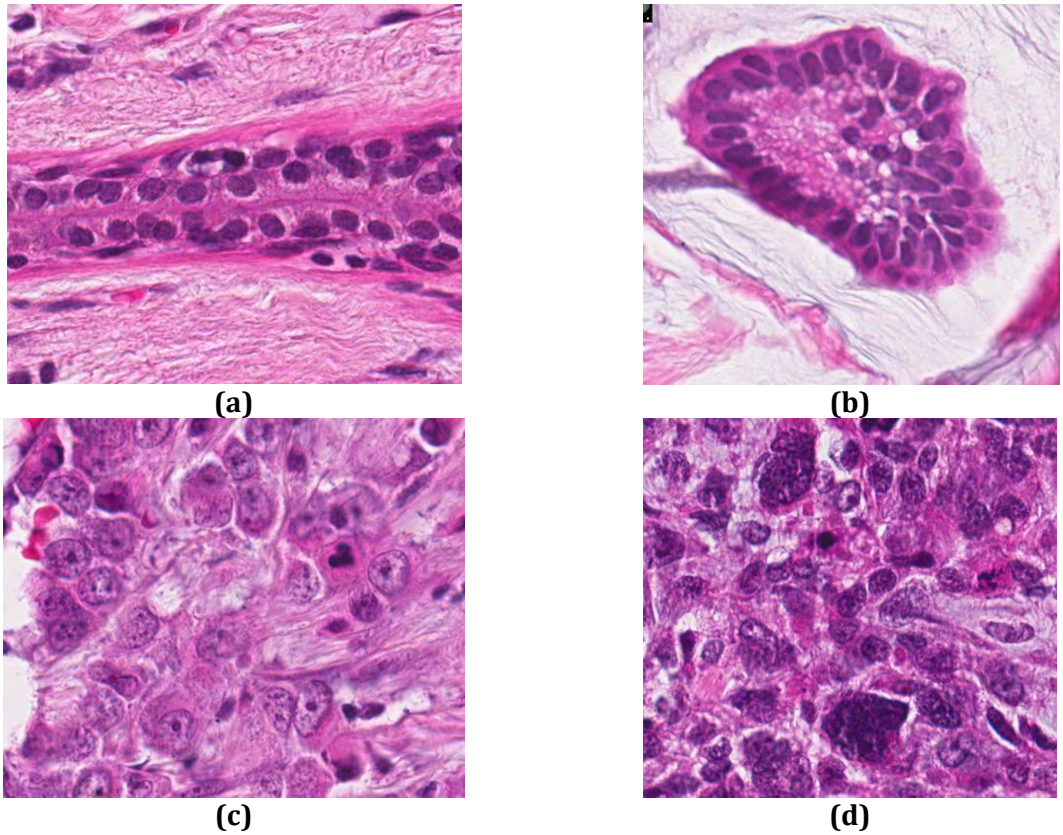


Figure 2. Scoring of nucleus pleomorphism. (a) Normal image, (b) Image with score 1 in nucleus pleomorphism, (c) Image with score 2 in nucleus pleomorphism, (d) Image with score 3 in nucleus pleomorphism.

Table 2 Scoring system of nucleus pleomorphism [14]

Score	Characteristic
1	Small nuclei with little increase in size respect to normal breast epithelial cells, regular outlines, uniform nuclear chromatin and low degree of variation in size
2	Increase in cell size with open vesicular nuclei, visible nucleoli, and moderate variability in term of shape and size
3	Vesicular nuclei, often with prominent nucleoli, present significant variation in shape and size, occasionally with very large and eccentric forms

Mitotic count is used to assess the speed of tumour cell growth. Mitosis process involved chromosome segregation, nuclear division and cytokinesis [31]. During mitosis, the nucleus becomes hyperchromatic due to an excessive nuclear staining. The mitotic cell (Figure 3) is more visible under a microscope [32] and appears darker via staining of Hematoxylin and Eosin (H & E). The scoring system of mitotic count is shown in Table 3.

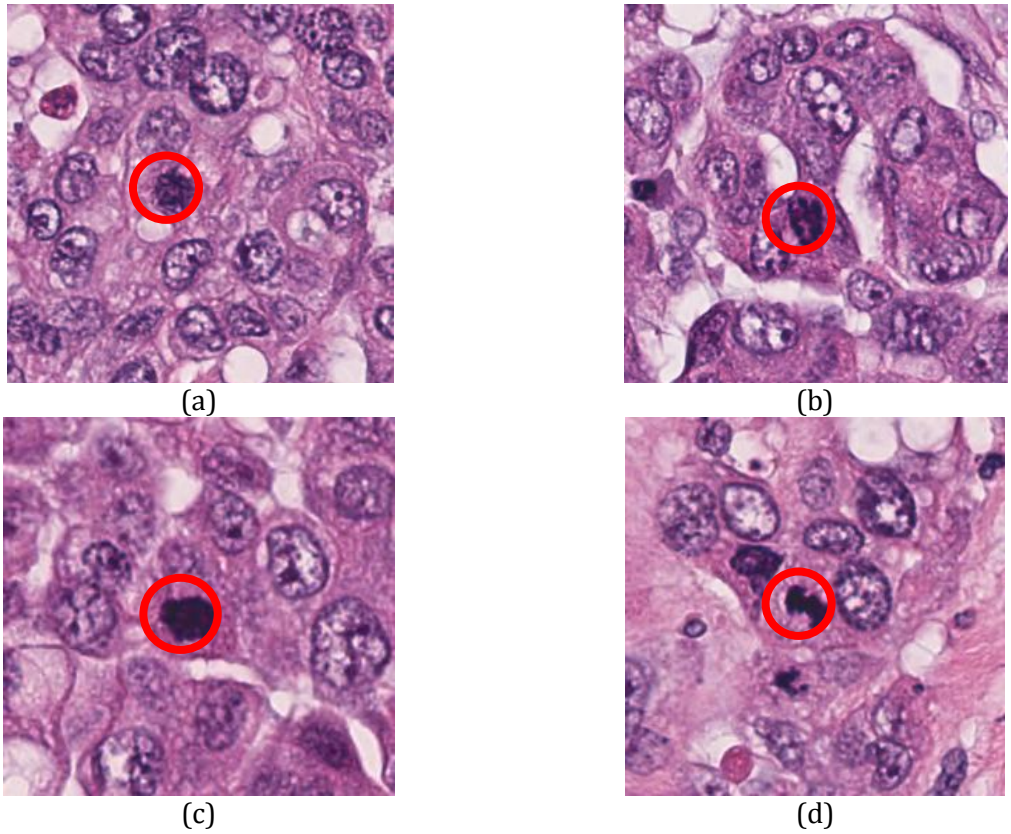


Figure 3. Examples of mitotic cells in histopathological images. In (a), (b), (c) and (d), the mitotic cells are shown in the red circles.

Table 3 Scoring system of mitotic count [14]

Score	Number of mitotic counts per 10 high power field (hpf)
1	0 - 9
2	10 - 19
3	20 or >20

3. QUANTITATION OF BREAST CARCINOMA FEATURES USING IMAGE PROCESSING TECHNIQUES

A pathologist examines breast tissue slides under a microscope where tubules, nucleus features and mitotic counts are evaluated manually. Slide examination on breast carcinoma tissue may is a cumbersome and tedious work [33]. In addition, inter- and intra-observers variability among pathologist exhibited a significant effect on the outcome of manual grading [33]. Few studies reported that manual grading is not reproducible [11, 34, 35]. Therefore, an automated-computerized system is essential to encounter the limitations aforementioned.

3.1 Assessment of Tubule Formation

In this section, a brief published work on tubule segmentation is discussed.

Ko *et al.* [8] proposed a texture based extraction of tubule in breast carcinoma. K-mean clustering technique was first applied on HSV and La*b* channels to identify the tubule candidates. Morphological closing and holes filling were implemented as post processing

techniques to eliminate artefacts and noises. The proposed algorithm was tested on 90 images with an overall accuracy of 90.12%.

Cheng *et al.* [36] implemented a simple thresholding method to identify the lumen candidates. Then, the region growing was applied to identify the lumen area in the study images. These algorithms can be applied on real-time processing in tubule.

Fakhrzadeh *et al.* [37] used an active contour [38-40] to extract the lumens candidates. This algorithm computes the evolving curve inside the connected component using Geodesic Distance Transform. The gland boundary was then segmented using watershed classifier. This study provided an accuracy of 89.0% based on 36 input images.

Ojansivu *et al.* [41] applied a texture based algorithm with Local Phase Quantization (LPO) and Local Binary Pattern (LBP) descriptors to segment tubule in the breast carcinoma images. The study found that by using the LPQ descriptor in addition to LBP descriptor alone, the overall accuracy can be improved by 2% (from 62% to 64%).

Naik and Doyle [42] implemented low, high and domain knowledge for features segmentation in the breast carcinoma. The low level information was based on the pixel values where the high level information was based on the relationship established between the pixels and the object of interested. Domain knowledge was based on the characteristic of the features of interested in histological images. This method had successfully identified the percentage of tubules in the breast carcinoma. The percentage was then used to calculate the tubule scores based on Nottingham Grading System (breast carcinoma) [12]. The scoring hold an accuracy of 81.91% in classification of cancer and non-cancer images.

Doyle and Agner [43] implemented texture and architectural based methods to segment tubules in the breast carcinoma. Gabor filter features were extracted and applied to the algorithm and produced accuracy of 95.80% in classification of cancer and non-cancer histopathology images. Apart from this, the manifold data of different grades of breast carcinoma show a smooth spatial transition through spectral clustering method.

Chekkoury *et al.* [44] used textural, topological and morphometric features based segmentation in breast carcinoma histopathological images. This fusion method has been proven to be more effective (accuracy of 87.14%) to segment the cancer features. This is because each technique holds a different characteristics or relationships between the structures and pixel values. Tubules candidates that did not fit into the proposed criteria were registered as artefacts, thus, eliminated from being segmented.

Nguyen *et al.* [45] developed a fusion method based on lumen domain knowledge and nuclei features. The lumens candidates were detected using the lumen-based method. Then, the nuclei detection was applied to determine the tumor nuclei in the images. The lumen candidates that have a close relationship with the tumor nuclei were identified and registered as true lumens. In addition, graph-cut based method was implemented to eliminate the possible faulty links established between the lumen candidates and the nearby tumor nuclei. This method resulted in a mean accuracy of 91.0%.

Bilgin *et al*. [46] used k-mean clustering for tubule segmentation. A cell-graph was generated based on each segmented image. Then, a global metric based on the cell-graph was determined and this information is for training purpose. The hierarchical cell graphs were proven to be accurate in term of classification in breast tissues. The study was tested on 446 images and obtained an overall accuracy of 81.8%.

3.2 Assessment of Nucleus Pleomorphism

In this section, a brief review on nucleus pleomorphism detection in histopathological images is discussed.

Cosatto *et al.* [9] implemented Hough transforms to detect enlarged nuclei in histopathological images. These nuclei may have low amount of H in its center as compared to the nucleus edge during the staining process. To tackle this limitation, a Hough Transform was used to detect elliptical nuclei in the nucleus. Then, the active contour algorithm was applied to identify the boundary of the nucleus. This algorithm was tested on 208 images with an F-measure of 89.0%.

Petushi *et al.* [47] used adaptive thresholding and morphological operation to segment the cell nuclei. The input RGB image was first converted into a grey-scale image. Then aforementioned methods were applied to obtain the region of interest (ie., the nucleic). Features extraction based on the nucleus candidates were used for classification. The proposed study implemented learning-based approaches for image classification using Quadratic classifier from the LNKnet software. This study was tested on 24 images with an overall accuracy of 95.6%.

Doyle *et al.* [48] implemented a cascaded (CAS) approach which has been proven to be more systematic for nucleus detection and cancer grading. This approach maximized the intra-homogeneity and inter-heterogeneity of the input data. The nucleus was detected and a relationship between neighborhood nuclei was established using Delaunay Triangular, Voronoi diagram, nuclear density calculation and Minimum Spanning Tree. This study was conducted on 214 images with an accuracy of 98.0% in detection of cancer vs non-cancerous.

Chekkoury *et al.* [44] proposed textural, topological and morphological features approach in malignancy detection. The color RGB input image was first converted to CMY color model. In a high resolution (40x magnification) nuclei may be blurred with weak or missing boundaries. Therefore, a Random Walker (RW) was applied to segment the nucleus. Then, textural, topological and morphological features were extracted from the nucleus candidates and classified using a Support Vector Machine (SVM). A total of 70 images were tested and an overall accuracy of 87.14% was obtained.

Dalle *et al.* [49] proposed a Gaussian modelling in pleomorphism detection. First, the distribution of the color in the input image was modelled using a Gaussian model. Then, the three levels of nucleus pleomorphism based on the NHG System were predefined with a specific color threshold. Then, the difference in color between the detected nucleus and the color thresholds was calculated. The nucleus was then assigned into respective grade based on the color thresholds.

3.3 Assessment of Mitotic Count

In this section, a brief literature review on mitotic cell detection is discussed.

Al-Kofahi *et al.* [10] implemented the multiscale Laplacian of Gaussian (LoG) with automatic scale selection to detect the nuclei in histopathology images. First, graph-cuts-based binarization is use to remove the foreground of the input images. Then, the proposed method aforementioned was applied. A second graph-cut-based method was implemented with the combination of alpha expansions and graph coloring to refine the detection accuracy. This algorithm was tested on 25 images and obtained accuracy of 86.3%. Irshad [50] implemented LoG together with thresholding, morphological and active contour model to detect the mitotic cells. Before implementation of these techniques, the color RGB input image was converted into a blue-ratio image. The classification was performed by using the decision tree method. Two image scanners: Aperio and Hamamatsu were used. Each scanner captured 50 images and the F-

measures of 72.0% and 63.0% were obtained respectively. Wang *et al.* [51] combined LoG and local dynamic thresholding on a blue-ratio color space of RGB input images to segment the mitotic cell candidates. A cascade approach was then applied on the mitotic cell candidates. The cascade approach consists of a convolutional neural network (CNN) and handcrafted features (ie., morphology, color and texture features). A random classifier with 50 trees was implemented to identify the true mitotic cells. The algorithm was tested on 35 images with an F-measure of 73.45%.

Nateghi *et al.* [52] implemented a Teaching-Learning-Based optimization (TLBO) to reduce the percentage of false positive in mitotic cell detection. In TLBO, the false positive mitotic candidates is represented by a set of cost function. The number of false positive could be eliminated via minimizing of the cost function. Support Vector Machine (SVM) was applied to classify 35 images with an output F-measure of 77.34%.
Irshad *et al.* [53] used a novel mitotic cell detection based on Scale-Invariant Feature Transform (SIFT) feature and Hierarchical Model and X (HMAX) biologically inspired approach. Features such as co-occurrence features, run-length features and SIFT were extracted from the blue-ratio images. Then, these features were used as input to the classifier to classify the true mitotic cells. This algorithm was tested on 25 images with an F-measure of 76.0%.

Pourakpour and Ghassemian [54] proposed a Gamma-Gaussian Mixture Model (GGMM) to detect non-mitotic and mitotic cells. In this model, the mitotic cells were represented by Gamma model and non-mitotic cells were represented by Gaussian Model. A SVM with RBF kernel classifier was applied on Aperio XT and Hamamatsu scanner images. The F-measure obtained for Aperio XT and Hamamatsu scanner images were 92.3% and 89.4% respectively. Khan *et al.* [55] also implemented GGMM approach to detect mitotic and non-mitotic cells. In addition, the authors proposed a Context Aware Post Processing (CAPP) to reduce the number of false positive. The false positive was reduced significantly with a small compensation of sensitivity. 35 breast histology images were used in this study and a sensitivity of 72.0% was obtained.

Nateghi and Habibollah [56] proposed a Genetic Optimization algorithm to reduce the number of false positive in mitotic cell detection. Features such as Gabor features, co-occurrence and run-length matrices were extracted from the mitotic cell candidates. A SVM was used as classifier to classify the mitotic candidates. This algorithm was tested on 35 images with an overall F-measure of 78.47%.

Tashk *et al.* [57] proposed a Maximum Likelihood Estimation (MLE) to identify the true mitotic cells. The study implemented a 2-D anisotropic diffusion as a pre-processing method. Then, MLE was applied to extract pixel-wise features in the input images. An object-wise completed local binary pattern (CLBP) was proposed to prevent misclassification. A SVM was then used to classify the mitotic cells. The average F-measures of 70.94% and 70.11% were obtained respectively for Aperio XT and Hamamatsu scanner images.

Logambal and Saravanan [58] proposed a Bayesian modelling and a local region thresholding method for mitotic cell detection. Features such as shape, intensity, gradient and texture were extracted from the mitotic candidates. In order to evaluate the performance of the proposed method, 35 histopathological images were captured from five breast carcinoma slides. The proposed method achieved a promising result with an output accuracy of 95.8%.

Sertel *et al.* [33] proposed a likelihood function estimation to identify the probability a pixel is belong to a mitotic cell group. The proposed method started with a pre-processing using histogram equalization. Then, an anisotropic diffusion is applied to smooth the heterogeneous regions and to normalize the color distribution in the input image. This algorithm was followed by a probability calculation and mitotic cells segmentation using a component-wise-2-step thresholding. This algorithm obtained an overall accuracy of 81.8%.

Ciresan *et al*. [59] proposed a Deep Neural Network (DNN) to classify the mitotic cells from the background. The DNN is a max-pooling (MP) convolutional neural network (CNN). DNN can operate on a color RGB input image. DNN has a better weight, non-linearity and connections as compared to the CNN. An F-measure of 78.2% was obtained when DNN was used to classify 50 images. Chen *et al.* [60] focused on the classification of mitotic cells. The study proposed a Deep Cascaded Neural Network (CasNN) as the classification model to identify mitotic cells in breast carcinoma. The study focused on the computation enhancement as the proposed method was 60 times faster as compared to the present method in 2012 ICPR MITOSIS data. The algorithm achieved an F-measure of 78.8%, which was slightly higher than Deep Neural Network (DNN) proposed by Ciresan *et al.* [59].

Lu and Mandal [61] proposed a Bayesian Modelling and a local-region thresholding to identify mitotic cells. The relationship function was first calculated on every pixel to identify the likelihood a pixel is belong to a mitotic or a non-mitotic group. Then, Bayesian Modelling and local-region thresholding were implemented to detect and segment the pixels that have high affinity toward mitotic group. A Model Explanation System (MES) classifier was then used to classify all the pixels into respective groups. The proposed method obtained a promising result by registered an overall sensitivity, which is greater than 80%.

Paul and Mukherjee [62] used Relative-Entropy Maximized Scale Space (REMSS) in the mitotic detection. This method could prevent over segmentation as compared to morphological scale space because the proposed method parameterizing only grey levels that hold a Relative-Entropy between the cells and its background. A random forest classifier was used to classify 40x magnification training data set and obtained an F-measure of 73.8%.

Chowdhury *et al.* [63] implemented a minimum weight bipartite graph matching to tract the mitotic cells. Median filter is used as pre-processing to remove high level noises in the input images. Then, an entropy thresholding was implemented to segment the cells from the background. After pre-processing and segmentation stage, the bipartite graph matching was applied to 10 microscopy images and a mean accuracy of 80.63% was obtained.

Nedzved *et al.* [64] used a fast grey-scale thinning algorithm to detect cells in the input images. The proposed algorithm was simple where the idea was based on binary image layer analysis that is by applying mathematical morphology and merging operation on grey-scale images. However, this study is lack of quantitative measurement results and the outcome of segmentation was highly dependent on the staining outcome.

Yang *et al.* [65] proposed a marker-controlled watershed to segment the cells based on mathematical morphology. This method was pertained to avoid over segmentation. A tracking method was applied based on a modified mean shift algorithm to further refine the segmentation results which then followed by the mean-shift algorithm and Kalman filter. A promising result was obtained with an overall segmentation accuracy of 98.8%.

Lee *et al.* [66] focused on detection of nuclei boundary using snake and local tunings. They implemented two iterative generalized Hough Transforms (GHTs) in the study. The first iterative was used to obtain the information on the size of the nuclei, whereas the second iterative was to segment the nuclei from the background. This algorithm was applied on cytological images with an overall accuracy greater than 80.0%.

Dalle *et al.* [49] used a combination method based on features and Gaussian model to detect mitotic cells. The low resolution input images were analyzed to detect neoplasm. The areas of neoplasm were extracted and underwent a higher magnification for further feature extraction

(ie., mean, standard deviation, solidity, eccentricity and area). These features were classified using probability estimation.

3.4 Quantitative Measurement System of Breast Carcinoma

The state-of-art methods in tubule detection, nucleus pleomorphism detection and mitotic count might be effective in quantifying breast carcinoma and lead to a promising result. However, there are no many studies proposed automated systems that replicate Nottingham Grading System to fully quantitatively measure breast carcinoma. Studies in [42, 53, 67] had developed full systems based on the Nottingham Grading System. However the proposed system only had been tested to a small number of dataset (ie., 12 images [42] and 6 images [49]). A large data set may result in a great variation in overall performance.

4. DISCUSSION

Computer technology especially on topics that are related to the use of image processing techniques has brought many changes in clinical practice of breast carcinoma disease. This initiated a digitalization era across the globe where vast imaging techniques are employed and integrated in clinical research. Many extensive works have been published and tested on the individual criterion of breast carcinoma features (ie., tubule formation, nucleus pleomorphism and mitotic count) based on the NHG system.

Based on the established methods discussed in the previous sections, there are studies that had provided promising results when using individual criterion for breast carcinoma detection. However, very few studies provide measurement for all three breast carcinoma criteria using NHG system. Thus, the review shows that there is research gap where the detection on individual criterion could be compiled to form a single-input-multi-output system based on the NHG system.

Quantitative measurement in image analysis in medical practice is becoming a common trend in hospital and health care lines. This is essential for the routine clinical practice and important in prognosis and treatment planning. A robust automated system with quantitative output analysis may highly increase the efficiency and suitability of the cancer prognosis. The NHG system is widely accepted and common in use as a global standard grading system for breast carcinoma. However, conventional manual grading based on the NHG system provides semi-quantitative scores. Assessment of tubule formation using NHG system is dependent on estimation done by the histopathologist. For example, the exact value in percentage for tubule formation is not possible to be determined. This problem becomes significant when the percentage of tubule formation lies on the boundary between two scores. Also, the scoring for nucleus pleomorphism in NHG system is based on qualitative description. There is lack of quantitative characteristic to determine the exact score in nucleus pleomorphism. The prognosis and treatment planning of the breast carcinoma are greatly dependent on the output grading. The cancer treatment to be delivered is directly affecting the morbidity and mortally of the patient.

An automated system that replicates the manual grading system such as on the NHG system to fully quantify the breast carcinoma features is hypothesized to provide a great contribution to the breast carcinoma grading. A cascade system with modular approaches can be employed instead of using a single algorithm to reflect the manual routine practice of the pathologist. Hybridization in algorithms may be the solution in the future trend to automate the manual grading system.

In general, image processing algorithms can be classified into two types: semi-automated and fully automated. A semi-automated algorithm requires some user interaction to initiate a

process, whereas a fully automated algorithm requires no user interaction. Although many pathologists request for a fully automated algorithm, but in real time application, this could be nearly impossible. In many cases, the selection of region of interest (ROI) as the input images and the verification of the output results require pathologist to perform the tasks manually. In other words, all algorithms are semi-automated. Therefore, in this context automation refers to an algorithm that requires a minimum user interaction [68, 69]. The main purpose of algorithm implementation is to reduce the workload of pathologist and to provide reproducible and high accuracy results.

5. CONCLUSION

This paper presents the overview of the breast carcinoma, breast carcinoma grading systems (NHG system) and the established image processing methods in assessing breast carcinoma features: tubule formation, nucleus pleomorphism and mitotic activity. The review highlights the research gaps arise from the established studies: (1) very few studies provide measurement for all three breast carcinoma used in the NHG system, (2) conventional grading based on the NHG system is a semi-quantitative method, (3) semi-automated algorithms with minimum user interaction could be a solution to encounter the vast variation in assessing breast histopathological images for breast carcinoma.

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