Journal of Advances in Medical and Pharmaceutical Sciences
9(3): 1-9, 2016, Article no.JAMPS.28336
ISSN: 2394-1111

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Development of Combined Genetic and Imaging Approaches for Differentiation of Cutaneous Malignant Melanoma and Benign Melanocytic Nevi

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Authors' contributions

This work was carried out in collaboration among both authors. Author SA designed the study and wrote the protocol. Author NAA collected all data, performed the statistical analysis, and wrote the first draft of the manuscript. Author NAA did the literature search and also wrote part of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2016/28336
Editor(s):
(1) Nissar Darmani, Professor of Pharmacology, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, California, USA.
Reviewers:
(1) Sandra A. Marinho, State University of Paraiba (UEPB), Brazil.
(2) Kowichi Jimbow, Sapporo Medical University, School of Medicine, Japan.
Complete Peer review History: http://www.sciencedomain.org/review-history/15828

Review Article

Received 14th July 2016
Accepted 10th August 2016
Published 17th August 2016

ABSTRACT

The morbidity and mortality rate is reduced by premature and exact diagnosis of melanoma, which is the deadliest type of skin cancer. Timely identification of melanoma needs extremely complex and subjective test and laboratory samples. It is not insignificant even for experienced dermatologists to identify, so lot of concentration must be given. Finding the difference between melanoma and mole is also an issue in the accuracy of clinical diagnosis of melanoma. Especially, early diagnosis of cutaneous melanoma is very hard for experienced dermatologists. Even though a lot of advanced imaging techniques and clinical diagnostic algorithms such as dermoscopy and the ABCD rule of dermoscopy respectively are available, clinical diagnosis of melanoma becomes very challenging. The accuracy is an issue of distress (estimated to be about 75--85%) especially

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with oblique pigmented lesions. Quantitative and objective evaluation of the skin lesion is achieved by the above methods with respect to the subjective clinical assessment. An effective diagnosis can be achieved by reducing the viewer variability's found in dermatologists' examinations. In order to improve some of existing methods and budding new techniques to ease accurate, fast and reliable diagnosis of cutaneous melanoma. In this paper different types diagnostic system of melanoma namely, preprocessing feature extraction, feature selection and classification is explained. The results of feature selection were optimized from advanced classes of classification techniques; namely, Two weighted *k*-nearest neighbor (*k*-NN) classifiers (*k* = 1, 30), a decision tree (DT), and the Random Forest (RF) algorithm are employed. Support Vector Machine has been very effective in computer-based melanoma diagnosis studies in the literature.

Keywords: Classification; composite biomarkers; cutaneous melanoma; dermoscopy and feature selection.

1. INTRODUCTION

Skin is the very sensitive and sensory part of the body that acts as protective layer of our body against the environmental pollutions. Skin acts as regulator of the human body temperature and transmitter of the sensation feelings to the brain. Melanoma is a Skin cancer which is not common disease such as other skin cancers types. This is a very dangerous disease and anyone can get melanoma at any time. It begins in the melanocytes which are in our skin. This cancer has some other names such as malignant melanoma and cutaneous melanoma. But some melanomas do not make melanin and can appear pink, tan, or even white. Melanomas can occur anywhere on the skin, but more likely to start on the men's trunk and on the women's legs. Melanoma is almost curable in its early stages like basal cell and squamous cell cancers. But it is easy to spread to other parts of the body if not caught early unlike basal or squamous cell cancer. Rossi et al. [1] have demonstrated that Cutaneous Melanoma (CM) is a complex multifactorial disease because of both environmental and genetic factors are involved in this cancer manifestation [1]. CM is serious neoplasm, derived from melanocytes, that accounts for most skin cancer deaths.

The complexity of cellular metabolism and regulatory pathways obstructs the formulation of melanoma mechanism as it has been shown by Dummer et al. [2]. Thus, though the derivation of gene signatures for various cancers, e.g., breast or colon cancer exist, a similar progress remains mysterious for malignant melanoma. Potentially this could be attributed to the intricate nature of the molecular basis of CM, which requests neatly stratified epidemiological cohorts to address effectively the issue of the high heterogeneity of the disease. In any case, genomic studies are limited by the shortage of similar melanoma cohorts, collecting and maintaining frozen tumor tissue thus rendering gene expression profiling studies of melanoma relatively scarce.

Melanoma is the most destructive and deadly form of skin cancer. Jemal et al. [3] have revealed that distant metastases Patients have a five-year survival rate of 16% and a median survival of four to six months. Until very recently, melanoma has been identified by the chemotherapy and other therapeutic attempts. However, the discovery that 40%–50% of melanomas harbor activating BRAF mutations as shown by Flaherty et al. [4] prompted the development of selective BRAF inhibitors. Sosman et al. [5] have monted that the first specific ones were the lead compound PLX4720, and the pharmacokinetically superior PLX4032/vemurafenib [6]. In order to identify genes that confer resistance to a melanoma drug called PLX-4720 is generally used. Drugs of this type work well in patients whose melanoma cells have a mutation in the BRAF gene, but cancer cells that survive the treatment can grow into new tumours, allowing the cancer to recur.

A great example of appropriate melanoma models at different steps of preclinical development is the extraordinarily quick bench-to-bedside history of this drug. Oncogenic BRAF with PLX4720 or PLX4032 resulted is Targeted which results inhibition of growth and invasion of three-dimensional melanoma spheroids into a collagen matrix and causes tumor regression of melanoma xenografts without evidence of toxicity [6]. This was mirrored in phase II and phase III patient trials and has finally lead FDA-approval of vemurafenib; however, despite these

unprecedented response rates, rapid onset of resistance is a major issue as it has been shown by Chapman et al. [7].

Melanoma model system has a vital property is that Reiteration of their proliferative, migratory, and invasive properties of melanoma cells. The selection of the model system which is used to study melanoma cell has the capability to retain features of the primary tumor can as well as tumor growth. Winnepenninckx et al. have shown that [8] genomic studies and gene expression profiling studies of melanoma are limited by the lack of similar melanoma cohorts, collecting and maintaining frozen tumor tissue [8]. In [8], Winnepenninckx et al studied patients to identify 254 genes, which expression was related with metastatic dissemination of cutaneous melanomas. Lately, Raskin et al. [9] used transcriptome profiling of primary melanomas, metastases, and normal skin samples. They revealed that the transcription factor HMGA2, previously unrecognized in melanoma pathogenesis, is significantly up-regulated in primary melanoma and metastases. Many significant emerging biological pathways and gene targets are identified in melanoma and reported by Dutton-Regester K. and N. K. Hayward [10].

Ogorzałek et al. [11] have revealed that the human interpretation of image content can be subjective and superior programmed techniques are used in the diagnostic process. In this context, expert computer systems have been proposed as alternatives to the naked-eye expert prediction. The extracted dermoscopy image features are associated with color in various color spaces (RGB, HIS, CIELab) and are used for automated lesion characterization [12]. Other common features are associated with asymmetry and border that also used for automated lesion characterization. The statistical and advanced classification methods like support vector machines [13] and neural network [14] have also been applied. Korotkov et al. [15] have presented a comprehensive review of image analysis techniques and computer based systems used for the early detection of CM appear.

So, the final goal is to provide a holistic description of the disease through the inter-connections of predictive models which are defined at different scales into systemic networks. This survey is used to study the associate macroscopic CM disease descriptors, i.e., imaging features from dermoscopic examinations, and low-level biological information, i.e., gene expression, to CM disease status and compare their information content. Though several numbers of methods have been proposed based on image analysis and existing methods for the diagnosis of melanoma lesions using notions from the traditional visual inspection, the ultimate goal is the derivation of a compressed set of imaging features, which filters out most of the confusing part from the initial imaging descriptor set. In addition, the resulting compact set of imaging features would be characterized by reduced computational cost. However, it is also important to consider issues of the existing methods with the factors, such as ease of use, data interpretation, cost, and applicability issues, such as genetic manipulation and drug delivery, when selecting a model system. Nimunkar et al. [16] applied wavelet transform with pyramid-structure on a set of 28 images to differentiate melanoma from dysplastic nevi. A vector of 34 features is formed by the decomposition of luminance color channel into three levels and different statistical ratios such as energy, entropy, etc. This was ultimately reduced to five features using statistical analysis. Patwardhan et al. [17] proposed an adaptive wavelet-based tree-structured method on a set of 60 images for classification of melanoma. The average energy, maximum energy and fractional energy ratios were used, where a vector comprising 231 features is created by the decomposition of luminance image into three levels. Then, a bimodal distribution was applied to select those features through statistical analysis based on population mode. As a result, the process yielded five optimal features.

Moreover, Garnavi et al. [18] have proposed a wavelet-based texture analysis method for classification of melanoma. The method applies tree - structured wavelet transform on different color channels of red, green, blue and luminance of dermoscopy images, and employs various statistical measures and ratios on wavelet coefficients. Feature extraction and a two-stage feature selection method, based on entropy and correlation were applied to a train set of 103 images. The resultant feature subsets were applied to four different classifiers: support vector machine, random forest, logistic model tree and hidden naive bayes to classify melanoma in a test set of 102 images, which resulted in an accuracy of 88.24% and ROC area of 0.918.

Manousaki et al. [19] have used an approach that has parameters of geometry, color and color texture as independent covariates for selecting melanoma from melanocytic nevi. For early melanoma diagnosis, experienced dermatologists have an accuracy of 64-80% using clinical diagnostic criteria, usually the ABCD rule, while automated melanoma diagnosis systems are still considered to be experimental and serve as adjuncts to the naked- eye expert prediction. In an attempt early melanoma diagnosis establishes a mathematical model with a melanoma probability and it is used to develop an image processing program with the aim to separate melanoma from melanocytic nevi.

In the work of Ganster et al. [20], a melanoma recognition system that involves image processing, segmentation, feature calculation and selection, as well as k-NN classification has been presented. A system for the computerized analysis of images obtained from epiluminescence microscopy (ELM) has been developed to enhance the early recognition of malignant melanoma. As an initial step, several basic segmentation algorithms together with a fusion strategy are used to find the binary mask of the skin lesion. A shape and radiometric features as well as local and global parameters are calculated to describe the malignancy of a lesion. Feature selection is performed by the application of statistical feature subset selection methods. The final kNN classification delivers a sensitivity of 87% with a specificity of 92%. In addition, Alcón et al. [21] also have presented an automatic imaging system that combines the outcome of the image classification with context knowledge such as skin type, age, gender to improve the classification accuracy. Malignant and benign lesions are classified through an automatic system for inspection of pigmented skin lesions. A personal risk factor is calculated by the image processing system for feature extraction, classification, and patient-related data decision support machinery. It has been shown that our algorithm is capable of recreating controlled lighting conditions and correcting for uneven illumination. A robust segmentation algorithm has been developed. As a result, the features are scale and rotation invariant. Therefore, the distance at which the digital image was taken is of no significant importance as long as the size of the feature of interest can be resolved on an imaging device.

Tittmann et al. [22] have developed a novel two-frequency approach for noninvasive evaluation of cancerous tissue with optimum depth and resolution. Thickly sliced tissue detects the relative attenuation (C-scan mode scanning) difference with relatively limited resolution by the usage of 50 MHz frequencies. Thus, suspect zones can be identified according to a quantitative criterion. The selection of suspect zones is used for preparation of thin, transversal slices from within the original thick slices. A very-high-resolution (1-μm) cell is obtained at around 600 MHz on these transversal sections and adjacent sections are prepared for histological study in parallel. The technique's feasibility and potential are demonstrated on both normal and cancerous (melanoma) skin tissue. Specimens isotropy is experimentally verified to ensure that conditions were coherent for use of a 5-layer, angular spectrum model made to simulate longitudinal velocity that is evaluated from semi quantitative V (z) data.

Moreover, Rahman et al. [23] have reported that the automated melanoma recognition of the dermoscopic images based on image retrieval is done by content and multiple expert fusion. In this context, the ultimate aim is to support the decision making by retrieving and displaying the relevant past cases as well as predicting the image categories (e.g., melanoma, benign and dysplastic nevi) by combining outputs from different classifiers. However, the most challenging aspect in this domain is detection of a lesion among the healthy surrounding skin and the lesion-specific local image features is extracted. A lesion is detected through threshold -based segmentation method on the intensity images generated from two different schemes. For the fusion-based image retrieval and classification, the lesion-specific local color and texture features are extracted and represented in the form of the mean and variance–covariance of color channels and in a combined feature space. The performance is evaluated by using both the precision-recall and classification accuracies. In order to do cancer research, clinical data (age, sex, size, or grade of tumor size, image extracted features) can be incorporated with gene expression data from microarray experiments. The skin tissue is taken as a uniform or homogeneous medium. Nevertheless, the skin tissue is inhomogeneous with multilayered structure. It consists of two primary layers that include a bottom layer – the dermis, and a top layer – the epidermis.

In the most of the work identification the multimodal datasets which are biomedical data from different sources is not considered.

Multimodal datasets is used in the context of personalized medicine and health data management. Their weightage is strengthened in the case of multi-factorial diseases, like CM, which are promoted by interplay between genetic factors and the environment. Linking different data can help toward a holistic approach of the disease, and for the evaluation and comparison of various subsets of markers (genetic/ environmental factors, imaging features).

In addition the classification accuracy will be reduced if most of the irrelevant features in the features set are not removed. The selection of imaging features which depends on the gene signature provides added value to the bias power of the selected imaging features. All of these problems are solved and motivated from the all above work. In addition, Valavanis et al. [24] have reported information about gain ratio measurements and exploration of the gene ontology tree, is used to identify a set of 32 uncorrelated genes with a essential role as regards molecular regulation of melanoma, in which the different pathological states are correlated heavily with expression across samples. These genes do the uncorrelated imaging features selection based on their ranking which is made according to mutual information measurements to the selected gene expression values. Genes and imaging features which are selected were used to train various classifiers that could distinguish malignant samples from malignant melanoma samples. In this classification task, imaging features were outperformed by the genes subset selected here contained much denser information on the expression of CM compared to the latter.

2. EXPERIMENTATION RESULTS

The incorporated dataset which is formed from two different sources (microarrays and imaging), which are described as follows. The methodology which is used to produce the dataset by using data imputation methods is described.

2.1 Microarrays Data and Preprocessing

Gene expression profiling dataset was found in the gene expression omnibus [25-26], GDS1375. RNA was cut off from 45 primary melanoma, 18 benign skin nevi, and 7 normal skin tissue specimens and used for gene expression analysis. The Affymetrix Hu133A microarray chip was used for expression profiling and contained 22 000 probes. The mean gene vector relating to the normal skin categories was subtracted from all replicate vectors of the other two categories followed by global normalization and log transformation of gene expression values. Differential expression ratios were calculated by dividing the each category signal intensities by the respective normal category's gene value. An FDR for multiple testing adjustments, p-value 0.001 and two-fold change thresholds were applied, and thus, 1701 genes were statistically preselected.

2.2 Imaging Data

The imaging dataset consists of skin lesion images set, 972 instances of nevus skin lesions and 69 melanoma cases. Three types of imaging features were calculated as follows: border Features, color features and textural features which are based on ABCD rule of dermatology, C rules, and D rules respectively [27]. Finally 31 features were produced (one feature was removed due to having zero variation across the samples).

2.3 Integrated Dataset

Moutselos et al. [28] have reported that microarray and imaging datasets are unified into single datasets with the use of missing value imputation methods. Before this method, the dataset corresponded to a sparse matrix containing 1104 samples (benign or malignant samples, either from microarray data or imaging data) and a total of 1732 features (gene expression or imaging features). Missing value imputation uses two algorithms: uniform data imputation and bootstrap data imputation [25]. The uniform imputation is conducted by uniform sampling within the range of each feature per class, and the bootstrap imputation is performed by independent bootstrapping of each variable separately per class, until all the missing values are replaced. Each algorithm was applied three times and a total of six datasets were derived. All of the derived datasets has dual scope: 1) apply statistics to enlighten the interrelations of imaging features and genes and their impact to the target variable (malignant versus benign) toward the selection of narrowed subsets of imaging features or genes, and 2) estimate more broadly the selected subsets of features when input to classification algorithms. Four classifiers

were constructed and evaluated in terms of generalization in all six datasets each (three uniforms and three bootstrap). Specifically, two weighted k-Nearest Neighbor (k-NN) classifiers (k = 1, 30), a Decision Tree (DT), and the Random Forest (RF) algorithm were used. Their performance was measured using three-cross validation resampling. Sensitivity (Sen) measurements (true positive/(true positive + false negative) for each of the two classes in all six datasets and in order to compare the selected genes subset and imaging features subset, mean values were calculated. GOR evenge analysis (MF and BP aspects) resulted in total of 179 genes found in the original list of 1701 differentially expressed genes. Out of this subset of genes, 32 genes had an IG ratio in the top 20% of all 1701 genes. These genes comprise a gene signature underlying CM manifestation, based on the available gene expression profiling data. Correlation redundancies (|correlation coefficient| > 0.8) were not found in the gene set. Every incremental genes subset, starting from the first ranked gene based on IG ratio up to all 32 genes, was calculated most of the variation content of the disease status and corresponds to measurement of TV > 0.8. Davies et al. [29] have shown that their analysis reveals mutations in two regions of the BRAF kinase domain. Mutations are very similarly distributed in cancer cell lines and primary cancers. They [29] have demonstrated that the total of 89% of mutations are within or immediately adjacent to the activation segment, a region of 10–30 amino acids bounded by almost invariant DFG and APE motifs.

The total variation criterion is used to reduce the dimensionality of the set of selected genes set. In total four gene or imaging features, subsets were derived by the methodologies previously described: 1) Thirty-two genes has the gene signature (functional analysis and IG ratios), 2) ten imaging features selected based solely on information content to disease status (IG ratios), 3) prioritization which depends on list of genes has a TV > 0.8 using MI values, is applied to select ten imaging features which are selected by the GA- based selection scheme. All four subset of features were input to the classifiers used here. Sensitivity results for the two classes (malignant, benign) obtained for all six instances of the integrated dataset and mean values, are presented for these four features subsets in Tables 1, 2, 3 and 4, respectively.

Table 1. Sensitivity measurements (%) for malignant and benign classes for classifiers using 32 selected genes (Gorevenge AND IG Ratios): Three cross-validation resampling and mean values

RF malignant Sen	RF benign Sen	DT malignant Sen	DT benign Sen	30-NN malignant Sen	30-NN benign Sen	1-NN malignant Sen	1-nn benign Sen	Set
97.12	100	95.12	100	96.12	100	98.13	100	Bootstrap 1
97.12	100	94.71	100	96.12	100	96.42	100	Bootstrap 2
99.17	100	93.81	100	96.12	100	99.12	100	Bootstrap 3
98.13	100	93.81	100	96.12	100	97.21	100	Uniform 1
98.15	100	100	100	96.12	100	98.36	100	Uniform 2
98.36	100	92.38	100	96.12	100	98.36	100	Uniform 3
98.008	100	94.971	100	96.12	100	97.93	100	Mean value

Table 2. Sensitivity measurements (%) for malignant and benign classes for classifiers using ten imaging features selected based solely on IG ratios: three cross-validation resampling and mean values

RF malignant Sen	RF benign Sen	DT malignant Sen	DT benign Sen	30-NN malignant Sen	30-NN benign Sen	1-NN malignant Sen	1-NN benign Sen	Set
30.58	96.12	44.32	93.12	0	100	25.16	92.53	Bootstrap 1
26.21	97.81	44.18	94.18	0	100	26.18	92.13	Bootstrap 2
30.18	96.18	51.81	95.24	0	100	33.12	93.13	Bootstrap 3
16.28	97.63	42.03	94.16	1.63	99.21	17.32	91.62	Uniform 1
11.23	98.41	35.18	95.18	5.13	99.15	22.58	90.61	Uniform 2
18.36	97.21	34.18	93.14	7.02	99.01	21.08	91.58	Uniform 3
22.14	97.22	41.95	94.17	2.29	99.56	24.24	91.93	Mean value

Table 3. Sensitivity measurements (%) for malignant and benign classes for classifiers using ten imaging features selected based on prioritizing Imaging features to the 26 selected genes (gorevenge, IG ratios, TV > 0.8): three cross-validation resampling and mean value

RF malignant Sen	RF benign Sen	DT malignant Sen	DT benign Sen	30-NN malignant Sen	30-NN benign Sen	1-NN malignant Sen	1-NN benign Sen	Set
14.36	99.10	37.18	93.12	0	100	51.45	93.12	Bootstrap 1
16.71	98.16	44.25	99.17	0	100	64.12	93.33	Bootstrap 2
18.18	97.12	42.13	95.24	0	100	54.39	94.06	Bootstrap 3
12.21	98.32	36.25	94.16	1.63	99.21	21.46	90.13	Uniform 1
7.03	99.41	42.13	95.42	5.13	99.09	21.46	90.13	Uniform 2
10.36	98.35	40.28	94.18	7.02	99.01	22.15	91.10	Uniform 3
13.141	98.41	40.37	95.215	2.296	99.551	39.171	91.978	Mean value

Table 4. Sensitivity measurements (%) for malignant and benign classes for classifiers using ten imaging features selected by the GA selection scheme: three cross-validation resembling and mean value

Set	1-NN	1-NN	30-NN	30-NN	DT	RF	RF	Malignant Sen
Malignant Sen	Benign Sen	Malignant Sen	Benign Sen	Malignant Sen	Benign Sen	Malignant Sen	Benign Sen	
22.32	98.26	45.18	94.13	14.36	98.12	49.23	96.13	Bootstrap 1
20.13	98.18	38.13	93.18	15.12	99.04	36.18	95.94	Bootstrap 2
15.13	97.21	38.18	94.36	10.53	99.12	43.13	94.84	Bootstrap 3
6.18	99.18	36.92	94.15	4.13	99.18	31.40	95.18	Uniform 1
11.16	99.31	32.45	93.337	9.42	99.32	36.51	94.36	Uniform 2
12.12	99.41	33.14	93.03	7.02	99.01	35.18	94.37	Uniform 3
14.506	98.591	37.33	93.697	10.096	98.96	38.605	95.136	Mean value

Results in Table 1 show that top genes are able to yield very good performance metrics. Classification accuracy will be high, when selected genes are input to the well performed 1-NN and RF classifier. Sensitivity measurements for the malignant class are little worse than the corresponding benign class and this shows the abundance of benign samples in the integrated dataset. When combining results in Tables 1, 2, 3 and 4, it is obvious that performance metrics obtained here by the top genes, are much higher than the ones obtained when imaging features are feeding the classifiers. Regarding the use of imaging features and the classifiers' performance, the much greater abundance of benign samples in the integrated dataset provides great effect here. Thus, along with the lower information content of imaging features, the classifiers perform moderately when recognizing malignant samples.

3. CONCLUSIONS AND FUTURE WORK

Cutaneous Melanoma diagnosis, skilled dermatologists have an accuracy of 64–80% using clinical diagnostic criteria, but automated melanoma diagnosis systems are still experimentally considered and served as adjuncts to the naked-eye expert prediction. In an attempt recent work of Cutaneous Melanoma diagnosis, developed an image processing program to differentiate melanoma from gene samples, with a mathematical model. In this paper the most significant systems for the automated detection of malignant melanoma and begin melanoma have been surveyed. The above said systems use a variety of methods which are the image acquisition, the feature definition and selection as well as the Cutaneous Melanoma classification from features. The most promising image acquisition techniques is feature extraction, since the extracted dermoscopy image features which are applied for automated lesion characterization with predictive value concerning CM. Malignant melanoma samples are separated from the benign ones by feeding a series of classifiers with the selected imaging features subset. The classification results obtained using gene signature for samples discrimination is compared. In order to increase the number of cases, more patients must be examined

particularly during the classification phase. The issue of selecting the most powerful variables for classification is very important and may also enable even better classification with examination of the differences between the two methods. The scope of the future work is the improvement of accuracy of clinical diagnosis of melanoma which is also an issue especially in distinguishing between melanoma and mole.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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(Received 2 February 2002)
(Accepted 16 May 2002)
(Published online 9 June 2002)

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/15828