Optical perception for detection of cutaneous T-cell lymphoma by multispectral imaging

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Abstract
In this study, the spectrum of each picture element of the patient’s skin image was obtained by multi-spectral imaging technology. Spectra of normal or pathological skin were collected from 15 patients. Principal component analysis and principal component scores of skin spectra were employed to distinguish the spectral characteristics with different diseases. Finally, skin regions with suspected cutaneous T-cell lymphoma (CTCL) lesions were successfully predicted by evaluation and classification of the spectra of pathological skin. The sensitivity and specificity of this technique were 89.65% and 95.18% after the analysis of about 109 patients. The probability of atopic dermatitis and psoriasis patients misinterpreted as CTCL were 5.56% and 4.54%, respectively.

Keywords: skin biopsy, cutaneous T-cell lymphoma, spectrum signature of the skin, multispectral imaging

1. Introduction
Cutaneous T-cell lymphoma (CTCL) refers to a group of lymphoproliferative disorders characterized by localization of neoplastic T lymphocytes to the skin and is an unusual type of non-Hodgkin lymphoma [1, 2]. The most represented form of CTCL was mycosis fungoides. Pathological changes in mycosis fungoides, refer to the process in which mutant T lymphocytes break out of the corium from the capillaries, continuing upwards to attack the epidermal layer [3]. It could be misdiagnosed as ordinary psoriasis, atopic dermatitis, or eczema. Early CTCL often lacks the histologic criteria necessary for a definitive diagnosis [4].

Updated methods for CTCL detection have been developed. Booken identified the Sézary syndrome as a unique CTCL, as determined by an expanded gene signature, including the diagnostic marker molecules CDO1 and DNM3.
Sézary syndrome gene expression [5]. Lin reported on a high-resolution genomic analysis combining DNA (23 samples) and mRNA (12 samples) data of peripheral blood isolates from CTCL patients across a spectrum of stages [6]. Wozniak clarified the differences between cutaneous anaplastic large-cell lymphoma and cutaneous peripheral T-cell lymphoma not otherwise specified by molecular pathogenesis [7]. Despite the importance and usefulness of these methods in deepening the understanding of CTCL, these techniques need to be performed by invasive skin biopsy or blood tests, and remain clinically unsuitable for real-time diagnosis.

The application of spectroscopy and illumination in biomedicine has recently been investigated [8–11]. The real-time property of multi-spectral image reproduction technology is shown to exhibit the greatest potential. The individual spectrum in different regions in the image is easily determined using multi-spectral technology to obtain the spectrum of each picture element in the entire image. Calculation of the different spectra can enhance the color contrast between the normal and the pathological images, thus increasing diagnostic efficiency [12–14].

2. Studied samples and empirical approach

All images of the patients and the pathological sections in this study were provided by the Dermatology Department of Chung Shan Medical University Hospital. Initially, pictures of three CTCL patients and one pre-cancerous CTCL (parapsoriasis) patient were taken. However, the initial symptoms of parapsoriasis were similar to those of psoriasis and atopic dermatitis; therefore, images of seven psoriasis and four atopic dermatitis patients were also taken to represent the control group. This study was reviewed and approved by the Chung Shan Medical University Hospital (IRB No CS12126) institutional review board.

In this study, we took pictures of various patients: three with early CTCL, one with pre-cancerous CTCL (parapsoriasis), six with psoriasis, and four with atopic dermatitis. After the spectra showing different pathological changes and the normal region were obtained. Principal component analysis (PCA) was conducted for the normal spectra and the pathological spectra of the three CTCL patients and then the eigenvector of CTCL (six basic functions) was obtained. The spectra of all patients with similar symptoms were then analyzed using the CTCL eigenvector, and the principal component score of all pathological and normal spectra was determined. Skin diseases with similar symptoms were distinguished according to the distribution of the principal component score to different regions. Thus, cutaneous lymphoma, psoriasis, and atopic dermatitis were identified.

Figures 1(a)–(c), and (d) show the pathological results of the three CTCL patients (a)–(c) and one pre-cancerous CTCL (parapsoriasis) patient (d). Patients A–C, and D are males aged 35, 47, 43, and 36 years, respectively. The above images, which are clearer than those taken with a camera, also reveal erythemas in the pathological regions. Figure 1(d) shows a localized, brownish patch over the right shoulder of

Figure 1. (a), (b), and (c) represent the images of the pathological skin of CTCL patients A, B, and C; (d) represents the pathological skin of pre-cancerous CTCL (parapsoriasis) patient D; (e)–(g), and (h) are the histopathological results of patient A–C, and D, respectively.
indicating psoriasiform hyperplasia of the epidermis, and a green arrow (→) denoting tortuous capillaries in the papillary dermis. Given the aforementioned histopathological mechanisms, the condition is confirmed to be psoriasis. Figure 3 shows images of pathological regions of atopic dermatitis belonging to (a) a 21-year-old male; (b) a 24-year-old male; (c) a 17-year-old female; and (d) an 18-year-old male. Figure 3(e) shows the section image of (c). The blue asterisk (☆) represents a normal basket weave stratum corneum layer; the blue arrow (→) indicates a granular layer; the white star (☆☆) denotes spongiotic epidermis; and the orange arrow (→) represents lymphocytes with exocytosis. The thicker horny layer, the present granular layer, and other histopathological mechanisms confirm that the patients have atopic dermatitis. In the pathological region of a cutaneous lymphoma patient, the characteristics that determine the pathological differences among the three kinds of skin diseases are the monoclonal and atypical lymphocytes gathered into the surface of the epidermis, which show epidermotropism. Lymphocytes increase, and abnormal lymphocytes collect in the epidermal layer. The stratum corneum of the pathological region in a psoriasis patient thickens. The papillary dermis shows dilated capillaries and normal lymphocytes accumulating in the epidermal layer. The stratum corneum of the pathological region of an atopic dermatitis patient thickens, and the epidermis shows edema and spongiosis. In these three pathological changes, keratinocytes show cell edema. The differences among the three pathological changes are obvious. However, patches of slight erythema are a common clinical characteristic, as shown in figures 1(a)–(c), 2(e), 3(a), (b), and (c).

In this study, multi-spectral imaging technology (MSI) was used to obtain the spectrum of each picture element of pathological skin. With color reproduction technology, the image can be simulated under a new light source by changing the new light source spectrum. PCA was performed on the obtained skin spectra to determine the eigenvalue of each spectrum. The principal component score was finally used to distinguish the different pathological spectra. The MSI technique is divided into three parts: the PCA for spectra data reduction, the calculation of transformation matrix to determine the relationship between the digital camera and the spectrophotometer (Konica Minolta CS1000A), and spectral reproduction of images. The experiment and the calculations are reported in [12–15]. To acquire a more accurate estimation of the spectra, the process of dealing with the RGB values of each picture element after capturing the image was corrected. Color correction was implemented to match the color performance of the camera with that of the spectrophotometer. From the...
spectrophotometer, the International Commission on Illumination/Commission internationale de l’éclairage (CIE) XYZ tristimulus values and corresponding RGB values from the spectra of 24 color checkers were calculated and established as standard values. From the camera, images under the same lighting conditions were captured, and the RGB values of each picture element were retrieved by the computer program. Finally, the color relationship between the two devices was determined by separately performing third-order polynomial regression for red, green, and blue components. The output format of commercial digital cameras was sRGB (JPEG image files) in which the reference white was illuminated by a CIE standard light source D65 that is different from the artificial lights used to measure the spectra of 24 color checkers [12–15]. Consequently, chromatic adaptation transformation was performed prior to third-order polynomial regression. Figure 4 presents the calculation results of the average spectrum of the normal skin and the skin with three kinds of pathological changes. The average spectrum of the latter has a lower reflection rate than that of the former. The reason is that pathological changes alter the structures of the stratum corneum, epidermal layer, and dermis, affecting the reflection of light on the skin surface. The very dark color of the pathological skin is also attributed to this alteration. The differences among the three types of skin disease are visually slight; therefore, the average spectra of CTCL, psoriasis, and atopic dermatitis are almost the same. Their main difference is in the adsorption of hemoglobin near the 530 nm wave band. An increase in hemochrome causes a reduction in the reflection rate in this wave band. The difference near the short wave (about 450 nm) mainly comes from the increase in the number of abnormal lymphocytes and the reduction in reflection rate. The cell nucleus of the cancer cell becomes enlarged, increasing the adsorption of the short wave and reducing the reflection rate [16].

Figure 4. The average spectrum calculation results of normal skin, CTCL, psoriasis, and atopic dermatitis.

3. Principal component score analysis of the spectrum signature

PCA is a commonly used method in multivariate statistics [17]. This technique has become important and has been applied to color technology since 1960. PCA involves finding a subspace that is less than the original variable, maintaining its data change in a multivariable data set, and projecting the original data into the subspace for analysis [18]. Principal axis analysis has two objectives: to define the principal axis direction of a large number of spectral information and to simplify the information data. For data simplification, the method transfers the high correlation variables to independent of each other variables after the reorganization of the original data. Most parts of variability of data can be explained by this PCA method [19]. The principal axis component score is expressed below:

$$y_j = a_{j1}(x_{11} - \overline{x_1}) + a_{j2}(x_{22} - \overline{x_2}) + \ldots + a_{jm}(x_{m1} - \overline{x_m})$$

(1)

where $x_{11}, x_{22}, \ldots, x_{m1}$ refers to the spectral intensity corresponding to the first, second, and up to the $m$th wave length. $\overline{x_1}, \overline{x_2}, \ldots, \overline{x_m}$ refers to the average spectral intensity of the first, second, and $m$th wave length. The coefficients $a_{j1}, a_{j2}, \ldots, a_{jm}$ are the coefficients of the eigenvector after the covariance matrix is determined for each spectrum. Based on Hotelling’s rule, the first principal component constitutes the most information in the original data, which can be regarded as the comprehensive index; the information that the second and third principal components constitute in the original data can be used to classify all groups [20]. We chose to mark ten positions in the normal and the pathological skin of four CTCL patients. Each position included 100 picture elements. The average spectrum of each position was determined to perform PCA to obtain different eigenvector groups. Six eigenvectors from each group of eigenvectors were used as the foundation base to obtain six eigenvalues. After PCA was accomplished to find the eigenvectors corresponding to two groups of the largest eigenvalue, equation (1) was used to calculate the eigenvalues of the normal and the pathological regions of each patient. Two groups of eigenvalues ($a_1, a_2$) were chosen to plot the scattergraph. The result is shown in figure 5(a). The figure shows that the spectral eigenvalue $a_1$ of most normal skin is less than 3.0, and the spectral eigenvalue $a_1$ of the pathological skin ranges from 2.7 to 4.3. The spectral eigenvalue of pathological and normal skin fall within different distribution ranges. The distribution trend of the spectral eigenvalue of the four CTCL patients may be related to skin color, as discussed in the following section. The trend of the principal component score scattergraph in figure 5(a) is not clearly exhibited because the difference in reflection spectrum among the CTCL patients is low. Therefore, an impact factor (difference gain factor) is added in the covariance matrix, as shown in equation (2). The difference gain factor is designed as the power of the covariance matrix. The principal component score scattergraph is expected to
demonstrate a clear trend

\[ [A^T A] \delta_m \mathbf{m}_m = \delta_m \mathbf{X}_m, \]

where \( A \) is the average spectrum of the patient’s skin, \( \gamma \) denotes the difference gain factor, \( \mathbf{x}_m \) represents the eigenvector, and \( \delta_m \) is the eigenvalue.

Figures 5(a)–(c) and (d) illustrate the principal component score scattergraph of the spectrum signature of the four patients with a difference gain factor from 1 to 4. Comparison between figures 5(a) and (b) reveals a marked difference between the normal and the pathological spectra in the eigen distribution of the four patients; that is, the distribution range of the normal and the pathological position can be clearly defined. When the difference gain factor is 3 or 4, as shown in figures 5(c) and (d), all spectrum eigen distributions are gradually combined. To determine the spectral eigen distribution of the four patients, we took pictures of the inside of the arms of four graduate students with different skin colors, as shown in figure 6(a). We took images of each arm in ten positions to calculate the average spectrum of each position. These average spectra were obtained using equations (1) and (2). We obtained the spectral eigen distribution of different skin colors, as shown in figure 6(b). In figure 6(b), we can obtain the spectral eigenvalues of different skin colors distributed in the radial direction in the principal component score scattergraph. Figures 5 and 6(a) show the distribution trend of the eigenvalue spectra. Based on the analysis of the spectral characteristics of the skin of CTCL patients, the
spectral eigenvalue distribution of the pathological skin is close to the original point, and the spectral eigenvalue distribution of the normal skin is far from the original point and is scattered. The different skin colors resulted in the distribution in the radial direction of the eigenvalue spectrum of four patients.

4. Color image analysis and reproduction of pathological region

Discrimination of CTCL disease can be demonstrated through a computer algorithm that system contains color image analysis, spectrum signature, and color image reproduction of patients’ images. After the PCA analysis, the average spectrum of normal and pathological skin of CTCL patients, six groups of obtained eigenvectors (namely six spectrums in form) and eigenvalues can be calculated. We then fit the average spectrum in the al regions of psoriasis and atopic dermatitis patients by using six groups of CTCL eigenvectors. The two obtained eigenvectors that constitute a larger proportion were analyzed by the principal component score scattergraph with the same principle as in figure 5(b), as shown in figure 7. As indicated in figure 7, PCA is performed again for the data of the individual group to determine the distribution. The range is shown in ellipsoid. The equation of the ellipsoid is expressed as follows:

$$\frac{(a_1 x + b_1 y + c_1)^2}{d_1^2} + \frac{(a_2 x + b_2 y + c_2)^2}{d_2^2} = 1,$$  \hspace{1cm} (3)

where $a_1$, $b_1$, $a_2$, and $b_2$ refer to the eigenvector coefficient of the inverse covariance matrix of the groups, the physical meaning of which is axis rotation; $c_1$ and $c_2$ represent the average of the data values of the groups. Groups make a parallel movement of all data points while PCA is conducted so that the center of an ellipse is moved to the original space; $d_1$ and $d_2$ refer to the feature values of the inverse covariance matrix, which refer to the long axis and half of the short axis of the ellipse. We found that the feature distribution of the pathological spectrum of psoriasis and atopic dermatitis patients could not fall within the CTCL distribution. The data of one psoriasis patient and one atopic dermatitis patient are presented in this study. Other psoriasis and atopic dermatitis patients demonstrated similar distribution trends. The pathological change in CTCL can be successfully distinguished using this method.

To assist doctors in effectively diagnosing CTCL, possible pathologic regions on the skin of a CTCL patient are shown by extraction of the image painting number, the change from color into a spectrum, PCA, discriminant of spectral eigenvalues, and color imaging reproduction. Figure 5(b) presents the feature distribution of the pathological spectra of three CTCL patients and one pre-cancerous CTCL (parapsoriasis) patient. This type of distribution is also related to the skin color. Therefore, we assumed that the feature distribution ranges of the pathological spectrum of four kinds of skin colors were as follows: no. 1 (patient A), $a_1 < 0.9503$, $0 < a_2 < 0.046$; no. 2 (patient B), $a_1 < 0.9871$, $-0.121 < a_2 < 0$; no. 3 (patient C), $a_1 < 0.9152$, $-0.1462 < a_2 < 0.0361$; and no. 4 (patient D), $a_1 < 0.6075$, $-0.1770 < a_2 < 0$. In skin color nos. 2, 3, and 4, the spectrum signature in the normal region is combined with that in the pathological region for some eigenvalues. Therefore, the suspected pathological regions are confirmed. Figure 8 shows the skin imaging result of a patient reproduced using this research method. Figures 8(a)–(d) correspond to patients A–D, respectively. Red dots represent CTCL pathological regions, namely, that the spectrum signature falls within the elliptic CTCL pathological region in figure 7. Pink points represent the suspected CTCL pathological region, namely, that the spectrum signature in its image painting number falls outside the elliptic CTCL pathological region but near the elliptic region in figure 7. Patients A and B have no pink regions unlike patient C. Thus, the conditions of patients A and B are more serious than patient C. As far as the distribution regions of the entire lesion, in the aspect of clinical diagnosis, CTCL manifest as erythematous plaque distribution on the skin. However, our computer program discriminant showed CTCL manifesting as extensive erythematous distribution. Thus, our proposed method can clearly and effectively determine a CTCL lesion. The case of patient D cannot be confirmed as a CTCL lesion based on section diagnosis because it belongs to pre-cancerous CTCL (parapsoriasis) lesion. However, we observed some CTCL lesions in the periphery of the brown pathological region on the shoulder of the patient through this technology. The method can be used in early detection of CTCL so that patients can promptly receive appropriate treatment. The graphical user interface panels of the program’s modular functions indicated in [15]. In order to determine sensitivity and specificity of this method, the database created four different skin-colors CTCL patients according to the above data. We used this technology to identify the possibility of CTCL.
discrimination and the possibility of atopic dermatitis and psoriasis patients misinterpreted as CTCL in the 109 patients (29 CTCL patients, 36 atopic dermatitis patients, and 44 psoriasis patients). Twenty-six patients were successfully recognize in the 29 CTCL patients. Four patients have been misinterpreted as a CTCL condition in the 80 non-CTCL patients. The sensitivity and specificity of optical perception CTCL are 89.65% and 95.18%, respectively. Two atopic dermatitis and psoriasis patients misinterpreted as CTCL condition among in 36 atopic dermatitis patients and 44 psoriasis patients, respectively. The probability of each lesion misinterpreted as CTCL were 5.56% and 4.54%, respectively.

5. Conclusion

In this study, we calculated the reflection spectra of the normal and the pathological skin by MSL. We also conducted a study on the spectrum signature of the skin. The normal and the pathological spectrum signature of CTCL patients can be distinguished using PCA. These distributions were also related to skin color. To determine CTCL, we fit the average spectrum in the pathological regions of psoriasis and atopic dermatitis patients by using six groups of the eigenvectors of CTCL. The spectrum signature in the pathological regions of psoriasis and atopic dermatitis patients were found to be in different regions. On the basis of this method, we rapidly and accurately distinguished CTCL from eczematous and psoriasis lesions by a computer program. Finally, we showed the skin pathological conditions of CTCL patients by using color and image reproduction, which can be useful to help doctors for diagnosis of early cancerous patients.

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