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Potential of ^{18}F -FDG PET toward personalized radiotherapy or chemoradiotherapy in lung cancer

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Abstract

Purpose We investigated the metabolic response of lung cancer to radiotherapy or chemoradiotherapy by ^{18}F -FDG PET and its utility in guiding timely supplementary therapy. **Methods** Glucose metabolic rate (MRglc) was measured in primary lung cancers during the 3 weeks before, and 10–

12 days (S2), 3 months (S3), 6 months (S4), and 12 months (S5) after radiotherapy or chemoradiotherapy. The association between the lowest residual MRglc representing the maximum metabolic response (MRglc-MMR) and tumor control probability (TCP) at 12 months was modeled using logistic regression.

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Results We accrued 106 patients, of whom 61 completed the serial ^{18}F -FDG PET scans. The median values of MRglc at S2, S3 and S4 determined using a simplified kinetic method (SKM) were, respectively, 0.05, 0.06 and 0.07 $\mu\text{mol}/\text{min}/\text{g}$ for tumors with local control and 0.12, 0.16 and 0.19 $\mu\text{mol}/\text{min}/\text{g}$ for tumors with local failure, and the maximum standard uptake values (SUVmax) were 1.16, 1.33 and 1.45 for tumors with local control and 2.74, 2.74 and 4.07 for tumors with local failure ($p < 0.0001$). MRglc-MMR was realized at S2 (MRglc-S2) and the values corresponding to TCP 95 %, 90 % and 50 % were 0.036, 0.050 and 0.134 $\mu\text{mol}/\text{min}/\text{g}$ using the SKM and 0.70, 0.91 and 1.95 using SUVmax, respectively. Probability cut-off values were generated for a given level of MRglc-S2 based on its predicted TCP, sensitivity and specificity, and MRglc ≤ 0.071 $\mu\text{mol}/\text{min}/\text{g}$ and SUVmax ≤ 1.45 were determined as the optimum cut-off values for predicted TCP 80 %, sensitivity 100 % and specificity 63 %.

Conclusion The cut-off values (MRglc ≤ 0.071 $\mu\text{mol}/\text{min}/\text{g}$ using the SKM and SUVmax ≤ 1.45) need to be tested for their utility in identifying patients with a high risk of residual cancer after standard dose radiotherapy or chemoradiotherapy and in guiding a timely supplementary dose of radiation or other means of salvage therapy.

Keywords F-FDG PET · Personalized radiotherapy · Individualized therapy · Lung cancer · Chemoradiotherapy

Introduction

Current standard radiotherapy administering a total dose of 60 Gy in 30 fractions over a period of 6 weeks (60 Gy/30 F/6 week) is still associated with local failure rates of 40–45 % even in combination with cisplatin-based concurrent chemotherapy in inoperable stage IIIA and IIIB non-small-cell lung cancer (NSCLC) [1]. Thus, there are about 40 % of patients who still have residual cancer at the end of standard-dose radiotherapy and chemotherapy, but we have no means of predicting which ones. If a timely biomarker capable of detecting residual cancer soon after standard radiotherapy were available, individualized therapy providing a timely supplemental dose of radiation or salvage surgery to patients with residual cancer may be feasible while patients with complete metabolic response implying complete tumor control are saved from escalated radiation doses beyond the standard dose and the associated toxicities and cost.

Warburg described accelerated glucose transport and metabolism in cancer, which is one of the most characteristic biochemical changes occurring with malignant cellular transformation [2]. A significant increase in the uptake of 2-deoxy-D-glucose and amino acids was reported by Isselbacher when cells were transformed in culture by polyomavirus and Simian vacuolating virus 40 (SV-40) [3]. The glucose analog, 2-deoxy-D-glucose allows the measurement of glucose metabolic rate (MRglc) that represents regional glucose utilization through quantitative ^{18}F -FDG PET [4]. Thus, biologic imaging could be useful in assessing metabolic response of tumor cells to radiotherapy or chemoradiotherapy [5–7]. It is also probable that such metabolic changes will occur much sooner than changes in tumor size [8, 9]. Therefore, changes in the metabolic status of cancer cells may be an early biomarker for subsequent response of the gross tumor including complete tumor control.

Radiation cell kill means loss of capacity for sustained proliferation (loss of cell viability) as a consequence of radiation-induced injury. Suit showed using cinephotographic analysis of proliferative activity of mammalian cells grown in vitro and subjected to single doses of radiation that a cell may undergo one, two, three, five, or even six divisions after irradiation before the progeny of that radiation-killed cell undergo pyknosis and lysis [10].

We hypothesize that cessation of glucose metabolism by tumor cells after radiotherapy or chemoradiotherapy is a biomarker representing a cell's inability to continue its vital function, i.e., glycolysis. MRglc measured with ^{18}F -FDG PET after radiotherapy or chemoradiotherapy depends upon the number and metabolic activity of the remaining tumor and host cells. No uptake indicates

with high probability that no living cells remain. Residual glucose uptake could reflect the presence of (a) reproductively dead but metabolically intact tumor cells (in full or part) admixed with (b) reproductively intact cells, and (c) host cells. As the dose of fractionated radiotherapy is increased, the number of reproductively intact tumor cells decreases while the sum of both tumor cell populations also decreases as reproductively dead but metabolically intact cells undergo lysis with time. There may not be a significant change in the host cell population [11]. Therefore, it may be possible to measure residual MRglc soon after radiotherapy or chemoradiotherapy in the clinical setting using an in vivo assay, which would represent the metabolic activities of only two cell populations: residual tumor cells that are metabolically alive but reproductively dead, and host cells. Such a MRglc value measurable in vivo using ^{18}F -FDG PET is likely to correspond to subsequent complete tumor control.

We have reported following a prospective study that the levels of residual MRglc quantified using ^{18}F -FDG PET 14 days after preoperative radiotherapy or chemoradiotherapy in patients with marginally operable stage IIB/IIIB NSCLC is inversely correlated with the probability of histopathologic complete tumor control [8]. A similar observation was also subsequently reported by others [9, 12]. In this follow-up prospective study, we wished to determine the lowest level of residual MRglc representing the maximum metabolic response (MRglc-MMR) after definitive radiotherapy or chemoradiotherapy in lung cancer and investigate its potential in predicting the probability of tumor control (TCP) at 12 months. We also determined the optimum cut-off value of MRglc-MMR based on its TCP, sensitivity (probability of having residual tumor) and specificity (probability of having no residual tumor). Specific aims were:

1. To investigate the time-course of metabolic response, measured with ^{18}F -FDG PET, to radiotherapy or chemoradiotherapy in lung cancer and determine the earliest time point at which MRglc-MMR is attainable.
2. To determine the correlation between the levels of MRglc-MMR after radiotherapy or chemoradiotherapy and subsequent complete tumor control at 12 months.
3. To determine the values of MRglc-MMR that correspond to TCP ≥ 95 %, TCP 90 %, TCP 75 % and TCP 50 % at 12 months.
4. To determine the optimum cut-off value of MRglc-MMR based on its predicted TCP, sensitivity and specificity.
5. To determine correlation between MRglc measured using a simplified kinetic method (SKM) and standard uptake value (SUV) before and after radiotherapy or chemoradiotherapy in lung cancer.

Materials and methods

This prospective study was performed with the approval of the Institutional Review Board of the Dana Farber Cancer Institute and in accordance with an assurance filed with and approved by the US Department of Health and Human Services. Written informed consent was obtained from each patient before enrollment.

Study design

The study design included serial measurement of MRglc using the SKM and SUV, semiquantitative measurement of ^{18}F -FDG uptake by PET in the primary lung cancers during the 3 weeks before (S1), and 10–12 days (S2), 3 months (S3), 6 months (S4) and 12 months (S5) after radiotherapy or chemoradiotherapy. CT of the chest was also performed at the time of the ^{18}F -FDG PET studies.

This study was intended to provide the most cogent and scientifically robust assessment of the association between early ^{18}F -FDG PET measurements and subsequent local control. For this purpose, we used multiple criteria for the determination of local tumor control or failure. *Local control* was determined with a combination of the following criteria: (a) absence or decrease in MRglc to the level of tumor bed background or to the uninvolved mediastinum lasting a minimum of 12 months, and (b) no increase in size of the primary tumor from the smallest sum of width, length and height on study (this included the baseline sum if that was the smallest on study) determine by serial CT scans for a minimum of 12 months and beyond by the latest follow-up CT scan. There was no time limit for detecting and defining local failure during a patient's survival time. Local recurrence detected even after 12 months of follow-up was counted as local failure. *Local failure* was determined with a combination of the revised response evaluation criteria in solid tumors (RECIST) and PET response criteria in solid tumors (PERCIST) on multiple restaging chest CT scans and ^{18}F -FDG PET scans for a minimum of 12 months [7, 13]. Biopsy was performed only if local tumor failure could not be determined even with multiple sets of serial follow-up ^{18}F -FDG PET and chest CT scans specified during the study protocol for a minimum follow-up period of 12 months.

Patients

Eligibility included inoperable stage I–III NSCLC and limited stage small-cell lung cancer (SCLC). Other criteria included performance status (PS) 0 or 1, adequate general condition for either chemoradiotherapy or radiotherapy with curative intent, age ≥ 18 years, and absence of pregnancy. Patients with bronchoalveolar carcinoma were excluded

from the study. Initial evaluation consisted of a complete history and physical examination with special attention to symptoms associated with primary or metastatic lung cancer; laboratory tests, including a complete blood cell count, blood urea nitrogen, creatinine, and liver function tests, CT of the chest and upper abdomen, whole-body ^{18}F -FDG PET, and brain MRI. When a PET/CT scanner became available, the combined scans replaced both the chest CT and whole-body ^{18}F -FDG PET scans.

Treatments

Radiation dose schedules were as follows. In patients with inoperable stage I NSCLC, a total dose of 70–75 Gy was given in daily fractional doses of 2.5 Gy, five fractions per week. In patients with inoperable stages II/III NSCLC, a total dose of 63–66.6 Gy was given in daily fractional doses of 1.8 Gy, five fractions per week in combination with concurrent chemotherapy. In patients with limited stage SCLC, a total dose of 63 Gy was given in 35 fractions, five fractions per week [14]. Radiation therapy was administered as either three-dimensional conformal radiation therapy or intensity-modulated radiation therapy. Chemotherapy consisted of concurrent platinum/etoposide (PE 50/50) in patients with stage II/III NSCLC and good PS (PS 0 or 1). However, patients ≥ 70 years of age with PS 1 or 2 were treated with weekly carboplatin/paclitaxel during radiotherapy and two additional cycles of high-dose consolidation carboplatin/paclitaxel. In patients with limited stage SCLC, radiotherapy was combined with concurrent cisplatin/etoposide.

^{18}F -FDG PET image acquisition and reconstruction

Whole-body ^{18}F -FDG PET studies were performed using an ECAT HR+ PET scanner (Siemens/CTI). Patients fasted for at least 6 h before scanning, and blood glucose levels were measured and recorded immediately before injection of ^{18}F -FDG. Patients with uncontrolled diabetes mellitus and fasting blood glucose >200 mg/dl were excluded. A maximum dose of 333 MBq (9 mCi) of ^{18}F -FDG was injected intravenously. Images were acquired in six or seven bed positions (10 min per bed position) from the skull base to the mid-thigh approximately 45 to 60 min after injection of ^{18}F -FDG. Transmission images were acquired using a rotating rod source with ^{68}Ge and were used to correct for tissue attenuation. Images were reconstructed using segmentation and emission subtraction with the ordered subsets expectation maximization (OSEM) algorithm (two iterations, eight subsets). A gaussian filter was used for image reconstruction.

Image analysis

Both primary tumors and involved regional lymph nodes were evaluated using $1.0\text{ cm} \times 1.0\text{ cm}$ and $0.5\text{ cm} \times 0.5\text{ cm}$ regions of interest (ROIs) on transaxial ^{18}F -FDG PET images. The ROIs were drawn on multiple transaxial slices of tumor, and the highest metabolic activity within the ROIs was measured using both the SKM and SUV for determination of regional glucose utilization. When little or no tumor-related radioactivity was discernible by visual analysis (posttherapy studies), the ROI was positioned on the basis of the CT scan data.

In an earlier study, we introduced and evaluated the SKM as a simplified method for quantifying regional MRglc and compared it with kinetic modeling (KM) and the widely used semiquantitative method, SUV index, in 13 patients with stage III NSCLC [15]. SKM measurements were found to reliably predict KM measurements, and furthermore correlations were better with the SKM than with SUV (the coefficients of determination, R^2 , were 0.96 and 0.53, respectively, before chemoradiotherapy, and 0.94 and 0.71, respectively, after chemoradiotherapy). Based on this finding, we chose the SKM as the primary measurement method in the current study. The lumped constant for the SKM measurements was set at 1.0 and was assumed to be constant over time. Details of the SKM have been reported by us elsewhere [15]. Although the SUV index showed lower coefficients of determination than the SKM when compared with the gold standard KM in our prior study, we elected to also determine SUVmax in this study for comparison with the SKM for measuring metabolic response and its robustness in predicting TCP and survival because of its methodological simplicity and availability.

For semiquantitative analysis of ^{18}F -FDG uptake, SUV parametric images were generated using computer software developed in our laboratory. The SUVmax was measured using the equation: $\text{SUVmax} = \text{T}_{\text{max}}/(D/W)$, where T_{max} is the maximum concentration of ^{18}F -FDG in tumor (microcuries per gram), D is injected dose of ^{18}F -FDG (microcuries) and W is body weight (grams) [16].

Statistical methods

The relationship between the levels of residual MRglc and TCP was modeled using a logistic function [8]:

$$\ln\left(\frac{\text{TCP}}{1 - \text{TCP}}\right) = \beta_0 + \beta_1 \ln(\text{MRglc})$$

The logarithm of MRglc was used because the distribution of MRglc values in our sample was approximately log-normal.

In our prior study, the level of MRglc after irradiation was significantly associated with pathologic tumor control, while the level of MRglc before irradiation and the difference between the

levels before and after irradiation were not [8]. These associations were studied again in the current investigation using univariate and multivariate analyses. The relationship between the level of MRglc-MMR after radiotherapy or chemoradiotherapy and TCP at 12 months was obtained by fitting the logistic model to the collected data. The MRglc level that corresponds to a 50 % chance of complete tumor control at 12 months (MRglc-TCP 50 %) and the corresponding 95 % confidence interval were estimated using Fieller's theorem [17]. In addition, MRglc-TCP 75 %, MRglc-TCP 90 % and MRglc-TCP 95 % were also estimated. The goodness-of-fit model was evaluated using the Pearson χ^2 test and the Hosmer-Lemeshow test. The measured values of MRglc were compared between groups with local tumor control and failure using the Mann-Whitney test.

Receiver operating characteristic (ROC) curve analysis was used to evaluate MRglc-MMR for its robustness in predicting complete tumor control at 12 months after radiotherapy or chemoradiotherapy [18]. In addition, we created a model probability cut-off graph to determine sensitivity (residual cancer) and specificity (no residual cancer) at below and above the cut-off value of MRglc-MMR, respectively. Thus, this graph provided a range of cut-off values of MRglc-MMR for identifying patients with a high probability of residual cancer and offering supplemental radiotherapy or other means of salvage therapy. The optimum cut-off value would differentiate all patients with residual cancer requiring supplemental therapy from patients in whom complete tumor control has already been achieved so that such additional therapy can be avoided in as many as possible.

Multivariable analysis was also performed to determine the significance of age, gender, tumor volume and stage, and tumor histology (SCLC vs. NSCLC) in predicting the degree of metabolic response. Backward elimination was performed to eliminate nonstatistically significant variables.

Overall survival was calculated according to the local tumor control status at 12 months using the Kaplan-Meier method and the log-rank test. In addition, we set the reference point at 12 months (landmark method) to avoid a known bias in favor of responders [19]. The pretherapy log-transformed levels of MRglc (S1) determined using the SKM and SUVmax and the degree of decline in MRglc between S1 and S2 were also correlated with survival. A minimum sample size of 48 patients (tumors) was required to detect with 80 % power an association between 100 % increase in MRglc measured at the earliest time point with a 25 % increase in the hazard of local failure at 1 year.

Results

Patient characteristics

We accrued 106 patients between January 2004 and August 2007. Patient demographics and tumor characteristics are presented in Table 1.

To provide unequivocal and scientifically robust assessment of the association between MRglc-MMR at the earliest time point and subsequent local control, we excluded from the analysis measurements that were incomplete or had problematic interpretation. A total of 45 patients were excluded from the analysis for the following reasons: (a) early death resulting from distant metastasis within 5 months without local recurrence ($n=10$), (b) early death from failure to thrive within 3 months and their local tumor control at 12 months could not be determined ($n=5$), (c) assessment of local tumor control at 12 months was influenced by salvage chemotherapy added for distant metastasis ($n=2$), (d) intercurrent disease ($n=10$), (e) withdrawal from study ($n=5$), (f) symptomatic pneumonitis preventing accurate measurement of MRglc-MMR at S2 ($n=6$), (g) granuloma hindering accurate measurement of MRglc-MMR at S2 ($n=2$), and (h) data corruption and technical difficulties in ^{18}F -FDG PET at S2 ($n=5$). Thus, the remaining 61 patients with 62 tumors were evaluable for the study goals.

The demographics and tumor characteristics of these 61 patients with 62 tumors were as follows: median age 70 years (range 44 to 90 years), 26 man and 35 women, 48 NSCLC and 14 SCLC, and 12 stage IA, 5 stage IB and 45 stage II/III. Of 62 tumors, 19 showed local failure and 43

showed complete control at 12 months. Local failure became self evident with serial restaging ^{18}F -FDG PET and chest CT within 12 months in 18 of 19 patients, and fine needle aspiration biopsy was necessary to confirm local recurrence in only one patient.

Time-course of metabolic response to radiotherapy or chemoradiotherapy

MRglc values of primary lung cancers at baseline and subsequent values of metabolic response measured with serial ^{18}F -FDG PET after radiotherapy or chemoradiotherapy are shown in Fig. 1. The median baseline MRglc value determined using the SKM was $0.29 \mu\text{mol}/\text{min}/\text{g}$ and the median baseline SUVmax was 6.9, and marked decreases were noted in response to successful radiotherapy or chemoradiotherapy.

As shown in Fig. 1, the median values of MRglc at S1, S2, S3, S4 and S5 determined using the SKM were, respectively, 0.23, 0.05, 0.06, 0.07 and $0.07 \mu\text{mol}/\text{min}/\text{g}$ for tumors with local control and 0.30, 0.12, 0.16, 0.19 and $0.21 \mu\text{mol}/\text{min}/\text{g}$ for tumors with local failure, and the SUVmax were 6.15, 1.16, 1.33, 1.45 and 1.32 for tumors with local control and 8.20, 2.74, 2.74, 4.07 and 3.87 for tumors with local failure ($p<0.0001$, S2 through S5 for both SKM and SUVmax). In patients with complete tumor control, residual MRglc reached its lowest value at S2 (MRglc-S2) and was steady at S3 through S5, while in patients with local failure it continued to rise after S2 reflecting steady tumor progression with time. In addition, there was no statistically significant difference in baseline values of MRglc between those in whom complete tumor control was and was not achieved at 12 months ($p=0.90$ and 0.06 , for SKM and SUVmax, respectively).

Maximum metabolic response after therapy and its association with TCP

The observed tumor control status of 62 tumors at 12 months, their individual corresponding MRglc values and SUVmax at S2, and their model predictions are shown in Online Resource 1.

The relationship between residual MRglc-S2 and tumor control status at 12 months was studied by dividing all 62 tumors into eight groups between the maximum and minimum metabolic responders, as shown in Table 2. Complete tumor control was achieved in 27 of 27 tumors with residual $\text{MRglc-S2} \leq 0.070 \mu\text{mol}/\text{min}/\text{g}$. As residual MRglc increased, the rate of complete tumor control declined. A similar association between the degree of metabolic response at S2 and the rate of tumor control was also observed using SUVmax. No statistically significant correlation was noted between the degree of decline in MRglc from baseline to S2 and subsequent tumor control at 12 months ($p=0.13$).

Table 1 Patient demographics and clinical characteristics

Characteristic	Value
Number of patients	106
Age (years)	
Median	71
Range	44–90
Sex	
Male	51
Female	55
Histologic type ^a	
NSCLC	89
SCLC	19
Tumor stage ^a	
I	26 (17 T1N0M0; 9 T2N0M0)
II	10 (4 T1-2N1M0; 6 T3N0M0)
IIIA	45 (40 T1-3N2M0; 5 T3N1M0)
IIIB	27 (27 T1-4N0-3M0)

^a Two patients had two separate primary tumors; thus, the total number of tumors was 108.

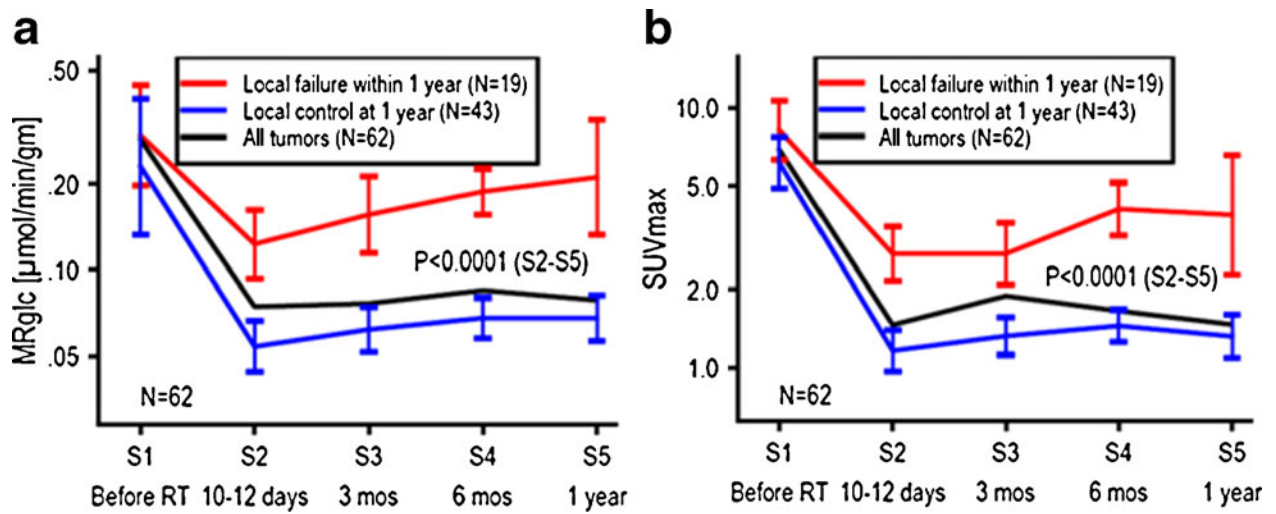


Fig. 1 Time-course of metabolic tumor response measured with ¹⁸F-FDG PET and analyzed using SKM (a) and SUVmax (b) before and at intervals after radiotherapy or chemoradiotherapy

TCP defined as no residual tumor at 12 months after treatment was modeled using logistic regression [8]. The logarithm of MRglc was used as an independent variable. The maximum likelihood estimates of the model parameters were determined: $\beta_0 = -4.5$ (95 % confidence interval, CI, -7.3 to -1.6) and $\beta_1 = -2.2$ (95 % CI -3.4 to -1.0). The MRglc-S2 values ($\mu\text{mol}/\text{min}/\text{g}$) corresponding to TCP 50 %, 75 %, 90 % and 95 % (with 95 % CI determined using Fieller’s theorem) were 0.134 (95 % CI 0.10 to 0.22), 0.082 (95 % CI 0.052 to 0.11), 0.050 (95 % CI 0.031 to 0.080) and ≤ 0.036 (95 % CI 0.019 to 0.066), respectively, as shown in Fig. 2a. The goodness-of-fit model was evaluated using the Pearson chi-square test and the Hosmer-Lemeshow test: Pearson chi-square 48.3 (53 degrees of freedom), probability greater than chi-square 0.66, Hosmer-Lemeshow chi-square 0.53 (data divided into ten groups based on the predicted probability), probability greater than chi-square 0.73. According to both tests, the model fitted the data well, as shown in Fig. 2b.

ROC curve and model versus probability cut-off

Metabolic response measured in terms of MRglc-S2 was evaluated for its robustness in predicting TCP by ROC curve analysis. As shown in Fig. 2c, the area under the ROC curve (0.85) suggests good predictive power of the model. A range of cut-off values of MRglc-S2 and their corresponding TCP, sensitivity (probability of having residual tumor) and specificity (probability of having no residual tumor) are shown in Table 3. $\text{MRglc} \leq 0.071 \mu\text{mol}/\text{min}/\text{g}$ by SKM and $\text{SUVmax} \leq 1.45$ were determined to be the likely optimum cut-off values, and the rationale for this is given in the Discussion.

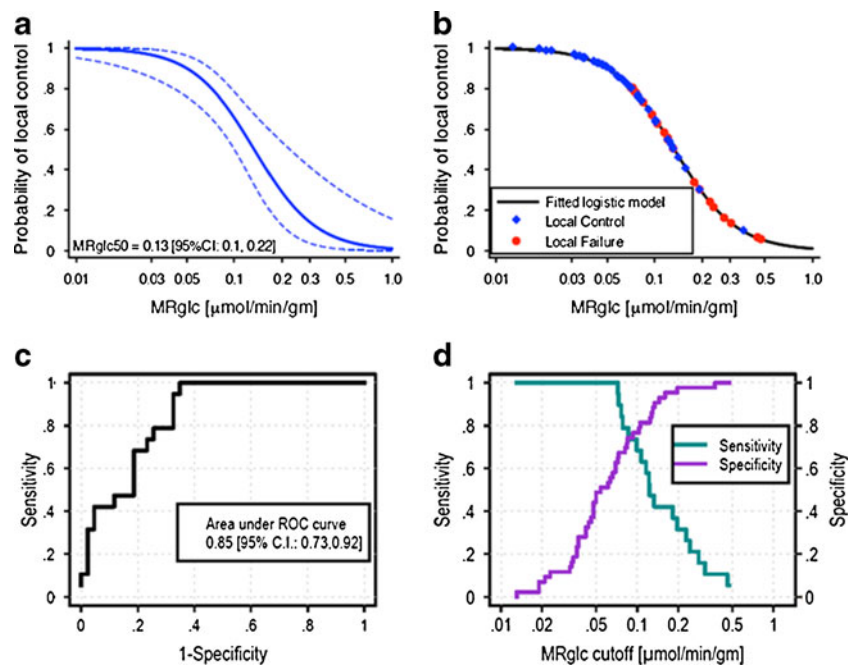
Correlation between glucose metabolic rates measured with SKM and SUVmax before and after therapies

The distributions of the SKM-determined values and SUVmax were approximately log-normal using a logarithmic

Table 2 Residual MRglc by SKM and SUVmax at S2 (10–12 days after radiotherapy or chemoradiotherapy) divided into eight groups from low to high levels and the corresponding tumor control status at 12 months in all 62 tumors

MRglc($\mu\text{mol}/\text{min}/\text{gm}$) by SKM at S2		Tumor control at 12 months (%)	SUVmax at S2		Tumor control at 12 months (%)
Group	Range		Group	Range	
≤ 0.030	0.013–0.023	5/5 (100 %)	≤ 0.62	0.39–0.62	5/5 (100 %)
≤ 0.050	0.032–0.050	16/16 (100 %)	≤ 1.15	0.63–1.15	16/16 (100 %)
≤ 0.070	0.054–0.069	6/6 (100 %)	≤ 1.35	1.16–1.35	4/4 (100 %)
≤ 0.090	0.072–0.086	5/10 (50 %)	≤ 1.93	1.36–1.93	8/12 (66 %)
≤ 0.110	0.093–0.107	3/5 (60 %)	≤ 2.21	2.01–2.21	3/5 (60 %)
≤ 0.130	0.116–0.130	3/6 (50 %)	≤ 2.74	2.22–2.74	2/6 (33 %)
≤ 0.150	0.133–0.145	2/3(66.6 %)	≤ 3.24	2.84–3.24	1/3 (33 %)
≤ 0.477	0.160–0.477	3/11 (27 %)	≤ 7.67	3.28–7.67	4/11 (36 %)

Fig. 2 Logistic model of TCP as a function of residual MRglc at S2 (a), Actual data points superimposed on the regression line (b), ROC curve showing sensitivity versus one minus specificity (c), and model probability cut-off curves showing sensitivity and specificity values (d). The area under the ROC curve was 0.85, suggesting good predictive power of the model



scale. Figure 3 shows the SKM-determined values and SUVmax of 62 tumors in 61 patients who completed the study. The correlation between SKM and SUVmax was strong with coefficients of determination (R^2) values of 0.89, 0.89, 0.79, 0.88 and 0.90 at S1, S2, S3, S4 and S5, respectively.

Confounding factors that may affect MRglc 10–12 days after therapy

There were only 14 SCLC, all of which were locally controlled at 1 year. There were 17 stage I NSCLC (12 stage IA tumors of 1.0–3.0 cm, 5 stage IB tumors larger than 3.0 cm) and only 2 developed local failures. Therefore, it was not possible to obtain separate results for SCLC and stage I NSCLC subgroups. However, a multivariable analysis of 1-year local control using penalized logistic regression showed that SCLC

histology and tumor stage (either overall or tumor stage 1 vs. higher) were not statistically significant predictors of 1-year local control after adjusting for MRglc at S2. In addition, the smallest value of MRglc by SKM in patients who were not locally controlled (a parameter which affected the choice of threshold SKM value) did not differ much between patients with stage I and those with higher stages (0.072 vs. 0.076 $\mu\text{mol}/\text{min}/\text{g}$). On the other hand, regression without the MRglc term showed that both SCLC and tumor stage were statistically significant predictors of 1-year local control. These results suggest that SCLC histology and tumor stage are no longer important for predicting 1-year local control after MRglc (quantified either by SKM or in terms of SUVmax) has been accounted for. Age (≥ 70 or < 70 years) and gender were not associated with higher values of MRglc-S2.

Table 3 Cut-off values of residual MRglc and SUVmax at S2 and their corresponding TCP, sensitivity and specificity

Cut-off values of MRglc ($\mu\text{mol}/\text{min}/\text{g}$) by SKM at S2	Cut-off values of SUVmax ^a at S2	TCP (%) ^b	Sensitivity ^b	Specificity ^b
≤ 0.036	≤ 0.92	95	100 %	19 %
≤ 0.050	≤ 1.14	90	100 %	44 %
≤ 0.061	≤ 1.32	85	100 %	53 %
≤ 0.071	≤ 1.45	80	100 %	63 %
≤ 0.092	≤ 1.75	70	74 %	74 %
≤ 0.134	≤ 2.48	50	42 %	91 %

^a SUVmax given as reference.

^b Values based on MRglc determined using the SKM.

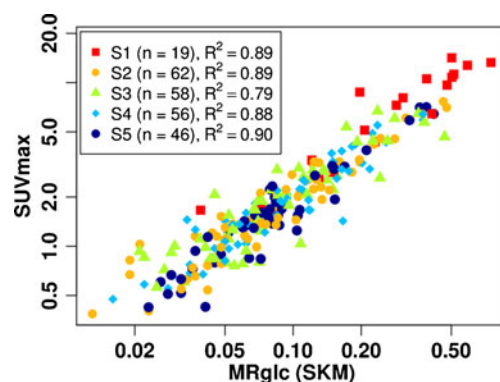


Fig. 3 Correlation between MRglc by SKM and SUVmax at S1 through S5

Overall survival according to local tumor control status

Neither the baseline value of MRglc (S1) nor the level of decline in MRglc in response to therapy between S1 and S2 showed statistically significant association with survival. However, using landmark method, patients who attained and maintained local tumor control at 12 months demonstrated longer overall survival than those with local failure ($p=0.02$).

Discussion

To address the high rate of local failure (40–45 %) and its consequence on long-term survival associated with the current standard radiation dose schedule, the RTOG (Radiation Therapy Oncology Group) 0617 trial compared the standard radiation dose schedule (60 Gy/30 F/6 week) with an escalated dose schedule (74 Gy/37 F/7.4 week) in combination with concurrent chemotherapy and with or without cetuximab in patients with inoperable stage IIIA or IIIB NSCLC [1, 20]. Overall survival rates at 12 months were 81 % with 60 Gy and 70 % with 74 Gy. Although this is an early result, there was no difference between the standard dose and escalated dose groups. Two new findings that we report from this study may help develop a new paradigm for therapy of patients with inoperable lung cancer. Therapy can be personalized by offering a complementary dose of radiation or other means of salvage therapy to patients with a high risk of residual cancer soon after standard dose radiotherapy and concurrent chemotherapy, while patients with a complete metabolic response implying complete tumor control (50 % of all patients) are saved from receiving escalated radiation doses beyond the standard radiation dose and the associated toxicities and cost.

Firstly, the earliest time-point at which the maximum metabolic response was found was 10 days after therapy. This is contrary to the conventional recommendation that a restaging ^{18}F -FDG PET scan be performed 3–4 months after therapy to measure the maximum metabolic response. Since early salvage therapy is likely more effective than late therapy in tumors with high metastatic potential [21], this new finding may have significant clinical implications. However, it is prudent to investigate whether or not the maximum metabolic response can be achieved even 1 week after radiotherapy or chemoradiotherapy since planning of supplementary radiotherapy and chemotherapy needs to take into account accelerated cancer cell proliferation which occurs during the treatment break. If metabolic response data from the latter part of the standard 6-week course of radiotherapy (i.e., the end of week 4) and concurrent chemotherapy were to be utilized for guiding patient selection and supplementary radiotherapy, the treatment break can be avoided. However, such an approach would have its own limitations because metabolic response

data obtained at the end of week 4 of standard radiotherapy (40 Gy/20 F/4 week) may be less than optimum compared with that obtainable after a full dose of standard radiotherapy (60 Gy/30 F/6 week) for guiding personalized and supplementary radiotherapy. Our results also showed no statistically significant correlation between the degree of decline in MRglc from baseline to S2 and subsequent tumor control at 12 months ($p=0.13$).

Secondly, the cut-off values of MRglc-MMR, shown in Table 3, indicate the potential utility of MRglc-MMR as a surrogate bioimaging biomarker measurable noninvasively 10–12 days after therapy for advancing a new paradigm, individualized and personalized therapy. If a cut-off MRglc value of ≤ 0.071 $\mu\text{mol}/\text{min}/\text{g}$ (SKM) or a SUVmax of ≤ 1.45 is chosen, it offers a sensitivity of 100 % and a specificity of 63 %, meaning that these values will identify all patients with residual cancer for salvage therapy while also including 37 % of patients in whom complete tumor control has already been achieved and who will receive additional therapy. In this situation, supplementary radiotherapy will be directed to a subvolume of the initial tumor outlined using a residual MRglc threshold of ≥ 0.072 $\mu\text{mol}/\text{min}/\text{g}$ or SUVmax > 1.45 , and can be expected to be tolerated well. To the best of our knowledge, this is also the first report of the potential utility of residual FDG uptake cut-off values at S2 for developing personalized therapy based on metabolic tumor response in patients with lung cancer. Nonetheless, the robustness of these threshold values for identifying patients with a high probability of residual cancer for salvage therapy needs to be validated in the setting of a clinical study before general use.

In the American College of Radiology Imaging Network (ACRIN) 6668/RTOG 0235 study, the association between SUVmax 12–16 weeks after therapy and local tumor control was investigated in patients with stage III NSCLC [22]. SUVmax 12–16 weeks after therapy was, as expected, highly correlated with local tumor control. Our study showed that the correlation between metabolic response data and local control rate was attainable as early as 10–12 days after therapy.

Therapy-induced pneumonitis contributes to an increase in residual MRglc after radiotherapy or chemoradiotherapy and interferes with accurate assessment of metabolic tumor response [23]. We excluded six patients from data analysis because of an overt pneumonitis process.

We have evaluated the use of 3'-deoxy-3'-[^{18}F]-fluorothymidine (^{18}F -FLT) PET in a cohort of patients showing an increase in MRglc at S2 through S4 study suggesting either local recurrence or inflammation [24]. ^{18}F -FLT PET was able to distinguish local recurrence from local inflammation correctly with a sensitivity of 83 % and a specificity of 89 %. Therefore, ^{18}F -FLT PET might be useful for supplementing ^{18}F -FDG PET in patients with a residual MRglc

value of ≥ 0.072 $\mu\text{mol}/\text{min}/\text{g}$ at S2 to improve the differentiation of patients with local tumor control from those with local failure. However, this hypothesis needs to be tested in future studies.

There is a large body of data supporting the notion that a supplementary dose of radiotherapy after a standard dose of 60 Gy/30 F/6 week would be effective in converting partial response to complete tumor response leading to lasting tumor control [25]. Nonetheless, it is important to take into account accelerated cancer cell proliferation during a treatment break and its adverse impact on local tumor control. The strategy to overcome accelerated cancer cell proliferation would include accelerated delivery of a supplementary dose of radiation and the use of concurrent chemotherapy. If our study data were to be applied in future studies, we recommend accelerated delivery of radiation by either a twice-daily treatment schedule administering 3.0 Gy per day as two fractions of 1.5 Gy with an interval of ≥ 6 h or a hypofractionated schedule administering a daily fractional dose of 3.0 Gy for 5 to 6 consecutive days including Saturday for a total supplementary dose of 15 to 18 Gy in 1 week [26]. In addition, concurrent cisplatin-based chemotherapy may be given with accelerated delivery of radiotherapy to enhance local tumor control [27].

A limitation of this study was the absence of the kinetic method, the “gold standard” that requires an 80-min dynamic data acquisition and full kinetic analysis for measurement of MRglc. However, such a method would be impractical in a busy clinical service. Our prior study demonstrated that MRglc measured with SKM had a very high correlation with that measured by kinetic modeling [15]. Other investigators have also shown a significant correlation between SKM, SUV indices and the kinetic method [28].

In conclusion, MRglc-MMR that can be obtained by ^{18}F -FDG PET 10–12 days after radiotherapy or chemoradiotherapy may be a robust biomarker capable of predicting TCP in lung cancer. The optimum cut-off values (MRglc ≤ 0.071 $\mu\text{mol}/\text{min}/\text{g}$ by SKM or SUV_{max} ≤ 1.45) need to be tested in clinical studies for their potential to identify patients with a high risk of harboring residual cancer soon after standard dose radiotherapy or chemoradiotherapy who can be offered a supplementary dose of radiation or other means of salvage therapy for improvement in local tumor control and survival.

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Conflicts of interest None.

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