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Quantitative PET-CT in Evaluating Response after Radiotherapy

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It is evident in the literature that F-18 fluorodeoxyglucose positron emission tomography enables us to evaluate tumor response to chemo-, radiotherapy or combined. Cellularity, proliferate rate and tumor size play essential roles in FDG uptake. Both pre- and post-treatment FDG PET-CT are useful in predicting response of treatment and status of residual tumor. Such an assessment is frequently achievable by the visual inspection. However, quantitative analysis of tumor FDG uptake is generally needed to precisely compare and predict tumor response in the earlier time. The commonly quantitative measurement used by PET is the standard uptake value (SUV) that reflects relative changes of tumor glucose use during treatment. Besides SUV, incorporation of glucose sensitivity into consideration may be potentially useful as a supplementary global index to reflect the true treatment response especially if patients are scanned with different serum glucose levels.

Key Words: F-18 FDG PET-CT, Glucose sensitivity, Therapeutic response.

INTRODUCTION

Integrated anatomic and functional assessment of the target region in cancerous patients provides complementary data to overcome inherent limitations of one another, and to achieve more meaningful information for better patient management and care[1]. A combined positron emission tomography and computerized tomography (PET-CT) not only offers a promising tool diagnosis, staging and radiation treatment planning but also in chemo-sensitivity and response evaluation of radiotherapy by (a) quantifying the high metabolic rate among various cancer types in metabolizing serum glucose using F-18 fluorodeoxyglucose (FDG) as its analog tracer in PET scanning[2,3] and (b) the potential ability of the concomitant mapping CT to measure the changes in tumor size[4,5]. Many radiopharmaceuticals have been applied in oncology[6]. In this review, it will be focused on F-18 FDG because it (a) can image cellular glycolysis that is one of the most distinctive biochemical features of malignant cells, (b) can be automatically and efficiently radiolabeled and (c) has a relatively longer half-life (110 minutes) not requiring for an on-site cyclotron[7]. Mathematically, the glucose metabolic rate is calculated using the three-compartment model of F-18 FDG tracer kinetics[8,9]. The common measurement used by PET is the standard uptake value (SUV). This is defined by tumor activity per dose injected per body mass, which is proportional to the glucose metabolic rate within the normal range of serum glucose concentration. For FDG imaging, the serum glucose is usually restricted to be less than 150 mg/dL for cancer detection. The metabolic response is defined by the percentage change of post-radiotherapy SUV from the pre-radiotherapy (RT) SUV[10] as: $\Delta M = (SUV_{post\text{-}RT}/SUV_{pre\text{-}RT} - 1) \times 100\%$.

Based on comments from the European Organization for Research and Treatment of Cancer (EORTC)[11], metabolic response is characterized as a SUV reduction by at least 25% or $\Delta M < -25\%$. Non-responders are classified as $\Delta M \geqq -25\%$. Similar criteria for size changes seen on anatomic imaging modalities have been proposed by the RECIST[12]. Both metabolic and size changes may have a continual spectrum. There is high correlation between changes of SUV of primary lung tumors following radiotherapy using F-18 FDG PET-CT imaging with changes in tumor size measured on the concomitant CT as demonstrated by our institution led by Wong et al in 2007[10]. After the demonstration of FDG PET in planning and treatment response of the radiotherapy, it appeared that it is time to move the metabolic concept onto a new more hypofractionated

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and more précised 4-D stereotypic radiotherapy to deliver maximum tumoricidal dose with minimal normal tissue damage and maximum convenience, comfort and treatment benefits to patients than the conventional external beam radiotherapy[13].

The purpose of this review is to illustrate applications of PET-CT in evaluating therapeutic response, to stimulate future research by revealing the thought process during the transformation from physical (PIGART) to biologic (BIGART) image guided adaptive radiotherapy.

Applications of CT-PET in Response Evaluation after Radiotherapy

Combined PET-CT is now not only gradually replacing single modality PET scan for diagnostic and staging evaluation of FDG-avid cancers but also is emerging as a tool for radiation treatment planning and monitoring of malignancies[14]. Yet, the visual interpretation of PET-CT images is still dominating the oncologic diagnosis and treatment evaluation. The semi-quantitative SUV analysis not only separates the mean SUV values of benign versus malignant tissue, but also is a simple representation of the underlying tumor metabolism. The size changes measured by the CT component depend primarily on the tumor shrinkage due to cellular death[15]. However, size changes after treatment are multifactor and may be affected by cystic, necrotic, fibrotic or hemorrhagic change within the tumor[15]. Without accurate respiratory gating during CT (4-D CT), size measurements of tumors within or around the lung may be altered by respiratory motion[16]. Thus, the impartial and dimensionless nature of quantitative measurement of maximum SUV change makes it a valuable adjunct to visual analysis of the PET component in the PET-CT imaging, especially without another dimension from respiratory gating (4-D CT).

The responses measured by PET-CT yield the combined effects of change in metabolism and physical size to reflect the change in underlying tissue after radiotherapy[17]. Moreover, the metabolic measurement of radiotherapy response by PET (SUV) has shown to be correlated with the traditional change in size on the concomitant CT during PET-CT imaging especially on the combined responding zone (PET<-25% and CT<-30%), which is the main focus of treatment evaluation[11,12]. Due to some discrepancy in the magnitude of responses between the biologic and physical criteria, PET imaging will impact clinically when metabolic response (SUV change) differs from changes in size seen on conventional anatomic modalities[17,18].

The primary factor for variations in SUV after treatment is the reduction of metabolism due to cellular death or less likely, in case of an effective treatment, augmentation of metabolism due to tumor progression[1]. The contribution of the prior research is to investigate the correlation and impact of metabolic change by the PET component using SUV with size change measured by CT[10]. This incorporation enables comprehensive anatomolecular criteria for treatment response. Prior results have demonstrated that the findings of PET and traditional CT response are correlated to reflect the anticipated clinical treatment effects[10]. The PET study measures the SUV change by searching the entire volume of interest to obtain the change in the maximum SUV[24,25]. The PET component measures metabolic activity in an averaged respiratory cycle and thus is less affected by respiratory motion than the size change measured by non-4D CT used in the commonly by PET-CT[16]. The combined changes of SUV (by PET) and size measurements (by CT) may potentially compliment each other[19]. This is particularly important biologically when the size of tumor does not shrink quickly or significantly in post-treatment CT scans (metabolic response). The expected deviations of SUV versus size change with PET-CT imaging can be obtained if the patients are scanned about 60-90 days after radiation, which reduces if not eliminates, the potential effects of post-radiation inflammation and had given enough time for the tumor to shrink[20]. It is also important to note that it would be rare to bring the post-radiotherapy SUV or size to absolute zero as there might have inflammatory cells and/or some granulation/scar tissue present at the original tumor site after treatment.

A comprehensive metabolic evaluation of tumor response may be obtained by PET supplemented with the change in size that might be evaluated by the CT component in PET-CT, resulting in the multi-dimensional multimodality evaluation (Fig. 1). This may play a vital role in the trend towards biologic imaging for tumor response evaluation in an earlier stage than conventional modalities after radiotherapy, with potential prognostic implications. There is ample evidence of prognostic implications of PET scan in tumors such as lymphoma and lung cancers and its prediction of relapse[21,22, and 23]. Moreover, in the evaluation of therapeutic response for lymphoma, there is growing interest in patient response early during treatment, just like PET for assessing neo-adjuvant treatment for lung cancers[23]. Early metabolic response using F-18 FDG during radiation therapy has also recently reported in cervical cancer[24]. With the introduction of the concept of maximum SUV and glucose sensitivity (g) (Fig. 2), which are both a dimensionless quantity depicting a facet of metabolic phenotypes (Fig. 3) and incorporating into size changes, it appeared

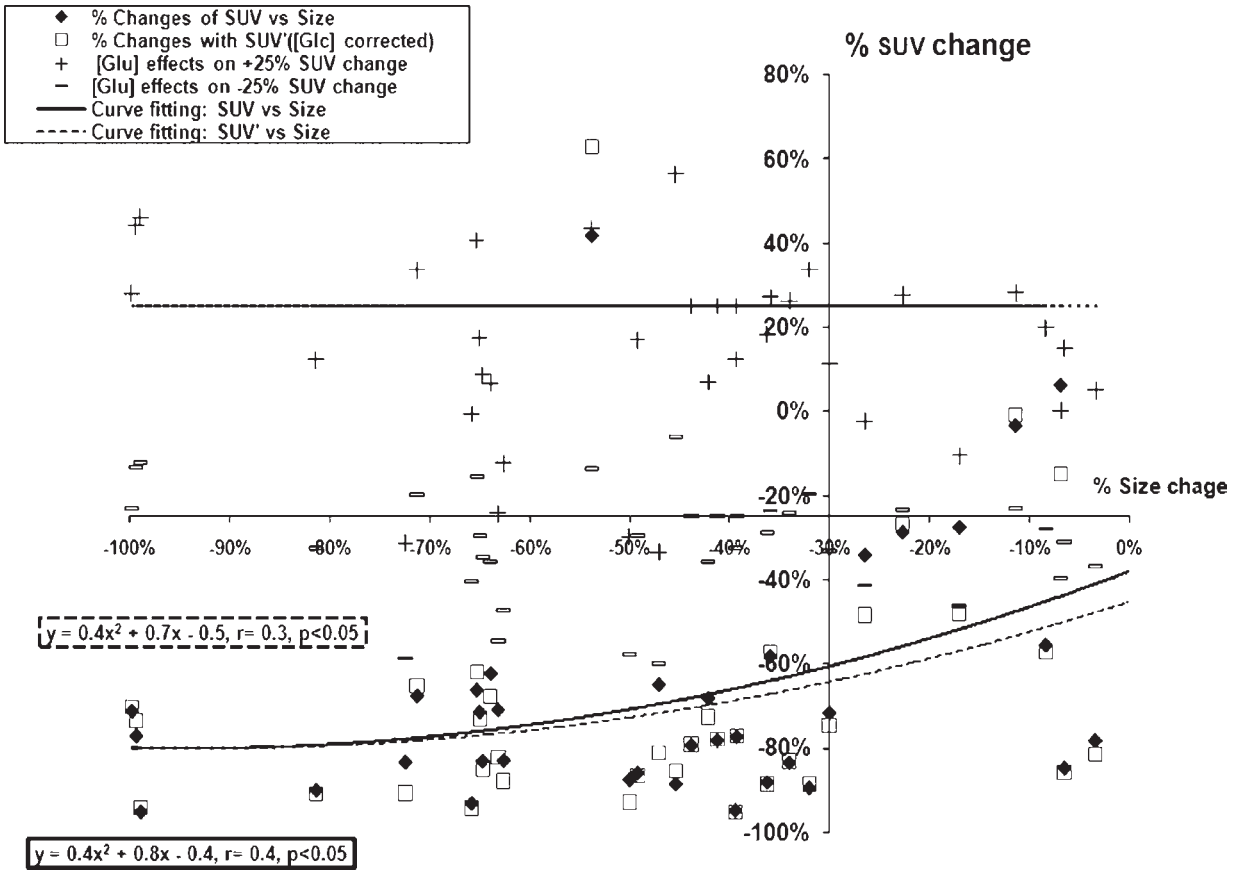

Fig. 1 The metabolic changes correlate with the traditional size change with some exceptions.

that the first step in improvement of PET-CT evaluation has been achieved[25-27] (Fig. 4).

The maximum SUV change is a useful parameter in oncologic PET-CT measurement for comparison and monitoring of treatment response, especially in a situation when size change is variable. The changes of SUV and size before and after radiotherapy allow additional dimension to the traditional single modality treatment monitoring evaluation using CT alone. Prior data indicated that glucose effects, measured by glucose sensitivity (g) may impact on the borderline response case[25,27]. The four quadrants formed by PET and CT response lines revealed four possible combinations or scenarios of metabolic and anatomical responses[27]. In the visible near future, the specific numerical results regarding glucose metabolism reflected by FDG PET in monitoring therapeutic response may be generalized to many cancers. This is an important consideration in view of the emerging biologic imaging guided adaptive radiotherapies[25-27].

It remains controversial in selection of the optimal timing for evaluating therapeutic response[28-30] as confounding transient "metabolic flare" has been observed in responding tumors following radiotherapy which is usually short-lasting in chemotherapy but not known in case of radiotherapy[29]. Earlier studies reported that an interval of 3-4 months after completion of radiotherapy for head and neck tumors was required to avoid false negative and positive results[31,32]. Recently, Kim et al. reported 1 month after completion of radiotherapy in patients with squamous cell carcinoma of the head and neck is not too early to evaluate the response of radiotherapy[30]. F-18 FDG PET performed 1 month after completion of radiotherapy can also reliable and accurately identify recurrence or residual disease[30]. In general, a waiting period of 4 weeks, preferably 6-8 weeks following radiotherapy is a reasonable compromise to reduce misinterpretation and yet fulfilled clinical requirement[28,30].

In summary, the correlation between changes in SUV and size using combined PET-CT imaging shows promise in the improved treatment response parameters. Incorpo-

$$MRglc = G[Glc][SUV]$$

$$\frac{d[SUV]}{d[Glc]} = g\frac{SUV}{[Glc]};\ g = \left|\frac{MRglc}{d[Glc]}\right|\left|\frac{[Glc]}{MRglc}\right| - 1$$

$$g = \frac{d\{\ln(SUV)\}}{d\{\ln[Glc]\}}$$

Thus glucose sensitivity, g is another dimensionless quantity, representing relative change of SUV over change of [Glc]. Both SUV and g represent metabolic phenotypes of tumors.

Fig. 2 The definition of glucose sensitivity factor by SUV and glucose concentration.

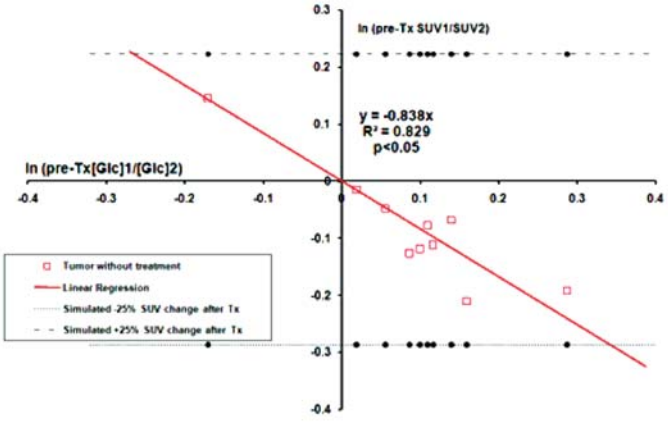

Fig. 4 The correction of glucose variation in treatment response evaluation.

rating metabolic change by PET into concomitant size change by CT is more sensitive and accurate in predicting local control than CT alone which may have a significant impact on the evaluation of response for different types of cancers.

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Glucose Sensitivity in Response Ratio (R)[25-27]

$$\frac{SUV_1}{SUV_2} = \left\{\frac{[Glc]_1}{[Glc]_2}\right\}^g \Rightarrow SUV_{pre-Tx^*} = SUV_{pre-Tx}\left\{\frac{[Glc]_{post-Tx}}{[Glc]_{pre-Tx}}\right\}^g$$

$$R = \ln(SUV_{post-Tx}/SUV_{pre-Tx}) - g\ln([Glc]_{post-Tx}/[Glc]_{pre-Tx})$$

Therefore, g=d{ln(SUV)}/d{ln[Glc]}= -0.8 from regression analysis of untreated lung cancers and
% SUV change=[exp (R)-1]×100%

Fig. 3 The determination of glucose sensitivity by logarithmic regression, showing also the variation of SUV due to the glucose effects.

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