Positron emission tomography/computerized tomography for tumor response assessment—a review of clinical practices and radiomics studies

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Contributions: (I) Conception and design: All authors; (II) Administrative support: W Lu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Even with recent advances in cancer diagnosis and therapy, treatment outcomes for many cancers remain dismal. Patients often show different response to the same therapy regimen, supporting the development of personalized medicine. 18F-fluodeoxyglucose positron emission tomography/computerized tomography (18F-FDG PET/CT) has been used routinely in the assessment of tumor response, in prediction of outcomes, and in guiding personalized treatment. These assessments are mainly based on physician's subjective or semi-quantitative evaluation. Recent development in radiomics provides a promising objective way for tumor response assessment, which uses computerized tools to extract a large number of image features that capture additional information not currently used in clinic that has prognostic value. In this review, we summarized the clinical use of PET/CT and the PET/CT radiomics studies for tumor response assessment. Finally, we discussed some challenges and future perspectives.

Keywords: 18F-fluodeoxyglucose positron emission tomography/computerized tomography (18F-FDG PET/CT); tumor response; radiomics, image analysis

Introduction

Size based evaluation, such as the World Health Organization criteria, or the Response Evaluation Criteria in Solid Tumors (RECIST) has been widely used for evaluation of tumor's response to treatment. Based on how the tumor shrinks anatomically after finishing the treatment, tumor response can be defined as complete response, partial response, stable, and progression. However, certain types of tumors, for example, lymphoma or sarcoma, may not show significant size decrease in spite of effective treatment. Hence, size based criteria may not be appropriate for assessing these tumors' treatment response.

Some current therapies target inhibiting abnormal cell growth signal, and thus are more cytostatic than cytocidal, which may not result in shrinking of the tumors, but with favorite clinical outcome. 18F-fluodeoxyglucose positron emission tomography/computerized tomography (18F-FDG PET/CT), as a functional imaging modality, is capable of detecting the effect of treatment at metabolic level and can be used to evaluate the treatment effect of the both cytocidal and cytostatic therapies. In addition, the size criteria is usually applied for late treatment response, i.e., after completion of whole cycle of chemotherapy or radiotherapy, rather than for early treatment response.

Clinically cancer patients often show different response to a chemoradiotherapy regimen. Thus, it is a laudable goal to develop an imaging modality for early treatment response, to guide individualized management of cancer. Given its ability to quantitatively detect tumor glucose metabolic change, 18F-FDG PET/CT can be potentially used for early treatment response to chemoradiotherapy, usually after the first cycle in one or 2 weeks. Studies from certain types of cancers, for example, esophageal cancer and lymphoma, have shown that in addition to predicting patient's late response to treatment and survival, early treatment response assessed by 18F-FDG PET/CT can potentially guide an individualized management for a better outcome.

In recent years, many studies proposed the use of computerized PET/CT image analysis tools to improve the evaluation of tumor response. Lu *et al*. (1), summarized these studies in the four steps of the analysis: image registration, tumor segmentation, image feature extraction, and response evaluation. Registering the baseline PET/CT and evaluation PET/CT images provides new opportunities to quantify changes at the original tumor site and to model changes as a function of spatial location. Segmenting the tumors allows measurements on the entire tumor rather than at single point or in small "peak" region. Various image features (recently termed radiomics), including volumetric, attenuation or uptake, geometric, and textural descriptors, allow comprehensive quantification of tumor characteristics and their changes due to therapy (2). Finally, advanced response predictive models that are based on various clinical and image features show higher accuracy than traditional response evaluation (3). In this review, we will focus on studies that examined advanced PET/CT image features or PET/CT radiomics for assessment of tumor response.

Clinic use of PET/CT for tumor response assessment

Given the limitations of RECIST criteria as mentioned above, PET Response Criteria in Solid Tumors (PERCIST) has been proposed (4). Its role in late treatment response (after finishing whole cycle of chemoradiotherapy) has been well documented for most of the cancers in the literature. The main drawback of the late response evaluation is that it is too late for the non-responders, who may benefit from an alternative or modified regimen, should they have been identified earlier. One of the unique features of FDG PET/CT compared to anatomical imaging modalities is its ability

to detect early treatment response, i.e., after the first cycle of chemoradiotherapy before any significant size change occurs.

In responders, in the early course of treatment, glucose metabolism in tumor tissue usually decreases to certain level. As there are still viable tumor cells, FDG uptake usually would not disappear. Change in 18F-FDG uptake between the pre- and the early follow-up scans are usually used to predict final histopathologic tumor response, and patient survival. This concept was first tested in breast cancer in 1993 (5). It was found that women with newly diagnosed breast cancer had a rapid and significant decline in standard uptake value (SUV), influx rate of 18F-FDG, and phosphorylation rate of 18F-FDG within 8 days of treatment. These parameters continued to decline with each treatment cycle in the responding patients, earlier than the size reduction. By contrast, the non-responders did not show a significant decline in the SUV. Since then, similar studies have been conducted in a wide range of tumors, for example, lymphoma and esophageal cancer.

For locally advanced esophageal cancer, current management is chemoradiotherapy followed by surgical resection. However, only approximately 50% patients would respond to the chemoradiotherapy. For the non-responders, the treatment is futile, associated with side effects, high cost, and poorer clinical outcome. Thus, it is essential to develop a tool to identify the 50% non-responders at an early stage. Weber *et al*. first conducted a study to assess early treatment response with 18F-FDG PET in locally advanced adenocarcinoma of esophageal (6). 18F-FDG PET was performed before and 2 weeks after initiation of chemoradiotherapy. All patients continued the whole cycle of 3 months of chemoradiotherapy, and then underwent surgery. The resected specimen was analyzed histopathologically. The results showed that a reduction of more than 35% in baseline SUV after 2 weeks allowed prediction of histopathologic response in 3 months after finishing the whole cycle treatment. The sensitivity and specificity was 93% and 95%, respectively in predicting response. Metabolic responders showed a significantly longer time to progression and significantly longer overall survival. This initial observation was validated by a subsequent prospective study (7). Using 35% decrease in SUV as the metabolic threshold, the sensitivity and specificity to predict histopathologic response was 80% and 78%, respectively. Similarly, metabolic responders had a significantly higher 3-y survival rate (70%) than metabolic non-responders (35%). Multivariate analysis showed that

metabolic response was the only predictor for recurrence.

Based on the above findings, it was hypothesized that it was feasible to use PET early response findings to guide treatment for a better clinical outcome. To do that, a clinical trial called MUNICON study was initiated (8). In the MUNICON study, a total of 110 patients were enrolled. PET early responders (more than 35% reduction of SUV after 2 weeks of induction chemotherapy) continued to finish the standard 3 months of chemotherapy before undergoing surgery, whereas PET non-responders discontinued the treatment after 2 weeks and were immediately sent for the surgery. Of the 110 patients, 49% were classified as responders, and 104 patients underwent resection. PET responders showed a complete histopathological response in 58%. After a median follow-up of 2.3 years, median overall survival was not reached in metabolic responders, whereas median overall survival was 25.8 months in non-responders. Median event-free survival was 29.7 months in responders and 14.1 months in non-responders. However, the trial did not randomize the non-responders into groups of continuing chemoradiotherapy followed by surgery as current management, and immediate surgery without further chemoradiotherapy to compare the difference of the two managements, although theoretically, the early surgical resection without continuing futile chemoradiotherapy would avoid side effects, and reduce the medical costs.

While, interval SUV reduction rate was applied to the treatment response in esophageal cancer, visual evaluation of FDG uptake is more commonly used in other cancers, for example, lymphoma. The successful application of FDG PET/CT in lymphoma early treatment response has led to the use of interim FDG PET/CT data to stratify patients for risk- and outcome-adapted treatment regimens. A 5 point scale (5-PS), also called Deauville scale, suited to assess differing degrees of response at mid- and end of treatment, has been developed to score PET images. The advantages of the Deauville scale include simplicity and high reproducibility. Score 1, no uptake; score 2, uptake ≤ mediastinum; score 3, uptake > mediastinum but ≤ liver; score 4, uptake moderately higher than liver; and score 5, uptake markedly higher than liver, and/or new lesions (9). Scores 1 and 2 are considered to represent complete metabolic response. Score 3 also likely represents complete metabolic response at interim. A score of 4 or 5 at interim suggests chemotherapy-sensitive disease, provided uptake has reduced from baseline (10). Using score 3, uptake > liver as positive on interim PET, for Hodgkin lymphoma, it

showed a 94% negative predictive value and a 73% positive predictive value (9,11).

Currently, in the clinical practice, only visual evaluation, or change in SUV_{max} is used for evaluation of treatment response. The former is subjective, and the latter bears a drawback: it simply represents the maximum activity within a pixel. Inflammatory change after chemoradiotherapy or macrophages within a cancer lesion can show increased FDG uptake and potentially influence the accuracy of PET evaluation in treatment response. PET/CT images contain much more information beyond visual evaluation and SUV_{max}. Thus, radiomics in PET/CT is proposed for a more comprehensive evaluation of treatment response by PET/CT.

PET/CT radiomics studies for tumor response assessment

Lambin *et al*. described radiomics as the automatic extraction of a large number of image features from medical images (12). The hypothesis of radiomics is that these image features could capture additional information not currently used that has prognostic value (12).

Radiomics in CT

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 (13,14), which overcomes some of the limitations of linear measurements. Changes in attenuation in contrast-enhanced CT (CECT) have been shown to correlate better with response than changes in tumor size in hepatocellular carcinoma (15) and gastrointestinal stromal tumor (16). One advantage of attenuation features is that they can take into consideration of tumor necrosis (15). It's worth mentioning that most PET/CT scans do not do contrast enhanced thin-section CT like in diagnostic CT imaging with deep-inspiration breath hold, although the CT on a PET/CT scanner is capable of doing that. In colorectal liver metastases, morphologic evaluation based on metastases changing from heterogeneous masses into

homogeneous hypo-attenuating lesions had a statistically significant association with pathologic response and survival while RECIST did not (17). Adding structure features (specifically 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 (18). CT texture features characterizing the spatial variations of tissue density or intratumour CT heterogeneity were shown to be prognostic factors in NSCLC (19,20) and esophageal cancer (21).

Aerts *et al.* reported a comprehensive radiomics study (22) using CT images in lung and head-and-neck cancer. They extracted 440 image features including (I) tumor intensity, (II) shape, (III) texture and (IV) wavelet features from 1,019 patients with lung or head-and-neck cancer. They constructed a multivariate Cox proportional hazards regression model using a radiomic signature consisting of the single best feature from each of the four groups: (I) 'Statistics Energy' describing the overall density of the tumor volume; (II) 'Shape Compactness' quantifying how compact the tumor shape is; (III) 'Grey Level Non uniformity', a measure for intratumour CT heterogeneity; and (IV) wavelet 'Grey Level Non Uniformity HLH' also describing intratumour CT heterogeneity. They showed that this signature had prognostic value (with a concordance index, a generalization of AUC, of 0.65, 0.69 and 0.69) in three validation data sets. Furthermore, they examined the association of the radiomic signature with gene-expression profiles and demonstrated that both intratumour CT heterogeneity features were strongly correlated with cell cycling pathways, indicating an increased proliferation for more heterogeneous tumors. Finally, they made these datasets publicly accessible.

Radiomics in PET

The majority of the published FDG-PET studies quantify therapeutic response in tumors with SUV_{max} (23-25). In these studies, changes in SUV_{max}, or sometimes SUV_{max} pre-therapy or post-therapy only, are correlated to post-therapy pathologic response, or survival, or both. SUV_{max} 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 (26-32), and has been shown to be prognostic in many cancers (26,27,29,30,32-34). Another limitation of SUV_{max} is that it exhibits dependence on image noise and image resolution (4,35-37). Recent studies suggest that new PET/CT features considering spatial information, such as tumor volume (38), total glycolytic volume (4), standardized added metabolic activity (total excess tumoral SUV above the tumor background) (39), SUV histogram distance (40), tumor shape (34,41), texture features (20,30,33,34,42,43), and cumulative SUV-volume histograms (34,44) are more informative than SUV_{max} and tumor diameters for the prediction of tumor response. We demonstrated that comprehensive spatial–temporal 18F-FDG PET features (intensity, texture, and shape features along with their changes due to therapy) were more useful predictors of pathologic tumor response to chemoradiotherapy (AUCs 0.78 to 0.85) than conventional SUV measures (AUC 0.76) in esophageal cancer (2). Based on selected features from both clinic parameters and those spatial-temporal PET features, we further constructed support vector machine (SVM) models which achieved 100% sensitivity and 100% specificity (AUC 1.00) for the prediction of pathologic tumor response with cross-validation (3).

Discussion

Most radiomics studies extracted a large number of image features (>100) first and then selected the most informative ones that are independent, robust, and prominent on the data (3,12,22). We called this approach feature discovery (analogy to gene discovery), in which the usefulness of a feature is not known *a priori*. Another approach is to extract only a few important image features that capture the underneath physiological processes during cancer therapy. These features are likely specific for each disease and therapy combination. For example, Wang *et al.* segmented the esophagus in CT using an atlas-based algorithm and measured the esophageal wall thickness, which is used qualitatively by radiologists in the diagnosis and assessment of tumor response to chemoradiotherapy (45). Other potentially informative features such as the variation in the wall thickness, and the asymmetry thickening of the wall, representing typical tumor growth in this disease, could be measured and tested for their prognostic value. We called this approach candidate feature approach (analogy to candidate gene approach), in which candidates are selected based on prior knowledge of their physiological,

biochemical or functional associations with the disease and therapy. Both approaches (feature discovery and candidate feature approach) can yield informative features. To assure that those features are truly useful, one should avoid overfitting of the training dataset and validate the results in high-quality validation datasets.

Unlike traditional simple response measures (RECIST, SUV_{max}), the advanced image features are more complex and more sensitive to the variation in scanner types, image acquisition parameters, and image noise. Some studies examined the stability and robustness of the advanced image features. Hunter *et al*. examined the test-retest and inter-machine stability of CT image features in NSCLC patients (46). They were able to identify a set of reproducible (concordance correlation coefficient >0.90), non-redundant (average mean similarity distance >0.1), and informative image features. Leijenaar *et al*. showed that the majority of the PET-derived image features had both a high test-retest (71%) and inter-observer (91%) stability, suggesting that further research in radiomics is warranted (43).

Gillies *et al*. recently published a seminar paper on radiomics and highlighted the biggest challenges of radiomics: reproducibility, data sharing and standards. The authors described an optimistic and clear vision of the future of radiomics (47).

Summary

This review first summarized the imperative clinical value of functional PET/CT imaging and then described recent PET/CT radiomics studies for tumor response assessment. There are many challenges as well as opportunities in PET/CT radiomics, which necessitate close collaborations between physicians, imaging scientists, biochemistry scientists, and information scientists. Two immediate challenges include delineating the tumor volume in multimodality (PET/CT) images, and validating the selected image features and resulting predictive models in large, multicenter patient data sets. In the long run, we believe that PET/CT radiomics have great potential to further our understandings of an individual's disease and how it responds to a therapy, leading to more precise and better decision making in cancer care.

Acknowledgments

Footnote

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