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Prognostic value of tumor volume for patients with advanced lung cancer treated with chemotherapy

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ABSTRACT

Background and objective: We aim to develop a reference system utilizing computed tomography to calculate changes in tumor volume of lung cancer patients after chemotherapy to assist physicians in clinical treatment and evaluation.
Methods: Image processing techniques were used to analyze the computed tomography of lung cancer, locate the tumor, and calculate the tumor volume. The medical indicator was then evaluated and analyzed. We examined the correlation between reduced tumor volume and survival duration of 88 patients after chemotherapy at Tri-Service General Hospital, Taiwan. The innovative survival prediction index was obtained by four statistical methods: receiver operating characteristic curve, Youden index, Kaplan-Meier method, and log rank test.
Results: From the image processing techniques, tumor volume from each patient were obtained within an average of 7.25 seconds. The proposed method was shown to achieve rapid positioning of lung tumors and volume reconstruction with an estimation error of 1.92% when calibrated with an irregularly shaped stone. In medical indicator evaluation and analysis, the area below the receiver operating characteristic curve is greater than 0.8, indicating good predictability of the medical index used herein. The Youden index spotted the best cut-off point of volume, and the correlation between the volume's cut-off point and survival time was confirmed again by Kaplan-Meier and log rank test. The p-values were all less than 0.05, presenting a high degree of correlation between the two, indicating that this medical indicator is highly reliable.
Conclusions: The proposed techniques can automatically find the location of tumors in the lung, reconstruct the volume, and calculate changes in volume before and after treatment, thus obtaining an innovative survival prediction index. This will help facilitate early and accurate predictions of disease outcomes during the course of therapy, and categorize patient stratification into risk groups for more efficient therapies.

1. Introduction

Lung cancer is the most common cause of cancerous death [1]. An irregular tumor is formed by continuous proliferation and division of cells that result from a mutation of pulmonary cells, and is further classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The latter accounts for about 85% of all lung cancers, and 25–30% of NSCLC patients are diagnosed as being in the terminal stage on their first visit, while 40%–50% of patients are found to have distant metastasis [2,3]. Tumor response is usually assessed using the standard World Health Organization (WHO) criteria [4] and the newly proposed unidimensional response evaluation criteria in solid tumor (RECIST) criteria [5,6]. Moreover, treatment effects are clinically divided into complete response, partial response, stable disease, and progressive disease.

Marten et al. [7] discussed the inadequacy of manual measurements compared to automated computed tomography (CT) volumetry in the assessment of treatment response for pulmonary metastases using RECIST criteria, and concluded that automated volumetry allowed for better reproducibility of response evaluation in pulmonary metastases and should be preferred versus manual measurements for patients. Sohaib et al. [8] showed that the CT volume measurement error is 1.0–5.1% for regularly shaped

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phantoms larger than 35 cm^3. In the assessment of treatment response, there is 90% agreement between one-dimensional (1D) and two-dimensional (2D) measurements and 100% agreement between 2D and three-dimensional (3D) measurements. The impact of CT assessment of tumor response using 1D, 2D, and 3D measurements on clinical decisions and patient outcome remains to be determined. Tran et al. [9] studied the agreement in treatment response classifications between 1D, 2D, and 3D methods of measuring metastatic lung nodules on chest CT, with the three methods of tumor measurement showing fair to poor agreement in treatment response classification. These findings have negative implications for accuracy, in which patients are classified under the WHO or RECIST criteria and managed under cancer treatment protocols.

Zhang et al. [10] explored whether changes in tumor size impact survival in advanced NSCLC after target therapy, especially in patients with a stable disease, and reviewed the applicability of the RECIST criteria in target therapy. The applicability of RECIST criteria was called into question in the evaluation of target therapy. A change in tumor size might predict survival in advanced NSCLC patients with target therapy and may be a surrogate endpoint for efficacy in target therapy. A prospective, observational prognostic factor study of the Trans-Tasman Radiation Oncology Group [11] investigated the hypothesis that primary tumor volume is prognostic independent of T and N stages in patients with NSCLC treated by definitive radiotherapy. Patients treated by non-surgical means were unable to show that lung tumor volume, overall, provided additional prognostic information beyond the T and N stages.

There is evidence that larger primary tumor volume adversely affects the outcome only within the first 18 months. A larger tumor size alone should not by itself exclude patients from curative (chemo) radiotherapy. Mozley et al. [12] used a 3D measurement of tumor volume to improve the assessment criteria of RECIST for late NSCLC patients and found that it had good reconstruction and accuracy. In a small number of tests, correlations with clinical effects have been higher for volumetric-based measures than for 1D or 2D diameters. The evidence indicates there are situations in which volumetric image analysis increases the value to the clinical practice of medicine, but the value in clinical practice settings and clinical trials has not been shown.

The clustering method of image segmentation splits the object into several regions with the same property according to its color and texture features. In the chest cavity CT image, the same tissues have similar features. Therefore, the samples in this study are applicable to the clustering method. In the clustering method, Ferahta et al. [13] added Shannon entropy in the magnetic resonance image with noise interference in the clustering algorithm, so that the number of clusters of image could be determined automatically. Iyer et al. [14] used fuzzy C-Means (FCM) and added other features, whereby the breast region with higher compactness was segmented in the breast X-ray detection image. Xu et al. [15] defined the concepts of association matrix and equivalent association matrix and calculated the association coefficients of intuitionistic fuzzy sets (IFSs). The corresponding clustering algorithm for IFSs was discussed, but its computer running time was longer than FCM. Boykov et al. [16] addressed the problem of minimizing energy functions that require estimating a spatially varying quantity (such as intensity or disparity) from noisy measurements. The proposed algorithms used graph cuts to fast approximate energy minimization. The result of segmentation of the computed tomography with complex texture and irregular shape is worse and inapplicable to the samples of this study.

This study adopted weighted FCM (WFCM) [17], which is based on adding the weight components to the centroid value of the standard FCM. The WFCM converges in fewer iteration counts with respect to fuzzy algorithms and produces better clustering results.

The boundary extraction is the key to the accuracy of tumor 3D reconstruction and volume correctness. In classical active contour models, Osher and Sethian [18] presented a group of schemes for moving surfaces under their curvature. These schemes counted on solving Hamilton-Jacobi equations with viscous terms, using approximation techniques from hyperbolic conservation laws. The schemes handled topological merging and breaking naturally, as well as the work in space dimensions. Li et al. [19] proposed a fuzzy level set algorithm to facilitate medical image segmentation, which is able to directly evolve from the initial segmentation by spatial fuzzy clustering. The controlling parameters of level set evolution are also estimated from the results of fuzzy clustering. Li et al. [20] proposed the distance regularized level set evolution (DRLSE), which corrects the re-initialization of level set methods and increases the contour extraction accuracy of level set methods. However, the aforesaid methods use an image gradient as a stop condition for curve evolution, and so the blurred image boundary detection capability is worse. Therefore, this study employs the method proposed by Chan et al. [21] and the Mumford-Shah model based on the active contour method and traditional level set method to propose a new level set method based on the areal feature of active contour without edges (ACWE). This method uses the zone information of the image as the stop condition of curve evolution, and so it is applicable to the samples in this study.

In this study, we utilized ACWE as a lung cancer tumor boundary extraction method to solve the irregular shape and blurred edge of a tumor. In addition, we applied the boundary contour obtained by the region's growth as the initial contour input of ACWE and calculated the region's growth center point as the seed of the next image's region growth, so as to automatically extract the tumor edge and use the contour to 3D reconstruction.

Changes in tumor volume and patients' survival time before treatment and after treatment were predicted with statistical methods. Thus, we proposed a survival prediction index for research and reference to physicians.

The patient's survival time was predicted by the percentage of tumor volume reduction in early treatment (about 4 months). The patients' tumor volume changes and survival time before and after treatment were obtained, in order to discuss their volume reduction variations in survival times of 1 year, 1.5 years, 2 years, 2.5 years, and 3 years.

All enrolled patients with a reduction in tumor volume after treatment were selected for statistical analyses, with the cut-off point of volume reduction percentage obtained by the receiver operating characteristic (ROC) curve [22] and Youden index [23]. The relationship between the volume reduction cut-off point and a patient's survival time was calculated by survival analysis (Kaplan-Meier) [24]. Finally, the log rank test [25] was implemented to check for apparent correlations between survival curves.

2. Method

We proposed an innovative system (Fig. 1) for automatic calculation of lung cancer tumor volume information, including image preprocessing, image segmentation, edge extraction, and 3D reconstruction. The survival prediction indicator was obtained statistically after the tumor volume is obtained.

2.1. Image pre-processing

2.1.1. Wiener filter

The Wiener filter was used to eliminate CT noise.

Fig. 2 is the Wiener filter, where $g(t)$ represents the filter, $x(t)$ is the input signal, the input signal contains real signal $s(t)$ and noise