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SHORT COMMUNICATION

An alternative parameter for early forecasting clinical response in NSCLC patients during radiotherapy: proof of concept study

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Objective: Positron emission tomography with ¹⁸F fludeoxyglucose integrated with CT (¹⁸F-FDG PET/CT) is a recommended imaging procedure in the evaluation of non-small-cell lung cancers (NSCLCs). Radiochemotherapy (RCT) is a mainstay for treatment of locally advanced NSCLC, for which overall survival still remains poor. Early evaluation of treatment response may help in decision-making to complete radiotherapy (RT) or to switch to other treatment modalities. The present study aimed to evaluate the performance of new metabolic parameters based on a simplified kinetic analysis on a single time point (SKA-S)-derived mathematical method, as compared with standard-ized uptake value (SUV) measurement during RT.

Methods: Four patients treated with RT or RCT for NSCLC were evaluated using ¹⁸F-FDG PET/CT during RT and after treatment completion. Whole-body ¹⁸F-FDG PET/CT was performed followed by four additional

list-mode acquisitions centered over the target lesion. Response was evaluated at four times (*i.e.* PET1-PET4) by calculating standard SUV values and T80%, the time taken to reach 80% of ¹⁸F-FDG metabolized fraction using a SKA-S-derived mathematical method.

Results: Data from SUV and T80% calculations were found to be controversial. T80% was found to be more predictive of clinical outcome.

Conclusion: Although results from this pilot study should be further confirmed in a large prospective study, the data suggest that T80% is a promising metabolic biomarker for assessing early response to RT.

Advances in knowledge: In this proof of concept study, we show that T80% defined from a mathematic model taking into account the net influx rate constant and vascular volume could be considered as a promising biomarker as compared with the maximum SUV.

INTRODUCTION

Locally advanced non-small-cell lung cancer (NSCLC) is a disease with a local control of about 17% at 1-year follow-up.¹ Positron emission tomography with ¹⁸F fludeoxyglucose integrated with CT (¹⁸F-FDG PET/CT) can be an option to define tumour extension and therapeutic response. Several studies^{2,3} have evaluated its role as a predictive factor for early response during radiochemotherapy or radiotherapy (RT). The maximum standard uptake value (SUV_{max}) is the parameter usually used, because it is expected to reflect the extent of glucose uptake by tumour tissues. However, SUV_{max} can generate misleading data because it does not

discriminate metabolized from non-metabolized glucose. In this respect, improving data interpretation from ¹⁸F-FDG PET/CT is critical because it may facilitate adapting irradiation plan or treatment switch in radiation-refractory tumours. We have developed an alternative parameter taking into account the net influx rate constant and vascular volume.⁴ T80% was defined as the time required to reach 80% of the amount of metabolized ¹⁸F-FDG, *i.e.* the higher the value, the lower the proliferation. This pilot study compared the performances of SUV_{max} and T80% to predict clinical outcome in patients with NSCLC undergoing RT.

METHODS AND MATERIALS

Five patients with histologically proven, locally advanced NSCLC were included in this proof-of-concept study. All received exclusive, concomitant or sequential radiochemotherapy with 60 or 70 Gy [three-dimensional conformal technique, 2 (Gy)/fraction at International commission on radiation units and measurements point]. For each patient, ^{18}F -FDG PET/CT was performed before, during (twice) and 1.5 months after RT. A CT scan was performed 1.5 months after RT. The PET/CT was interpreted by a nuclear physician. The tumour responses were assessed using CT by a thoracic radiologist according to response evaluation in solid tumours criteria 1.1.⁵ All patients provided informed consent.

Quantitative measurements

The previously published protocol has been used.⁴ Briefly, our first whole-body ^{18}F -FDG PET/CT was performed according to the current recommendations for cancer imaging.⁶ This allowed us to define precisely the target hypermetabolic foci chosen for the four additional list-mode acquisitions: t_1 , t_2 , t_3 , t_4 . PET image data sets were corrected for random, scattered, decay and iterative reconstruction effects (ordered subset expectation maximization algorithm) using CT data for attenuation correction. Co-registered images were displayed on a workstation (Xeleris™; GE Healthcare, Fairfield, CT) with three-dimensional representation as well as axial, coronal and sagittal slices.

Venous blood sampling was performed at four different time intervals: t_1 , t_2 , t_3 , t_4 .

Blood activity was measured using a Cobra Gamma Counter (Cobra II-Auto Gamma, Packard Instrument Co. Meriden, CT). Its 3-inch crystal configuration has a high sensitivity for

detecting high-energy annihilation photons. Calibration was performed immediately prior to sample measurements.

To determine the kinetic patterns and unmetabolized fraction of ^{18}F -FDG within the lesion, we used a mathematical approach. Indeed, if $FDG(t)$ denotes the tissue concentration of ^{18}F -FDG (Bq ml^{-1}) in a target tissue and $C_p(t)$ the concentration of ^{18}F -FDG in the plasma, once the steady-state is achieved, we have the well-known balance equation:

$$FDG(t) = k_i \int_0^t C_p(\tau) d\tau + VC_p(t) \quad (1)$$

K_i (min^{-1}) is the so-called “net influx rate constant”, *i.e.* a composite rate of metabolized ^{18}F -FDG extracted from the plasma and V (without unit) the vascular volume fraction in tissue.

As previously published, we determined a simplified kinetic analysis model adapted to provide different parameters to better clarify the quantification of ^{18}F -FDG PET/CT, including the T80% (time required to reach 80% of the amount of metabolized ^{18}F -FDG).⁴ This model integrates a model of clinical measurement errors and considers the arterial input function model $C_p(t)$, as proposed by Hunter et al.⁷ Note that T80% characterizes the rate of metabolism after estimating the parameters K_i and V from (1) using the data provided by the four blood samples and is obtained from Equation (1) as the single solution of equation:

$$\frac{K_i \int_0^t C_p(\tau) d\tau}{K_i \int_0^t C_p(\tau) d\tau + VC_p(t)} = 0.8$$

Details are available in a previous work.⁴

Table 1. Patient characteristics

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Age (years)	39	67	60	84	81
Sex	M	M	F	M	M
Smoking ($\pm$)	+	+	–	+	+
Primary site	RLL	RLL	RUL	RLL	RH
cTNM	T3N2M0	T3N2M0	T4N0M0	T2N1M0	T3N3M0
Pathology	SCC	SCC	SCC	UC	SCC
Treatment modality	Induction chemo: 1 cycle and CRC	SRC	SRC	ERT	SRC
Total dose (Gy)	66	60	70	66	60
Chemotherapy	CDDP docetaxel	Carboplatin paclitaxel	CDDP gemcitabine	–	Carboplatin paclitaxel
Chemotherapy response	PR	SD	PR	–	SD
Pulmonary infection during radiotherapy ($\pm$)	+	–	–	–	–

CDDP, neoadjuvant cisplatin; CRC, concomitant radiochemotherapy; ERT, external radiation therapy; F, female; M, male; PR, partial response; RH, right hilar; RLL, right lower lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; SD, stable disease; SRC, sequential radiochemotherapy; UC, undifferentiated carcinoma.

Figure 1. Correlation between standardized uptake value (SUV), T80% and clinical outcome. SUV_{max}, maximum SUV.

RESULTS

Patient characteristics are provided in Table 1. Patient #4 died from respiratory distress after RT completion and could not undergo all the examinations for pharmacodynamic end points. Patient #1 did not undergo PET3 due to poor compliance, and Patient #3 did not undergo PET4 due to a major progression. SUV_{max} and T80% values according to clinical outcomes are displayed in Figure 1. For Patient #1, a high SUV_{max} value usually associated with progressive disease was observed, whereas elevated T80% value was indicative of tumour response. During this period, the patient developed a lung infection at the tumour site, which was successfully treated. At PET4, evolution of T80% values (*i.e.* from 66 down to 28) strongly suggested tumour progression, whereas conversely SUV_{max} evolution (*i.e.* from 11.45 to 5.95) was showing response. This discrepancy was further observed at PET5, SUV_{max} indicating prolonged response, whereas T80% was still decreasing, suggesting disease progression. This was eventually confirmed for the primary lung tumour and mediastinal nodes on a CT scan performed 4.5 months after the end of RT. Given this result of mediastinal progression, we decided to perform a new *a posteriori* measurement for PET4 and PET5 to take into account the mediastinal area as well. Results confirmed a pathological measure with a decreased T80% values showing a fast progression that SUV_{max} failed to evidence. For patient #2, both T80% and SUV_{max} first suggested no efficacy at 8 Gy but a response after 50 Gy treatment. However, further monitoring of SUV_{max} and T80% values immediately after treatment completion showed controversial data. Although SUV_{max} indicated a prolonged

response, T80% revealed progressive disease, as confirmed on the CT scan 4.5 months later. This patient eventually died of disease progression 11 months after RT completion. For Patient #3, SUV_{max} was found to decrease during RT, whereas elevated T80% values suggested progressive disease. This was confirmed 1 month later, with the patient subsequently dying of disease progression. For Patient #4, decreased SUV_{max} (*i.e.* 10.5 to 5.5) suggested tumour response, whereas T80% suggested stabilized disease. Although the patient died too quickly for further clinical assessment. For Patient #5, both SUV_{max} and T80% values showed stabilized disease, whereas CT scan revealed tumour progression 3 months after treatment completion. Table 2 summarizes the times of progression diagnosis. No statistical analysis was performed because of the small patient sample size.

DISCUSSION

Our group has previously demonstrated how T80% parameter can be used as a prognostic tool and could help to better discriminate malignant from non-malignant lesions as compared with standard SUV_{max} calculation.⁴ Here, we further compared the predictive values of standard SUV_{max} and T80% to interpret ¹⁸F-FDG PET/CT imaging: in a pilot subset of patients with lung cancer. Although preliminary, our data showed that T80% should be considered as a promising biomarker for early disease response assessment during RT and tend to provide more accurate predictions as compared with SUV_{max}. Globally, our results showed stable or linear decrease in SUV_{max} during RT, an observation in line with published results.^{2,8} Interestingly, in Patient #1, infectious pneumonitis led to very high SUV_{max} observed during PET2 imaging. Other studies have already observed an early increase in SUV_{max} during RT^{7,9} attributed to radiation-induced tumour inflammation, greater tumour metabolic activity or infectious disease. By contrast, in Patient #1, T80% value during PET2 indicated a tumour response, thus suggesting that this new parameter is less affected by infectious disease than SUV_{max}. Globally, T80% values successfully predicted early progression in three out of five patients with poor clinical outcome indeed, whereas SUV_{max} always wrongly suggested tumour response. Overall, this pilot study highlights the discrepancy between SUV_{max} and T80% predictions, probably because of the unmetabolized fraction neglected with standard calculations. The role of ¹⁸FDG-PET/CT in NSCLC diagnosis or treatment as a predictive factor for survival has been repeatedly assessed,^{10,11} and the clinical relevance of SUV_{max} remains debated today.^{12–14} In addition, only few studies have focused on the use of PET with SUV_{max} during RT to predict survival in patients with NSCLC.^{2,3} Overall, the possible lack of robustness

Table 2. Comparison between study results and CT follow-up for relapse time relative to radiotherapy (RT) completion

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
T80% prediction	Progression 6 weeks post RT	Progression 6 weeks post RT	Progression during RT	Progression during RT	No response during RT
SUV _{max} prediction	Still reduction 3 months post RT	Still response 3 months post RT	Still response at the end of RT	Response during RT	Stable during RT
Actual clinical outcome	Progression 6 months post RT on CT scan	Progression 6 months post RT on CT scan	Progression 1 month post RT on CT scan	Sudden death	Progression 3 months post RT on CT scan

SUV_{max}, maximum standardized uptake value.

of SUV_{max} is an issue, calling for the determination of alternative markers. One reason could be the very calculation to determine SUV_{max} , as an oversimplification skipping the issue of unmetabolized ^{18}F -FDG. Moreover, theoretically it has to be measured after ^{18}F -FDG concentrations have reached a plateau, a requirement that is not always met in clinical practice.⁷ Hamberg et al¹⁵ showed an unpredictable error in SUV_{max} interpretation according to the time of measurement, thus highlighting how sampling time was critical. Other SUV-based PET parameters and textural features have been evaluated [SUV ratios, metabolic tumour volume (MTV), metabolic tumour burden (MTB), total lesion glycolysis (TLG)] as an alternative to SUV_{max} in the assessment of response to RT. The use of these metabolic parameters have shown very promising results in combination with TNM stage but need to be validated in further

clinical studies.¹⁶ Here, we proposed T80% as a new kinetic analysis model, taking into account unmetabolized ^{18}F -FDG. In this proof-of-concept study, our data support the hypothesis that this alternative T80% parameter could make PET interpretation more reliable and robust in lung cancer, irrespective of time and pneumonitis context, with a better and earlier response assessment than standard SUV_{max} . These preliminary results will have to be validated in a further prospective study with a larger patient population.

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