Chapter 9

Early Metabolic Response Evaluation After Stereotactic Radiotherapy for Lung Cancer: Pilot Experience with 18F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography

M. Dahele *†, M. Freeman †‡, S. Pearson *, A. Brade*†, B.C.J. Cho *†, A. Hope *†, K. Franks *†, T. Purdie *†, J.P. Bissonnette *†, D.A. Jaffray *†, A. Bezjak *†, A. Sun*†

*Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, Canada

†Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

‡Department of Medical Imaging, Princess Margaret Hospital, University Health Network, Toronto, Canada

Clin Oncol (R Coll Radiol) 2011;23:359-363.

Abstract

The early response of lung tumours to stereotactic radiotherapy was prospectively evaluated with 18F-fluorodeoxyglucose positron emission tomography - computed tomography. Three months after treatment, the maximum standardised uptake value and the tumour diameter fell by 64 and 30%, respectively. This imaging strategy therefore remains under ongoing evaluation with the aim of identifying predictive and prognostic factors.

Introduction

Lung cancer is the leading cause of cancer death in men and women [1]. In North America, about 80% of patients have non-small cell lung cancer (NSCLC), about 20% of which are early stage tumours (e.g. stage I, T1-T2N0M0) [2]. The standard treatment for these is surgical resection with reported 5-year survival rates in excess of 50% and local failure rates as low as 5-10% [3]. However, some patients are medically inoperable due to co-morbid disease [4] or decline surgery and so effective non-surgical treatments are needed. Conventional external beam radiotherapy has been disappointing, with local failure rates up to 70% and overall 5-year survival 0-42% [5]. Stereotactic body radiotherapy (SBRT) is a treatment technique that is typically used to deliver higher doses of radiotherapy per fraction (e.g. 5-20 Gy versus 2-3 Gy) in fewer total fractions (e.g. 3-10 versus 20-30 or more) than usual. Several non-randomised reports and a meta-analysis now indicate that it is superior to conventional radiotherapy for early stage NSCLC and local control rates comparable with surgery seem to be within reach [6-8].

Response assessment after SBRT typically makes use of computed tomography (CT)-based anatomic changes. However, maximum tumour shrinkage can take several months and treatment-induced lung changes (e.g. apparently fibrotic masses) can confound the evaluation [9]. An accurate and timely response assessment has become even more important as SBRT is being proposed as a possible alternative to surgery in patients with medically operable, early stage disease [10]. In this context, identifying or predicting treatment failure could still allow definitive ‘salvage’ therapy. MacManus et al. [11] showed that the addition of metabolic imaging to CT improves the response assessment after conventional radiotherapy or chemoradiotherapy for NSCLC [11]. Here we describe a pilot experience with 18F-fluorodeoxyglucose

positron emission tomography-CT (FDG PETCT) for response assessment 3 months after SBRT for lung tumours. The decision to image 3 months after SBRT was made in the absence of clear data to favour another time point, and with the aim of identifying early indicators of response that would still allow patients to undergo 'salvage' procedures with curative intent.

Materials and Methods

Patients were enrolled on research ethics board-approved institutional lung SBRT studies that allowed 18F-FDG PET-CT imaging at baseline (before SBRT) and 3 months after SBRT in addition to follow-up CT scans at 6 month intervals. Thirty consecutive patients (17 women, 13 men, median age 69.5 years, range 52-85 years) who received lung SBRT for a diagnosis of medically inoperable stage I primary lung cancer (n=31 tumours) were evaluated. In 12/31 (39%) lesions where there was a relative contraindication to biopsy, the diagnosis was clinical (e.g. based upon serial enlargement of the index lesion ± metabolically active lesion on PET scan). The remainder were confirmed malignant (n=18) or suspicious (n=1). Smaller, central T1 lesions were treated with 50 Gy in 10 fractions (n=1) or 60 Gy in eight fractions (n= 3) and those close to ribs received 48 Gy in four fractions (n=16). Other more peripheral lesions received 54 or 60 Gy in three fractions (n=11).

Imaging Methodology Baseline and post-SBRT 18F-FDG PET-CT imaging was carried out on a dedicated diagnostic PET/CT scanner. A blood sample was taken before injection to confirm an acceptable blood sugar level (<9.7 mmol/l). After fasting for a period of 6 h, patients were injected with 5 MBq/kg 18F-FDG. Whole body images were acquired 60 min after tracer administration. The unenhanced CT scan was carried out first, from the patient's auditory meatus to the upper/mid-thighs, using the following acquisition parameters: 130 kVp, 110 mAs, CARE Dose, 5.0mm slice width, 4.0mm collimation, 0.8 s/rotation, 7.2mm feed/rotation with a reconstruction slice thickness of 2.5mm. The CT data were reconstructed using a filtered backprojection algorithm and a 512 x 512 matrix, with a transaxial field of view of 50 cm. After the CT scan, the emission scan was obtained in three-dimensional mode starting at the mid-thighs towards the head, for five to eight bed positions of 3 min each. CT images were used to generate the transmission maps for attenuation correction of the PET acquisitions. PET data were reconstructed with an

iterative reconstruction algorithm with scatter correction (eight subsets, two iterations). The follow-up thoracic CT scans beyond 3 months were acquired at 2.5mm slice thickness and intravenous contrast was used unless contraindicated.

Response Evaluation Baseline and 3 month response evaluation was carried out by two observers working together, without prior knowledge of the treatment dose. All baseline and post-SBRT PET-CT scans were reviewed. The maximum tumour diameter was measured in the axial plane on the CT component of the PET-CT scan, using 'lung' window/level settings (1500, -600) and the anatomic response was categorised using RECIST criteria [12]. Metabolic activity was obtained by designating the entire tumour volume a region of interest, and using this to derive the maximum standardised uptake value (SUVmax) [13]; the SUVmax was not adjusted for partial volume effect. Subsequent follow-up CT scans were reviewed on the Fusion eFilm 2.1.2 platform.

Comparing Radiation Doses The biological effective dose (BED) is frequently used to compare the potency of different radiotherapy regimens. The equation is given below, and although it may not accurately reflect the effects of SBRT it is not infrequently used for illustrative purposes. The BED for acute tumour effects using the treatment regimens in this series are: 48 Gy in four fractions=105.6 (n=16); 54 Gy in three fractions=151.2 (n=6); 60 Gy in three fractions=180 (n=5); 60 Gy in eight fractions=105 (n=3) and 50 Gy in 10 fractions=75 (n=1)

$$BED = D(1+d/[\alpha/\beta])$$

where D = prescribed radiation dose (Gy); α/β ratio (Gy) reflecting the characteristic radiation response of the particular tissue of interest (e.g. conventionally 10 Gy for the acute effect on
tumour).

Data Analysis The non-parametric Mann-Whitney test and Pearson's correlation were used. A P-value <0.05 was taken as representing statistical significance.

Results

Baseline Characteristics The median baseline SUVmax for all lesions was 5.8 (1-14.7). In the 12 lesions diagnosed clinically, the median baseline SUVmax was 6.9 (2.5-14.7), compared with 5.2 (1-12.5) in those with a positive or suspicious biopsy. The respective median maximum diameters at baseline were 2.2 (1.3-4.4) and 2.2 (1-4.5) cm. The post-SBRT PET-CT scan was carried out at 3 months (median 83 days, range 65-104 days). The median interval between the baseline PET-CT scan and (1) the last fraction of radiotherapy, was 32.5 days (16-109 days, all except one between 16 and 51 days) and (2) the post-SBRT scan, was 118 days (91-189 days, all except one between 91 and 140 days). The median clinical follow-up was 326 days (81-486 days), measured from the last fraction of SBRT.

Change in Dimension and Metabolic Activity Figures 1 and 2 illustrate the change in maximum tumour diameter and SUVmax, respectively, as measured on the baseline and post-SBRT PET-CT scans. The median maximum diameters at baseline and post-SBRT were 2.2 (1-4.5) and 1.5 (0-3.4) cm, respectively ($P< 0.05$). The median absolute and relative reductions in diameter were 0.7 cm (+0.1 cm to -3.2 cm, where the 'plus' denotes an increase and 'minus' a reduction) and 30% (+9% to -100%), respectively. At 3 months after SBRT, 15 tumours (48%) had not achieved a reduction in maximum diameter of at least 30%, the conventional RECIST criterion of response.

The median SUVmax at baseline and after SBRT was 5.8 (1-14.7) and 1.7 (0-4.8) ($P< 0.05$). The baseline SUVmax and the maximum lesion diameter were significantly correlated ($P<0.05$). The median absolute and relative reductions in SUVmax were 3.6 (+0.5 to -11.6) and 64% (+50% to -100%). The baseline SUVmax and the subsequent percentage reduction were significantly correlated ($P<0.05$) as were the percentage reduction in maximum diameter and SUVmax ($P<0.05$). The time between the last fraction and 3 month PET-CT and the percentage reduction in SUVmax were not ($r=0.02$). Only one lesion failed to achieve a reduction in SUVmax (see below); of the remaining lesions, the minimum reduction in SUVmax was 32%. In the group with anatomically 'stable disease', the median reduction in SUVmax was 60% (+50% to -92%). The single lesion that demonstrated an increase in SUVmax of 50% measured only 1.1 and 1.2 cm in maximum diameter before and 3 months after SBRT

and had a very low SUVmax on both occasions: 1 and 1.5, respectively. There were three complete anatomic, and also metabolic, responses at the time of the initial follow-up PET-CT scan. Although not originally described in the context of SBRT, if the data were evaluated using the European Organization for Research and Treatment of Cancer definition of metabolic response (≥25% reduction in metabolic activity) then 30/31 (97%) tumours had a metabolic response. In total, 22/31 had a reduction in metabolic activity of ≥50% and 12/31 a reduction of ≥75%.

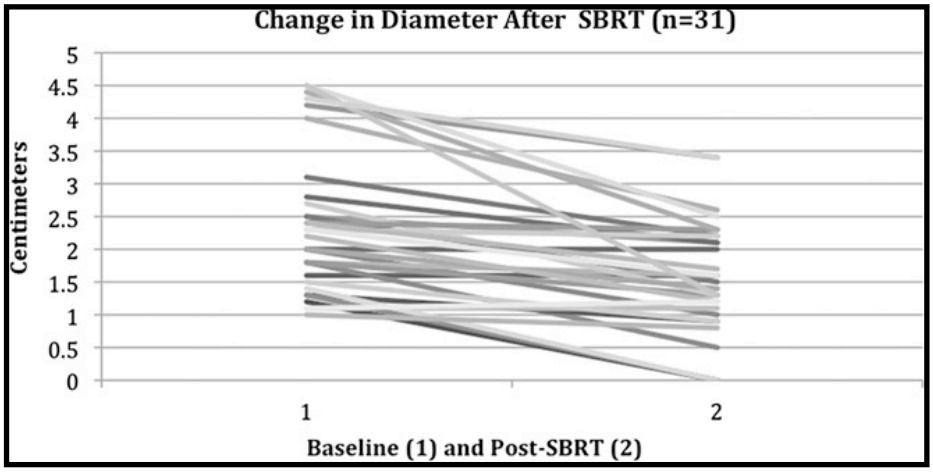

Figure 1 The maximum diameter of 31 lung tumours before and after stereotactic body radiotherapy (median interval between last fraction of stereotactic body radiotherapy and follow-up imaging 83 days).

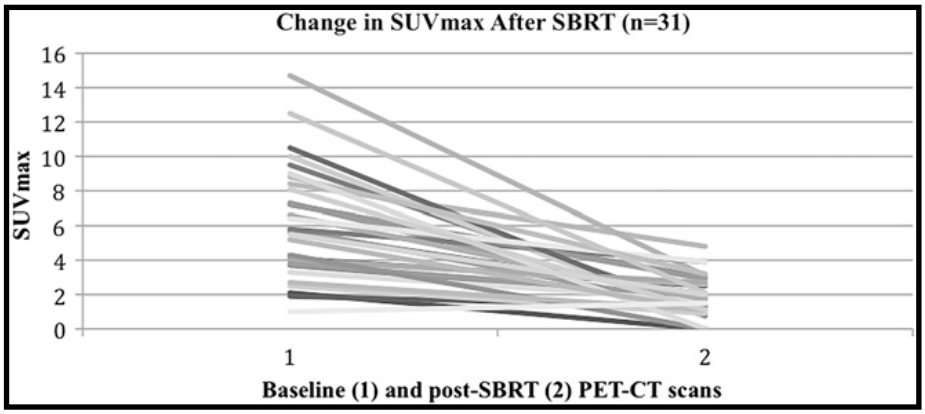

Figure 2 The maximum standardised uptake value (SUVmax) of 31 lung tumours before and after stereotactic body radiotherapy (median interval between last fraction of stereotactic body radiotherapy and follow-up imaging 83 days).

To explore the influence of dose on metabolic response, two subgroups of tumours were compared, one receiving a 'low' BED of about 105 (48 Gy in four fractions and 60 Gy in eight fractions, n=19) and one a 'high' BED of about 150-180 (54 or 60 Gy in three fractions, n= 11) BED (the only tumour to receive 50 Gy in 10 fractions with a BED of 75 is not included). The median reduction in SUVmax for both was 64%. However, there was one outlying tumour in the 'high' BED group that showed an increase in SUVmax of 50%, from 1 to 1.5.

Computed Tomography Changes after Stereotactic Body Radiotherapy and Local Control Although all tumours were evaluable at about 3 months after SBRT, we found that during the follow-up period, parenchymal lung changes attributed to SBRT that hindered anatomic response assessment developed in seven patients. Three additional patients achieved a complete anatomic response during the follow-up period having shown a 33, 74 and 83% reduction in SUVmax 3 months after SBRT. On the basis of an expanding lesion at the primary tumour site (first noted 7 months after SBRT), one patient was deemed to have progressed after an initial anatomic and metabolic response.

Discussion

Prospective pilot experience with FDG PET imaging before and 3 months after SBRT showed that in nearly all cases (30/31=97%) the metabolic activity of the tumour fell considerably after SBRT (median reduction 64%), whereas the CT-based anatomic response showed a more modest change (median reduction 30%). This is consistent with the results of Chao et al. [14]. It was observed that the median reduction in SUVmax was similar for lesions that were stable or partial responders by RECIST criteria. Having seen in this pilot evaluation quantifiable changes of varying magnitude in metabolic activity about 3 months after lung SBRT, this imaging strategy is now the subject of ongoing prospective evaluation with the aim of trying to identify and refine metrics that can inform early response prediction and provide prognostic information.

Several authors have described their experience with metabolic imaging after SBRT in patients with varying stages of NSCLC. Feigenberg et al. [15] obtained FDG-PET scans a median of 3 months after SBRT, concluding that the PET response (defined as

a drop in the SUVmax by 3 months) correlated with local failure, and seemed to be a good early surrogate for response. However, in the present series, a local failure was seen after a metabolic response, consistent with Coon et al. [16], who described two patients with an initial reduction in SUVmax and subsequent local progression. With such high early local control rates after SBRT, the subsequent rate of local failure is low, underscoring the importance of larger studies with sufficient follow-up to accurately determine the role of FDG PET as a predictive tool. Extension of this study will allow the results to be contrasted with those of other groups, including Burdick et al. [17], who recently reported that pre-treatment SUVmax did not predict for treatment outcome after lung SBRT. In addition to low event rate and adequate follow-up, there are additional cautionary notes when evaluating PET in stereotactic lung radiotherapy. For example: (1) prolonged elevation of FDG uptake may be observed after SBRT and should not automatically be assumed to represent local failure [18-20]; (2) consistent with others [9], we saw examples of radiological changes in the lung during follow-up. Although post-treatment inflammation might also be expected to confound the assessment of metabolic activity, we found that in this small series all lesions remained evaluable on CT about 3 months after SBRT and there was a high rate of reduction in metabolic activity at this time point. More marked changes generally became apparent at subsequent evaluations. However, this was not a specific end point of the present study and both longer follow-up and greater patient numbers are necessary to describe in more detail the characteristics, incidence, timing and evolution of parenchymal changes in our population. Our initial experience is broadly consistent with Matsuo et al. [21] who reported that mass-like consolidation was seen a median of 5 months after treating 27/40 (68%) tumours with SBRT and Trovo et al. [22] who described most patients as having no radiographic evidence of lung injury 6 weeks after lung SBRT and patchy and diffuse consolidation developing 2-6 months after treatment [22]. Interestingly, in a study that showed no difference in the incidence of clinical or early radiographic lung changes between patients treated with SBRT delivered with volumetric modulated arc therapy or three-dimensional conformal radiotherapy, Palma et al. [23] reported that 57% of patients had radiological changes of pneumonitis 3 months after SBRT. Standardised evaluation metrics and improved appreciation of the temporal evolution of pulmonary changes, including their association with the dose-volume histogram, treatment technique and treatment planning strategies will be needed to better understand SBRT

and its effect on radiological appearance and physiological function. (3) It is acknowledged that most of the tumours were relatively small and therefore susceptible to partial volume effects and underestimation of SUVmax [24]. How much this could have contributed to the observed reduction in SUVmax over time has not been quantified.

Currently, the most appropriate way to describe anatomic and metabolic response after lung SBRT is not known. The SUVmax is a widely used quantitative end point. However, it may be affected by a number of factors, including lesion size, background activity and motion, as well as technical factors relating to scanner performance and patient preparation. This is especially relevant when comparing longitudinal and multi-centre data and highlights the importance of robust quality assurance for imaging studies [25]. We recognise that using the European Organization for Research and Treatment of Cancer criteria that are generally applied to tumours after chemotherapy is open to debate and that there are other response indicators, such as visual response assessment [11], that could have been considered. Recent data suggest that in addition to quantitative metrics, such as SUVmax, alternative means of PET image analysis, including feature-based approaches (e.g. intensity-volume histograms, shape and texture), may provide insight into tumour response [26] and there is significant interest in the use of volumetric CT-based response evaluation as a predictive tool, which may also merit further evaluation in this patient population [27].

In terms of some of the potential limitations of this study, we include the following observations: (1) In static, three dimensional PET imaging, breathing-induced lesion motion can result in the loss of PET data, depending in part upon such factors as lesion location, size, motion amplitude and breathing pattern [28]. More advanced PET imaging techniques, including four-dimensional PET (-CT) may enable at least partial recovery of ‘lost’ information and improve the interpretation of PET studies for moving lesions [29]. The PET-CT images in the present study were not carried out with this technology, which is gradually becoming more widely available. (2) Although about 40% of the lesions were not pathologically confirmed as NSCLC, this is not unique [7,17]. In addition, the median SUVmax was higher in those patients without a biopsy, and the range was comparable between the two groups, as was the

lesion diameter. (3) The timing of baseline and follow-up studies may also be relevant. However, although the interval between the last radiotherapy fraction and post-SBRT PET-CT varied, we did not see a strong correlation between the percentage reduction in metabolic activity and this interval. (4) Finally, we carried out the baseline and 3 month CT measurement on the CT component of the PET-CT scan. Although not possessing the same imaging characteristics as a diagnostic CT scan of the thorax, all such measurements were consistent across the study group.

In this preliminary evaluation of the early metabolic response to lung SBRT, we have observed that activity in most lung tumours decreases substantially, and that this occurs to a greater extent than a reduction in size. With modest follow up we have observed one local tumour failure after a previous metabolic and anatomic response, highlighting the pitfalls of response prediction. Although we did not see a dose-response effect in this preliminary report, this might be obscured by the fact that both the 'low' and 'high' groups had a BED of more than 100 for acute tumour effect, which has previously been suggested as being associated with a more favourable outcome [30]. With this initial information we are now continuing this imaging strategy with the aim of trying to identify PET metrics for response assessment and prognosis.

Acknowledgements

Funding was provided in part by the Addie MacNaughton Chair in Thoracic Radiation Oncology, Princess Margaret Hospital, and by the Elekta Synergy Research Group.

References

1. Lung Cancer Statistics. Canadian Cancer Society. Available at: http://www.cancer.ca/Canadawide/About%20cancer/Cancer%20statistics/Stats%20at%20a%20glance/Lung%20cancer.aspx?sc_lang=en; 2008. Accessed 26 October 2008.

2. Morgensztern D, Goodgame B, Baggstrom MQ, Gao F, Govindan R. The effect of FDG-PET on the stage distribution of non-small cell lung cancer. J Thorac Oncol 2008;3:135-139.

3. El-Sherif A, Gooding WE, Santos R, et al. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. Ann Thorac Surg 2006;82:408-415.

4. Ghosh S, Sujendran V, Alexiou C, Beggs L, Beggs D. Long term results of surgery versus continuous hyperfractionated accelerated radiotherapy (CHART) in patients aged >70 years with stage 1 non-small cell lung cancer. Eur J Cardiothorac Surg 2003;24:1002-1007.

5. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II nonsmall cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax 2001;56:628-638.

6. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-1076.

7. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-692.

8. Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol 2010;95:32-40.

9. Guckenberger M, Heilman K, Wulf J, Mueller G, Beckmann G, Flentje M. Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol 2007;85:435-442. Erratum in:2008;86:293.

10. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. Radiat Oncol 2009;4:1.

11. MacManus 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;21:1285-1292.

12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-216.

13. 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;35:1773-1782.

14. Chao KK, Grills IS, Kestin LL, et al. Radiographic and metabolic response of solitary lung tumors to image guided stereotactic radiotherapy. Proceedings of the 49th Annual ASTRO Meeting. Int J Radiat Oncol Biol Phys 2007;69:89S.

15. Feigenberg SJ, Yu JQ, Eade T, et al. PET response following stereotactic body radiotherapy for non-small cell lung carcinoma correlates with local control. ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2007;25:18013.

16. Coon D, Gokhale AS, Burton SA, Heron DE, Ozhasoglu C, Christie N. Fractionated stereotactic body radiation therapy in the treatment of primary, recurrent, and metastatic lung tumors: the role of positron emission tomography/computed tomography-based treatment planning. Clin Lung Cancer 2008;9:217-221.

17. Burdick MJ, Stephans KL, Reddy CA, Djemil T, Srinivas SM, Videtic GM. Maximum standardized uptake values from staging FDG-PET/CT does not predict treatment outcome for early-stage non-small-cell lung cancer treated with stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:1033-1039.

18. Farsad M, Vicenzi L, Castellucci P, et al. Evaluation of treatment response of lung cancer after stereotactic radiotherapy: role of 18F-FDG PET. J Nucl Med 2007;48:353P.

19. 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;76:789-795.

20. Matsuo Y, Nakamoto Y, Nagata Y, et al. Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer. Radiother Oncol 2010;97:200-4.

21. Matsuo Y, Nagata Y, Mizowaki T, et al. Evaluation of mass-like consolidation after stereotactic body radiation therapy for lung tumors. Int J Clin Oncol 2007;12(5):356-362.

22. Trovo M, Linda A, El Naqa I, Javidan-Nejad C, Bradley J. Early and late lung radiographic injury following stereotactic body radiation therapy (SBRT). Lung Cancer 2010;69(1):77-85.

23. Palma DA, Senan S, Haasbeek CJ, Verbakel WF, Vincent A, Lagerwaard F. Radiological and clinical pneumonitis after stereotactic lung radiotherapy: a matched analysis of three dimensional conformal and volumetric-modulated arc therapy techniques. Int J Radiat Oncol Biol Phys 2011;80:506-13.

24. Soret M, Bacharach SL. Buvat I.Partial-volume effect in PET tumor imaging. J Nucl Med 2007;48(6):932-945.

25. Boellaard R, O'Doherty MJ, WeberWA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010;37(1):181-200.

26. El Naqa I, Grigsby P, Apte A, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. Pattern Recognit 2009;42(6):1162-1171.

27. Buckler AJ, Mulshine JL, Gottlieb R, Zhao B, Mozley PD, Schwartz L. The use of volumetric CT as an imaging biomarker in lung cancer. Acad Radiol 2010;17(1):100-106.

28. Liu C, Pierce 2nd LA, Alessio AM, Kinahan PE. The impact of respiratory motion on tumor quantification and delineation in static PET/CT imaging. Phys Med Biol 2009;54(24):7345-7362.

29. Park SJ, Ionascu D, Killoran J, et al. Evaluation of the combined effects of target size, respiratory motion and background activity on 3D and 4D PET/CT images. Phys Med Biol 2008;53(13):3661-3679.

30. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2(7 Suppl. 3): S94-S100.