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Diagnostic spectroscopic and computer-aided evaluation of malignancy from UV/VIS spectra of clear pleural effusions

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HIGHLIGHTS

- Differentiation and classification of UV/VIS spectra of pleural effusions are given.
- Method uses features extracted from normalized and discretized UV/VIS signals.
- 104 Samples of pleural effusions were clinically collected and evaluated.
- The accuracy for malignant cases was higher than 95% by using the proposed method.
- For non-malignant cases the maximal accuracy of 100% was obtained by both methods.

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ABSTRACT

The automated, computer-aided method for differentiation and classification of malignant (M) from benign (B) cases, by analyzing the UV/VIS spectra of pleural effusions is described. It was shown that by two independent objective features, the maximum of Katz fractal dimension (*KFDmax*) and the area under normalized UV/VIS absorbance curve (*Area*), highly reliable M–B classification is possible. In the *Area–KFDmax* space M and B samples are linearly separable permitting thus the use of linear support vector machine as a classification tool. By analyzing 104 samples of UV/VIS spectra of pleural effusions (88 M and 16 B) collected from patients at the Clinic for Lung Diseases and Tuberculosis, Military Medical Academy in Belgrade, the accuracy of 95.45% for M cases and 100% for B cases are obtained by using the proposed method. It was shown that by applying some modifications, which are suggested in the paper, the accuracy of 100% for M cases can be reached.

1. Introduction

Recently, it was reported that by using an originally invented and patent protected method [1] the on-line differentiation of malignant (M) from benign (B) cases from UV/VIS spectra of body liquids is possible. Classification to M and B cases,

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obtained by using this method, highly corresponds to the clinically approved diagnosis, regardless of the histological type of the malignant disease. Moreover, by using the multifractal (MF) analysis [2,3] it was found that even more accurate off-line objective classification of UV/VIS spectra of ascites[1] can be obtained [4]. Consequently, the UV/VIS spectral analysis of ascites [1], combined with their MF analysis [4], can be suggested as successful and safe screening method in the evaluation of intraperitoneal fluids [4]. The required instrumentation for UV/VIS spectroscopy is not so expensive while this method is simple and the examination procedure is relatively fast [1,5,6]. The main advantage of this method is its reliability without the need of biopsy, which is a highly invasive procedure. The suggested method could be of special importance in uncertain and urgent cases in patients with intraperitoneal fluids. Note that the combination of several well-known signal processing tools (for instance, using the mean, standard deviation, first derivative, etc.) in an appropriate way permits also satisfactory good objective classification of collected UV/VIS spectra [7]. Regarding the other body liquids, for instance pleural effusions, standard medical procedures for cancer diagnosis usually are complex and time consuming [8–19]. From these reasons, the invention and introduction of additional methods for the examination of pleural effusions in clinical praxis, in order to facilitate and accelerate the diagnosis, is highly welcome.

1.1. Clinical background

Pleural effusions may occur as a consequence of different diseases and conditions, most often as their side effects, and are classically divided into "transudates" and "exudates". Some investigations [8] found that even 30%–50% of patients with congestive heart failure, malignant disease, pneumonia, pulmonary thromboembolism, and tuberculosis, have pleural effusions. The most common cause of transudates is the congestive heart failure. On the other hand, the most common causes of exudative pleural effusions are the inflammatory process in the lungs and pleura (non-specific or tuberculosis caused), malignant lung disease, and pulmonary embolism [9,10]. In order to better understand the causes of pleural effusion it is highly important to have the medical history and the information of living conditions of patients [9]. A variety of diagnostic procedures are applied, for instance, imaging, tumor marker tests, genetic testing, etc. Cytology and histology are usual procedures for the confirmation of malignancy, but they need biopsy, which is an aggressive diagnostic procedure.

Cytological findings of malignant cells in effusion clearly indicate the cause of the pleural effusion. In patients with suspected metastasis the cytology is more sensitive than "blind" pleural biopsy. In patients with clinical and histopathological proven pleural tumor, the cytological analysis of pleural fluid was positive in 71% of cases, and pleural biopsy in 45% [11]. In the diagnosis of malignancy the appearance of false negative results is about 58%, but they are significantly reduced with the large number of analyzed samples [12–14]. False-positive results are seen in less than 1% of benign effusions [14,15]. False-positive and suspicious results are the consequence of mesothelial cell atypia caused by pulmonary infarction, tuberculosis and chemotherapy [16]. The immunocytochemistry is a very sensitive and highly specific method for the detection of malignant cells [17]. Furthermore, there are many publications where the tumor markers were subject of the diagnostic accuracy [18,19]. For unexplained pleural effusion the thoracoscopy is used when necessary. This is the most aggressive diagnostic procedure and it is applied through diagnostic (medical thoracoscopy) and video-assisted thoracoscopy (VATS). The first procedure is the popular one for pulmonologist to analyze the undiagnosed pleural effusion. It can be done under local anesthesia and mild analgosedation outside the operating room. Diagnostic accuracy ranges from 80% to 100% [19]. VATS is a diagnostic and therapeutic method developed *via* thoracic-surgical experiences of laparoscopic techniques, and it is now in routine practice. The main indication for thoracoscopy is a progressive undiagnosed pleural effusion.

1.2. UV/VIS spectroscopy diagnostic method

When applying the UV/VIS diagnostic method in the analysis of pleural effusions, characteristic spectra are obtained, with significant differences between malignant (M) and benign (B) cases [1]. Typical UV/VIS spectra of M and B cases of pleural effusions are presented in Fig. 1. The UV/VIS spectrum of malignant pleural effusions, Fig. 1(a), is characterized by relatively high and narrow absorbance in the region between 200 and 320 nm (absorbance A is between 3 and 4), usually with two well-defined and well-shaped local peaks in this region. The peaks are wide and quasi symmetrical. In the spectral region between 350 and 500 nm, a low plateau is observed, with an absorbance value closer to or lower than 1, Fig. 1(a) [1]. Conversely, for non-malignant (B) case, Fig. 1(b), the absorbance curve is wider in the same wavelength range (200–320 nm) having an array of sharp peaks with the absorbance values mostly above 4 and never lower than 3.5 [1]. Over 320 nm the absorbance is slow decaying having high plateau with an absorbance value up to 2 in the spectral region between 350 and 500 nm [1]. In both cases, some local maximum in absorbance may be observed within the range between 400 and 430 nm, as is depicted in Fig. 1(a), due to impurities in body liquid caused by hemoglobin. Serious clinical studies presented in Refs. [20,21] suggest that the analysis of UV/VIS spectra of body liquids can be of significant importance as an additional tool for safe and reliable screening in cases of several types of cancer.

The aim of this work is the development of automated, computer-aided method for the objective differentiation and classification of UV/VIS spectra of pleural effusions, which can replace or extend the possibility of exact evaluation of

[1] In medical terminology the term *ascites* describes the accumulation of body liquids (fluids) in the peritoneal cavity. Ascites may indicate liver cirrhosis, and also some metastatic cancer.