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Exploring feature-based approaches in PET images for predicting cancer treatment outcomes

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ABSTRACT

Accumulating evidence suggests that characteristics of pre-treatment FDG–PET could be used as prognostic factors to predict outcomes in different cancer sites. Current risk analyses are limited to visual assessment or direct uptake value measurements. We are investigating intensity–volume histogram metrics and shape and texture features extracted from PET images to predict patient's response to treatment. These approaches were demonstrated using datasets from cervix and head and neck cancers, where AUC of 0.76 and 1.0 were achieved, respectively. The preliminary results suggest that the proposed approaches could potentially provide better tools and discriminant power for utilizing functional imaging in clinical prognosis.

1. Introduction

Recent years have witnessed increased use of positron emission tomography (PET) in radiotherapy treatment planning and monitoring. In particular, [^{18}F] fluoro-2-deoxy-d-glucose (FDG), a glucose metabolism analog, has been frequently used in clinical practice for tumor detection, staging, and radiotherapy target definition of different cancer sites [1–3]. Recently, there has been accumulating evidence that pre-treatment FDG uptake could be used as a prognostic factor for predicting radiotherapy treatment outcomes [4–10]. This was motivated by the fact that tumor uptake is dependent on the characteristics of its microenvironment [11]. More recently, heterogeneity in FDG uptake in head and neck tumors has been reported in animal models [12]. The heterogeneity was attributed to the distribution of different tissue components within the tumor region. Typically, quantitative analysis of FDG uptake is conducted based on observed changes in the standardized uptake value (SUV). However, sole SUV measurements are potentially impacted by the initial FDG uptake kinetics and radiotracer distribution, which are dependent on the initial dose and the elapsing time between injection and image acquisition. In addition, some commonly reported SUV measurements might be sensitive to changes in tumor volume definition (e.g., maximum SUV). These factors and others might make such approach prone to significant intra- and inter-observer variability [6,7]. Alternatively, there have been some efforts in the literature directed towards utilizing variations in the FDG distribution, characterized by its heterogeneous shape and texture, as potentially more robust prognostic metrics. Visual assessment was investigated to evaluate heterogeneity in FDG for patients with locally advanced rectal carcinoma [6] and cervix cancer [13]. Another visual pattern analysis technique was applied in Hicks et al. [7] for grading tumor response and normal tissue toxicity in patients with non-small cell lung cancer. Spatial heterogeneity metric based on deviation from an idealized ellipsoid structure (i.e., eccentricity) was found to have strong association with survival in patients with sarcoma [14,15].

In this work, we are exploring two feature-based approaches for summarizing and extracting reliable information from PET images. This information would be used to derive prognostic metrics in outcome analysis and could potentially be incorporated into the clinical planning process to modify patients' treatment based on their predicted failure risk. For instance, this could be done by intensifying the treatment dose for patients who are at high risk of failure and providing less toxic regimens than standard for patients who are at lower risk.

The first approach is a histogram-based approach referred to as intensity–volume histogram (IVH), which is analogous to the

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dose–volume histogram (DVH) concept used for evaluating treatment plan in radiotherapy [16,17] but is applied to functional imaging datasets instead of dose distributions. The IVH approach would summarize the 3D functional imaging intensity information into a single curve for each anatomic structure of interest, which will be used to derive intensity–volume metrics, as discussed later. The IVH may be represented in two forms: the cumulative integral IVH and the differential IVH. Considered here is only the cumulative IVH, which is a plot of the volume of a given structure as a function of image intensity (or normalized SUV) that is equal to or higher than a certain value.

The second approach extracts shape and texture features from PET images to characterize anatomical structure of interest. This would provide the analyst with objective morphological descriptors of PET uptake in these regions. As a proof of principle, we will mainly focus on commonly well-established features in the pattern recognition community. Hence, in addition to geometrical shape features such as eccentricity and solidity for shape description [15,18], we also explore second-order histogram statistics or co-occurrence matrix features for texture analysis [19]. These features possess strong discriminant power and ability to mimic human perception of texture variability. Therefore, they have been widely applied in many complex industrial and medical pattern recognition tasks [20–25]. In PET imaging, texture analysis has been previously applied to evaluate the performance of reconstruction algorithms [26]. In addition, we demonstrate that complementary information among extracted features can be combined to capture differences in tumor metabolic activities between patients who respond to treatment and patients who do not respond to treatment. To our knowledge, this is the first report that utilizes a systematic pattern analysis approach for predicting cancer patients' treatment outcomes based on PET imaging.

2. Methods and materials

As demonstrative examples, we analyzed two datasets of cervix cancer patients and head and neck cancer patients who received chemoradiotherapy as part of their treatment. All patients, in both sets, underwent pre-chemoradiotherapy diagnostic FDG–PET in our institute. The PET images were acquired using a hybrid PET/CT Siemens biograph with an in-plane spatial resolution of 5.3×5.3 mm/pixel and a slice thickness of 3.4 mm. The images were reconstructed using ordered-subsets' expectation maximization algorithm with compensation for attenuation using CT-derived μ-maps. The cervix cancer dataset consisted of 14 patients. These data were analyzed for the endpoint of disease persistence (i.e., tumor did not get eradicated as a result of the treatment), 3 months post-radiotherapy. Half of the cervix patients had persistent disease after chemoradiotherapy treatment as diagnosed on their follow-up PET scans. The head and neck dataset consisted of nine patients. Each patient underwent a CT simulation scan and diagnostic PET/CT scan providing three images per case (27 images in total). The dataset was analyzed for endpoint of overall survival rate. The patients had a median follow-up period of 30 months (range: 9–48 months). Four of the head and neck patients died during the follow-up period. Note that traditional disease staging evaluation was not predictive of response in these patients. Interested reader could find review literature on the current role of PET imaging for cervix cancer in Grigsby et al. [8] and in head and neck cancer in Greven [27].

The pre-treatment scans were transferred using the digital imaging and communications in medicine (DICOM) protocol into the research treatment planning system CERR, which stands for computational environment for radiotherapy research [28], where the intensity values were converted into SUV. SUV is a decay-corrected measurement of activity per unit volume of tissue (MBq/mL) adjusted for administered activity per unit of body weight (MBq/kg) [29]. All patients had a maximum SUV greater than 2. An experienced oncologist outlined and recorded the clinical target volume (CTV), which includes a margin around the tumor to account for subclinical invasion of microdisease extensions. The gross tumor volume (GTV) delineation in the cervix cancer case was performed by thresholding the SUVs within the CTV at 40% of the maximum value [30], which is the current standard clinical practice in our institute. Fig. 1 shows samples of contoured PET images for the cervix cancer case. In the case of head and neck cancer, the tumor delineation of the PET's GTV was performed manually by the physician (see Fig. 2) because the 40% maximum SUV is implicated as an unreliable criteria for the

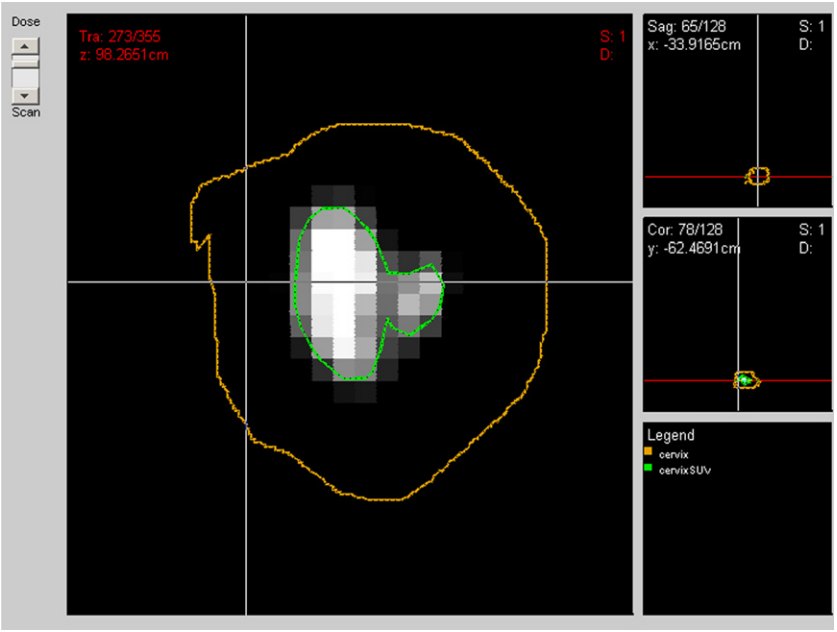

Fig. 1. A pre-treatment PET scan of a cervix cancer case of a patient with persistent tumor at 3 months follow-up post-radiotherapy treatment. The cervix clinical tumor volume (CTV) (brown) and the 40% maximum SUV delineated gross tumor volume (GTV) (green) were outlined by the physician.