Radiation-Induced Lung Injury on PET/CT: Analysis of FDG Uptake Response within Specific Isodose Regions of Irradiation in Non-small Cell Lung Cancer Patients

PET/BT'de Radyasyona Bağlı Akciğer Hasarı: Küçük Hücreli Dışı Akciğer Kanseri Hastalarında Belirli Eş Doz Radyasyon Bölgelerinde FDG Tutulum Yanıtının Analizi

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ABSTRACT Objective: Inflammatory response associated with radiation-induced lung injury (RILI) results in an increased 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT). In this study, we aimed to analyze the degree of FDG uptake within specific isodose regions (IR) of the irradiated lung using standardized uptake value (SUV) measurements, and to correlate posttreatment FDG uptake with radiotherapy (RT) dose parameters, patient characteristics and the imaging time interval after RT completion. **Material and Methods:** Data from 30 patients with non-small cell lung cancer (NSCLC) who underwent FDG PET/CT imaging at least 12 weeks (72-668 days) after completion of RT were evaluated. In each patient, side-by-side visual registration of the treatment planning CT slices including IR curves with the corresponding PET/CT slices was performed. Using SUV measurements, FDG uptake levels were analyzed within specific IRs of the irradiated lung. The statistical difference between SUVmax of each IR was determined. The RT dose parameters, patient characteristics and time interval between RT and PET/CT were tested for correlation with SUVmax of IRs. **Results:** The mean SUVmax in the IRs of the lung that received 2000-4000cGy was 1.51 ± 0.66 (mean ± SD) (min-max: 0.69-2.84), 4000-6000cGy was 2.67 ± 1.16 (min-max: 0.71-6.0), and >6000Gy was 3.55 ± 1.09 (min-max: 1.2-5.72). We found statistically significant differences between the SUVmax values of all IRs (SUV2000 vs. SUV4000, p= 0.001; SUV2000 vs.6000, p= 0.002; SUV4000 vs. 6000, p= 0.001). No statistically significant correlation was found between SUVmax and the other variables. **Conclusion:** The findings of this study showed that, although some overlap occurs between IRs, the degree of radiation-related parenchymal FDG uptake gets higher with increasing dose levels. Persistent high FDG uptake levels may be observed in radiation fibrosis areas on PET/CT even several months after RT.

Key Words: Lung injury; radiotherapy; positron-emission tomography; fluorodeoxyglucose F18; lung neoplasms

ÖZET Amaç: Radyasyona bağlı akciğer hasarı (RBAH) ile ilişkili inflamatuvar yanıt pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) artmış 18F-florodeoksiglukoz (FDG) tutulumu ile sonuçlanır. Bu çalışmada, standardize tutulum değeri (standard uptake value; SUV) ölçümlerini kullanarak ışınlanmış akciğerin belirli izodoz alanlarında (İA) FDG tutulumunun derecesini incelemeyi ve tedavi sonrası FDG tutulumu ile radyoterapi (RT) doz parametreleri, hasta özellikleri ve RT tamamlandıktan sonra görüntüleme zamanı aralığı arasında bağıntı kurmayı amaçladık. **Gereç ve Yöntemler:** RT tamamlandıktan en az 12 hafta (72-668 gün) sonra FDG PET/BT yapılan küçük hücreli dışı akciğer kanserli (KHDAK) 30 hastanın verileri değerlendirildi. Her hastada, PET/BT kesitlerine karşılık gelen ve İA eğrilerini içeren tedavi planlama BT kesitlerinin yan yana görsel kaydı yapıldı. SUV ölçümleri kullanılarak, ışınlanmış akciğerin belirli İA içindeki FDG tutulum düzeyleri incelendi. Her ışınlanmış bölgenin SUVmax arasındaki istatistiksel fark belirlendi. İA'nın SUVmax ile korelasyonu için RT doz parametreleri, hasta özellikleri ve RT ile PET/BT arasındaki zaman aralığı istatistiksel olarak test edildi. **Bulgular:** 2000-4000 cGy alan akciğer İA'daki ortalama SUVmax 1.51 ± 0.66 (mean ± SS) (min-max: 0.69-2.84) idi, 4000-6000 cGy ve >6000 alanlarda sırasıyla 2.67 ± 1.16 (min-max: 0.71-6.0) ve 3.55 ± 1.09 (min-max: 1.2-5.72) idi. Tüm İA'nın SUVmax değerleri arasında istatistiksel olarak anlamlı farklar bulduk (SUV2000 ile SUV4000, p= 0.001; SUV2000 ile SUV6000, p= 0.002; SUV4000 ile SUV6000, p=0.001). SUVmax ve diğer değişkenler arasında istatistiksel olarak anlamlı ilişki bulunmadı. **Sonuç:** Bu çalışmanın sonuçları, izodoz alanları arasında bir miktar çakışma olmakla birlikte, radyasyonla ilişkili parankimal FDG tutulumunun derecesinin artan dozlarla arttığını göstermiştir. RT bitiminden aylar sonra bile, radyasyona bağlı fibrozis gelişen alanlarda yüksek düzeylerde FDG tutulumunun sebat ettiği görülebilmektedir.

Anahtar Kelimeler: Akciğer hasarı; radyoterapi; pozitron emisyon tomografi; fluorodeoksiglukoz F18; akciğer tümörleri

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Radiation therapy (RT) is an integral part of treatment strategy in the management of patients with locally advanced non-small cell lung cancer (NSCLC). Nevertheless, it presents a challenge because of high sensitivity of lung tissue to irradiation and it is inevitable to encounter treatment-related side-effects such as radiation-induced lung injury (RILI). RILI may occur as an inflammatory reaction or radiation pneumonitis (RP), at an early stage after irradiation, and as fibrosis after several months or years.[1] Imaging techniques, mainly X-ray and computed tomography (CT), have so far been used in the early diagnosis of RILI and the spectrum of CT changes occurring after RT have been well-described in literature.[2-6]

CT-integrated positron emission tomography (PET/CT) with 18F-fluorodeoxyglucose (FDG) is currently a well-known modality for revealing metabolic aspects of tumors. However FDG, as a glucose analog, is taken up by high-glucose-consuming cells and its uptake is not a specific marker of malignancy. In addition to most types of cancer, various inflammatory conditions such as acute inflammation, granulomatous diseases and autoimmune diseases show FDG uptake levels as high as RP.[7-11] Recent studies have focused on providing an objective measure of the inflammatory response to irradiation with either quantitative or visual assessment of FDG uptake by PET/CT.[8,12] The increased FDG uptake reflecting inflammatory parenchymal activity may persist for several months due to numerous factors influencing the degree of lung injury such as varied patient characteristics,[13] prior or concomitant chemotherapy[14,15] or radiation dose-lung volume relationships.[6,16,17] Therefore, it is reasonable to expect that the extent and degree of FDG uptake may have different manifestations on PET/CT.

The evidence from the previous studies showed that the probability and severity of RILI, particularly radiation pneumonitis, depend mainly on the irradiation dose and the percentage of lung volume receiving a dose above a threshold of 20 Gy.[18-20]

In this retrospective study, we aimed to analyze the changes of the FDG uptake levels between specific isodose regions within the irradiated lung tissue but beyond the initial tumor uptake area. Furthermore, we correlated the degree of FDG uptake in irradiated lung tissues of patients with NSCLC with RT dose parameters and characterized its relationship with the time interval between RT and FDG PET/CT and with some patient characteristics.

MATERIALS AND METHODS

PATIENT SELECTION

For this retrospective study, we reviewed consecutive files of lung cancer patients who underwent an oncologic PET/CT in Uludag University Medical Faculty Hospital PET/CT center between January 2008 and March 2010. Post-radiation FDG PET/CT reports of the patients were reviewed to identify PET/CT scans on which at least some degree of radiation-related lung tissue findings had been reported.

Amongst them, only the patients who had undergone treatment planning CT and both staging and post-RT FDG PET/CT imaging at least 12 weeks after the completion of 3-dimensional conformal RT (3D-CRT) were selected. The patients with underlying lung disease, metastatic disease within the lungs and residual masses that cannot be easily separated from adjacent areas of RILI were excluded. Finally, a total of 30 patients (all male, aged 31-73 yrs., mean: 61) were found eligible and included in this study. Patient characteristics were summarized in Table 1.

ETHICAL CONSIDERATIONS

The methods used (RT and PET/CT) were part of the clinical routine. Patients were informed about the clinical reasons to undergo the investigations and treatment. Retrospective data analysis and reporting comply with the institutional laws.

FDG PET/CT PROTOCOL

PET/CT imaging was performed with a dedicated scanner (Biograph 6 LSO, Siemens Medical Systems, Germany) approximately 60 minutes after administration of 10 to 15 mCi of FDG. Patients fasted for at least six hours and their blood glucose

TABLE 1: Patient characteristics.

Characteristic	Value
Age (yrs) Mean (Min-max)	61 (31-73)
Gender (Male/Female)	30/0
Histopathology (n)	
Adenocarcinoma	10 (33%)
Squamous cell carcinoma	13 (43%)
NSCLC –unspecified	7 (23%)
Tumor location (n)	
Central	14 (47%)
Periphery	16 (53%)
Stage (n)	
Stage IIIa	9 (30%)
Stage IIIb	21 (70%)
Chemotherapy (n)	
Yes/No	30/0
Smoking status (Yes/Never) **(n)**	22/8

levels were checked before the imaging. Intravenous contrast material and breath-hold techniques were not used. Attenuation-corrected PET images were reconstructed with an ordered subset expectation maximization iterative reconstruction algorithm. The CT slice thickness of PET/CT was 5 mm. Fused PET/CT images were generated for visual and semi-quantitative evaluation on an "e.soft" workstation (Siemens Medical Systems, Germany).

IMAGE ANALYSIS AND QUANTITATION

A total of 60 pre- and post-treatment PET/CT images of 30 patients were re-evaluated by two Nuclear Medicine physicians in consensus. The diagnosis of RILI was based on characteristic CT findings, such as mass-like consolidation beyond the tumor area, ground-glass opacity, and nodular areas of increased opacity or fibrosis, on PET/CT images. Visual evaluation and semiquantitative image analyses were performed on transaxial slices of post-RT PET/CT. For this purpose, three different transaxial slices reflecting the most representative of RILI visually were chosen from each transaxial data depending on the extent of area affected. The isodose distribution of 2000, 4000 and 6000 cGy curves were overlaid at the same slice level of transaxial treatment planning CT scan. The lung CT axial images with superimposed isodose distribution curves obtained from radiation planning CT were then transferred to PET/CT workstation. SUV values were calculated on post-RT PET/CT images that correspond to specific isodose regions. Slice-to-slice matching was performed visually. In patients with therapy-related lung volume changes, the most appropriate post-RT PET/CT slice corresponding to the planning CT slice was chosen to be analyzed. Considering general patchy distribution and heterogeneity of FDG uptake, we calculated mean of multiple SUVmax values throughout the RILI areas. For this purpose, depending on the area influenced, 3-6 small regions of interests (ROI) were drawn at the most intense FDG uptake regions within available isodose regions on irradiated lung to define SUVmax in each ROI, and the arithmetic mean of SUVmax (m-SUVmax) were then calculated on all three transaxial slices (Figure 1). For each patient, therefore, multiple m-SUVmax values were calculated separately and termed as SUV2000, SUV4000 and

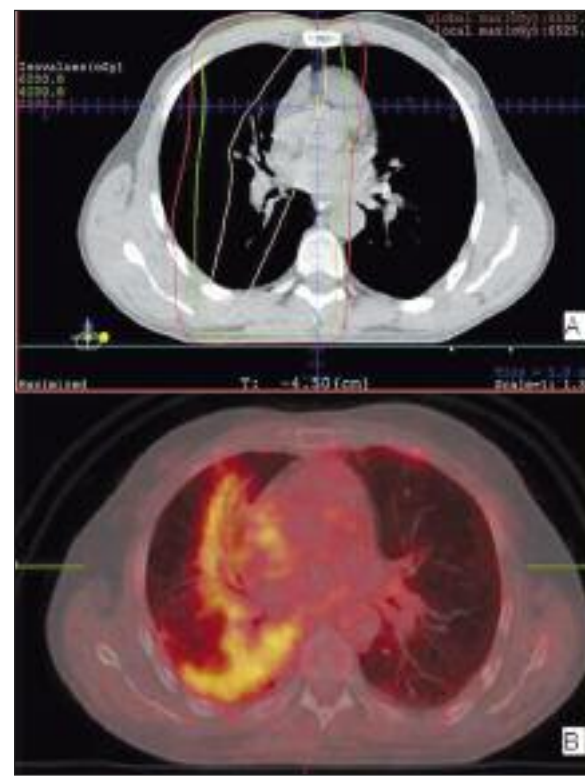

FIGURE 1: Treatment planning CT with (A) isodose curves and (B) corresponding PET/CT slices showing intense FDG uptake in the treated volume. Isodose curves were colored as follows: light brown: 6000 cGy, green: 4000 cGy, red: 2000 cGy.

TABLE 2: Descriptive statistics

Time interval between RT and PET	(d)
Median (min-max)	133 days (72-668)
Mean±SD	171±125
Karnofsky Performance Scoring	(%)
Median (min-max)	90 (40-100)
Mean±SD	75±39
RT dose parameters	(cGy) Mean, Median (min-max)
Ipsilateral Lung	
Total dose	6300
Mean lung dose	3280, 3304 (1133-5036)
Minimum dose	40, 25 (8-265)
Maximum dose	6504, 6432 (5604-7518)
V20 dose volume (%)	59, 59 (22-89)
V40 dose volume (%)	47, 47 (9-77)
Whole Lung	
Prescribed Total dose (GTV)	6300
Minimum dose	13, 8 (0-81)
Maximum dose	6578, 6536 (6185-7204)
Mean Dose	1916, 1861 (31-2900)
V20 dose volume (%)	36, 35 (23-55)
V40 dose volume (%)	26, 25 (14-37)
Smoking (Pack Year)	
Median (min-max)	45 (0-144)
Mean±SD	48±42
SUV2000	
Median (min-max)	1.29 (0.69-2.84)
Mean±SD	1.51±0.66
SUV4000	
Median (min-max)	2.75 (0.71-6.01)
Mean±SD	2.67±1.16
SUV6000	
Median (min-max)	3.62 (1.24-5.72)
Mean±SD	3.55±1.09

SUV6000. On some slices, depending on the radiation treatment planning, one or more isodose regions of 2000, 4000 or 6000 cGy did not exist.

RADIATION TREATMENT AND CHEMOTHERAPY

Radiation therapy was applied by using linear accelerators (Siemens Mevatron KD2 and MD2). 3D dose calculations were done on the 5 mm CT slices using CT simulator (Somatom Emotion Duo, Siemens, Germany). Radiation therapy was planned by using Computerized Radiotherapy Planning System (Xio, CMS, Germany). Patients treated with a curative intend were irradiated using digitally constructed fields to cover initially primary tumor and locoregional lymph nodes (CTV) with 1.8 Gy per fraction, five days a week (Monday through Friday). Forty-five Gy was administered for the initial phase and boost (to cover primary tumor and invaded lymph nodes (GTV)) dose of 18 Gy was given using 6, 15 or 25 MV photon beams. All patients received a prescribed GTV dose of 63 Gy. Target volumes were defined using the ICRU Report 50.[21] The dosimetric parameters of 3D-CRT were also detailed in Table 2.

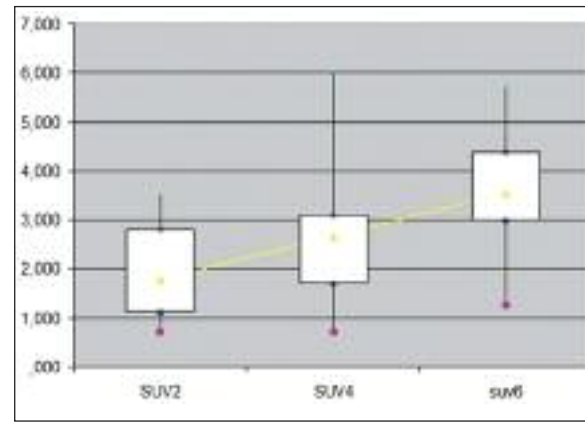

FIGURE 2: Box and whisker diagram shows m-SUVmax distributions according to the specific isodose regions. Upper and lower limits show the highest and lowest SUVmean measured, respectively. The group labels indicate as follows; SUV2: m-SUVmax distributions measured within 2000-4000 cGy areas, SUV4: m-SUVmax distributions measured within 4000-6000 cGy areas, SUV6: m-SUVmax distributions measured within 6000 cGy areas.

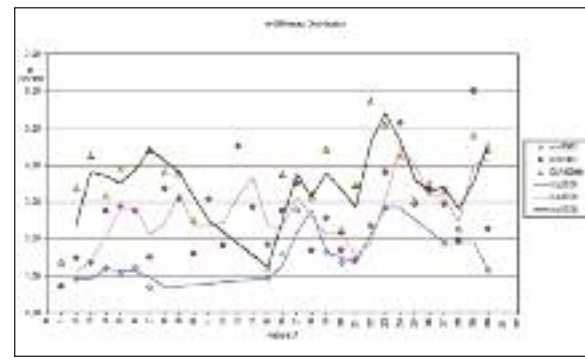

FIGURE 3: Patient based m-SUVmax distribution and their moving average (ma) curves. The labels indicate as follows; SUV2000: m-SUVmax measured within 2000-4000 cGy areas, SUV4000: m-SUVmax measured within 4000-6000 cGy areas, SUV6000: m-SUVmax values measured within 6000 cGy areas. The ma2000, ma4000, and ma6000 indicate the moving average curves of the corresponding m-SUVmax.

All patients underwent concurrent and/or adjuvant chemotherapy. The most commonly used chemotherapy regimens were a combination of taxan (docetaxel or paclitaxel) and platinum (cisplatinum or carboplatinum) based.

STATISTICAL ANALYSIS

The descriptive statistics of time interval, performance scoring, smoking amount, RT dose variables, and m-SUVmax values were summarized in Table 2. Correlations between m-SUVmax and these variables were determined by Spearman's rank correlation. Wilcoxon Signed Ranks test was used to compare m-SUVmax values between each isodose region. Descriptive statistics were represented as median, minimum and maximum values since nonparametric tests were used. The data was processed by SPSS 13, and p values below 0.05 were considered as statistically significant.

RESULTS

The patient characteristics and descriptive statistics of the 30 cases evaluated in this study are summarized in Table 1 and Table 2, respectively. Briefly, the median of Karnofsky performance status score was 90 (min-max: 40-100) in all patients. The median time interval between RT completion and FDG-PET/CT imaging session was 133 days (min-max: 72-668). All patients received a prescribed total tumor dose of 63 Gy. The percentage of V20 and V40 dose volumes, volumes of total lung receiving at least 20 Gy and 40 Gy in ipsilateral lungs were 59% and 47%, respectively.

IMAGE CHARACTERISTICS AND ANALYSIS OF FDG UPTAKE VS. RT DOSE

Visually, both PET and CT findings were generally confined to the field of irradiation typically conforming to the treated volume. Although not too many, some CT features of RILI corresponded to intense FDG uptake were observed outside the high dose treatment regions. Visual patterns of CT and PET were not compared in a one-to-one manner because such an analysis was beyond the scope of this study which deals with the comparison of radiation dose parameters and FDG uptake levels.

The m-SUVmax in the lung that received 2000-4000 cGy was 1.29 (0.69-2.84), (median (min-max)), 4000-6000 cGy was 2.75 (0.71-6.0), and >6000 cGy was 3.62 (1.2-5.72). On Figure 2, Box and Whisker plots show the m-SUVmax distribution according to the different isodose regions. On Figure 3, patient-based m-SUVmax distributions and their moving average curves were presented. Although some overlap existed, there were statistically significant differences between the m-SUVmax values of all isodose regions (SUV2000 vs. SUV4000, p=0.001; SUV2000 vs.6000, p=0.002; SUV4000 vs. 6000, p=0.001) (Table 3). The isodose regions receiving 6000 cGy had the greatest elevation of m-SUVmax when compared to the others, while the regions receiving 2000 cGy had the least.

No statistically significant correlation was found between m-SUVmax values of different isodose regions and the time interval between RT and PET/CT. Similarly, there was no statistically significant correlation between m-SUVmax values and RT dose parameters as well as age, Karnofsky performance status score, tumor type and tumor location.

DISCUSSION

Based on our experience to date, neither average SUV, i.e. commonly used standard "SUVmean" method reflecting mean standard uptake value within ROI, nor do SUVmax, denoting the maximum value in a pixel within the ROI, always reflect the visual findings due to the heterogeneity of the FDG uptake distribution in the areas of RILI. Thus, we used a unique parameter, the "m-SUVmax" which is, depending of the affected area, the arithmetic mean of SUVmax of 3-6 selected ROIs showing the

TABLE 3: Statistical comparison of m-SUVmax values of all isodose regions

	Isodose Regions		
	SUV2000	**SUV4000**	**SUV6000**
Median (Min-Max)	1.29 (0.69-2.84)	2.75 (0.71-6.0)	3.62 (1.24-5.72)
SUV2000 vs. SUV4000		p=0.001	
SUV2000 vs. SUV6000		p=0.002	
SUV4000 vs. SUV6000		p=0.001	

most intense FDG uptake. Instead of SUVmean or SUVmax, we have developed and used this parameter to avoid, to some extent, the intraobserver and interobserver variations on values, considering that it can visual findings on RILI areas the best. This method seems to preclude the disadvantages of both SUVmax which does not always reflect general uptake pattern and standard SUVmean which is mainly ROI-size-dependent.

RILI is a common side effect after curative RT for lung cancer and the RT-related inflammatory metabolic response results in an increased FDG uptake on PET/CT. It is known from the literature that radiation-induced changes in the lung can vary according to the irradiation technique and the dose-volume relationships.[17-20] In the present study, using SUV measurements, the changes of the FDG uptake within specific isodose regions in the irradiated lung tissue, but beyond the initial tumor uptake area were analyzed semi-quantitatively. The evidence from the study showed that, although some overlap occurs, the degree of FDG uptake is significantly different among specific isodose regions of irradiated lung volume. We found greater elevation of m-SUVmax in the regions that received higher radiation doses similar to earlier reports in which SUVmean was preferred as a semi-quantitative parameter.[9,10] In the study of Guerrero et al. the data supported a linear relationship between the radiation dose and the normalized FDG uptake in the lung in patients with esophageal cancer.[9] Another study showed that among patients whose SUV mean was increased by three times in the region 10-19 Gy, 75% of patients developed RP later.[10] In both studies, post-RT FDG PET/CT imaging time interval was no longer than 12 weeks. Thus, FDG PET/CT was reported to play an important role in predicting acute RP.[10]

As the isodose regions, such as 1000, 2000, 3000 cGy, were very closely overlaid to each other, in the majority of cases, we preferred to study with only 2000, 4000 and 6000 cGy isodose curves to avoid overlap of FDG uptake values of these regions. A considerable amount of overlap of m-SUVmax values within different isodose regions were observed in the present study. Inflammatory causes other than RT, individual alterations in response, daily setup variations, and respiratory motion may contribute to the high and/or variable FDG uptake values.[22]

In accordance with the general clinical practice, evaluation of the metabolic response to radiotherapy in NSLC patients is commonly performed approximately three months after the end of RT. The median time interval between RT completion and FDG-PET/CT imaging session was 133 days, ranging between 72-668 days, in our study. We found no statistically significant correlation between the degree of FDG uptake and the time interval of PET/CT after RT. This may be associated with the limited sample size in the study and relatively small proportion of cases imaged at the late post-radiation period. Furthermore, in contrast to the presence of classic fibrosis patterns on corresponding CT, high FDG uptake levels reflecting active inflammatory process on the same areas may also explain the lack of statistically significant correlation in our study. RP refers to the acute changes within 4-12 weeks which is seen as ground-glass opacity or consolidation in the lung.[2,3,23] These may resolve completely, but radiation fibrosis develops within 6-12 months more commonly and typically appears as traction bronchiectasis, volume loss and scarring on CT scan.[2,3,23,24] In this study, we observed that despite late post-RT imaging periods, FDG uptake may still persist to a variable but generally high degree. Inflammation is characterized by increased glucose metabolism, which leads to elevated FDG uptake. Tendency to infection due to anatomical distorting late effects of radiation may be speculated as one of the reasons for this persistence. The other reasons that may be speculated as the high uptake of FDG in fibrosis areas on PET/CT were non-neoplastic inflammatory cellular elements, such as macrophages, lymphocytes and metaplastic epithelial cells, and squamous metaplasia induced by chemoradiotherapy.[25] Assessment of lung inflammation with 18F-FDG PET during acute lung injury is documented in a recent review.[26] As noted by de Prost et al., in patients with pulmonary fibrosis, the highest FDG PET SUVs coregistered with high-resolution CT patterns, such as honey-

combing, which is classically understood as representative of irreversible parenchymal scarring. It was hypothesized that this finding reflected high fibroblastic activity, suggesting an opportunity for pharmacologic manipulation.[26] Although the present study does not have a long term follow up, the high FDG uptake levels imply that the affected areas may undergo fibrosis, and supportive care, such as steroids, oxygen therapy, and pulmonary rehabilitation exercises to manage respiratory symptoms, should be taken into account in these patients.

Although RP usually occurs within the irradiated lung, RP outside the treatment portals has been reported.[3,7] In this study we have focused on the metabolic response on the affected lung beyond the tumor area, and contralateral lung was not analyzed from this point of view.

As stated earlier, sex, age, smoking history, pre-existing pulmonary disease, performance score and pulmonary function before radiotherapy have been reported to affect the risk for radiation pneumonitis.[13,20,27] Wang et al. reported that that there was no statistically significant difference between the clinical parameters (sex, age, smoking history, induction chemotherapy, concurrent chemotherapy regimens and Karnofsky performance score) and the incidence of acute radiation pneumonitis.[27] Similarly, we did not find a statistically significant relationship between the degree of FDG uptake and presence or degree of the aforementioned clinical risk parameters such as Karnofsky performance score, age and smoking status.

We acknowledge some important limitations in this study. Concurrent or adjuvant chemotherapy, especially with carboplatin or paclitaxel combinations, has been reported to potentiate the effects of radiation toxicity.[14,15] Parashar et al. reported that patients who received any chemotherapy had a five times greater risk of developing RP than in patients who did not receive this treatment.[15] However, in a prospective randomized study evaluating therapeutic significance of concurrent paclitaxel and radiotherapy (group 1) versus radiotherapy alone (group 2) in NSCLC by Ulutin and Pak, Grade 3 pulmonary toxicity was observed in 16% of patients in group 1, whilst Grade 1 and 2 pulmonary toxicity in group 2 was 19%, and treatment-related toxicity rates were found to be nearly close to each other.[28] Clinical trials demonstrated that these effects were consistent with the radiosensitization properties of these chemotherapeutic agents and might be an explanation for the toxicities.[29] In the present study, as all patients had received chemotherapy, the additional effects of chemotherapy on RILI were not evaluated statistically.

The reported incidence of clinical manifestations associated with RP is 7-8% and the symptoms are usually mild, despite imaging findings that may appear more prominent.[6,23,30] Due to the retrospective nature of this study, we were unable to correlate FDG PET/CT findings with patients' symptoms. Such a correlation could help the clinician to predict the severity of RILI. In a recent study, Faria et al. studied two common ways of assessing radiation-induced late lung toxicity after curative radiotherapy.[31] They reported that although all patients presented some degree of radiographic abnormalities, there was no correlation with lung symptoms. Because, contrary to X-ray based imaging systems, FDG PET reflects metabolic aspects of RILI, one may have expected to find a better correlation between FDG PET with clinical symptoms than that of the previous ones.

Another limitation of the present study is the patient selection method. Because we reviewed the PET/CT scan reports at first and selected only cases in whom at least some degree of radiation-related lung injury findings had been reported on PET/CT scans, some cases with RILI who has no marked FDG uptake or have not been mentioned in the reports would have been missed. If such cases were to be included in the study, then we would expect a considerable relationship between the time elapsed after RT and FDG response.

The use of a single post RT PET/CT scan is a limitation, itself. A timeline interpretation with serial scanning may allow more accurate information on its clinical importance, but it would not be feasible for our retrospective study.

CONCLUSION

The evidence from our study showed that, although some overlap occurs between isodose regions, the degree of radiation-related parenchymal FDG uptake gets higher with increasing dose levels. Persistent high FDG uptake levels may be observed within radiation fibrosis areas even several months after RT. Although a statistically significant relationship was not found in the present study, a meaningful association would be expected between the time elapsed after RT and FDG response with a larger patient group. In addition to its relationship with RT dosimetric factors, the diagnostic and prognostic importance of the PET patterns of RILI phenomenon remain to be studied further.

REFERENCES

1. Nestle U, Hellwig D, Fleckenstein J, Walter K, Ukena D, Rübe C, et al. Comparison of early pulmonary changes in 18FDG-PET and CT after combined radiochemotherapy for advanced non-small-cell lung cancer: a study in 15 patients. Front Radiat Ther Oncol 2002;37:26-33.
2. Park KJ, Chung JY, Chun MS, Suh JH. Radiation-induced lung disease and the impact of radiation methods on imaging features. Radiographics 2000;20(1):83-98.
3. Choi YW, Munden RF, Erasmus JJ, Park KJ, Chung WK, Jeon SC, et al. Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. Radiographics 2004;24(4):985-97.
4. Linda A, Trovo M, Bradley JD. Radiation injury of the lung after stereotactic body radiation therapy (SBRT) for lung cancer: A timeline and pattern of CT changes. Eur J Radiol 2009; doi:10.1016/j.ejrad.2009.10.029
5. 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.
6. Takeda T, Takeda A, Kunieda E, Ishizaka A, Takemasa K, Shimada K, et al. Radiation injury after hypofractionated stereotactic radiotherapy for peripheral small lung tumors: serial changes on CT. AJR Am J Roentgenol 2004; 182(5):1123-8.
7. Hassaballa HA, Cohen ES, Khan AJ, Ali A, Bonomi P, Rubin DB. Positron emission tomography demonstrates radiation-induced changes to nonirradiated lungs in lung cancer patients treated with radiation and chemotherapy. Chest 2005;128(3):1448-52.
8. Hart JP, McCurdy MR, Ezhil M, Wei W, Khan M, Luo D, et al. Radiation pneumonitis: correlation of toxicity with pulmonary metabolic radiation response. Int J Radiat Oncol Biol Phys 2008;71(4):967-71.
9. Guerrero T, Johnson V, Hart J, Pan T, Khan M, Luo D, et al. Radiation pneumonitis: local dose versus [18F]-fluorodeoxyglucose uptake response in irradiated lung. Int J Radiat Oncol Biol Phys 2007;68(4):1030-5.
10. Song H, Yu JM, Kong FM, Lu J, Bai T, Ma L, et al. [18F]2-fluoro-2-deoxyglucose positron emission tomography/computed tomography in predicting radiation pneumonitis. Chin Med J (Engl) 2009;122(11):1311-5.
11. Kubota K. From tumor biology to clinical Pet: a review of positron emission tomography (PET) in oncology. Ann Nucl Med 2001;15(6): 471-86.
12. Mac Manus MP, Ding Z, Hogg A, Herschtal A, Binns D, Ball DL, et al. Association Between Pulmonary Uptake of Fluorodeoxyglucose Detected by Positron Emission Tomography Scanning After Radiation Therapy for Non-Small-Cell Lung Cancer and Radiation Pneumonitis. Int J Radiat Oncol Biol Phys 2010; doi:10.1016/j.ijrobp.2010.04.021
13. Dehing-Oberije C, De Ruysscher D, van Baardwijk A, Yu S, Rao B, Lambin P. The importance of patient characteristics for the prediction of radiation-induced lung toxicity. Radiother Oncol 2009;91(3):421-6.
14. Mao J, Kocak Z, Zhou S, Garst J, Evans ES, Zhang J, et al. The impact of induction chemotherapy and the associated tumor response on subsequent radiation-related changes in lung function and tumor response. Int J Radiat Oncol Biol Phys 2007;67(5): 1360-9.
15. Parashar B, Edwards A, Mehta R, Pasmantier M, Wernicke AG, Sabbas A, et al. Chemotherapy Significantly Increases the Risk of Radiation Pneumonitis in Radiation Therapy of Advanced Lung Cancer. Am J Clin Oncol 2010; doi: 10.1097/COC.0b013e3181d6b40f
16. Koenig TR, Munden RF, Erasmus JJ, Sabloff BS, Gladish GW, Komaki R, et al. Radiation injury of the lung after three-dimensional conformal radiation therapy. AJR Am J Roentgenol 2002;178(6):1383-8.
17. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. Int J Radiat Oncol Biol Phys 2005;63(1):5-24.
18. Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, Das SK, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51(3):650-9.
19. Allen AM, Henning GT, Ten Haken RK, Hayman JA, Martel MK. Do dose-volume metrics predict pulmonary function changes in lung irradiation? Int J Radiat Oncol Biol Phys 2003; 55(4):921-9.
20. Claude L, Pérol D, Ginestet C, Falchero L, Arpin D, Vincent M, et al. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: clinical and dosimetric factors analysis. Radiother Oncol 2004;71(2):175-81.
21. International Commission on Radiation Units and Measurements. Prescribing recording, and Reporting Photon Beam Therapy; ICRU Report 50. Bethesda, MD: ICRU; 1993.
22. Dawson LA, Sharpe MB. Image-guided radiotherapy: rationale, benefits, and limitations. Lancet Oncol 2006;7(10):848-58.
23. Movsas B, Raffin TA, Epstein AH, Link CJ Jr. Pulmonary radiation injury. Chest 1997; 111(4):1061-76.
24. Bluemke DA, Fishman EK, Kuhlman JE, Zinreich ES. Complications of radiation therapy: CT evaluation. Radiographics 1991;11(4):581-600.
25. Ohtsuka T, Nomori H, Watanabe K, Naruke T, Orikasa H, Yamazaki K, et al. False-positive findings on [18F]FDG-PET caused by non-neoplastic cellular elements after neoadjuvant chemoradiotherapy for non-small cell lung cancer. Jpn J Clin Oncol 2005;35(5):271-3.

26. de Prost N, Tucci MR, Melo MF. Assessment of lung inflammation with 18F-FDG PET during acute lung injury. AJR Am J Roentgenol 2010;195(2):292-300.

27. Wang S, Liao Z, Wei X, Liu HH, Tucker SL, Hu CS, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66(5): 1399-407.

28. Cüneyt Ulutin H, Pak Y. Preliminary results of radiotherapy with or without weekly paclitaxel in locally advanced non-small cell lung cancer. J Cancer Res Clin Oncol 2003;129(1):52-6.

29. Chen Y, Okunieff P. Radiation and third-generation chemotherapy. Hematol Oncol Clin North Am 2004;18(1):55-80.

30. Roach M 3rd, Gandara DR, Yuo HS, Swift PS, Kroll S, Shrieve DC, et al. Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. J Clin Oncol 1995;13(10):2606-12.

31. Faria SL, Aslani M, Tafazoli FS, Souhami L, Freeman CR. The challenge of scoring radiation-induced lung toxicity. Clin Oncol (R Coll Radiol) 2009;21(5):371-5.