# Classification of Lung Cancer Subtypes Based on Autofluorescence Bronchoscopic Pattern Recognition: A Preliminary Study

# Abstract

**Background and Objectives:** Lung cancer is the leading cause of cancer deaths worldwide. With current use of autofluorescent bronchoscopic imaging to detect early lung cancer and limitations of pathologic examinations, a computer-aided diagnosis (CAD) system based on autofluorescent bronchoscopy was proposed to distinguish different pathological cancer types to achieve objective and consistent diagnoses.

**Methods:** The collected database consisted of 12 adenocarcinomas and 11 squamous cell carcinomas. The corresponding autofluorescent bronchoscopic images were first transformed to a hue (H), saturation (S), and value (V) color space to obtain better interpretation of the color information. Color textural features were respectively extracted from the H, S, and V channels and combined in a logistic regression classifier to classify malignant types by machine learning.

**Results:** After feature selection, the proposed CAD system achieved an accuracy of 83% (19/23), a sensitivity of 73% (8/11), a specificity of 92% (11/12), a positive predictive value of 89% (8/9), a negative predictive value of 79% (11/14), and an area under the receiver operating characteristic curve of 0.81 for distinguishing lung cancer types.

**Conclusions:** The proposed CAD system based on color textures of autofluorescent bronchoscopic images provides a diagnostic method of malignant types in clinical use.



**Keywords:** lung cancer, autofluorescent bronchoscopy, computer-aided diagnosis, color texture

# Introduction

Lung cancer is the most common cancer and the leading cause of cancer deaths worldwide [1, 2]. One reason for the high mortality rate of lung cancer is the difficulty of early detection/diagnosis, which leads to a high prevalence of late-stage lung cancer at the time of diagnosis. Recent implementation of low-dose computed tomographic (CT) screening in high-risk groups of patients produced early detection of early-stage peripheral lung cancer and a significant reduction in mortality [3]. However, low-dose CT screening cannot detect endobronchial lesions, and a bronchoscopic study is the most important method for the early detection of endobronchial/tracheal lesions [4, 5].

Due to the low detection rate of early lung cancer using traditional white-light bronchoscopy (WLB), new bronchoscopic imaging techniques, including autofluorescent imaging (AFI) and narrow-band imaging (NBI), have become important in detecting endobronchial premalignant lesions in the bronchial mucosa [6-8]. In addition, advantages of AFI include the synchronous localization of tumors, an ability to estimate the extent of the mass, and better estimation of the resection margins [9]. A meta-analysis comparing AFI to WLB and AFI with WLB to WLB, both showed higher detection rates and sensitivities but variable specificity [10].

In clinical settings, advanced stages of adenocarcinomas (ACs) and squamous cell carcinoma (SCC) require different treatment choices. In eastern advanced lung ACs,

the epidermal growth factor receptor (EGFR) is mutated in a higher portion of patients, and there is a good response to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) [11, 12]. Because of the diversity of treatment choices, confirmation of the correct histologic type is the first step in determining the best treatment for lung cancer patients, followed by a molecular diagnostic panel of the lung cancer. Using an immunohistochemical (IHC) panel to confirm the correct histologic type is the most frequently used method, but it takes several days. In lung cancer patients with endobronchial lesions found by a bronchoscopic study, the initial bronchoscopic images might help make a diagnosis of the histologic type and facilitate subsequent cancer staging and treatment. However, the main limitation of bronchoscopic examinations is the variance among different observers [13]. Extracting diagnostic imaging features from bronchoscopy can be useful by providing more-complete tumor characterization. Thus, the use of computer-aided diagnosis (CAD) can be a practical way to provide objective diagnostic suggestions. After extracting quantitative image features and combining them in a logistic regression classifier, different types can be modeled and presented via probabilities [14, 15]. So far, there is no literature about whether a CAD system can help recognize different cell types from WLB or AFI images.

Previously, a CAD system was applied to classify normal mucosa and tumors using WLB [16]. An accuracy of 80% was achieved based on quantitative image

features. To the best of our knowledge, this is the first study to explore predictions of different cancer types with AFI. In this study, a CAD system was proposed to analyze textures of multiple color channels in autofluorescent bronchoscopy to classify lung cancer types, i.e., ACs and SCC. The color space of the original images was transformed to provide a better interpretation of color information and compared to the original one. From an analysis of color textures, complementary features were combined via a logistic regression classifier. Establishment of the CAD system is expected to provide more-objective recommendations for recognizing lung cancer types in clinical use.

# Materials and Methods

### Patient information

This retrospective study was approved by the institutional review board of Shuang Ho Hospital (New Taipei City, Taiwan), and informed consent was waived. From September 2015 to April 2017, 70 patients from Shuang Ho Hospital were screened using BF-F260 (Olympus Optical, Tokyo, Japan). Among these cases, 36 patients had normal mucosa, and 34 had positive findings of neoplastic changes under WLB and AFI. All 34 abnormal mucosa samples had a pathologic diagnosis by bronchoscopic biopsies. Among them, only 23 endobronchial tumors could clearly be recognized with WLB and AFI without confounding by bleeding. Two small-cell

carcinoma patients, two unknown carcinomas, and one tracheal tumor were excluded due to the limited sample sizes. Demographic information of the patient database included 12 AC patients (aged 42~83 years) and 11 SCC patients (aged 50~90 years). Figure 1 shows an example of an AC and SCC.

To delineate the tumor area in an AFI, the background airway mucosa should be greenish with a consistent texture with no secretions or blood. Any abnormal or atypical expression of color which was not green detected by AFI was delineated as a suspected tumor area for further processing.

**Multichannel features**

Conventional CAD systems quantify features of medical images in gray-scale [17, 18]. These medical images include CT, ultrasound, magnetic resonance imaging (MRI), and so on. CAD systems focus on brightness variations in lesions and brightness contrasts between lesions and background tissues and can achieve substantial accuracy in classifying benign and malignant tumors. In this study, lung cancers were detected by AFI which presents lung tissues in color images. To utilize meaningful color information, multichannel features were extracted from the color channels for tissue characterization. Hue (H), saturation (S), and value (V) transformation was the first step in converting unintuitive red (R), green (G), and blue (B) channels into more

describable features. Then, textural features were individually extracted from the H, S, and V channels.

*HSV transformation*

Color information plays an inevitable role in AFI for detecting abnormal tissues. The choice of the color space can dramatically influence processing results. The RGB color space arises naturally from color camera hardware such as AFI. However, other color models such as the HSV scheme are preferable for extracting more corresponding colors of images for subsequent analyses [19]. HSV is one of the useful color models which defines color through three channels of hue, saturation, and value. Hue represents the fluorescent parts of an image. Saturation indicates the level of fluorescence, and value is the luminance of tissues. Extracting features from the HSV color space is expected to provide more-significant color information for diagnosing malignant types. Figure 2 shows the HSV color space composition.

***Textural** features*

Texture analyses are widely used for pattern recognition in medical images [17, 18]. Most systems extract textural information from sonographic or MRI patterns presented by gray-scale values. After combining textural features, patterns of benign and malignant tumors can be recognized by a classifier. Based on the success of previous studies [17, 18], this study further extracted textural features from HSV color

channels for classifying malignant types. After delineating the tumor area in autofluorescent bronchoscopy, tissues inside the tumor area were analyzed for tissue characterization.

The tumor area enclosed by the contour is a cluster of similar biological structures shown as fluorescence. The fluorescence color texture was then extracted to analyze correlations between pixel values in individual channels, i.e., H, S, and V. In each channel, a gray-level co-occurrence matrix (GLCM) [20] of second-order statistics describes the joint frequencies of pair-wise combinations. By scanning each pixel and its adjacent pixels, co-occurrence matrices $P$=[$p(i,j|d,\theta)$] are constructed to show frequencies of two adjacent pixels at distance $d$ and direction $\theta$. Gray-scale pixel values are $i$ and $j$, respectively. In practice, distance $d$=1 and four offset directions, $\theta$=0°, 45°, 90°, and 135°, were used in the experiment (Fig. 3). For rotation invariance, these four directions were combined into a single matrix, and the statistics listed below are the 14 GLCM textural features:

$$\textit{Autocorrelation} = \sum_i \sum_j (p_x - \mu_x)(p_y - \mu_y) \Big/ \sigma_x \sigma_y; \quad (1)$$

$$\textit{Contrast} = \sum_n n^2 \left\{ \sum_i \sum_j p\,(i,j) \right\}, |i-j| = n; \quad (2)$$

$$\textit{Correlation} = \frac{\sum_i \sum_j (i-\mu_x)(j-\mu_y) p(i,j)}{\sigma_x \sigma_y}; \quad (3)$$

$$\textit{Cluster prominence} = \sum_i \sum_j \left(i + j - \mu_x - \mu_y\right)^4 p(i,j); \quad (4)$$

$$\textit{Cluster shading} = \sum_i \sum_j \left(i + j - \mu_x - \mu_y\right)^3 p(i,j); \quad (5)$$

*Dissimilarity* = $\sum_i \sum_j p(i,j)|i-j|;$ (6)

*Energy* = $\sum_i \sum_j p(i,j)^2;$ (7)

*Entropy* = $-\sum_i \sum_j p(i,j)\log(p(i,j));$ (8)

*Homogeneity* = $-\sum_i \sum_j \frac{1}{1+i-j} p(i,j);$ (9)

*Difference variance* = $\sum_i i^2 p_{x-y}(i);$ (10)

*Difference entropy* = $-\sum_i p_{x+y}(i)\log(p_{x+y}(i));$ (11)

*Information measure of correlation* = $\frac{HXY - HXY1}{max\{HX, HY\}}$, $HXY = (8)$, $HXY1 = -\sum_i \sum_j p(i,j)\log(p_x(i)p_y(j))$, $HX = entropyofp_x$, $HY = entropyofp_y$; (12)

*Inverse difference normalized* = $\sum_i \sum_j \frac{1}{1+|i-j|} p(i,j)$; and (13)

*Inverse difference moment* = $\sum_i \sum_j \frac{1}{1+(i-j)^2} p(i,j);$ (14)

where $\mu_x$, $\mu_y$, $\sigma_x$, and $\sigma_y$ are the means and standard deviations of the distributions of $p(i,j|d,\theta)$:

$$\mu_x = \sum_i i \sum_j p(i,j), \mu_y = \sum_j j \sum_i p(i,j) \text{ and} \tag{15}$$

$$\sigma_x^2 = \sum_i (i - u_x)^2 \sum_j p(i,j), \sigma_y^2 = \sum_j (j - u_y)^2 \sum_i p(i,j). \tag{16}$$

**Statistical analysis**

Multichannel features were evaluated if they were statistically significant in distinguishing malignant types. This study first used the Kolmogorov-Smirnov test [21] to determine if the features were normally distributed. According to the determined normal or non-normal distribution, the corresponding Student's *t*-test [21] and Mann-Whitney U-test [21] were used to test features. Results showed a statistically significant difference between malignant types for features with a $p$ value of <0.05. In the construction stage of the prediction model, textural features extracted from the HSV channels were grouped. Utilizing backward elimination in the binary logistic regression model [22], only one feature was eliminated each time. The feature with a minimum predictive residual error sum of squares was the one eliminated.

In the training stage, the most relevant subset features for tumor diagnosis have the lowest error rates. Next, the leave-one-out cross-validation method [23, 24] validated the performance. **Leave-one-out cross-validation is a kind of k-fold cross-**

**validation where k equals the number of collected cases. In each iteration, k-1 are used for training and the model is then tested on the remaining observation. The estimate of the accuracy is considered to be almost unbiased but it may have high variance. The cross-validation method is widely used when the collected cases are rare.** Ground truthing of the classifier was biopsy-proven lesion types. After the logistic regression, each tumor was given a predicted malignancy probability based on its features. Tumor types were classified according to a probability threshold. Consequently, five performance indices including the accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained. The Chi-squared test in SPSS software (vers. 16 for Windows; SPSS, Chicago, IL, USA) judged the performance difference between the two feature sets. The receiver operating characteristic (ROC) curve presented trade-offs between sensitivity and specificity. Az, the area under a ROC curve, was tested by a bivariate Chi-squared test in ROCKIT software (C. Metz, University of Chicago, Chicago, IL, USA).

# Results

**This study proposed using HSV color space to extract textural features to distinguish malignant types in autofluorescent bronchoscopic images. In the experiment, the performances of HSV features and the RGB features were**

**compared to demonstrate the equipped color information of HSV. A total of 42 features were calculated (14 for each channel). Among them, two HSV features including the information measure of the correlation in the S channel and correlation in the V channel had significant *p* values of <0.05 as shown in Table 1. Only these two features were then combined in the classifier to establish the prediction model with an accuracy of 83% (19/23), a sensitivity of 73% (8/11), a specificity of 92% (11/12), and Az=0.82. For RGB features, the information measure of the correlation in the R and G were significant (Table 2). Combining the features achieved an accuracy of 57% (13/23), a sensitivity of 73% (8/11), a specificity of 42% (5/12), and Az=0.67. In the comparison, the HSV features have significantly better specificity (*p*-value=0.0094) than RGB features.** Among 12 AC cases, only one was misclassified with a probability of 90% (cases having probabilities of >50% were regarded as being SCC). The trade-offs between sensitivity and specificity were shown in ROC curves as Fig. 4. Illustrations of two misclassified cases are shown in Fig. 5a (misclassified AC) and 5c (misclassified SCC).

## Discussion

AFI can provide early detection of endobronchial lesions, but there is no previous study concerning the use of AFI to differentiate the pathological classification. In this

study, we used a CAD with a new algorithm to make diagnoses of different pathological types from AFI data. In clinical interpretations, this method might save time for subsequent pathological diagnoses.

Compared to traditional WLB, AFI had better sensitivity and specificity to detect early endobronchial lesions. However, classifying carcinoma in situ and subtypes highly depends on a histological examination of biopsy specimens, which are only a portion of the abnormal tissues. To present a more-complete assessment of malignant types, the CAD system was proposed based on color textural features in AFI. In addition, inter-observer variabilities among different observers can be reduced via the use of the CAD system. In the experiment, using GLCM textural features from HSV-transformed images, the CAD system achieved an accuracy of 83% (19/23), a sensitivity of 73% (8/11), and a specificity of 92% (11/12) which was better than RGB features. **Similar to the human perception of color, the HSV model separates the luminance component (V) of a color from its chrominance components (H and S). Hue is the color type and Saturation refers to the intensity of specific hue. HSV has been widely used in natural image processing including segmentation, clustering, and feature generation. Sural et al. used HSV to develop a framework for features used in image segmentation and color histogram generation, the two important approaches to content based image retrieval [25]. In the medicine use, HSV is also**

**more useful for the definition of existing trauma colors than RGB [26]. Additionally, using HSV in the segmentation on digital microscope images for acute lymphoblastic leukemia achieved accuracy over 99% [27]. In our result, utilizing the more intuitive HSV features, the diagnostic interpretation with regard to tumor characteristics in AFI can be better described and thus induce better performance.**

**AFI is a novel modality in hospitals thus this preliminary study is the first study exploring using image processing and logistic regression classifier to establish a prediction model. Only malignant lung cancers were enrolled in the discrimination also limit the cohort size. Due to the limited data available in the experiment, no substantial number of patients can be a subset (training set) used to tune the classifier and also the other subset for validation. Instead, this preliminary study used leave-one-out cross-validation to evaluate the proposed CAD system. The generalization ability should be further confirmed after applying it to a sufficient number of patients in the future experiment.**

Compared to a previous CAD system which was applied to classify normal mucosa and tumors using WLB [18], this study achieved a similar accuracy (83% vs. 80%). The difference is that this study used HSV textures in AFI to classify different malignant types. Although the number of collected image cases was limited, distinguishing

malignant types is more challenging. With respect to misclassified cases, the reason for misclassifying the AC in Fig. 5a may have been the insignificant size of the tumor area. Because of the image resolution, restricted exhibition of tissue details in the tumor area provided incomplete diagnostic information. In Fig. 5b, the lesion occurred close to the boundary of the image. Similarly, the lack of a complete tumor area may have induced an incorrect diagnosis. In future studies, automatic lesion detection can be integrated into the proposed CAD system for both lesion detection and diagnosis. The system can provide a way to simultaneously alert users as to where a lesion is and to which type it belongs.

# Conclusions

**This study proposed a CAD system based on image features extracted from autofluorescent bronchoscopic images to achieve a diagnostic accuracy of 83% in classifying lung cancer types. This preliminary study provides a method of using HSV textures for malignant tissue characterization.**

# Conflict of interest statement

The authors declare that there are no conflicts of interest related to this paper.

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**Figure Captions**

Fig. 1. Examples of (a) an adenocarcinoma and (b) a squamous cell carcinoma shown in autofluorescent bronchoscopy.

Fig. 2. The HSV color space is composed of hue (H), saturation (S), and value (V) channels.

Fig. 3. Spatial correlations between neighboring pixels were analyzed in four directions: 0°, 45°, 90°, and 135° at distance=1.

Fig. 4. **Performance comparisons between HSV and RGB features using receiver operating characteristic (ROC) curves.**

Fig. 5. A misclassified (a) adenocarcinoma and (c) squamous cell carcinoma in autofluorescent bronchoscopy and the respective corresponding delineated tumor areas (b) and (d).

Table 1. Significant HSV textural features and corresponding *p* values evaluated using Student's *t*-test

| Feature | AC | SCC | *p* value |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Information measure of correlation (S) | -0.854±0.015 | -0.821±0.039 | <0.05* |
| Correlation (V) | 0.984±0.003 | 0.976±0.013 | <0.05* |

* A *p* value of <0.05 indicates a statistically significant difference.

AC, adenocarcinoma; SCC, squamous cell carcinoma; S, saturation; V, value; SD, standard deviation.

**Table 2. Significant RGB textural features and corresponding *p* values evaluated using Student's *t*-test**

| **Feature** | **AC** | **SCC** | ***p* value** |
|---|---|---|---|
| | **Mean±SD** | **Mean±SD** | |
| **Information measure of correlation (R)** | **-0.866±0.017** | **-0.839±0.036** | **<0.05*** |
| **Information measure of correlation (G)** | **-0.845±0.037** | **-0.791±0.047** | **<0.05*** |

*** A *p* value of <0.05 indicates a statistically significant difference.**

**AC, adenocarcinoma; SCC, squamous cell carcinoma; R, Red; G, Green; SD, standard deviation.**

**Table 3. Performance comparisons between HSV and RGB textural features in classifying lung cancer types.**

| | **HSV** | **RGB** | **HSV vs. RGB (*p* value)** |
|---|---|---|---|
| **Accuracy** | **83% (19/23)** | **57% (13/23)** | **0.0545** |
| **Sensitivity** | **73% (8/11)** | **73% (8/11)** | **1.0000** |

| | | | |
|---|---|---|---|
| **Specificity** | **92% (11/12)** | **42% (5/12)** | **0.0094*** |
| **Az** | **0.82** | **0.67** | **0.0715** |

*** $p<0.05$ indicates a statistically significant difference.**