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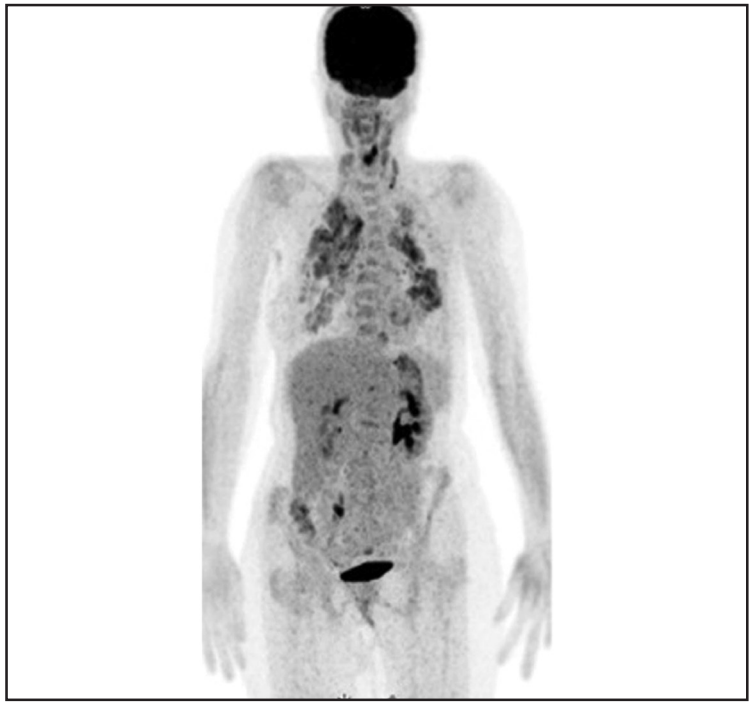

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Erselcan T, Hasbek Z, Tandogan I, Gumus C, Akkurt I. Modification of Diet in Renal Disease equation in the risk stratification of contrast induced acute kidney injury in hospital inpatients. Nefrologia 2009 doi: 10.3265/Nefrologia.2009.29.5.5449.en.full.

Article in a journal published ahead of print: Ludbrook J. Musculovenous pumps in the human lower limb. Am Heart J 2009;00:1-6. (accessed 20 February 2009).

Lang TF, Duryea J. Peripheral Bone Mineral Assessment of the Axial Skeleton: Technical Aspects. In: Orwoll ES, Bliziotes M (eds). Osteoporosis: Pathophsiology and Clinical Management. New Jersey, Humana Pres Inc, 2003;83-104.

Books: Greenspan A. Orthopaedic Radiology a Pratical Approach. 3th ed. Philadelphia, Lippincott Williams Wilkins 2000, 295-330.

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CONTENTS

Original Article
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Factors That Impact Evaluation of Left Ventricular Systolic Parameters in Myocardial Perfusion Gated SPECT with 16 Frame and 8 Frame Acquisition Models

16 ve 8 Frame Görüntüleme Modelli Miyokard Perfüzyon Gated SPECT Çalışmasında Sol Ventrikül Sistolik Parametrelerinin Değerlendirilmesini Etkileyen Faktörler

Mojtaba Ansari[1], Hoda Hashemi[2], Mehdi Soltanshahi[2], Mohsen Qutbi[2], Zahra Azizmohammadi[1], Faraj Tabeie[2], Hamid Javadi[3], Esmail Jafari[4], Maryam Barekat[5], Majid Assadi[4]

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Abstract

Objective: Evaluating the effects of heart cavity volume, presence and absence of perfusion defect, gender and type of study (stress and rest) on the difference of systolic parameters of myocardial perfusion scan in 16 and 8 framing gated SPECT imaging.

Methods: Cardiac gated SPECT in both 16 and 8 framing simultaneously and both stress and rest phases at one-day protocol was performed for 50 patients. Data have been reconstructed by filter back projection (FBP) method and left ventricular (LV) systolic parameters were calculated by using QGS software. The effect of some factors such as LV cavity volume, presence and absence of perfusion defect, gender and type of study on data difference between 8 and 16 frames were evaluated.

Results: The differences in ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV) in both stress and rest were statistically significant. Difference in both framing was more in stress for EF and ESV, and was more in rest for EDV. Study type had a significant effect on differences in systolic parameters while gender had a significant effect on differences in EF and ESV in rest between both framings.

Conclusion: In conclusion, results of this study revealed that difference of both 16 and 8 frames data in systolic phase were statistically significant and it seems that because of better efficiency of 16 frames, it cannot be replaced by 8 frames. Further well-designed studies are required to verify these findings.

Keywords: Perfusion gated SPECT, 16 frames, 8 frames, systolic parameters

Öz

Amaç: Kalp boşluk hacmi, perfüzyon defekti varlığı veya yokluğu, cinsiyet ve inceleme tipinin (istirahat-stres) 16 ve 8 frame modeli ile gated SPECT görüntülemede miyokard perfüzyon sintigrafisi sistolik parametrelerindeki farklılık üzerindeki etkilerini incelemektir.

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Öz

Yöntem: Elli hastada eş zamanlı olarak hem 16 hem 8 frame hem stres hem dinlenme fazları ile tek-gün protokolü ile kardiyak gated SPECT uygulandı. Veriler geri filtreleme yansıması (FBP) yöntemi ile rekonstrükte edildi ve QGS yazılımı kullanılarak LV sistolik parametreleri hesaplandı. LV boşluk hacmi, perfüzyon defekti varlığı ya da yokluğu, cinsiyet ve inceleme tipi gibi bazı faktörlerin 16 ve 8 frame modeli ile gated SPECT görüntülemede miyokard perfüzyon sintigrafisi sistolik parametrelerindeki farklılık üzerindeki etkileri incelendi.

Bulgular: EF, EDV ve ESV'de hem stres hem istirahattaki fark istatistik olarak anlamlı idi. Her iki frame ile EF, EDV ve ESV'de artmış fark sırasıyla stres, istirahat ve streste idi. İnceleme türünün sistolik parametreler üzerinde anlamlı etkisi vardı, benzer şekilde cinsiyetin istirahat halinde her iki bölme yöntemi arasında EF ve ESV farkı üzerinde anlamlı etkisi görüldü.

Sonuç: Sonuç olarak, bu çalışma sonuçları hem 16 hem 8 frame ile elde edilen sistolik verinin istatistiksel olarak anlamlı olduğunu ortaya koymaktadır ve 16 frame modelinin daha etkin olması nedeniyle 8 frame ile değiştirilemeyeceğini öne sürmektedir. Bu bulguların ileride iyi planlanmış çalışmalar ile doğrulanması gerekmektedir.

Anahtar kelimeler: Perfüzyon gated SPECT, 16 frame, 8 frame, sistolik parametre

Introduction

Currently, gated SPECT is used for evaluation of left ventricular (LV) systolic and diastolic functions and data are acquired by the electrocardiographic signal using a specific number of interval, from R wave to next R wave (1).

Each image is generated by counts which are accumulated during each of these intervals. Each interval (cardiac cycle) can be divided into several frames. The choice of best framing interval in myocardial perfusion gated SPECT is still an unresolved issue. It is suggested that using 8-frames leads to better count density in each frame while higher framing intervals, like 16-frames, yield more accurate results (2).

It is reported that 8-frame gated SPECT is likely to underestimate the ejection fraction (EF) as compared to other standard modalities like magnetic resonance imaging (MRI) (3,4) or equilibrium radionuclide angiography (ERNA) (5). It was stated that 8-frame gated SPECT generated smaller end-diastolic volume (EDV), larger end-systolic volume (ESV) and lower EF as compared to 16-frame gated SPECT (1,2). In a study, systolic parameters of 8, 16, 32 frames had been compared to results of ERNA. It showed that LVEF in gated SPECT underestimates as compared to ERNA and also this underestimation reduces by increasing the number of frames. This study showed that by increasing the frame, the LVEDV, LVESV, and LVEF were increased, decreased and increased, respectively (5). Vallejo et al. (6) showed that in the presence of perfusion defects, quantitative gated SPECT (QGS) overestimated the volume as compared to MRI as a standard modality.

Total perfusion deficit (TPD) is a parameter showing both the extent and severity of myocardial perfusion abnormality, and it is calculated by QGS (7). Kurisu et al. (8) used TPD as a quantitative parameter of myocardial perfusion for evaluating accuracy of QGS measurements and showed that TPD can impact systolic parameters and results in differences in ESV, EDV and EF.

The aims of this study include evaluating the effect of heart cavity volume, presence and size of perfusion defect, gender and type of study (stress and rest) on the differences in systolic parameters in myocardial perfusion scan in 8 and 16 frames gated SPECT imaging.

Materials and Methods

This is a cross-sectional study. The patients were chosen randomly between people admitted for myocardial perfusion SPECT in Nuclear Medicine Department of a referral university affiliated hospital in Iran. The exclusion criteria included patients with severe arrhythmias (more than one ectopic beat in 6 heart cycles) (9), cardiomyopathy, a history of myocardial infarction, and patients in whom the modality is unable to determine their heart range due to abnormalities (10).

After injection of 740 MBq of Tc-MIBI, acquisition for each patient was started after at least 60 minutes of rest and at least 30 minutes after exercise peak or pharmacologic stress.

Gated SPECT, then, was performed in both 8 and 16 frames at the same time for both rest and stress phases with a one-day protocol by using Dual head modality, high-resolution collimator and energy window of 20% for 140 KeV.

Myocardial perfusion SPECT was acquired in 64*64 matrix with 32 projections and 30 seconds for each projection.

Data were reconstructed by using filter back projection and cut off: 0.5. LVEF, LVESV and LVEDV were calculated by QGS software. V2 software was used for image reconstruction with different gating frame (10). Attenuation correction and scatter correction were not used. LVEF, LVESV and LVEDV were obtained automatically (9).

For obtaining quantitative perfusion defect as summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS), polar map was used. SDS ≥2 and SDS >7 were considered as ischemia and severe ischemia, respectively (10).

LV cavity volume was obtained by ungated images and the mean volume of 8 and 16 frames in both rest and stress, separately, was considered as the heart cavity volume.

In addition, mean EDV of 8 and 16 frames in stress and rest, separately, was used as a criterion for the left ventricle volume.

After completion of sample size, the difference of systolic parameters of the two aforementioned methods and effects of size of the heart cavity, presence and size of perfusion defect, gender and type of study (stress and rest) on data difference were evaluated with SPSS (T test) and Bland-Altman analysis. P-value less than 0.05 was considered as statistically significant.

Ethics Committee Approval and Informed Consent

This study complies with the Declaration of Helsinki, and it was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (registration number: 75/1394-1395) and informed consent was obtained from all participants.

Results

In 56 evaluated patients in this study, 4 patients were excluded due to inability of the modality to find the heart range, 1 patient due to silent MI and 1 patient due to arrhythmia. The study group consisted of 50 patients including 20 males and 30 females. Nine patients underwent stress with exercise test and 41 patients with pharmacologic stress. The mean age was 54.02 years with 11.11 standard deviation (SD) and a range of 30-79 years.

The mean SSS and mean SDS were calculated as 7.1 with 3.02 SD and 4.5 with 2.9 SD, respectively.

The EDV in stress phase was 79.12±30.44 for 16 frames and 78.08±29.67 for 8 frames, while this value in rest phase was determined as 82.40±30.12 for 16 frames and 81.82±29.60 for 8 frames.

The ESV in stress phase was calculated as 27.44±15.29 for 16 frames and 29±16.17 for 8 frames, and as 28.06±15.85 for 16 frames and 30.90±17.18 for 8 frames in rest phase.

The EF in stress phase was identified as 0.67±0.07 for 16 frames and 0.63±0.08 for 8 frames, while the EF in rest phase was 0.66±0.11 for 16 frames and 0.64±0.07 for 8 frames (Table 1).

The Pearson correlation coefficient between 8 and 16 gated framings in stress and rest phase was determined as 0.957 and 0.956, respectively, and in total it was calculated to be 0.852.

EF was higher in both stress and rest phases with both types of framing in females than males, while EDV and ESV were larger in both stress and rest phases with both types of framing in males (Figure 1, 2, 3).

EF difference between these two types of framing was obtained at 95% confidence interval of 3.05%±2.1 in stress and at 95% confidence interval of 2.92%±1.8 in rest (Figure 1, 2, 3).

95% confidence interval for difference of EDV between 8 and 16 framing was 1.73 mL±1.12 in stress and 1.98 mL±1.14 in rest. Also, 95% confidence interval for difference of ESV between 8 and 16 framing was -2.34 mL±1.9 in stress and -1.92 mL±1.6 in rest.

In the evaluation of systolic factors between 8 and 16 framings, the difference of LVEF, LVEDV, LVESV in both stress and rest phases were statistically significant (EF: p-value <0.001, ESV: p-value=0.005).

Evaluation of the effects of phase (stress and rest) on the difference of systolic parameters between two types of framing revealed that the effect of this variable on ΔEF

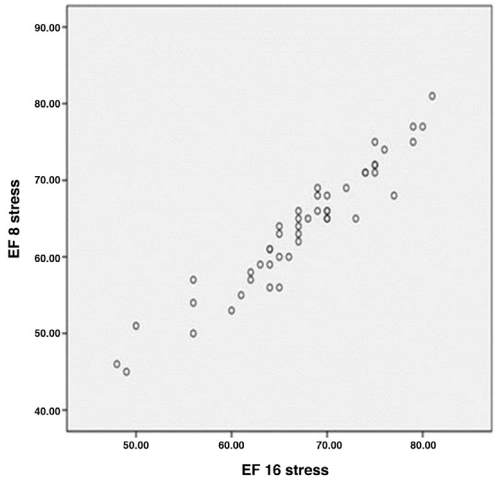

Figure 1. Comparison of ejection fraction between 8 and 16 frames in stress
EF: Ejection fraction

Table 1. Mean values of systolic and diastolic parameters in 8 and 16 frames

	EF stress	EDV stress	ESV stress	EF rest	EDV rest	ESV rest
Female (16-frame)	69.9±8	71.9±24	23.5±11	69.4±12	74.3±25	24.1±12
Female (8-frame)	66.4±8	69.8±23	25.4±12	66.1±10	72.1±24	26.0±13
Male (16-frame)	63.9±7	96.0±35	35.1±17	63.6±10	99.7±34	35.8±18
Male (8-frame)	60.4±6	95.1±33	37.1±18	60.2±7	98.2±34	37.8±19

EF: Ejection fraction, EDV: End-diastolic volume, ESV: End-systolic volume

(p-value=0.036, more difference was seen in stress), ΔEDV (p-value=0.04, more difference was seen in rest) and ΔESV (p-value=0.04, more difference was seen in stress) was statistically significant.

In evaluating effect of gender on difference in systolic parameters between 8 and 16 frames, the impact of this variable on ΔEF in rest (p-value=0.038) and on ΔESV in stress (p-value=0.030) between 8 and 16 frames was statistically significant. Mean ΔEF between 8 and 16 frames in rest phase was 3.48% for males and 2.066% for females, and this correlation for ΔESV was inverse (males<females). Effect of gender on ΔEDV was not statistically significant between 8 and 16 frames in stress (p=0.441) and in rest (p=0.083), and on ΔESV in stress (p=0.88).

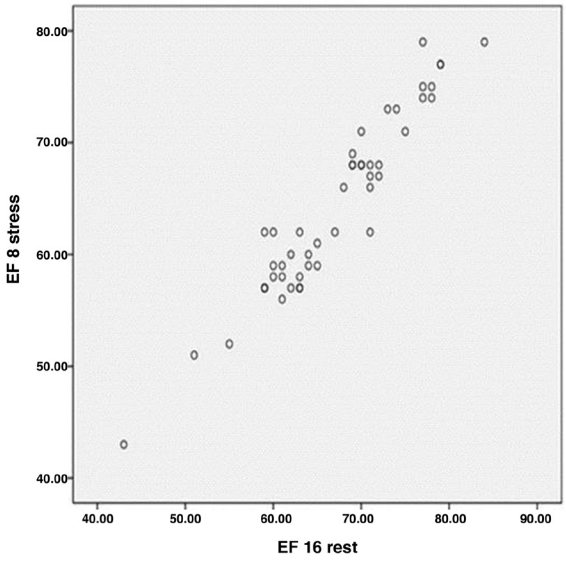

Figure 2. Comparison of ejection fraction between 8 and 16 frames in rest
EF: Ejection fraction

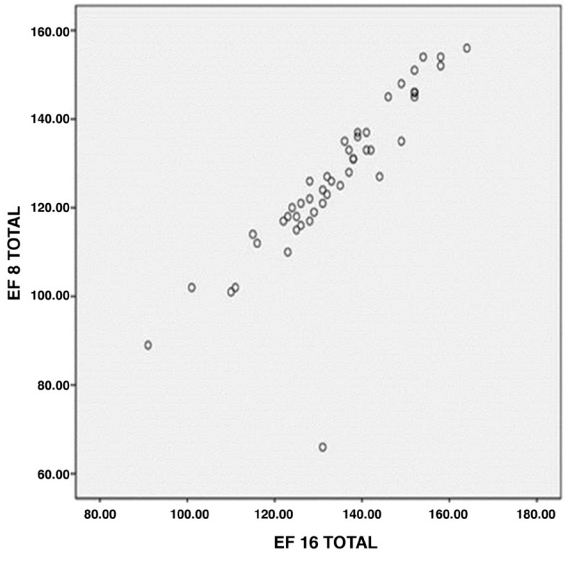

Figure 3. Comparison of ejection fraction between 8 and 16 frames in stress and rest
EF: Ejection fraction

With the unification of volumetric variable between both genders, there was no statistically significant in the difference of systolic parameters in both 8 and 16 frames between males and females.

Evaluation of the effects of (presence and absence of) perfusion defect on difference in systolic parameters between 8 and 16 frames showed that this variable did not have a statistically significant impact in both stress and rest on ΔEDV (stress: p=0.693; rest: p=0.78), ΔEF (stress: p=0.513; rest: p=0.964), ΔESV (stress: p=0.533; rest: p=0.159).

SSS and SDS had no significant effect on the related variable of systolic parameters between 8 and 16 frames.

The mean LV volume (non-gated) of 8 and 16 frames in stress had significant correlation with ΔESV in stress (Spearman correlation coefficient: 0.359, p=0.011) and rest (Spearman correlation coefficient: 0.290, p=0.041). Also, mean LV volume (non-gated) of 8 and 16 frames in rest had significant correlation with ΔESV in stress (Spearman correlation coefficient: 0.337, p=0.017) and rest (Spearman correlation coefficient: 0.333, p=0.018). The mean LV volume (non-gated) of 8 and 16 frames had no significant correlation with ΔEF and ΔEDV in both stress and rest.

The mean LVEDV of 8 and 16 frames in stress showed significant correlation with ΔESV in stress (Spearman correlation coefficient: 0.336, p=0.017) and rest (Spearman correlation coefficient: 0.324, p=0.022). However, mean LVEDV of 8 and 16 frames did not show a significant correlation with ΔEF and ΔEDV.

In our observation, 4 patients showed EF drop more than 5 percent after stress as compared to rest condition in both 8 and 16 frames imaging.

Discussion

The results of 8 and 16 frames gated imaging in both stress and rest of 50 patients were compared in this study. The difference of EF, EDV and ESV in both stress and rest was statistically significant between 8 and 16 frames. EF in 16 frames was higher than 8 frames in both stress and rest. ΔEF in stress was more than rest in comparison of 16 frames and 8 frames. In both stress and rest, EDV was larger in 16 frames than 8 frames and ESV in 8 frames. ΔEDV in rest and ΔEF and ΔESV in stress were more in 16 frames as compared to 8 frames.

When gated SPECT was introduced, 8-interval framing has been used as the standard modality (11). Eight frames were chosen because of the need to achieve a high count in each

frame for determination of cardiac walls and assessment of regional wall motion without prolonging the acquisition time (12). However, Germano et al. (9) reported that EF was underestimated by using 8 frames as compared to 16 frames, a finding that was confirmed by studies comparing EF obtained by gated SPECT with other reference standards such as ERNA and MRI (5,13,14,15).

EF in females and EDV and ESV in males were higher in both stress and rest and in both types of 8 and 16 frames imaging that is consistent with Trägårdh et al. (16) study. Nevertheless, Moslehi et al. (17) reported that the difference in systolic parameters was only observed in stress EF. Inaccurate estimates of volumes in small hearts might lead to higher EF and smaller ESV and EDV in women (18).

Since 16 frames had been introduced for obtaining diastolic factors, several studies evaluating differences in measurement of systolic factors obtained with 8 and 16 frames have been performed, with contradictory results. Only a few studies assessed the differences related directly to framing in the same patient. Navare et al. (2) have exchanged results of 16 frames to 8 frames and then by using QGS algorithms, they reported that higher LVEDV, smaller LVESV and higher LVEF in 16 frames than 8 frames and suggested to using 16 frames instead of 8 frames. These results are similar to the findings in the present study. Kumita et al. (19) had acquired 32 frames and then at each projection angle, they combined it into 16-frame and 8-frame gated data set. EDV, ESV and EF had been calculated by using QGS algorithms and had been compared with ERNA. Combining the 32-frame data into 16-frame and 8-frame data sets generated a smaller LVEDV and a larger LVESV, and LVEF was significantly lower in accordance with the decreasing number of frames. Compared with ERNA studies, the Bland-Altman method showed underestimated LVEFs and larger 95% limits of agreement in lower framing gated SPECT. Kurisu et al. (1) reported that 8 frames compared to 16 frames underestimates diastolic parameters as well as systolic parameters, and suggested that framing rate should be taken into consideration when interpreting these parameters or comparing data from different studies.

Several methods have been introduced for image reconstruction. Schaefer et al. (20) used QGS and 4D-MSPECT algorithm for comparison of 16 and 8 gated framing in 120 patients and observed smaller difference for EF with domain difference of 7% by using QGS as compared to 17% in 4D-MSPECT. Domain differences of ESV and EDV based on Bland-Altman analysis were 10 mL against 21 mL and 12 mL against 32 mL in QGS as compared to 4D-MSPECT, respectively. In addition, QGS was more accurate in determining heart range.

Montelatici et al. (10) compared 8 and 16 framing, independently, at the same time and reported underestimation of EF and EDV and overestimation of ESV in 8 frames in both stress and rest. However, the differences were very limited and smaller than that reported in other studies. Also, there was a compliance in both 8 and 16 frames for finding patients with stress-induced EF drop that indicated the lack of the superiority of one method over the other. These results are similar to the results of the present study in the way that Montelatici et al. (10) reported the mean ΔEF of 16 and 8 frames in stress as 2.8% with 95% confidence interval of 2.5-3.2 and in rest as 2.7% with 95% confidence interval of 2.3-3.1. In the present study, mean ΔEF of 16 and 8 frames in stress was calculated as 3.05% with 95% confidence interval of 1-5.1 and in rest as 2.92% with 95% confidence interval of 1.4-1.7. The higher difference in the present study as compared to the aforementioned study may be attributed to the smaller sample size.

Presence or absence of perfusion defect, SSS or SDS had no significant effect on differences of the variables related to systolic parameters between 8 and 16 frames, which are consistent with Montelatici (10) study. But Sciagrà et al. (21) confirmed that there is a significant relationship between infarct size and LV volumes and LVEF. Furthermore, in addition to infarct size, the infarct location influences LVEF and volumes, with lower LVEF values in anterior compared to lateral or inferior infarctions of the same extent, and higher EDV and ESV in anterior compared to inferior or lateral infarctions. Also, this study showed a significant correlation with LV volumes and LVEF. Vallejo et al. (6) reported that QGS overestimated the EDV in the presence and absence of perfusion defect. However, in the presence of a perfusion defect, overestimation was worse. ESV and LVEF were also overestimated in the presence of a perfusion defect.

Study Limitations

The main limitation of the study is the lack of the assessment of clinical impact of the acquired data. In other words, it is possible that the difference between 16 and 8 frames does not have an effect on treatment approach. Another limitation was the lack of comparison with a gold standard test. Finally, it is possible that the observed difference between 16 and 8 frames does not indicate the superiority of one method over the other.

Conclusion

In conclusion, according to our results, although the difference of systolic factors in 16 and 8 gated framings by using the similar protocol were estimated less than previous studies, the difference is still significant. Further studies are required to evaluate the effect of this difference on treatment approach.

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Ethics

Ethics Committee Approval: This study complies with the Declaration of Helsinki, and it was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (registration number: 75/1394-1395).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: External and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practice: M.A., M.Q., Z.A., Concept: M.A., M.Q., Z.A., Design: M.A., H.H., M.Q., Z.A., F.T., Data Collection or Processing: M.A., M.Q., M.S., Z.A., F.T., H.J., Literature Search: H.J., E.J., M.B., M.A., Writing: E.J., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Utility of FDG PET/CT in the Management of Primary Testicular Lymphoma

Primer Testis Lenfomasında FDG PET/BT'nin Yararlılığının Değerlendirilmesi

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Abstract

Objective: Primary testicular lymphoma (PTL) is a form of extra-nodal lymphoma originating from the testicles. Currently, positron emission tomography (PET) with glucose analogue 18F-fluorodeoxyglucose (18F-FDG) is the most popular and widely used modality for evaluating tumor metabolism, and PTL usually displays increased 18F-FDG uptake. Despite the rapid increase in clinical applications of FDG PET/ computed tomography (CT), its role in PTL has neither been clearly defined nor reviewed systematically. This study reviews the usefulness and limitation of FDG PET/CT in the diagnosis and treatment of PTL.

Methods: This study included 12 patients with PTL between 2004 and 2015. We retrospectively examined PET/CT results along with patient outcome. The maximum standardized uptake value (SUV_{max}) was calculated.

Results: The mean overall survival (OS) and disease-free survival (DFS) was 44.5 months and 35.5 months, respectively. The mean SUV_{max} was identified as 18.5 in recurrent/metastatic group. The 1-year and 3-year OS was 94% and 69%, while the 1-year and 2-year DFS was 93.5% and 56%, respectively.

Conclusion: FDG PET/CT is very helpful in both staging and evaluating treatment response. Although it is not a perfect tool in the initial diagnosis, it might aid in the differential diagnosis of challenging testicular tumors. Pre-treatment and post-treatment FDG uptake values may also have a prognostic value in patients with PTL.

Keywords: Primary testicular lymphoma, SUV_{max}, FDG PET/CT

Öz

Amaç: Primer testis lenfoması (PTL) testis kaynaklı bir ekstranodal lenfomadır. ^{18}F-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) tümör metabolizmasını değerlendirmede yaygın olarak kullanılmaktadır ve PTL yüksek FDG tutulumu gösterir. FDG PET/BT'nin klinik uygulamalarının gün geçtikçe artmasına rağmen, PTL'deki rolü tam olarak tanımlanmamış ve sistematize edilmemiştir. Bu çalışma FDG PET/BT'nin PTL tanı ve tedavisindeki yararlılık ve kısıtlamalarını araştırmaktadır.

Yöntem: Çalışma 2004-2015 yılları arasında 12 PTL hastasını içermektedir. Olguların geriye dönük olarak FDG PET/BT sonuçları ve gidişatları incelenmiştir. Maksimum standart tutulum değeri (SUV_{maks}) hesaplandı.

Bulgular: Ortalama toplam sağkalım (OS) ve hastalıksız sağkalım (DFS) sırasıyla 44,5 ay ve 35,5 ay idi. Ortalama SUV_{maks} rekürrent/metastatik grupta 18,5 idi. OS 1. yılda %94, 3. yılda %69; DFS 1. yılda %93,5, 2. yılda %56 idi.

Sonuç: FDG PET/BT evreleme ve tedaviye yanıt takibinde çok faydalıdır. Testis tümörlerinin ayırıcı tanısının zor olduğu olgularda yararlı olabilir. Fakat ilk tanıda iyi bir yöntem değildir. Tedavi öncesi veya sonrası FDG tutulum değerleri prognostik bir önem taşıyabilir.

Anahtar kelimeler: Primer testis lenfoması, SUV_{maks}, FDG PET/BT

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Introduction

Primary testicular lymphoma (PTL) is a form of extra-nodal lymphoma originating from the testicles (1). PTL constitutes approximately 1-2% of all non-Hodgkin lymphomas (NHL) and accounts for 1-9% of all testicular tumors (2). Most patients are older than 60 years of age, with PTL being the most frequent testicular neoplasm in this age group (3). Approximately 80-98% of PTLs are diffuse large B-cell lymphomas (DLBCL) (4,5). The typical initial symptom is a firm, painless testicular mass with an average tumor size of 6 cm (5). Synchronous bilateral involvement occurs in 6-10% while systemic disease is present in 20-30% of the patients (6). The median overall survival (OS) of PTL is reported to be 4-5 years (7). The most common metastatic sites are contralateral testicle, central nervous system (CNS), skin, adrenal glands, bone marrow, lung and pleura (8).

Diagnostic imaging modalities include ultrasound and magnetic resonance imaging (MRI), which allow simultaneous evaluation of both testicles, paratesticular space and spermatic cord (9). When PTL is suspected, inguinal orchiectomy is required for achievement of successful treatment and establishment of correct histopathologic diagnosis with adequate pathologic specimen. An experienced pathologist is required for difficult cases, since distinguishing some cases from seminoma can be challenging (10). In meta-analysis studies, 60-79% of the patients have stage I/II disease at initial presentation (11). Recommended staging is the same as in other forms of aggressive NHL by positron emission tomography/computed tomography (FDG PET/CT) and bone marrow biopsy, with the addition of specific CNS staging with lumbar puncture for cerebrospinal fluid analysis and cranial MRI (12). The most frequent metastatic location is CNS with a reported incidence of approximately 45% (13). 64% of CNS relapses involve the brain parenchyma (11).

Currently, PET with glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most popular and widely used modality for evaluating tumor metabolism, and PTL usually displays increased ^{18}F-FDG uptake (14). Despite the rapid increase in clinical applications of FDG PET/CT, its role in PTL has neither been clearly defined nor reviewed systematically. This study reviews the usefulness and limitation of FDG PET/CT in the diagnosis and treatment of PTL.

Materials and Methods

This is a retrospective cohort study conducted with 12 PTL patients of DLBC variant treated by surgery (orchiectomy) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) between 2004 and 2015 at our institution. Patients with histopathologically confirmed PTL, who have been treated with R-CHOP protocol and had a follow-up of at least two years, with an initial staging or follow-up FDG PET/CT were included. Patients with systemic involvement at initial presentation and who received alternative therapy regimens other than R-CHOP as first line therapy protocol were excluded from the study.

FDG PET/CT was obtained for primary staging in 8 cases and for evaluation of treatment response in 4 cases. Baseline staging, re-staging or follow-up PET results and patient outcome were retrospectively extracted from patient files. The patients having pathologically increased FDG uptake on baseline or follow-up FDG PET/CT constituted recurrent/metastatic group. The semi-quantitative parameter of maximum standardized uptake value (SUV_{max}) was calculated on FDG PET/CT. OS was accepted as the time from initial diagnosis to death of any cause or last follow-up. Disease-free survival (DFS) was defined as the period from diagnosis to detection of first relapse or last follow-up.

Ethics Committee Approval and Informed Consent

The study was approved by Gülhane Training and Research Hospital Institutional Ethics Committee (protocol number: 14044, date: 2014). Informed consent was obtained from all participants.

FDG PET/CT Imaging Protocol

Patients fasted for at least 6 hours and their blood glucose level were below 150 mg/dL before the injection of an activity of 370-555 MBq of ^{18}F-FDG calculated according to the patient's bodyweight. Images were acquired one hour later with an integrated PET/CT scanner (Discovery 690-GE Healthcare). Unenhanced low dose CT and PET emission data were performed from mid-thigh to the vertex of the skull in the supine position with the arms raised above the head. CT data was obtained by an automated dose modulation of 120 kVp (maximal 100 mA), a collimation of 64×0.625 mm, a measured field of view (FOV) of 50 cm, and a noise index of 20%. These data were reconstructed to images of 0.625 mm transverse pixel size and 3.75 mm slice-thickness. PET data was in 3D mode with a scan duration of 2 min per bed position and an axial FOV of 153 mm. A standard technique (random, scatter and attenuation) and an iterative reconstruction (matrix size 256×256, Fourier rebinning, VUE Point FX [3D] with 3 iterations, 18 subsets) corrected the emission data.

Visual and Quantitative Assessment of FDG PET/CT

A standard protocol on a dedicated workstation (Volumetrix for PET/CT and AW volume share 4.5, GE Healthcare, Waukesha, WI, USA) calculated the semiquantitative PET/CT parameters used in the study. The SUV_{max} corrected for body weight was computed with standard methods from the activity of the highest density voxel in three-dimensional tumor region of transaxial whole body images on attenuation-corrected PET/CT images. The corresponding CT scan of lesions were demarcated as a frame if the boundaries of an uptake were difficult to define for the calculation of SUV_{max}.

Statistical Analysis

The data were analyzed by IBM Corp. Released 2013 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) number and percentage values were used for the description of categorical data; mean, median, standard deviation (SD), minimum (min) and maximum (max) values were used for the description of continuous data. ROC curve was drawn to evaluate the diagnostic accuracy of SUV_{max} and a cut-off level was determined. Sensitivity and specificity rates were calculated according to the chosen cut-off value. Kaplan-Meier test was used for survival analysis.

Results

The mean patient age was 57±15 years (21-77) and the mean SUV_{max} value was 18.5±7 (9.8-30.8). Mean OS and DFS were identified as 44.5 months (12-101) and 35.5 months (9-101), respectively. Mean SUV_{max} was 15.9 in the recurrent/metastatic group. Complete remission was achieved in 5/12 of the cases (42%). On the other hand, 7/12 (58%) developed recurrence and/or metastasis during follow-up 5 (42%) of which died. Median time to progression was 18.6 months. OS at the 1st year was 94%, 87.5% at the 2nd, 69% at the 3rd, and 62.5% at the 5th years. DFS at the first year was 93.5%, 56% at the second year, and 44% at the 3rd year.

There was a statistically significant difference between recurrent/metastatic group and non-metastatic (complete remission) group according to SUV_{max} values ($p<0.001$). ROC curve was drawn to evaluate the diagnostic value of SUV_{max} (Figure 1). Cut-off value of SUV_{max}, its associated sensitivity and specificity rates are demonstrated in Table 1.

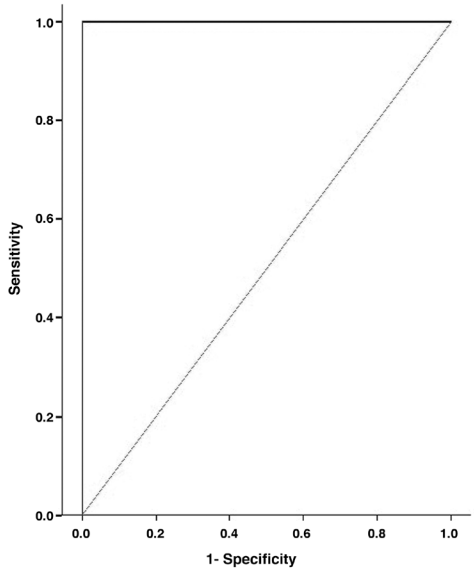

Figure 1. ROC curve represents the diagnostic accuracy of SUV_{max}

Kaplan-Meier method was used to compare DFS and OS of recurrent/metastatic and non-metastatic groups, and curves were plotted for OS (Figure 2) and DFS (Figure 3).

Table 1. Cut-off value of SUV_{max}, its associated sensitivity and specificity are demonstrated

Cut-off value	Sensitivity (%)	Specificity (%)	Area under curve
11.4	89	100	0.99 (p=0.001)

SUV_{max}: Maximum standardized uptake value

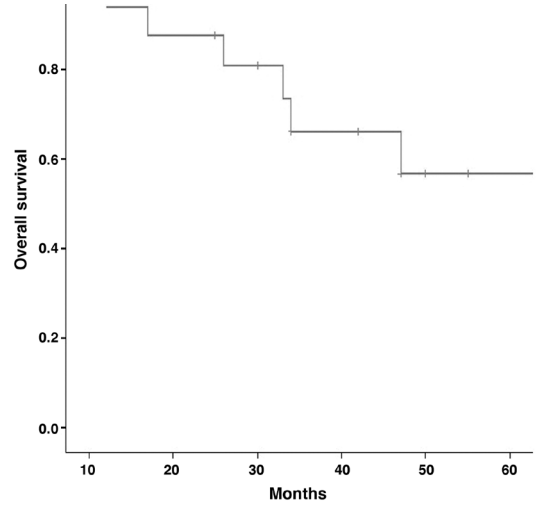

Figure 2. Kaplan-Meier curve shows the plot associated with overall survival

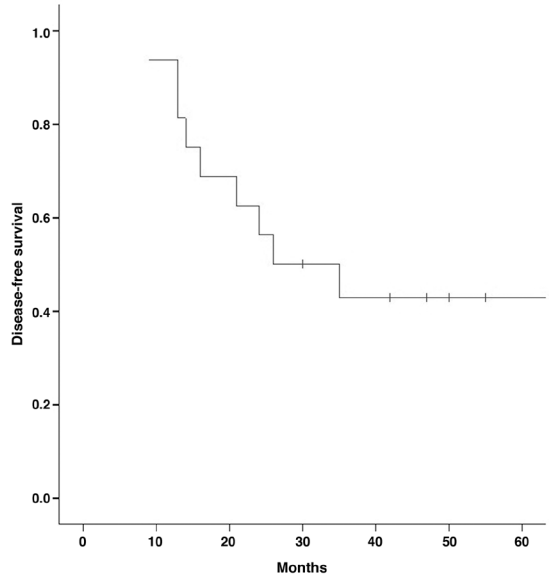

Figure 3. A Kaplan-Meier curve indicates disease-free survival in patients with primary testicular lymphoma

Discussion

The mean age of our patient population was 57 years, which is lower than the mean age reported in the literature. The mean tumor size was 6.5 cm and the mean SUV_{max} was 18,5, which were both in line with previous studies. Local recurrence was detected in 60% of the cases and bilateral involvement was present in 16%. Nearly 50% of the tumors metastasized to CNS, and CNS metastasis and/or testicular recurrence was the cause of death in all our cases. All these findings including median OS, median time to progression and other prognostic data presented herein are in accordance with the literature.

Early diagnosis of PTL is essential for timely treatment before the occurrence of widespread metastases and invasion of neighboring tissues. Clinical diagnosis of PTL is sometimes difficult and delayed due to its nonspecific symptoms. FDG PET/CT has a limited value in the initial diagnosis and differentiation of PTL from other malignant testicular tumors or non-malignant lesions. PTL is a highly cellular tumor and shows increased glucose metabolism, causing homogenous marked asymmetric testicular FDG uptake (14). The semi-quantitative FDG uptake values measured by SUV_{max} were reported to be between 10 and 30 for PTL (14). This value is higher than the average SUV_{max} of the normal testicle that has been reported as approximately 2.5 in large case series (14). PTL may be distinguished from other testicular diseases such as seminoma according to its uptake pattern and SUV_{max} value. However, FDG PET/CT is not a perfect tool in the diagnosis of PTL.

Detection of PTL with extra-testicular involvement at primary (baseline) staging is important for appropriate therapy since systemic involvement alternates therapy protocol. Standard baseline (initial) staging for PTL includes MRI and sometimes bone marrow biopsy to exclude systemic lymphoma (13). Conventional initial staging in PTL might not show extra-testicular lesions, especially occult systemic lymphoma in some patients. FDG PET/CT is more sensitive than conventional staging methods in this regard and may disclose higher rates of concomitant systemic disease at initial diagnosis. The supremacy of this modality is attributed to the ability to screen the whole-body, and the fusion of anatomic detail provided by the CT component with metabolic information. This advantage remains true also for re-staging during follow-up. The clinical significance of identifying recurrence and/or metastasis at the follow-up is apparent. Currently, FDG PET/CT is the choice of imaging modality for primary staging and re-staging. In our study, we also observed that FDG PET/CT is an excellent tool in disease-staging both initially and during follow-up.

PTL is one of the most malignant testicular tumors that respond well to treatment. Changes in metabolic imaging with FDG PET/CT can be detected soon after initiation of therapy. Early evaluation of the initial treatment response is very important, since salvage treatment may improve outcome. Follow-up (evaluation of treatment response) FDG PET/CT fulfills this easily with its unique advantages over conventional techniques. The whole body can be assessed in one session prior to anatomic changes and active foci can be distinguished from fibrotic or inflammatory tissue as well as detection of small lesions located outside areas imaged by conventional techniques. Dramatic disappearance of increased FDG uptake in the tumor with therapy indicates treatment success.

Kawai et al. (15) demonstrated that FDG PET 3 weeks after the first chemotherapy showed a significant decrease in FDG uptake of the tumor as compared to pre-treatment uptake. The reduction in FDG uptake significantly correlated with the decrease in tumor size as detected by follow-up MRI (15). These results indicate that metabolic imaging with FDG PET can accurately evaluate treatment response at an early stage, sometimes preceding changes on MRI. Early therapeutic monitoring might have an impact on deciding whether the treatment regimen should be maintained or changed. If patients with a poor early response were identified, treatment could be modified at an early stage before delivering additional cycles of ineffective therapy. In our study, we detected that follow-up FDG PET provided valuable information for treatment evaluation.

The 5-year survival rate is reported as 35% with a mean survival of 13 months for patients with PTL (16). The 5-year survival rate was identified as 53% in our study, with a mean survival of 18 months. Early quantitative measurement of metabolic response with FDG PET was declared to provide valuable prognostic information in systemic aggressive lymphoma types (15). FDG PET/CT might also provide prognostic information in patients still under therapy and predict long-term outcome in PTL. The OS of patients with low to moderate FDG uptake was reported to be significantly longer than that of patients with high FDG uptake (17). PTL with high FDG uptake tended to exhibit poor treatment response as compared to that with low to moderate uptake (18). This prognostic information yielded by FDG PET over SUV_{max} values was very accentuated in our study. The SUV_{max} of the recurrent/metastatic group was significantly high ($p<0.001$) and it was a strong predictor of outcome. To the best of our knowledge, although there are no published studies on this issue in the literature, FDG uptake value might represent tumor aggressiveness in PTL. Further clinical trials are required to define the optimal strategy to utilize FDG PET information as a prognosticator and to improve outcome in patients with PTL.

Conclusion

The utility of FDG PET/CT is currently increasing in the management of PTL. This review summarizes the usefulness and limitations of FDG PET/CT in the diagnosis and treatment of PTL. FDG PET/CT is valuable in both primary staging and restaging. It is also valuable in evaluating

treatment response after initial chemotherapy and altering treatment strategy at a very early stage, if required. Pre- and post-treatment FDG uptake values reflected by SUV_{max} might have a prognostic value in patients with PTL. FDG PET/CT might be useful for differential diagnosis of challenging testicular tumors. Nevertheless, it is not the proper modality for initial diagnosis.

Ethics

Ethics Committee Approval: The study was approved by Gülhane Training and Research Hospital Institutional Ethics Committee (protocol number: 14044, date: 2014).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.O., S.İ., E.A., E.A., N.A., Concept: K.O., S.İ., E.A., E.A., N.A., Design: K.O., S.İ., E.A., E.A., N.A., Data Collection or Processing: K.O., S.İ., E.A., E.A., N.A., Analysis or Interpretation: K.O., S.İ., E.A., E.A., N.A., Literature Search: K.O., S.İ., E.A., E.A., N.A., Writing: K.O., S.İ., E.A., E.A., N.A.

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Usefulness of ^{18}F-FDG PET/CT in Cutaneous Melanoma Patients with Negative Sentinel Lymph Nodes and High Clark Levels

Sentinel Lenf Nodu Negatif Yüksek Clark Seviyeli Kutanöz Melanom Hastalarında ^{18}F-FDG PET/BT'nin Değeri

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Abstract

Objective: We investigated the utility of PET/CT in cutaneous melanoma (CM) patients with pathological negative sentinel lymph nodes (SLN), within the first year.

Methods: The results of PET/CTs and SLN biopsy (SLNB) in 65 patients (39 male and 26 female, mean age 53.8) with a PET/CT in the first postoperative year were evaluated. Within this cohort, the utility of early PET/CT imaging was assessed in patients with negative SLNB. McNemar test was used to compare PET/CT findings with SLNB results.

Results: Out of 43 patients with pathologically positive SLNs, 23 patients (53.5%) had positive and 20 patients (46.5%) had negative findings on PET/CT within the first postoperative year. On the other hand, PET/CT results of 22 patients with negative SLNBs were found to be negative in 19 patients (86.4%) and positive in 3 patients (13.6%). For the patients with negative SLNB results, the detection rate of distant metastasis with PET/CT was significantly lower ($p<0.001$) than that in patients with positive SLNBs.

Conclusion: Our results showed that ^{18}F-FDG PET/CT will most likely (86.4%) be negative during the first postoperative year in patients with a negative SLNB. Therefore, it is concluded that this modality would not provide any significant clinical contribution within this time frame.

Keywords: ^{18}F-FDG, melanoma, sentinel lymph node biopsy

Öz

Amaç: Çalışmamızda sentinel lenf nodu (SLN) patoloji sonucu negatif olan malign melanom (MM) tanılı hastalarda PET/BT'nin ilk bir yıl içerisindeki yararını araştırdık.

Yöntem: Ameliyat sonrası ilk bir sene içerisinde PET/BT çekimi yapılan 65 hastanın (39 erkek; 26 kadın, yaş ortalaması: 53,8) PET/BT çekimleri ve SLN biyopsi sonuçları değerlendirildi. Bunların içerisinden SLN biyopsi sonucu negatif olan hastalarda erken dönemde PET/BT görüntülemenin gerekliliği araştırıldı. McNemar testi, pozitif veya negatif PET/BT sonuçlarını pozitif ve negatif SLNB sonuçları ile karşılaştırmak için kullanıldı.

Bulgular: SLNB sonuçları pozitif olan 43 hastanın postoperatif 1. yılda yapılan PET/BT çekimlerinin sonuçları 23 hastada (%53,5) pozitif, 20 hastada (%46,5) ise negatif olarak bulundu. Diğer taraftan SLN biyopsi sonucu negatif olan 22 hastanın

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Öz

postoperatif 1. yılda yapılan PET/BT çekimlerinin sonuçları 19 hastada (%86,4) negatif, 3 hastada (%13,6) ise pozitif olarak bulundu. SLN biyopsi sonucu negatif olan hastalar için postoperatif 1. yılda yapılan PET/BT ile uzak metastaz saptanma oranı SLN biyopsi sonucu pozitif olan hastalardan anlamlı olarak daha düşük (p<0,001) bulundu.

Sonuç: Çalışmamızda, SLN biyopsi sonucu negatif olan hastalarda postoperatif ilk bir yılda yapılan ^{18}F-FDG PET/BT çekimlerinin sonuçlarının büyük bir olasılıkla (olguların %86,4'ünde) negatif olması nedeniyle bu hasta grubunda bu periyotta yapılan ^{18}F-FDG PET/BT çekimlerinin önemli bir klinik katkı sağlamayacakları sonucuna varılmıştır.

Anahtar kelimeler: ^{18}F-FDG, melanom, sentinel lenf nodu biyopsisi

Introduction

PET/CT is introduced as an important scintigraphic imaging method for both the diagnosis and restaging of maligant diseases as well as the evaluation of treatment outcomes. Although it is a valuable method, it is a costly procedure with considerable radiation exposure to tissues. That is why, it might be feasible to avoid PET/CT scanning in unnecessary conditions in terms of overall patient health.

The use of ^{18}F-FDG PET/CT for both staging and follow-up of patients with cutaneous melanoma (CM), which is a disease that threatens life and spreads easily with lymphatic metastases, has been previously reviewed by clinicians (1,2,3,4).

Sentinel lymph node (SLN) biopsy (SLNB) has an important role in disease staging of these patients. Although PET/CT has been proven to be useful in the staging of CM, it should only be used in patients when truly indicated. The utility of PET/CT to detect systemic recurrences during follow-up has yet to be investigated. SLNB results might have clues to determine the exact timing of this examination.

The purpose of this study was to evaluate the necessity and utility of PET/CT imaging that was performed within the first year in patients with a diagnosis of CM, whose SLN(s) have previously been biopsied by either blue dye injection or lymphoscintigraphy and had negative results for metastasis.

Materials and Methods

Between January 2005 and December 2010, the results of 425 PET/CT examinations of 360 patients, who have been diagnosed histopathologically as CM and referred to our department for restaging by PET/CT imaging, were evaluated retrospectively. Within 360 patients, 96 patients who had postoperative pathology results of their SLNBs were included in the study. Patients had been selected for SLNB according to NCCN guidelines.

Accordingly, patients with melanoma greater than 1 mm in depth along with those between 0.76 mm and 1.0 mm in thickness had been considered for SLND if they had positive deep margins, lymphovascular invasion, age less than 40 years, significant vertical growth phase, increased mitotic rate, and Clark's level IV or higher (5).

In order to reach the maximum number of examinations possible within the same interval, only the results of 65 patient's [39 male and 26 female, mean age=53.8 (minimum=27; maximum=85)] PET/CT studies that have been performed in the first postoperative year were evaluated as well as their SLNB pathology results.

Within this cohort, 22 patients with negative SLNB results were determined and the utility of early PET/CT imaging in this subgroup was further evaluated.

The lesions were located mostly at the feet (n=14), back (n=9) and arms (n=7). The rest of the lesions were found on sites such as the scalp, ears, cheeks, abdomen, legs and hands in decreasing order. According to histopathologic subtypes, most patients were diagnosed with superficial spreading type of CM followed by nodular and acrolentiginous types in decreasing frequency (Table 1).

The Breslow thickness of the detected lesions varied between 0.6-17.0 mm. Thus, the Clarks levels were between 3 and 5.

PET/CTs were performed at our department by a high-resolution PET scanner (Siemens Biograph LSO HI-RES PET/CT, Illinois, USA) integrated 6 section multidetectors (for attenuation correction and location).

The patients fasted for at least 4 hours and their finger-tip blood glucose levels were under 150 ng/mL. They rested to obtain complete biodistribution of ^{18}F-FDG in the body for about 1 hour after an intravenous injection of 13-15 mCi of ^{18}F-FDG. After micturition they were taken into the imaging suite and were laid on the scanner bed in the supine position.

Following a low-dose CT scan without iv. radiological contrast agent injection PET scanning was performed, covering all areas of the body. Then, CT and PET data were reconstructed by iterative methods after performing attenuation correction for PET images by using tissue attenuation map derived from corresponding CT data. Fusion images of PET and CT at three spatial planes (axial, coronal, and sagittal) approximately 0.5 cm in thickness cross-sectional images as well as maximum intensity projection (MIP) images were displayed and evaluated by an

Table 1. Patient characteristics

Patient	Sex	Age	Location of primary tumor	Histopathology
1	M	72	Back	Malignant melanoma
2	F	77	Arm	Malignant melanoma
3	M	39	Knee	Verrucous melanoma
4	F	60	Abdomen	Malignant melanoma
5	M	57	Ear	Superficial spreading
6	F	57	Thigh	Malignant melanoma
7	F	73	Cheek	Desmoplastic
8	M	40	Abdomen	Malignant melanoma
9	M	68	Foot	Acral lentiginous
10	M	51	Arm	Malignant melanoma
11	F	40	Scalp	Nodular melanoma
12	M	34	Back	Superficial spreading
13	M	52	Thigh	Malignant melanoma
14	M	54	Arm	Nodular melanoma
15	M	40	Waist	Malignant melanoma
16	M	41	Scalp	Malignant melanoma
17	M	71	Arm	Nodular melanoma
18	F	33	Abdomen	Malignant melanoma
19	F	26	Hand	Malignant melanoma
20	F	69	Thigh	Malignant melanoma
21	M	58	Back	Malignant melanoma
22	M	63	Abdomen	Malignant melanoma
23	F	35	Back	Superficial spreading
24	M	53	Back	Superficial spreading
25	M	79	Foot	Acral lentiginous
26	M	64	Scalp	Malignant melanoma
27	M	69	Foot	Acral lentiginous
28	M	74	Inguinal	Superficial spreading
29	M	37	Hand	Malignant melanoma
30	F	36	Arm	Malignant melanoma
31	F	47	Abdomen	Superficial spreading
32	M	54	Foot	Superficial spreading
33	M	46	Arm	Superficial spreading
34	M	85	Back	Superficial spreading
35	M	76	Back	Malignant melanoma
36	M	68	Waist	Malignant melanoma
37	M	27	Scalp	Malignant melanoma
38	M	40	Back	Malignant melanoma
39	F	38	Hand	Malignant melanoma
40	F	57	Foot	Malignant melanoma
41	M	54	Foot	Malignant melanoma
42	F	68	Foot	Malignant melanoma
43	F	42	Arm	Malignant melanoma
44	F	46	Scalp	Malignant melanoma
45	M	68	Arm	Malignant melanoma
46	M	33	Abdomen	Malignant melanoma
47	M	42	Foot	Malignant melanoma
48	M	55	Thorax	Nodular melanoma
49	F	64	Back	Malignant melanoma
50	M	69	Foot	Nodular melanoma
51	M	69	Foot	Subungual
52	F	34	Thigh	Nevoid mm
53	F	65	Hand	Malignant melanoma
54	M	75	Heel	Acral lentiginous
55	F	52	Scalp	Malignant melanoma
56	M	67	Ear	Nodular melanoma
57	M	67	Foot	Acral lentiginous
58	M	62	Foot	Malignant melanoma
59	F	59	Foot	Superficial spreading
60	F	43	Hand	Malignant melanoma
61	F	42	Back	Superficial spreading
62	M	54	Hand	Acral lentiginous
63	F	31	Thigh	Malignant melanoma
64	M	54	Arm	Nodular melanoma
65	F	39	Abdomen	Malignant melanoma

M: Male, F: Female

experienced nuclear medicine specialist on a high-resolution monitor. When it is deemed necessary, PET images without attenuation correction were interpreted by the examiner. In the interpretation, excluding the physiological FDG uptake, the foci showing more intensive involvement as compared to the environmental background activity were evaluated as metastasis and the result was expressed as a positive PET/CT finding. In addition, a semi-quantitative parameter indicating the rate between the average activity in the body and intensity of activity in the selected area i.e. "maximum standard uptake value (SUV_{max})" was also used for pathological uptake evaluation.

Preoperative lymphoscintigraphy by intracutaneous injection of 0.5 mCi Tc-99m-labelled albumin nano-colloids around the tumor or the tumor's excision scar was combined with

the intraoperative use of a hand-held gamma probe and patent blue dye mapping technique in order to identify and harvest the SLN.

Statistical Analysis

McNemar test was used in order to compare the positive or negative PET/CT results of the study group with the positive and negative results of their SLNBs. Statistical results were expressed as percent and frequency. Any "p" value less than 0.05 was accepted as statistically significant.

Ethics Committee Approval and Informed Consent

This study was approved by the İstanbul University Cerrahpaşa Medical Faculty Ethics Committee (date: 12 July 2010, file number: 20697) and signed written informed consent was obtained from all research subjects.

Results

Study patients were divided into 7 groups according to the time interval between the surgery of the primary lesion and the initial PET/CT (Table 2). Some patients in these groups had more than one PET/CT scans during their course of follow-up.

In the first postoperative year, PET/CT results were positive in 26 (40%) and negative in 39 (60%). Of the same patients, SLNB results were positive in 43 (66.2%) and negative in 22 (33.8%) (Table 3).

Within the first postoperative year, PET/CT results of 43 patients with a positive SLNB were found to be also positive in 23 patients (53.5%) (Figure 1A, 1B) and negative in 20 patients (46.5%). On the other hand, PET/CT results of 22 patients with a negative SLNB were found to be also negative in 19 patients (86.4%) and positive in 3 patients (13.6%). One of the three patients with a negative SLNB and positive PET/CT finding was a 47-year-old female patient with superficial spreading melanoma localized in the abdomen, the tumor being Clark level III with a thickness of 0.6 mm without ulceration. The second was a 76-year-old male patient with malignant melanoma of the back while the third patient was a 60-year-old male patient with the primary tumor localized at the foot showing a histopathology of Clark level V subungual melanoma, tumor thickness of 0.6 mm with ulceration (Figure 2A, 2B, 2C, 2D).

For the patients with negative SLNB results, the detection rate of distant metastasis with PET/CT was significantly lower ($p<0.001$) than that in patients with positive SLNB results (Table 4).

Table 2. Patient distribution according to time of PET/CT scanning

PET/CT scanning	Number of patients
1st postoperative year	65
1st and 2nd postoperative year	30
2nd and 3rd postoperative year	22
3rd and 4th postoperative year	12
4th and 5th postoperative year	5
5th and 6th postoperative year	6
6th and 7th postoperative year	3

Discussion

In a study on the routine use of ^{18}F-FDG PET in patients with early stage CM and positive SLNB results by Horn et al. (6), ^{18}F-FDG PET was reported to be positive in 27% of these cases. However, only 12% of these have been verified as true CM metastases. According to this result, even in case of positive SLNB results, FDG PET imaging did not have a clinically important impact for staging. On the contrary, our results demonstrated that 53.5% of patients with a positive SLNB also had a positive PET/CT scan in terms of metastatic lesions, which indicates that in approximately half of the study patients any possibly metastatic lesion could be detected by PET/CT. Therefore, PET/CT is a feasible method in these patients to detect possible distant metastatic lesions.

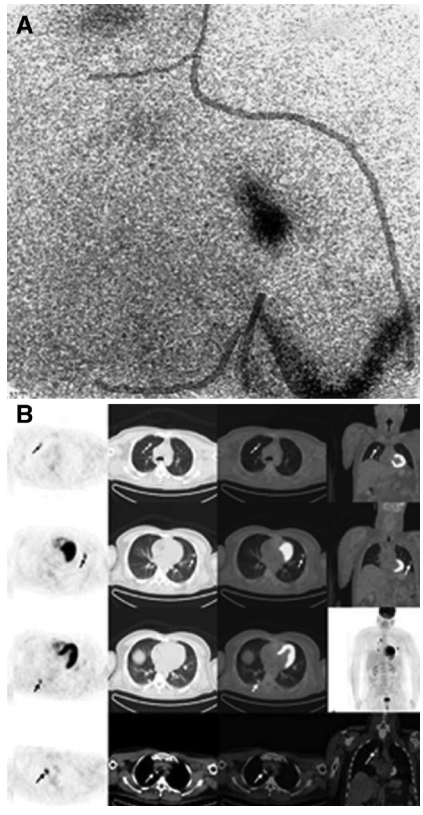

Figure 1. Preoperative lymphoscintigraphy image of a patient with a positive axillary sentinel lymph nodes biopsy (A) along with metastatic lun nodules and mediastinal lymph nodes of the same patient in PET/CT scan performed within the 1st postoperative year (B)

Table 3. Sentinel lymph nodes biopsy results and PET/CT results of all patients

Patient	SLN	PET
1	+	-
2	-	-
3	+	+
4	+	+
5	+	+
6	+	+
7	+	+
8	+	+
9	+	+
10	+	+
11	+	+
12	+	-
13	+	+
14	-	-
15	+	-
16	+	+
17	-	-
18	+	+
19	+	-
20	+	-
21	+	-
22	+	-
23	-	-
24	+	-
25	-	-
26	-	-
27	-	-
28	-	-
29	+	+
30	-	-
31	-	+
32	-	-
33	+	-
34	-	-
35	-	+
36	+	+
37	+	+
38	+	+
39	+	+
40	+	+
41	+	-
42	+	+
43	+	-
44	+	-
45	+	+
46	+	+
47	-	-
48	+	+
49	+	-
50	+	-
51	-	+
52	-	-
53	+	-
54	+	-
55	-	-
56	-	-
57	-	-
58	+	-
59	+	-
60	+	-
61	-	-
62	+	-
63	-	-
64	+	+
65	-	-

SLN: Sentinel lymph nodes

Table 4. The correlation of sentinel lymph nodes biopsy and PET/CT results

Patient results	PET/CT (+)	PET/CT (-)
SLN biopsy (+)	n=23 (53.5%)	n=20 (46.5%)
SLN biopsy (-)	n=3 (13.6%)	n=19 (86.4%)

p<0.001, SLN: Sentinel lymph nodes

Constantinidou et al. (7) have reported that PET scan was positive on two patients none of which was related to melanoma out of 30 patients who were referred for PET/CT within 100 days postoperatively with positive SLNB results, and the value of PET was determined to be limited for staging, although they have indicated that FDG PET was a highly sensitive and specific method in identifying distant metastases.

The positive SLNB rate is reported as approximately 20% in most studies on CM patients. In our study group, this

rate was determined to be much higher (66.2%) which may be attributed to the significantly advanced disease stage of our patients, having Clark levels mostly greater than 4.

Wagner et al. (8) performed 18F-FDG PET or PET/CT scans in 46 CM patients in order to determine the rate of distant metastasis, within 6 weeks after positive SLNBs. Of these 46 patients, 6 had an inconclusive PET/CT. The distant metastases were detected in 5 (12.5%) of the remaining 40 patients with negative PET results by other methods within 12 months. In this study, FDG PET was found inadequate in detecting distant metastases during initial staging of these patients with positive SLNB results. These results may be due to the lack of macroscopic metastatic disease detectable by PET scan performed within six weeks after positive SLNBs.

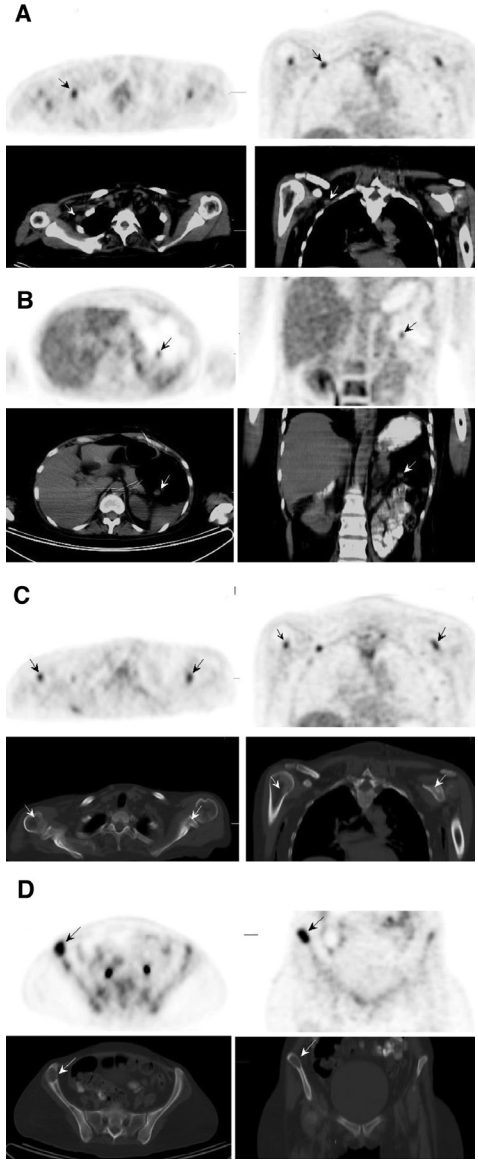

Figure 2. PET/CT images performed within the 1st postoperative year of a patient with primary tumor localized at the foot with a negative sentinel lymph nodes biopsy, showing right axillary lymph node metastasis (A), mesenteric metastasis (B), and bone metastasis (C and D)

In other similar studies, PET/CT was found to be ineffective in early stages of CM even in patients with positive SLNBs. Actually, it is thought that this insufficiency could be more pronounced in t patients with negative SLNBs, which was the case in our study. In line with these findings, our results indicated that 86.4% of the 18F-FDG PET/CTs performed in the first postoperative year in patients with negative SLNB results were also negative.

In another study evaluating the accuracy of SLNB and 18F-FDG PET imaging for determining early lymph node metastasis by Libberecht et al. (9), preoperative PET imaging and SLNB were performed in five patients diagnosed with CM over 1 mm Breslow thickness and without clinically detected lymph node metastases and recurrence. In this study, no lymph node involvement or distant metastasis were detected by PET while micrometastasis was histologically detected in the SLN in 2 of the 5 patients (40%) included in the study during the 10 month study period. The false negative finding of lymph node metastasis by PET in this small group of patients indicated that PET had a limited role for this group of patients without palpable lymph nodes. Accordingly, even when there was micrometastasis in the SLN(s), it was determined that the probability of distant organ metastasis detection by PET performed within 10 months would be low. In other words, keeping the limited number of patients in mind, 18F-FDG PET together with SLNB was found to be negative in 60% of their patients.

In a retrospective study of 61 patients with early stage CM, Klode et al. (10) reported that only 1 of 17 metastatic SLNs was detected in 14 patients (23%) by preoperative 18F-FDG PET/CT. In that study, the sensitivity and the negative predictive value of 18F-FDG PET as a diagnostic test was calculated as 5.9% and 78%, respectively. It was concluded that 18F-FDG PET was not an appropriate method for evaluation of early regional lymphatic metastases and that 18F-FDG PET would be more applicable for AJCC stage III-IV CM patients.

Some of the aforementioned studies have reported that 18F-FDG PET imaging was not sensitive in detecting SLN metastases. For example, in a study on patients diagnosed with early-stage CM Wagner et al. (8) reported the true positivity rate of FDG PET as 11%. We could not make a similar evaluation since we did not evaluate 18F-FDG uptake particularly for SLN(s). Moreover, in that study distant metastasis could be detected only in 12.5% of patients by early 18F-FDG PET imaging. According to our study, recurrence or distant metastasis could be demonstrated in 53.5% of cases with a positive SLNB within the first year by 18F-FDG PET/CT.

It was an interesting finding that in 3 patients whose SLN was negative, the PET/CT results were positive. Unfortunately, we could not depict any underlying reason to explain it. There was diversity in terms of their age, gender, site and type of lesions.

Study Limitations

The main limitation of our study was not to perform histopathologic verification for foci of ^{18}F-FDG uptake in the study group. However, the patients were followed-up for long periods and secondary malignancy was not detected in any patients, that could have been interpreted as a false positive metastatic disease for CM.

Conclusion

The existing published articles have focused on the utility of ^{18}F-FDG PET or PET/CT to demonstrate distant metastases in patients with positive SLNBs, and this imaging method was not recommended at early stages of this disease for this particular purpose. Keeping that in mind, we tried to understand if this method is useful in the initial workup of CM patients with negative SLNBs.

In conclusion, ^{18}F-FDG PET/CT performed within the first year after excision of the primary lesion in patients with CM was positive in 53.5% of patients with a positive SLNB, and was negative in 86.4% of patients with a negative SLNB.

It is well known that, SLNB does not provide direct information on the presence or absence of distant metastases (6). Nevertheless, our study also demonstrated that the presence of distant metastases within the first year was more than two-fold higher in patients with regional SLN involvement as compared to patients without SLN metastasis.

The results of our study showed that results of ^{18}F-FDG PET/CT performed during the first year follow-up of patients histologically diagnosed with CM and had negative SLNB had a good correlation. Accordingly, ^{18}F-FDG PET/CT was found to be negative during the first year follow-up of patients with a negative SLNB. Therefore, it is concluded that ^{18}F-FDG PET/CT scanning will not provide any significant clinical contribution. The results also suggested that both local and distant metastases could be demonstrated by ^{18}F-FDG PET/CT in more than half of the patients with a positive SLNB result and that PET/CT scanning was important in terms of re-staging.

Ethics

Ethics Committee Approval and Informed Consent: This study was approved by the İstanbul University Cerrahpaşa Medical Faculty Ethics Committee (date: 12 July 2010, file number: 20697) and signed written informed consent was obtained from all research subjects.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Concept: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Design: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Data Collection or Processing: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Analysis or Interpretation: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Literature Search: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S., Writing: Ö.V.T., F.A.Ç., Z.R.K.D., Ç.Ö., H.B.S.

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Original Article
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The Contribution of Fluorine ^{18}F-FDG PET/CT to Lung Cancer Diagnosis, Staging and Treatment Planning

Flor ^{18}F-FDG PET/BT'nin Akciğer Kanseri Tanı, Evreleme ve Tedavi Planlamasına Katkısı

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Abstract

Objective: Lung cancer is the most common cause of cancer-related death throughout the world, and the correct choice of treatment based on early diagnosis and staging increases the chance of survival. The present study aims to investigate the contribution of fluorine 18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to the management of lung cancer.

Methods: In this study, 50 patients who underwent ^{18}F-FDG PET/CT for lung cancer diagnosis and staging between February 2012 and February 2014 were included. The maximum standardized uptake value (SUV_{max}) of the primary lung lesion along with other findings of ^{18}F-FDG PET/CT and the results of histopathologic and conventional examinations were evaluated retrospectively. The mean survival time of patients was determined, and the findings were compared by using statistical methods.

Results: Histopathologic examinations revealed 51 lung cancers in 50 patients. The sensitivity, accuracy and positive predictive value of ^{18}F-FDG PET/CT in detecting primary malignancy were 94%, 94%, 100%, respectively. Adenocarcinoma (n=23, 16.8±13.5) and squamous cell carcinoma (n=15, 17.9±5.6) did not differ significantly regarding their mean SUV_{max} values (p=0.2). A statistically significant positive correlation (r=0.4) was identified between tumor size and SUV_{max} value for 51 tumors (p=0.002). The ^{18}F-FDG PET/CT result was true negative in nine, false positive in six, true positive in two, and false negative in four patients who underwent histopathologic evaluation of their lymph nodes. The ^{18}F-FDG PET/CT changed treatment planning in 34% of the patients. No significant relationship was identified between SUV_{max} value of the tumor and patient survival in patients (p=0.118).

Conclusion: The present study concluded that PET/CT was an efficient method in the diagnosis and staging of lung cancer since it provided useful information in addition to conventional methods. It was also observed that PET/CT scanning resulted in a change in therapeutic plans in the majority of patients. However, there was no statistically significant relationship between survival and the SUV_{max} of the primary mass.

Keywords: Lung cancer, positron emission tomography, survival analysis

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Öz

Amaç: Akciğer kanseri, tüm dünyada kansere bağlı ölümlerin en sık nedenidir. Erken tanı ve evrelemeye bağlı doğru tedavi seçimi akciğer kanserinde sağkalımı artıran bir faktördür. Amacımız akciğer kanseri yönetimine flor 18-fluorodeoksiglukoz-pozitron emisyon tomografisi/bilgisayarlı tomografinin (^{18}F-FDG PET/BT) katkısını araştırmaktır.

Yöntem: Çalışmamıza Şubat 2012-Şubat 2014 tarihleri arasında akciğer kanseri tanı ve evrelemesi amacıyla ^{18}F-FDG PET/BT yapılan 50 hasta dahil edildi. ^{18}F-FDG PET/BT'de akciğerde saptanan primer lezyonun maksimum standart tutulum değeri (SUV_{maks}) ve diğer bulguları ile histopatolojik ve konvansiyonel yöntem sonuçları retrospektif olarak değerlendirildi. Hastaların ortalama sağkalım süresi belirlendi. İstatistiksel yöntemler kullanılarak bulgular karşılaştırıldı.

Bulgular: Elli hastada histopatolojik olarak toplam 51 akciğer kanseri saptandı. ^{18}F-FDG PET/BT'nin primer maligniteyi saptamada duyarlılık, doğruluk ve pozitif prediktif değeri sırasıyla %94, %94, %100 saptandı. Adenokarsinom (n=23, 16,8±13,5) ve skuamöz hücreli karsinom (n=15, 17,9±5,6) ortalama SUV_{maks} değeri açısından anlamlı bir farklılık göstermedi (p=0,2). Elli bir tümör için tümör boyutu ile SUV_{maks} değeri arasında istatistiksel olarak anlamlı pozitif korelasyon (r=0,4) mevcuttu (p=0,002). ^{18}F-FDG PET/BT, histopatolojik olarak lenf nodu değerlendirilen hastaların; dokuzunda gerçek negatif, altısında yanlış pozitif, ikisinde gerçek pozitif ve dördünde yanlış negatifti. ^{18}F-FDG PET/BT, hastaların %34'ünde tedavi planını değiştirdi. Tümörün SUV_{maks} değeri ile hasta sağkalımı arasında anlamlı bir ilişki yoktu (p=0,118).

Sonuç: Çalışmamızda PET/BT'nin konvansiyonel yöntemlere ek önemli bilgiler sağlayarak akciğer kanseri tanı ve evrelemesinde etkin bir yöntem olduğu sonucuna varıldı. Ayrıca PET/BT'nin evrelemeye katkısıyla hastaların önemli bir kısmında tedavi planında değişikliğe neden olduğu görüldü. Ancak primer kitlenin SUV_{maks} değeri ile hastaların sağkalımı arasında istatistiksel olarak anlamlı ilişki saptanmadı.

Anahtar kelimeler: Akciğer kanseri, pozitron emisyon tomografi, sağkalım analizi

Introduction

Lung cancer is the most frequent malignancy throughout the world since 1985 (1) and the leading cause of cancer-related death in both men and women (2). Curative treatment can be offered to lung cancer patients with early diagnosis, in whom computed tomography (CT) is the first diagnostic tool (3). One of the most important prognostic factors in lung cancer is tumor stage. Hence, proper staging is very important when determining prognosis and choosing appropriate treatment. T-staging is based on CT findings, although this modality may be unable to distinguish a tumor from atelectasis or show disease extent. Fluorine 18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) is an effective method for the diagnosis, staging, evaluation of treatment response, follow-up for recurrence and re-staging of lung cancer. In our retrospective study, we investigated the contribution of ^{18}F-FDG PET/CT to lung cancer diagnosis, staging and management, as well as the prognostic and survival effects of the maximum standardized uptake value (SUV_{max}) of the primary lesion in an ^{18}F-FDG PET/CT.

Materials and Methods

The present study included 50 patients who have been referred to Ege University Faculty of Medicine, Department of Nuclear Medicine between February 2012 and February 2014, and who have undergone ^{18}F-FDG PET/CT scanning for the diagnosing and staging of lung cancer. Patients were injected intravenously with 250-400 MBq of ^{18}F-FDG at least four hours after fasting for ^{18}F-FDG PET/CT imaging. Approximately one hour after the tracer injection, PET and CT scans were obtained using a PET-CT scanner (biograph high-definition 16-slice CT, Siemens Healthcare, Erlangen, Germany), and the PET and CT images were loaded onto three-dimensional workstations. Visual and semi-quantitative evaluation of the lesions observed on ^{18}F-FDG PET/CT were carried out. In case of non-physiologically enhanced areas of activity associated with soft/bone tissue on CT, the finding was identified as "PET lesion", and these PET lesions were interpreted as malignant if either the SUV_{max} value >2.5 or when the FDG uptake was significantly higher than the background tissue. Adrenal gland lesions with a higher FDG uptake than the liver were considered as malignant. A total of 30 patients or their close relatives were accessed to assess survival. One of those 30 patients had synchronous double primary lung cancers. The correlation between the SUV_{max} value of the primary lesion and patient survival was evaluated. The findings of ^{18}F-FDG PET/CT were compared with radiologic and histopathologic results as well as the final clinical decisions and the determined stages.

Statistical Analysis

The IBM SPSS V 21.0 software was used for statistical analysis. Kolmogorov-Smirnov and Shapiro-Wilk (S-W) tests were utilized for normality analysis of data distribution, and Mann-Whitney U test was applied to determine the differences between the two groups in case of non-normal distribution. A Spearman's rho correlation test was utilized to investigate the correlation between the parameters, and the Kaplan Meier method was used for survival analysis. The differences in survival curves taking different variables into account were tested by using the log-rank test.

Results

This study included 50 patients (46 males, four female, mean age 63.0±8.6) who underwent ^{18}F-FDG PET/CT. A histopathologic diagnosis of lung cancer was obtained in all patients. There were 51 tumors in 50 patients since one patient had synchronous double primary lung cancers that have been diagnosed as adenocarcinoma. The histopathologic results of the lung lesions revealed 23 adenocarcinomas, 15 squamous cell carcinomas (SCC), four small-cell lung cancers (SCLC), two large-cell neuroendocrine carcinomas, one adenoid cystic carcinoma, one carcinoid tumor and five non-SCLC [(NSCLC), with no specific classifications]. Patient and tumor characteristics are summarized in Table 1. In terms of detecting malignancy, the ^{18}F-FDG PET/CT yielded true positive results in 48 and false negative findings in three cases out of the 51 tumors. The tumor size and histopathologic features of these three false negative lesions were 0.6 cm adenocarcinoma (SUV_{max}: 1.4), 1.3 cm adenocarcinoma (SUV_{max}: 1.6) and 1 cm carcinoid tumor (SUV_{max}: 0.8). In the patient who had synchronous double primary lung

Table 1. Patient-tumor characteristics and the impact of positron emission tomography/computed tomography on patient management

No	Sex	Histologic subtype	Tumor diameter (cm)	Tumor SUV_{max}	Patient survival (month)	Impact of PET/CT scan on patient management
1	M	AC	1	9.3	6	-
2	M	AC	2.7	18.6	8	-
		AC	0.6	1.4	5	-
3	M	AC	6.4	61.8	11	-
4	M	SCC	4.5	29.6		-
5	M	AC	4.4	34.2	20	-
6	M	NSCLC	5.9	13.7		-
7	M	SCC	3.5	14.3		-
8	M	LCNEC	1.6	15.8	15	-
9	M	CARCINOID	1	0.8	17	-
10	M	AC	5.5	21.3	8	+ (4a)'
11	M	NSCLC	3.3	19.7	7	+ (2)*
12	M	AC	5.2	19.4		+ (4b)'
13	M	SCC	6	15.5	19	-
14	M	AC	3.7	10.9	15	-
15	M	SCC	11.5	14.5	1	-
16	M	AC	12.3	14.4	8	-
17	F	SCLC	6.1	14.8		-
18	M	SCC	4	14.9	6	-
19	M	AC	2	12.3	7	-
20	M	AC	1.5	10.3		-
21	M	SCLC	3.6	10	1	+ (2)*
22	M	SCC	9.5	19.2	14	-
23	M	LCNEC	2.7	17	15	+ (4c)'
24	M	AC	3.7	20.9		+ (3)*
25	M	SCC	4.6	24.7	12	-
26	M	SCC	11	20.5		+ (2)*
27	M	SCC	8	26.7		+ (3)*
28	F	AC	2.3	9.8		-
29	M	SCC	3	7		+ (6)'

Table 1. Continued

No	Sex	Histologic subtype	Tumor diameter (cm)	Tumor SUV_{max}	Patient survival (month)	Impact of PET/CT scan on patient management
30	F	NSCLC	5	9.3	5	-
31	M	AC	4.3	16.3		-
32	M	NSCLC	9	25.5		+ (3)*
33	M	NSCLC	6.2	21	3	-
34	M	SCC	5.9	17.6		+ (1)*
35	M	SCC	5.5	14.2	6	-
36	M	SCLC	9.5	11.1	0	-
37	M	SCC	7	17.8	14	+ (3)*
38	M	SCLC	10	24.5		-
39	M	SCC	5	16.9	19	+ (3)*
40	M	AC	9	11.5		-
41	M	AC	5.6	40.5		+ (5)'
42	M	AC	9.5	18.5		+ (5)'
43	F	AC	2.8	20.1	5	-
44	M	AC	2.9	9.5	4	+ (1)*
45	M	AC	1.5	4	3	-
46	M	AC	1.3	1.6		-
47	M	SCC	5.4	16.4	3	+ (2)*
48	M	ACC	4.5	19.6	4	-
49	M	AC	1.2	4.1	2	-
50	M	AC	2.4	17		-

F: Female, M: Male, AC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small-cell lung cancer, LCNEC: Large-cell neuroendocrine carcinomas, ACC: Adenoid cystic carcinoma, NSCLC: Non-small-cell lung cancers, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value.
*Patients were classified as "at a potentially operable stage (stage 1-3A)" by conventional staging, 'Patients were classified as "at a potentially inoperable stage (stage 3B-4)" by conventional staging, (1): PET/CT detected N1 lymph node metastasis, (2): PET/CT detected N3 lymph node metastasis, (3): PET/CT detected distant metastasis, (4): The areas considered as distant metastases (4a: axillary lymph node, 4b: surrenal gland, 4c: liver) in the patients who were identified with M1 disease by conventional staging were interpreted as benign by ^{18}F-FDG PET/CT, (5): Distant metastases were detected by PET/CT, (6): The pulmonary mass that was interpreted as benign by conventional methods was evaluated as malignant by ^{18}F-FDG PET/CT

cancers, the adenocarcinoma of 0.6 cm (SUV_{max}: 1.4) had a false negative finding whereas the 2.7 cm-sized (SUV_{max}: 18.6) adenocarcinoma was detected. The sensitivity, accuracy and positive predictive value of ^{18}F-FDG PET/CT in detecting primary malignancy were calculated as 94%, 94% and 100%, respectively. The mean SUV_{max} values of adenocarcinoma (n=23) and SCC (n=15) lesions was 16.8±13.5 and 17.9±5.6, respectively. These two types of lung cancer were similar in terms of SUV_{max} values (p=0.2).

The correlation between tumor diameter and SUV_{max} was evaluated for all tumors. The mean tumor diameter of the 51 tumors was 5.0±2.9 cm. Tumor sizes ranged from 0.6 cm to 12.3 cm. A statistically significant positive correlation (r=0.4) was identified between tumor size and SUV_{max} (p=0.002). Two patients had post-obstructive atelectasis due to the tumor, and the ^{18}F-FDG PET/CT was able to distinguish between the tumor and the atelectasis owing to an intense FDG uptake in the tumor area. Thus, the tumor size was correctly calculated (Figure 1). The histopathologic results of the lymph nodes were compared with nodal staging according to ^{18}F-FDG PET/CT. Histopathologic evaluation of the lymph nodes was performed on 21 patients. The ^{18}F-FDG PET/CT findings were interpreted as true negative in nine, false positive in six, true positive in two and false negative in four patients. In this regard, 11/21 (52%) of the patients were correctly staged by ^{18}F-FDG PET/CT, while 4/21 (19%) patients were incorrectly down-staged and 6/21 (28%) were incorrectly up-staged by PET-CT. Within the group of 15 histopathologically N0 patients, the ^{18}F-FDG PET/CT was N0 in nine (true negative) while it was false positive in the remaining six patients. ^{18}F-FDG PET/CT identified subcarinal, right hilar and left interlobar hypermetabolic lymph nodes in one of the six patients with a false positive result (Figure 2). Thus, the patient was staged as N3 on ^{18}F-FDG PET/CT. Histopathologically, these lymph nodes were assessed as anthracosis and the

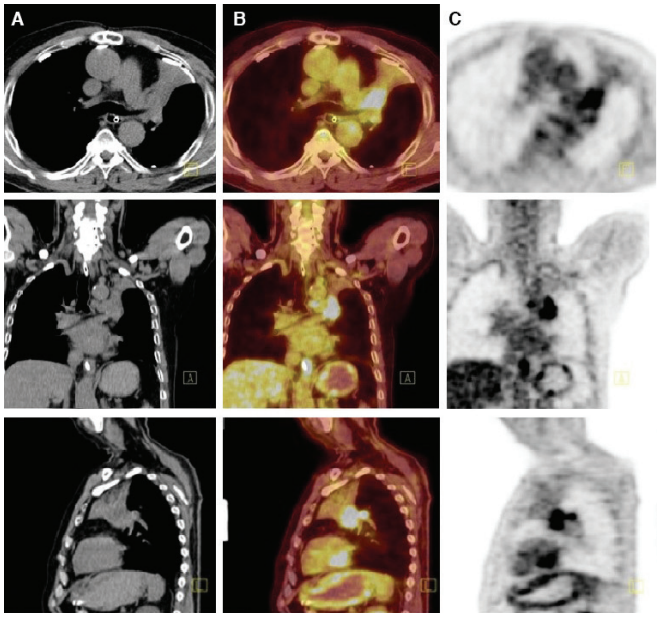

Figure 1. Axial, coronal, and sagittal CT images (A), fused PET/CT images (B) and PET images (C) of the patient with small cell lung carcinoma. The tumor size could not clearly be assessed on CT images. The fused PET/CT images enables differentiation of tumor and atelectasis areas due to intense FDG uptake of the tumor area [tumor maximum standardized uptake value (SUV_{max}): 10, atelectasis SUV_{max}: 3.7], thus, the tumor size has been correctly calculated

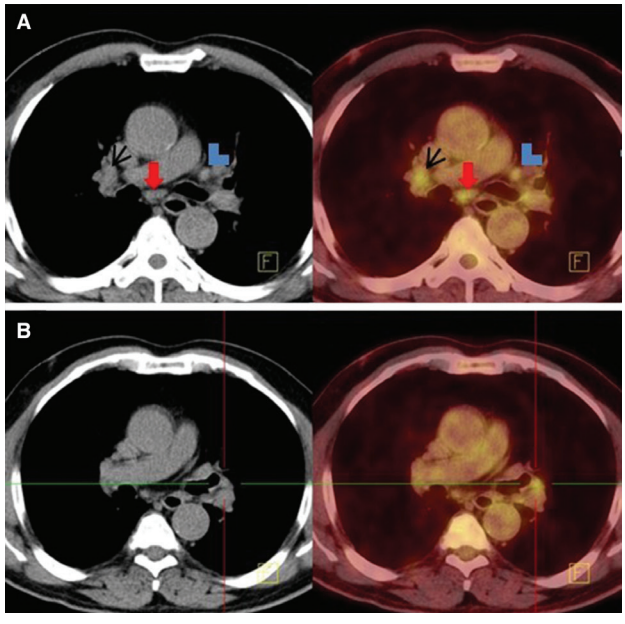

Figure 2. A and B demonstrate axial sections of CT and fused PET/CT images in the patient with lung adenocarcinoma. Right hilar [black arrow in A, maximum standardized uptake value (SUV_{max}): 4.1], subcarinal (red arrow in A, SUV_{max}: 4.2) and left interlobar hypermetabolic lymph nodes (in B, SUV_{max}: 3.8) seen on fused PET/CT were evaluated as anthracosis using histopathologic sampling. The hypermetabolic subaortic lymph node (blue arrowhead in A, SUV_{max}: 4.1) was histopathologically reactive

patient was down-staged. When assessed on a patient-by-patient basis, hilar and interlobar lymph nodes were most commonly recorded as false-positives on ^{18}F-FDG PET/CT (in 66% of patients with false-positive lymph nodes). A total of 20 distant metastatic sites (eight bone, five liver, three surrenal gland, two brain, one spinal, one pons metastases) were detected in 14 patients (28% of all patients) by ^{18}F-FDG PET/CT . Of these metastases, 12/20 (60%) could only be detected by ^{18}F-FDG PET/CT. When evaluated on a patient-by-patient basis, in 14% (7/50) of all patients, distant metastases were detected only by ^{18}F-FDG PET/CT.

^{18}F-FDG PET/CT led to a change in treatment plan based on conventional methods in 17/50 (34%) patients. Through conventional staging, 11 of these 17 patients were classified as "at a potentially operable" stage (stage 1-3A), five were classified as "at a potentially inoperable" stage (stage 3B-4), and one patient had a lesion that was assessed to be benign by conventional methods. Within the group of 11 patients classified as "at a potentially operable" stage, four had N3 lymph node metastases and five had distant metastases as identified by ^{18}F-FDG PET/CT. As a result, these patients underwent chemotherapy thus avoiding unnecessary surgery in 9/50 (18%) patients. In the other two patients, N1 lymph node metastasis was detected by ^{18}F-FDG PET/CT, and neoadjuvant chemotherapy was started prior to the operation. Within the group of five patients who were classified as "at a potentially inoperable" stage, three were identified with M1 disease by conventional staging. The areas considered as distant metastases in these three patients were interpreted as benign by ^{18}F-FDG PET/CT and thus were accepted as candidates for curative treatment. The other two patients were categorized as stage 3B by conventional methods and were thus planned for chemotherapy and localized radiotherapy. However, distant metastases were detected by ^{18}F-FDG PET/CT in these two patients who underwent chemotherapy and palliative radiotherapy. Another patient had a lesion that was interpreted as benign by conventional methods while the ^{18}F-FDG PET/CT evaluated this mass as malignant, and the patient was started on chemotherapy. The impact of ^{18}F-FDG PET/CT on patient management is listed in Table 1. Finally, the correlation between SUV_{max} value of the primary lesion and patient survival was evaluated in 30 patients, one of whom was the patient who had synchronous double primary lung cancers. Primarily, the median SUV_{max} (median SUV_{max}= 15.6) was calculated and accepted as the "cut-off" value. The mean survival time was 10.3±2.2 months in patients with SUV_{max} <15.6, and 15.9±1.6 months in those with SUV_{max} ≥15.6. There was no significant difference between the two groups in terms of survival (p=0.118) (Figure 3).

Discussion

Lung cancer is the most common cause of cancer-related death worldwide, and early diagnosis is important for the application of curative treatments. ^{18}F-FDG PET/CT is used commonly to differentiate benign and malignant lung lesions. Gupta et al. (4) reported the sensitivity and specificity of ^{18}F-FDG PET/CT in benign-malignant distinction of indeterminate solitary pulmonary nodules as 93% and 88%, respectively. ^{18}F-FDG PET/CT might yield a false positive result in inflammatory conditions, tuberculosis or granulomatous lesions. A false negative ^{18}F-FDG PET/CT result is generally associated with nodules measuring less than 1 cm, carcinoid tumors or bronchoalveolar carcinomas (BAC) (5,6,7,8,9). In our study, ^{18}F-FDG PET/CT provided a true positive result in 94% and a false negative result in 6% of 51 lesions. The tumors with a false negative ^{18}F-FDG PET/CT included two adenocarcinomas (0.6 cm and 1.3 cm) and one carcinoid tumor (1 cm). The small size and presence of a carcinoid tumor may have contributed to the false negative results. In the present study, the sensitivity, accuracy and positive predictive value of ^{18}F-FDG PET/CT in the detection of primary malignancy were calculated as 94%, 94% and 100%, respectively. These results are consistent with that reported in the literature. Several studies indicated that the mean SUV and SUV_{max} differ according to histologic subtypes of lung cancer. In particular, it has been reported that the SUV_{max} of carcinoid tumors and BAC are low (10,11). Vesselle et al. (12) found that the SUV_{max} of BAC was lower than all other subtypes, and that non-BAC adenocarcinomas had lower SUV_{max} values than SCC. The majority of studies in the literature report that the SUV_{max} of adenocarcinomas is lower than that of SCCs (13,14). However, in our study, no statistically significant difference was identified between adenocarcinoma (16.8±13.5) and SCC (17.9±5.6) in terms of mean SUV_{max} (p=0.2). Several studies showed that tumor size is a prognostic factor for survival in NSCLC (15). The correlation between tumor size and SUV_{max} has been previously assessed (16,17). Zhu et al. (18) reported a moderate positive correlation between SUV_{max} value and tumor size (r=0.642, p<0.001). In our study, a positive correlation (p=0.002) was identified between tumor size and SUV_{max}, in line with findings of the earlier studies.

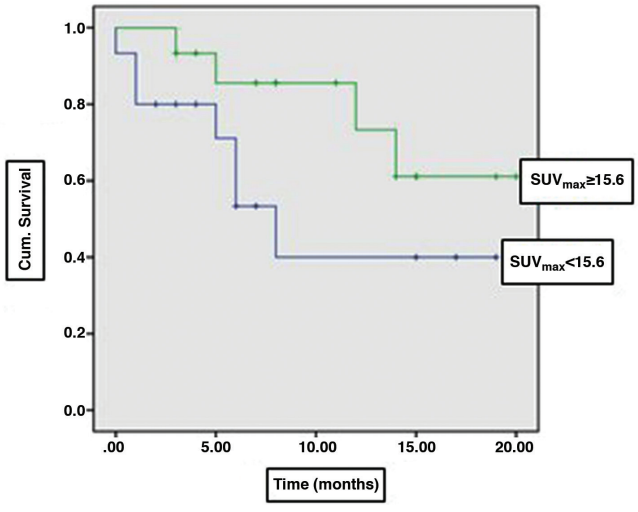

Figure 3. Survival curves of patients according to their maximum standardized uptake value (SUV_{max}) values; there was no significant difference in terms of mean survival time between SUV_{max} values below 15.6 (10.3±2.2 months) and those above 15.6 (15.9±1.6 months) (p=0.118)

The detection of both lymph node and distant metastases is essential for proper staging in lung cancer. The sensitivity of ^{18}F-FDG PET/CT in lymph nodes greater than 1 cm is high, although the accuracy and specificity rates are low (19). In a study by Detterbeck et al. (20), the false positive rate of PET in mediastinal lymph nodes was reported to be 13-22%, and the false negative rate as 5-8%. In our study, histopathologic lymph node evaluation was carried out in 21 of the 50 patients, and 52% of the 21 patients were correctly staged by ^{18}F-FDG PET/CT whereas the rate of patients incorrectly down-staged or up-staged by ^{18}F-FDG PET/CT were detected as 19% and 28%, respectively. In our study, the false positive and false negative lymph node rates in ^{18}F-FDG PET/CT were found to be higher than that reported in the literature. This finding may be attributed to the fact that histopathologic evaluation was not performed in all lymph nodes evaluated as either positive or negative by ^{18}F-FDG PET/CT. Furthermore; sarcoidosis, amyloidosis, anthracosis, tuberculosis and organized pneumonia may cause false positive results in lymph nodes. In one patient with a false positive lymph node on ^{18}F-FDG PET/CT, histopathologic sampling revealed anthracosis. In addition, pulmonary infections or granulomatous diseases such as tuberculosis or sarcoidosis that are frequent in our country might have contributed to these outcomes. Further investigation of lymph node and distant organ metastases, particularly in patients being considered for surgical therapy, could prevent unnecessary surgery. Van Tinteren et al. (21) reported that performing an ^{18}F-FDG PET/CT in addition to conventional methods as part of preoperative staging of NSCLC might avoid unwarranted surgery in one-fifth of patients. In a study on patients with NSCLC, an ^{18}F-FDG PET/CT led to a change in disease stage as determined by conventional methods in 50.6% (41.1% up-staged, 9.5% down-staged) of patients, and alteration in treatment planning in 42.3% (22). In our study, the ^{18}F-FDG PET/CT resulted in a change in the treatment plan as decided by conventional methods in 34% of all patients, and unnecessary surgery was prevented in 18% of the patients. In 6% of the

patients, the ^{18}F-FDG PET/CT was interpreted as negative for areas identified as metastasis through conventional methods, leading patients to possible curative therapy. In various studies, SUV_{max} of the primary tumor detected by ^{18}F-FDG PET/CT was used to predict lung cancer prognosis and assess patient survival (23,24). Ahuja et al. (25) found that patients with primary tumors showing a high FDG uptake had lower survival rates than those with a low uptake, while Hoang et al. (26) found no significant association between FDG uptake of the primary tumor and survival in patients with advanced NSCLC. In a meta-analysis published by IASLC in 2008, the SUV_{max} of the primary tumor was a strong determinant of prognosis in NSCLC. However, the need to support this finding with multivariate analysis was emphasized (27). The present study evaluated the relationship between SUV_{max} of the primary tumor and patient survival and no significant difference was identified between those with SUV_{max} below 15.6 (10.3±2.2 months) and above 15.6 (15.9±1.6 months) in terms of mean survival time (p=0.118). Several previous studies support our findings, although a larger number of authors argue that SUV_{max} could be used to predict prognosis and assess survival in case of lung cancer. Our results might be related to the limited number of patients in the study as well as the differences between the two groups (e.g. age, genetic factors, stage, tumor pathology).

Conclusion

Despite the limitations of our study, such as limited number of patients, most of the results are consistent with previous studies. In our study, it is concluded that ^{18}F-FDG PET/CT contributes to both the diagnosis and management of lung cancer by providing valuable information in addition to conventional methods.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Clinical and Laboratory Researches of Ege University Faculty of Medicine with decision number: 14-4.2/16 dated: 12.06.2014.

Informed Consent: Informed consent was waived due to the retrospective design of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.B., Design: E.B., A.A., Data Collection or Processing: E.B., G.Ç., A.A., Analysis or Interpretation: E.B., G.Ç., A.A., Literature Search: E.B., A.A., Writing: E.B., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report
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Laryngeal Tuberculosis Mimicking Laryngeal Carcinoma on ^{18}F-FDG PET/CT Imaging

^{18}F-FDG PET/BT Görüntülemede Maligniteyi Taklit Eden Laringeal Tüberküloz

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Abstract

Laryngeal tuberculosis is a rare presentation of tuberculosis. It can mimic laryngeal carcinoma with its clinical and imaging findings. A 51-year old woman underwent ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) imaging for clinically suspected carcinoma of the larynx. PET/CT revealed lung lesions consistent with tuberculosis in additional to hypermetabolic focus on larynx. The patient was histopathologically diagnosed with lung and laryngeal tuberculosis.

Keywords: Tuberculosis, laryngeal cancer, positron emission tomography/computed tomography

Öz

Laringeal tüberküloz, tüberkülozun nadir bir formudur. Klinik ve radyolojik bulguları larinks karsinomunu taklit edebilir. Klinik olarak larinks karsinomu şüphesi olan 51 yaşında bir kadın hastaya ^{18}F-fluorodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ile görüntüleme yapıldı. PET/BT larinksteki hipermetabolik odağa ilave olarak tüberkülozla ilişkili akciğer lezyonlarını ortaya çıkardı. Hasta histopatolojik olarak akciğer ve larinks tüberkülozu tanısı aldı.

Anahtar kelimeler: Tüberküloz, larinks kanseri, pozitron emisyon tomografi/bilgisayarlı tomografi

Introduction

Laryngeal tuberculosis is an infrequent manifestation of extrapulmonary tuberculosis. It occurs in only 1% of all cases (1,2). Usually, it is seen as a complication of pulmonary tuberculosis, nevertheless, solitary laryngeal involvement is possible. Clinical, laryngoscopic and radiological findings of laryngeal tuberculosis have a tendency to mimic laryngeal cancer (3,4). There are no specific findings of extrapulmonary tuberculosis in ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), which can also mimic malignancy (5). Herein we present a case of laryngeal tuberculosis who underwent ^{18}F-FDG PET/CT imaging with a preliminary diagnosis of laryngeal carcinoma without any clinical pulmonary manifestations.

Case Report

A 51-year-old woman was referred to our otolaryngology clinic with a history of cough, hoarseness, and sore throat. Her prior medical history was unremarkable. She had been

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smoking for the past 20 years. The laryngoscopy revealed diffuse swelling and a lesion involving both arytenoids and the marginal portion of the epiglottis, which suggested carcinoma of the larynx. Histopathologic examination of the lesion demonstrated necrosis and was interpreted as suspicious for malignancy, thus recommending a second biopsy.

Contrast-enhanced computed tomography (CT) scan of the neck demonstrated edema and asymmetry of the epiglottic vallecula. Thorax CT showed multiple nodules that resembled pulmonary metastases on both lungs. The patient underwent ^{18}F-FDG PET/CT imaging for diagnosis and staging. PET/CT imaging showed hypermetabolic focus on left aryepiglottic fold and interarytenoid area maximum standard uptake values (SUV_{max}): 8.9 without any anatomical correlation. In addition, there were multiple hypometabolic nodules (SUV_{max}: 1.5) and hypermetabolic infiltrations (SUV_{max}: 6) on both lungs along with mildly hypermetabolic cervical lymph nodes (Figure 1, 2). The second laryngeal biopsy revealed necrotizing granulomatous inflammation suggesting tuberculosis (Figure 3). PCR assay was positive for mycobacterium tuberculosis. The patient was diagnosed as lung and laryngeal tuberculosis, and was started on antituberculosis medication.

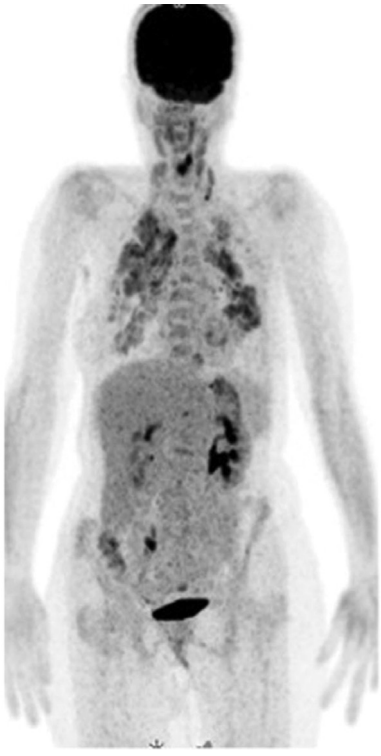

Figure 1. Whole body ^{18}F-FDG PET/CT imaging revealed high FDG accumulation in the larynx, lung parenchyma and milimetric cervical lymph nodes

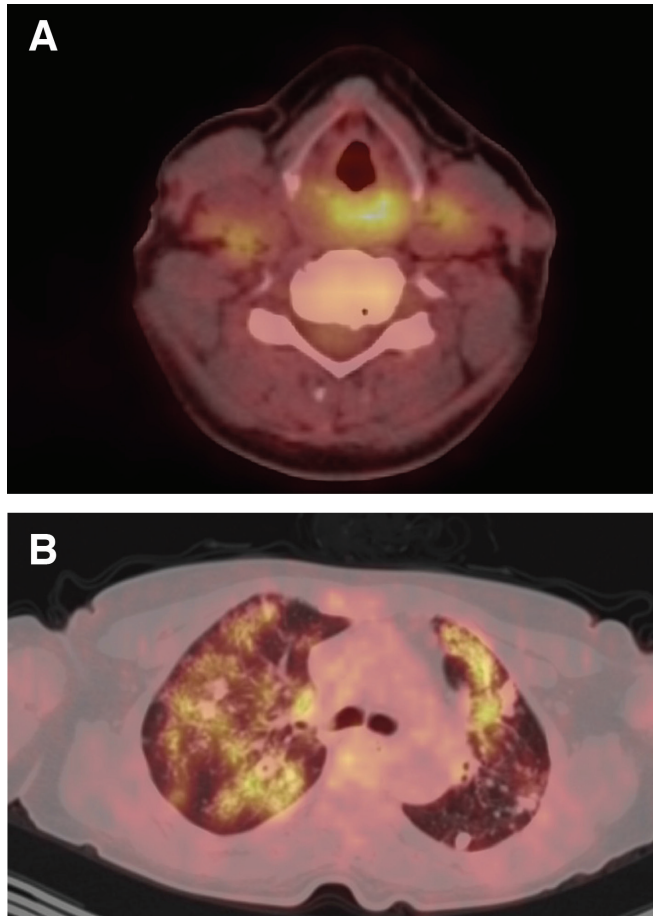

Figure 2. PET/CT fusion images showed hypermetabolic foci in the left aryepiglottic fold and interarytenoid area maximum standard uptake values (SUV_{max}): 8.9 (A). On transaxial thorax fusion images, there were multiple hypometabolic nodules (SUV_{max}: 1.5) and hypermetabolic infiltrations (SUV_{max}: 6) on both lungs, indicating tuberculosis (B)

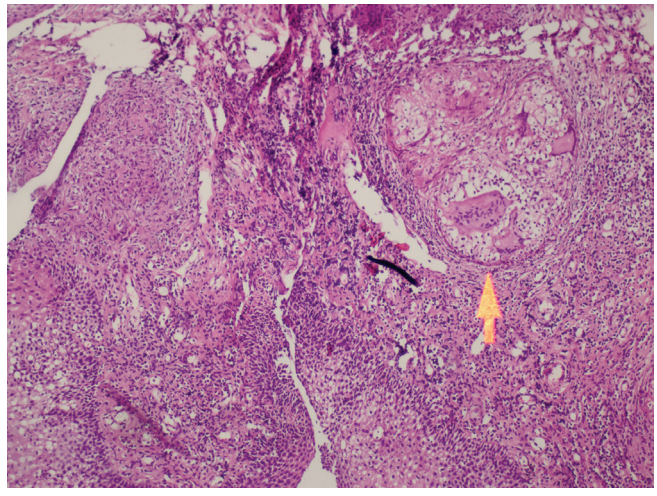

Figure 3. Photomicrograph showing giant cell granuloma (hematoxylin&eosin x200)

Literature Review and Discussion

Although a rare clinical condition, laryngeal tuberculosis is the most common granulomatous disease of the larynx. Primary laryngeal disease is rare and it usually occurs due to hematogenous dissemination or direct extension of a pulmonary tuberculosis infection (6). The chief complaints in our patient were cough, hoarseness and sore throat. The most common presenting symptom is hoarseness, which is reported to be present in 80-100% of patients. Other symptoms include odynophagia, dysphagia, dyspnea, stridor, cough and hemoptysis (7). These symptoms are also associated with laryngeal carcinoma. On physical examination, laryngeal tuberculosis can manifest as edema, hyperemia, ulcerations, nodule or an exophytic mass. Vocal cords are the most affected site followed by the ventricular strip, epiglottis, subglottic region and posterior commissure (8). CT and MR imaging demonstrate the diffuse nature of the disease and the involvement of the paralaryngeal spaces more accurately than laryngoscopy. Consistent with other studies, Moon et al. (9) detected focal thickening or a mass in the vocal cords, epiglottis and paralaryngeal tissue on CT imaging. ^{18}F-FDG PET/CT is a non-invasive imaging method that is being widely used for the differentiation of benign and malignant lesions. However, ^{18}F-FDG may also accumulate in inflammatory cells. ^{18}F-FDG uptake has previously been reported in tuberculomas and other tuberculosis related lesions (10). In a study, 88 cases with extrapulmonary tuberculosis was reported to show high ^{18}F-FDG uptake on PET imaging with a SUV_{max} ranging from 1.3 to 23.2 (11). In our case, PET/CT imaging showed high ^{18}F-FDG uptake in the extrapulmonary tuberculosis focus with a SUV_{max} of 8.9. In addition, there were multiple hypometabolic nodules (SUV_{max}: 1.5) and hypermetabolic infiltrations (SUV_{max}: 6) on both lungs, which were consistent with pulmonary tuberculosis that has not been previously diagnosed. As a whole body scanning method, ^{18}F-FDG PET/CT facilitates the detection of extra pulmonary tuberculosis. Although it is a rare condition, extrapulmonary tuberculosis of the head and neck should be kept in mind as part of differential diagnosis, especially in regions where pulmonary tuberculosis is common.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.B., Ş.T.G., Concept: A.C., Y.Y., Design: A.C., Data Collection or Processing: A.C., S.G., F.D., Y.Y., Analysis or Interpretation: A.C., Y.Y., Literature Search: A.C., Writing: A.C., Y.Y.

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Case Report
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I-131 Radiation-Induced Myelosuppression in Differentiated Thyroid Cancer Therapy

Diferansiye Tiroid Kanser Tedavisinde I-131 Radyasyona Bağlı Miyelosüpresyon

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Abstract

Radioactive iodine (RAI) treatment of differentiated thyroid cancer has been used in clinical practice for almost 60 years and is generally accepted to be a safe and efficacious treatment. Severe toxicity in the form of radiation pneumonitis, sometimes progressing to fibrosis, and bone marrow suppression are reported but remain rare. We present a case of severe myelosuppression requiring hospitalization and transfusion support in an otherwise well, young female patient who had received 175 mCi I-131 for low-volume micronodular lung disease one month prior, with a cumulative lifetime administered activity of 575 mCi. The most important risk factors for myelosuppression following RAI are the activity received, the amount of functioning thyroid tissue present, and the lifetime cumulative activity received.
Keywords: Iodine radioisotopes, bone marrow, thyroid neoplasms

Öz

Radyoaktif iyot (RAİ) diferansiye tiroid kanseri tedavisinde yaklaşık 60 yıldır klinik uygulamada kullanılmaktadır ve genellikle güvenli ve etkili bir tedavi olarak kabul edilir. Fibrozise ilerleyebilen radyasyon pnömonisi ve kemik iliği süpresyonu gibi ciddi yan etkiler bildirilmiştir ancak nadiren rastlanır. Bu makalede bir ay önce düşük volümlü mikronodüler akciğer hastalığı için 175 mCi I-131 tedavisi, hayat boyu uygulanan kümülatif aktivite 575 mCi, aldıktan sonra ciddi miyelosüpresyon nedeniyle hastane yatışı ve transfüzyon desteği ihtiyacı olan genç bir kadın hasta sunulmaktadır. RAİ sonrası miyelosüpresyon için en önemli risk faktörleri alınan aktivite miktarı, mevcut fonksiyonel tiroid dokusu ve alınan hayat boyu kümülatif aktivite miktarıdır.
Anahtar kelimeler: İyot radyoizotopları, kemik iliği, tiroid neoplazmları

Introduction

Well-differentiated thyroid cancers (DTC), although they generally confer a good prognosis, sometimes follow an aggressive disease course (1,2). When they do occur, DTC metastases are best treated with high-dose I-131 if surgical resection is impossible or otherwise ill-advised (3). Radioiodine remnant ablation and high-dose RAI treatment of metastatic disease has been shown to improve disease-specific mortality in intermediate and high-risk patients (1). Curative-intent treatment can be envisaged with low-volume micronodular lung or small nodal disease although bone metastases are often resistant to treatment (3). The goal of RAI therapy is to deliver very high doses (>100 Gy) to the tumor while keeping the dose to the bone marrow below 2 Gy (4). Myelosuppression is the

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most important and dose-limiting toxicity of high-dose I-131 therapy but remains rare in clinical practice. Bone marrow suppression is dose-dependent and highly related to the volume of functional thyroid tissue and lifetime total activity received (3,5). Pulmonary fibrosis is another potentially fatal complication of high-dose I-131 when the tumor burden in the lungs is important (2). Other more common acute toxicities include nausea and vomiting, epigastric discomfort and sialadenitis; however, these are self-limiting conditions (2). Generally, the accepted safe tolerance for the blood (or bone marrow) is a total absorbed dose of 2 Gy or, as a surrogate, less than 80 mCi whole-body retention at 48 h with lung metastases and 120 mCi at 48 h without lung lesions (6,7). Dosimetry, although described in the literature, involves estimates and assumptions, remains time-consuming and expensive, and is not routinely performed at our institution (1). However, dosimetric calculations can lead to the safe administration of higher treatment doses for about a quarter of patients; and conversely can identify the small number of patients in which empiric doses must be reduced (4). Most centers, including ours, have gravitated towards an empiric, fixed-dose treatment regimen using 30-200 mCi for RAI. Although certain authors have suggested that empiric dosing often exceeds maximum tolerated activities in older patients, most institutions do not report clinically significant adverse outcomes (2,6). In keeping with our experience, some authors note that while myelosuppression is common in patients treated with single-treatment activities up to 300 mCi, it is almost invariably mild (2).

Case Report

All of the procedures and treatments described in the case report have been performed according to clinical practice standards at our institution after obtaining the patient's informed consent. Following the initial diagnosis, the patient underwent a total thyroidectomy and lymph node dissection for a 5 cm x 3.5 cm x 2.2 cm diffuse sclerosing variant of papillary thyroid cancer on Feb 9th 2000, at age 19. There were positive margins and all eleven sampled lymph nodes were positive for malignancy. The patient was thyroglobulin antibody-positive and further thyroglobulin measurements were not performed. She underwent radioiodine remnant ablation with 150 mCi I-131 on April 18th 2000 and follow-up post-therapy whole-body scanning revealed no iodine-avid disease outside of the thyroid bed. Subsequent whole-body I-131 scans and high resolution ultrasound of the neck remained negative and the patient was considered to be disease-free until December 2004 when routine iodine-scintiscanning revealed abnormal foci of uptake in the thyroid bed, the left neck and the superior mediastinum. The patient was admitted for high dose I-131 and received 150 mCi on September 17th 2004. Post-therapy scanning revealed the same three pre-treatment foci, and additional uptake at both lung bases, compatible with functioning DTC lung metastases. In 2005 and 2006 serial chest CTs demonstrated slowly progressing scattered milimetric lung nodules bilaterally. Several ultrasound scans of the neck failed to show any local disease. The patient was retreated for progressive micronodular lung metastases with 100 mCi I-131 on September 6th 2006. Post-therapeutic scanning revealed persistent but improved cervical foci and diffuse increased uptake in both lungs. In view of false-negative tracer-dose I-131 scanning, a decision was taken at this time to re-treat the patient in 9 months' time empirically with high-dose radioiodine. She then received 175 mCi I-131 on July 24th 2007, for a total lifetime activity of 575 mCi. Post-therapy scanning approximately 1 week later again showed lung uptake, but it was much improved as compared to 2006. No complete blood count (CBC), chemistry panel or other blood work was ordered at the time of admission for RAI treatment as this was not part of the institution's protocol, and the patient was discharged in good clinical condition to follow up with her endocrinologist. About one month post-treatment on August 26th 2007, the patient presented to her local community hospital complaining of fatigue, heavy menses, epistaxis, headache and multiple pre-syncopal episodes in the preceding week. Upon investigation she was found to have pancytopenia with a platelet count of 12.000 per microliter, a hemoglobin (Hg) of 85 g/L, a white blood cell (WBC) count of 1.5 per microliter and neutrophils of 0.7 per microliter. The first CBC performed at our institution on the following day is explained in detail in Table 1. Although no recent values were available for a trend comparison, a CBC in 2002 (5 years prior) was completely within normal limits and the most recent CBC in 2004 (3 years prior) was remarkable only for a slightly low platelet count of 112.000 per microliter (reference range 150-400.000 per microliter). Her TSH was appropriately suppressed and free T4 was just above the upper limit of normal. Blood pressure (112/71 mmHg), heart rate (64 BPM) and serum biochemistry were normal and she was afebrile when she was transferred to our institution for further treatment. Upon admission, packed red blood cell (RBC) and platelet transfusions were given and the granulocyte colony-stimulating factor analog, filgrastim (300 mcg SQ QD) and erythropoietin (48.000 units SQ QWeek) were started. The Hg and WBC trends from the admission are illustrated in Graphic 1; the jumps in Hg represent RBC transfusions. The full virological work-up was negative. Vitamin B12 and folate levels were normal. The immunoglobulin profile, beta-2 microglobulin and iron studies were unremarkable. The patient had an inappropriately low level of circulating reticulocytes, given her anemia. The hematology consult team, having failed to identify any other cause of the pancytopenia, settled on a working diagnosis of RAI-induced bone marrow suppression. The patient's admission was complicated by a febrile neutropenic episode which was empirically treated for a number of days with ticarcillin/clavulanate and gentamycin; however, a source of infection was never identified and the

fever resolved. A single episode of hypotension also arose and responded well to intravenous fluid challenge. RBCs, platelets and WBCs showed slow recovery towards the end of the admission period. She was discharged 17 days later in good condition with blood counts still below normal, to be followed up closely with her endocrinologist and other specialists. Extensive post-discharge testing was negative, including anti-nuclear antibodies, physical and chemical urinalysis, Westergren sedimentation rate, erythrocyte sedimentation rate, C-reactive protein and extractable nuclear antigen antibody screening. Follow-up consultations with hematology, rheumatology and other specialists failed to turn up any alternative diagnoses such as connective tissue diseases which could explain the cytopenia. The cytopenias spontaneously recovered as assessed in subsequent follow-ups (Graphic 1). The last thyrogen-stimulated 2 mCi I-123 scan in October 2014 did not demonstrate active thyroid tissue. At the last clinical follow-up in June 2015, the patient had no evidence of recurrence of thyroid disease or signs of marrow suppression.

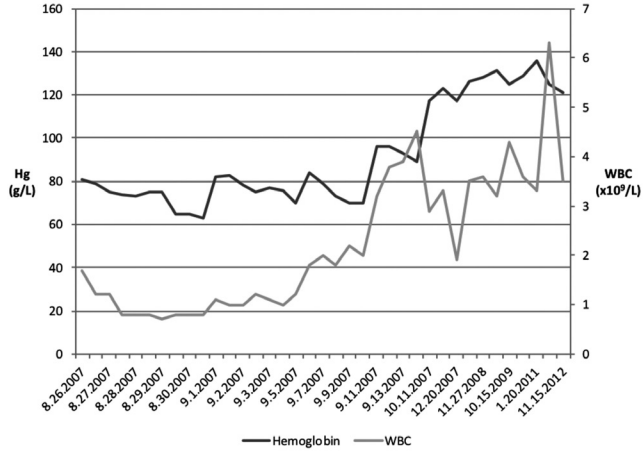
Table 1. Complete blood count on presentation

CBC	Result	Flag	Reference range
Hemoglobin	75	Low	120-152 g/L
Red blood cells	2.27	Low	4.10-5.10x10^{12}/L
Hematocrit	0.2	Low	0.360-0.450
Mean corpuscular volume	88.1		80.0-96.0 fL
Mean corpuscular hemoglobin	33		27.0-33.0 pg
Mean corpuscular hemoglobin concentration	375	High	310-370 g/L
Red cell distribution width coefficient of variation	12.5		11.5-14.5 c/v
Red cell distribution width standard deviation	39.9		36.1-53.3 fL
Platelets	32	Panic low	150-400x10^9/L
Mean platelet volume	9.4	Low	9.9-11.8 fL
White blood cells	1.2	Panic low	4.0-11.0x10^9/L
Automated differential			
Immature granulocytes	0.8		N/A %
Neutrophils (%)	55.6		45.0-75.0%
Lymphocytes (%)	36.1		25.0-45.0%
Monocytes (%)	5		2.0-12.0%
Eosinophils (%)	2.5		0.0-6.0%
Basophils (%)	0		0.0-2.0%
Neutrophils (#)	0.7	Low	1.8-7.5x10^9/L
Lymphocytes (#)	0.4	Low	1.2-3.5x10^9/L
Monocytes (#)	0.1	Low	0.2-0.8x10^9/L
Eosinophils (#)	0		0.0-0.5x10^9/L
Basophils (#)	0		0.0-0.2x10^9/L

CBC: Complete blood count

Discussion

Following oral RAI administration, blood radioiodine concentrations follow 2 distinct phases. In the first phase (0-48 h) inorganic free iodine is absorbed through the GI mucosa and is quickly removed from plasma by thyroid tissue and the kidneys. The second phase (2-10 d) sees a rise in plasma RAI activity as radioiodinated thyroid hormone is released by functioning tissue (5). The area under the curve of the free inorganic iodine time-activity profile in phase 1 is variable and related to the total body iodine stores and renal function. However, due to the relatively brief rise and fall of plasma radio-iodine concentrations in phase 1, the dose to the bone marrow is largely related to the amount of radioiodinated thyroid hormone formed and released in the second phase. The peak of the second phase is also highly variable, relating to the amount of functioning thyroid tissue present, both malignant and benign. Therefore, the burden of tumor (or normal functioning thyroid tissue in the case of a first ablative dose post-thyroidectomy) is the major factor in determining the total dose to the bone marrow for a given administered activity (6). As opposed to exogenous thyroid hormone withdrawal, rhTSH stimulation seems to increase overall RAI clearance rates by as much as 30%, although the clinical implications of this are unclear (6,8,9). Administration of high doses of I-131 as opposed to limited dose fractionation has several purported advantages (1). The general consensus is that the first treatment is potentially the most efficacious as radio-resistant clones are naturally selected by the exposure (2). Tumor heterogeneity



Graphic 1. Hematologic parameters
WBC: White blood cells, Hg: Hemoglobin

is an important consideration, as RAI-concentrating abilities of DTC can vary widely within a single lesion (1). The loss of crossfire effect following the destruction of RAI-avid tissue will tend to diminish the effectiveness of subsequent RAI administrations (1,2). Also, dedifferentiation with loss of radioiodine-avidity and finally anaplastic transformation are poor-prognosis events in DTC (2). The risk of leukemia, aplastic anemia and myelodysplastic syndrome post high-dose RAI seems to be more strongly correlated with cumulative dose to the bone marrow than with the activity of any given treatment. This too would support the notion that fewer doses with more activity per dose is likely to be beneficial to the patient (1,10). However, there have been data suggesting that lifetime cumulative doses of RAI have a protracted and clinically significant impact on peripheral blood counts (5). In our patient, the last dose of radioiodine (175 mCi) and the burden of functioning disease as assessed by post-therapeutic scintiscanning was not out of the ordinary for our institution. Her CBCs in the years prior had been normal or near-normal. This is the first patient we have encountered who presented following RAI therapy with such profound myelosuppression. At our hospital, larger doses are given for larger tumor volumes and to older patients with putatively less bone marrow reserve on a routine basis. It must be noted that at a total lifetime administered activity of 575 mCi, our patient was on the higher-end of the 600-800 mCi lifetime ceiling suggested by some authorities. This total lifetime administered activity is also on the very high end of the range which we encounter at our institution. Extensive work-up failed to identify another cause for our patient's pancytopenia. Although the high variability of bone marrow absorbed dose in relation to a given activity of I-131 can be influenced by many factors, the profound hematologic toxicity encountered in this patient lends credence to the theory that the cumulative effect of multiple doses can persist over time (5). In conclusion, although there is no way to definitively diagnose the condition, we suspect that our patient was suffering from radiation-induced bone marrow suppression secondary to RAI administration. The most important risk factors for myelosuppression following RAI are the activity received, the amount of functioning thyroid tissue present, and the lifetime cumulative activity received. It may therefore be wise to monitor patients' blood counts more closely when they: 1) Are receiving more than 150 mCi and have a significant RAI-avid tumor burden as proven by prior scintiscanning or 2) Have a cumulative lifetime dose approaching 500 mCi or more. More research will be needed to fully elucidate these risk factors and the impact on potential RAI-induced myelosuppression.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.P., G.A., G.C., M.T., Concept: S.P., G.A., G.C., M.T., Design: S.P., G.A., G.C., M.T., Data Collection or Processing: S.P., G.A., G.C., M.T., Analysis or Interpretation: S.P., G.A., G.C., M.T., Literature Search: S.P., G.A., G.C., M.T., Writing: S.P., G.A., G.C., M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Interesting Image
Mol Imaging Radionucl Ther 2018;27:88-90 DOI:10.4274/mirt.78941

A Case of Hypertrophic Pulmonary Osteoarthropathy in Both Upper and Lower Extremities: A Rare Involvement

Üst ve Alt Ekstremitede Hipertrofik Pulmoner Osteoartropati Olgusu: Nadir Bir Görünüm

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Abstract

Hypertrophic pulmonary osteoarthropathy (HPOA) is a paraneoplastic manifestation of gastric and, more frequently, lung carcinomas. It is characterized by extremity pain, clubbing, arthritis and periostitis of the long bones. Periostitis is the hallmark of HPOA and can be revealed with bone scintigraphy. Whole-body bone scintigraphy (WBBS) is very sensitive during the active lesion period and WBBS findings usually precede that of plain radiography. WBBS can also show improvement in the first 6 months following treatment, thus making it an important technique in the management and follow-up of these patients. While HPOA findings are usually seen in the lower extremities, involvement of both upper and lower extremities is a rare condition. In this case report, it is aimed to present findings of a 67-year-old male patient with lung cancer and complaint of extremity pain. We report on this patient to draw attention to HPOA of both upper and lower extremities.

Keywords: Hypertrophic pulmonary osteoarthropathy, lung cancer, upper extremity

Öz

Hipertrofik pulmoner osteoartopati (HPOA), mide ve özellikle akciğer kanserlerinde görülebilen bir paraneoplastik sendromdur. Çomak parmak, artrit, ekstremite ağrısı ve uzun kemiklerde periostit ile karakterizedir. Periostit HPOA'nın ayırıcı bulgularındandır ve sintigrafi ile gösterilebilir. Sintigrafik bulgular çoğunlukla radyolojik bulgulardan önce ortaya çıkar. Tüm vücut kemik sintigrafisi (TVKS) aktif lezyon döneminde oldukça duyarlıdır. TVKS ile tedavi sonrası ilk 6 ayda bulgularda gerileme gösterilebilir. Dolayısıyla TVKS, bu hastaların tanı ve takibinde önemli bir yer tutar. HPOA bulguları çoğunlukla alt ekstremitede görülür; hem üst hem alt ekstremite tutulumu nadir görülen bir durumdur. Bu olgu takdimi, ekstremite ağrısı ile başvuran akciğer kanseri hastalarında, hem alt hem üst ekstremitede nadiren görülen HPOA tablosuna dikkat çekmek amacıyla sunulmaktadır.

Anahtar kelimeler: Hipertrofik pulmoner osteoartopati, akciğer kanseri, üst ekstremite

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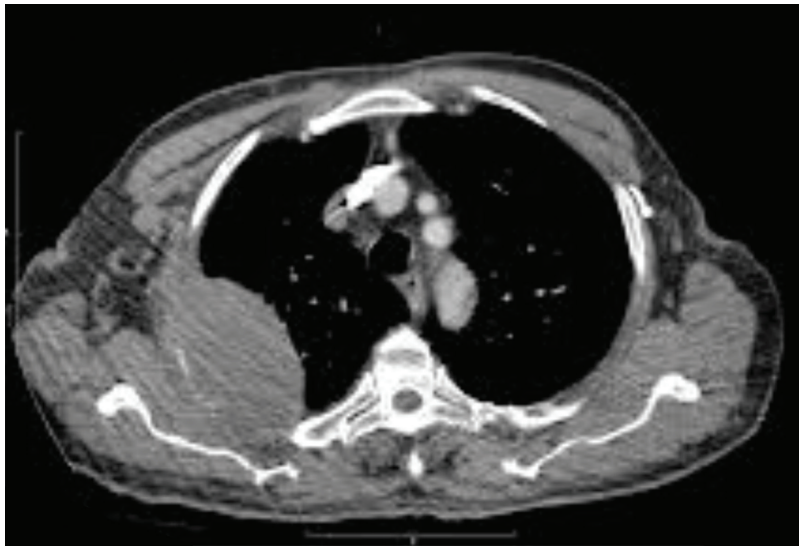

Figure 1. A 67-year-old male patient suffering from chest pain, cough, shortness of breath and extremity pain was referred to the department of radiology for imaging. Computed tomography of the chest showed a large mass in the right lung and biopsy cytology results were positive for adenocarcinoma. The patient was then referred to the department of nuclear medicine for whole-body bone scintigraphy (WBBS) due to extremity pain.

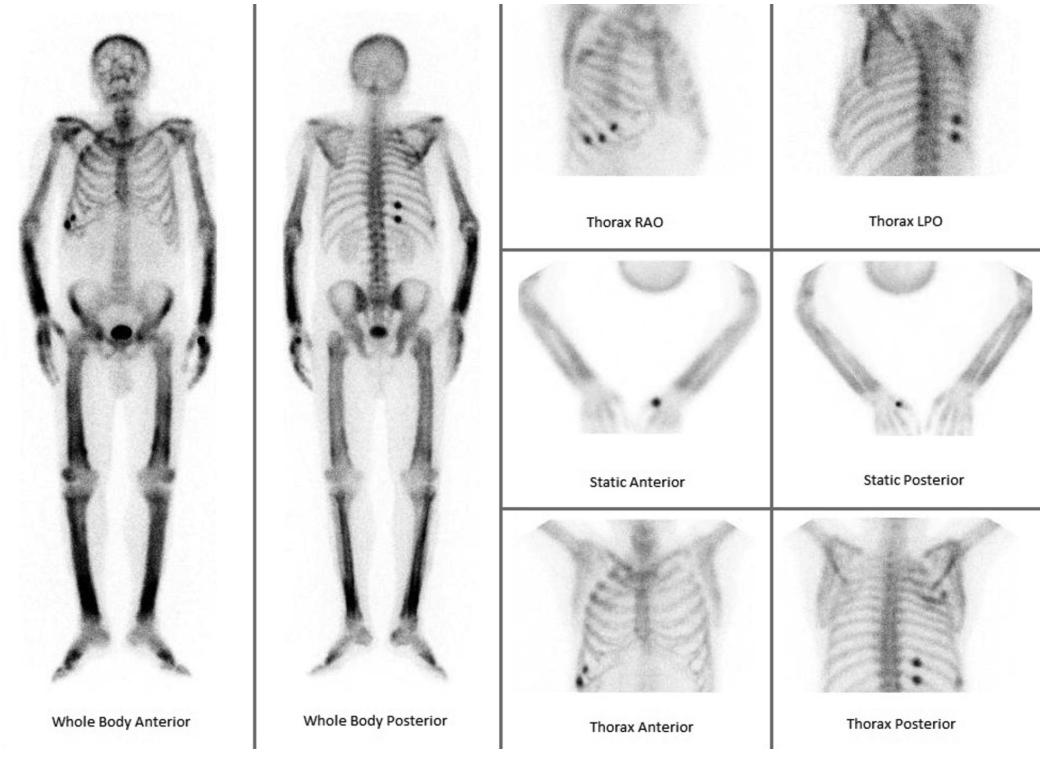

Figure 2. The WBBS showed non-homogeneous cortical uptake in bilateral upper and lower extremity bones, consistent with hypertrophic pulmonary osteoarthropathy (HPOA). Multiple focal spots were also seen on right hemithorax costae, possibly due to trauma. HPOA is a paraneoplastic manifestation of gastric and, more frequently, lung carcinomas. It is characterized by extremity pain, clubbing, arthritis and periostitis of the long bones. HPOA findings in lower extremities have been previously reported (1,2,3). However, involvement of both upper and lower extremities is a rare condition. Periostitis is the hallmark of HPOA and can be revealed with bone scintigraphy (4). WBBS is very sensitive during the active lesion period and WBBS findings usually appear before radiography findings. WBBS can also display the improvement within the first 6 months following treatment, thus making it an important technique in the management and follow-up of these patients.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.O., N.C., P.A., R.Ş., S.N., Concept: B.O., N.C., P.A., R.Ş., S.N., Design: B.O., N.C., P.A., R.Ş., S.N., Data Collection or Processing: B.O., N.C., P.A., R.Ş., S.N., Analysis or Interpretation: B.O., N.C., P.A., R.Ş., S.N., Literature Search: B.O., N.C., P.A., R.Ş., S.N., Writing: B.O., N.C., P.A., R.Ş., S.N.

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Disseminated Multi-system Sarcoidosis Mimicking Metastases on ^{18}F-FDG PET/CT

^{18}F-FDG PET/BT'de Metastazı Taklit Eden Dissemine Multisistem Sarkoidoz

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Abstract

A 60-year-old female with no significant medical history presented with hematuria. A computed tomography (CT) scan revealed extensive lymphadenopathy with hypodensities in the liver and spleen, and she was referred for an ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT (PET/CT) study to assess for malignancy of unknown primary. PET/CT revealed extensive ^{18}F-FDG avid lymphadenopathy as well as innumerable intensely ^{18}F-FDG avid lung, liver and splenic nodules, highly concerning for malignancy. A PET-guided bone marrow biopsy of the posterior superior iliac spine revealed several non-necrotizing, well-formed granulomas, consistent with sarcoidosis. The patient was managed conservatively and remained clinically well over the subsequent 9 years of follow-up.

Keywords: Sarcoidosis, artifact, mimic, lymphadenopathy, metastases, ^{18}F-fluorodeoxyglucose, positron emission tomography

Öz

Tıbbi anamnezinde özellik olmayan 60 yaşında bir kadın hematüri ile başvurdu. Bilgisayarlı tomografide (BT) yaygın lenfadenopatiyle birlikte karaciğer ve dalakta hipodens alanlar saptanması üzerine primeri bilinmeyen malignite değerlendirilmesi amacıyla ^{18}F-fluorodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/BT (PET/BT) için yönlendirildi. PET/BT'de ^{18}F-FDG tutan yaygın lenfadenopatiler ve ölçülemeyecek kadar fazla yoğun ^{18}F-FDG tutan akciğer, karaciğer ve dalak nodülleri saptandı, malignite açısından şüpheli bulundu. PET-kılavuzluğunda posterior superior spina iliacadan yapılan kemik iliği biyopsisinde sarkoidoz ile uyumlu non-kazeifiye granülomlar saptandı. Hasta konservatif olarak takip edildi ve 9 yıllık takip süresinde klinik sorun oluşmadı.

Anahtar kelimeler: Sarkoidoz, artefakt, taklit etme, lenfadenopati, metastaz, ^{18}F-fluorodeoksiglukoz, pozitron emisyon tomografi

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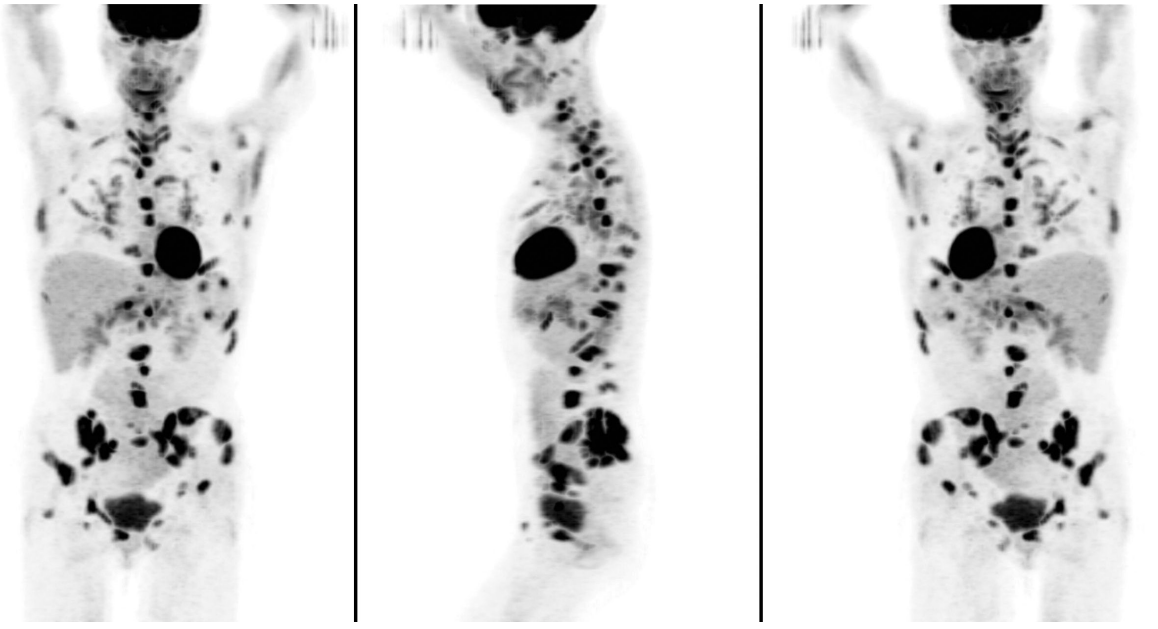

Figure 1. A 60-year-old woman, non-smoker with no significant medical history presented with recurrent hematuria. Computed tomography (CT) abdomen/pelvis identified intra-abdominal, retroperitoneal and inguinal lymphadenopathy, and small hepatic/splenic hypodensities, prompting referral for positron emission tomography/CT (PET/CT) to assess for malignancy of unknown origin. Maximum intensity projection images revealed widespread foci of intense ^{18}F-FDG uptake throughout the skeleton and soft-tissues.

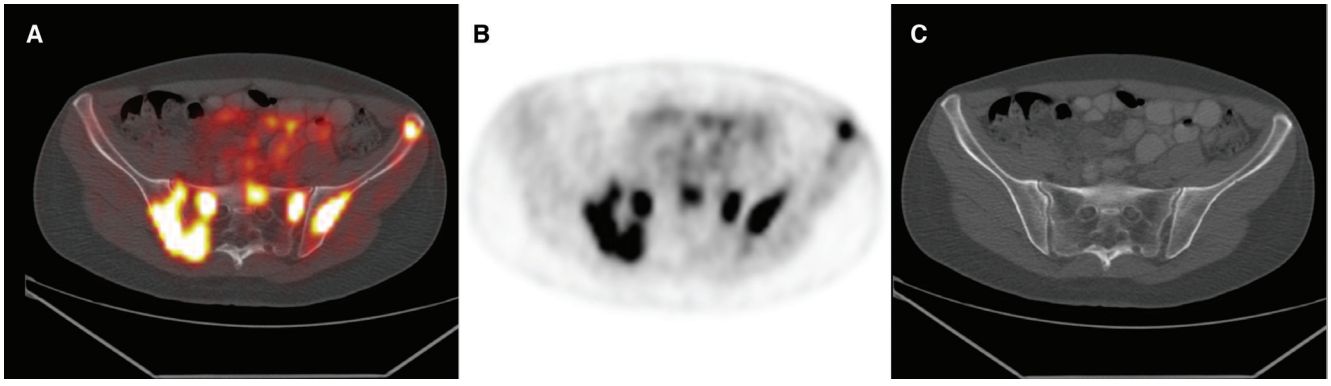

Figure 2. Transaxial (A) PET/CT fusion, (B) PET, and (C) CT images revealed extensive bone involvement of the skull base, right clavicle, spine, multiple ribs, sternum, proximal left humerus, right femur and extensively throughout the pelvis with maximum standardized uptake value (SUV_{max}) 8.3.

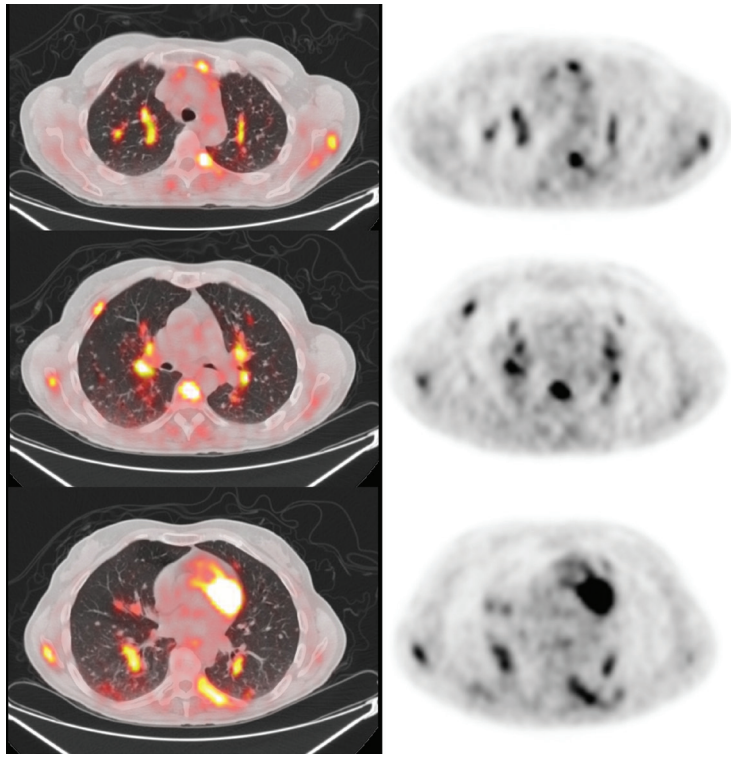

Figure 3. Intense ^{18}F-FDG uptake was also noted in numerous peribronchovascular and subpleural nodules in both lungs (largest was 1.0 cm in diameter with SUV_{max} 3.2).

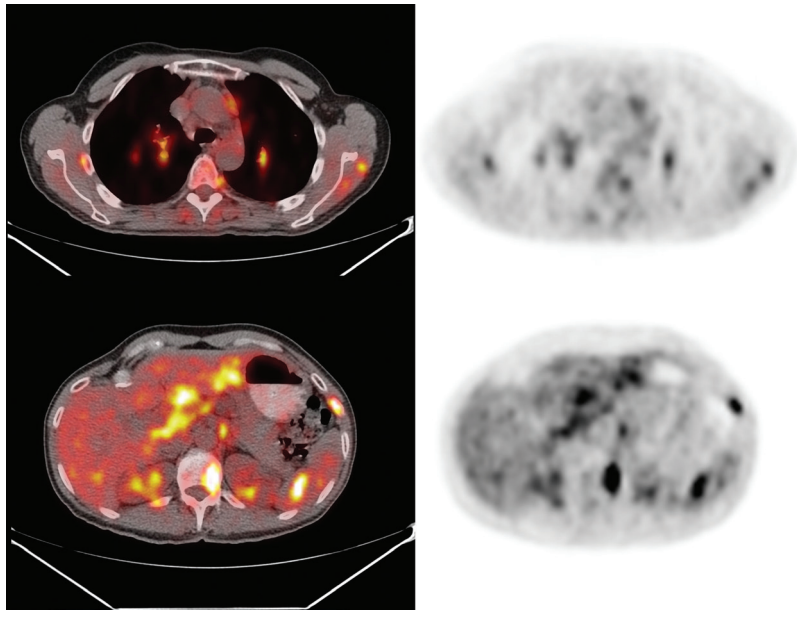

Figure 4. There was widespread adenopathy including left retromandibular, mediastinal, hilar, abdominal, retroperitoneal and inguinal nodes (largest mediastinal node measured 1.4 cm, and the most metabolically active was a right perihilar lymph node with SUV_{max} 5.2). The innumerable liver and spleen hypodensities identified on CT were intensely ^{18}F-FDG avid with SUV_{max} 4.3 in the liver and 5.9 in the spleen. No primary malignancy was identified, but findings were interpreted as highly concerning for disseminated metastatic disease. The patient remained asymptomatic. PET-guided bone marrow biopsy of the left posterior superior iliac spine revealed several non-necrotizing, well-formed granulomas. These granulomas were paratrabecular in distribution and were composed of tightly apposed epithelioid histiocytes, with occasional multinucleated giant cells, consistent with sarcoidosis.

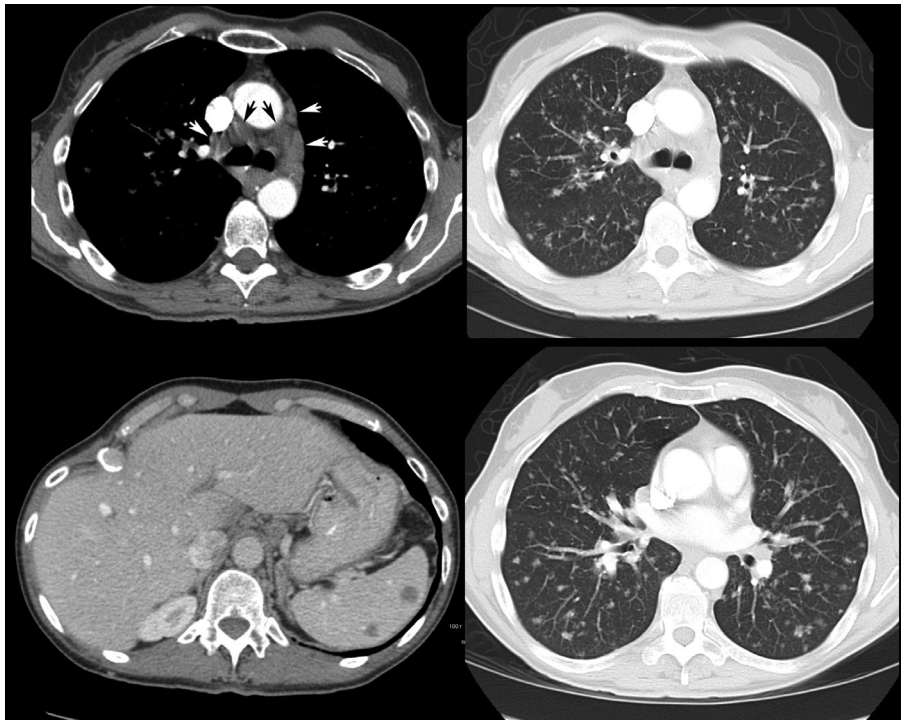

Figure 5. Follow-up diagnostic CT of chest/abdomen/pelvis performed 6 months later, again revealed extensive poorly marginated lung nodules, thoracic and abdominal lymphadenopathy, and splenic and hepatic hypodensities, unchanged as compared to prior PET/CT and consistent with stable granulomatous disease. The patient was managed conservatively with observation and remained malignancy-free over the subsequent 9 years of clinical and imaging follow-up. Sarcoidosis is a chronic multisystem granulomatous disorder of unknown etiology, which is characterized pathologically by non-caseating granulomas that can present almost anywhere in the body (1,2,3,4). ^{18}F-FDG uptake in the granulomas of sarcoidosis can be very intense, likely due to metabolic activity of activated macrophages (2,3,5). ^{18}F-FDG-avid lesions of skeletal sarcoidosis cannot be reliably differentiated from metastases or other benign bone processes (Paget's disease, fibrous dysplasia, giant cell tumors, osteomyelitis) on the basis of semi-quantitative (SUV), visual or other analysis, and therefore remain a pitfall of oncologic PET/CT interpretation (6,7,8,9,10). ^{18}F-FDG uptake in pulmonary sarcoidosis lesions has been described and the severity of pulmonary involvement has been shown to be associated with ^{18}F-FDG activity in persistently symptomatic sarcoidosis patients (11). CT studies show presence of hepatic and splenic nodules in approximately 5-15% of sarcoidosis patients and splenic nodules tend to be larger than hepatic nodules (12). Intense ^{18}F-FDG uptake in hepatic and splenic sarcoidosis lesions has been previously described (13). This case shows an uncommon presentation of disseminated sarcoidosis in the skeleton, lymph nodes, as well as organs such as the lungs, liver and spleen. This impressive pattern of disseminated ^{18}F-FDG uptake can be easily mistaken for extensive metastatic disease when interpreting oncologic PET/CT studies.

Ethics

Informed Consent: All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: W.M., M.P., C.R., S.P., Concept: W.M., M.P., C.R., S.P., Design: W.M., M.P., C.R., S.P., Data Collection or Processing: W.M., M.P., C.R., S.P., Analysis or Interpretation: W.M., M.P., C.R., S.P., Literature Search: W.M., M.P., C.R., S.P., Writing: W.M., M.P., C.R., S.P.

Conflict of Interest: William Makis, Mark Palayew, Christopher Rush and Stephan Probst declare that they have no conflicts of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

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Hypermetabolic Hurthle Cell Adenoma on ^{18}F-FDG PET/CT

^{18}F-FDG PET/BT'de Hipermetabolik Hurthle Hücreli Adenom

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Abstract

Thyroid incidentalomas are frequently reported on ^{18}F-FDG PET/CT scan. High risk of malignancy is thought to be associated with increased metabolic activity and high standardized uptake value. Likewise, thyroid nodules with focal FDG avidity have a higher potential to be malignant. However, some benign nodules such as follicular and Hurthle cell adenomas can also present with focal hypermetabolic activity. We report a case of a 59-year-old lady diagnosed with gastric carcinoma, who had a hypermetabolic thyroid nodule on FDG PET/CT scan. Despite the complex texture of the nodule and intense focal avidity, the histopathology was consistent with Hurtle cell adenoma.

Keywords: Thyroid, Incidentaloma, ^{18}F-FDG PET/CT, Hurthle cell adenoma

Öz

^{18}F-FDG PET/BT görüntülemede tiroid insidentalomalarına sık rastlanır. Yüksek malignite riski artmış metabolik aktivite ve yüksek standart tutulum değeri ile ilişkilendirilmektedir. Fokal FDG tutulumu olan tiroid nodüllerinde malignite olasılığı benzer şekilde artmaktadır. Ne var ki, foliküler ve Hurthle hücreli adenom gibi bazı benign nodüller fokal hipermetabolik aktivite gösterebilir. Bu yazıda gastrik adenokarsinom tanısı almış ve FDG PET/BT'de hipermetabolik tiroid nodülü saptanan 59 yaşında bir kadın hasta sunulmaktadır. Nodülün sert yapısı ve yoğun fokal tutuluma rağmen histopatoloji değerlendirmesi Hurthle hücreli adenom ile uyumlu idi.

Anahtar kelimeler: Tiroid, insidentaloma, ^{18}F-FDG PET/BT, Hurthle hücreli adenom

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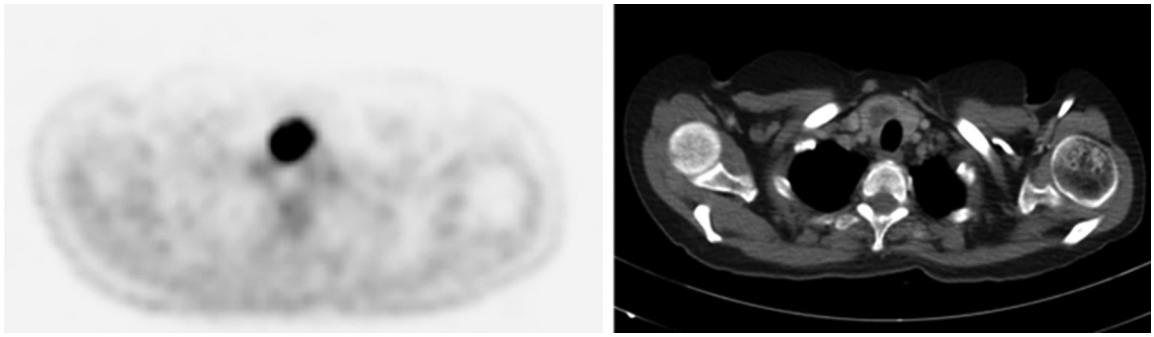

Figure 1. A 59-year-old female patient with a diagnosis of gastric carcinoma was referred for staging ^{18}F-FDG PET/CT scan. Imaging was performed 60 minutes after a dose of 294 MBq, on an integrated 16-slice PET/CT scanner, with scanning from the vertex to the mid-thigh. ^{18}F-FDG PET/CT scan axial views of the lower neck showed a hypermetabolic, heterogeneously enhancing right thyroid nodule with low attenuation [2.7 cm, standardized uptake value (SUV) 17.5]. The left thyroid lobe was unremarkable both radiologically and metabolically.
Ultrasound correlation and targeted biopsy of the right thyroid nodule was recommended. The patient was clinically and biochemically euthyroid. Fine needle aspiration cytology was consistent with follicular neoplasm, Bethesda category IV. Thereafter, the patient underwent partial thyroidectomy.

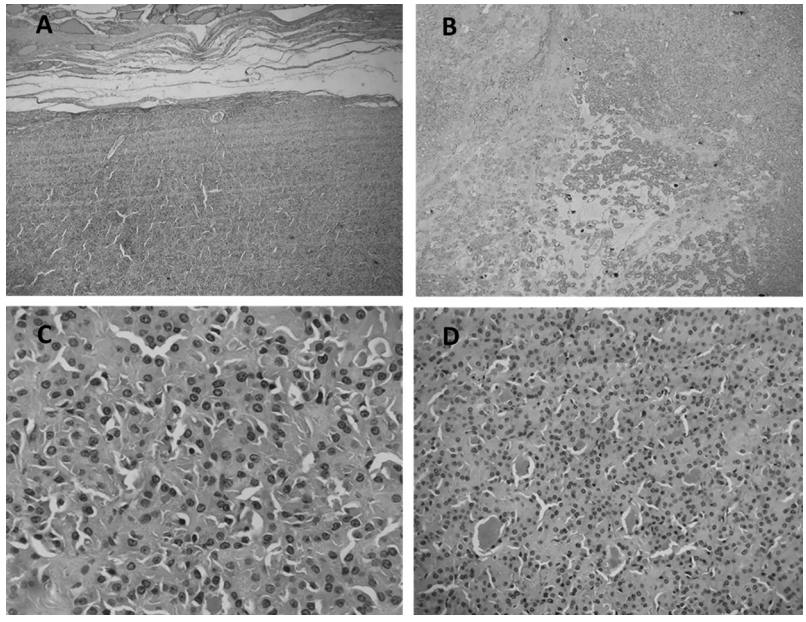

Figure 2. Histopathology evaluation revealed Hurthle cell adenoma (2.5 cm). Figure 2 displays histopathological characteristics of a well circumscribed neoplasm with a thin walled capsule (A). The low power view of adenoma at 4x (B) shows the cells arranged in sheets. Individual cells have abundant granular oncocytic cytoplasm with round large nuclei and prominent nucleoli (C, D). Thyroid incidentalomas are frequently detected on FDG PET/CT scan during oncological work-up. A normal thyroid gland shows homogenous, mild FDG uptake on PET/CT images (1). High, focal metabolic activity usually has a higher tendency to be malignant (2). In the absence of frank local invasion or adenopathy, it is difficult to characterize a thyroid nodule on CT scan (3). Heterogeneous complex textured thyroid nodules with an average size of 2.0 cm are radiologically concerning for malignancy (4).
At our institution, the prevalence of thyroid incidentalomas identified by FDG PET/CT is 1.7% (5), which is in line with the prior literature (2). FDG uptake in a lesion is dependent on the rate of glycolysis. Malignant lesions take up FDG in significantly higher fractions as compared to benign lesions. Focal FDG uptake in the thyroid has a reported malignancy rate ranging from 24 to 74% (6,7,8). Diffuse increased thyroid uptake is usually related to benign causes such as Graves' disease and thyroiditis (2). Our institutional experience has shown 48% of the focal FDG avid thyroid incidentalomas to be malignant.
The case presented herein had a complex thyroid nodule and the appearance was concerning for metastatic involvement. Despite the higher clinical suspicion of malignancy, our final histopathology was consistent with a benign pathology, i.e Hurthle cell adenoma. Hurthle cells are oxyphillic variant of follicular cells, and depict granular cytoplasm due to the high content of intra-cytoplasmic mitochondria (9). The intense metabolic activity in this nodule on FDG PET/CT scan can be explained on the basis of this abundance of intra-cytoplasmic mitochondria.
Most prior studies suggest that high SUV is associated with thyroid malignancy. However, some conflicting results have also been reported with overlapping SUV of benign and malignant thyroid incidentalomas (10). It has been reported that 1.5–2.1% of benign thyroid nodules might show high SUV in FDG PET/CT scans (11). In view of these false positive findings, high metabolic activity on FDG PET/CT cannot accurately distinguish between benign and malignant nodules. Our case is an example where intense avidity of a thyroid nodule on FDG PET/CT was deceptive for being a malignant lesion.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H., S.R., A.A., Concept: A.H., Design: A.H., S.R., Data Collection or Processing: A.H., S.R., A.A., Analysis or Interpretation: A.H., S.R., A.A., Literature Search: A.H., S.R., Writing: A.H., S.R.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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