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Hot Topic

Therapeutic implications of molecular imaging with PET in the combined modality treatment of lung cancer

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ABSTRACT

Molecular imaging with PET, and certainly integrated PET-CT, combining functional and anatomical imaging, has many potential advantages over anatomical imaging alone in the combined modality treatment of lung cancer. The aim of the current article is to review the available evidence regarding PET with FDG and other tracers in the combined modality treatment of locally advanced lung cancer. The following topics are addressed: tumor volume definition, outcome prediction and the added value of PET after therapy, and finally its clinical implications and future perspectives.

The additional value of FDG-PET in defining the primary tumor volume has been established, mainly in regions with atelectasis or post-treatment effects. Selective nodal irradiation (SNI) of FDG-PET positive nodal stations is the preferred treatment in NSCLC, being safe and leading to decreased normal tissue exposure, providing opportunities for dose escalation. First results in SCLC show similar results. FDG-uptake on the pre-treatment PET scan is of prognostic value. Data on the value of pre-treatment FDG-uptake to predict response to combined modality treatment are conflicting, but the limited data regarding early metabolic response during treatment do show predictive value. The FDG response after radical treatment is of prognostic significance. FDG-PET in the follow-up has potential benefit in NSCLC, while data in SCLC are lacking. Radiotherapy boosting of radioresistant areas identified with FDG-PET is subject of current research.

Tracers other than ^{18}FDG are promising for treatment response assessment and the visualization of intratumor heterogeneity, but more research is needed before they can be clinically implemented.

Background

Lung cancer accounts for 219,000 new cancer cases and 159,000 deaths a year in the United States, representing 15% of cancer cases and 28% of cancer deaths in 2009.[1] As patients often present with primary irresectable disease, the majority of patients with localized disease is currently treated with multimodality treatment using a combination of surgery, chemotherapy (CTx), radiotherapy (RT) and targeted agents. Although survival has significantly improved with combined modality treatment, still, about one third of locally advanced lung cancer patients experience local failure as their first site of relapse.[2] Furthermore, these combined treatment strategies are often associated with dose limiting toxicity, prohibiting further intensification of treatment. This could potentially be overcome by targeted antitumor therapy with increasingly conformal RT techniques and targeted agents. Furthermore, progress is made in strategies directed at individualization and early adaptation of therapy dependent on the treatment response, which may lead to optimization of the therapeutic ratio in each individual. After completion of curative treatment, improvement of outcome could be accomplished by an early detection of local progression, increasing the possibility for those patients to be offered salvage therapy.

With the introduction of these techniques, however, accurate definition of the tumor volume to be treated becomes increasingly important. This emphasizes the need for imaging techniques enabling accurate definition of the presence and extent of tumor before, during and after curative treatment in cancers of the respiratory tract. While CT and MRI are the most accurate imaging modalities with respect to anatomical information, they often lack the potential to distinguish between vital tumor and non-malignant tissue. Here, molecular imaging with positron emission tomography (PET), providing metabolic information, has additional

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value. Different radiopharmaceuticals have been evaluated for the imaging of malignant tumors, of which ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is by far most commonly used. FDG-PET scanning utilizes the difference in accumulation of FDG between normal and cancerous tissues, based on an enhanced glucose metabolism in cancer cells. Other PET tracers, visualizing specific molecular pathways in tumors such as proliferation (e.g. ^{11}C-methionine, ^{11}C-choline, ^{18}F-fluorothymidine) hypoxia (e.g. ^{18}F-FMISO) or expression of certain receptors (Her2Neu, EGFR) are increasingly being used in the evaluation of malignancies.

Thus, metabolic imaging with PET, and certainly integrated PET-CT, combining functional and anatomical imaging, has many potential advantages over anatomical imaging alone in the combined modality treatment of lung cancer. PET using FDG is at present most widely applied in the clinical practice of non-small cell lung cancer (NSCLC). Its use in small cell lung cancer (SCLC) is rapidly emerging.

The aim of the current article is to review the available evidence on the use of PET in the combined modality treatment of locally advanced lung cancer. For NSCLC and SCLC separately, the role of PET imaging will be addressed with respect to the following topics:

1. Definition of the tumor volume to be treated, both with respect to the primary tumor and the locoregional lymph nodes
2. Outcome prediction on basis of PET before or early after the start of treatment, and the added value of PET after therapy

With regard to both these topics, the clinical implications of the use of PET are addressed, and future perspectives are provided.

Because ^{18}F-FDG is by far most commonly applied in clinical practice, the majority of evidence comes from this tracer. Therefore, where "PET" is used in this article, this refers to "^{18}F-FDG-PET", unless otherwise stated. Wherever other tracers have shown additional value, or are regarded as promising in the near future, they will be discussed.

Search strategy

A comprehensive literature search was conducted using the "Pubmed" database. Included search terms were: "Non small cell lung cancer", "Small cell lung cancer", "NSCLC", "SCLC", "Target volume definition", "Delineation", "Gross tumor volume (GTV)", "Clinical target volume (CTV)", "Tumor heterogeneity", "Selective nodal irradiation", "Prognostic value", "Outcome prediction", "Follow-up", "Combined modality treatment", "Chemotherapy", "Radiotherapy" or "Radiation" in combination with "PET", "Positron emission tomography" or "Molecular imaging".

Reference lists of relevant articles were searched for further studies.

Only publications in the English language and published online before February 1, 2010 were included.

Non-small-cell lung cancer (NSCLC)

NSCLC represents more than 80% of lung cancer cases.[3] Combined chemoradiotherapy is the standard treatment for locally advanced (stage III), inoperable NSCLC.[4] The added value of PET to select patients for combined modality treatment has been studied extensively[5–7], and it was shown that PET staging results in superior outcome due to stage migration: up to 30% of stage III patients are diagnosed with distant metastases.[8,9] This clearly affects patient outcome as it withholds toxic therapy in individuals who will not benefit from it.

Below, we will discuss the role of PET in the RT planning and evaluation of combined chemoradiotherapy for stage III NSCLC.

Definition of the tumor volume to be treated

Primary tumor

Although FDG-PET has a high sensitivity for the detection of the primary tumor, an important drawback is its lack of anatomic detail, which limits its ability to define the exact tumor boundaries. The spatial resolution of current PET scanners is limited to 4–6 mm[10], which is far lower than that of modern CT scanners, with a resolution down to 1 mm. There are cases, however, where anatomic imaging modalities such as CT are compromised in their ability to define the exact tumor border, such as in patients with atelectasis or tumors near the thoracic wall.[11] Multiple studies have shown a large interobserver variation in delineation of the tumor on CT.[11,12] This interobserver variation is significantly diminished by using the information of a FDG-PET scan, co-registered with CT.[13–16] Overall, volumes delineated using PET-CT are smaller.[14] Differences between PET and CT were mainly found in the regions with atelectasis.[14,17,18]

Various quantitative methods have been developed for automatic tumor delineation using PET instead of visual interpretation of the PET signal. The most straightforward method uses an absolute threshold of the standardized uptake value (SUV). The SUV_{max} threshold of 2.5 is often used for this purpose.[19] An absolute threshold should be used with caution, however, as the SUV is associated with considerable variety due to both technical and biological factors.[20] An alternative method is the use of a relative threshold, e.g. a certain percentage of the SUV_{max}. Recently, more complex methods have been developed, including the application of an individualized threshold based on the source-to-background ratio (SBR) or the watershed clustering method.[21–23] An example of the difference in interobserver variation between manual and autocontour based delineation is provided in Fig. 1. Nestle et al. compared absolute ($SUV_{max} \geqslant 2.5$), relative (40% SUV_{max}) and individual (SBR algorithm) quantitative methods and a visual interpretation method with CT-volumes.[24] There were large differences in the resulting volumes, particularly in patients with a heterogeneous pattern of FDG-uptake.

Although autocontour based delineation methods have thus proven their utility in reducing interobserver variability, all quantitative methods harbor the risk of including metabolic active but not cancerous tissue in the GTV. Therefore, it has been suggested that those methods should be used complementary to visual interpretation, and not as a substitute for it.[25,26]

Ideally, validation of the delineated tumor volume should be obtained by correlating it with the tumor volume at pathologic examination, being the gold standard. The currently available data are based on two-dimensional correlations in early stage disease.[27–29] With the use of a relative threshold, a better correlation was found for CT than for PET (correlation coefficient 0.87 vs. 0.77).[27] Yu et al. found the best correlation with integrated PET-CT based on an absolute threshold ($SUV_{max} \geqslant 2.5$).[28] A correlation coefficient of 0.90 was found between the maximal tumor diameter obtained with SBR-based autodelineation and pathology.[29] Promising attempts are made to develop a three-dimensional model, but results in large patient cohorts are to be awaited.[30–32]

The methods described above are aimed at an accurate definition of the gross tumor volume (GTV) in order to ensure that this region is adequately covered by the RT treatment fields. Characteristics associated with radioresistance, such as hypoxia, cell density and proliferation, however, are known to be heterogeneous across the tumor.[33–35] FDG-PET scans may allow the identification of therapy-resistant areas within the tumor. It would be logical to selectively boost the radioresistant areas, whilst decreasing the dose to the less resistant zones, resulting in higher tumor control with similar side effects.[36–39] It has been demonstrated that regions with high FDG uptake prior to radiotherapy correspond well with the location of recurrent/persistent tumor after sequential

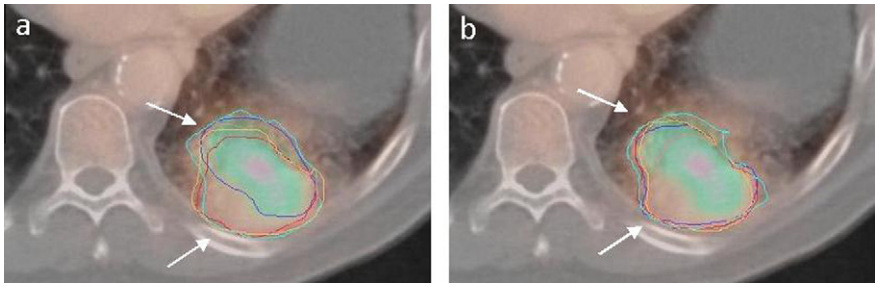

Fig. 1. Example of a manual (a) and autocontour based (b) delineation of the primary tumor For autocontouring, the SBR based method was used. Arrows indicate changes in interobserver variation in delineation between the two methods. Reprinted from: van Baardwijk A, Bosmans G, Boersma L, et al. PET-CT-based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumor and involved nodal volumes. *Int J Radiat Oncol Biol Phys* 2007;68:771–778. Copyright 2010, with permission from Elsevier.

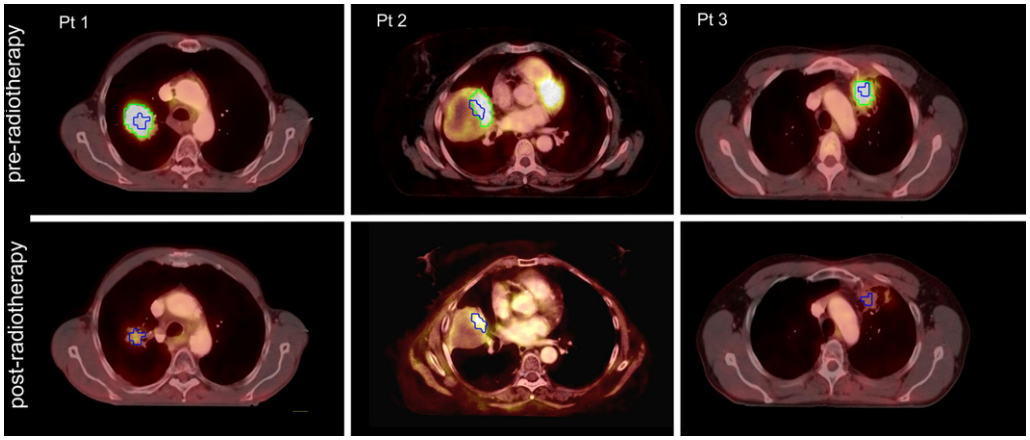

Fig. 2. Correlation between pre-treatment high FDG-uptake areas and location of residual disease. Representative FDG-PET-CT images of three patients pre- and post-radiotherapy. The light gray lines indicate the 50% SUV_{max} FDG high-uptake area pre-radiotherapy. The dark lines indicate the residual metabolic-active areas post-radiotherapy, also transposed on the pre-radiotherapy scan. Visual evaluation shows a large correspondence between the residual areas post-radiotherapy with the high FDG-uptake areas pre-radiotherapy. Reprinted from: Aerts HJ, van Baardwijk AA, Petit SF, et al. Identification of residual metabolic-active areas within individual NSCLC tumors using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. *Radiother Oncol* 2009;91:386–392. Copyright 2010, with permission from Elsevier.

chemo-radiotherapy or RT alone (Fig. 2).[40,41] Furthermore, those regions remain stable during a course of RT (Fig. 3).[42] Thus, selective boosting of areas of assumed radioresistance identified with FDG-PET before the start of RT appears to have a good rationale. It remains important, however, to consider that other biologic characteristics within the GTV, such as inflammation, may be associated with increased FDG-uptake as well, that are not directly related to increased radioresistance.[43]Therefore, further research in this field is strongly encouraged.

The additional value of FDG-PET scanning in defining the primary tumor volume is thus beyond doubt. However, the drawbacks of FDG-PET should be kept in mind. Due to the poor resolution, blurring does occur, particularly at the tumor edges.[20] Those blurring effects at the tumor boundary are even more pronounced by motion artefacts. Although the long acquisition time of PET is disadvantageous with respect to defining an absolute tumor edge and quantitating metabolic activity, it may have additional value in determining the extent of tumor motion. The acquisition time of several minutes results in a tumor volume incorporating the averaged position of the tumor over multiple respiratory and cardiac cycles. In a phantom study, PET-based treatment volumes resulted in an adequate coverage of the tumor, while CT-based volumes harbored the risk of a geographical miss.[44] Respiratory gating or 4D imaging techniques allow the incorporation of the extent of tumor movement, while optimizing image quality and quantitation as the blurring effect is reduced.[45] Those techniques are presently being evaluated in clinical studies.[45,46]

Microscopic disease extension

The poor spatial resolution of PET precludes a direct evaluation of the presence and extent of microscopic disease around the macroscopic tumor border. Definition of the area of potential microscopic spread in patients treated with chemoradiotherapy is important as this region should be covered in the radiation field. The only way to quantitate microscopic spread beyond the tumor border visible on imaging is by correlating imaging with the findings at pathologic examination. Until now, this correlation has only been performed between CT and pathology.[47–49] Furthermore, no correction was applied for deformation of the lung lobe after surgery. Methods for the correlation of both PET and CT with pathology, which do take into account deformation, are under development.[30,31] First results indicate an average microscopic spread in vivo of 9 mm[31], suggesting that currently applied margins might be too small to cover microscopic disease.

Lymph nodes

Accurate identification of nodal metastases has become of particular importance since routine elective nodal irradiation, i.e. the prophylactic irradiation of clinically uninvolved lymph nodes, is no longer recommended in NSCLC.[50,51] FDG-PET has a higher sensitivity and specificity for the detection of lymph node involvement in NSCLC than CT (sensitivity: 83% vs. 62%; specificity: 97% vs. 91%, respectively).[52] Both PET- and CT-based selective irradiation of involved lymph nodes has proven its safety in NSCLC, with the occurrence of isolated nodal failures (INF) in less than 5% of

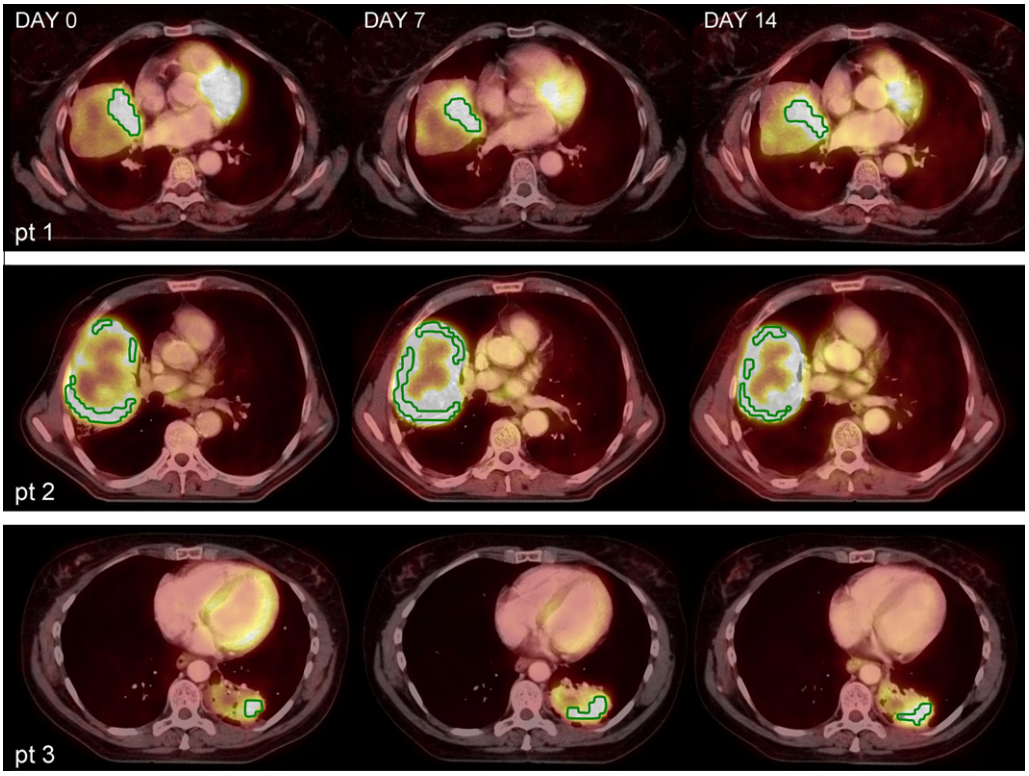

Fig. 3. Stability of high FDG-uptake areas during a course of RT PET-CT images of three patients before treatment (Day 0) and during treatment (Days 7 and 14). Lines indicate 60% of maximal standardized uptake value (SUV_{max}) threshold. Visual inspection showed that location of the hotspot remained at the same location during treatment; however, the volume of the hotspot changed. Reprinted from: Aerts HJ, Bosmans G, van Baardwijk AA, et al. Stability of 18F-deoxyglucose uptake locations within tumor during radiotherapy for NSCLC: a prospective study. *Int J Radiat Oncol Biol Phys* 2008;71:1402–1407. Copyright 2010, with permission from Elsevier.

patients.[53–56] One study found INF in up to 15% with PET-based SNI.[57] However, the accuracy of the identification of lymph nodes in this study was questionable, as only visual interpretation of non-coregistered FDG-PET images was used. In general, the PET-based treatment volumes are smaller than CT-based volumes.[58,59] Selective nodal irradiation (SNI) has shown not only to be safe, but also to result in a reduction of radiation fields based on CT, and even further based on FDG-PET.[55] A modeling study showed that treating only FDG-positive mediastinal areas decreases radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation dose-escalation.[55,59] An example of the difference resulting from RT planning with PET-CT compared to CT alone is illustrated in Fig. 4.

Although PET-defined SNI appears to be safe, ideally, pathological confirmation should be obtained. Pathological validation of the CT-and PET-based nodal treatment volumes was performed in 998 lymph nodal stations from 105 patients.[60] The coverage of all pathologic lymph nodes was 89% with PET-based treatment volumes compared to 75% with CT ($p = 0.005$). Nevertheless, a false negative rate with PET up to 14% has been reported in operable patients.[61] A possible explanation for the low amount of isolated nodal failures is the incidental irradiation of clinically negative lymph node stations through coverage by the beam penumbra of conventional RT fields. The Michigan group showed that risk factors of nodal metastases, such as a large tumor size and central location, were associated with a considerable dose to the high-risk nodal regions.[62] Therefore, caution is warranted with the application of new RT technologies, such as stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT) and particle therapy, as they are associated with a more conformal dose distribution.

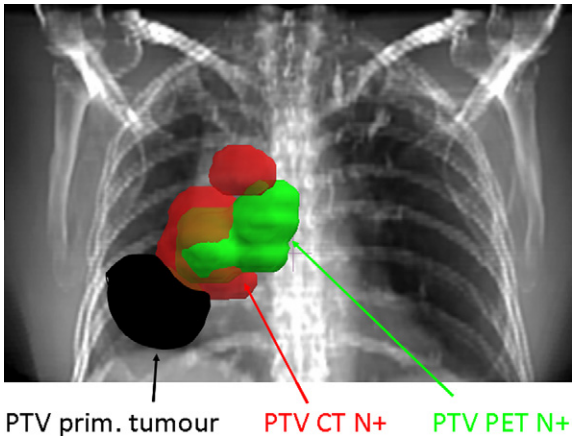

Fig. 4. Example of the effects of RT planning with PET-CT compared to CT alone Projection of the planning target volume (PTV) of a 66-yearold female with a large cell carcinoma of the right lower lobe with pathological lymph nodes on CT scan in areas 4R and 3R and on FDG-PET scan in area 7. Although the lung exposure was lower with PET-CT than with CT (V20 25 vs. 30% and MLD 15.4 vs. 19.3 Gy, respectively), the esophageal exposure was higher with PET-CT because of the involvement of level 7 (MED 16.9 vs. 14.1 Gy, V55 18 vs. 4%, D_{max} 60.1 vs. 58.6 Gy, respectively, for PET-CT and CT). Reprinted from: De Ruysscher D, Wanders S, Minken A, et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small-cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. *Radiother Oncol* 2005;77:5-10. Copyright 2010, with permission from Elsevier.

Different methods can be used for delineation of the involved lymph nodes on PET. Nestle et al. compared the nodal volumes resulting from visual delineation and absolute ($SUV_{max} \geqslant 2.5$),

relative (40% SUV_{max}) and individual (SBR-based) thresholds.[63] There were no clinically relevant differences in resulting volumes. SBR-based contouring of lymph nodes generally showed a good correlation with pathology.[29] Regardless of the delineation method, the question remains how to incorporate the lymph nodes in the treatment volume. There are no data available on the microscopic extension of disease outside lymph nodes. This residual uncertainty can be overcome by encompassing the whole anatomical mediastinal region in the treatment volume, as was done in the Maastricht studies described above.[55,58,59]

As for the primary tumor, the exact anatomical localization of the mediastinal lymph nodes may be blurred because of respiratory motion. Ideally, individually determined margins should be applied to cover the lymph nodes in all respiratory phases, as there is a large intra- and inter-individual variation in lymph node motion, not related to the motion of the primary tumor.[64–66]

Clinical implications and future perspectives

The incorporation of PET in RT planning has shown the potential for dose escalation through a reduction of the radiation fields, mainly because of avoidance of irradiating PET negative lymph nodes.[58,59,67] With individualized radiation dose escalation based on normal tissue constraints, patients treated with sequential chemoradiation had survival rates comparable to results with concurrent chemoradiation schedules while less toxicity was observed.[68] These results imply that PET-based RT planning might ultimately lead to higher cure rates, and randomized prospective studies are warranted to investigate this further.

Further optimization of the treatment volume could be obtained by accurate definition of the appropriate margin around the delineated tumor to cover microscopic disease. This information should become available from pathology correlation studies.

Recently, an increasing tendency has emerged to move away from the concept of homogeneous irradiation. Studies have been performed to investigate the feasibility of selectively boosting areas with residual FDG-uptake after 40–60 Gy, with diverging results.[69,70] Prospective trials are awaited to investigate whether radiation dose redistribution leads to better treatment outcome, for which preparations are currently being performed.[37,71] In the studies mentioned before, ^{18}FDG was used as a tracer for radioresistant areas. Other tracers, e.g. for hypoxia (^{18}F-FMISO, ^{18}F-HX4) or proliferation (^{18}F-FLT) could be used complementary to or instead of FDG.[72–76] These tracers deserve further investigation for this purpose.

Conclusion

FDG-PET has an important additional role to anatomic imaging in defining the primary tumor volume. Automatic delineation with adaptive techniques, such as SBR-based methods is to be preferred above absolute thresholding. Models are under development that correlate imaging findings with pathology in three dimensions. These could finally allow validation of different thresholds for SUV-based contouring and evaluation of microscopic spread and intra-tumor heterogeneity. Selective boosting of radioresistant areas identified with FDG-PET is subject of current research.

Selective irradiation of FDG-PET positive nodal stations is safe and leads to decreased normal tissue exposure, providing opportunities for dose escalation. With the increased use of more conformal radiation techniques, the safety of PET-based SNI should be re-evaluated. Disparities in treatment volumes resulting from different contouring methods are smaller than for the primary tumor.

Outcome prediction on basis of PET before or early after the start of treatment, and the added value of PET after therapy

Despite the improved outcome of inoperable stage III NSCLC achieved with combined chemoradiotherapy, the majority of inoperable stage III NSCLC patients still show disease progression after treatment, with 23–43% having an isolated local recurrence as their first site of progression.[77–81] As the treatment is associated with considerable toxicity, it would be of great value to select patients before or early during treatment, with the highest probability to benefit from treatment and to adjust the treatment in the other patient group.

Early response assessment with conventional chest X-ray and CT is limited by their poor discriminating capacity between residual tumor and treatment induced changes.[82,83] PET scanning allows for the assessment of changes in glucose consumption of the tumor during chemo- and radiotherapy. Several studies have shown a correlation between the SUV and tumor cell proliferation[84–86], supporting the hypothesis that an early change in FDG uptake has predictive value.

Prognostic value of pre-treatment PET

Most evidence regarding the prognostic value of pre-treatment PET comes from studies in heterogeneous patient populations with both early and late stage disease, treated with different modalities. A meta-analysis was performed within the IASLC lung cancer staging project. 11/13 eligible studies in stage I–IV NSCLC identified a high SUV as a poor prognostic factor for survival, with a combined HR for survival of 2.27 (95% CI: 1.43–3.04) for low vs. high SUV.[87] The threshold was variable between the studies, ranging from 5 to 20. Those differences are due to both technical and patient related factors, such as different scanners, time intervals between injection and scanning and fasting times. Furthermore, the relationship between SUV and prognosis is rather gradual than fixed at a single cut-off point.

Regarding the ability of PET to predict response to combined modality treatment, the first study in patients with advanced disease treated with (chemo-)radiotherapy showed a positive correlation between the tumor to muscle ratio (TMR) and response, but no significant correlation with outcome.[88] Two later studies revealed SUV_{mean} and SUV_{max} to be significantly associated with overall survival.[89,90] In the first population, both tumor grade and UICC stage showed a stronger correlation with survival than the SUV[89], while in the second study, SUV_{max} was the strongest predictor.[90] By contrast, the most recent study in the largest cohort of stage III and IV NSCLC patients thus far ($n = 214$), did not show a significant relationship with survival.[91] This study was not included in the IASLC meta-analysis mentioned above.

Outcome prediction on basis of early PET response during combined modality treatment

Because FDG is preferentially accumulated in viable tumor cells[92,93], FDG-PET imaging is an attractive method to visualize early treatment response. In advanced NSCLC, the predictive value of an early metabolic response to palliative chemotherapy, as well as to radical treatment with (chemo)radiotherapy has been evaluated. Prospective observational studies have consistently shown that in advanced NSCLC treated with palliative chemotherapy, the metabolic response after 1–3 cycles of chemotherapy is strongly correlated with outcome.[94–97]

With respect to radical treatment, metabolic response to induction chemotherapy prior to radiotherapy or surgery in locally advanced NSCLC patients has been shown to correlate with outcome in multiple studies.[95,98–100] One study, however, did not show a predictive value.[101] While the evidence regarding the predictive value of a metabolic response to induction chemotherapy is abundant, far less is known about its value early during the course of radical treatment itself. Two studies investigated the predictive value of response during radiotherapy alone or chemoradiation. The first study was a pilot study in 15 patients treated with RT alone or chemoradiotherapy. A significant correlation was found

between the response after 45 Gy of RT and the response 3 months after RT.[102] The second study, investigating the predictive value of response during concurrent chemoradiotherapy[103], showed a significant difference in long-term survival between patients with and without a metabolic response after 3 weeks of concurrent chemoradiotherapy. An overview of the studies evaluating outcome prediction on basis of early PET response to combined modality treatment is provided in Table 1. A study evaluating response during radical RT revealed a large intra-patient heterogeneity in the evolution of SUV_{max} during and after radical RT.[104] Different time patterns were seen for responders and non-responders, but due to the limited patient numbers, the predictive value of the SUV_{max} changes could not be assessed.

To make FDG response assessment a valuable tool in routine clinical practice, a clear definition of response should be prescribed, as the intra-patient variability of repeated tumor SUV-measurements is in the range of 10–15%.[105–107] Furthermore, early response should be assessed at a fixed time interval. Ideally, the interval should be short enough to switch to a potentially more successful treatment as early as possible, but with a time interval sufficient to allow for a reliable response assessment. In 1999, the EORTC published consensus guidelines on which cut-off points should be used to define response at different time intervals[108], which are still widely applied in clinical practice. Weber et al. defined a metabolic response after the first cycle of chemotherapy as a decrease in FDG uptake of more than twice the standard deviation, calculated to be 20%. This definition correlated with final response according to RECIST, as well as with time to progression and overall survival.[96] The Melbourne group demonstrated that visual response assessment on PET with the use of standardized response criteria correlated with survival and was superior to response assessment on CT using WHO response criteria.[109] In 2009, the PET Response Criteria in Solid Tumours (PERCIST version 1.0) have been proposed resulting from a review of qualitative and quantitative methods of metabolic response assessment.[110] PERCIST recommends to correct SUV for lean body mass (SUL) as this accounts for variations due to differences in body composition.

A comparison between the EORTC criteria and PERCIST is provided in Table 2. Overall and most importantly, the same definition of response criteria should be used by different groups to be able to compare metabolic response studies across different centers.

Concerning the type of measurement, semiquantitative methods, such as the relative change in SUV, appear to perform equally well as more complex quantitative methods such as change in the net-influx constants (*Ki*) or metabolic rate of glucose (MRglu).[95–97] This facilitates the use of early PET response for outcome prediction in daily clinical practice.

Added value of PET after combined modality treatment

The accuracy of PET after treatment is assumed to be lower than at initial staging because of therapy induced inflammatory and perfusion changes.[111] Nevertheless, PET still has a high accuracy in detecting recurrent lung cancer, with a sensitivity up to 98% and a specificity of 62–92%[111–113], and is more accurate than CT in the distinction of tumor from post-RT effects.[109,114,115] Here, the added value of a post-treatment PET is addressed with regard to the prognostic value of a PET early after treatment and the role of PET in the follow-up after combined modality therapy.

We identified four studies addressing the prognostic value of PET after radical treatment in locally advanced NSCLC patients, consisting of (chemo-)RT.[79,88,104,116] Four studies evaluated the predictive value of PET after induction chemoRT before surgery.[100,117–119] Details of the studies evaluating the prognostic value after radical (chemo)RT and the predictive value after induction (chemo)RT are provided in Table 3. These studies were unambiguous in their conclusion that the FDG response after radical treatment has prognostic value. Mac Manus proved the superiority of PET response above CT. Response on PET and CT was identical in only 40% of patients. In multivariate analysis, only the PET response was significantly associated with survival.[109]

Clear cut-offs should be prescribed to define the different prognostic subgroups. In the aforementioned studies, however, there is a large heterogeneity in the way FDG-uptake after therapy was measured. Some studies reported an absolute threshold post-treatment[88,100,117,119], while others stratified patients according to the relative change in SUV.[79,104,109,116,118] In none of the studies a direct comparison was made between the different methods. Until more data are available we recommend the use of the EORTC criteria for PET response[108] for prognostic stratification, as the results of the larger studies are mainly based on these criteria.

Another important aspect is the timing of the PET-CT. The median time interval in the studies described above was 14–70 days. It is recommended to perform a PET-CT scan not earlier than 3–6 months after treatment to avoid false positive results due to post-therapy inflammatory changes.[111,120] The time interval should not be excessive either, as the final aim is to select patients for further therapy. Hicks et al. observed no confounding effect through post-RT inflammatory changes for response assessment with a PET-CT scan performed 70 days after radical RT.[121] As different time-points have not been compared directly, we recommend the use of the time point 70 days post-treatment.

It should be noted that the results described above only apply for patients treated with conventional or hyperfractionated RT with or without chemotherapy. In hypofractionated SBRT, where 3–5 large fractions are applied, persistently elevated SUV_{max} of >3.5 have been described up to one year post treatment.[122,123] These different findings may be explained by localized normal tissue changes induced by SBRT, such as segmental atelectasis or focal fibrosis, not distinguishable from persistent or recurrent tumor.

PET in the follow-up of NSCLC could improve outcome when progressive disease can be detected early enough to allow radical retreatment. There are no convincing data supporting that early

Table 1
Prediction of outcome on basis of early PET response to combined modality treatment.

Study	*N*	Stage	Timepoint of PETscan	Radical treatment	Definition of cut-off	Predictive value
Hellwig (2004)[99]	47	IIB–III	After induction therapy[a]	Surgery	SUV_{max} = 4	OS: yes
Hoekstra (2005)[95]	47	IIIA	1 and 3 Cycles	Surgery or RT	Residual MR_{glu} = 0.13	OS: yes
Pottgen (2006)[100]	50	III	3 Cycles	ChemoRT ± Surgery	NR	Histopathologic tumor response: yes
Kong (2007)[102]	15	I–III	45 Gy	(chemo)RT	CMR/PMR	CMR/PMR 3 months after treatment: yes
(Decoster) 2008[98]	31	III	3 Cycles	RT	CMR	PFS: yes OS: trend
Tanvetyanon (2008)[101]	89	I–III	2 Cycles	Surgery	30% Decrease in SUV_{max}	OS: no
Zhang (2009)[103]	46	III	40–50 Gy	ChemoRT	50% Decrease in SUV_{max}	OS: yes

N, number of patients; NR, not reported; CMR, complete metabolic response; PMR, partial metabolic response; OS, overall survival; PFS, progression free survival.
[a] Data on number of cycles are not provided. Induction therapy consisted of chemotherapy only or chemotherapy followed by RT.

Table 2
Comparison of response criteria according to EORTC and PERCIST.

	EORTC	PERCIST
Progressive Metabolic Disease (PMD)	>25% Increase in SUV of tumor defined on pre-treatment scan, or >20% increase in the longest dimension of FDG-uptake, or Appearance of new FDG-uptake in metastatic lesions	>30% Increase in SUL peak and absolute increase of SUL units ⩾0.8 from baseline scan in pattern typical of tumor and not of infection /treatment effect, or Visible increase in extent of FDG-uptake (> 75% increase in total lesion glycolysis), or Appearance of new FDG-avid lesions typical of cancer and not related to infection /treatment effect
Stable Metabolic Disease (SMD)	<25% Increase or <15% decrease in SUV of tumor defined on pre-treatment scan, and <20% increase in the longest dimension of FDG-uptake	No CMR, PMR or PMD
Partial Metabolic Response (PMR)	>15% Decrease in SUV of tumor defined on pre-treatment scan (after 1 cycle) > 25% decrease in SUV of tumor defined on pre-treatment scan (after >1 cycle)	>30% Decrease in SUL peak and absolute drop in SUL units ⩾0.8 of the most intense lesion before and after treatment (not necessarily the same lesion) No new FDG-avid lesions typical of cancer
Complete Metabolic Response (CMR)	Complete resolution of FDG-uptake within tumor defined on pre-treatment scan, not distinguishable from surrounding normal tissue	Complete resolution of FDG-uptake within measurable target lesion, less than mean liver activity and indistinguishable from surrounding background blood-pool levels Disappearance of all other lesions to background blood-pool levels No new FDG-avid lesions typical of cancer

SUL: Standardized uptake value corrected for lean body mass.

Table 3
Value of post-treatment PET.

Study	*N*	Stage	Interval[a]	Radical treatment	Definition of threshold	Prognostic value
Post (chemo)RT						
Ichiya (1996)[88]	20	III–IV	<3 weeksks	RT or chemoRT	TMR > 5	RFS: yes
Hebert (1996)[166]	12	NR	NR	RT	CR, visually interpreted	Probable[b]
Mac Manus (2005)[79]	88	I–III	70 days (median)	RT or chemoRT	CMR	OS: yes Distant M: yes Local failure: yes
Van Baardwijk (2007)[29,93]	20	I–III	71 days (median)	RT or chemoRT	CMR or PMR	OS: yes
After Neoadjuvant treatment						
Choi (1998)[117]	29	IIB–IIIA	2 weeks	ChemoRT	$MR_{glu} \leqslant 0.040$	Predictive value pTCP ⩾ 95%
Ryu, 2002[119]	26	III	2 wks	ChemoRT	$SUV_{mean>}3$	Pathological complete response: yes
Pottgen (2006)[100]	43	III	NR[c]	ChemoRT	$SUV_{maxpost}/SUV_{maxpre}$[d]=0.38–0.55	Histopathologic tumor response: yes
Eschmann (2007)[118]	70	III	2 weeks	ChemoRT	CR, PR, SD, PD, visually interpreted > 80% decrease in SUV_{max}	OS: yes

TMR, tumor to muscle ratio; RFS, relapse free survival; NR, not reported; OS, overall survival; CMR, complete metabolic response; PMR, partial metabolic response; MR_{glu}, metabolic rate of glucose; pTCP, probability of pathologic tumor control; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[a] Between end of treatment and PETscan.
[b] Patients with a complete response remained locally controlled, while 50% of the patients with a partial or no response showed progression.
[c] Interval between the end of induction treatment was not reported. The interval between the start of induction chemotherapy and the PETscan was around 83 days.
[d] Ratio between the SUV_{max} post induction chemoradiotherapy and the SUV_{max} after 3 cycles of induction chemotherapy.

detection of progression with chest X-ray or CT scan improves survival.[82,124–126] This might be different for FDG-PET scanning, as PET is more accurate than CT in the distinction of tumor from post-RT effects[109,114,127], and is known to be prognostic for outcome.[87,93,128–130] A prospective study was performed to evaluate whether PET-CT 3 months after therapy can detect potentially curable progression in locally advanced NSCLC[131], which was the case in a small proportion (3%) of patients, who were all asymptomatic. An economic evaluation showed that a PET-CT scan 3 months after (chemo-)radiotherapy is potentially cost-effective, and is more cost-effective than CT alone.[132] As the advantage was confined to the asymptomatic patients, a PET-CT scan in this group only is probably as effective and more cost-effective.

Other tracers

As response assessment early during and after therapy is complicated by the limited ability of FDG to discriminate between inflammation and tumor activity, it is worthwhile to investigate alternative tracers, corresponding more specifically with tumor proliferative activity.

The uptake of ^{18}F-fluorothymidine (^{18}F-FLT), a marker of DNA synthesis, has been correlated with tumor proliferative activity in various tumor sites including NSCLC.[133–138] Recent (pre)clinical studies have demonstrated that FLT can detect changes in proliferation during and after irradiation in colorectal tumors and breast cancer cell lines.[139–141] One pilot study in NSCLC has shown the feasibility of FLT to image proliferation during chemo-radiotherapy.[76]

Amino-acid tracers theoretically have an advantage over FDG in that it more specifically accumulates in viable cancer cells.[142] However, data on its usefulness in evaluating treatment response are scarce. One study compared ^{18}F-FDG and the amino-acid tracer ^{11}C-methionine (^{11}C-Met) for evaluation of treatment response in lung cancer, but this study focussed on early stage patients treated with stereotactic RT.[123] In this study, FDG and Met showed an equal accumulation in inflammatory tissue, a finding supported by the results of other research groups.[143–145] ^{18}F-fluoromethyltyrosine (^{18}F-FMT), another amino-acid tracer, has recently been put forward. Two animal studies showed a rapid response to antitumor therapy, and less accumulation in inflammatory cells.[146,147]

Clinical implications and future perspectives

The clinical impact of patient selection before or early during treatment is beyond doubt, as it avoids ineffective treatment with the associated side-effects and enables alternative therapy in case of an inadequate early response. Additional research is needed to define clear cut-off points for FDG uptake to stratify patients into different treatment modalities. With regard to early response assessment, attention should be paid to other tracers, in particular proliferation markers, as they are less susceptible to uptake in inflammatory tissue.[76]

A final option for improvement in outcome is the use of PET in the follow-up. Currently available data do show a potential benefit of PET in the follow-up compared to CT. Ideally, different follow-up strategies should be compared in a randomized controlled trial to provide definitive insight in the added value of PET in the follow-up of NSCLC patients after combined modality therapy.

Conclusion

In the overall NSCLC patient group, pre-treatment FDG-uptake is of prognostic value. Results on its ability to predict response to combined modality therapy in advanced stage NSCLC are conflicting. The most recent study in the largest patient cohort did not show a significant correlation with survival.

The predictive value of an early metabolic (FDG) response during induction chemotherapy has been established. Less is known about the predictive value of a metabolic response during radical (chemo-)RT, but the limited available data show a correlation with survival. The FDG response after radical treatment is of proven prognostic significance. A time interval of 70 days after the end of treatment is recommended for response assessment on basis of the EORTC criteria.

An FDG-PET scan in the follow-up after combined modality therapy can detect progression amenable for radical retreatment in a limited number of patients.

Tracers other than FDG are promising for treatment response assessment, but more research is needed before they can be clinically implemented.

Small cell lung cancer (SCLC)

SCLC is a tumor with a poor prognosis, characterized by a rapid growth rate. Traditionally, staging of those patients has been limited to the distinction between limited (LD) and extensive disease (ED).[148] Approximately 25% of patients present with limited-disease (LD), defined as disease confined to one hemithorax, including the mediastinum and bilateral supraclavicular fossae.[149–151] Even in this patient group, surgery is rarely an option because of the advanced stage of locoregional disease. Concurrent chemo-radiation is currently the first choice treatment. Literature is sparse on the role of PET in LD-SCLC. The available literature suggests that FDG-PET has additional value above standard staging procedures in SCLC[152–159], with a reported sensitivity and specificity up to 100% and 95%.[160] Staging with PET can positively influence the outcome of chemoradiotherapy for LD-SCLC patients by means of stage migration. Upstaging from LD to ED by FDG-PET scanning occurs in 6–33%[152–154,161–164] and downstaging in 3–40%.[153,154,161,163]

Definition of the tumor volume to be treated

Primary tumor

In order to define the tumor volume, PET should be assessed for its ability to distinguish malignant from surrounding normal tissue. Studies addressing this issue are focussed on NSCLC.[13–16] The same holds true for correlation studies with pathology.[28,30,31,48,49] Therefore, we can only assume that similar caveats apply as described above for NSCLC. In short, a major limitation of PET is the low spatial resolution. Hence, the major gain is to be expected in regions where anatomical imaging techniques lack the capacity to discriminate malignant from normal tissue, e.g. in areas with atelectasis. Another question refers to which method should be applied for PET-based tumor delineation. Again, comparison and validation of different methods has exclusively been performed in NSCLC.[24,29] No conclusions can be drawn regarding which method is to be preferred, except that adaptive techniques are likely to be more accurate than the use of an absolute or relative SUV-based threshold.[22,23] Obviously, blurring effects due to motion hinder exact tumor delineation. Respiration correlated imaging techniques have the potential to include individual tumor motion in the treatment volume, in conjunction with optimal image quality, as blurring effects are significantly reduced.[45,46]

Microscopic disease extension

As described previously, the only way to define microscopic disease extension beyond the tumor border visible on imaging is to correlate imaging with pathology. There are no data on image correlation with pathology available for SCLC.

Lymph nodes

The available data suggest that an FDG-PET scan can identify metastases to regional lymph nodes in 14–25% of patients whose mediastinal CT scan is negative.[152,156,163] With the high sensitivity and specificity of PET in SCLC, it is likely that the use of PET scans improves the coverage of mediastinal lymph node areas in LD-SCLC.

Until recently, few prospective data concerning selective nodal irradiation (SNI) in SCLC were available. A report from the International Atomic Energy Agency (IAEA) meeting emphasized the need for prospective clinical evidence regarding SNI in SCLC.[165] CT-based SNI resulted in an unacceptable amount (11%) of isolated nodal failures outside the treatment volume.[166] These findings imply that results on the safety of SNI in NSCLC cannot straightforwardly be extrapolated to SCLC. Since the publication of the IASLC report, two studies have become available evaluating FDG-PET-based SNI in SCLC. In a planning study, a difference in the treatment plan resulting from PET- and CT-based SNI was found in 24% of patients.[167] Radiation fields increased in 10% and decreased in 14% of patients, respectively. No significant changes in the radiation exposure of the normal tissue were observed. In the subsequent prospective study, 3% of the patients experienced an isolated nodal failure after a minimal follow-up of 18 months, comparable to results in NSCLC. A remarkably low percentage (12%) of grade III esophagitis was found, while this occurs in about 30% of patients receiving elective nodal irradiation or CT-based SNI.[166,168] This finding deserves further investigation. The low rate of isolated nodal failures and toxicity thus supports the use of PET-based SNI in LD-SCLC.

A few points of caution should be taken into consideration. First, incidental irradiation of surrounding nodal stations might partially

explain the low rates of isolated nodal failures with SNI. Therefore, results should be re-evaluated with the application of more conformal techniques (SBRT, IMRT, particle therapy). A second point of attention consists of the methods for target volume definition. In the available study, the mediastinal nodal regions involved on PET were included in the treatment field.[169] As our literature search did not yield any study evaluating autocontouring methods for lymph node delineation in SCLC, we recommend SNI of the whole mediastinal nodal station involved on PET.

Clinical implications and future perspectives

As in most SCLC cases, the bulk of disease is located in the hilar and mediastinal regions, reduction of the treatment volume can mainly be reached by omitting elective nodal irradiation. If the finding of low esophageal toxicity, as described in the first study with PET-based SNI[169] holds true, PET based SNI indeed provides opportunities for treatment intensification. With regard to RT planning, another point of consideration is the concept of subboosting areas of supposed radioresistance. FDG-PET, as well as PET with other tracers, could help to identify those regions within the tumor. Although this concept is readily evolving in NSCLC, no such trend is observed until now in SCLC. Although it is reasonable to assume that characteristics associated with radioresistance are also heterogeneous in SCLC[33–35], the distribution of the disease load in NSCLC is different from SCLC, as for most SCLC cases, the majority of the tumor load is found in the nodal stations. Studies on the evolution and stability of regions with high FDG-uptake in NSCLC are entirely focussed on the primary tumor, and no such information is available with respect to lymph nodes. These issues should be addressed when heterogeneous dose escalation is taken into consideration in SCLC.

Conclusion

There are no data available on the role of FDG-PET in defining the borders of the primary tumor. In contrast with CT-based SNI, first results indicate that SNI of FDG-PET positive nodal stations appears to be safe and results in remarkably limited toxicity. With the increased use of more conformal radiation techniques, the safety of PET-based SNI should be re-evaluated. It is recommended to encompass the whole anatomical mediastinal region containing FDG-positive nodes in the treatment volume.

Outcome prediction on basis of PET before or early after the start of treatment, and the prognostic value of PET after therapy

The majority of SCLC patients still shows disease progression short after the completion of chemoradiotherapy, with over 30% having an isolated local recurrence as their first site of progression.[168] Furthermore, the treatment is associated with considerable toxicity, with grade 3 esophagitis in up to 27% of patients.[117,170–172] Therefore, the ability to predict the benefit from treatment would be of great clinical value. Recent data have made clear that the traditional staging system with two categories (limited and extensive disease) is on its own not an adequate predictor of survival and is not sufficient to stratify patients for the most optimal therapy.[173,174] Since recently, it is recommended to use the TNM staging for SCLC, as it has proven to result in a better stratification of patients in prognostic subgroups.[175,176] FDG uptake on PET before, during or after therapy could have a role as additional prognostic and predictive marker in SCLC.

Prognostic value of pre-treatment PET

Evidence concerning the prognostic value of FDG-uptake before treatment in SCLC is scarce. One study was identified that addressed this subject.[177] The majority of patients had LD and were treated with concurrent chemoradiotherapy. Overall, as well as for the subgroup with LD, patients with a high SUV_{max} (i.e., higher than the median) had a significantly worse overall survival than patients with a low SUV_{max} (LD: 20.1 vs. 35.3 months). Three prognostic subgroups could be defined on basis of FDG-uptake and disease stage. Those results imply that different treatment strategies are required for LD with low and high SUV_{max}. Randomized clinical studies are warranted to answer whether FDG-uptake in combination with anatomical staging is predictive of outcome and can be used to select the appropriate therapy for each patient group.

Outcome prediction on basis of early PET response during combined modality treatment

The predictive ability of an FDG response early after the start of chemotherapy has been evaluated in two studies, both after one cycle of chemotherapy.[178,179] However, patients with both LD and ED were investigated. Therefore, the results reflect the predictive value of an FDG response early during palliative chemotherapy or radical chemoradiotherapy. Furthermore, both studies used CT response after completion of therapy as a reference, and not survival. Both studies concluded that the metabolic response was correlated with the response according to RECIST.

Several important questions need to be addressed in future studies to make early response assessment with PET during treatment a valuable clinical tool. Those questions include the type of measurement, the definition for response, and the most optimal time interval for the measurement of early response. Regarding response criteria, the use of the EORTC recommendations[108], a 20% threshold[96], as well as the criteria for visual response assessment by MacManus are valid[109]: Fischer et al. compared the visual method with the EORTC criteria in SCLC response evaluation after one cycle of chemotherapy and found no significant difference.[178] Regarding the type of measurement and the time interval, no separate data on SCLC are available. As long as no such data are available, the most practical alternative is to adhere to the NSCLC recommendations. Those are the use of relatively simple semi-quantitative measurements such as SUV_{max}[95–97], and a time interval of 1–3 cycles of chemotherapy.[95–97]

Caution is warranted, however, when projecting results obtained in NSCLC at SCLC. As mentioned before, those are two distinct types of disease with different clinical behavior. SCLC is characterized by a rapid response to chemo- and radiotherapy. Therefore, a response to therapy could be more rapidly visible on CT than it is in NSCLC, which might restrict the beneficial effect of PET. This hypothesis is supported by the study of Fischer et al., who found that early response assessment after one cycle of chemotherapy with CT and PET showed a comparable correlation with the final evaluation on basis of RECIST.[178]

Added value of PET after combined modality treatment

Two retrospective studies evaluated the prognostic value of PET after treatment in SCLC patients[157,180], with one specifically aimed at LD.[180] The first study included both LD and ED, and both treated and untreated patients, with treated LD patients representing 50% of the study population. It is hard to draw separate conclusions on this group, but overall, there was a significant negative correlation between PET positivity or SUV_{max} and overall survival.[157]

The study evaluating exclusively LD patients has some limitations: only 73% was treated with chemoradiotherapy, the remaining patients with palliative chemotherapy.[180] Furthermore, the time interval between the end of treatment and PET-scanning was variable (3–125 days). Finally, the definition of PET positivity was rather broad. With those limitations in mind, the study showed a significant difference in progression free survival between PET positive and negative patients, with a trend for overall survival.

A prerequisite for PET in the follow-up to have a positive impact on the final outcome is that progression should be detected at a time that radical retreatment is still an option. The rapid growth rate and early dissemination make it less likely for progression to be detected in a "curable" stage in SCLC than in NSCLC. Although no studies have addressed the role of FDG-PET in the follow-up of SCLC, it can therefore be questioned whether PET scanning is advantageous with respect to outcome.

Clinical implications and future perspectives

It is obvious that the currently available data are insufficient to modify or adapt treatment on basis of pre-treatment FDG uptake or an early metabolic response in SCLC patients. Research in the field of early response assessment is of particular importance to define the additional benefit of PET above CT given the rapid response of SCLC to chemo- and radiotherapy.

Finally, the role of PET after combined modality therapy of LD-SCLC should be addressed. Given the early dissemination of SCLC, most benefit is to be expected with a tracer that allows response evaluation early after treatment. Given the high uptake in inflammatory regions, FDG might not be ideal for this purpose. Therefore, other tracers should be evaluated.

Conclusion

Studies evaluating the prognostic value of PET, its ability to predict response to combined modality treatment and the added value of PET after treatment in SCLC are scarce. Available results mainly come from studies in patients with both limited and extensive disease. Overall, results do show some predictive value of an FDG response before and during therapy, as well as prognostic value of FDG uptake after treatment. No studies have evaluated the impact of PET in the follow-up of SCLC.

General conclusions

Molecular imaging with PET, using different tracers, has the potential to distinguish between vital tumor and non-malignant tissue and to identify intra-tumor characteristics. The additional value of FDG-PET in defining the primary tumor volume has been established, mainly in regions with atelectasis or post-treatment effects. Three dimensional models that correlate imaging findings with pathology are being developed for NSCLC, which could allow validation of different thresholds for SUV-based contouring, evaluation of microscopic spread and intra-tumor heterogeneity. FDG-PET has the ability to identify regions within the tumor that are associated with radioresistance, and it has been proved that these regions remain stable during a radiotherapy course. Therefore, boosting of radioresistant areas identified with FDG-PET appears to be feasible and is subject of current research. Selective irradiation of FDG-PET positive nodal stations in NSCLC is safe and leads to decreased normal tissue exposure, providing opportunities for dose escalation. For this reason, it is the preferred treatment in NSCLC. First results in SCLC suggest that the same holds true for SCLC. Data on the predictive value of pre-treatment FDG-uptake and an early metabolic response during combined modality treatment are conflicting and limited, respectively. The FDG response after radical treatment is of prognostic significance. A time interval of 70 days between end of treatment and PET scanning is recommended for response evaluation in NSCLC. A PET scan in the follow-up of NSCLC potentially improves survival through the detection of progression with radical treatment options. Data on its value in the follow-up of SCLC are lacking.

Tracers other than ^{18}FDG are promising for treatment response assessment and the visualization of intra-tumor heterogeneity, but more research is needed before they can be clinically implemented.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;**59**:225–49.
2. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;**28**:2181–90.
3. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. *Lung Cancer* 2001;**31**:123–37.
4. Jett JR, Schild SE, Keith RL, Kesler KA. Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;**132**:266S–76S.
5. Hoekstra CJ, Stroobants SG, Hoekstra OS, et al. The value of [18F]fluoro-2-deoxy-D-glucose positron emission tomography in the selection of patients with stage IIIA-N2 non-small cell lung cancer for combined modality treatment. *Lung Cancer* 2003;**39**:151–7.
6. Mac Manus MP, Hicks RJ, Ball DL, et al. F-18 fluorodeoxyglucose positron emission tomography staging in radical radiotherapy candidates with nonsmall cell lung carcinoma: powerful correlation with survival and high impact on treatment. *Cancer* 2001;**92**:886–95.
7. Mac Manus MP, Wong K, Hicks RJ, Matthews JP, Wirth A, Ball DL. Early mortality after radical radiotherapy for non-small-cell lung cancer: comparison of PET-staged and conventionally staged cohorts treated at a large tertiary referral center. *Int J Radiat Oncol Biol Phys* 2002;**52**:351–61.
8. Hicks RJ, Kalff V, MacManus MP, et al. (18)F-FDG PET provides high-impact and powerful prognostic stratification in staging newly diagnosed non-small cell lung cancer. *J Nucl Med* 2001;**42**:1596–604.
9. MacManus MP, Hicks RJ, Matthews JP, et al. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;**50**:287–93.
10. Nestle U, Weber W, Hentschel M, Grosu AL. Biological imaging in radiation therapy: role of positron emission tomography. *Phys Med Biol* 2009;**54**:R1–R25.
11. Van de Steene J, Linthout N, de Mey J, et al. Definition of gross tumor volume in lung cancer: inter-observer variability. *Radiother Oncol* 2002;**62**:37–49.
12. Steenbakkers RJ, Duppen JC, Fitton I, et al. Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: a 'Big Brother' evaluation. *Radiother Oncol* 2005;**77**:182–90.
13. Mah K, Caldwell CB, Ung YC, et al. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2002;**52**:339–50.
14. Steenbakkers RJ, Duppen JC, Fitton I, et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. *Int J Radiat Oncol Biol Phys* 2006;**64**:435–48.
15. Ashamalla H, Rafla S, Parikh K, et al. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**:1016–23.
16. Fox JL, Rengan R, O'Meara W, et al. Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? *Int J Radiat Oncol Biol Phys* 2005;**62**:70–5.
17. Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;**59**:78–86.
18. Nestle U, Walter K, Schmidt S, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 1999;**44**:593–7.
19. Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol* 1998;**16**:1075–84.
20. Nestle U, Kremp S, Grosu AL. Practical integration of [18F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC): the technical basis, ICRU-target volumes, problems, perspectives. *Radiother Oncol* 2006;**81**:209–25.
21. Geets X, Lee JA, Bol A, Lonneux M, Gregoire V. A gradient-based method for segmenting FDG-PET images: methodology and validation. *Eur J Nucl Med Mol Imaging* 2007;**34**:1427–38.
22. Black QC, Grills IS, Kestin LL, et al. Defining a radiotherapy target with positron emission tomography. *Int J Radiat Oncol Biol Phys* 2004;**60**:1272–82.
23. Daisne JF, Sibomana M, Bol A, Doumont T, Lonneux M, Gregoire V. Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms. *Radiother Oncol* 2003;**69**:247–50.
24. Nestle U, Kremp S, Schaefer-Schuler A, et al. Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. *J Nucl Med* 2005;**46**:1342–8.
25. Macmanus MP, Hicks RJ. Where do we draw the line? Contouring tumors on positron emission tomography/computed tomography. *Int J Radiat Oncol Biol Phys* 2008;**71**:2–4.
26. Bayne M, Hicks RJ, Everitt S, et al. Reproducibility of "intelligent" contouring of gross tumor volume in non-small-cell lung cancer on PET/CT images using a standardized visual method. *Int J Radiat Oncol Biol Phys* 2010;**77**:1151–7.

27. Wu K, Ung YC, Hornby J, et al. PET CT thresholds for radiotherapy target definition in non-small-cell lung cancer: how close are we to the pathologic findings? *Int J Radiat Oncol Biol Phys.* 2009.
28. Yu HM, Liu YF, Hou M, Liu J, Li XN, Evaluation YuJM, et al. 18F-FDG PET, integrated 18F-FDG PET/CT and pathological analysis in non-small cell lung cancer. *Eur J Radiol* 2009;**72**:104–13.
29. van Baardwijk A, Bosmans G, Boersma L, et al. PET-CT-based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumor and involved nodal volumes. *Int J Radiat Oncol Biol Phys* 2007;**68**:771–8.
30. Dahele M, Hwang D, Peressotti C, et al. Developing a methodology for three-dimensional correlation of PET-CT images and whole-mount histopathology in non-small-cell lung cancer. *Curr Oncol* 2008;**15**:62–9.
31. Stroom J, Blaauwgeers H, van Baardwijk A, et al. Feasibility of pathology-correlated lung imaging for accurate target definition of lung tumors. *Int J Radiat Oncol Biol Phys* 2007;**69**:267–75.
32. Siedschlag C, van Loon J, van Baardwijk A, et al. Analysis of the relative deformation of lung lobes before and after surgery in patients with NSCLC. *Phys Med Biol* 2009;**54**:5483–92.
33. Cooper RA, Carrington BM, Loncaster JA, et al. Tumour oxygenation levels correlate with dynamic contrast-enhanced magnetic resonance imaging parameters in carcinoma of the cervix. *Radiother Oncol* 2000;**57**:53–9.
34. Foo SS, Abbott DF, Lawrentschuk N, Scott AM. Functional imaging of intratumoral hypoxia. *Mol Imaging Biol* 2004;**6**:291–305.
35. Zhao S, Kuge Y, Mochizuki T, et al. Biologic correlates of intratumoral heterogeneity in 18F-FDG distribution with regional expression of glucose transporters and hexokinase-II in experimental tumor. *J Nucl Med* 2005;**46**: 675–82.
36. Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. *Lancet Oncol* 2005;**6**:112–7.
37. Bentzen SM. Dose painting and theragnostic imaging: towards the prescription, planning and delivery of biologically targeted dose distributions in external beam radiation oncology. *Cancer Treat Res* 2008;**139**: 41–62.
38. Galvin JM, De Neve W. Intensity modulating and other radiation therapy devices for dose painting. *J Clin Oncol* 2007;**25**:924–30.
39. Das SK, Miften MM, Zhou S, et al. Feasibility of optimizing the dose distribution in lung tumors using fluorine-18-fluorodeoxyglucose positron emission tomography and single photon emission computed tomography guided dose prescriptions. *Med Phys* 2004;**31**:1452–61.
40. Aerts HJ, van Baardwijk AA, Petit SF, et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. *Radiother Oncol* 2009;**91**:386–92.
41. Abramyuk A, Tokalov S, Zophel K, et al. Is pre-therapeutical FDG-PET/CT capable to detect high risk tumor subvolumes responsible for local failure in non-small cell lung cancer? *Radiother Oncol* 2009;**91**:399–404.
42. Aerts HJ, Bosmans G, van Baardwijk AA, et al. Stability of 18F-deoxyglucose uptake locations within tumor during radiotherapy for NSCLC: a prospective study. *Int J Radiat Oncol Biol Phys* 2008;**71**:1402–7.
43. Christensen JD, Colby TV, Patz Jr EF. Correlation of [18F]-2-fluoro-deoxy-D-glucose positron emission tomography standard uptake values with the cellular composition of stage I nonsmall cell lung cancer. *Cancer* 2010;**116**: 4095–102.
44. Caldwell CB, Mah K, Skinner M, Danjoux CE. Can PET provide the 3D extent of tumor motion for individualized internal target volumes? A phantom study of the limitations of CT and the promise of PET. *Int J Radiat Oncol Biol Phys* 2003;**55**:1381–93.
45. Nehmeh SA, Erdi YE. Respiratory motion in positron emission tomography/computed tomography: a review. *Semin Nucl Med* 2008;**38**:167–76.
46. Grgic A, Nestle U, Schaefer-Schuler A, Kremp S, Kirsch CM, Hellwig D. FDG-PET-based radiotherapy planning in lung cancer: optimum breathing protocol and patient positioning–an intraindividual comparison. *Int J Radiat Oncol Biol Phys* 2009;**73**:103–11.
47. Chan R, He Y, Haque A, Zwischenberger J. Computed tomographic-pathologic correlation of gross tumor volume and clinical target volume in non-small cell lung cancer: a pilot experience. *Arch Pathol Lab Med* 2001;**125**: 1469–72.
48. Giraud P, Antoine M, Larrouy A, et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. *Int J Radiat Oncol Biol Phys* 2000;**48**:1015–24.
49. Grills IS, Fitch DL, Goldstein NS, et al. Clinicopathologic analysis of microscopic extension in lung adenocarcinoma: defining clinical target volume for radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;**69**:334–41.
50. Belderbos JS, Kepka L, Spring Kong FM, Martel MK, Videtic GM, Jeremic B. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2008;**72**:335–42.
51. Senan S, De Ruysscher D, Giraud P, Mirimanoff R, Budach V. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. *Radiother Oncol* 2004;**71**:139–46.
52. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003;**139**:879–92.
53. Senan S, Burgers S, Samson MJ, et al. Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;**54**:999–1006.
54. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**66**:126–34.
55. De Ruysscher D, Wanders S, van Haren E, et al. Selective mediastinal node irradiation based on FDG-PET scan data in patients with non-small-cell lung cancer: a prospective clinical study. *Int J Radiat Oncol Biol Phys* 2005;**62**:988–94.
56. Sulman EP, Komaki R, Klopp AH, Cox JD, Chang JY. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol* 2009;**4**:5.
57. Sura S, Greco C, Gelblum D, Yorke ED, Jackson A, Rosenzweig KE. (18)F-fluorodeoxyglucose positron emission tomography-based assessment of local failure patterns in non-small-cell lung cancer treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;**70**:1397–402.
58. De Ruysscher D, Wanders S, Minken A, et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. *Radiother Oncol* 2005;**77**:5–10.
59. van Der Wel A, Nijsten S, Hochstenbag M, et al. Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2–N3M0 non-small-cell lung cancer: a modeling study. *Int J Radiat Oncol Biol Phys* 2005;**61**:649–55.
60. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al. The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. *Radiother Oncol* 2000;**55**:317–24.
61. Gomez-Caro A, Garcia S, Reguart N, et al. Incidence of occult mediastinal node involvement in CN0 non-small-cell lung cancer patients after negative uptake of positron emission tomography/computer tomography scan. Eur J Cardiothorac Surg.
62. Zhao L, Chen M, Ten Haken R, et al. Three-dimensional conformal radiation may deliver considerable dose of incidental nodal irradiation in patients with early stage node-negative non-small cell lung cancer when the tumor is large and centrally located. *Radiother Oncol* 2007;**82**:153–9.
63. Nestle U, Schaefer-Schuler A, Kremp S, et al. Target volume definition for 18F-FDG PET-positive lymph nodes in radiotherapy of patients with non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2007;**34**:453–62.
64. Thomas JG, Kashani R, Balter JM, Tatro D, Kong FM, Pan CC. Intra and interfraction mediastinal nodal region motion: implications for internal target volume expansions. *Med Dosim* 2009;**34**:133–9.
65. Bosmans G, van Baardwijk A, Dekker A, et al. Time trends in nodal volumes and motion during radiotherapy for patients with stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;**71**:139–44.
66. Pantarotto JR, Piet AH, Vincent A, de Koste JR, Senan S. Motion analysis of 100 mediastinal lymph nodes: potential pitfalls in treatment planning and adaptive strategies. *Int J Radiat Oncol Biol Phys* 2009;**74**:1092–9.
67. van Baardwijk A, Bosmans G, Boersma L, et al. Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. *Int J Radiat Oncol Biol Phys* 2008;**71**:1394–401.
68. van Baardwijk A, Wanders S, Boersma L, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol* 2010;**28**(8):1380–6.
69. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. *Int J Radiat Oncol Biol Phys* 2009;**73**:1228–34.
70. Gillham C, Zips D, Ponisch F, et al. Additional PET/CT in week 5–6 of radiotherapy for patients with stage III non-small cell lung cancer as a means of dose escalation planning? *Radiother Oncol* 2008;**88**:335–41.
71. Petit SF, Aerts HJ, van Loon JG, et al. Metabolic control probability in tumour subvolumes or how to guide tumour dose redistribution in non-small cell lung cancer (NSCLC): an exploratory clinical study. *Radiother Oncol* 2009;**91**:393–8.
72. Rasey JS, Koh WJ, Evans ML, et al. Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: a pretherapy study of 37 patients. *Int J Radiat Oncol Biol Phys* 1996;**36**:417–28.
73. Thorwarth D, Eschmann SM, Scheiderbauer J, Paulsen F, Alber M. Kinetic analysis of dynamic 18F-fluoromisonidazole PET correlates with radiation treatment outcome in head-and-neck cancer. *BMC Cancer* 2005;**5**:152.
74. Mees G, Dierckx R, Vangestel C, Van de Wiele C. Molecular imaging of hypoxia with radiolabelled agents. *Eur J Nucl Med Mol Imaging* 2009;**36**:1674–86.
75. Sovik A, Malinen E, Skogmo HK, Bentzen SM, Bruland OS, Olsen DR. Radiotherapy adapted to spatial and temporal variability in tumor hypoxia. *Int J Radiat Oncol Biol Phys* 2007;**68**:1496–504.
76. Everitt S, Hicks RJ, Ball D, et al. Imaging cellular proliferation during chemo-radiotherapy: a pilot study of serial 18F-FLT positron emission tomography/computed tomography imaging for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**:1098–104.
77. Ataman OU, Barrett A, Filleron T, Kramar A. Optimization of follow-up timing from study of patterns of first failure after primary treatment. An example from patients with NSCLC: a study of the REACT working group of ESTRO. *Radiother Oncol* 2006;**78**:95–100.

78. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;**17**:2692–9.
79. Mac Manus MP, Hicks RJ, Matthews JP, Wirth A, Rischin D, Ball DL. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2005;**49**:95–108.
80. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004;**46**:87–98.
81. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95–01 Study. *J Clin Oncol* 2005;**23**:5910–7.
82. Korst RJ, Gold HT, Kent MS, Port JL, Lee PC, Altorki NK. Surveillance computed tomography after complete resection for non-small cell lung cancer: results and costs. *J Thorac Cardiovasc Surg* 2005;**129**:652–60.
83. Korst RJ, Kansler AL, Port JL, Lee PC, Altorki NK. Accuracy of surveillance computed tomography in detecting recurrent or new primary lung cancer in patients with completely resected lung cancer. *Ann Thorac Surg* 2006;**82**:1009–15. discussion 15.
84. Higashi K, Ueda Y, Ayabe K, et al. FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features. *Nucl Med Commun* 2000;**21**:707–14.
85. Higashi K, Ueda Y, Yagishita M, et al. FDG PET measurement of the proliferative potential of non-small cell lung cancer. *J Nucl Med* 2000;**41**:85–92.
86. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. *Clin Cancer Res* 2000;**6**:3837–44.
87. Berghmans T, Dusart M, Paesmans M, et al. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol* 2008;**3**:6–12.
88. Ichiya Y, Kuwabara Y, Sasaki M, et al. A clinical evaluation of FDG-PET to assess the response in radiation therapy for bronchogenic carcinoma. *Ann Nucl Med* 1996;**10**:193–200.
89. Eschmann SM, Friedel G, Paulsen F, et al. Is standardised (18)F-FDG uptake value an outcome predictor in patients with stage III non-small cell lung cancer? *Eur J Nucl Med Mol Imaging* 2006;**33**:263–9.
90. Borst GR, Belderbos JS, Boellaard R, et al. Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. *Eur J Cancer* 2005;**41**:1533–41.
91. Hoang JK, Hoagland LF, Coleman RE, Coan AD, Herndon 2nd JE, Patz Jr EF. Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography imaging in patients with advanced-stage non-small-cell lung carcinoma. *J Clin Oncol* 2008;**26**:1459–64.
92. Higashi K, Clavo AC, Wahl RL. Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. *J Nucl Med* 1993;**34**:414–9.
93. van Baardwijk A, Dooms C, van Suylen RJ, et al. The maximum uptake of (18)F-deoxyglucose on positron emission tomography scan correlates with survival, hypoxia inducible factor-1alpha and GLUT-1 in non-small cell lung cancer. *Eur J Cancer* 2007;**43**:1392–8.
94. Nahmias C, Hanna WT, Wahl LM, Long MJ, Hubner KF, Townsend DW. Time course of early response to chemotherapy in non-small cell lung cancer patients with 18F-FDG PET/CT. *J Nucl Med* 2007;**48**:744–51.
95. Hoekstra CJ, Stroobants SG, Smit EF, et al. Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol* 2005;**23**:8362–70.
96. Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003;**21**:2651–7.
97. de Geus-Oei LF, van der Heijden HF, Visser EP, et al. Chemotherapy response evaluation with 18F-FDG PET in patients with non-small cell lung cancer. *J Nucl Med* 2007;**48**:1592–8.
98. Decoster L, Schallier D, Everaert H, et al. Complete metabolic tumour response, assessed by 18-fluorodeoxyglucose positron emission tomography (18FDG-PET), after induction chemotherapy predicts a favourable outcome in patients with locally advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 2008;**62**:55–61.
99. Hellwig D, Graeter TP, Ukena D, Georg T, Kirsch CM, Schafers HJ. Value of F-18-fluorodeoxyglucose positron emission tomography after induction therapy of locally advanced bronchogenic carcinoma. *J Thorac Cardiovasc Surg* 2004;**128**:892–9.
100. Pottgen C, Levegrun S, Theegarten D, et al. Value of 18F-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. *Clin Cancer Res* 2006;**12**:97–106.
101. Tanvetyanon T, Eikman EA, Sommers E, Robinson L, Boulware D, Bepler G. Computed tomography response, but not positron emission tomography scan response, predicts survival after neoadjuvant chemotherapy for resectable non-small-cell lung cancer. *J Clin Oncol* 2008;**26**:4610–6.
102. Kong FM, Frey KA, Quint LE, et al. A pilot study of [18F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. *J Clin Oncol* 2007;**25**:3116–23.
103. Zhang HQ, Yu JM, Meng X, Yue JB, Feng R, Ma L. Prognostic value of serial [(18)F]fluorodeoxyglucose PET-CT uptake in stage III patients with non-small cell lung cancer treated by concurrent chemoradiotherapy. Eur J Radiol 2009 Aug 18. Epub ahead of print.
104. van Baardwijk A, Bosmans G, Dekker A, et al. Time trends in the maximal uptake of FDG on PET scan during thoracic radiotherapy. A prospective study in locally advanced non-small cell lung cancer (NSCLC) patients. *Radiother Oncol* 2007;**82**:145–52.
105. Krak NC, Boellaard R, Hoekstra OS, Twisk JW, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. *Eur J Nucl Med Mol Imaging* 2005;**32**:294–301.
106. Minn H, Zasadny KR, Quint LE, Wahl RL. Lung cancer: reproducibility of quantitative measurements for evaluating 2-[F-18]-fluoro-2-deoxy-D-glucose uptake at PET. *Radiology* 1995;**196**:167–73.
107. Nakamoto Y, Zasadny KR, Minn H, Wahl RL. Reproducibility of common semi-quantitative parameters for evaluating lung cancer glucose metabolism with positron emission tomography using 2-deoxy-2-[18F]fluoro-D-glucose. *Mol Imaging Biol* 2002;**4**:171–8.
108. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 1999;**35**:1773–82.
109. Mac Manus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol* 2003;**21**:1285–92.
110. Wahl RL, Jacene H, Kasamon Y, From LodgeMA, ST RECI. To PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;**50**(Suppl 1):122S–50S.
111. Bruzzi JF, Munden RF. PET/CT imaging of lung cancer. *J Thorac Imaging* 2006;**21**:123–36.
112. Hicks RJ, Kalff V, MacManus MP, et al. The utility of (18)F-FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: impact on management and prognostic stratification. *J Nucl Med* 2001;**42**:1605–13.
113. Rubins J, Unger M, Colice GL. Follow-up and surveillance of the lung cancer patient following curative intent therapy: ACCP evidence-based clinical practice guideline (2nd edition). *Chest* 2007;**132**:355S–67S.
114. Duhaylongsod FG, Lowe VJ, Patz Jr EF, Vaughn AL, Coleman RE, Wolfe WG. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). *J Thorac Cardiovasc Surg* 1995;**110**:130–9. discussion 9-40.
115. Patz Jr EF, Lowe VJ, Hoffman JM, Paine SS, Harris LK, Goodman PC. Persistent or recurrent bronchogenic carcinoma: detection with PET and 2-[F-18]-2-deoxy-D-glucose. *Radiology* 1994;**191**:379–82.
116. Hebert ME, Lowe VJ, Hoffman JM, Patz EF, Anscher MS. Positron emission tomography in the pretreatment evaluation and follow-up of non-small cell lung cancer patients treated with radiotherapy: preliminary findings. *Am J Clin Oncol* 1996;**19**:416–21.
117. Choi NC, Herndon 2nd JE, Rosenman J, et al. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *J Clin Oncol* 1998;**16**:3528–36.
118. Eschmann SM, Friedel G, Paulsen F, et al. 18F-FDG PET for assessment of therapy response and preoperative re-evaluation after neoadjuvant radio-chemotherapy in stage III non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2007;**34**:463–71.
119. Ryu JS, Choi NC, Fischman AJ, Lynch TJ, Mathisen DJ. FDG-PET in staging and restaging non-small cell lung cancer after neoadjuvant chemoradiotherapy: correlation with histopathology. *Lung Cancer* 2002;**35**:179–87.
120. Keidar Z, Haim N, Guralnik L, et al. PET/CT using 18F-FDG in suspected lung cancer recurrence. Diagnostic value and impact on patient management. *J Nucl Med* 2004;**45**:1640–6.
121. Hicks RJ, Mac Manus MP, Matthews JP, et al. Early FDG-PET imaging after radical radiotherapy for non-small-cell lung cancer: inflammatory changes in normal tissues correlate with tumor response and do not confound therapeutic response evaluation. *Int J Radiat Oncol Biol Phys* 2004;**60**:412–8.
122. Henderson MA, Hoopes DJ, Fletcher JW, et al. A pilot trial of serial 18F-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;**76**:789–95.
123. Ishimori T, Saga T, Nagata Y, et al. 18F-FDG and 11C-methionine PET for evaluation of treatment response of lung cancer after stereotactic radiotherapy. *Ann Nucl Med* 2004;**18**:669–74.
124. Benamore R, Shepherd FA, Leighl N, et al. Does intensive follow-up alter outcome in patients with advanced lung cancer? *J Thorac Oncol* 2007;**2**:273–81.
125. Edelman MJ, Schuetz J. Follow-up of local (stage I and stage II) non-small-cell lung cancer after surgical resection. *Curr Treat Options Oncol* 2002;**3**:67–73.

126. Walsh GL, O'Connor M, Willis KM, et al. Is follow-up of lung cancer patients after resection medically indicated and cost-effective? *Ann Thorac Surg* 1995;**60**:1563–70. discussion 70-2.
127. Patz Jr EF, Connolly J, Herndon J. Prognostic value of thoracic FDG PET imaging after treatment for non-small cell lung cancer. *AJR Am J Roentgenol* 2000;**174**: 769–74.
128. Ahuja V, Coleman RE, Herndon J, Patz Jr EF. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer* 1998;**83**:918–24.
129. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol* 2004;**22**:3255–60.
130. Kased N, Erasmus JJ, Komaki R, Cox JD. Prognostic value of posttreatment [18F] fluorodeoxyglucose uptake of primary non-small cell lung carcinoma treated with radiation therapy with or without chemotherapy: a brief review. *J Thorac Oncol* 2008;**3**:534–8.
131. van Loon J, Grutters J, Wanders R, et al. Follow-up with 18FDG-PET-CT after radical radiotherapy with or without chemotherapy allows the detection of potentially curable progressive disease in non-small cell lung cancer patients: a prospective study. *Eur J Cancer* 2009;**45**:588–95.
132. van Loon J, Grutters JP, Wanders R, et al. 18FDG-PET-CT in the follow-up of non-small cell lung cancer patients after radical radiotherapy with or without chemotherapy: an economic evaluation. *Eur J Cancer* 2010;**46**:110–9.
133. Apisarnthanarax S, Alauddin MM, Mourtada F, et al. Early detection of chemoradioresponse in esophageal carcinoma by 3′-deoxy-3′-3H-fluorothymidine using preclinical tumor models. *Clin Cancer Res* 2006;**12**:4590–7.
134. Buck AK, Halter G, Schirrmeister H, et al. Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG. *J Nucl Med* 2003;**44**:1426–31.
135. Muzi M, Vesselle H, Grierson JR, et al. Kinetic analysis of 3′-deoxy-3′-fluorothymidine PET studies: validation studies in patients with lung cancer. *J Nucl Med* 2005;**46**:274–82.
136. Wagner M, Seitz U, Buck A, et al. 3′-[18F]fluoro-3′-deoxythymidine ([18F]-FLT) as positron emission tomography tracer for imaging proliferation in a murine B-cell lymphoma model and in the human disease. *Cancer Res* 2003;**63**:2681–7.
137. Yamamoto Y, Nishiyama Y, Ishikawa S, et al. Correlation of 18F-FLT and 18F-FDG uptake on PET with Ki-67 immunohistochemistry in non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2007;**34**:1610–6.
138. Yap CS, Czernin J, Fishbein MC, et al. Evaluation of thoracic tumors with 18F-fluorothymidine and 18F-fluorodeoxyglucose-positron emission tomography. *Chest* 2006;**129**:393–401.
139. Pan MH, Huang SC, Liao YP, et al. FLT-PET imaging of radiation responses in murine tumors. *Mol Imaging Biol* 2008;**10**:325–34.
140. Roels S, Slagmolen P, Nuyts J, et al. Biological image-guided radiotherapy in rectal cancer: is there a role for FMISO or FLT, next to FDG? *Acta Oncol* 2008;**47**:1237–48.
141. Wieder HA, Geinitz H, Rosenberg R, et al. PET imaging with [18F]3′-deoxy-3′-fluorothymidine for prediction of response to neoadjuvant treatment in patients with rectal cancer. *Eur J Nucl Med Mol Imaging* 2007;**34**:878–83.
142. Kubota R, Kubota K, Yamada S, et al. Methionine uptake by tumor tissue: a microautoradiographic comparison with FDG. *J Nucl Med* 1995;**36**:484–92.
143. Nettelbladt OS, Sundin AE, Valind SO, et al. Combined fluorine-18-FDG and carbon-11-methionine PET for diagnosis of tumors in lung and mediastinum. *J Nucl Med* 1998;**39**:640–7.
144. Tsuyuguchi N, Sunada I, Ohata K, et al. Evaluation of treatment effects in brain abscess with positron emission tomography: comparison of fluorine-18-fluorodeoxyglucose and carbon-11-methionine. *Ann Nucl Med* 2003;**17**:47–51.
145. van Waarde A, Jager PL, Ishiwata K, Dierckx RA, Elsinga PH. Comparison of sigma-ligands and metabolic PET tracers for differentiating tumor from inflammation. *J Nucl Med* 2006;**47**:150–4.
146. Murayama C, Harada N, Kakiuchi T, et al. Evaluation of D-18F-FMT, 18F-FDG, L-11C-MET, and 18F-FLT for monitoring the response of tumors to radiotherapy in mice. *J Nucl Med* 2009;**50**:290–5.
147. Yamaura G, Yoshioka T, Fukuda H, et al. O-[18F]fluoromethyl-L-tyrosine is a potential tracer for monitoring tumour response to chemotherapy using PET: an initial comparative in vivo study with deoxyglucose and thymidine. *Eur J Nucl Med Mol Imaging* 2006;**33**:1134–9.
148. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep.* 1973;**4**:31–42. Part 3.
149. de Jong WK, Schaapveld M, Blaauwgeers JL, Groen HJ. Pulmonary tumours in the Netherlands: focus on temporal trends in histology and stage and on rare tumours. *Thorax* 2008;**63**:1096–102.
150. Bunn Jr PA, Carney DN. Overview of chemotherapy for small cell lung cancer. *Semin Oncol* 1997;**24**. S7-69–S7-74.
151. Ihde DC. Small cell lung cancer. State-of-the-art therapy 1994. *Chest* 1995;**107**:243S–8S.
152. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;**22**:3248–54.
153. Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2004;**31**:1614–20.
154. Chin Jr R, McCain TW, Miller AA, et al. Whole body FDG-PET for the evaluation and staging of small cell lung cancer: a preliminary study. *Lung Cancer* 2002;**37**:1–6.
155. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. *Ann Oncol* 2007;**18**:338–45.
156. Niho S, Fujii H, Murakami K, et al. Detection of unsuspected distant metastases and/or regional nodes by FDG-PET in LD-SCLC scan in apparent limited-disease small-cell lung cancer. *Lung Cancer* 2007;**57**:328–33.
157. Pandit N, Gonen M, Krug L, Larson SM. Prognostic value of [18F]FDG-PET imaging in small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2003;**30**:78–84.
158. Shen YY, Shiau YC, Wang JJ, Ho ST, Kao CH. Whole-body 18F–2-deoxyglucose positron emission tomography in primary staging small cell lung cancer. *Anticancer Res* 2002;**22**:1257–64.
159. Vinjamuri M, Craig M, Campbell-Fontaine A, Almubarak M, Gupta N, Rogers JS. Can positron emission tomography be used as a staging tool for small-cell lung cancer? *Clin Lung Cancer* 2008;**9**:30–4.
160. Ung YC, Maziak DE, Vanderveen JA, et al. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. *J Natl Cancer Inst* 2007;**99**:1753–67.
161. Azad A, Chionh F, Scott AM, et al. High Impact of (18)F-FDG-PET on management and prognostic stratification of newly diagnosed small cell lung cancer. *Mol Imaging Biol* 2009;**12**(4):443–51.
162. Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. *Am J Clin Oncol* 2004;**27**:164–71.
163. Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. *J Nucl Med* 2003;**44**:1911–7.
164. Schumacher T, Brink I, Mix M, et al. FDG-PET imaging for the staging and follow-up of small cell lung cancer. *Eur J Nucl Med* 2001;**28**:483–8.
165. Videtic GM, Belderbos JS, Spring Kong FM, Kepka L, Martel MK, Jeremic B. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: small-cell lung cancer (SCLC). *Int J Radiat Oncol Biol Phys* 2008;**72**:327–34.
166. De Ruysscher D, Bremer RH, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol* 2006;**80**:307–12.
167. van Loon J, Offermann C, Bosmans G, et al. 18FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study. *Radiother Oncol* 2008;**87**: 49–54.
168. Turrisi 3rd AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;**340**:265–71.
169. Vanloon J, De Ruysscher D, Wanders R, et al. Selective Nodal Irradiation on Basis of (18)FDG-PET Scans in Limited-Disease Small-Cell Lung Cancer: A Prospective Study. *Int J Radiat Oncol Biol Phys* 2010;**77**(2):329–36. Part 1.
170. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006;**24**:1057–63.
171. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, Kester A, Rutten I, Lambin P. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. *Ann Oncol* 2006;**17**:543–52.
172. Pijls-Johannesma MC, De Ruysscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited stage small cell lung cancer. Cochrane Database Syst Rev 2005:CD004700.
173. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol* 1999;**17**:2092–9.
174. Shepherd FA, Ginsberg RJ, Haddad R, et al. Importance of clinical staging in limited small-cell lung cancer: a valuable system to separate prognostic subgroups. The University of Toronto Lung Oncology Group. *J Clin Oncol* 1993;**11**:1592–7.
175. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007;**2**:1067–77.
176. Vallieres E, Shepherd FA, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;**4**:1049–59.
177. Lee YJ, Cho A, Cho BC, et al. High tumor metabolic activity as measured by fluorodeoxyglucose positron emission tomography is associated with poor prognosis in limited and extensive stage small-cell lung cancer. *Clin Cancer Res* 2009;**15**:2426–32.
178. Fischer BM, Mortensen J, Langer SW, et al. PET/CT imaging in response evaluation of patients with small cell lung cancer. *Lung Cancer* 2006;**54**: 41–9.
179. Yamamoto Y, Kameyama R, Murota M, Bandoh S, Ishii T, Nishiyama Y. Early assessment of therapeutic response using FDG PET in small cell lung cancer. *Mol Imaging Biol* 2009;**11**:467–72.
180. Onitilo AA, Engel JM, Demos JM, Mukesh B. Prognostic significance of 18 F-fluorodeoxyglucose – positron emission tomography after treatment in patients with limited stage small cell lung cancer. *Clin Med Res* 2008;**6**:72–7.