Value of $^{18}$F-Fluoro-2-Deoxy-D-Glucose-Positron Emission Tomography/Computed Tomography in Non-Small-Cell Lung Cancer for Prediction of Pathologic Response and Times to Relapse after Neoadjuvant Chemoradiotherapy

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Abstract

Purpose: To determine the value of combined positron emission tomography/computed tomography (PET/CT) during induction chemotherapy (CTx) followed by chemoradiotherapy (CTx/RTx) for non–small-cell lung cancer to predict histopathologic response in primary tumor and mediastinum and prognosis of the patient.

Experimental Design: Fifty consecutive patients with locally advanced non–small-cell lung cancer received induction therapy and, if considered resectable, proceeded to surgery (37 of 50 patients). Patients had at least two repeated $^{18}$F-2-fluoro-2-deoxy-d-glucose (FDG)-PET/CT scans either before treatment ($t_0$) or after induction CTx ($t_1$) or CTx/RTx ($t_2$). Variables from the PET/CT studies (e.g., lesion volume and corrected maximum standardized glucose uptake values ($SUV_{\text{max,corr}}$)) were correlated with histopathologic response (graded as 3, 2b, or 2a: 0%, >0-10%, or >10% residual tumor cells) and times to failure.

Results: Primary tumors showed a percentage decrease in $SUV_{\text{max,corr}}$ during induction significantly larger in grade 2b/3 than in grade 2a responding tumors (67% versus 34% at $t_0$, 73% versus 49% at $t_2$; both $P < 0.005$). $SUV_{\text{max,corr}}$ at $t_2$ was significantly correlated with histopathologic response in tumors smaller than the median volume ($7.5 \text{ cm}^3$; $r = -0.54$, $P = 0.02$). In the mediastinal lymph nodes, $SUV_{\text{max,corr}}$ values at $t_2$ predicted an ypN$_0$ status with a sensitivity and specificity of 73% and 89%, respectively ($SUV_{\text{max,corr}}$ threshold of 4.1, $r = -0.54$, $P = 0.0005$). Freedom from extracerebral relapse was significantly better in grade 2b/3 patients (86% at 16 months versus 20% in 2a responders, $P = 0.003$) and in patients with a greater percentage decrease in $SUV_{\text{max,corr}}$ in the primary tumor at $t_2$ in relation to $t_0$ than in patients with lesser response (83% at 16 months versus 43%; $P = 0.03$ for cutoff points between 0.45 and 0.55).

Conclusions: $SUV_{\text{max,corr}}$ values from two serial PET/CT scans, before and after three chemotherapy cycles or later, allow prediction of histopathologic response in the primary tumor and mediastinal lymph nodes and have prognostic value.

About one third of patients with non–small-cell lung cancer are found to have locally advanced tumor stages IIIA and IIIB at initial diagnosis (1). For these patients, the main therapeutic options with the potential for cure are definitive high-dose radiotherapy combined with chemotherapy or induction treatment followed by surgery. Induction treatment protocols using either preoperative chemotherapy or combined chemoradiotherapy followed by resection result in cure rates of 25% to 35% at 3 years for locally advanced non–small-cell lung cancer (2–6).

Pathologic complete response in the primary tumor and nodal downstaging of initial N$_2$ or N$_3$ involvement to ypN$_0$ status in the mediastinum have both been shown to be strong predictors of favorable long-term survival after neoadjuvant chemotherapy or chemoradiotherapy (2, 4, 6–12). It has been consistently found that higher response rates can be achieved in the mediastinum (30-70%) than in the primary tumor region (15-30%; refs. 9, 13, 14). Patients with tumor-free lymph nodes in the mediastinum at the time of resection had survival rates of 30% to 40% whereas those with residual nodal disease only had survival rates of 0% to 11% at 5 to 6 years (2, 3, 7, 8, 10–12, 15).
Computed tomography (CT) as well as positron emission tomography (PET) with $^{18}$F-2-fluoro-2-deoxy-D-glucose (FDG) has gained an accepted value as initial staging investigations in lung cancer (16, 17). The median sensitivity and specificity of FDG-PET for identifying mediastinal node involvement was 85% and 90%, respectively, in the meta-analysis of Gould et al. (17).

A dual modality PET/CT allows the fusion of all diagnostic information from CT and PET scans with utmost accurate spatial alignment, which helps to detect primary tumors and metastases by morphologic and functional characteristics (18). Early studies of PET/CT have shown that the diagnostic accuracy in the initial mediastinal staging of lung cancer is improved by PET/CT in comparison with CT and PET viewed side by side (19, 20).

Some data on response prediction following neoadjuvant treatment protocols have been presented based on PET scans alone (21–25) or on evaluation of PET and CT scans side by side (26, 27). But none of these investigations has analyzed both, mediastinal response in addition to the response in the primary tumor. This may reflect that factors like elevated background activity in the mediastinum or partial volume effects which reduce the measured maximum standard glucose uptake values ($\text{SUV}_{\text{max}}$) render the accurate detection of small mediastinal lymph node metastases by PET alone difficult (28, 29).

In the present study, we analyzed whether histopathologic response at both sites, the primary tumor and mediastinal lymph node metastases, as well as times to treatment failure can be predicted by using the functional and morphologic information from FDG-PET/CT scans done initially and during the course of neoadjuvant CTx/RTx.

**Patients and Methods**

This is a retrospective study of 50 consecutive patients with potentially operable, locally advanced non–small-cell lung cancer (stages IIIA/IIIB) who were treated with neoadjuvant chemoradiotherapy in the department of radiotherapy of the University Hospital Essen between January 2002 and December 2004. Histologic diagnosis was confirmed by cytology or conventional histopathology. Initial routine staging procedures consisted of a clinical examination including lung function tests, bronchoscopy and mediastinoscopy, and CT or magnetic resonance imaging of the brain with and without contrast. Patients got at least two PET/CT scans as a component of the initial staging or during the course of induction therapy. However, 20 patients who did not get an initial PET/CT by the institution, which conducted induction chemotherapy, had a chest and abdomen CT as well as a bone scintigraphy.

Neoadjuvant treatment started with three cycles of induction chemotherapy consisting of cisplatin (50 mg/m$^2$, d1 + 8, q21) with either paclitaxel (175 mg/m$^2$, d1) or etoposide (150 mg/m$^2$, d4 – 6), or vinorelbine (25 mg/m$^2$, d1 + 5, q21; ref. 30). Three weeks after completion of the third chemotherapy cycle, concurrent chemoradiotherapy was started. Irradiation was given either fractionated with $5 \times 2$ Gy per week or hyperfractionated accelerated with 1.5 Gy twice daily up to a total dose of 44 to 45 Gy. Radiotherapy was planned on the basis of a planning CT or PET/CT after induction chemotherapy. The clinical target volume included the gross tumor volume with a margin of 1 cm, the ipsilateral hilar and ipsilateral paratracheal and pretracheal lymph nodes, as well as the infracarinal nodes in all patients. Other mediastinal lymph node groups were included in the clinical target volume only if involvement was found by the pretreatment evaluations or by restaging during treatment. The three-dimensional dose distribution and dose-volume histograms were calculated by a radiotherapy treatment planning system (ECLIPSE, Varian Medical Systems). Treatment was done using megavoltage equipment (>10 MV photons).

Concurrent chemotherapy consisted of cisplatin (45-50 mg/m$^2$, d2 + 9) with either vinorelbine (20 mg/m$^2$, d2 + 9) or etoposide (50 mg/m$^2$, d4 – 6).

After completion of chemoradiotherapy, only patients who did not show disease progression on repetitive PET/CT scans were referred to thoracic surgery aiming at resection with curative intent.

**PET/CT investigations.** Pretreatment baseline PET/CT scans, as part of the initial staging, were done about 3 days before the start of induction chemotherapy (time point $t_1$). Thoracic PET/CT examinations were done after induction chemotherapy and before radiotherapy as part of the treatment planning procedure (time point $t_2$) and a whole body PET/CT scan was recorded at the end of simultaneous CTx/RTx (time point $t_3$) to exclude tumor progression locally or at distant sites and to evaluate the patients' resectability. The time points $t_1$, $t_2$, and $t_3$ were at days 56 and 83 (median values) after the start of chemotherapy, respectively. Written informed consent was obtained from all patients.

Dual-modality PET/CT was done on a biograph (Siemens Medical Solutions, Hoffman Estates, IL), which is based on a dual-slice helical CT and a full-ring PET scanner (31). In-plane spatial resolutions of CT and PET are 0.45 and <6.5 mm, respectively.

A commercial radiation therapy pallet was mounted on the PET/CT patient table to facilitate adequate positioning of the patient corresponding to the radiotherapy settings using standard immobilization devices.

A topogram was used to define the axial imaging range. CT scans were acquired in spiral mode with a reconstructed 2.4-mm slice width, pitch 1.6, 130 kV, and 130 mA. All patients were given i.v. contrast media (100 mL, 3 mL/s). To avoid high-density focal artifacts from bolus injection, the contrast volume was applied by an adaptive pressure pump. A standardized breathing protocol was used (32). After completion of the CT scan, the bed moved automatically to the PET field-of-view and emission data were acquired. The CT images were used for the attenuation correction of the emission data (33). PET imaging was conducted 1 hour after the administration of 360 ± 20 MBq of FDG (three-dimensional mode, 3.5 min/bed position). As all patients were monitored to be normoglycemic, no plasma glucose correction was planned. When positioned on the table attachment, patients were scanned with elevated arms over two to three bed positions covering a range from the base of the skull down to the base of the lungs. The combined PET/CT exam took <24 minutes. Pretreatment PET/CT scans covered the patient down to the middle of the femoral bones and took about 40 minutes. Image reconstruction of the corrected emission data was done after Fourier rebinning (AWOSEM, two iterations, eight subsets, 5-mm Gaussian filter).

**Interpretation of scans.** Using the Syngo fusion platform (Siemens Medical Solutions), PET/CT images were visually evaluated for regions of focally increased glucose metabolism. In all lesions, standardized uptake values ($\text{SUV}$) were determined according to the following formula: $\text{SUV} = \frac{\text{tissue activity per milliliter}}{\text{injected activity per body weight}}$. We used the maximum value of SUV in the structures of interest ($\text{SUV}_{\text{max}}$) for further quantitative assessment and potential differentiation of lesions.

$\text{SUV}_{\text{max}}$ was determined in the PET study after both the primary tumor and the dominant lymph node had been delineated as regions of interest on the fused CT scan by an experienced radiation oncologist. The “dominant” lymph node was defined as a lymph node in an involved mediastinal lymph node region with increased FDG uptake (i.e., an uptake above the background level) as the first criterion and with maximum size as a subsequent criterion in cases with several lymph nodes with similar SUV. The dominant lymph node was identified on the first done PET/CT scan and followed up in the subsequent scans. $\text{SUV}_{\text{max}}$ was corrected for background and partial...
volume effects according to the following formula: \[ SUV_{\text{max,corr}} = \text{background SUV}_{\text{mean}} + \frac{\text{(measured SUV}_{\text{max}} - \text{background SUV}_{\text{mean}})}{\text{recovery coefficient}} \times (28) \].

The background was determined as mean SUV in a representative area around each tumor or lymph node, respectively. The recovery coefficients were obtained from the plots published by Kessler et al. (34) using the geometric mean diameter of each lesion determined in the central axial plane of the CT scan and the spatial resolution of the biograph scanner.

**Histologic evaluation—grading of response.** For all primary tumors, the regression score described by Junker et al. (35) was used to describe the chemoradiotherapy-induced morphologic changes based on the extent of vital tumor tissue, the degree of necrosis, foam cell reaction, fibrosis, and scarring: grade 1, no or only spontaneous tumor regression; grade 2a, evidence of therapy-induced tumor regression with >10% residual tumor cells; grade 2b, evidence of therapy-induced tumor regression with 10% residual tumor cells; and grade 3, no evidence of vital tumor, complete regression. In addition, we have assigned grade 0 to all patients who did not proceed to curative surgery. Reasons for not being operated on were the assessment of irresectability due to persistent bulky tumor, medical reasons, or patient refusal.

**Data analysis.** A linear model was used to analyze the time dependence of SUV_{\text{max,corr}} and the volumes of the primary tumor and the dominant mediastinal lymph node during the course of therapy in dependence on the different histopathologic response categories. This analysis was done with the general linear model procedure of the SAS software system (SAS Institute, Inc., Cary, NC; ref. 36). The time points \( t_0 \) (before the start of chemotherapy around day 0), \( t_1 \) (after three cycles of chemotherapy around day 56), and \( t_2 \) (after neoadjuvant chemoradiotherapy around day 83) were fixed values of the classification variable “time.” The classification variable “regression grade” had the fixed values 0, 1, 2a, 2b, and 3. To analyze the within-patient effects of the classification variable time as well as the interaction of both effects on the response variables SUV_{\text{max,corr}} or tumor volume, a repeated measures analysis was done. All patients had PET/CT scans at two or three time points. All of the information is used by the model to estimate the individual log(predicted SUV_{\text{max,corr}}(t_0)) value and to contribute to the estimated effects of time, regression grade, and the interaction between time and regression grade on log(SUV_{\text{max,corr}}(t_i)). A test of normality was done for the SUV_{\text{max}} and tumor volume data by computing a Shapiro-Wilk test (36). Both variables were log-normally distributed.

In addition, a Spearman rank correlation was done between the different quantitative end points \[ \log(SUV_{\text{max,corr}}(t_i)) \] at times \( t_0 \) to \( t_2 \); \( \Delta \log(SUV_{\text{max,corr}}(t_i)/C_0) \), the change in log SUV_{\text{max,corr}} between time points \( t_0 \) and \( t_2 \); \( \log(\text{volume}(t_0)/\text{volume}(t_2)) \); \( \log(\text{volume}(t_0)/\text{volume}(t_2)) \); \( \Delta \log(\text{volume}(t_0)/\text{volume}(t_2)) \), the change in log volume between time points \( t_0 \) and \( t_2 \) and the graded histopathologic response.

Overall survival and times to extracerebral progression were estimated according to the Kaplan-Meier method. For the latter, extracerebral relapses as the site of first relapse were counted as an event whereas all other patients were censored at the times of a competing event (death, cerebral relapse; ref. 37). Comparison of the Kaplan-Meier curves was made by the log-rank test. Receiver operating characteristic (ROC) analyses were done to evaluate the overall performance of SUV_{\text{max,corr}} values and the relative remaining SUV_{\text{max,corr}} \[ \text{SUV}_{\text{max,corr}}(t_2)/\text{SUV}_{\text{max,corr}}(t_0) \] as a prognostic test for histopathologic response and times to extracerebral failure. The ROC curves were calculated with the SPSS software package (version 11.0, SPSS, Inc., Chicago, IL).

**Results**

Fifty consecutive patients, 35 male and 15 female, have been treated according to the neoadjuvant schedule between January 2002 and December 2004; median age was 56 years (range, 34-78 years). Thirty-seven patients had curative thoracic surgery with either pneumonectomy (13 patients) or lobectomy (24 patients).

Thirty-seven patients showed involved mediastinal nodes at initial staging. Clinical mediastinal involvement was established in 31 patients by mediastinoscopy, in 4 cases by PET/CT, and in 2 patients by CT alone. The other 13 patients had T4 tumors. Twenty-seven of the 37 resected patients had clinical mediastinal involvement at the start of therapy. In the resection specimens after neoadjuvant therapy, lymph nodes showed residual tumor in 13 patients and were free from tumor in 24 patients. A histopathologic complete remission in both the primary site and the mediastinum was observed in 10 of 37 patients who were resected. Thirteen patients had no resection, of whom four did not proceed to thoracotomy due to inoperability for medical reasons (limited respiratory function, reduced performance status) or patient refusal. Seven patients were deemed irresectable by the thoracic surgeon due to persistent bulky T4 tumors. These patients were treated further on a definitive chemoradiotherapy protocol. Two patients showed progressive disease (malignant pericardial effusion, distant lymph node metastasis) during neoadjuvant chemotheraphy or chemoradiotherapy, respectively, and received palliative therapy.

In total, there were 120 PET/CT data sets from 50 patients. Each patient got at least two PET/CT scans. Pretreatment PET/CT scans (at \( t_0 \)) have been done in 30 patients; scans at time points \( t_1 \) and \( t_2 \) were done in 47 and 43 patients, respectively. A pathologic complete response (regression grade 3) of the primary tumor was observed in 13 of the resected patients whereas 12, 12, and 0 of the resection specimens had a grade 2b, 2a, and 1 response, respectively. The number of patients with PET/CT scans done at \( t_0 = t_1 = t_2 \) to \( (t_0, t_1, t_2) \) group by regression grade are, resected patients with regression grade 3: 5/0/5/5; regression grade 2b: 1/2/4/5; regression grade 2a: 1/1/5/5; and nonresected patients: 0/0/6/7 patients.

**Primary tumor.** Partial volume and background corrected SUV_{\text{max}} values in the primary tumor are shown in Fig. 1A at the three different time points before and during neoadjuvant therapy. To analyze the time course of the SUV_{\text{max,corr}} values during therapy in comparison with \( t_0 \) data from the 30 patients with PET/CT scans done at \( t_0 \) were plotted according to the histopathologic regression grade of the primary tumor. The SUV_{\text{max,corr}} values were log-normally distributed with a median of 1.0 [50% confidence interval (CI), 6.8-13.6] at the start of treatment. Between patients, analysis with a linear model showed a significant time effect with decreasing SUV_{\text{max,corr}} values at \( t_1 \) or \( t_2 \) in comparison with \( t_0 \) for patients with regression grades 2b and 3 (P < 0.02, F test) but no significant time effect for regression grade 2a and the nonresected patients.

In a second step, a repeated measures analysis was done to analyze the within-patient effect of time, the independent effect of regression grade, and the interaction of both on the log(SUV_{\text{max,corr}}(t_i)) values. This repeated measures analysis estimates and adjusts for an individual log(predicted SUV_{\text{max,corr}}(t_i)) value at \( t_0 \) for each patient and allows the inclusion of log(SUV_{\text{max,corr}}(t_i)) values of all 120 PET/CT scans of the 50 patients without omissions. Figure 1B shows the results of the repeated measures analysis. The log(SUV_{\text{max,corr}}(t_i))/predicted SUV_{\text{max,corr}}(t_0)) values are

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The group means of the relative remaining SUV\text{max,corr} values are given for the different histopathologic response groups at remaining SUV\text{max,corr} at this plot. The regression grade according to repeated measures analysis. Treatment (significantly smaller relative decrease of SUV\text{max,corr}(t) for tumors of regression grades 2a and 3 are plotted, terming as ΔSUV(t, t₀) values from tumors with grade 2a response was well separated from the higher response grades 2b and 3 with SUV\text{max,corr}(t₁)/predicted SUV\text{max,corr}(t₀) values of 66% and 51% at t₁ and t₂, respectively (P < 0.005, F test at both time points). The values of tumors in nonresected patients (grade 0 response) were 74% and 72% at t₁ and t₂ (P < 0.005, F test). This repeated measures analysis by the linear model also showed that there was significant between-patient variability in log(SUV\text{max,corr}(t₀)) (P < 0.0001, F test) but no dependence of log(SUV\text{max,corr}(t₀)) on regression grade (P = 0.075, F test).

The following additional analyses were done with the measured values from the primary tumors without using linear model analysis.

Figure 2A shows the measured percentage remaining SUV\text{max,corr} values at t₂ (SUV\text{max,corr}(t₂)/SUV\text{max,corr}(t₀)) of 16 resected patients with PET/CT scans done at t₀ and t₂. For seven additional patients who had PET/CT scans only at t₀ and t₁, SUV\text{max,corr}(t₂)/SUV\text{max,corr}(t₀) values were estimated using the relation SUV\text{max,corr}(t₂) = 0.89 × SUV\text{max,corr}(t₁), which was obtained from patients with PET/CT scans at t₁ and t₂. Using ROC analysis of the performance of the SUV\text{max,corr}(t₂)/SUV\text{max,corr}(t₀) values for prediction of grade 2b or grade 3 response, an area under the curve of 0.86 (95% CI, 0.63-1.00; P = 0.008) was observed (Fig. 2B). This high area under the curve value is significantly larger than 0.5 and classifies the SUV\text{max,corr}(t₂)/SUV\text{max,corr}(t₀) as a test with good performance. The sum of sensitivity and specificity of the test was greatest for cutoff values between 0.38 and 0.55, with sensitivities ranging from 0.70 to 0.94 and specificities ranging from 0.71 to 0.86. In addition, a ROC curve was done to assess the value of the SUV\text{max,corr}(t₁)/SUV\text{max,corr}(t₀) to predict grade 2b/3 response in comparison with grade 1a/2a response. Of the 37 resected patients, 20 had a PET/CT scans at t₀ and t₁ and 3 at t₀ and t₂. For the latter, SUV\text{max,corr}(t₁) was estimated by SUV\text{max,corr}(t₁) = 1.12 × SUV\text{max,corr}(t₀). The area under the curve for the SUV\text{max,corr}(t₁)/SUV\text{max,corr}(t₀) values predicting grade 2b or grade 3 response was 0.88 (95% CI, 0.7-1.0; P = 0.005). Therefore, the relative SUV\text{max,corr} value remaining at t₁ is of similar value to predict grade 2b/3 response as the relative value remaining at t₂.

In addition, we analyzed the predictive value of the absolute SUV\text{max,corr} at t₂. However, we observed high SUV\text{max,corr}(t₂) values in some larger residual tumors with
grade 3 histopathologic regression. Therefore, differences in SUV_{max,corr(t_2)} values between tumors with grade 2b-3 regression and tumors with lower regression grades have been analyzed in two separate classes of tumor sizes smaller or equal or larger than the median volume of 7.5 cm³, respectively (Fig. 2C). In tumors <7.5 cm³, the SUV_{max,corr(t_2)} values from tumors with regression grades 2b or 3 are significantly smaller than from tumors with regression grades 1 or 2a (r = -0.51, P = 0.02, Spearman rank correlation). The area under the ROC curve for the prediction of regression grades 2b or 3 from SUV_{max,corr(t_2)} was 0.8 (95% CI, 0.55-1.0; P = 0.03). A maximum sum of sensitivity and specificity was obtained at a cutoff point of SUV_{max,corr(t_2)} = 3.3 (sensitivity 0.8, specificity 0.8). On the other hand, tumors >7.5 cm³ did not show any difference in the SUV_{max,corr} values between regression grades 2b/3 and 1/2a (r = 0.00, P > 0.5).

Tumor volumes Vol_{TU(t_i)} at times t_0 to t_2 were estimated from the maximum orthogonal diameters d_1 and d_2 in the axial center plane according to the relation (d_1 x d_2)^{3/2} x 0.52 as a second end point from the PET/CT. The volumes were log-normally distributed. The initial median volume of the primary tumors was 32 cm³ (50% CI, 13-69 cm³). Using repeated measures analysis with a linear model, the time dependence of log(Vol_{TU(t_i)}/predicted Vol_{TU(t_0)}) denoted by ΔVol_{TU(t_i, t_0)}, was statistically highly significant (P < 0.0001, F test) but not the interaction effect between time and regression grade (P = 0.14, F test). The ΔVol_{TU(t_i, t_0)} curves were similar for the regression grades 2a, 2b, and 3 with Vol_{TU(t_i)}/predicted Vol_{TU(t_0)} values of 22%, 35%, and 24% at t_1, respectively, and 20%, 24%, and 21% at t_2, respectively. However, nonresected tumors showed only little decrease in tumor volume at times t_1 and t_2 and were well separated from resected tumors (P = 0.004, F test). This underscores that the interdisciplinary decision against resection was influenced by a limited volume reduction. The rank correlation between the Vol_{TU(t_2)}/Vol_{TU(t_0)} and the histopathologic response grade (r = -0.26, P = 0.3, F test) was low.

Mediastinal lymph nodes. The median SUV_{max,corr(t_0)} value in the dominant mediastinal lymph node among all patients with PET/CT at t_0 was 3.1 (50% CI, 2.7-6.1). Median size of the dominant lymph nodes at t_0 was 1.6 cm³. A volume <1.0 cm³ was found in 25% of the dominant lymph nodes, resulting in partial volume correction factors >1.25. The median SUV background level in the mediastinum was 1.7 (50% CI, 1.5-2.0), nearly twice as high as the background around the primary tumor (median 0.8; 50% CI, 0.6-1.0).

Despite mediastinoscopic staging, the histopathologic involvement of the dominant lymph node was not proved as

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**Figure 2.** A, ratio of the measured SUV_{max,corr} after neoadjuvant chemoradiotherapy (at t_2) and pretreatment SUV_{max,corr} (at t_0) as function of histopathologic regression grade. Of measured values of 16 resected patients with PET/CT scans done at t_0 and t_2, iii, for seven additional patients who had PET/CT scans only at t_0 and after induction chemotherapy at t_2, SUV_{max,corr(t_2)} values were estimated using the relation SUV_{max,corr(t_2)} = 0.89 x SUV_{max,corr(t_0)}. A threshold range (light gray horizontal bar) of SUV_{max,corr(t_2)}/SUV_{max,corr(t_0)} between 0.38 and 0.55 discriminated best between tumors with grade 2a and grade 2b/3 response. B, ROC curve for 23 operated patients with SUV_{max,corr(t_2)}/SUV_{max,corr(t_0)} in relation to histopathologic regression grade. Cutoff points for SUV_{max,corr(t_2)}/SUV_{max,corr(t_0)} with respect to sensitivity and 1-specificity are indicated in italics; area under the curve: 0.86 (P = 0.008). C, absolute values of SUV_{max,corr} after neoadjuvant chemoradiotherapy as function of regression grade for tumors smaller and larger than the median volume of 7.5 cm³ determined at t_2. In contrast to large tumors, tumors smaller than the median show significantly different SUV_{max,corr(t_2)} values for regression grades 2a and 2b/3, respectively. A threshold range of SUV_{max,corr(t_2)} between 2.9 and 3.9 discriminates best between histopathologic response groups for small tumors (horizontal bar).
directly as in the primary tumor. To evaluate the time course of SUV\textsubscript{max,corr}(t\textsubscript{i}) only in dominant lymph nodes with a very high risk of tumor involvement, we restricted estimation of SUV\textsubscript{max,corr}(t\textsubscript{i}) values to resected patients with a positive mediastinoscopy if done. In addition, the SUV\textsubscript{max,corr}(t\textsubscript{i}) value at t\textsubscript{0} had to be >3.8. In cases without a PET/CT scan at t\textsubscript{0}, SUV\textsubscript{max,corr}(t\textsubscript{i}) had to be >3.3. This resulted in 20 patients in whom response in the mediastinum was analyzed. Thirteen of these patients (65%) had a pathologic complete response in the mediastinal lymph nodes whereas in seven patients, residual lymph node involvement was found. The effect of time on \( \Delta \text{SUV}(t_0, t) \) was significant \((P < 0.0001, F \text{ test})\). However, no difference in \( \Delta \text{SUV}(t_i, t) \) values of patients with pathologic complete response and those with residual lymph node metastases was found using repeated measures analysis with a linear model \((P = 0.95, F \text{ test})\). Figure 3 presents SUV\textsubscript{max,corr}(t\textsubscript{i}) values in the dominant lymph nodes normalized to those estimated for the primary tumor in the same patient at t\textsubscript{0} by the repeated measures linear model \((\text{SUV}_{\text{max,corr}}(t\textsubscript{i})/\text{predicted SUV}_{\text{TU}}(t\textsubscript{0}))\). Within a patient, the SUV\textsubscript{max,corr}(t\textsubscript{i})/\text{predicted SUV}_{\text{TU}}(t\textsubscript{0}) values in the lymph nodes were on average 24% lower than in the primary tumors at the same time points \((P = 0.008, F \text{ test})\). Again the time effect was significant \((P = 0.0001, F \text{ test})\) and the time courses of SUV\textsubscript{max,corr}(t\textsubscript{i})/\text{predicted SUV}_{\text{TU}}(t\textsubscript{0}) in the dominant lymph node and the primary tumor were parallel and no differences were found \((P = 0.97, F \text{ test} \text{ for the interaction effect: time by tumor site})\).

In addition, the prognostic value of the SUV\textsubscript{max,corr}(t\textsubscript{2}) value for the histopathologic evidence of residual tumor in the dominant lymph node after neoadjuvant treatment has been investigated (Fig. 4). Thirty of the 37 resected patients (81%) had a PET/CT scan at t\textsubscript{2}. In the remaining seven patients, SUV\textsubscript{max,corr}(t\textsubscript{2}) was estimated by SUV\textsubscript{max,corr}(t\textsubscript{1}) \times 0.89. The rank correlation coefficient between ypN\textsubscript{0} (yes/no) and SUV\textsubscript{max,corr}(t\textsubscript{2}) was \( r = -0.54 \) \((P = 0.0005)\). Area under the curve in the ROC analysis accounted for 0.84 \((95\% \text{ CI}, 0.69-0.99; P = 0.002)\). The sum of sensitivity and specificity was maximized at a cutoff point of SUV\textsubscript{max,corr}(t\textsubscript{2}) = 4.1 \((\text{sensitivity } 0.73, \text{ specificity } 0.89)\).

**Patient follow-up and survival.** At the time of last examination, the median follow-up of all patients was 17 months (range, 8-39 months) and 19 months (range, 12-39 months) for the resected patients. During this time, 24 patients have experienced a relapse of their disease, of whom 6 had brain metastases as the first site of failure whereas the remaining patients had an extracerebral local or distant disease progression. The estimated 1- and 2-year overall survival rates for the entire group of 50 patients were 86% \((95\% \text{ CI}, 0.80-0.91)\) and 63% \((95\% \text{ CI}, 0.55-0.71)\). No statistically significant difference in overall survival was observed for group with grade 2b/3 versus grade 2a/1 histopathologic regression versus no resection \((P = 0.37, \text{ log-rank test})\). The corresponding 1- and 2-year survival rates are similar with 88% versus 92% versus 77% and 70% versus 61% versus 51%, respectively. Two intercurrent deaths not related to disease progression were observed in patients with grade 2b/3 response. SIIV change was not a variable predictive for survival during follow-up neither in the homogeneously treated group of resected patients with PET/CT at t\textsubscript{0} nor in the group of all patients resected or definitively treated with chemoradiotherapy with PET/CT at t\textsubscript{0}. The performance of the SUV\textsubscript{max,corr}(t\textsubscript{2})/PET/CT at t\textsubscript{0} for prediction of survival of resected patients at the end of follow-up (yes/no) was explored by ROC analysis. Area under the curve as a global summary statistic over all cutoff levels was 0.54 \((95\% \text{ CI}, 0.25-0.83; P = 0.75, \text{ Wilcoxon test})\). Using 0.5 as a cutoff point, survival at 1 and 2 years of resected patients with
SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ values of <0.5 was 0.88 and 0.79 and with values of >0.5 was 0.86 and 0.86, respectively ($P > 0.5$, log-rank test).

Because the brain is a major site of recurrence, which is not sufficiently treated by the neoadjuvant treatment regimen, we separately analyzed the actuarial risk of extracerebral disease progression in patients homogeneously treated with neoadjuvant chemoradiotherapy and surgery ($n = 37$). Extracerebral relapses were observed between 12 and 15 months. A significant difference in the freedom from extracerebral disease progression was observed for patients with histopathologic grade 2b/3 response versus grade 1/2a responders (86% versus 20%; $P = 0.003$; Fig. 5A).

In addition, the performance of the SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ values for prediction of freedom from extracerebral relapse as the first event within follow-up (yes/no) was explored by ROC analysis. Minimum follow-up of the 23 included resected patients with PET/CT at $t_0$ was 12 months. Area under the curve was 0.74 (95% CI, 0.49-0.98; $P = 0.045$, sequential one-sided Wilcoxon test) and, therefore, determining SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ is of value to predict freedom from extracerebral relapse (Fig. 6). The sum of sensitivity and specificity was largest for SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ cutoff levels between 0.45 and 0.55. For a better consideration of censoring due to limited follow-up and intercurrent events, the Kaplan-Meier curves for freedom from extracerebral disease progression of patients with SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ values of <0.5 and >0.5 are given in Fig. 5B. As expected from the correlation of SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ with regression grade, there was a significant trend towards a better freedom from extracerebral disease progression for patients with lower SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ ($P = 0.03$, log-rank test; Fig. 5B). This result did not change for cutoff levels between 0.45 and 0.55. Differences in the performance of the SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ to predict survival and freedom from extracerebral progression are caused by intercurrent deaths and unrelated cerebral relapses. In patients with SUV$_{\text{max,corr}}(t_2)/$SUV$_{\text{max,corr}}(t_0)$ values of <0.5, intercurrent deaths and cerebral metastases were observed in 12% and 25%, respectively.

Discussion

In this study, SUV$_{\text{max,corr}}$ values of the primary tumors and mediastinal lymph nodes of locally advanced non–small-cell lung cancer have been measured during a 12-week neoadjuvant treatment protocol of chemotherapy and chemoradiotherapy by PET/CT and correlated with histopathologic response and prognosis of the patients. On the basis of the morphologic CT information and the maximum FDG uptake, the dominant lymph node in the mediastinum could be identified and followed up consecutively. Furthermore, CT provided necessary and reliable information about primary tumor and dominant lymph node with respect to partial volume correction. The entire information from the dual modality scan enabled us to evaluate the association between morphologic and functional
changes and histopathologic response of the primary tumor and mediastinal lymph nodes during the course of neoadjuvant treatment.

Shrinkage of the primary tumor or lymph nodes was not significantly related to the histopathologic response, which is well in accordance with the data from Cerfolio et al. (27). Earlier studies have already given hints that CT information alone is not an important predictor of pathologic remission (3, 7, 13, 38).

According to our data, PET/CT scans after chemothera and following combined chemoradiotherapy show similar findings and provide the clinician with similar information about the prediction of histopathologic response; i.e., combined chemoradiotherapy with a limited preoperative dose is not capable of converting post-chemotherapy nonresponders into patients with histopathologic complete remission at an early time point post-radiotherapy. For squamous cell carcinomas of the esophagus, it has been shown that the FDG signal of serial PET scans before and as early as 2 weeks after initiation of preoperative chemoradiotherapy allows identification of histopathologic responders (39). Consequently, an early modification of the treatment regimen may be reasonable in patients who do not show response to the induction treatment.

In this study, the remaining SUV max,corr(t 2) shows a good correlation with the histopathologic response in the smaller tumors (size < median volume of the total sample: 7.5 cm 3). It has been found earlier that a larger residual tumor mass even without tumor cells after chemoradiotherapy can have an overall uptake remaining at high levels, which are suggestive for malignant tissue, and decreases the specificity for differentiation of residual cancer from scarring tissue or fibrosis (21). In this study, SUV values up to 5.5 have been found in complete responders. According to the results of this study, even SUV max,corr(t 2) values of ~10 can be associated with histopathologic complete response in larger tumors which can be attributed to metabolically active cells of an inflammatory reaction in the connective tissue which surrounds the therapy-induced areas of necrosis. Investigators have repeatedly underscored that especially with a radiotherapy-containing induction regimen this inflammatory reaction may lead to false-positive FDG-PET findings (21, 40). There is still a need for more specific markers for monitoring viability of tumor cells during neoadjuvant chemoradiotherapy or resistance-promoting mechanisms such as hypoxia or proliferation. 18F-Fluoro-3-deoxy-3-fluorothymidine is a promising tracer to measure tumor proliferative activity and viability during treatment with high specificity but with limited sensitivity (41).

In the primary tumors, the percentage of remaining FDG signal normalized to the initial SUV max,corr(t 0) to reduce the influence of the intertumoral heterogeneity has turned out as a better variable for prediction of response. Other groups have also found that the value of relative SUV changes as a successful variable for the prediction of histopathologic response not only in lung cancer but also in gastrointestinal malignancies (23, 27, 39, 42). This study underscores the limits of resolution of the ΔSUV values as a test to predict histopathologic response. A dynamic range of around 70% decrease of the initial SUV during neoadjuvant therapy can be observed. PET/CT therefore cannot distinguish grade 2b from grade 3 response (pathologic complete response), as has been shown in our results. However, both response groups have similar good prognosis after neoadjuvant treatment and therefore discrimination may not be necessary in the clinic (6). Another predictive variable from PET scanning is the metabolic rate according to the data of Choi et al. (43). Their group conducted a PET study 2 weeks after the end of neoadjuvant chemoradiotherapy for patients with stage IIIA non–small-cell lung cancer. Pathologic tumor response at the primary site was related to the metabolic rate of glucose when using a logistic model fit.

Here, we have analyzed FDG uptake in the mediastinal lymph nodes in relation to the SUV in the primary tumor. Even after partial volume correction, the dominant lymph nodes show on average a lower SUV max than the primary tumors. This can be explained by a lower tumor cell density. Dominant lymph nodes without residual nodal disease showed a relative decrease of the initial SUV to ~40% at t 2. Patients with residual tumor in the mediastinum, however, showed a similar decrease in the dominant lymph node. This can be explained by the higher responsiveness of lymph nodes so that even lymph nodes with residual tumor cells may have regression to <40% tumor cells. The best variable to predict histopathologic response in the lymph nodes was SUV max,corr after neoadjuvant chemoradiotherapy, which showed a statistically significant correlation with nodal downstaging. Despite marked background activity, PET/CT made a reliable identification and follow-up of the initially involved lymph nodes during neoadjuvant treatment possible.

Besides histopathologic response, some groups have recently started to correlate SUV changes during chemothera or chemoradiotherapy with prognosis after therapy, not only in lung cancer but also in head and neck, breast, gastrointestinal, lymphoma, sarcoma, and germ-cell tumors (39, 44–46), indicating that PET responses are associated with survival or relapse times. In the present study, a significant correlation between SUV response and time to extracerebral relapse could be shown in a homogeneously treated population with neoadjuvant chemoradiotherapy and resection. In contrast to survival, this end point is not confounded by intercurrent deaths not related to response to induction therapy, which occurred in three patients of this study. In addition, the brain represents a well-known sanctuary site which is not responsive to the aggressive trimodality approach (47). Because of the high risk of extracerebral recurrences in non–small-cell lung cancer patients (37), which will not be modified by induction treatment, time to extracerebral recurrence should be the clinical end point most closely related to locoregional treatment effect. Resected patients with good histopathologic regression (grade 2b/3) had a significantly longer time to extracerebral relapse in comparison with the other patients. SUV max,corr(t 2)/SUV max,corr(t 0) values could predict times to extracerebral relapse and identify cutoff points discriminating patient groups of different prognosis with high sensitivity and specificity. Following ROC analysis, cutoff levels between 0.45 and 0.55 discriminated best between patients with and without extracerebral relapse. According to our previous experience, patients with clinical evidence of multilevel N 2 or N 3 disease after neoadjuvant RTx/CTx were not resected but treatment was continued with definitive RTx/CTx (2, 48, 49). PET/CT response was not only able to predict times to extracerebral progression in the whole cohort of patients treated with neoadjuvant chemoradiotherapy but could also identify patients with good and poor prognosis in the subgroup of
patients which were selected for surgery and resected after neoadjuvant therapy.

Other groups have also shown that quantitative SUV changes during treatment have a prognostic effect in palliative chemotherapy of lung cancer (44) or esophageal cancer (39). The cutoff levels for \( \text{SUV}_{\text{max,corr}}(t)/\text{SUV}_{\text{max,corr}}(t_0) \) values were 70% (39) or 80% (44). Whereas such cutoff levels are adequate for patient groups with systemic disease during palliative chemotherapy, in which a progression of the systemic disease component immediately translates into a reduction of the overall survival or very early at about 2 weeks after start of treatment in the time course of neoadjuvant treatment in a curative setting, the data of the present study show that lower cutoff levels of 0.45 to 0.55 from PET/CT later after the third course of neoadjuvant CTx/RTx suited best to discriminate relapsing and nonrelapsing patients. In conclusion, the diagnostic information of serial PET/CT scans during the 3-month induction therapy phase is high enough to ascribe a substantial benefit for clinical patient management to PET/CT. Quantitative evaluation of routine PET/CT scans before and after neoadjuvant chemoradiotherapy allows exclusion of locoregional or distant disease progression and gives important prognostic information. Unsuccessful resections in patients with residual disease in multiple lymph node stations may be avoided because this will not improve prognosis of the patient (50). Residual disease in the mediastinum might then be targeted by a high-dose conformal radiotherapy boost. Further prospective evaluation of the effect of FDG-PET/CT on prognostic stratification and early management decisions in the group of patients with locally advanced non–small-cell lung cancer is warranted.

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Value of $^{18}$F-Fluoro-2-Deoxy-d-Glucose-Positron Emission Tomography/Computed Tomography in Non–Small-Cell Lung Cancer for Prediction of Pathologic Response and Times to Relapse after Neoadjuvant Chemoradiotherapy

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