

Is ^{18}F -FDG-PET/CT a Valid Non-Invasive Predictor for Regression Grade after Neoadjuvant Treatment in Patients with NSCLC Stage III?

Natalie Desiree Klass¹, Richard P. Baum², Michael Schmuecking^{1,2}, Norbert Presselt³, Klaus-Michael Mueller⁴, Thomas G. Wendt⁵, Reiner Bonnet^{6,7}

¹Department of Radiation-Oncology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

²Department of Nuclear Medicine, Zentralklinik Bad Berka, Bad Berka, Germany

³Department of Thoracic Surgery, Zentralklinik Bad Berka, Bad Berka, Germany

⁴Institute of Pathology, University of Münster, Münster, Germany

⁵Department of Radiation Oncology, University of Jena, Jena, Germany

⁶Department of Pneumology, Zentralklinik Bad Berka, Bad Berka, Germany

⁷LUCAS-MD Study Group, Germany

Email: desiree.klass@insel.ch

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Abstract

Introduction: CT alone cannot provide sufficient information referring to response after neoadjuvant therapy in a timely manner. To evaluate the role of ^{18}F -FDG-PET after neoadjuvant chemoradiation as a valid, non-invasive predictor for early therapy response and its effect on survival as compared to histopathologic tumor response, data of 32 of 210 randomized patients with NSCLC stage IIIA/IIIB, who were treated in a prospective randomized controlled multicenter trial (LUCAS-MD), were re-evaluated. **Material and Methods:** For 32 patients with NSCLC stage IIIA (44%) IIIB (56%) neoadjuvant treatment consisted of two to three cycles of chemotherapy (225 mg/m² paclitaxel and carboplatin AUC 6 d1q22) and concomitant chemoradiation (50 mg/m² paclitaxel and carboplatin AUC 2 d1, d8, d15; 1.5 Gy b.i.d. up to 45 Gy). Documentation of involved lymph node stations as detected by ^{18}F -FDG-PET/CT and lymph node sampling during surgery according to the IASLC lymph node mapping (2009). Evaluation of histological regression grade (RG) according to Junker *et al.* (2001) and correlation with ^{18}F -FDG-PET/CT for primary tumor and each lymph node station. Calculation of disease free survival using Kaplan-Meier estimates and log rank tests. **Results:** Actuarial tumor specific survival for the 32 patients with concomitant chemoradiation plus chemotherapy: complete vs. incomplete metabolic remission prior to surgery after 60 months:

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40% vs. 24% ($p = 0.018$). RG III/Ib (no/less than 10% of vital tumor cells) vs. RG IIa/I (more than 10% vital tumor cells) after 60 months: 46% vs. 15% ($p = 0.006$). 18/32 (56%) patients had RG III/Ib, 8/32 (25%) patients had regression grade III. 1/8 pts. with RG III were in the ^{18}F -FDG-PET/CT false positive, 10 pts. with RG IIb (*i.e.* all pts. with RG IIb) were in the ^{18}F -FDG-PET/CT false negative. One patient with RG IIa was in the ^{18}F -FDG-PET/CT false negative. Hence, the cut-off level in detecting vital tumor cells by ^{18}F -FDG-PET/CT after neoadjuvant chemoradiation for NSCLC is about 10%. Conclusion: Histological regression grading correlates well with metabolic remission as detected by ^{18}F -FDG-PET. Thus, ^{18}F -FDG-PET precedes CT in measuring the tumor response and may predict long-term therapeutic outcome in patients with stage III NSCLC. Invasive staging procedures may be avoided and patients who will not profit from resection due to insufficient downstaging after neoadjuvant treatment will be easily detected by using ^{18}F -FDG-PET as standard imaging in workup and evaluation of treatment response.

Keywords

NSCLC, ^{18}F -FDG-PET, Neoadjuvant Treatment, Non-Invasive Predictor

1. Introduction

Lung cancer is still one of the most frequent and lethal solid tumors in most countries. 80% of all lung cancers are represented by non-small-cell lung cancer. About one third of those patients present with locally advanced disease at diagnosis (stage IIIA and B). In this heterogeneous group the average 5-year-survival rate has been in the range of 15% - 27% at best [1]-[5]. A very important factor for survival is a good local and regional, especially mediastinal control [1] [2] [4] [5]. At diagnosis, 50% of all cases show lymph node metastases. In over 70% of the first hilar lymph nodes followed by mediastinal and then supraclavicular lymph nodes are involved. This fact also depends on the histology of the tumor: 33% of squamous cell tumors, 54% of adenocarcinomas and 57% of non-differentiated tumors present lymph node metastases at diagnosis. At the same time even very small tumors tend to metastasize quite early so that lung cancer is a systemic disease.

The initial tumor extension is decisive for further therapy stratification. Although lots of molecular and immunological factors such as RAS mutation, p53 and EML4-ALK were found, none of them play a role in therapy management according to multimodality treatment vs. definitive chemoradiation in NSCLC [6]-[8].

In these cases positron emission tomography (PET) offers the possibility to display cellular tumor metabolism by using ^{18}F -FDG (2-[^{18}F]-fluoro-2-deoxy-D-glucose) with high sensitivity and specificity. In contrast to computed tomography (CT) the stage of disease can be determined in a more exact way which leads to an optimized therapy management for the patients [9]-[14].

1.1. Goals of Therapy

50% - 80% of all patients with stage IIIA or IIIB disease die because of systemic relapse, only 20% - 37% of all patients because of local relapse. These data show that surgery, radiotherapy, antibody therapy and chemotherapy lead to a sufficient local control in locally advanced lung cancer. However, to improve overall survival, not only loco-regional control but also systemic tumor control has to be optimized. The sequence of systemic and loco-regional therapy is still topic of ongoing discussions, but there is a trend that concurrent chemoradiation might be superior to sequential treatment [10] [15]-[18].

In cases of resectable NSCLC stage III the aim of induction therapy is to reduce initial tumor volume and thereby to improve resectability. This procedure is also called *downstaging*. An optimal downstaging allows a R0 resection in primary tumor and initially positive lymph nodes. Second aim is systemic tumor control, achieved by systemic therapy. Some data, based on a small number of patients, hypothesize that complete remission in mediastinal lymph node metastases is predictive for systemic tumor control [4] [19].

1.2. Improvement of Diagnostic Imaging Is Inevitable

At this point problems concerning diagnostic imaging become clear: data prove that the correct evaluation of

initial tumor extent and tumor response to chemotherapy in cases of NSCLC by using CT alone is imprecise [14] [20] [21]. Furthermore, there is no correlation detectable between histological tumor regression and therapy response, but histological response after induction therapy is a very important predictor for systemic tumor control [22]–[29]. To evaluate the morphologic regression grading the classification according to Junker *et al.* is usually used [25]–[27].

In our study we examined the following questions:

- Is there a correlation between morphological regression and metabolic remission?
- Is there an improved overall survival (OS) stratified by regression grading and molecular remission as detected by ^{18}F -FDG-PET?
- Can ^{18}F -FDG-PET be used as a valid non-invasive predictor according to local and systemic control?

2. Material and Methods

Patients with histologically confirmed stage III NSCLC (American Joint Committee on Cancer [AJCC] sixth edition) out of a randomized multicenter phase III trial (LUCAS-MD) were included in this retrospective analysis. Details of baseline characteristics, treatment, and follow-up findings were entered prospectively into a database, managed by Alcedis GmbH (Giessen, Germany). All patients provided written informed consent to participate in this study, and the Institutional Review Board as well as the local ethics committee approved the study. Data confidentiality was preserved according to the Revised Helsinki Declaration of Bioethics in 2008.

2.1. Inclusion Criteria

So far, we retrospectively re-evaluated data of 32 of 210 randomized patients with NSCLC stage IIIA/IIIB who were treated in a prospective randomized controlled multicenter trial (LUCAS-MD) between 2000 and 2005. Follow-up time was 60 months.

Patients with a performance status ECOG 0–1, age between 18–70, functional resectability, and adequate hematologic, renal and hepatic function were included.

After diagnostic workup by CT and/or MRI, randomization to one of the two arms was done (Figure 1). To evaluate the significance of PET in therapy of NSCLC, ^{18}F -FDG-PET was done for every patient after randomization prior to treatment.

2.2. Neoadjuvant Treatment

All patients received the same neoadjuvant treatment. The only difference was the point in time of concurrent chemoradiation therapy (early vs. late concurrent chemoradiation therapy). Neoadjuvant treatment consisted of 2–3 cycles of paclitaxel (225 mg/m² d1q22) and Carboplatin (AUC = 6, d1q22) followed by concurrent chemoradiation (radiotherapy according to ICRU 62: total dose 45 Gy, single dose 1.5 Gy b.i.d., concomitant 50 mg/m² paclitaxel and carboplatin AUC = 2 d1, d8, d15). For radiation treatment planning the target volume delineation was based on ^{18}F -FDG-PET. If available $^{99\text{m}}\text{Tc}$ -MAA SPECT/CT was used to optimize radiation treatment plans, referring to individual lung function [30].

2.3. CT and ^{18}F -FDG-PET

Within 5 days all patients received CT and ^{18}F -FDG-PET in tidal breathing position. The positioning was the same as during radiotherapy. Fusion of PET and CT was done by a fusion software, installed on a HERMES computer (Nuclear diagnostics, Sweden). It was mandatory to fuse the images to ensure the detailed localization of PET positive lymph nodes according to IASLC recommendations. Alternatively ^{18}F -FDG-PET/CT was done: these patients were examined on a dual-modality PET/CT tomograph (biograph duo, Siemens Medical Solutions). The CT component of the biograph BGO duo corresponds to a Somatom Emotion Duo (Siemens Medical Solutions), a 2-row spiral CT system with a maximum continuous scan time of 100 s and a maximum rotation speed of 75 rpm. The PET components of the combined PET/CT tomograph are based on a full-ring lutetium orthosilicate (LSO) PET system. PET scan emission images were recorded for 4 min per bed position; for non-uniform attenuation correction, CT images were used (acquisition parameters: 140 kV, 90 mA, 0.8 s, tube rotation, 5 mm thickness). PET images were acquired from the skull base to the middle part of the thigh. The CT transmission images were used for attenuation correction of the PET emission data. After scatter and attenuation

correction, PET emission data were reconstructed using an attenuation-weighted ordered subsets expectation maximization approach with 2 iterations and 8 subsets on 128×128 matrices and with a 5-mm Gaussian post-reconstruction filtering.

Just before surgery a second ^{18}F -FDG-PET was also mandatory (**Figure 1**). During surgery lymph node sampling according to IASLC recommendations was done, to correlate histology with the results found in CT and ^{18}F -FDG-PET [31] [32].

2.4. Histology

The surgical specimens were morphologically analyzed regarding to therapy-induced changes of the tumor tissue. Initially, the formalin-fixed resection samples were inspected macroscopically. From the primary lesion, regions with likely vital tumor tissue or former, now regressively altered, tumor tissue, as well as all resected mediastinal lymph nodes were embedded in paraffin. Hematoxylin-eosin and van Gieson stains were available for analysis of the specimens. In order to determine the degree of tumor regression, the type and extent of the vital tumor tissue, and the degree of tumor necrosis were taken into account. These findings were classified according to the following regression grading according to Junkers *et al.* (**Table 1**) [25]–[27].

2.5. Statistics

The primary objective of this study was to assess overall survival (OS) stratified by regression grading and molecular remission as detected by PET. All time-to-event end points were calculated from the start of induction chemotherapy. Survival rates were calculated using the Kaplan-Meier product limit methodology. The influence of response to induction chemotherapy on OS was compared using a two-sided log-rank test (Mantel 1966, Breslow 1975, Kaplan Meier 1958). A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics included

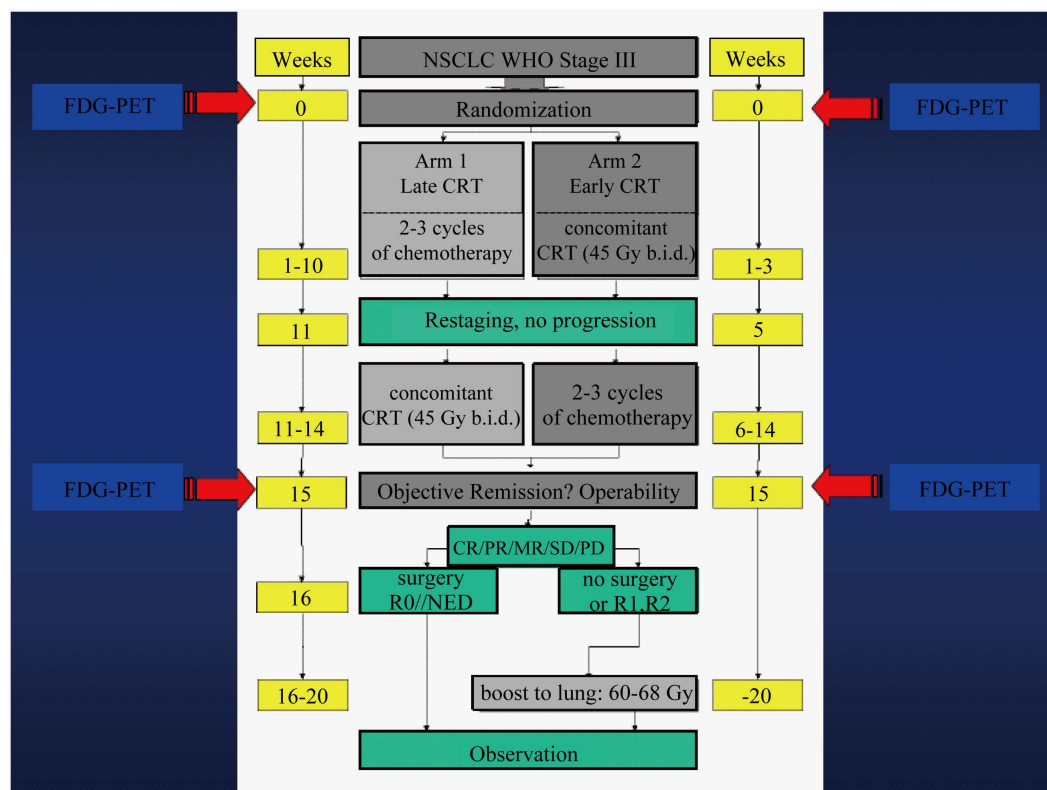


Figure 1. Trial design: mandatory ^{18}F -FDG-PET after randomization and in 15th week after end of neo-adjuvant therapy, correlation of ^{18}F -FDG-PET results with regression grading in surgical specimens (lymph node sampling according to IASLC recommendations).

Table 1. Grading of tumor regression according to Junker *et al.*

Grading of tumor regression in non-small cell lung cancer, Junker <i>et al.</i> , 2001	
Grading I	No tumor regression or only spontaneous tumor regression in the sections of the primary lesion and mediastinal lymph nodes
Grading IIa	Morphologic evidence of therapy-induced tumor regression with at least 10% residual tumor cells in the sections of the primary lesion and/or mediastinal lymph nodes presenting more than focal microscopic disease
Grading IIb	<10% residual tumor cells in the sections of the primary lesion and/or mediastinal lymph nodes presenting focal microscopic disease
Grading III	Complete tumor regression with no evidence of vital tumor tissue in the section of the primary lesion and mediastinal lymph nodes

absolute and relative frequencies for categorical variables, and the median and range for quantitative variables. Additionally, due to the small number of patients, the statistical power was estimated by Gail and Gart [33] [34].

3. Results

18/32 (56%) patients had a regression grading (RG) III or IIb. 8/32 (25%) patients had RG III. 1 of those 8 patients with RG III was false positive in ^{18}F -FDG-PET/CT due to inflammation which was histologically confirmed. All patients (10) with RG IIb (<10% residual tumor cells) were false negative in ^{18}F -FDG-PET/CT. One patient with RG IIa (15% of vital tumor cells) was false negative in ^{18}F -FDG-PET/CT: Hence, the cut-off level in detecting vital tumor cells by ^{18}F -FDG-PET/CT after neoadjuvant chemoradiation for NSCLC is about 10%.

Actuarial tumor specific survival, stratified to RG IIb and III vs. RG I and IIa was significantly increased after 60 months: 46% vs. 15 %, respectively ($p = 0.006$) (Figure 2). Patients who showed a complete metabolic remission lived significantly longer than those with no remission. Survival time after 60 months was 40% vs. 24%, respectively ($p = 0.018$) (Figure 3). Tumor specific survival according to RG in lymph nodes only was far better for patients with RG IIb or III (41% after 60 months) vs. those with RG I or IIa (0% after 18 months): $p = < 0.001$ (Figure 4). In lack of larger numbers of patients the statistical power is 70%.

Figure 5 shows an example of a patient with no metabolic response after neoadjuvant treatment (no change, NC according to WHO criteria). Initial imaging detected a cT4 cN2-3 cM0 tumor, according to ^{18}F -FDG-PET/CT. After neoadjuvant treatment a RG I was found in surgical specimen, ypT2a ypN3, with concordant results for lymph node metabolism and over-estimation of the T-status in the post-therapeutic ^{18}F -FDG-PET/CT: cT4 cN3 cM0.

Figure 6 shows an example of a patient with complete metabolic response. Pre-therapeutic ^{18}F -FDG-PET/CT detected a NSCLC cT3-4 cN3 cM0. After neoadjuvant chemoradiation complete metabolic remission was seen in ^{18}F -FDG-PET. CT still showed primary tumor with a diameter of 2.3 cm. Exemplarily this case demonstrates that ^{18}F -FDG-PET may be superior to CT according to therapy response. Histology proved complete regression, RG III: ypT0 ypN0.

Examples for histological regression grading can be seen in Figure 7.

4. Discussion

Moon *et al.* showed very nicely in 52 patients with stage IV NSCLC that metabolic response evaluated by ^{18}F -FDG-PET/CT has a potential in identifying a subgroup of patients who may benefit from immediate maintenance therapy after first-line chemotherapy. The parameter used in this study for risk-stratification was a decrease in total lesion glycolysis (TLG) with a cut-off value of <50% [35]. Also, Kim *et al.* emphasized the role of ^{18}F -FDG-PET/CT for prognostic stratification in 19 patients with advanced NSCLC (stage III and IV) using DeltaSUV (max) to retrospectively identify non-responders to chemotherapy [36]. The strong correlation between histological regression grading and overall survival was shown by the German Lung Cancer Cooperative Group (GLCCG), proving that patients showing regression grading IIb or III had significantly better progression free survival and overall survival [37].

The aim of our study was to correlate ^{18}F -FDG-PET/CT with histological regression as described by Junker *et al.* [25]. Univariate analysis showed significantly improved survival for patients with complete metabolic response in ^{18}F -FDG-PET or regression grade IIb/III in specimen.

The evaluation of response to treatment in CT is insecure and not contemporary, as shown in several studies.

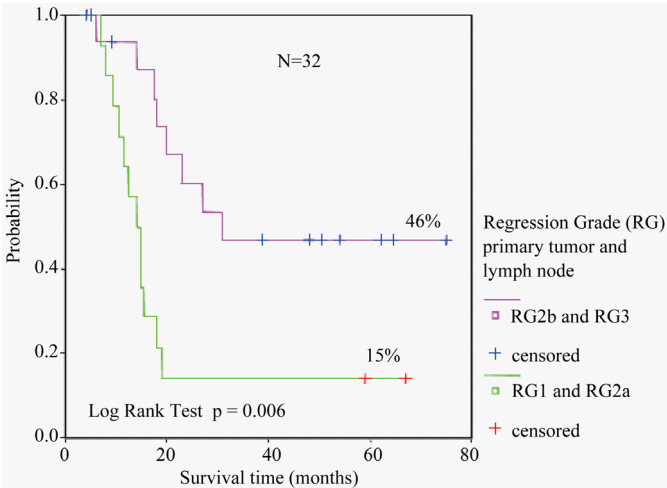


Figure 2. Tumor specific survival according to regression grading of primary tumor and lymph nodes.

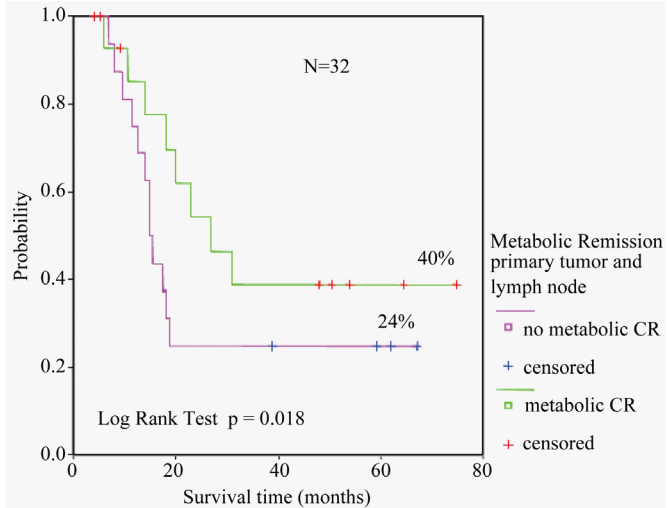


Figure 3. Tumor specific survival according to metabolic response.

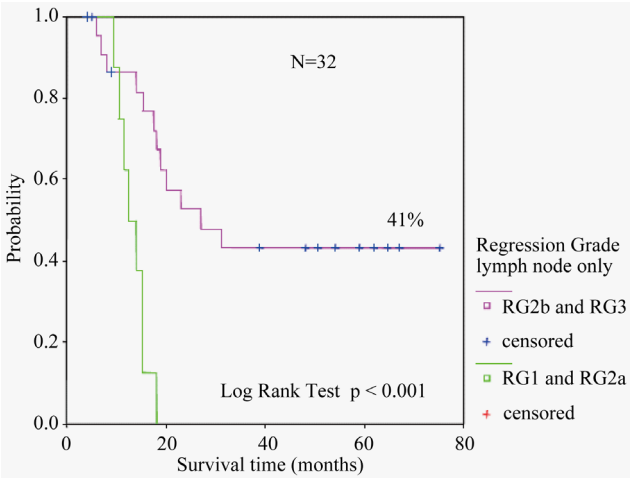


Figure 4. Tumor specific survival according to metabolic response.

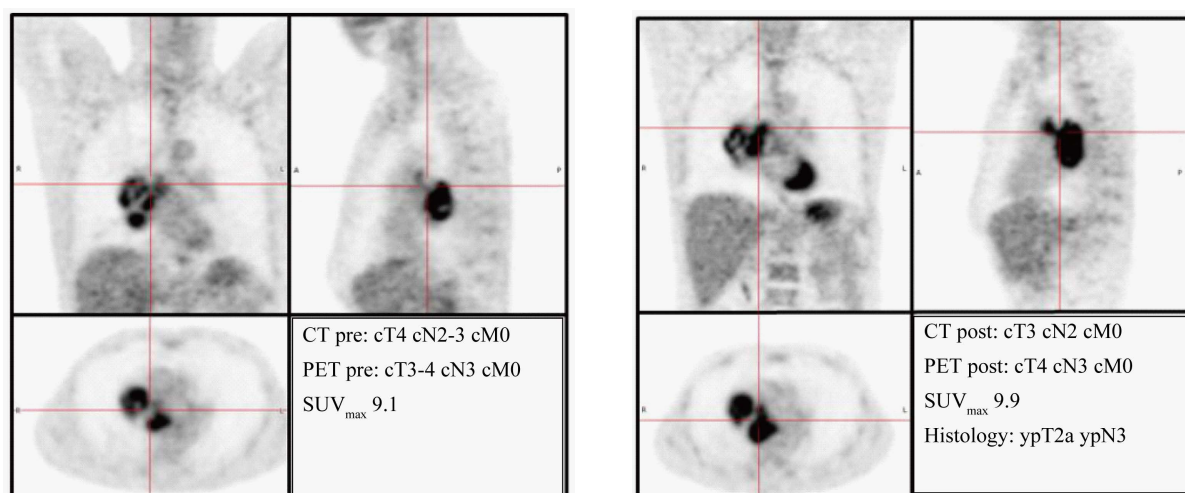


Figure 5. Example for no metabolic response after neoadjuvant treatment.

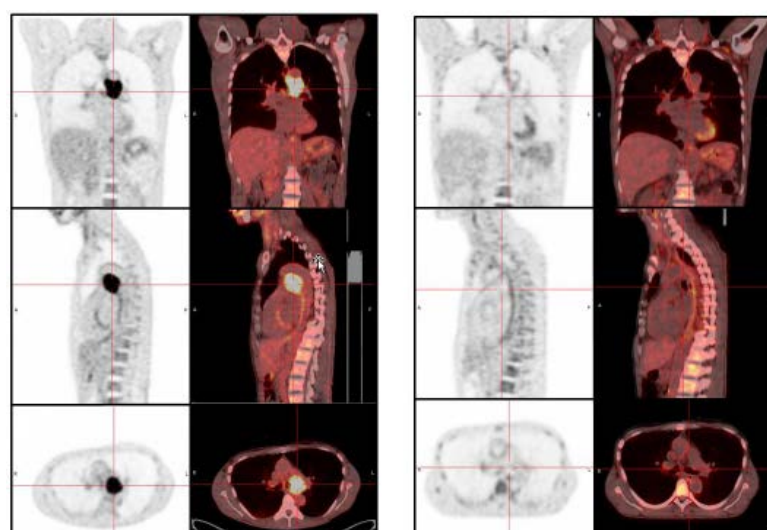


Figure 6. Example for metabolic response. Pre-therapeutic ^{18}F -FDG-PET/CT, cT3-4 cN3 cM0, SUV_{max} 23.5 in primary tumor and SUV_{max} 10.2 in lymph node metastasis 4L. After neoadjuvant treatment complete metabolic remission, physiologically normal SUV_{max} 1.5 - 2.0 in mediastinum. In CT primary tumor showed still a diameter of 2.3 cm. Histology: ypT0 ypN0.

Thus, CT alone as a morphologic imaging is an improper non-invasive predictor to loco-regional, but also systemic tumor control [22]-[24] [29].

Nevertheless, ^{18}F -FDG-PET/CT has its limitations. There are false positive and false negative findings which should be discussed critically.

False positive findings in ^{18}F -FDG-PET according to primary tumor are mostly due to inflammation or side effects by radiotherapy which could be proved by histology, as shown not only by Poettgen *et al.* but also in our data [38] [39]. Patients with false positive findings in mediastinum represent a special problem, if ^{18}F -FDG-PET should play an important role as non-invasive predictor to loco-regional and systemic tumor control and basis for future therapy decisions. The PET based strategy, not to operate patients remaining positive in ^{18}F -FDG-PET after neoadjuvant treatment, because of lacking mediastinal remission and high risk of dying due to systemic tumor progression means that those patients with false positive findings in PET may be deprived of a curative option.

Otherwise it is going to be discussed whether patients with complete metabolic response in primary tumor and

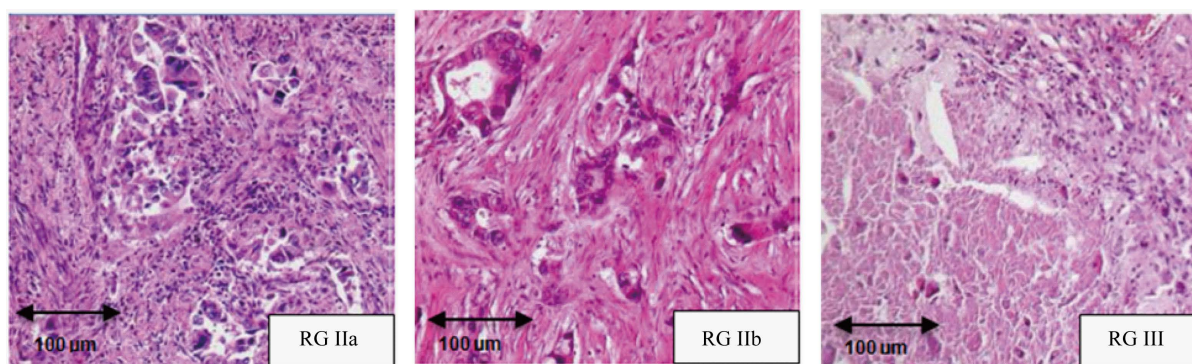


Figure 7. (a) 4 months after neoadjuvant chemoradiation of an adenocarcinoma. Regression grading IIa: multiple pleomorphic tumor areas and inflammation induced desmoplastic reaction; (b) Regression grading IIb in adenocarcinoma after neoadjuvant chemoradiation with less than 10% of vital tumor cells; (c) Regression grading III with complete tumor necrosis after neoadjuvant chemoradiation.

in initially positive lymph nodes will benefit from additional resection according to overall survival. In this context the false negative findings in PET may represent a problem. In our patient population especially patients with regression grade IIb are concerned. In our study we summed up regression grade IIb and III for correlation with complete metabolic remission. Hence, false negative means a detection of <10% of vital tumor cells in histology while in ^{18}F -FDG-PET a complete metabolic remission was found. In all of our patients showing a RG IIb in primary tumor (vital tumor cells <10%), ^{18}F -FDG-PET was negative. This is correlative to data by Fischer *et al.* who showed a detection limit of PET in the magnitude of 10^5 to 10^6 malignant cells [40] [41]. Hence, false negative results may occur if there is a low vital tumor cell density leading to very low PET signals in the voxels [42]. According to data by Fischer *et al.* false negative results are also possible due to small or well-differentiated malignancies, such as bronchioalveolar carcinoma or carcinoid [40] [41]. For a subgroup analysis the current number of patients is far too low. A correlation of patients with identical histology and grading is needed for that. Even if ^{18}F -FDG-PET shows complete metabolic remission, <10% of tumor cells found in specimen does not mean complete response. Those cells might have an accelerated repopulation, leading to a loco-regional recurrence in quite a short time if not treated. Thus, discordant findings in ^{18}F -FDG-PET and histology can be explained.

There is a growing body of evidence that in future newer techniques like deep inspiration breath hold acquisition or high resolution PET/CT with time-of-flight (TOF) technology may lead to higher sensitivity in detection of smaller lesions or lesions with low density of tumor cells [43]–[45].

Similar results according to correlation of ^{18}F -FDG-PET with histology were found in patients with induction chemotherapy alone. Betticher *et al.* achieved by using docetaxel-cisplatin as neoadjuvant chemotherapy a pathologic complete remission rate in 15% of their patients, comparable with data by Martini *et al.* who used neoadjuvant mitomycin, vindesine, vinblastine and cisplatin leading as well to a complete remission rate of 15% [46] [47]. In contrast, our complete remission rate was 28%. This shows a gap of >10% and might indicate a positive impact for an intensified neoadjuvant protocol consisting of 2–3 cycles of chemotherapy and concurrent chemoradiation as standard neoadjuvant treatment. Assuming a number of 540 patients the intensified treatment regimen consisting of concomitant chemoradiation plus chemotherapy will be statistically superior to the other neoadjuvant treatment regimens.

Our preliminary data underline that a second ^{18}F -FDG-PET/CT may also play an important role as a non-invasive, post-therapeutic intervention after chemoradiation, for an optimized therapeutic management as published by Hellwig *et al.* [48].

The final evaluation of regression grading in over 210 patients of the LUCAS-MD trial and in 232 patients included in the SAKK 16/00 trial (all together 442 patients) will show if an intensified neoadjuvant protocol is justified. However, a prospective randomized trial is needed to evaluate the hypothesis that an intensified approach is superior to chemotherapy alone or sequential neoadjuvant chemoradiation.

5. Conclusion

Histological regression grading after neoadjuvant treatment correlates well with metabolic remission as detected

by ^{18}F -FDG-PET, especially according to lymph nodes. Thus, ^{18}F -FDG-PET precedes CT in measuring the tumor response and may predict long-term therapeutic outcome in patients with stage III NSCLC. By correlating a high number of patient's histology with ^{18}F -FDG-PET, it will be possible to define a realistic cut-off level for detecting vital tumor cells, especially for the newer PET/CT systems. Our preliminary data suggest that the cut-off-level of vital tumor cells is about 10%. This detection threshold of ^{18}F -FDG-PET may have an important influence on molecular radiotherapy planning and target volume definition.

We could also prove that patients with metabolic complete remission (CR) or morphological regression grading IIb/III showed an improved overall survival. ^{18}F -FDG-PET can be used as a quality control after neoadjuvant treatment, and may change the initial treatment schedule. Invasive staging procedures could be avoided, and patients, who will not profit from resection due to insufficient downstaging, could be easily detected.

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