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New PET/CT Features for the Evaluation of Tumor Response

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Abstract

With the emerging multi-modality imaging performed at multiple time points for each patient, it becomes more important to analyze the serial images quantitatively, select and combine both complementary and contradictory information from various sources, for accurate and personalized evaluation of tumor response to therapy.

CT Features

Assessment of the change in tumor burden or tumor response is an important feature of the clinical evaluation of cancer therapeutics [1]. Traditionally, response of solid tumors to cancer therapy is evaluated visually or measured with anatomic changes in tumor diameters using CT imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria [1–3]. Briefly, RECIST [1] defines complete response (CR) as disappearance of all target lesions, partial response (PR) as at least 30% decrease in the sum of (largest) diameters (in the axial plane) of target lesions from the baseline, progressive disease (PD) as at least 20% increase and an absolute increase of at least 5 mm in the sum of diameters, and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Recent studies show that new CT features, including volumetric, attenuation, morphologic, structure, and texture descriptors, have advantages over the RECIST and WHO criteria in certain tumor types. Both RECIST and WHO criteria are linear measurements of tumor size, which have limitations related to technical variability, tumor morphology, and reader decisions. With the thin-section CT, it is possible to measure tumor volume using segmentation methods with adequate spatial resolutions [4,5], which overcomes some of the limitations of linear measurements. Changes in attenuation in contrast-enhanced CT (CECT) has been shown correlate better with response than changes in tumor size in hepatocellular carcinoma [6] and gastrointestinal stromal tumor [7]. One advantage of attenuation features is that they can take into consideration of tumor necrosis [6]. In colorectal liver metastases, morphologic evaluation based on metastases changing from heterogeneous masses into homogeneous hypoattenuating lesions had a statistically significant association with pathologic response and survival while RECIST did not [8]. Adding structure features

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(presence or absence of marked central necrosis) to morphology, attenuation, and size features in CECT was found more accurate than response assessment by RECIST in renal cell carcinoma [9]. CT texture features characterizing the spatial variations of tissue density were shown to be prognostic factors in non-small cell lung cancer (NSCLC) [10] and esophageal cancer [11].

PET Features

In recent years, FDG-PET imaging, which measures functional (metabolic activity) changes, has shown advantages over anatomic imaging as a response evaluation tool in many malignancies [3,12–16]. For example, in NSCLC [12,17] and esophageal cancer [14,18–22], FDG PET imaging has shown superior results in predicting survival and pathologic response to chemoradiotherapy (CRT) compared with conventional CT imaging. Both the European Organization for Research and Treatment of Cancer (EORTC) [23] and the PET Response Criteria in Solid Tumors (PERCIST) [3] developed guidelines for the methodology of evaluating tumor response with serial FDG-PET, with the goal of achieving standardization in clinical trials. Despite these encouraging results, the reported accuracy for predicting response to CRT using PET/CT is often not high enough (<90%) for clinicians to make critical treatment decisions confidently. For example, a pooled sensitivity of 67% (range: 33% – 100%) and specificity of 68% (range: 30% – 100%) were reported in 20 studies for esophageal cancer [21]. Furthermore, none of these studies have demonstrated both high sensitivity and high specificity.

Almost all of the published (to our knowledge) FDG-PET studies quantify therapeutic response in tumors with *SUVmax* - the maximum standard uptake value (SUV) of FDG within a tumor [24–26]. In these studies, changes in *SUVmax*, or sometimes *SUVmax* before (pre-) CRT or after (post-) CRT, are correlated to post-CRT pathologic response, or survival, or both. *SUVmax* is a single point estimate which ignores changes in the distribution of FDG uptake within a tumor and in the extent of metabolic abnormality. However, it is known that most solid tumors consist of various malignant and non-malignant components so that they show significant heterogeneity in both the degree and distribution of FDG uptake. Heterogeneity in FDG uptake is associated with important biological and physiologic parameters [27–31], and has been shown to be prognostic in many cancers [27,28,30–34]. Another limitation of *SUVmax* is that it exhibits dependence on image noise and image resolution [3,35–37]. Recent studies suggest that new PET/CT features considering spatial information, such as tumor volume [38], tumor shape [33,39], total glycolytic volume [3], and texture features [31–33,40,41] are more informative than *SUVmax* and tumor diameters for the prediction of tumor response. Particularly, Tan et al. demonstrated that comprehensive spatial-temporal ¹⁸F-FDG PET features (intensity, texture, and shape) were more useful predictors of pathologic tumor response to CRT than conventional SUV measures in esophageal cancer [42].

Future Works

The new PET/CT response features characterize different properties of a tumor suggesting that they contain complementary information. Therefore, it would be advantageous to

combine multiple features instead of traditional response criteria that are based on cutoff values of a single measure [3, =21]. Vaidya et al. showed that multivariable logistic regression improved the prediction of local failure for NSCLC by combining complementary PET and CT features [10]. Zhang et al. constructed support vector machine models using spatial-temporal ^{18}F -FDG PET features [42]. With cross-validation, the models achieved 100% sensitivity and 90% specificity for the prediction of pathologic tumor response to CRT in patients with esophageal cancer [43].

Though not widely used in clinic, quite a few new PET tracers, including FLT that measures cell proliferation [44,45], FMISO that measures hypoxia [46, 47], and others [48,49] have brought enthusiasm in the evaluation of tumor response for various disease sites. The aforementioned concepts and methods are generally applicable to any tracer and therapy where PET/CT is used for response evaluation.

Challenges for implementing the new methodology with the more comprehensive PET/CT features include delineating the tumor volume in multi-modality (PET/CT) images, identifying a few features that truly capture biological changes correlated with tumor response for a specific disease and therapy, validating the results in large, multicenter patient datasets, vendor implementation and ultimately clinic acceptance.

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