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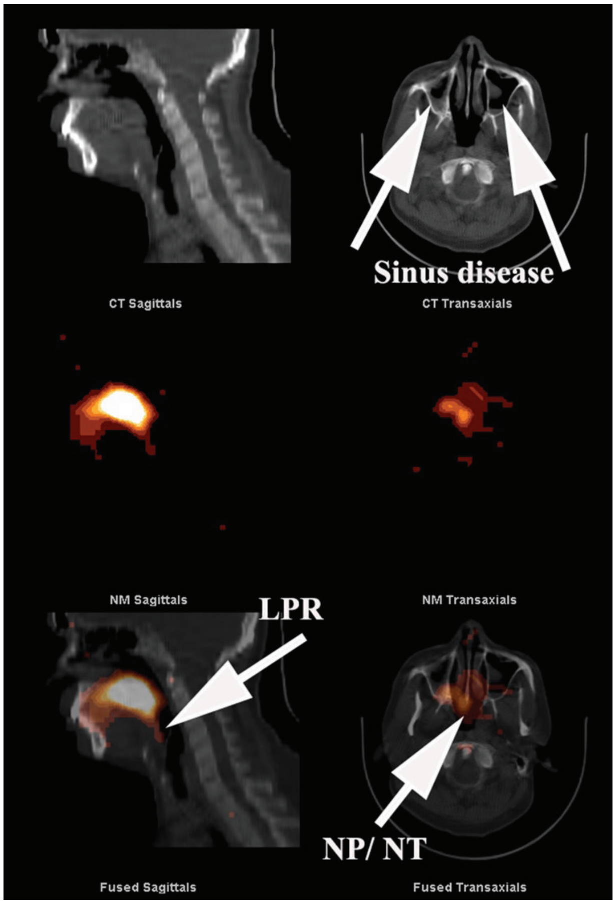

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Molecular Imaging and Radionuclide Therapy (Mol Imaging Radionucl Ther, MIRT) is a double-blind peer-review journal published in English language. It publishes original research articles, invited reviews, editorials, short communications, letters, consensus statements, guidelines and case reports with a literature review on the topic, interesting images in the field of molecular imaging, multimodality imaging, nuclear medicine, radionuclide therapy, radiopharmacy, medical physics, dosimetry and radiobiology. MIRT is published three times a year (February, June, October). Audience: Nuclear medicine physicians, medical physicists, radiopharmaceutical scientists, radiobiologists.

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Molecular Imaging and Radionuclide Therapy (Mol Imaging Radionucl Ther, MIRT) publishes original research articles, short communications, invited reviews, editorials, case reports with a literature review on the topic, interesting images, consensus statements, guidelines, letters in the field of molecular imaging, multimodality imaging, nuclear medicine, radionuclide therapy, radiopharmacy, medical physics, dosimetry and radiobiology. MIRT is published by the Turkish Society of Nuclear Medicine three times a year (February, June, October).

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Sample References

Journal Article: Sayit E, Söylev M, Capa G, Durak I, Ada E, Yilmaz M. The role of technetium-99m-HMPAO-labeled WBC scintigraphy in the diagnosis of orbital cellulitis. Ann Nucl Med 2001;15:41-44.

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.

Website: Smith JR. 'Choosing Your Reference Style', Online Referencing 2(3), http://orj.sagepub.com (2003, accessed October 2008).

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MIRT
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CONTENTS

Review

49 Guide for Nuclear Medicine Applications During the COVID-19 Outbreak
COVID-19 Salgını Sırasında Nükleer Tıp Uygulamaları İçin Kılavuz
Aslı Ayan, F. Suna Kıraç; Ankara, İzmir, Turkey

Original Articles

59 The Predictive Value of Proportional Evaluation Based on the Metabolic Activity of Cervical Lymph Nodes on PET/CT Imaging in Patients with Larynx Cancer
Larinks Kanserli Hastalarda PET/BT Görüntülemede Servikal Lenf Nodlarının Metabolik Aktivitesine Dayanan Oransal Değerlendirmenin Prediktif Değeri
Sevda Sağlampınar Karyağar, Savaş Karyağar, Osman Güven, Onur Üstün, Yavuz Atar, Yavuz Uyar; İstanbul, Turkey

65 The Impact of Primary Tumor and Locoregional Metastatic Lymph Node SUV_{max} on Predicting Survival in Patients with Rectal Cancer
Rektal Kanserli Hastalarda Primer Tümör ve Lokorejyonel Metastatik Lenf Nodu SUV_{maks}'ın Sağkalım Üzerine Belirleyici Etkisi
Göksel Alçın, Yasemin Şanlı, Gülçin Yeğen, Esra Kaytan Sağlam, Tevfik Fikret Çermik; İstanbul, Turkey

72 Fungal Pneumonia in the Immunocompetent Host: A Possible Statistical Connection Between Allergic Fungal Sinusitis with Polyposis and Recurrent Pulmonary Infection Detected by Gastroesophageal Reflux Disease Scintigraphy
İmmünokompetan Hastada Fungal Pnömoni: Polipozis ile Alerjik Fungal Sinüzit ve Gastroözefageal Reflü Sintigrafisi ile Saptanan Tekrarlayan Pulmoner Enfeksiyon Arasında Olası İstatistiksel Bağlantı
Leticia Burton, Karl Baumgart, Daniel Novakovic, John Beattie, David Joffe, Gregory Falk, Hans Van der Wall; Sydney, Australia

Interesting Images

79 Intense ^{18}F-Flourodeoxyglucose Uptake in Brachial Plexus of Patients with Brachial Plexopathy
Brakial Pleksopatili Hastada Brakial Pleksusta Yoğun ^{18}F-Florodeoksiglukoz Tutulumu
Çiğdem Soydal, Pınar Akkuş, Mine Araz, Güngör Utkan; Ankara, Turkey

82 Findings of Gynecomastia That Developed in Follow-up Secondary to Bicalutamide Treatment on Bone Scan
Kemik Sintigrafisinde Bicalutamide Tedavisine Sekonder Takipte Gelişen Jinekomasti Bulguları
Kemal Ünal, Nahide Gökçora; İstanbul, Ankara, Turkey

85 Lymphoblastic Involvement of the Bone Marrow as a Cause of Superscan Appearance in ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
^{18}F-Florodeoksiglikoz Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi'de Supersken Görünümünün Bir Nedeni Olarak Kemik İliğinin *Lenfoblastik Tutulumu*
Zehra Pınar Koç, Pelin Özcan Kara, Aydan Akdeniz, Mehmet Yaldız; Mersin, Turkey

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Review
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Guide for Nuclear Medicine Applications During the COVID-19 Outbreak

COVID-19 Salgını Sırasında Nükleer Tıp Uygulamaları İçin Kılavuz

Aslı Ayan[1], F. Suna Kıraç[2]
[1]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Nuclear Medicine, Ankara, Turkey*
[2]*Chairman of TSNM Radiation Safety and Quality Control Working Group, İzmir, Turkey*

Abstract

A viral pneumonia rapidly spread from Wuhan, China to all countries in late 2019. In February 2020, WHO named as Coronavirus Disease 2019 (COVID-19) and declared the pandemic on March 11, 2020. To prevent the spread of COVID-19, Ministry of Health of Republic of Turkey and international institutions have published documents defining hygiene rules. After the lung computerized tomography (CT) findings which are important in the diagnosis of COVID-19 are described, protection measures against infection were defined in radiology departments. There is no publication involving protection measures for diagnostic and therapeutic procedures in nuclear medicine (NM) (appointment, patient acceptance, imaging and treatment procedures, disinfection etc). There are two reports on CT findings suggesting COVID-19 in ^{18}F–fluorodeoxyglucose positron emission tomography/CT scan. These lung findings detected in hybrid images will be helpful in the early diagnosis of pulmonary involvement. Infected cases may be asymptomatic and can unintentionally disseminate the virus to surrounding people. This advisory guide has been prepared to avoid infection risk in NM clinics. During the COVID-19 outbreak, staff must use proper personal protective equipment and patients should be evaluated as the elective case according to clinical status. A questionnaire should be made for COVID-19. In cancer cases requiring urgent treatment, radionuclide treatment (RNT) should be planned according to the COVID-19 test result. If the result is negative, RNT can be applied; but if not or if the symptoms are present, RNT must be postponed. Following imaging procedures, scanners and room surfaces should be cleaned by personnel with proper disinfection training.

Keywords: Coronavirus, COVID-19 outbreak, nuclear medicine staff, positron emission tomography/computerized tomography, infection protection rules, disinfection

Öz

2019'un sonlarında, viral pnömoni Wuhan, Çin'den hızla tüm ülkelere yayıldı. Şubat 2020'de Dünya Sağlık Örgütü Coronavirus Disease 2019 (COVID-19) olarak adlandırdı ve 11 Mart 2020'de pandemi geliştiğini açıkladı. COVID-19 enfeksiyonunun yayılmasını önlemek için, TC. Sağlık Bakanlığı ve uluslararası kurumlar hijyen kurallarını tanımlayan broşürler yayınladı. Bilgisayarlı tomografi (BT) görüntülerinde COVID-19 tanısında önemli olan akciğer bulgularının tanımlanmasıyla radyoloji bölümlerinde enfeksiyondan korunma önlemleri açıklanmıştır. Nükleer tıpta tanı ve tedavi işlemleri için (randevu vermek, hasta kabulü, görüntüleme ve tedavi işlemleri, dezenfeksiyon gibi) korunma önlemlerini içeren yayın yoktur. ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/BT taramada COVID-19'u düşündüren BT bulguları hakkında iki yayın vardır. Hibrid görüntülerde saptanan bu akciğer bulguları akciğer tutulumunun erken tanısında faydalı olacaktır. Enfekte olgular asemptomatik olabilir ve farkında olmadan virüsü çevresindeki kişilere yayabilir. Öneri niteliğindeki bu kılavuz Nükleer Tıp kliniklerinde enfeksiyon riskini önlemek amacı ile hazırlanmıştır. COVID-19 salgını sırasında, personel uygun kişisel koruyucu ekipman kullanmalı ve hastalar klinik durumlarına göre elektif olgu olarak değerlendirilmelidir. COVID-19 açısından anket yapılmalıdır. Acil tedavi gereken kanser olgularında, COVID-19 test sonucuna göre radyonüklit tedavi (RNT) planlanmalıdır. Sonuç negatif ise RNT uygulanabilir. Sonuç pozitif ise veya semptomlar varsa, RNT ertelenmelidir. Görüntüleme işlemlerinden sonra, tarayıcılar ve oda yüzeyleri dezenfeksiyon konusunda uygun eğitim almış personel tarafından temizlenmelidir.

Anahtar kelimeler: Koronavirüs, COVID-19 salgını, nükleer tıp personeli, pozitron emisyon tomografi/bilgisayarlı tomografi, enfeksiyondan korunma kuralları, dezenfeksiyon

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Introduction

In late 2019, a new coronavirus was isolated from a group of patients admitting with viral pneumonia in Wuhan, China. With the increasing global people movement, the major concern over the possibility of this novel virus spreading and reaching pandemic levels has unfortunately now come true. In the first group of patients, the virus was believed to be transmitted from the wet "seafood market" in Wuhan. Since then, numerous reports which are related with human-to-human transmission have been published. It has rapidly spread to all countries world-wide. New countries affected by the virus are reported every day. The novel virus is one member of the coronavirus family and Coronavirus Disease 2019 (COVID-19) spreads from human-to-human like flu (1).

Due to the increasing number of patients in our country since Mid-March 2020, more attention has been given to infection control measures especially in hospitals that have the potential to spread the virus not only among patients but also healthcare personnel. These measures should be implemented at the national level, not just at the hospital level and regional. It is important to comply with the general hygiene rules for public persons and health professionals. After the World Health Organization (WHO) declared that the COVID-19 global pandemic has developed on March 11, 2020, general hygiene rules have been published by Republic of Turkey Ministry of Health and international related institutions to prevent the spread of disease and to avoid new infected cases (Annex 1) (2). However, more strict and branch-specific protection rules are necessary, since healthcare professionals are more likely to come in contact with the infected and/or probable infected cases. Because the lung findings in the computerized tomography (CT) images are useful in the diagnosis of COVID-19, although there are articles about how they can be careful to reduce to the risk of outbreaks in the radiology departments, there are very few application recommendations for nuclear medicine (NM) clinics (1,3,4). Despite the similarities, there are pertinent differences between radiology and NM regarding the urgency of diagnostic and therapeutic applications, the length of patient contact, the ability for portable imaging instruments and the duration of scans, which necessitate a separate set of advice. Therefore, just like infection protection algoritms prepared by other medical specialities, preventive applications guide has become mandatory in the NM clinics, too.

NM departments are the clinics that necessarily apply the principles of infection protection published by WHO in their daily practices due to the ionizing radiation protection measures (distance, time, shielding). Similar to the radiology departments, NM specialists, nurses and technicians are generally at the highest risk of exposure to the COVID-19. COVID-19 is believed to be mainly transmitted through respiratory droplets and close contact with infected patients or with the asymptomatic carriers in the incubation period. Also, it may be transmitted indirectly through touching in contaminated surfaces or objects. There have been no reports of airborne transmission of the COVID-19 virus to date. However, it can not be denied that some aerosol-forming process such as supportive oxygen therapy or intubation, would be able to cause transmission in the healthcare units. There are some experiences providing important recommendations and measures, which have been vested from prior coronavirus epidemics of SARS and MERS outbreaks which in the same class with COVID-19, to combat the current outbreak (1,3).

Nuclear medicine department is partially lucky compared to other branches because the majority of imaging methods and radionuclide treatment (RNT) performed are elective and tend to be outpatient. In addition, NM workers will have the chance to take the necessary precautions, since the new studies will usually be performed in the patients who have already been hospitalized and secreened for COVID-19. Nevertheless, the absence of portable single photon emission computerized tomography (SPECT) or positron emission tomography (PET)/CT instruments is the most important risk. Setting appointments over the phone will help to identify infected and probable patients, it partially will prevent COVID-19 contamination to the patients and staff, and also the development of outbreak in NM clinics. However, the risk of encountering the virus will not be zero by patients who have not been diagnosed yet, with no suspicious history in terms of disease, but any form of asymptomatic infection at the time of admission. Therefore, this guideline including some suggestions has been prepared with a goal for providing the protection of patients and healthcare workers in the NM clinics that continue to perform the diagnostic and therapeutic procedures even under the risk of contamination by COVID-19 virus which is defined as pandemic by WHO.

The recommendations set out in this guide should be adapted to the clinics' own working conditions, fields of activity and the number of patients.

Patient Registration

1. In the patients whose new appointments will be arranged, the clinician or assisstant physician responsible for the patient referring to the NM clinic should be asked to give detailed information on COVID-19 and the patients's previous illnesses.

2. During recourse and enrollment to the department, the patients travelling to the country with known COVID-19 outbreak should be encouraged to self-report, especially when they are symptomatic (Annex 2) (2).

a. The first registration, if possible, should first be accepted by phone and an inquiry should be made in this regard.

b. If it is not possible to make an appoinment by phone, the necessity to fill the notification form prepared for patients to declare their own information in the NM secretariat will be useful in the identifying infected and suspicious cases (Annex 2).

3. During admission, the fever measurement of the patients who registered for outpatient-treatment, and who will undergo a diagnostic procedure may be useful in distinguishing asymptomatic patients. In the large departments dealing with outpatient or referral service to the healthcare provider, thermal screening by thermal scanning and mass screening systems that measure the skin temperature at high-speed using temperature measurement equipment as used in airports must be considered.

4. Healthcare staff should well know the symptoms of COVID-19 infection such as fever, dry cough, fatique and shortness of breath. Additionally, they should be aware that patients are asymptomatic carriers of the virus and that history of contact with a suspicious case is important for probable infection.

5. If there is a suspicious case for COVID-19 when setting an appoinment over the phone, the responsible NM specialist should be informed by the interviewing staff. After that, the competent authority must be notified immediately and the patient should be transferred to the competent hospital.

6. Advisory staff who are arranging the patient procedures in nuclear medicine, making an appoinment and providing the necessary documents exchange should be properly trained for the risk of COVID-19 transmission. It is strongly recommended to use anti-virus protective equipments such as disposable head caps, disposable masks, disposable gloves and hospital-only work clothes.

7. When such patients are identified, they should be placed in a separate waiting area and must be consulted to the infectious diseases specialist or local line accross, our country 184, should be called in the case of strong suspect.

8. Taking into consideration of current information, the patients should use a surgical mask in order to minimize the potential risk of transmission while waiting for results of assessments.

9. If possible, it is recommended to postpone all patient procedures (for diagnostic or therapeutic purposes) until the results of the COVID-19 tests are obtained.

10. When the COVID-19 endemia develops, giving disposable masks to all patients to put on while they are in the department should be considered. This practice must be applied at the expense of the patient's objection.

11. If there is more than one receptionist, it is recommended that the work desks are placed at a distance of 1 m, and similarly, a barrier may be created in front of the counseling desk with a distance of 1 m between the desk and the patients or accompanying persons.

Registration Reception Hall Waiting Area

1. Waiting areas must be close to hand washing facilities, masks should be in easy reach. Patients can be encouraged/provided to follow basic hygiene practices.

2. Since the risk of coronavirus transmission increases within one (1) m, the waiting area should have enough space in order to provide enough distance while waiting. The concept of sufficient distance should be designed according to the daily patient load of each clinic. In NM clinics that cannot provide 1 m distance measure between the patients, keeping the admitted patient and/or accompanying persons outside the clinic for providing the social isolation distance; or that to take in the patients individually and in a way that will not cause a confluence in the waiting area, or limiting the number of new appointments based on the size of the waiting area is recommended.

3. The reception hall and waiting area should be good ventilated by equipment with a high-efficiency particulate air filter.

If the Patient has been Called for Procedure

1. NM staff welcoming patients such as NM technicians or nurses are individuals who will be in the most close contact with infected patients.

2. Because physical contact is unavoidable during catheter insertion intravenously and it may take a long time, it is very important to identify probably infected patients before this step.

3. Therefore the informations in terms of COVID-19 infection should be added into the cases' anamnesis (Annex 2).

4. If COVID-19 outbreak is defined in the country, it is mandatory that workers use proper personal protective equipment (PPE). PPE (level 1 protective equipment) is

generally sufficient in the NM clinics. Level 1 protective equipment includes a disposable surgical mask, special work clothes, disposable latex gloves and/or disposable insulating clothing. Additionally, staff wearing contact lenses must switch to glasses to protect health. Wearing eyeglasses can shield their eyes from probable transmission by contaminated hands or infected respiratory droplets (5). However, level 2 PPE should be used during the examination and imaging of the confirmed or probable patient, and during cleaning of the equipment used to the patient with a suspicious or confirmed disease. Unlike level 1, level 2 PPE requires the use of N95 or equivalent mask, disposable protective suit, googles or face shield (3). Especially the beard and/or mustache interfere with the N95 masks or respirators fitting to entire face and thereby virus transmission risk increases. It is important to be clean shaved for complete protection against infection (6).

5. However, the procedures performed with full PPE are difficult and may affect the ability of personnel to handle the same patient load as before.
6. These practices may change depending on the number of positive cases in the hospital and the departmental success to catch infected or suspicious patients who have been admitted to the department for any procedure or the number of confirmed or probable COVID-19 cases referred.

Recommendations for The Waiting Rooms of Radioactive Patients

Most of NM imaging and procedures require a processing time from several minutes to several hours following radiopharmaceutical administration. During this time,

1. 1 m distance between patients placed in the separate radioactive patient areas (PET patients) or in the common waiting rooms (for gamma camera patients) should be maintained to prevent novel coronavirus transmission among patients.
2. Waiting rooms of radioactive patients should be good ventilated by an equipment with a high-efficiency particulate air filter.
3. The crowded rooms may increase possible transmission risk due to cases who are asymptomatic and have an inappropriate history. It is adviced to limit the number of patients according to the size of radioactive patient room.
4. Similar measures as those defined for the non-radioactive patients and accompanying persons in the registration hall should be applied to all other stages after radiopharmaceutical administration. First of all, all of them should be supported to wear a protective mask.

When the Patient is Scanned

1. Once patients' scan is complete, scanners and room surfaces should be disinfected to avoid potential spread.
2. As a general rule of Public Health Units;
   a. In the absence of visible pollution after scanning, disinfectants produced for especially the hospitals or the 1/1000 (1000 parts per million) parts of chlorine solutions containing are recommended to use in the disinfection of scanning instruments and clinical rooms used (7).
   b. Terminal cleaning procedures must be applied in case of the presence of patient secretions, urine or stool contamination (7).
   c. Adequate and appropriate training is recommended for cleaning staff to work properly.

The Safety of Nuclear Medicine Staff

1. The same precautions and tests recommended to the patients at the time of admission should also be valid for NM personnel (eg technicians, nurses, NM specialists) who are in close contact with the patient.
2. Personnel who is in contact with patients must wear a whole apron, gloves, surgical mask, protective eye glasses and shoe covers.
3. Personnel should be trained in the use of these equipments and be warned to correct their mistakes seen during usage.
4. Similar measures such as isolation at home, should be taken for the staff who has symptoms like fatique, fever, cough, or a history of travelling in areas with more widespread local transmission of COVID-19 or a history of contact with travellers visiting infected areas or contact with confirmed cases, for reducing the risk of virus transmission.
5. It would be appropriate for senior clinician and/or supervisors to advice workers not come to work if they feel unwell.
6. Due to the possibility of the presence of asymptomatic infected personnel, employees can be prevented being together by adjusting rest time.
7. If COVID-19 spread increases, the larger NM departments, may consider dividing their staff into alternative working groups to reduce the risk of viral transmission among the healthcare providers causing department work to fail.

8. All staff should receive proper training to ensure maximum compliance for measures.
9. Clinical staff should stay under observation at home to monitor the daily symptoms if they have come into contact with a probable case in less than 1 meter distance without PPE or if they directly or indirectly exposed to the patient's respiratory secretions. If test result of the suspicious infected case who contacted with, is negative, the observation is terminated. But, if test result is confirmed as positive, the observation at home should continue for 14 days. Staff who have symptoms should be managed in accordance with the applications for COVID-19 probable case according to the COVID-19 Disease Guide and the COVID-19 case flow-chart published by the Ministry of Health of Republic of Turkey.
10. An emergency and business continuity plan should be prepared.

Recommendations for Diagnostic and Therapeutic Applications with Radionuclides During Outbreak

A. Myocardial Perfusion Scintigraphy (MPS)

1. Taking into consideration asymptomatic patients, patient in a good clinical condition without any strict contraindication criterion, performing pharmacological stress test (especially with vasodilatator agents) shortens the procedure time instead of treadmill exercise test. This recommendation can keep safe the staff and also the patient from possible transmission.
2. Since the pharmacological stress test will be performed at a less distance than 1 m, particular attention should be paid to the use of PPE. If possible, it is recommended to wear a disposable clothing over the lead apron, and to properly disinfect the materials and the clothes used during the procedure. Additionally, patient must wear a protective mask during the entire procedure.
3. Cardiac arrhytmias, myocarditis, low ejection fraction and sudden death cases have been reported due to SARS-Cov-2 (COVID-19) infection (8). There is no published MPS scintigraphy study including COVID-19 cases, yet. Another important issue here is that hydroxychloroquine preparations (hydroxychloroquine is a drug known with strong antimalarial effect. However, today it is used in the treatment of autoimmune disease rather than malaria treatment) has been reported to be effective in COVID-19 treatment and even for prophylaxis, may cause similar cardiac findings. The side effects of hydroxychloroquine drugs are not dose dependent in each case and may also develop idiosyncratic side effects in individuals who are sensitive to 4-aminoquinoline compounds. Therefore, it should be taken into account that side effects of the drugs may be thought as the cardiac manifestations of the disease. Additionally, it may cause serious retinopathy and skin lesions (9,10,11). It is recommended to be used prophylactically with the decision of the expert and under the supervision of specialist in the healthcare workers at high risk of disease.

B. Lung Perfusion Scintigraphy

The most common symptoms in COVID-19 patients are high fever, cough, myalgia and fatigue. Pneumonia involving multiple lobes, bilaterally has been reported in the published studies. The SARS-Cov-2 pneumonia resulting extensive inflammation and infiltration is localized particularly in the posterior and peripheral zones of the lungs (12,13) (Table 1). However, patients especially who are at risk for pulmonary embolism (PE) such as deep vein thrombosis, malignancy, and presence of immobilization may be considered as PE because of that typical complaints are not detected and no severe infiltration findings in lungs in the early stages.

PE can lead to non-specific findings such as arterial hypoxemia and hypocapnia in the patients. These findings are also seen in chronic obstructive pulmonary disease, lung cancer or pulmonary fibrosis besides PE. The pulmonary X-rays will be helpful in the differential diagnosis of non-PE diseases. But its sensitivity is very low (40%). Although the sensitivity (82%) and specificity (96%) of perfusion-only study is inferior to combined ventilation/ perfusion study, these values are still high in the diagnosis of pulmonary embolism.

1. In the clinics where there is no SPECT/CT equipment, patients suspicious for PE should be referred to lung CT scanning in terms of the possible COVID-19 pneumonia, even if their body temperature is not high. After that if necessary, pulmonary perfusion scintigraphy should be performed following CT. Planar or SPECT perfusion study should be evaluated together with clinical findings and simultaneous CT images (14,15,16).
2. If SPECT/CT camera is available, hybrid imaging have to be performed; careful examination in terms of ground-glass opacities and pneumonic infiltration in the CT slices obtained, especially posterior and peripheral, subpleural zones, will provide useful informations in the the early diagnosis.
3. Lung ventilation scintigraphy must not be performed if there are findings mimicking COVID-19 pneumonia such as non-segmental perfusion defects, non-wedge-

Table 1. CT findings and their distributions in the lung lobes that can be observed during COVID-19 infection

CT findings according to the disease stage		Localization ratios
Early stage 0-4th days	Ground-glass opacities*, partial crazy paving**, a small number of lobes involved	Bilateral involvement 87.5% Posterior involvement 80.4% Multilobar involvement 78.8% Peripheral lesions 76%
Progressive stage 5-8th days	Ground-glass opacities, increased crazy paving findings	
Peak stage 10-13th days	Consolidation	
Resolution stage ≥14 days	Gradual resolution of findings	

*Ground-glass opacities are present in 88% of cases, **Crazy paving: ground glass opacity overlapping interlobular and intralobular septal thickening areas, CT: Computerized tomography

shaped perfusion defects, resembling lung parenchymal disease.

a. There is a risk of transmission of all viral and bacterial infections, including COVID-19, by means of ventilation devices.

b. Additionally, the lung ventilation procedure can cause aerosolization and the formation of microdroplets. Therefore, lung ventilation study should not be performed in patients with probable PE during the pandemic (6).

c. If necessary, perfusion-only study should be settled in these cases as defined above.

4. Pneumonia and PE findings sometimes overlap. Diagnostic lung CT imaging should be performed in both conditions.
5. The flow-chart recommended in probable cases should be followed.

The Tc-99m macroagregated albumin (MAA) particles used for lung perfusion scintigraphy are 15-100 µm in size and the particle distribution accurately shows regional lung perfusion. Since MAA particles block pulmonary capillaries and precapillary arterioles, the number of particles injected is important. Normally 100.000-500.000 (ideally 400.000) particles are injected during perfusion study. However, 60.000 particles are sufficient for obtaining uniform distribution of activity reflecting regional perfusion. Taking into account that the number of pulmonary capillaries and precapillary arterioles present in the lungs, the administration of up to 400.000 MAA particles will result in obstruction in a very small fraction of pulmonary vessels. But it is recommended to inject the minimum number of MAA particles (60.000 particles) which sufficient for good quality images (14,15). In this way, developing widespread microemboli will be prevented and kept pulmonary functions in the patients with the possibility of COVID-19 pneumonia which can cause severe damage in the lungs.

C. Hybrid Imagings

1. There is increasing number of reports which describe CT findings of COVID-19 associated pneumonia. Recently a manuscript containing 4 (four) cases about random CT findings suggesting COVID-19 in the ^{18}F–fluorodeoxyglucose (FDG) PET/CT scans and a case report including a patient who underwent FDG PET/CT scan due to a lesion in the lung were published. COVID-19 was detected in one case in each publication (17,18,19).
2. If interlobular septal thickening and ground-glass density areas with high metabolic activity are detected in the cases who underwent to ^{18}F- FDG PET/CT imaging for other reasons, these cases should be referred to the relevant institutions or departments.
3. Similar lung CT findings for COVID-19 pneumonia observed in the SPECT/CT slices of the thorax should be reported to the Infection Control Committee or to the call centers in the hospital by NM specialists.
4. Based on these cases, a more careful evaluation of PET/CT or SPECT/CT images of each patient, especially the lungs in the CT components, and reporting the lung findings observed by NM specialists will offer very useful informations to the clinicians in the early diagnosis of COVID-19 lung involvement (12,13). Because such patients may be asymptomatic, and being unaware, can spread the virus to the surrounding people and to the people who they are in contact with. Imaging findings are similar to previous coronaviruses such as MERS or SARS. These nonspecific findings become meaningful in terms of COVID-19 infection if they comply with suspicious case definition.
5. Information about the patient's clinical history will be useful in the diagnosis for evaluation of radiology and NM images, as in routine practice. Risk factors such as chronic illness, the history of contact with confirmed

patients and visiting to the places where COVID-19 infection spread should be investigated.

6. Staff performing injection and imaging of these patients must be questioned in detail for a history of contact with patient (such as duration, proximity, whether using PPE) .

Table 1 shows the CT findings and their distributions regarding to lung lobes that can be observed during COVID-19 infection.

D. Radionuclide Treatments

Although cancer patients have a higher risk than healthy people, there is still no published chronic disease and algorithm for COVID-19 infection in these patients. It is accepted that the presence of other being older than 65 years will rise the infection risk. Although there is a small number of reports on surgical treatments in cancer cases suspicious for COVID-19 infection or infected (20,21), any published report regarding RNT is not present, yet. If necessary, the guide for surgery of these cases may be applied. According to these rules;

1. The patients referred for RNT, should be evaluated electively based on their clinical condition.
   a. A questionnaire should be made for symptoms and signs of COVID-19 infection, and answers should be recorded (Annex 2).
   b. It should be questioned whether there are any infected or suspicious cases at home or in their immediate vicinity. It should be recommended to postpone the appointment and refer to the relevant institution or unit for the diagnosis of COVID-19, if there is a suspicion for coronavirus infection.
2. If the patient preparation for I-131 treatment or whole body scanning is not urgent, treatment should be postponed and replacement treatment should be given for euthyroidism in hypothyroid patients who are in the preparation period. If urgent treatment is necessary, recombinant TSH (rTSH) can be preferred, instead of hypothyroidism in these cases.
3. Patients who had an appointment for RNT other than I-131 should also follow the recommendations defined for patients who will be arranged new appoinments.
4. For all RNT including I-131, in case of requiring urgent treatment, the questionnaire for COVID-19 infection should be applied at initial referral and must be recorded.
   a. If there is fever (>37.3), a history of travel to the outbreak area or contact with an infected person, social isolation at home is recommended for fourteen days before treatment. At the end of this period, reevaluation should be done.
   aa. Treatment can be planned for the patients who COVID-19 is negative or without having symptoms following 14 days of isolation.
   aaa. The patients with positive test results for COVID-19 or who have symptoms should be directed to the authorized units for infection treatment at first. After COVID-19 treatment, re-evaluation should be made and a novel appointment for RNT have to be arranged.
5. A flow-chart similar to cancer cases should be followed in patients whose I-131 treatment is planned due to hyperthyroidism. Antithyroid treatment should continue until COVID-19 is identified as negative.
6. During treatment, COVID-19 positive and negative cases, and also personnel applying treatment should be followed the measures suggested for people at high transmission risk but no with cancer diagnosis, and hygiene rules (5,6,12).
7. Dose rate values of the patients regarding COVID-19 test positive soon after RNT should be recorded by the Radiation Protection Officer at the time of hospital discharge and the epicrisis related to treatment process should be given (22,23).
8. In case of deterioration in the general condition of these patients (use of a ventilator, intubation, hemodialysis) or death, relevant national and international guidelines should be consulted for measures and practices to be taken in terms of radiation safety and infection transmission (22,23,24,25,26.27,28).

E. Disinfection Procedures in Nuclear Medicine Departments

1. Visual materials such as brochures and in-hospital broadcasts may be used to promote hand washing and good respiratory hygiene measures in the department.
2. All gamma camera gantries and image monitoring station mouses and keyboards, sphygmomanometer cuffs, all surfaces (tables, seats, chairs and beds), should be wiped with disinfectant regularly and after each contact with suspicious patients.
3. Make sure disinfectant bottles in the work area are easy accesible and refilled regularly.
4. The risk encountered at the time of cleaning is not the same as contacting an infected patient who coughs or sneezes. However, cleaning personnel who makes clean all areas in the department during work and

out of working hours should be specifically trained for professional cleaning of potentially contaminated surfaces after high-risk patient contact (3,7). During cleaning time, cleaning personnel should;

a. Use proper PPE. Informations should be given on how to put on and take off this equipment and practical training should be done.
b. Informed about not touching their faces, especially mouth, nose and eyes.
c. Wear water-proof disposable gloves and use a surgical mask, eye protective or face shield, shoes cover.
d. Wear glasses instead of lenses (5).
e. Use alcohol-based hand disinfectants before and after wearing their gloves.
f. Use alcohol-based disinfectants with a virucidal effect before and after wearing surgical mask.
g. If there is a possibility of visible contamination with respiratory secretion or other body fluids; in addition to surgical masks and eye protection equipment, disposable protective clothing that covers the entire body should be worn prior to cleaning work.

Take-home Messages

- For outpatient cases, the imaging process should be carried out in accordance with hospital policy. If imaging is really necessary, special patient waiting rooms equipped with high-efficiency particulate air filters are recommended.
- An algorithm must be developed to ensure that probable cases are identified in a timely manner.
- All staff must receive appropriate training to ensure maximum compliance measures.
- Staff should be contacted and given the message that they should stay at home even in the presence of mild COVID-19 symptoms.
- In case of signs of illness suggesting COVID-19 or confirmed infection in your personnel, emergency and business continuous workflow plans should be adapted in order to prevent the disruption of function.

Conclusion

Although there are many issues raised for NM applications concerning the current COVID-19 outbreak, NM departments can make a significant contribution to reducing the effect of COVID-19 infection on patients and staff, if adequately prepared for PPE and disinfection procedures. The lessons learned from the current experience and the data obtained from the case groups will help to improve preparedness and address possible deficiencies in case of new outbreaks in the future.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.A., F.S.K., Design: F.S.K., A.A., Data Collection or Processing: A.A., F.S.K., Analysis or Interpretation: F.S.K., A.A., Literature Search: A.A., F.S.K., Writing: F.S.K., A.A.

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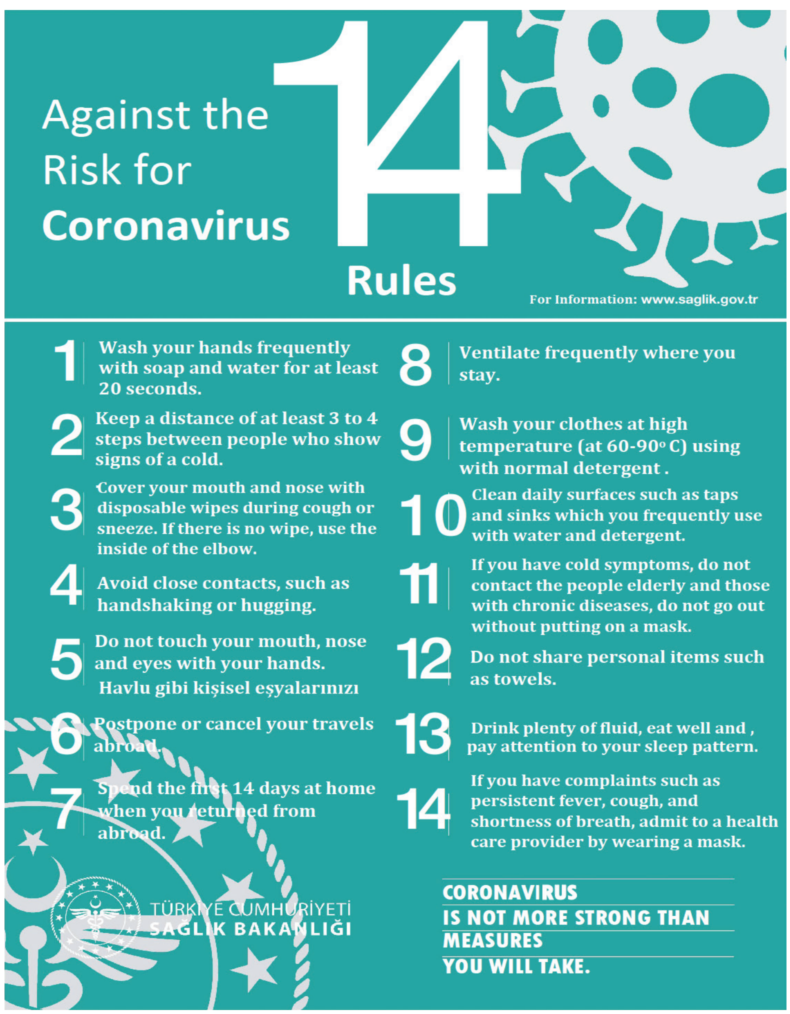
References

1. Huang HL, Allie R, Gnanasegaran G, Bomanji J. COVID19-Nuclear Medicine Departments, be prepared! Nucl Med Commun 2020;41:297-299.
2. www.saglik.gov.tr Date of access: March 21,2020.
3. Liang T, Handbook of COVID-19 Prevention and Treatment https://COVID-19.alibabacloud.com/Date of access: March 20, 2020.
4. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Reviw of Imaging Findings in 919 Patients. Am J Roentgenol 2020:1-7.
5. https://www.aao.org/eye-health/coronavirus Erişim T: 23 Mart 2020.
6. Bunyan D, Ritchie L, Jenkins D, Coia JE. Respiratory and facial protection: a critical review of recent literature. J Hosp Infect 2013;85:165-169.
7. Environmental cleaning and disinfection principles for COVID-19. Australian Government Department of Health Publications. 10.03.2020
8. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J 2020.
9. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy- implications of research advances for rheumatology care. Nat Rev Rheumatol 2018;14:693-703.
10. Jorge A, Melles RB, Zhang Y, Lu N, Rai SK, Young LH, Costenbader KH, Ramsey-Goldman R, Lim SS, Esdaile JM, Clarke AE, Urowitz MB, Askanase A, Aranow C, Petri M, Choi H. Hydroxychloroquine prescription trends and predictors for excess dosing per recent ophthalmology guidelines. Arthritis Res Ther 2018;20:133-140.
11. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents 2020:105938.
12. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020;295:210-217.
13. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19: An Update-Radiology Scientific Expert Panel. Radiology 2020:200527.
14. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, Allescia G, Tonelli L, Sostman HD, Giuntini C. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med 1996;154:1387-1393.
15. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B; EANM Committee. EANM guidelines for ventilation/perfusion scintigraphy Part

1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging 2009;36:1356-1370.
16. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P SPECT and MDCT. Eur J Nucl Med Mol Imaging 2009;36:1528-1538.
17. Qin C, Liu F, Yen TC, Lan X. 18F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. Eur J Nucl Med Mol Imaging. 2020,47:1281-1286.
18. Zou S, Zhu X. FDG PET/CT of COVID-19. Radiology 2020:200770.
19. Deng Y, Lei L, Chen Y, Zhang W. The potential added value of FDG PET/CT for COVID-19 pneumonia. Eur J Nucl Med Mol Imaging 2020.
20. Chen YH, Peng JS. Treatment strategy for gastrointestinal tumor under the outbreak of novel coronavirus pneumonia in China. Zhonghua Wei Chang Wai Ke Za Zhi 2020;23:1-6.
21. Xu Y, Liu H, Hu K, Wang M. Clinical Management of Lung Cancer Patients during the Outbreak of 2019 Novel Coronavirus Disease (COVID-19)]. Zhongguo Fei Ai Za Zhi 2020;23:136-141.
22. Ayan A, Dönmez S, Aras F, Günalp B, Kıraç S, Alıç Özaslan I, Değer M, Demir M, Ince M, Kovan B, Köseoğlu K, Poyraz L, Toklu T, Uysal B, Yeyin N. Radiation Safety Process in Case of Changing Medical Condition of Patients Who Received Radionuclide Therapy or Radioactive Substances: Emergency Medical Procedures. Nucl Med Semin 2016;3:168-171.
23. Kıraç FS, Ayan A. The Radiation Safety Process for Non-Radiation Workers in Case of Death of Radionuclide Therapy Patient. Nucl Med Semin 2019;5:165-168.
24. Ayan A, Dönmez S, Günalp B, Kıraç S, Aras A, Değer M, Demir M, İnce M, Kovan B, Köseoğlu K, Alıç Özaslan İ, Poyraz L, Toklu T, B Uysal B, Yeyin N. Radiation Safety Procedures For Non-Radiation Workers in Case of Application Radionuclide Therapy in the Dialysis Patients. Nucl Med Semin 2016;3:176-178.
25. Aras F, Kıraç S, Ayan A, Değer M, Demir M, Dönmez S, Günalp B, Ince M, Kovan B, Köseoğlu K, Alıç Özaslan İ, Poyraz L, Toklu T, Uysal B, Yeyin N. Radiation Safety Process for the Patient and People Around during Diagnostic Radionuclide Studies. Nucl Med Semin 2016;3:172-175.
26. Parthasarathy KL, Komerek M, Quain B, Bakshi SP, Qureshi F, Shimaoka K, Rao U, Adamski JS, Bender MA. Necropsy of a cadaver containing 50 mCi of sodium131 iodide. J Nucl Med 1982;23:777-780.
27. Woods CM, DePaolo F, Whitaker RD. Guidelines for Handling Decedents Contaminated with Radioactive Materials (HHS/CDC, April 2007). https://emergency.cdc.gov/radiation /pdf/radiation-decedent-guidelines.pdf. Date of access: Jan 21,2019.
28. Greaves C, Tindale W. Radioiodine therapy: care of the helpless patient and handling of the radioactive corpse. J Radiol Prot 2001;21:381-392.

Annex 1



Annex 2

REPUBLIC OF TURKEY
MINISTRY OF HEALTH

FOR OUTPATIENT CASES
PROBABLE COVID-19 CASE INQUIRY GUIDE

Triage is performed by a healthcare professional dressed in accordance with the COVID-19 case algorithm (apron, medical mask, face shield, or goggles)

Question		
Do you have a history of fever? Body temperature is measured if not known	◯ Yes	◯ No
Do you cough?	◯ Yes	◯ No
Do you have a difficulty in breathing or dispnea?	◯ Yes	◯ No

If the answer to any of the above questions is YES
PATIENT wears a MASK and is directed to the reserved area for COVID-19.

If the answer to any of the above questions is NO, following questions are asked to the PATIENT

Question		
Have you been abroad in the last 14 days?	◯ Yes	◯ No
Has someone in the home come from abroad abroad in the last 14 days	◯ Yes	◯ No
Any of your relatives was hospitalized due to respiratory disease in the last 14 days	◯ Yes	◯ No
Has anyone from your relatives been diagnosed with the COVID-19 disease in the last 14 days?	◯ Yes	◯ No

If the answer to any of the above questions is YES, PATIENT wears a MASK and is directed to the reserved area for COVID-19 because there is a risk of COVID-19.

If the answer to all of the above questions are NO, it is considered low risk in terms of COVID-19 and patient is directed to the relevant department for evaluation in the direction of his complaint.

Original Article
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The Predictive Value of Proportional Evaluation Based on the Metabolic Activity of Cervical Lymph Nodes on PET/CT Imaging in Patients with Larynx Cancer

Larinks Kanserli Hastalarda PET/BT Görüntülemede Servikal Lenf Nodlarının Metabolik Aktivitesine Dayanan Oransal Değerlendirmenin Prediktif Değeri

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Abstract

Objectives: We aimed to evaluate the proportional values of maximum standardized uptake value (SUV_{max}) for cervical lymph nodes on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for prediction of the presence of metastasis in patients with larynx squamous cell cancer (LSCC).

Methods: This retrospective study involved 43 patients with LSCC. All patients underwent resection of the primary tumor and neck dissection within 4 weeks after undergoing ^{18}F-FDG PET/CT examinations. Receiver operating characteristic (ROC) analysis was performed to evaluate the lymph node SUV_{max}/primary tumor SUV_{max} (SUV_{max}LN/SUV_{max}PT), lymph node SUV_{max}/aortic SUV_{max} (SUV_{max}LN/SUV_{max}A), and lymph node SUV_{max}/liver SUV_{max} (SUV_{max}LN/ SUV_{max}L) ratios for diagnosis of lymph node metastasis.

Results: SUV_{max}LN/SUV_{max}A, SUV_{max}LN/SUV_{max}L, and SUV_{max}LN/SUV_{max}PT rates were significantly higher in metastatic lymph nodes compared to non-metastatic nodes. ROC analysis for metastasis showed that the cut-off thresholds were 3.87 for SUV_{max}LN; 1.78 for SUV_{max}LN /SUV_{max}A; 1.08 for SUV_{max}LN/SUV_{max}L; and 0.36 for SUV_{max}LN/SUV_{max}PT. The diagnostic sensitivity, specificity and AUC were 83.7%, 77%, 0.856 for SUV_{max}LN; 79.7%, 84%, 1.78 for SUV_{max}LN/SUV_{max}A; 84.1%, 76%, 0.833 for SUV_{max}LN/SUV_{max}L; and 53.6%, 76%, 0.666 for SUV_{max}LN/SUV_{max}PT, respectively.

Conclusion: SUV_{max}LN/SUV_{max}A, SUV_{max}LN/SUV_{max}L, and SUV_{max}LN/SUV_{max}PT ratios can be safely used for diagnosis of cervical lymph node metastasis in patients with LSCC.

Keywords: Cervical lymph node, metabolic activity, larynx cancer, positron emission tomography/computed tomography

Öz

Amaç: ^{18}F-florodeoksiglikoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) servikal lenf nodlarının maksimum standardize uptake değerine (SUV_{maks}) dayalı oransal değerlerin skuamöz hücreli larenks kanserli (LSHK) hastalarda metastaz varlığını tahmin etmedeki gücünü değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif çalışmaya LSHK olan 43 hasta alındı. Tüm hastalara ^{18}F-FDG PET/BT görüntülemeden sonraki 4 hafta içinde primer tümör rezeksiyonu ve boyun diseksiyonu yapıldı. Metastatik lenf nodlarının tanısı açısından lenf nodu SUV_{maks}/primer tümör SUV_{maks} (SUV_{maks}LN/SUV_{maks}PT), lenf nodu SUV_{maks}/aortik SUV_{maks} (SUV_{maks}LN/SUV_{maks}A), lenf nodu SUV_{maks}/karaciğer SUV_{maks} (SUV_{maks}LN/SUV_{maks}L) oranları alıcı işletim karakteristiği (ROC) analizi yapılarak değerlendirildi.

Bulgular: SUV_{maks}LN/SUV_{maks}A, SUV_{maks}LN/SUV_{maks}L, SUV_{maks}LN/SUV_{maks}PT oranları metastatik lenf nodlarında metastatik olmayanlara göre anlamlı derecede yüksek idi. ROC analizinde metastaz tespiti açısından eşik değerler, SUVmaxLN için 3,87; SUV_{maks}LN/SUV_{maks}A için 1,78; SUV_{maks}LN/SUV_{maks}L için 1,08; SUV_{maks}LN/SUVmaxPT için 0,36 olarak bulundu. Tanısal duyarlılık, özgüllük ve AUC değerleri SUV_{maks}LN, SUV_{maks}LN/SUV_{maks}A, SUV_{maks}LN/SUV_{maks}L, SUV_{maks}LN/SUV_{maks}PT için sırasıyla %83,7, %77, 0,856; %79,7, %84, 1,78; %84,1, %76, 0,833; %53,6, %76, 0,666 idi.

Sonuç: SUV_{maks}LN/SUV_{maks}A, SUV_{maks}LN/SUV_{maks}L, SUV_{maks}LN/SUVmaksPT oranları, LSHK hastalarında metastatik servikal lenf nodlarının tanısında güvenle kullanılabilir.

Anahtar kelimeler: Servikal lenf nodu, metabolik aktivite, larenks kanseri, pozitron emisyon tomografisi/bilgisayarlı tomografi

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Introduction

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is being increasingly carried out to determine the stage and localization of metastatic disease in patients with larynx squamous cell cancer (LSCC). The correct diagnosis of metastatic cervical lymph nodes is important in terms of determining prognosis and providing adequate treatment. In clinical practice, CT and/or magnetic resonance imaging (MRI) are generally recommended for the assessment of tumor extension and cervical lymph node involvement (1).

Several studies in the literature reported that ^{18}F-FDG PET/CT had reliable diagnostic value for a depiction of lymph node metastasis of head and neck squamous cell (HNSCC) compared with conventional CT/MRI (2,3). Meta-analyses of ^{18}F-FDG PET/CT showed that the pooled per-patient, per-neck-side, and per-neck-level sensitivities/specificities were 0.91/0.87, 0.84/0.83, and 0.80/0.96, respectively. Across 13 studies (3460 neck levels) for which per-neck-level data were available, sensitivity and specificity were 0.84/0.96 respectively for ^{18}F-FDG PET/CT and 0.63/0.96 for conventional imaging (CT and MRI), respectively (4).

Cut-off value of 2.5 for the maximum standardized uptake value (SUV_{max}) is used commonly to differentiate between benign and malignant lesions on ^{18}F-FDG PET/CT imaging. But many biological and technical factors can affect SUV_{max} value, such as patient's weight, blood glucose level, postinjection uptake time, respiratory motion, tumor behavior, lesion size, motion artefacts, variability of the scanner, image-reconstruction parameters and contrast agent used (5,6). These factors may affect SUV values by 5% to 50% and cause false negativity or positivity (7).

In the literature, there are many studies on proportional values such as SUV_{max}LN/ SUV_{max}PT, SUV_{max}LN/SUV_{max}A, and SUV_{max}LN/SUV_{max}L for the prediction of metastatic lymph nodes in various malignancies, mainly lung cancer and breast cancer. However, the number of studies about LSCC is limited (8,9,10,11,12). In this study, we aimed to evaluate the proportional values of the SUV_{max} for cervical lymph nodes on ^{18}F-FDG PET/CT imaging for the prediction of the presence of metastasis in patients with LSCC.

Materials and Methods

This retrospective study involved 43 patients (42 men,1 woman; mean age=60.20±8.12 years, range=46-83) with LSCC.

The following criteria were defined for patient selection:

- Patients with diagnosis ofprimary LSCC made by a biopsy.

- Patients who did not undergo any treatment for LSCC before ^{18}F-FDG PET/CT imaging and had no secondary malignancy.

- Patients who did not undergo any diagnostic excisional or incisional cervical lymph node biopsy for metastasis evaluation before ^{18}F-FDG PET/CT imaging.

- Patients who underwent resection of the primary tumor and neck dissection within 4 weeks after undergoing ^{18}F-FDG PET/CT imaging.

^{18}F-FDG PET/CT imaging was performed at our institution between November 2013 and January 2018. Ethics Committee Approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with the decision number "1066" and date "12.04.2018". The written informed consent was obtained from all patients at the time of imaging.

^{18}F-FDG PET/CT studies were carried out using an integrated PET/CT scanner, which consisted of a full-ring HI-REZ LSO PET and a 6-slice CT (Siemens Biograph 6; Siemens, Chicago, USA). All patients were instructed to fast for at least 6 h before the ^{18}F-FDG injection. Blood glucose levels were measured before the study and the injection was given only when the blood glucose levels were below 11.11 mmol/L. The patients were injected with 370 to 555 MBq ^{18}F-FDG, according to body weight. After 60 minutes of waiting on a semireclined relaxed chair, the patients were imaged using an integrated PET/CT scanner. The CT portion of the study was performed without injection of intravenous contrast medium to define anatomical landmarks and attenuate correction on PET images. CT was acquired first with the following parameters: 50 mAs, 140 kV, and 5 mm section thickness. Whole-body CT was performed in a craniocaudal direction. PET images were acquired in a three-dimensional mode, from the vertex to mid-thigh, with six to eight bed positions of 3 min each, and PET data were collected in a caudocranial direction. Image reconstruction used "ordered subsets expectation maximization" algorithm of 2 iterations and 8 subsets. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany). ^{18}F-FDG PET/CT images were retrospectively interpreted by 3 experienced nuclear medicine physicians. The observers were blinded to the results of preoperative diagnostic imaging examinations such as MRI or ultrasonography and to the histopathological evidence of lymph node dissections. All cervical lymph nodes on CT which increased tracer uptake compared with background activity were accepted as metastatic. Semi-quantitative analysis of ^{18}FDG uptake was performed, through creation of a region of interest (ROI) over the primary lesion and lymph nodes. SUV_{max} was also determined by manually placing a cylindrical ROI over the arcus aorta and right lobe of the liver. Lymph node SUV_{max} values were divided by the SUV_{max} of the primary tumour, arcus aorta (mediastinal blood pool) and liver to calculate the following:

- Lymph node SUV_{max}/primary tumour SUV_{max} (SUV_{max}LN/SUV_{max}PT)
- Lymph node SUV_{max}/aortic SUV_{max} (SUV_{max}LN/SUV_{max}A)
- Lymph node SUV_{max}/Liver SUV_{max} (SUV_{max}LN/SUV_{max}L)

Operations were performed in our head and neck surgical clinic based on clinical and imaging findings. Modified radical neck dissection was performed in all patients. Lymph nodes and tumors were dissected from the specimens and stained with hematoxylin and eosin for histologic analysis. Serial histologic sections were used. We compared results of preoperative examinations using ^{18}F-FDG PET/CT with those of the corresponding histopathologic examinations. If one lymph node showed increased uptake on ^{18}F-FDG PET/CT images and had some findings on CT such as ≥10 mm diameter or round shape or hypoechogenicity or irregular margin or loss of fatty hilum findings and if histopathology showed lymph node with metastasis in the same neck level, this lymph node was accepted as a true positive finding for ^{18}F-FDG PET/CT. If metastatic lymph node number on histopathology was lower than lymph node numbers that were accepted as metastatic on ^{18}F-FDG PET/CT, the lymph node showing the lowest uptake was accepted as false positive. If metastatic lymph node number on histopathology was higher than lymph node number accepted as metastatic on ^{18}F-FDG PET/CT, it was recorded as false-negative lymph node for ^{18}F-FDG PET/CT.

Statistical Analysis

While evaluating the findings of the study, IBM SPSS Statistics 22 program (IBM SPSS, Turkey) was used for statistical analysis. The normal distribution of the parameters was evaluated by the Shapiro-Wilk test and it was found that the parameters did not show normal distribution. The Mann-Whitney U test was used to compare the parameters between the two groups. Receiver operating characteristic (ROC) curve analysis was performed to identify the best cut-off value and to evaluate whether SUV_{max}LN and also SUV_{max}LN/SUV_{max}PT, SUV_{max}LN/SUV_{max}A and SUV_{max}LN/SUV_{max}L ratios provided diagnosis of lymph node metastasis. For the calculation of sensitivity and specificity, the screening test was used. A p value <0.05 was accepted as statistically significant.

Results

Patients general characteristics are given in Table 1. Histopathological examination revealed 71 metastatic lymph nodes in 21 patients (mean=3.5; range=1-12). On ^{18}F-FDG PET/CT imaging, 68 lymph nodes showing

Table 1. General characteristics of patients

Total number of patients (n)	43
Laryngectomy	
-Partial	14
-Total	29
Neck dissection	
-Bilateral	39
-Unilateral	4
Histopathologic evaluation of lymph nodes	
-Metastatic	21
-Nonmetastatic	22

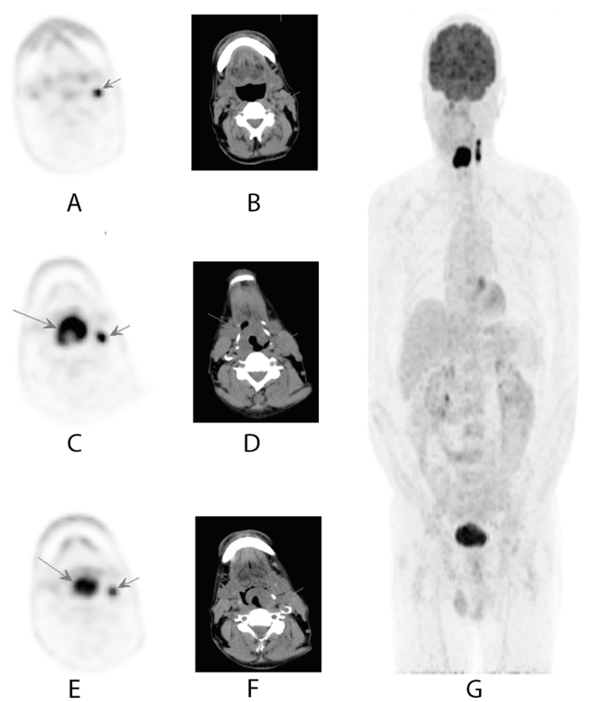

Figure 1. ^{18}F-FDG PET/CT with axial slice PET (A, C, E), axial slice CT (B, D, F) and whole-body PET (F) images of a 59-year-old patient with larynx squamous cell cancer. ^{18}F-FDG PET/CT imaging showed primary laryngeal hypermetabolic lesion and hypermetabolic lymph nodes at left upper and middle jugular region compatible with metastasis. He underwent total laryngectomy and left modified neck dissection. Histopathological examination revealed three metastatic lymph nodes

FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography

Table 2. Diagnostic performance of the quantitative metabolic parameters				
	Metastatic (n=69)	**Non-metastatic (n=25)**	**Total (n=94)**	**p**
	Avg ± SD (median)	**Avg ± SD (median)**	**Avg ± SD (median)**	
$SUV_{max}LN$	11.51±7.99 (10.14)	4.16±3.96 (3.25)	9.48±7.71 (5.87)	**0.000***
$SUV_{max}LN/SUV_{max}L$	2.77±1.73 (2.5)	1.21±1.03 (0.8)	2.35±1.72 (1.6)	**0.000***
$SUV_{max}LN/SUV_{max}A$	4.13±2.71 (3.5)	1.82±1.69 (1.2)	3.51±2.68 (2.3)	**0.000***
$SUV_{max}LN/SUV_{max}PT$	0.48±0.52 (0.4)	0.3±0.23 (0.2)	0.43±0.47 (0.3)	**0.014***

*p<0.04, Avg: Average, SD: Standard deviation, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, A: Aortic, L: Liver, PT: Primary tumor

increased FDG uptake were evaluated by histopathological examination and metastasis was detected (Figure 1), but the histopathological examination of 26 lymph nodes showing ^{18}F-FDG involvement showed no metastasis. There was no pathological involvement on ^{18}F-FDG PET/CT in 3 lymph nodes with metastasis in 1 patient.

In patients with metastatic lymph nodes, the primary tumor SUV_{max} values were significantly higher than non-metastatic patients (26.76±10.43 vs 17.73±8.14; p=0.001). Mean $SUV_{max}LN$, $SUV_{max}LN/SUV_{max}L$ ratio, $SUV_{max}LN/SUV_{max}A$ ratio, and $SUV_{max}LN/ SUV_{max}PT$ ratio were significantly higher in patients with metastatic lymph nodes than non-metastatic nodes (Table 2).

For diagnosis of lymph node metastasis with ROC analysis, the cut-off point for $SUV_{max}LN$ was 3.87 (AUC 0.856, p: 0.000) with the sensitivity of 83.7%, specificity 77%, positive predictive value (PPV) 89.1% and negative predictive value (NPV) 58% (Figure 2). The cut-off point for $SUV_{max}LN/SUV_{max}L$ was 1.08 (AUC 0.833, p=0.000), with a sensitivity of 84.1%, specificity of 76%, PPV 90.6%, and NPV 63.3% (Figure 3). The cut-off point for $SUV_{max}LN/SUV_{max}A$ was 1.78 (AUC 0.822, p=0.000) for the diagnosis of lymph node metastasis. The sensitivity of this value was 79.7%, specificity was 84%, PPV was 93.2%, and NPV was 60% (Figure 4). The cut-off point for $SUV_{max}LN/SUV_{max}PT$ was 0.36 (AUC 0.666, p: 0.014) for the diagnosis of lymph node metastasis, with a sensitivity of 53.6%, specificity 76%, PPV 86.1%, and NPV 37.3% (Figure 5). When $SUV_{max}LN$ >2.5 was taken as a criterion for the detection of metastatic lymph nodes, the sensitivity was 95.7%, the specificity was 26.9%, PPV was 78%, and NPV was 70%.

Discussion

Quantitative data obtained using ^{18}F-FDG PET/CT can be useful for lymph node assessment in addition to visual evaluation. In general practice, if a lymph node shows ^{18}F-FDG uptake and SUV_{max} value is more than 2.5, it is more

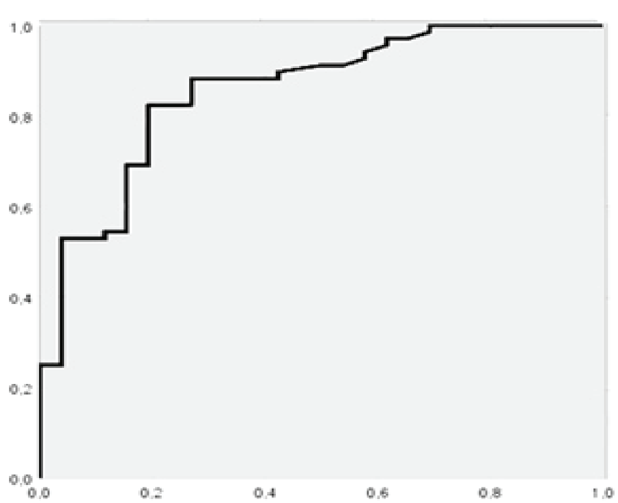

Figure 2. ROC curve for $SUV_{max}LN$ in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node

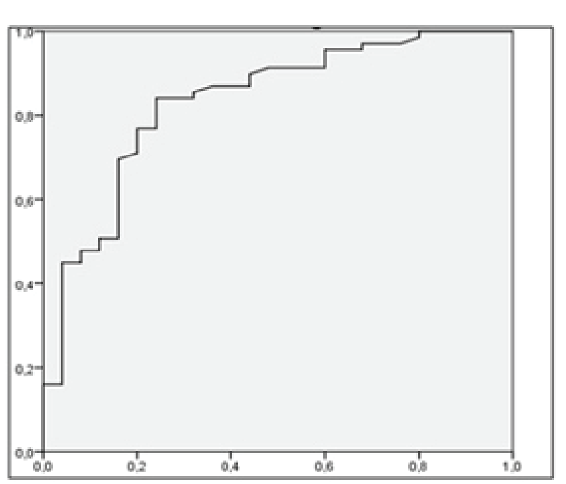

Figure 3. ROC curve for $SUV_{max}LN/SUV_{max}L$ in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, L: Liver

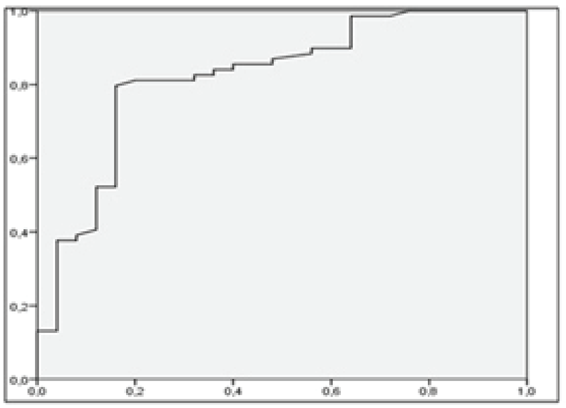

Figure 4. ROC curve for $SUV_{max}LN/SUV_{max}A$ in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, A: Aortic

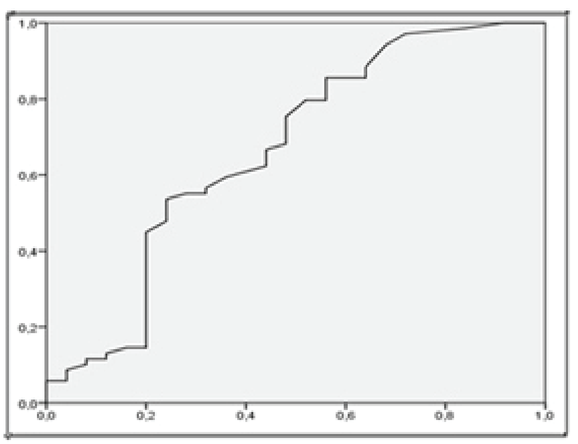

Figure 5. ROC curve for SUVmaxLN/SUVmaxPT in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUVmax: Maximum standardized uptake value, LN: Lymph node, PT: Primary tumor

likely to be malignant (13). But, SUV_{max} value does not have sufficient diagnostic capability to detect metastatic lymph nodes in head and neck cancer. In our study, if SUV_{max} >2.5 was taken as the criterion for detection of metastatic lymph node, the sensitivity would be 95.7% and the specificity would be 26.9%. To increase diagnostic accuracy for detecting metastatic lymph nodes, different lymph node SUVmax cut-off value and proportional ratios reproduced from lymph node SUVmax are used (12,14,15,16,17).

In our study, the mean SUV_{max} values, $SUV_{max}LN/SUV_{max}L$ ratio, $SUV_{max}LN/ SUV_{max}A$ ratio, and $SUV_{max}LN/SUV_{max}PT$ ratio of metastatic lymph nodes were significantly higher than non-metastatic lymph nodes. In the ROC analysis, the cut-off point for $SUV_{max}LN$ was 3.87 for the diagnosis of lymph node metastasis, with a sensitivity of 83.7% and specificity of 77%. A study by Marshall et al. (16) included 114 patients with head and neck cancer and found that SUV_{max} cut-off was 3.9 and that yielded a sensitivity of 85% and specificity of 73%. Suenaga et al. (17) used a SUV_{max} cut-off value of 3.65 and found that sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT on a level by level basis were 72.9, 96.8, and 92.1%, while sensitivity, specificity, and accuracy of CT were 52.9, 98.6, and 89.6%, respectively (17).

In our study, cut-off values for $SUV_{max}LN/SUV_{max}L$ and $SUV_{max}LN/ SUV_{max}A$ were 1.08 and 1.78, respectively. The sensitivity and specificity for these cut-off values were 84.1%-76% and 79.7%-84%, respectively. These proportional values were proven to have higher AUC compared to $SUV_{max}LN/SUV_{max}PT$ ratio and have high diagnostic power for the diagnosis of metastatic lymph node. We think that this situation is due to the variance in SUV_{max} of the primary tumor due to the size or histopathological features of the tumor. The specificity of all 3 proportional values we examined in our patient group was higher when SUV_{max} >2.5 criterion was used. Lim et al. (12) studied 74 patients with HNSCC and found that nodal SUV_{max} ≥3.16 yielded a sensitivity of 74.4% and specificity of 84.9% in detecting metastatic nodes and also that nodal $SUV_{max}LN/SUV_{max}L$ ratio ≥0.90 yielded a sensitivity of 74.1% and specificity of 93.4%.

Study Limitations

There are some limitations of the present study. It was a retrospective study with a limited number of patients. As the study was retrospective, there were technical impediments to the matching of the lymph nodes detected on ^{18}F-FDG PET/CT imaging and histopathological examination. Because the precise spatial correlation between ^{18}F-FDG PET/CT and histopathology was impossible and one to one matching between them showed increased uptake on ^{18}F-FDG PET/CT and metastatic lymph nodes on histopathologic evaluation could not be attributed due to the retrospective study design; analysis of results of the study should use this model. Therefore, there is a need for prospective studies with larger samples.

Conclusion

$SUV_{max}LN/SUV_{max}A$, $SUV_{max}LN/SUV_{max}L$, and $SUV_{max}LN/ SUV_{max}PT$ ratios can be used safely for diagnostic evaluation of metastasis in cervical lymph nodes on ^{18}F-FDG PET/CT imaging in patients with LSCC.

Ethics

Ethics Committee Approval: Ethics Committee Approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with the decision number "1066" and date "12.04.2018".

Informed Consent: The written informed consent was obtained from all patients at the time of imaging.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Ü., Y.A., Y.U., Concept: S.S.K., S.K., O.G., Design: S.S.K., S.K., O.G., Data Collection or Processing: S.S.K., S.K., O.G., O.Ü., Y.A., Y.U., Analysis or Interpretation: S.S.K., S.K., O.G., Literature Search: S.S.K., S.K., O.G., Writing: S.S.K., S.K., O.G.

References

1. Steuer CE, El-Deiry M, Parks JR, Higgins KA, Saba NF. An Update on Larynx cancer. CA Cancer J Clin 2017;67:31-50.
2. Kim SY, Kim JS, Doo H, Lee H, Lee JH, Cho KJ, Choi SE, Nam SY, Roh JL. Combined [18F] fluorodeoxyglucose positron emission tomography and computed tomography for detecting contralateral neck metastases in patients with head and neck squamous cell carcinoma. Oral Oncol 2011;47:376-380.
3. Ceylan Y, Ömür Ö, Hatipoğlu F. Contribution of ^{18}F-FDG PET/CT to staging of Head and Neck Malignancies. Mol Imaging Radionucl Ther 2018;27:19-24.
4. Sun R, Tang X, Yang Y, Zhang C. ^{18}F-FDG PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis. Oral Oncol 2015;51:314-320.
5. Adams MC, Turkington TG, Wilson JM, Wong TZ. A systematic review of the factors affecting accuracy of SUV measurements. Am J Roentgenol 2010;195:310-320.
6. Boellaard R. Standards for PET image acquisition and quantitative data analysis. J Nucl Med 2009;50(Suppl 1):11-20.
7. Weiss GJ, Korn LR. Interpretation of PET Scans: Do Not Take SUVs at Face Value. J Thoracic Oncol 2012;7:1744-1746.
8. Mattes MD, Moshcinsky AB, Ahsanuddin S, Rizk NP, Foster A, Wu AJ, Ashamalla H, Weber WA, Rimner A. Ratio of Lymph Node to Primary Tumor SUV on PET/CT Accurately Predicts Nodal Malignancy in Non-Small Cell Lung Cancer. Clin Lung Cancer 2015;16:253-258.
9. Lee AY, Choi SC, Jung KP, Park JS, Lee SM, Bae SK. Characteristics of Metastatic Mediastinal Lymph Nodes of Non-Small Cell Lung Cancer on Preoperative F-18 FDG PET/CT. Nucl Med Mol Imaging 2014;48:41-46.
10. Sun YW, Choi YC, Song Y. Prediction of Axillary Nodal Status according to the Axillary Lymph Node to Primary Breast Tumor Maximum Standardized Uptake Value Ratio on ^{18}F-fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography. J Breast Dis 2016;4:92-99.
11. Gedik GC, Kara PO, Kara T, Sari O, Kara F. Evaluation of FDG uptake in pulmonary hila with FDG PET/CT and contrast-enhanced CT in patients with thoracic and non-thoracic tumors. Ann Nucl Med 2010;24:593-599.
12. Lim RSM, Ramdave S, Beech S, Billah B, Karim MN, Smith JA, Safdar A, Sigston E. Utility of SUVmax on ^{18}F-FDG PET in detecting cervical nodal metastases. Cancer Imaging 2016;16:39-47.
13. Plaxton NA, Brandon DC, Corey AS, Harrison CE, Karagulle Kendi AT, Halkar RK, Barron BJ. Characteristics and Limitations of ^{18}F-FDG PET/CT for Imaging of Squamous Cell Carcinoma of the Head and Neck: A Comprehensive Review of Anatomy, Metastatic Pathways, and Image Findings. AJR Am J Roentgenol 2015;205:519-531.
14. Matsubara R, Kawano S, Chikui T, Kiyosue T, Goto Y, Hirano M, Jinno T, Nagata T, Oobu K, Abe K, Nakamura S. Clinical significance of combined assessment of the maximum standardized uptake value of ^{18}F-FDG PET with nodal size in the diagnosis of cervical lymph node metastasis of oral squamous cell carcinoma. Acad Radiol 2012;19:708-717.
15. Murakami R, Uozumi H, Hirai T, Nishimura R, Shiraishi S, Ota K, Murakami D, Tomiguchi S, Oya N, Katsuragawa S, Yamashita Y. Impact of ^{18}F-FDG PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2007;68:377-382.
16. Marshall RA, Som PD, Uliel L, Buckstein M, Gupta V, Miles B, Gandikota N, Corcuera-Solano I, Misiukiewicz K, Sikora AG, Kostakoglu L. Combined Evaluation of ^{18}F-FDG PET/CT and CT Imaging Characteristics of Cervical Lymph Nodes to Increase the Interpretation Accuracy for Nodal Metastatic Involvement in Head and Neck Cancer. Otolaryngol (Sunnyvale) 2015;5:213.
17. Suenaga Y, Kitajima K, Kanda T, Otsuki N, Nibu K, Sasaki R, Itoh T, Sugimura K. ^{18}F-FDG PET/CT imaging for detection of nodal metastases in patients with squamous cell carcinoma of the pharynx and larynx: comparison with CT. Jpn J Radiol 2016;34:203-210.

Original Article
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The Impact of Primary Tumor and Locoregional Metastatic Lymph Node SUV_{max} on Predicting Survival in Patients with Rectal Cancer

Rektal Kanserli Hastalarda Primer Tümör ve Lokorejyonel Metastatik Lenf Nodu SUV_{maks}'ın Sağkalım Üzerine Belirleyici Etkisi

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Abstract

Objectives: The aim of this study was to evaluate the impact of maximum standard uptake value (SUV_{max}) of the primary tumor and locoregional metastatic lymph node in predicting survival in patients with the preoperative rectal adenocarcinoma.

Methods: One hundred and fifteen patients [mean age ± standard deviation (SD): 58.7±11.4 years] with biopsy-proven rectal adenocarcinoma underwent ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging for the staging were included in this study. All patients were followed-up for a minimum of 12 months (mean ± SD: 29.7±13.5 months). Tumor-node-metastasis 2017 clinical staging, SUV_{max} of the primary rectal tumor and locoregional lymph nodes on the PET/CT studies were evaluated.

Results: All patients had increased FDG activity of the primary tumor. The mean ± SD SUV_{max} of the primary tumor and locoregional metastatic lymph node were 21.0±9.1 and 4.6±2.8, respectively. Primary tumor SUV_{max} did not have an effect on predicting survival (p=0.525) however locoregional metastatic lymph node SUV_{max} had an effect ($p<0.05$) on predicting survival. Clinical stage of the disease was a factor predicting survival ($p<0.001$).

Conclusion: ^{18}F-FDG PET/CT is an effective imaging modality for detecting primary tumors and metastases in rectal adenocarcinoma and clinical stage assessment with PET/CT had an effect on predicting survival. Furthermore, in our study locoregional lymph node SUV_{max} was defined as a factor in predicting survival.

Keywords: Rectal adenocarcinoma, ^{18}F-FDG PET/CT, staging, SUV_{max}, prognosis

Öz

Amaç: Çalışmamızın amacı preoperatif rektum adenokanserli olan hastalarda sağkalımı öngörmede primer tümör ve lokorejyonel metastatik lenf nodu maksimum standart alım değeri (SUV_{maks}) değerinin etkinliğini değerlendirmektir.

Yöntem: Bu çalışmaya, biyopsiyle kanıtlanmış rektal adenokarsinoma ile evreleme amaçlı ^{18}F-florodeoksiglikoz (FDG) pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) görüntüleme yapılan 115 hasta [ortalama yaş ± standart sapma (SS): 58,7±11,4 yıl] dahil edildi. Tüm hastalar en az 12 ay (ortalama ± SS: 29,7±13,5 ay) takip edildi. Tümör-nodül-metastaz 2017 klinik evreleme, primer rektal tümör SUV_{maks} ve lokorejyonel lenf nodu SUV_{maks}değerlendirildi.

Bulgular: Tüm hastalarda primer tümöre ait artmış FDG tutulumu saptandı. Primer tümör ve lokorejyonel metastatik lenf nodu ortalama SUV_{maks}'ları sırasıyla 21,0±9,1 ve 4,6±2,8 idi. Primer tümör SUV_{maks}'ın sağkalımı öngörmede bir etkisi saptanmamış olup (p=0,525) lokorejyonel metastatik lenf nodu SUV_{maks}'ın sağkalımı öngörmede etkisi saptandı ($p<0,05$). Hastalığın klinik evresi sağkalımı öngören bir faktördü ($p<0,001$).

Sonuç: ^{18}F-FDG PET/BT rektum kanserinde primer tümör ve metastazlarının saptanmasında etkili bir görüntüleme yöntemi olup lokorejyonel lenf nodu SUV_{maks} değerlerinin prognostik değerinin bulunduğu ve rektum kanserinin tedavi öncesi preoperatif evrelemede hastaların tedavi yönetimine önemli katkılar sağlayacağı düşünülmüştür.

Anahtar kelimeler: Rektum kanseri, ^{18}F-FDG PET/BT, evreleme, SUV_{maks}, prognoz

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Introduction

Colorectal cancer is the third most common cancer in men and the second most common in women (1). Furthermore, it is one of the most important causes of cancer-related morbidity and mortality, globally (2). The primary treatment is surgical resection of the primary tumor and coupled with a (neo) adjuvant therapy increases the rates of survival of colorectal carcinoma (3). The importance of clinical staging with positron emission tomography/computed tomography (PET/CT) is established (4), the effect of the maximum standard uptake value (SUV_{max}) acquired with ^{18}F-fluorodeoxyglucose (FDG) PET/CT on survival in initial staging has been evaluated by several studies. Primary tumor SUV_{max} is related to survival in some studies (5,6) however, some authors reported that primary tumor SUV_{max} was not associated with survival (7). On the other hand, the effect of metastatic locoregional lymph node FDG uptake level on survival has not been sufficiently studied. The aim of this study was to analyze the effect of the primary tumor and locoregional metastatic lymph node SUV_{max} and stage of disease detected with ^{18}F-FDG PET/CT on the survival of patients with rectal adenocarcinoma.

Materials and Methods

The study was approved by the Local Ethics Committee of İstanbul University İstanbul Medical Faculty of (2015/1867). The patients with histologically proven rectal adenocarcinoma who underwent FDG-PET/CT staging were assessed retrospectively. Clinical follow-up was performed until September 2015.

Localization of tumor was categorized as upper, mid rectal and distal rectal. Clinical staging was achieved using tumor-node-metastasis (TNM) staging provided by the American Joint Committee on Cancer Colon and Rectum Cancer Staging 8th Edition after assessing pathology reports, CT and PET/CT images.

PET/CT Protocol

Patient Preparation

Patients with blood glucose levels lower than 200 mg/dL after at least 6 h of fasting were admitted for the procedure. Patients received an intravenous injection of 5.4 MBq/kg ^{18}F-FDG and then rested for approximately 60 min before undergoing imaging. Patients were instructed to discontinue oral antidiabetic 'metformin' use 3 days before PET/CT imaging. Long-acting insulin treatment was allowed 12 hours before ^{18}F-FDG injection. Patients were administered oral contrast media 12 hours before imaging. All of the patients were instructed to refrain any muscular activity to avoid muscle uptake during the distribution phase of injected ^{18}F-FDG.

PET/CT Imaging

PET/CT scan was performed using a Biograph 6 True Point HD LSO (Siemens Healthcare, Molecular Imaging, Knoxville, Tennessee, USA) integrated device. Initially, a CT scan (130-136 keV; 60-90 mAs) from vertex to upper thighs was performed in a single step which was used for attenuation correction of PET/CT images. The PET images were iteratively reconstructed with 5 mm thickness (TrueX option, subsets=21, iterations=3). A PET emission scan was acquired using whole-body mode following the CT scan. Six to 9 bed positions were used with an acquisition time of 3 minutes for each bed position. Additional imaging of the lower extremities was carried out in patients with multiple metastases. The PET data were reconstructed using 3D PET reconstruction with a system matrix derived from point source measurements.

Image Analysis

All images were examined on an LCD monitor as attenuation-corrected and uncorrected multiplanar PET, CT and PET/CT fusion cross-sections (maximum intensity projection) using the eSOFT software. ^{18}F-FDG-PET/CT studies were reviewed for abnormally increased tracer uptake foci by a nuclear medicine physician with minimum 5 years of experience. Each focal uptake identified in PET images was correlated in the corresponding CT sections and a PET/CT scan was considered to be positive if one or more areas of abnormal ^{18}F-FDG uptake were noted with a corresponding abnormality in CT. Furthermore, focally increased ^{18}F-FDG accumulations of lymph nodes higher than the background activity, a short axis of 6 mm or larger, round shaped and fatty hilum loss were considered as pathological lymph nodes. Pathological FDG uptake in the liver was assumed as metastasis. The quantification was made by calculating the SUV that was used as a relative measure of ^{18}F-FDG uptake. The simple expression for SUV was the ratio of tracer activity concentration (C) in the region of interest and the decay-corrected amount of injected activity (kBq) per weight of the patient (gr): SUV=C (kBq/mL)/[injection activity (kBq)/patient's weight (g)].

Histopathological Analysis

All patients had primary tumor resection and lymph node dissection. Besides primary tumor and lymph nodes pathology, largest tumor diameter, venous invasion, angiolymphatic invasion, perineural invasion, surgical margins, and K-ras mutation status were evaluated in the pathology department.

Statistical Analysis

The normality of the data distribution was assessed with the Shapiro-Wilk test. Non-parametric data were presented as median and minimum-maximum ranges, while parametric data as means ± standard deviation (SD). Nominal and categorical variables were presented as frequencies and percentages. The parametric distribution was compared with the Student t-test in independent groups, and with the Mann-Whitney U test in the rest. Survival was evaluated by the Kaplan-Meier method. Categorical variables were evaluated with chi-square and Fisher's Exact Contingency tests. The tests were two-sided. $p<0.05$ was accepted as significant. Statistical analysis was performed with SPSS statistical software, version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The receiver operating characteristics (ROC) was applied to determine the threshold value for the optimal inventory SUV_{max}. Sensitivity, specificity, positive-negative predictive values and accuracy rates were calculated for different threshold values.

Results

We reviewed data of 115 patients that underwent ^{18}F-FDG PET/CT for initial staging. Thirty nine (34%) patients were female and 76 (66%) patients were male. The mean ± SD of patients was 58.7±11.4 (range=31-82 y). All patients underwent surgery and their histopathologic diagnosis was rectal adenocarcinoma. According to TNM, 66 patients had pN stage 0, 37 had pN stage 1 and 20 had pN stage 2 disease. Eleven patients had stage 1, 42 had stage 2, 39 had stage 3 disease and 23 had metastatic disease in initial staging (Table 1) (8). Subsequent to initial ^{18}F-FDG PET/CT scan, all patients were followed-up for a 12-75 (29.7) months period and the estimated 5-year survival was found to be 61.8 ±2.9 months (Figure 1). Increased pathological ^{18}F-FDG uptake in primary tumor was observed on PET/CT in all patients. The mean ± SD SUV_{max} of the primary tumor was 21.0±9.1 (7.6-55). There was no significant relation between primary tumor SUV_{max} and disease-free survival (DFS) or primary tumor SUV_{max} and overall survival (OS) (p=0.760 and p=0.525) (Table 2).

Fifty eight out of 115 patients (50.4%) had locoregional lymph node with increased ^{18}F-FDG uptake in initial PET/CT. Histologically proven metastatic LNs were found in 39 out of 115 patients (33.9%). Thirty of the PET/CT findings were true positive, 28 false positive, 48 true negative and 9 false negative. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{18}F-FDG PET/CT were 76.9%, 63.1%, 51.7%, 84.2% and 67.8%, respectively.

The mean ± SD SUV_{max} of metastatic lymph nodes were 4.6±2.8 (1.7-14.9). There was a significant correlation between locoregional metastatic lymph node SUV_{max} and DFS or OS (p=0.049 and p=0.045, respectively). Also in accordance with the ROC curve (Figure 2) when the cut-off point for the lymph node SUV_{max} was taken as 3.55; the sensitivity and specificity were 66.7% and 54.5% for DFS, 72.7% and 54.2% for OS, respectively. Metastatic lymph node SUV_{max} was higher in the patient group who died compared with the individuals who survived [5.8 (2.5-14.9) vs 3.5 (1.7-12.0)].

The lymph node SUV_{max} was higher in the patients as the stage of the disease increased and it was found to be statistically significant (p=0.002). The mean ± SD SUV_{max} of the metastatic lymph nodes was 2.5±0.6 for stage 1, 3.2±1.8 for stage 2, 4.7±2.0 for stage 3 and 6.7±3.9 for stage 4.

K-ras mutation was assessed in 22 patients and 11 of patients had K-ras mutation (50%). There was no association between K-ras mutation and the primary tumor SUV_{max} or metastatic tumor SUV_{max} (p=0.358 and p=0.643, respectively). There was no correlation between tumor localization, angiolymphatic invasion, perineural invasion of the primary tumor and DFS or OS (p>0.05). A higher maximum diameter of the primary tumor and the number of metastatic lymph node or positive venous invasion of tumor predicted worse DFS in patients (p=0.012, p=0.03, p=0.024, respectively).

Table 1. Patient characteristics

Characteristics	**All patients n=115 (%)**
Sex	
Female	39 (33.9)
Male	76 (66.1)
Age (years)	58.7±11.4
Histopathologic tumor type	
Adenocarcinoma	115 (100)
TNM stage, AJCC*	
1	11 (9.5)
2	42 (36.5)
3	39 (34.0)
4	23 (20.0)
pT stage, AJCC*	
2	22 (19.1)
3	76 (66.1)
4	17 (14.8)
pN stage, AJCC*	
0	66 (57.4)
1	37 (32.2)
2	12 (10.4)

*AJCC: American Joint Committee on Cancer 8th edition, TNM: Tumor-node-metastasis

N-stage was determined to be significant on DFS and OS (p=0.001, p=0.021, respectively). According to TNM stage, 23 patients had metastases (17 liver, 10 thorax, 11 non-regional lymph nodes, 3 peritoneum and 1 bone metastases) at diagnosis. Metastatic disease had predictive value on both DFS and OS (p<0.001).

Discussion

Rectal cancer is a common malignancy and a common cause of mortality; thus, accurate staging of rectal cancer is extremely important in determining the prognosis of the disease and the treatment protocol (9). The overall predicted 5-year survival rate after diagnosis is less than 60% but it is significantly dependent on disease stage (10).

One of the most used techniques to detect prognosis in clinical practice is ^{18}F-FDG PET/CT (11); providing a semi-quantitative measure of the metabolism of the tumoral lesion that is a comparative rate of tumoral proliferation (12). In patients with lung cancer and esophageal cancer, the SUV_{max} is a predictive value for survival. Primary tumor ^{18}F-FDG uptake in non-small cell lung cancer was demonstrated to be the most potent prognostic factor in the curative treatment patient group (13). As the same, the initial ^{18}F-FDG uptake was predictive of survival in esophageal cancer (14). In the light of this data, primary tumor SUV_{max} of rectal cancer for predicting survival has been investigated in previous studies and SUV_{max} has been asserted as a prognostic factor (15). However, in a study to assess the prognostic value of preoperative

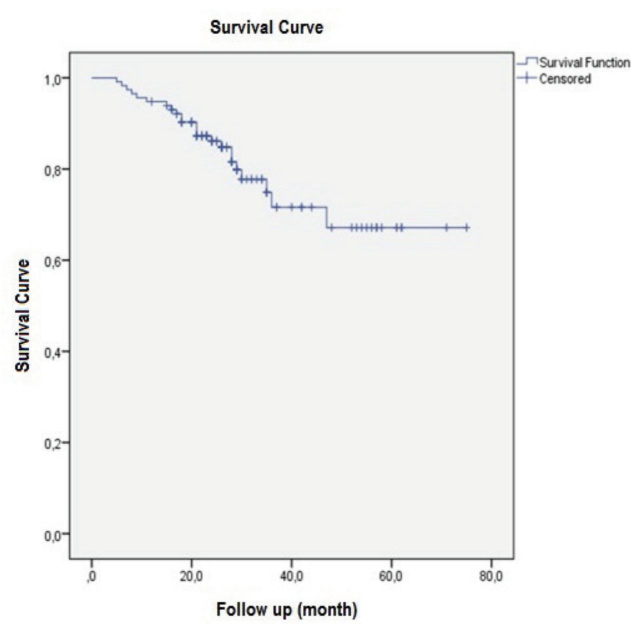

Figure 1. Kaplan-Meier survival analysis of all patients

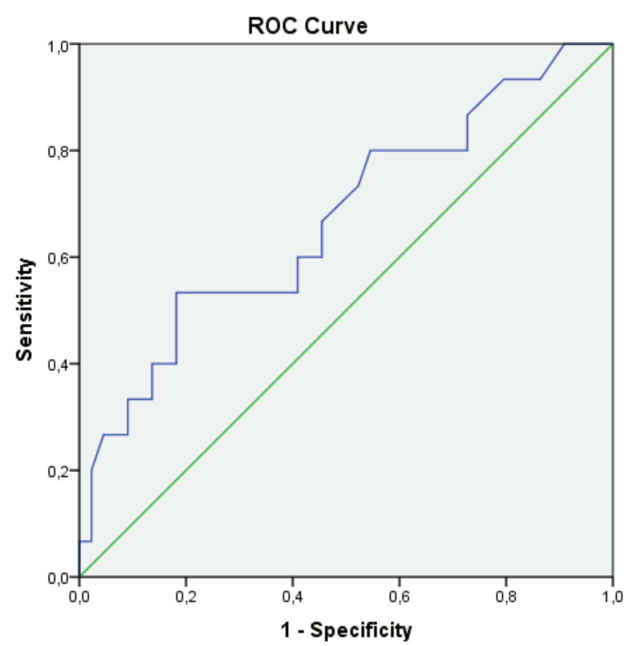

Figure 2. ROC analysis of lymph node SUV_{max} (blue) with DFS
ROC: Receiver operating characteristic, SUV_{max}: Maximum standard uptake value, DFS: Disease-free survival

Table 2. Correlation between histopathological features, SUV_{max} values and survival rates

	Values	p value for DFS and OS, respectively
Primary tumor SUV_{max} (mean ± SD)	21.0±9.1 (7.6-55)	p=0.760, p=0.525
Lymph node SUV_{max} (mean ± SD)	4.6±2.8 (1.7-14.9)	**p=0.049, p=0.045**
Maximum diameter of the primary tumor (mm)	36.9±16 (15-82)	**p=0.012**, p=0.092
Number of metastatic lymph nodes	1.21±2.5 (0-16)	**p=0.030**, p=0.605
Positive perineural invasion (%)	50	p=0.765
Positive angiolymphatic invasion (%)	78	p=0.292
Positive venous invasion (%)	33	**p=0.024**
Positive K-ras mutation	50	p=1

SUV_{max}: Maximum standard uptake value, SD: Standard deviation, DFS: Disease-free survival, OS: Overall survival

^{18}F-FDG PET/CT, Lee et al. (16) detected that SUV_{max} was not a significant predictor of recurrence or DFS. In a rectal cancer patient group that received neoadjuvant radiation therapy, Oku et al. (17) found that pretreatment ^{18}F-FDG PET/CT SUV_{mean} was unrelated to disease recurrence or response to therapy. In the study by Bang et al. (18), SUV_{mean}, SUV_{peak}, and SUV_{max} were not associated with recurrence or neoadjuvant radiation and chemotherapy in locally advanced rectal cancer. In a study of 100 patients by Deantonio et al. (7); higher level of metabolic parameters was significantly associated with higher clinical tumor stage that was considered as more aggressive, but none of the analyzed metabolic parameters had any significant correlation with DFS or OS. In a study conducted by Ogawa et al. (19); it was shown that OS did not differ significantly between low and high SUV_{max} and SUV_{mean} groups. On the other hand, Dehdashti et al. (20) found that high ^{18}F-FDG uptake (≥14.3) on initial PET/CT correlated with better DFS and better neoadjuvant therapy response, and so on better outcomes contrary to prior studies. Regarding the patient results in our study, increased FDG uptake of the primary tumor was shown in all patients. As the preoperative ^{18}F-FDG PET/CT parameters could be able to predict survival outcomes in rectal cancer, we evaluated the impact of primary tumor SUV_{max} on survival and it was shown that there was no correlation between primary tumor SUV_{max} and survival.

^{18}F-FDG PET/CT is not widely used in routine practice, but is a useful test for the detection of metastatic lymph nodes and distant metastasis (21). As is well known, one of the most important prognostic factors in rectal cancer is lymph node metastasis (22) and correct diagnosis of lymph node metastasis in staging might improve the therapy (23). Bae et al. (24) evaluated the diagnostic accuracy of ^{18}F-FDG PET/CT in diagnosis of lymph nodes in patients with rectal cancer with optimal SUV_{max} cut-off values according to lymph node size. It was shown that lower cut-off SUV_{max} improved the diagnostic performance of ^{18}F-FDG PET/CT, especially in small lymph node evaluation. In our study, lymph node size was not considered in determining optimal SUV_{max} cut-off values but the lymph node metastasis revealed by ^{18}F-FDG PET/CT was always confirmed histologically and the optimal cut-off values of the SUV_{max} were calculated using ROC analysis. As we took a cut-off SUV_{max} lymph node value of 2.5 in the ROC analysis regarding DFS (area under the curve 0.671; p=0.049; 95% CI: 0.506-0.836; Figure 2), the sensitivity and specificity at this value were 80.0% and 45.5%, respectively. Chen et al. (25) identified a cut-off SUV value of 1.15 in the ROC analysis regarding DFS and the sensitivity and specificity at that value were 84.2% and 59.2%, respectively, pointing out similar sensitivity but slightly higher specificity than the results of our study.

The other significant finding in our study was that the high SUV_{max} of the lymph nodes was predictive of low survival. In this respect, prior literature studies have put forward several and conflicting data about the relationship between survival and PET parameters such as primary tumor SUV_{max}, MTV and post-treatment metabolic changes (7,18,26,27) Chen et al. (25) showed that preoperative SUV lymph node measured on ^{18}F-FDG PET/CT could predict the recurrence in patients with colorectal carcinoma. In our study, we assessed only the patients with rectal carcinoma. Furthermore, in addition to DFS, OS was evaluated, as well. The higher level of lymph node SUV_{max} in preoperative ^{18}F-FGD PET/CT was significantly related to the more advanced clinical stage of the disease that was associated with more aggressive disease and poor survival outcomes. Morphological criteria such as lymph node size and number, which were higher in advanced stages, were considerable in this issue due to partial volume effect in small lymph nodes <10 mm in size leading to underestimation of true SUV (28).

Bang et al. (18) showed that lymphatic and venous involvements were not significantly associated with 3-year DFS, whereas in our study positive venous invasion had a prognostic impact (worse DFS). Chen et al. (29) reported that the mutated K-ras tumors were associated with higher ^{18}F-FDG accumulation and higher SUV_{max} was a predictor of K-ras mutations. We should note that in our study, due to the retrospective nature, only 20 patients' K-ras results were interpreted and there was no correlation between K-ras results and ^{18}F-FDG PET/CT metabolic parameters. Furthermore, it has been reported that there is a heterogeneity of K-ras status among the primary rectal tumor (30). As a result, the correlation analysis might be biased because of the small patient group and dissected specimens for mutational testing could not reflect the real status of the total tumor, and ^{18}F-FDG PET/CT displayed the entire status of tumor (31).

In this retrospective study, we found that primary tumor SUV_{max} in preoperative staging ^{18}F-FDG PET/CT scan had no effect on predicting survival. On the other hand, the SUV_{max} of lymph nodes in ^{18}F-FDG PET/CT was predictive regarding survival. Our results showed that the staging system which was still used in clinical practice was effective on predicting survival of patients with rectal cancer.

Study Limitations

There were some limitations in this study. First of all, it was a retrospective, single-institution study; thus, the findings of ^{18}F-FDG-PET/CT as a prognostic factor in preoperative rectal cancer required strengthening in a prospective, multicenter study with a larger patient number. Another weakness was the small sample size of patients and the heterogeneity of the clinical stages of the disease in the patient group that might have biased the outcome of this study. Additionally, we chose the SUV_{max} cut-off values from the ROC curves for the balance of sensitivity and specificity. However, these choices could be improved with a larger and homogeneous patient group.

Conclusion

The results showed that primary tumor SUV_{max} obtained in initial ^{18}F-FDG PET/CT was not predictive of survival in patients with rectal cancer. On the other hand, the lymph node SUV_{max} had negative effect on survival. For this reason, we suggest the use of high lymph node SUV_{max} as a new parameter for clinical practice, which has a negative impact on survival.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University İstanbul Medical Faculty of Local Ethics Committee (2015/1867).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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References

1. Nishihara R, Ogino S, Chan AT. Colorectal-cancer incidence and mortality after screening. N Engl J Med 2013;369:2355.
2. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O, Bray F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-387.
3. Hong TS, Ryan DP. Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer-The New Standard of Care? JAMA Oncol 2018;4:e180070.
4. Ozis SE, Soydal C, Akyol C, Can N, Kucuk ON, Yagcı C, Erkek AB, Kuzu MA. The role of 18 F-fluorodeoxyglucose positron emission tomography/ computed tomography in the primary staging of rectal cancer. World J Surg Oncol 2014;12:26.
5. Huang J, Huang L, Zhou J, Duan Y, Zhang Z, Wang X, Huang P, Tan S, Hu P, Wang J, Huang M. Elevated tumor-to-liver uptake ratio (TLR) from 18F-FDG-PET/CT predicts poor prognosis in stage IIA colorectal cancer following curative resection. Eur J Nucl Med Mol Imaging 2017;44:1958-1968.
6. Nakajo M, Kajiya Y, Tani A, Jinguji M, Nakajo M, Kitazono M, Yoshiura T. A pilot study for texture analysis of 18F-FDG and 18F-FLT-PET/CT to predict tumor recurrence of patients with colorectal cancer who received surgery. Eur J Nucl Med Mol Imaging 2017;44:2158-2168.
7. Deantonio L, Caroli A, Puta E, Ferrante D, Apicella F, Turri L, Sacchetti G, Brambilla M, Krengli M. Does baseline [18F] FDG-PET/CT correlate with tumor staging, response after neoadjuvant chemoradiotherapy, and prognosis in patients with rectal cancer? Radiat Oncol 2018;13:211.
8. Weiser MR. AJCC 8th Edition: Colorectal Cancer. Ann Surg Oncol 2018;25:1454-1455.
9. Engelen SM, Beets-Tan RG, Lahaye MJ, Kessels AG, Beets GL. Location of involved mesorectal and extramesorectal lymph nodes in patients with primary rectal cancer: preoperative assessment with MR imaging. Eur J Surg Oncol 2008;34:776-781.
10. National Institute for Health and Clinical Excellence. Improving outcomes in colorectal cancer. Manual update. London: National Institute for Health and Clinical Excellence; 2004.
11. Tagliabue L. The emerging role of FDG PET/CT in rectal cancer management: is it time to use the technique for early prognostication? Eur J Nucl Med Mol Imaging 2013;40:652-656.
12. Kijima S, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. World J Gastroenterol 2014;20:16964-16975.
13. Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, Putnam JB, Herbst RS, Moran CA, Podoloff DA, Roth JA, Cox JD. [18F] fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. J Clin Oncol 2005;23:1136-1143.
14. Pan L, Gu P, Huang G, Xue H, Wu S. Prognostic significance of SUV on PET/CT in patients with esophageal cancer: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2009;21:1008-1015.
15. Riedl CC, Akhurst T, Larson S, Stanziale SF, Tuorto S, Bhargava A, Hricak H, Klimstra D, Fong Y. 18F-FDG PET scanning correlates with tissue markers of poor prognosis and predicts mortality for patients after liver resection for colorectal metastases. J Nucl Med 2007;48:771-775.
16. Lee JE, Kim SW, Kim JS, Choi KY, Kang WK, Oh ST, Yoo IeR, Kim SH. Prognostic value of 18-F-fluorodeoxyglucose positron-emission tomography-computed tomography in resectable colorectal cancer. World J Gastroenterol 2012;18:5072-5077.
17. Oku S, Nakagawa K, Momose T, Kumakura Y, Abe A, Watanabe T, Ohtomo K. FDG-PET after radiotherapy is a good prognostic indicator of rectal cancer. Ann Nucl Med 2002;16:409-416.
18. Bang JI, Ha S, Kang SB, Lee KW, Lee HS, Kim JS, Oh HK, Lee HY, Kim SE. Prediction of neoadjuvant radiation chemotherapy response and survival using pretreatment [(18)F] FDG PET/CT scans in locally advanced rectal cancer. Eur J Nucl Med Mol Imaging 2016;43:422-431.
19. Ogawa S, Itabashi M, Kondo C, Momose M, Sakai S, Kameoka S. Prognostic value of total lesion glycolysis measured by 18F-FDG-PET/CT in patients with colorectal cancer. Anticancer Res. 2015;35:3495-3500.
20. Dehdashti F, Grigsby PW, Myerson RJ, Nalbantoglu I, Ma C, Siegel BA. Positron emission tomography with [(18)F]-3'-deoxy-3'fluorothymidine (FLT) as a predictor of outcome in patients with locally advanced resectable rectal cancer: a pilot study. Mol Imaging Biol 2013;15:106-113.
21. Cerny M, Dunet V, Prior JO, Hahnloser D, Wagner AD, Meuli RA, Schmidt S. Initial Staging of Locally Advanced Rectal Cancer and Regional Lymph Nodes: Comparison of Diffusion-Weighted MRI With 18F-FDG-PET/CT. Clin Nucl Med 2016;41:289-295.
22. Zhou L, Wang JZ, Wang JT, Wu YJ, Chen H, Wang WB, Cao F, Cheng

GX. Correlation analysis of MR/CT on colorectal cancer lymph node metastasis characteristics and prognosis. Eur Rev Med Pharmacol Sci 2017;21:1219-1225.

23. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(Suppl 4):22-40.
24. Bae SU, Won KS, Song BI, Jeong WK, Baek SK, Kim HW. Accuracy of F-18 FDG PET/CT with optimal cut-offs of maximum standardized uptake value according to size for diagnosis of regional lymph node metastasis in patients with rectal cancer. Cancer Imaging 2018;18:32.
25. Chen R, Wang Y, Zhou X, Huang G, Liu J. Preoperative PET/CT 18F-FDG Standardized Uptake by Lymph Nodes as a Significant Prognostic Factor in Patients with Colorectal Cancer. Contrast Media Mol Imaging 2018;2018:5802109.
26. Leccisotti L, Gambacorta MA, de Waure C, Stefanelli A, Barbaro B, Vecchio FM, Coco C, Persiani R, Crucitti A, Tortorelli AP, Giordano A, Valentini V. The predictive value of 18F- FDG PET/CT for assessing pathological response and survival in locally advanced rectal cancer after neoadjuvant radiochemotherapy. Eur J Nucl Med Mol Imaging 2015;42:657-666.
27. Alongi F, Fersino S, Mazzola R, Fiorentino A, Giaj-Levra N, Ricchetti F, Ruggieri R, Di Paola G, Cirillo M, Gori S, Salgarello M, Zamboni G, Ruffo G. Radiation dose intensification in preoperative chemo-radiotherapy for locally advanced rectal cancer. Clin Transl Oncol 2017;19:189-196.
28. Rahmim A, Qi J, Sossi V. Resolution modeling in PET imaging: theory, practice, benefits, and pitfalls. Med Phys 2013;40:064301.
29. Chen SW, Chiang HC, Chen WT, Hsieh TC, Yen KY, Chiang SF, Kao CH. Correlation between PET/CT parameters and KRAS expression in colorectal cancer. Clin Nucl Med 2014;39:685-689.
30. Baldus SE, Schaefer KL, Engers R, Hartleb D, Stoecklein NH, Gabbert HE. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. Clin Cancer Res 2010;16:790-799.
31. Kawada K, Nakamoto Y, Kawada M, Hida K, Matsumoto T, Murakami T, Hasegawa S, Togashi K, Sakai Y. Relationship between 18F-fluorodeoxyglucose accumulation and KRAS/BRAF mutations in colorectal cancer. Clin Cancer Res 2012;18:1696-1703.

Original Article
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Fungal Pneumonia in The Immunocompetent Host: A Possible Statistical Connection Between Allergic Fungal Sinusitis with Polyposis and Recurrent Pulmonary Infection Detected by Gastroesophageal Reflux Disease Scintigraphy

İmmünokompetan Hastada Fungal Pnömoni: Polipozis ile Alerjik Fungal Sinüzit ve Gastroözefageal Reflü Sintigrafisi ile Saptanan Tekrarlayan Pulmoner Enfeksiyon Arasında Olası İstatistiksel Bağlantı

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Abstract

Objectives: Fungal pneumonia in the immune competent host is a rarity with few reported cases in the literature. We present a series of 7 cases of recurrent fungal pneumonia in association with allergic fungal rhinosinusitis and gastroesophageal reflux disease (GERD). We hypothesised that recurrent infection may have been transported from the infected paranasal sinuses into the lung by GERD as the process was terminated by surgical fundoplication in 2 of these patients.

Methods: Patients were recruited into the study if they were immune competent and had recurrent fungal pneumonia and GERD. Allergic fungal rhinosinusitis was proven by biopsy. GERD was investigated by a scintigraphic test that assessed local oesophageal disease, lung aspiration and head and neck involvement with a hybrid gamma camera and X-ray computed tomography.

Results: All patients were shown to have GERD with 5/7 showing paranasal sinus contamination and 7/7 showing laryngopharyngeal involvement and 6/7 lung aspiration. One patient had characteristics strongly predictive of aspiration. Fundoplication led to cessation of fungal lung infection in two patients.

Conclusion: Recurrent fungal pneumonia in the immune competent host should raise the possibility of re-infection from the paranasal sinuses, especially in patients with GERD.

Keywords: Allergic, fungal, rhinosinusitis, pneumonia, reflux, scintigraphy

Öz

Amaç: İmmünokompetan hastada fungal pnömoni literatürde az sayıda olguda bildirilmiştir. Bu yazıda alerjik fungal rinosinüzit ve gastroözofageal reflü hastalığı (GÖRH) ile ilişkili tekrarlayan fungal pnömonisi olan 7 olgu sunulmuştur. Bu hastaların 2'sinde cerrahi fundoplikasyon ile tekrarlayan fungal pnömoni atakları sonlandığı için, tekrarlayan enfeksiyonun enfekte paranazal sinüslerden GÖRH ile akciğere taşındığını varsaydık.

Yöntem: Tekrarlayan fungal pnömonisi ve GÖRH olan immünokompetan hastalar çalışmaya alındı. Alerjik fungal rinosinüzitin varlığı biyopsi ile kanıtlandı. GÖRH, lokal özofagus hastalığı, akciğer aspirasyonu ve baş-boyun tutulumunu bir hibrit gamma kamera ve X-ışını bilgisayarlı tomografi ile değerlendiren bir sintigrafik test ile araştırıldı.

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Bulgular: Tüm hastalarda GÖRH olduğu gösterildi. Yedi hastanın 5'inde paranazal sinüs kontaminasyonu, tamamında laringofaringeal tutulum ve 6'sında akciğer aspirasyonu gösterildi. Bir hastada aspirasyonun olduğunu güçlü bir şekilde öngören özellikler vardı. Fundoplikasyon iki hastada fungal akciğer enfeksiyonunun kesilmesine yol açtı.

Sonuç: İmmünokompetan hastalarda tekrarlayan fungal pnömoni, özellikle GÖRH olan hastalarda paranazal sinüslerden re-enfeksiyon olasılığını düşündürmelidir.

Anahtar kelimeler: Alerjik, mantar, rinosinüzit, pnömoni, reflü, sintigrafi

Introduction

The Aspergillus species of fungus is widespread and generally acquired by inhalation of airborne spores. The immunocompetence of the host is a critical factor in the establishment of invasive infection. More rarely, infection may occur in the immunocompetent host, as has been described by a number of authors (1,2,3). Such cases have been described since 1959 (4). These cases include patients with chronic fungal infections of the maxillary sinuses, mediastinum, lymph nodes and direct pulmonary involvement. The cohort in which the biggest of these series has been described (3) have consisted relatively young men and women. In that series 9 of 18 patients had allergic fungal sinusitis with polyposis with a background of chronic rhinosinusitis.

This paper presents 7 patients with recurrent pulmonary infections who are distinguished from most previous reports in terms of a connection between recurrent fungal pneumonia and allergic fungal sinusitis with polyposis. Several of these patients had undergone lobectomy to eradicate the primary infection of the lungs with subsequent recurrence elsewhere in the lungs. All patients gave a history of symptomatic gastroesophageal reflux disease (GERD), and were tested with a scintigraphic reflux study (5,6) to evaluate the presence of disease within the oesophagus, paranasal sinuses and the possibility of aspiration of refluxate into the lungs. The findings led to exploration of a possible connection between these conditions and surgical intervention, supporting the conclusions.

Based on this case series, we hypothesised that there might be a connection between severe GERD with aspiration into the lungs, recurrent pulmonary fungal infections and allergic fungal sinusitis with polyposis

Materials and Methods

Patient Group

Consecutive patients with fungal pneumonia were referred to a single Nuclear Medicine practice as part of a large research study to evaluate extra-oesophageal manifestations of GERD over a period of 3 years. All patients had established GERD on the basis of 24-hour pH, manometry and impedance monitoring and most had undergone upper gastrointestinal endoscopy and ear, nose and throat assessment with laryngoscopy. The presence of allergic fungal sinusitis with polyposis had been confirmed by biopsy of tissue from the paranasal sinuses, although culture had been unsuccessful in 3 of 7 cases. There was no evidence of invasion or mycetoma formation in these patients. Microscopy of lung tissue obtained by lobectomy or bronchoscopy confirmed semi-invasive fungal disease (7 aspergillus species) in all patients. Immunological testing had confirmed immune competence in all patients. Patients with fungal disease being treated for malignancy or following organ transplantation were excluded from the study.

All patients were on proton pump inhibitor (PPI) therapy at the time of the study and were clinically assessed with the Belafsky Reflux symptom index score (7).

Ethical Considerations

A database of patients with either proven or suspected GERD/Laryngopharyngeral reflux (approved by the Institutional Ethics Committee of University of Notre Dame 015149S) was maintained prospectively.

Statistical Analysis

All statistical analysis was performed on the Statistical Package for the Social Sciences (SPPS Version 24, IBM, New York, USA).

Scintigraphic Reflux Study

Patients were fasted for 12 hours and medications ceased for the 24-hours prior to the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, USA) with markers on the mandible and stomach to ensure regions of interest were in the field of view of the camera. Patients consumed 50-100 mL of water with 60-100 MBq of Technetium Phytate followed by flushing with 50 mL of water to clear the mouth and oesophagus from radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 2 minutes at 15 secs per frame into a 64x64 matrix while upright. This was followed by a 30-minute dynamic in the supine position. Delayed images were obtained at 2 hours to assess the presence of aspiration of tracer activity into the lungs. Following acquisition of the planar image of the lungs, a single photon emission computed tomography (SPECT) study of the head, neck and lungs was obtained and registered with X-ray computed tomography (CT) of the region. These images were reconstructed, fused and displayed in standard projections. Dynamic images were analysed by time activity curves over the pharynx/laryngopharynx, upper and lower half of the oesophagus and by a background region over the right side of the chest, away from the stomach and oesophagus. Delayed images were analysed by a line profile over the lungs. Time activity curves were graded as showing no GERD, falling, flat or rising curves. Area under the curve and maximal amplitude compared to background were estimated. Liquid gastric emptying half-time was determined from the 30-minute supine acquisition with a single exponential fit to the data.

Results

Patient data. A total of 7 patients were included in the study with an average age of 62 years (range= 47-74 years). There were 5 females and 2 males. The average length of history of sinusitis was 7 years (range=4-8 years). All had been treated for recurrent biopsy-proven allergic fungal sinusitis with polyposis of the paranasal sinuses and lung infection over a period of approximately 4-5 years. Five of 7 patients were on concurrent therapy for asthma, although lung function testing had shown no reversible component. Three patients had undergone lobectomy of the lungs to eradicate the infection without success. All patients had undergone paranasal sinus surgery with recurrence of infection within weeks of the surgery. Biopsy of tissue from the paranasal sinuses/lungs failed to grow the fungus in media in 3 patients, although microscopy confirmed semi-invasive disease in all 7 patients. Antifungal antibiotics utilised in treatment included erbinafine, fluconazole, itraconazole, voriconazole, posaconazole and griseofulvin.

High resolution CT scanning of the lungs demonstrated pulmonary fibrosis in 3 patients, with bronchiectasis in 2 of these and a further patient with bronchiectasis.

All 7 patients had previously been investigated for GERD with 24-hour pH manometry and impedance that confirmed reflux disease and been commenced on long-term PPI and other therapy (Nexium-5, Somac-3, Losec-1, Ranitidine-4, Tazac-1, Motilium-1). Four patients had no symptoms of heartburn, globus or regurgitation, while 3 gave a history of daily symptoms. The average Belafsky score (7) was 20.0 (range: 0-35.0).

Two of the seven patients who had undergone lobectomy for recurrent fungal pneumonia and shown lung aspiration of refluxate in the scintigraphic studies underwent laparoscopic fundoplication. These patients became disease free in the lungs within 3 months while on antifungal therapy and at follow-up showed reduced parameters of reflux and no further lung aspiration of refluxate.

Scintigraphic findings. All 7 patients showed evidence of significant intermittent or continuous full-column GER (Figure 1) with pharyngeal/ laryngopharyngeal contamination by refluxate. The average amplitude of the refluxate was 4.8 times higher than background and the average frequency of reflux to the larygopharynx in supine position was 22 episodes in 30 minutes (range=10-50 episodes). Liquid gastric emptying was normal in 2 patients (half-clearance time <16.0 minutes) while 5 were abnormal with half-clearance times ranging from 18.0 to 124.0 minutes (mean=56.8 minutes). Sample analysis is shown in Figure 1.

Analysis of the pattern of time-activity curves for the pharynx/laryngopharynx showed 5 rising curves when upright with 2 showing a falling pattern. When supine, 4 showed rising curves and 3 falling curves.

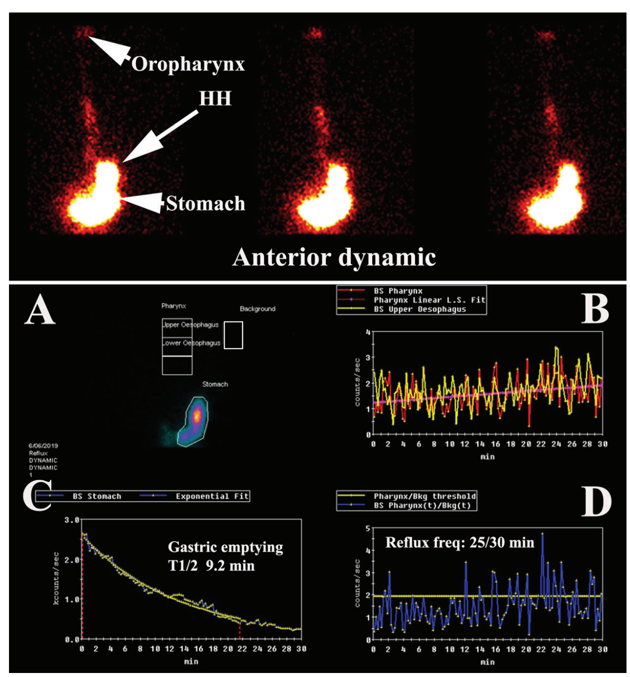

Figure 1. Initial anterior dynamic image with the analysis of the dynamic image in the panel below. Three 15 second frames of the supine dynamic image are shown in the panel above with the oropharynx and stomach labelled. The patient also has a hiatus hernia. The analysis in the panel below shows the regions of interest in A and the time-activity curves for the pharynx/laryngopharynx (red) and osesophagus (yellow) and the curve fitted to the pharynx/laryngopharyngeal curve (pink) in B. Liquid gastric emptying is shown in C with a single exponential curve fitted to the time-activity curve for the stomach. The frequency of reflux to the pharynx/laryngopharynx is shown in D

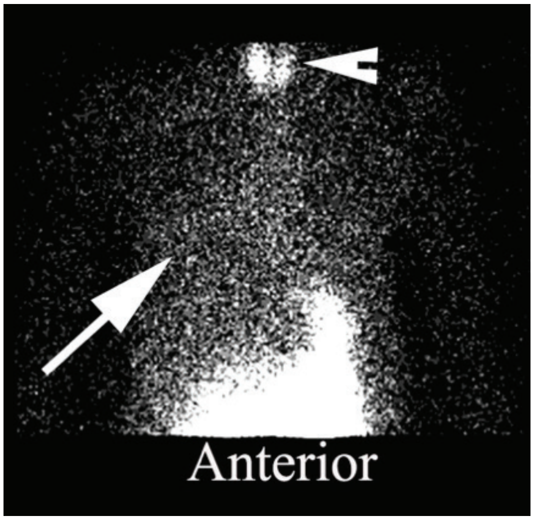

Figure 2. Delayed image of the anterior thorax obtained at two hours demonstrating aspiration of refluxate into predominantly the right lung (arrow). Radiopharmaceutical breakdown in the delayed image sometimes leads to free pertechnetate formation, which is taken up by the thyroid gland and is apparent in this study (arrowhead)

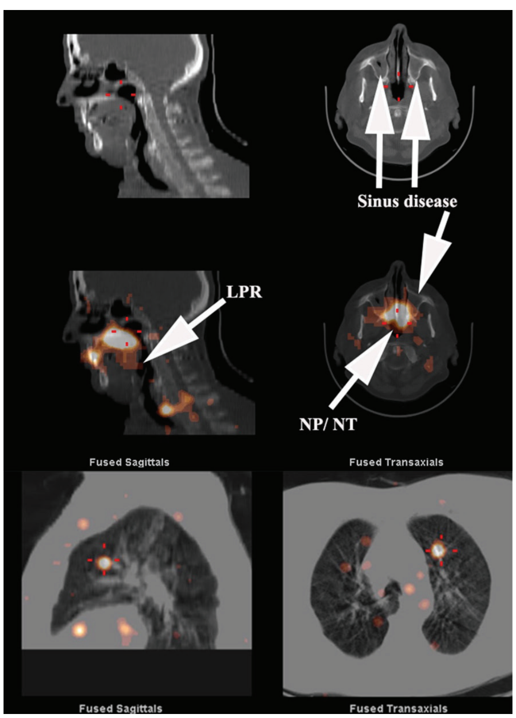

Figure 3. SPECT/CT image of head, neck and lungs. The CT image shows evidence of soft tissue thickening within the maxillary sinuses (arrows) consistent with sinus disease. The fused image in the middle panel demonstrates LPR, NP, NT and maxillary sinus contamination by refluxate. The lower panel shows aspirated refluxate within the lung tissue. Some misregistration is inevitable in the lungs due to respiratory motion and frequent coughing in many of these patients.

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate

Six of the 7 cases showed evidence of pulmonary aspiration of refluxate in the delayed study (Figure 2) and the patient who did not show had rising time-activity curves for thelaryngopharyngeal region in the upright and supine positions.

SPECT/CT imaging of the head, neck and lungs (Figure 3-5) demonstrated laryngopharyngeal contamination by refluxate in all 7, nasopharyngeal in 6 and maxillary sinus contamination in 5 patients. One patient had right middle ear contamination by refluxate. Lung aspiration of refluxate was confirmed in 6 patients.

Discussion

This series raises a number of troubling issues pertaining to the relationship between rhinosinusitis and GERD. What is the role of GERD in sustaining the inflammatory process in the paranasal sinuses? Is it a primary cause or a promoter or is it a bystander phenomenon? How can one establish whether GERD involves the paranasal sinuses? What is the

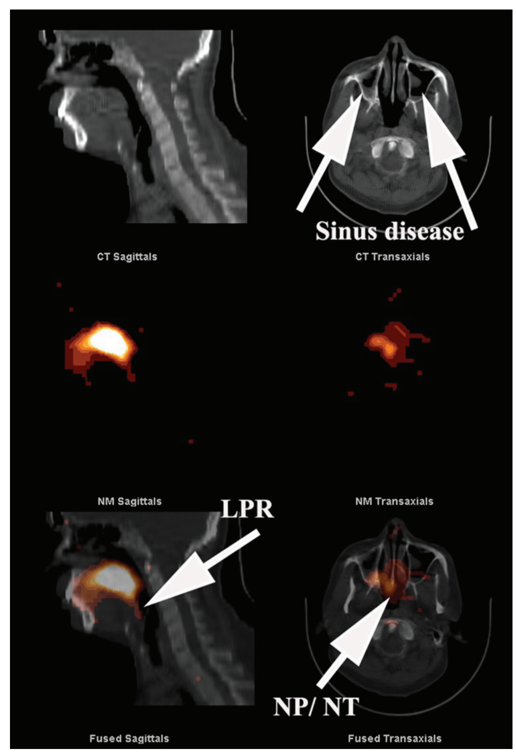

Figure 4. SPECT/CT image of head and neck. The upper panel of CT images with evidence of polyposis of both maxillary sinuses consistent with sinus disease. The fused images in the lower panel demonstrate evidence of LPR as well as contamination of the NP, NT and both maxillary sinuses. The central panel shows the scintigraphic images from the region in the absence of anatomical landmarks

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate relationship between chronic fungal sinusitis and recurrent fungal pneumonia? Five of seven patients in this series were diagnosed as having asthma and treated for asthma although lung functions tests showed no reversibility after bronhcodilators. Many of these troubling issues can be explained by the scintigraphic reflux studies as both local disease in the oesophagus and extra-oesophageal structures can be physically visualised and at least semi-quantitated as shown. All 7 patients showed laryngopharyngeal contamination by refluxate with 6 also demonstrating lung aspiration. Laryngopharyngeal reflux was supported by the Belafsky scores of~20.0.

The majority of the patients in this case series gave a good history of established rhinosinusitis (8) predating the episodes of fungal pneumonia. They also had established and treated gastroesophageal reflux. It raises the question of how fungal infection can establish itself in the paranasal

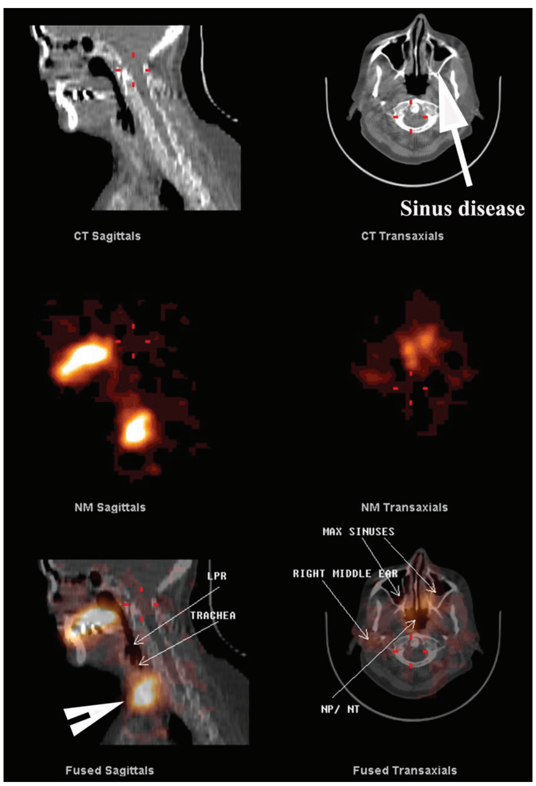

Figure 5. SPECT/CT image of head and neck. The upper panel of CT images demonstrates evidence of sinus disease in the left maxillary sinus. Fused images in the lower panel confirm the presence of refluxate contaminating the LPR, trachea, maxillary sinuses, NP, nasal NT and the right middle ear. The middle panel demonstrates the scintigraphic images and the difficulty in ascribing anatomical sites to these images without the CT study. Note uptake in the thyroid gland (arrowhead) in the fused sagittal image due to breakdown of the radiopharmaceutical in the delayed images

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate

sinuses in an immune competent host. The combination of pseudostratified ciliated epithelium which is held together by tight junctions and protein secretions that have antimicrobial properties generally protects the host from infection (9). Breakdown of this barrier occurs in response to either allergic or inflammatory stimuli with secretion of epithelial-derived thymic stromal lymphopoietin, which in an up-regulated state may damage tight junctions, together with other toxic molecules such as the interleukins and interferon (9,10). All seven patients in this study had established GERD with the scintigraphic study showing paranasal sinus contamination by refluxate in the majority. There is a body of evidence that shows pepsin in refluxate as an agent capable of damaging nasal epithelium, which may have contributed or potentiated chronic rhinosinusitis (11). The seminal question is whether fungi initiate the inflammatory change or exploit a pre-existing inflammatory condition. The balance of opinion is that fungi initiate the inflammatory changes and then exploit the breakdown in defensive barriers (12). Luong et al. (13) demonstrated that common etiologic fungal antigens induced peripheral blood mononuclear cells to secrete elevated levels of interleukin 4 and 5 in patients with allergic fungal rhinosinusitis compared to normal controls. Inflammatory changes may also be promoted by coexistent staphylococcus aureus infection of the paranasal sinuses with the elevated IgE response to enterotoxin A and B, superantigens which are secreted by the bacterium (14). Pathogenic organisms such as fungi create a favourable environment for growth in the paranasal sinuses and subsequently produce conditions (eg. biofilms) that help evade the host immun system, antibiotic therapy and even surgical intervention (15).

The key finding that supports the hypothesis of recurrent infection of the lungs from established fungal disease of the paranasal sinuses is the response to laparoscopic fundoplication. It clearly implies a fundamental role for GERD with extra-oesophageal manifestations in the paranasal sinuses and subsequent aspiration of refluxate into the lungs. This is a complex issue as virtually all patients were on maintenance PPI therapy for the clinically diagnosed reflux disease. As has been shown, patients on high-dose PPI therapy, will continue to experience non-acid or even alkaline reflux which may be asymptomatic (16). This raises the possibility that PPI therapy in this cohort may have reduced the sterilisation effect of acid reflux on fungal disease in the paranasal sinuses and encouraged growth of the fungus in an alkaline environment. The change in pH of growth medium has been shown to induce fungal gene expression involved in the regulation of extracellular enzymes that may promote growth (17). While Aspergillus species are capable of growth across the entire range of pH from 2 to 11, they have been shown to be more tolerant to alkaline pH for growth (18). Furthermore, the alkaline pH with co-existent gastric mucositis may have reduced the absorption of many of the anti-fungal antibiotics utilised in these patients, with the exception of fluconazole (19).

GERD could play the role of transporter, particularly in its extra-oesophageal reach through the paranasal sinuses, laryngopharynx and airways as happened in all 7 patients. This system would need to be operational for a significant period, particularly when the patient was supine and the protective mechanisms against reflux were minimised, most likely during sleep (20,21). The possibility of assessing extra-oesophageal manifestations of GERD has until recently been a matter of deductive reasoning or based on observation of inflammatory change in the laryngopharynx on laryngoscopy (22). More recently, 24-hour impedance/pH monitoring has shown some promise although reproducibility has been an issue (23). The scintigraphic reflux technique utilised in the current study allows direct visualisation of refluxate within the sinuses, laryngopharynx and lungs (Figure 3, 4, 5) in addition to demonstrating disease within the oesophagus. Entry of refluxate into the paranasal sinuses was evident in 5 of 7 patients and aspiration into the lungs in 6 of 7 with recurrent fungal pneumonia. The scintigraphic reflux study assesses patients for lung aspiration after a sampling period of 2 hours, during which the patient is supine for only 30 minutes. Previous work has shown that rising time activity curves for the pharynx/laryngopharynx and upper oesophagus have a positive predictive value of 90% for lung aspiration of refluxate (5). The only patient who did not show aspiration in the 2-hour study had this pattern of activity for the laryngopharynx and upper oesophagus. It does suggest a high likelihood of aspiration during prolonged recumbency, especially during sleep (20,21).

The inability to eradicate fungal disease from the lungs has suggested more complex pathology, as even pulmonary lobectomy of the infected sites has not solved the problem. There has appeared to be a source of recurrent fungal infection, raising the strong possibility that the disease in the paranasal sinuses may have been the source, and the passage of refluxate through the sinuses, the main transport mechanism for infected tissue into the lungs. The only method of breaking the cycle of infection and re-infection has appeared to be to disrupt recurrent gastro-oesophageal reflux with surgical fundoplication. This technique effectively reduces the volume of reflux and interrupts what has appeared to be a recurrent transport system from the sinuses into the lungs in this particular group of patients.

Diagnosis of aspergillosis within the paranasal sinuses has proven to be problematic as engendering fungal growth in external media has sometimes been unproductive. However, microscopy of biopsies from the sinuses with silver staining or molecular techniques has demonstrated semi-invasive disease of the mucosa with a diagnosis of allergic fungal sinusitis with polyposis. This is important, as studies of normal (uninfected) paranasal sinuses has shown a biome in which fungal elements may be inhaled as airborne contaminants and trapped in the paranasal mucous, being shuttled to the oropharynx for removal (24). One of the significant problems with molecular techniques is the detection of molecular material of inactive microorganisms (24). The inability to culture fungi from biopsy material may be related to the formation of biofilms, which inhibits growth in culture media, as has been shown in a number of reviewed studies (24). The type of biofilm (eg. haemophilus influenza versus staphylococcus aureus) may affect the severity of disease by protecting pathogenic organisms from the effects of antibiotics in chronic rhinosinusitis and even affect the success of surgery (15,25,26).

Conclusion

Fungal pneumonia in the immunocompetent host is rare. It may well begin in the paranasal sinuses, as has been shown in one of the larger series and when coupled with the appropriate pre-conditions become chronic and increase the risk of spread to the lungs. This series offers a good case to support the hypothesis that recurrent fungal pneumonia may be due to re-infection of the lungs from allergic fungal sinusitis with polyposis by passage of GER through the paranasal sinuses and into the lungs.

Ethics

Ethics Committee Approval: Institutional Ethics Committee of University of Notre Dame 015149S.

Informed Consent: Consent forms were filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.V.W., G.F., Concept: L.B., J.B., Design: L.B., D.J., Data Collection or Processing: H.V.W., K.B., L.B., D.N., Analysis or Interpretation: H.V.W., Literature Search: L.B., G.F., Writing: L.B., H.V.W., D.N., G.F.

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References

1. Hillerdal G, Benson L, Lindgren A, Hjertquist SO. Disseminated pulmonary aspergillosis in a previously healthy young woman. Scand J Infect Dis 1984;6:217-222.
2. Karam GH, Griffin FM Jr. Invasive pulmonary aspergillosis in nonimmunocompromised, nonneutropenic hosts. Rev Infect Dis 1986;8:357-363.
3. Karim M, Alam M, Shah AA, Ahmed R, Sheikh H. Chronic invasive aspergillosis in apparently immunocompetent hosts. Clin Infect Dis 1997;24:723-733.
4. Finegold S, Will D, Murray F. Aspergillosis, a review and report of twelve cases. Am J Med 1959;27:463-482.
5. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015;21:3619-3627.
6. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 2015;36:625-630.
7. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-277.
8. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994;111:580-588.
9. Patel NN, Kohanski MA, Maina IW, Workman AD, Herbert DR, Cohen NA. Sentinels at the wall: epithelial-derived cytokines serve as triggers of upper airway type 2 inflammation. Int Forum Allergy Rhinol 2019;9:93-99.
10. Lavigne P, Lee SE. Immunomodulators in chronic rhinosinusitis. World J Otorhinolaryngol Head Neck Surg 2018;4:186-192.
11. Southwood JE, Hoekzema CR, Samuels TL, Wells C, Poetker DM, Johnston N, Loehrl TA. The Impact of Pepsin on Human Nasal Epithelial Cells In Vitro: A Potential Mechanism for Extraesophageal Reflux Induced Chronic Rhinosinusitis. Ann Otol Rhinol Laryngol 2015;124:957-964.
12. Plonk DP, Luong A. Current understanding of allergic fungal rhinosinusitis and treatment implications. Curr Opin Otolaryngol Head Neck Surg 2014;22:221-226.
13. Luong A, Davis LS, Marple BF. Peripheral blood mononuclear cells from allergic fungal rhinosinusitis adults express a Th2 cytokine response to fungal antigens. Am J Rhinol Allergy 2009;23:281-287.
14. Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis-more than a fungal disease? J Allergy Clin Immunol 2013;132:487-489.
15. Foreman A, Wormald PJ. Different biofilms, different disease? A clinical outcomes study. Laryngoscope 2010;120:1701-1706.
16. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398-1402.
17. Caddick MX, Brownlee AG, Arst HN Jr. Regulation of gene expression by pH of the growth medium in Aspergillus nidulans. Mol Gen Genet 1986;203:346-353.
18. Wheeler KA, Hurdman BF, Pitt JI. Influence of pH on the growth of some toxigenic species of Aspergillus, Penicillium and Fusarium. Int J Food Microbiol 1991;12:141-149.
19. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM. Clinical Relevance of the Pharmacokinetic Interactions of Azole Antifungal Drugs with Other Coadministered Agents Clin Infect Dis 2009;48:1441-1458.
20. Lee KK, Birring SS. Cough and sleep. Lung 2010;188(Suppl 1):91-94.
21. Orr WC. Sleep and gastroesophageal reflux: what are the risks? Am J Med 2003;15(Suppl 3):109-113.
22. Habermann W, Schmid C, Neumann K, Devaney T, Hammer HF. Reflux symptom index and reflux finding score in otolaryngologic practice. J Voice 2012;26:123-127.
23. Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F; Groupe Français De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour ph impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 2013;11:366-372.
24. Boase S, Foreman A, Cleland E, Tan L, Melton-Kreft R, Pant H, Hu FZ, Ehrlich GD, Wormald PJ. The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection. BMC Infect Dis 2013;13:210.
25. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. Am J Rhinol Allergy 2010;24:169-174.
26. Foreman A, Psaltis AJ, Tan LW, Wormald PJ. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Allergy Rhinol (Providence) 2010;1:10.

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Intense ^{18}F-Flourodeoxyglucose Uptake in Brachial Plexus of Patients with Brachial Plexopathy

Brakial Pleksopatili Hastada Brakial Pleksusta Yoğun ^{18}F-Florodeoksiglukoz Tutulumu

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Abstract

Brachial plexopathy is a significant cause of pain and disability in patients with breast cancer. Major causes of brachial plexopathy in patients with breast cancer are metastatic invasion or radiation damage to the plexus. Differentiation between the two pathologies is important for appropriate treatment planning. The complicated anatomy of the plexus makes this a difficult area to image accurately. Magnetic resonance imaging (MRI) is the imaging modality of choice for diagnostic evaluation of these cases. We presented a case to demonstrate the role of ^{18}F-flourodeoxyglucose positron emission tomography/computerized tomography for confirming metastatic brachial plexopathy when MRI findings were suspicious and for differentiating radiation-induced brachial plexopathy from metastatic plexopathy.
Keywords: Brachial plexopathy, metastatic breast cancer, ^{18}F-fluorodeoxyglucose positron emission tomography

Öz

Brakial pleksopati, meme kanserli hastalarda ağrı ve hareket kısıtlılığının önemli bir nedenidir. Brakial pleksopatinin en sık görülen nedenleri metastatik invazyon ve radyasyon hasarıdır. Tedavi planının doğru yapılabilmesi için bu iki sebebin ayrımı önemlidir. Pleksusun karışık anatomisi nedeniyle bu bölgenin doğru görüntülenmesi zordur. Bu olgularda tanısal değerlendirme için tercih edilen görüntüleme yöntemi manyetik rezonans görüntülemedir (MRG). MRG'nin şüpheli olduğu durumlarda metastatik brakial pleksopati tanısını koymada ve radyasyona bağlı pleksopati ile metastatik pleksopatinin ayrımında ^{18}F-florodeoksiglikoz pozitron emisyon tomografi/bilgisayarlı tomografi'nin önemini gösteren bir olgu takdim ediyoruz.
Anahtar kelimeler: Brakial pleksopati, metastatik meme kanseri, ^{18}F-fluorodeoksiglukoz positron emisyon tomografisi

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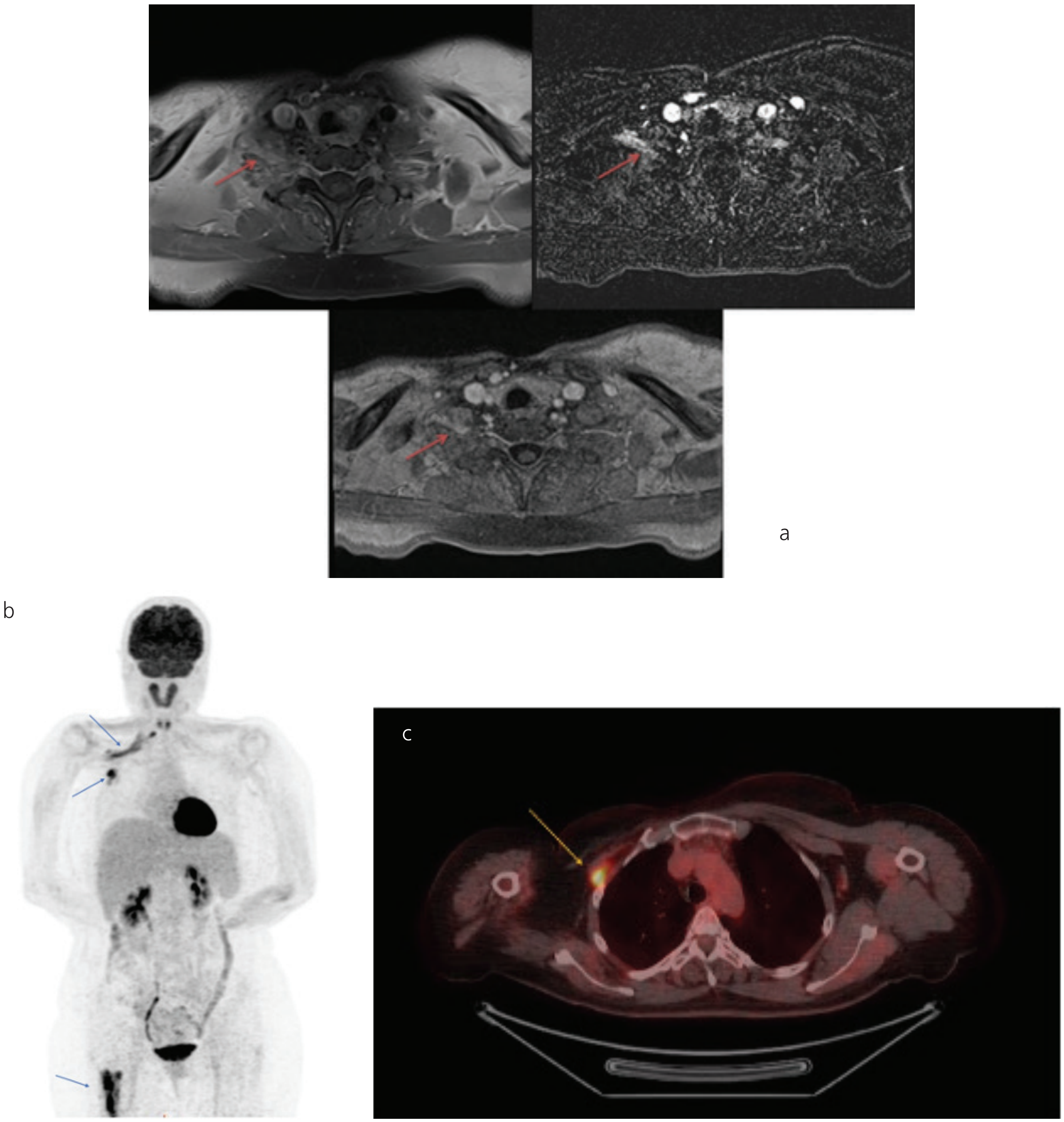

Figure 1. A 50-year-old woman diagnosed as having infiltrating ductal carcinoma of the right breast had undergone surgery (modified radical mastectomy and lymph node dissection), followed by adjuvant chemotherapy and radiotherapy six years ago. She presented to her oncologist with pain and restriction of movement of the right upper limb lately. Magnetic resonance imaging (MRI) was used for evaluation of brachial plexus and minimal thickening of plexus nerves was detected, which could be caused by radiation damage (Figure 1a, red arrows). The patient was referred for ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET/CT) for restaging of disease after it was observed that tumor marker level increased. ^{18}F-FDG PET/CT was performed and maximum intensity whole body and fused transaxial images of thorax revealed linear pattern of pathological FDG uptake in the right lateral aspect of the upper chest, right axillary and interpectoral lymph nodes and right femur (Figure 1b and c, blue and yellow arrows).

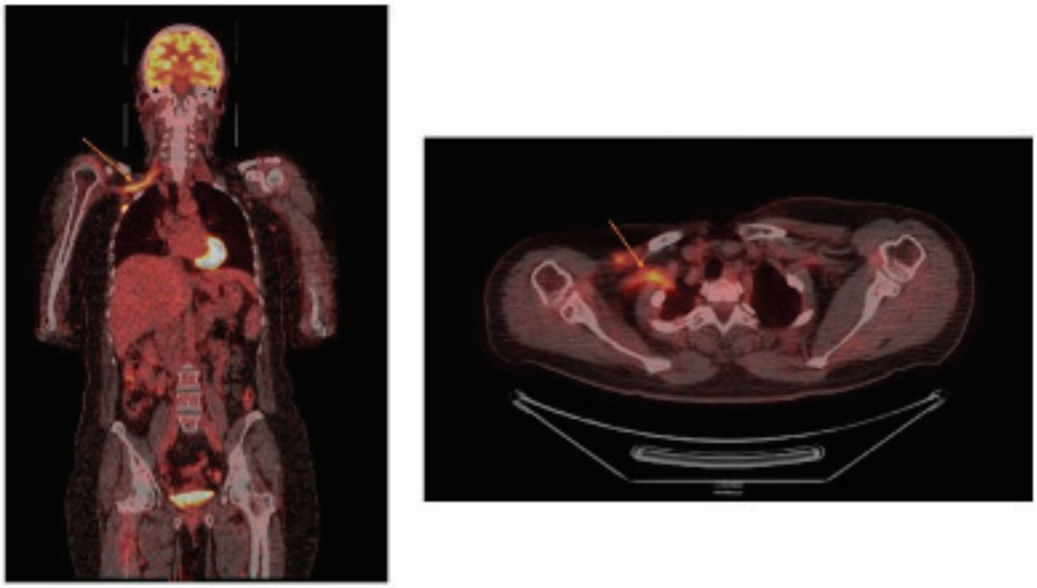

Figure 2. The coronal and transaxial fused PET/CT images revealed a linear pattern of FDG uptake in right brachial plexus (orange arrows).
Brachial plexopathy is a rare condition with an incidence of less than 0.5%. Metastatic breast and lung cancers are the most common nontraumatic causes of brachial plexopathy following radiation induced plexopathy (1). MRI is the modality of choice for diagnosis of brachial plexopathy and preferred to other imaging modalities for characterization of brachial plexopathy due to its multipl planar capabilities and superior soft-tissue contrast. In MRI, radiation fibrosis shows diffuse thickening and minimal enhancement along the brachial plexus and MRI cannot always readily differentiate radiation-induced plexopathy from metastatic plexopathy (2). ^{18}F-FDG PET/CT is a useful tool in the evaluation of patients with suspected metastatic plexopathy, particularly when MRI findings are suspicious (3). The typical pattern as seen in MIP and coronal images is linear uptake, extending from the superomedial aspect (supra/infra clavicular) to the lateral aspect of axilla closely related to the subclavian/axillary vessels (4). ^{18}F-FDG PET/CT plays an important role in diagnosing neoplastic plexopathy, differentiating it from radiation-induced plexopathy and monitoring response to treatment.

Ethics

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Wood JJ, Gawler J, Whittle RJ, Staunton MD. Brachial plexopathy in breast carcinoma - An unsolved problem. Eur J Surg Oncol 1991;17:265-269.
2. Thyagarajan D, Cascino T, Harms G. Magnetic resonance imaging in brachial plexopathy of cancer. Neurology 1995;45:421-427.
3. Ahmad A, Barrington S, Maisey M, Rubens RD. Use of positron emission tomography in evaluation of brachial plexopathy in breast cancer patients. Br J Cancer 1999;79:478-482.
4. Madhavi T, Chandan D, Anurag S, Chandra Sekhar B. Metastatic brachial plexopathy in a case of recurrent breast carcinoma demonstrated on 18F-FDG PET/CT. Nucl Med Mol Imaging 2014;48:85-86.

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Findings of Gynecomastia That Developed in Follow-up Secondary to Bicalutamide Treatment on Bone Scan

Kemik Sintigrafisinde Bicalutamide Tedavisine Sekonder Takipte Gelişen Jinekomasti Bulguları

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Abstract

Prostate cancer is a common neoplastic disease especially in elder patients. Metastatic prostate disease has low five-year survival rate. Bicalutamide is an androgen receptor antagonist that acts as an inhibitor by competizing androgen receptors in the target tissue and used as a treatment option in prostate cancer. Bone scan was performed on a 79-year-old male with prostate cancer in our department. Blood pool images showed bilateral hyperemia in the breast regions which was not present on the previous scan one year ago. On physical examination, there was bilateral painful gynecomastia. It was learned that the patient was given Bicalutamide therapy after the first bone scan. Blood pool images may detect this side effect and should be evaluated with physical examination in case of clinical doubt.

Keywords: Bicalutamide, gynecomastia, bone scan, prostate cancer

Öz

Prostat kanseri, ileri yaşlarda görülme sıklığı artan ve uzak metastazı olan hastalarda 5 yıllık sağkalım oranı önemli ölçüde düşük seyreden bir neoplazidir. Bicalutamide, prostat kanserli hastalarda kullanılan ve hedef dokudaki androjen reseptörleri ile kompetisyona girerek inhibitör etki gösteren bir ilaçtır. Prostat kanseri nedeniyle takip edilen 79 yaşındaki erkek hastaya bölümümüzde kemik sintigrafisi çekildi. Kan havuzu görüntülerinde bir yıl önceki incelemesinde gözlenmeyen, her iki meme bölgesinde hiperemi gelişimi görüldü. Hastanın fizik muayenesinde bilateral ağrılı jinekomasti tespit edildi. İlk sintigrafisinden sonra hastaya Bicalutamide tedavisi başlandığı öğrenildi. Kan havuzu görüntüleri bu yan etkiyi tespit edebilir ve klinik şüphe halinde fizik muayene ile birlikte değerlendirilmelidir.

Anahtar kelimeler: Bicalutamide, jinekomasti, kemik sintigrafisi, prostat kanseri

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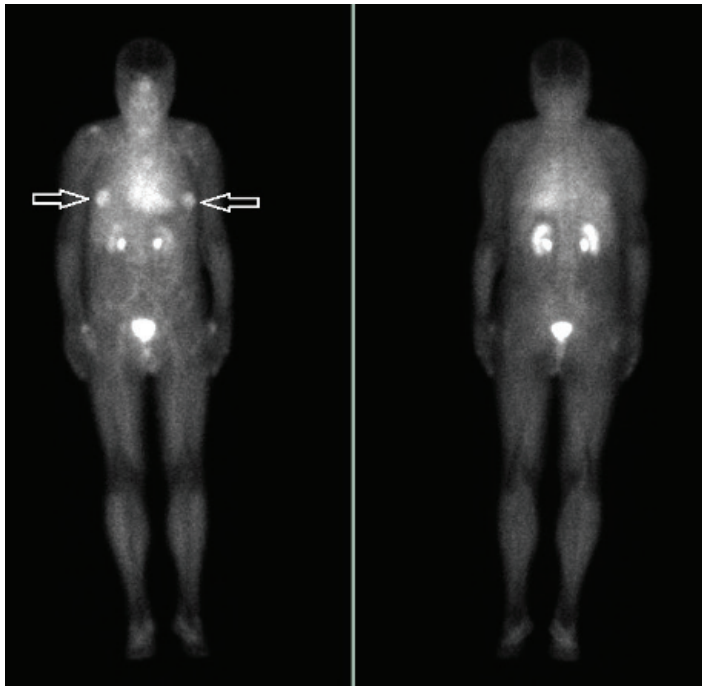

Figure 1. A 79-year-old male patient with prostate cancer underwent bone scan for the detection of bone metastases in our department. Blood pool images were taken immediately after the administration of Tc-99m labeled methylene diphosphonate and bone phase imaging was performed after 3 hours following the injection of radiopharmaceutical. In the blood pool phase, intense hyperemia was observed in regions corresponding to both areolar areas.

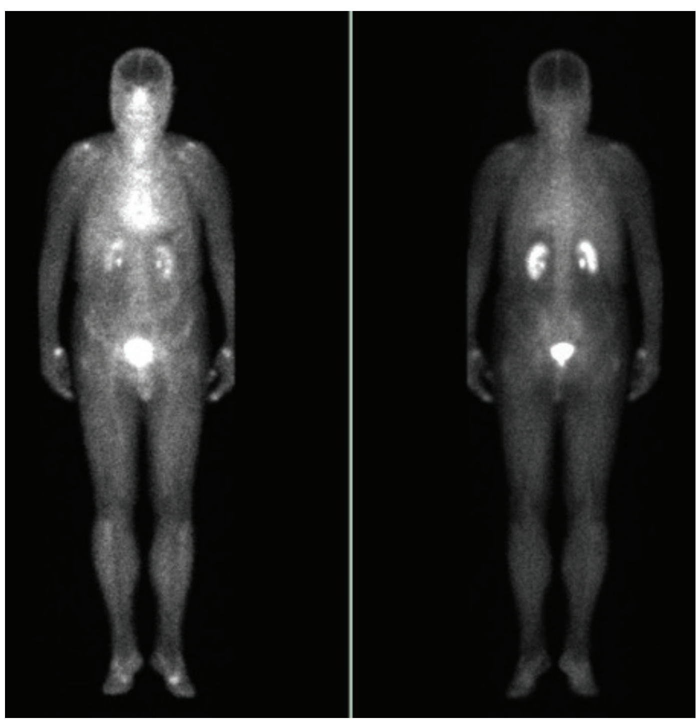

Figure 2. Previous scintigraphic examination of the patient one year before this scan and Bicalutamide treatment showed no sign of hyperemia in these areas.

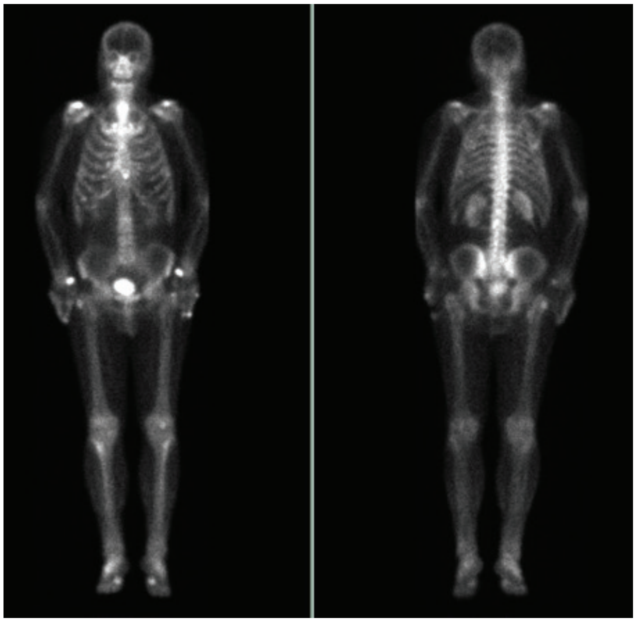

Figure 3. Bone phase images were consistent with stable degenerative changes and bone metastasis was not observed.

Physical examination of the patient revealed bilateral painful gynecomastia. In the drug questionnaire, it was learned that the patient was given Bicalutamide therapy after the first bone scan. No other drug use or any disease that might cause gynecomastia was found. Bicalutamide is a nonsteroidal drug used in patients with prostate cancer, which can be administered in combination with LHRH analogues. It has a competitive inhibitor effect on cytosolic androgen receptors in the target tissue (1,2). Gynecomastia, breast pain, fatigue and decreased libido are common side effects of Bicalutamide (3,4). When an increase in estrogen/androgen ratio in the breast tissue occurs, this may cause gynecomastia and breast pain (5). When inflammation or swelling occurs in breast regions, this may be seen on blood pool images. If these hyperemic tissues or lesions have no effect on nearby bones, clearance of the radiopharmaceutical happens and normal distribution of the tracer is seen on late bone phase images. We routinely perform 2-phase imaging in oncology patients to analyze the possible hyperemic status of bone lesions for the differential diagnosis of benign or malignant pathologies. Physical examination may help narrowing the differential diagnosis among gynecomastia, other soft tissue lesions or radioactivity contamination, when this sign is seen. It is also important to keep in mind that gynecomastia can sometimes be seen unilaterally. There are also several reports in the literature about incidental gynecomastia and other nuclear medicine procedures apart from bone scan, such as sodium fluoride positron emission tomography (PET), myocardial single photon emission computed tomography or single photon emission computerized tomography PET imaging (6,7,8). Blood pool images may detect this side effect and should be evaluated with physical examination in case of clinical doubt.

Ethics

Informed Consent: Written informed consent of the patient was obtained from patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Ü., Concept: K.Ü., Design: K.Ü., Data Collection or Processing: K.Ü., N.G., Analysis or Interpretation: K.Ü., N.G., Literature Search: K.Ü., Writing: K.Ü.

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

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References

1. Akaza H. Combined androgen blockade for prostate cancer: review of efficacy, safety and cost-effectiveness. Cancer Sci 2011;102:51-56.
2. Iversen P, Melezinek I, Schmidt A. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. BJU Int 2001;87:47-56.
3. Fagerlund A, Cormio L, Palangi L, Lewin R, Santanelli di Pompeo F, Elander A, Selvaggi G. Gynecomastia in Patients with Prostate Cancer: A Systematic Review. PLoS One 2015;10:e0136094.
4. Sieber PR. Treatment of bicalutamide-induced breast events. Expert Rev Anticancer Ther 2007;7:1773-1779.
5. Braunstein GD. Aromatase and gynecomastia. Endocr Relat Cancer 1999;6:315-324.
6. Kothekar E, Raynor WY, Al-Zaghal A, Werner TJ, Alavi A. Incidental 18F-NaF Uptake in Drug-Induced Gynecomastia. Clin Nucl Med 2019;44:303-304.
7. Farag AA, Andrikopoulou E, Hage FG. Spironolactone-induced bilateral gynecomastia in a man detected by SPECT myocardial perfusion imaging. J Nucl Cardiol 2017;24:742.
8. Wang HY, Jeng LB, Lin MC, Chao CH, Lin WY, Kao CH. 18F-FDG PET/CT in detection of gynecomastia in patients with hepatocellular carcinoma. Clin Imaging 2013;37:942-946.

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Lymphoblastic Involvement of the Bone Marrow as a Cause of Superscan Appearance in ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography

^{18}F-Florodeoksiglikoz Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi'de Supersken Görünümünün Bir Nedeni Olarak Kemik İliğinin Lenfoblastik Tutulumu

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Abstract

The ^{18}F-fluorodeoxylucose (FDG) positron emission tomography (PET) is the gold standard imaging modality in the staging of lymphoma. The superscan appearance in the FDG PET/computerized tomography (CT) imaging might be because of benign diseases or malignant infiltrations. This case report presents lymphomatous blastic infiltration as a cause of superscan appearance in ^{18}F-FDG PET/CT.
Keywords: Superscan, FDG, PET/CT, lymphoma

Öz

^{18}F-florodeoksiglikoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) lenfoma evrelemesinde altın standard görüntüleme yöntemidir. FDG PET/BT'de supersken görünümü benign hastalıklardan dolayı veya dokuların malign hastalıklarla tutulmasından kaynaklanabilir. Bu olgu sunumunda FDG PET/BT'de lenfomatöz blastik infiltrasyon sonucu olan supersken görünümü sunulmaktadır.
Anahtar kelimeler: Supersken, FDG, PET/BT, lymphoma

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Figure 1. Multiple intensity projection image of the fluorodeoxylucose (FDG) positron emission tomograph/computerized tomography (PET/CT) demonstrating significant uptake in bone marrow, spleen and lymph nodes and faint physiological activity in brain and liver without other soft tissue. Fifty-four-year-old female patient presented with anemia, leukopenia and trombositopenia. The patient was referred for ^{18}F-FDG PET/CT imaging and bone marrow biopsy procedure. The PET/CT imaging was performed after a fasting period of 12 hours and the blood glucose level was 111 mg/dL. The imaging was performed 60 minutes after intravenous administration of 7.7 mCi ^{18}F-FDG in craniocaudal direction in 3D acquisition mode for 1 min per bed position with nondiagnostic CT scan for attenuation correction with oral contrast administration. The imaging revealed multiple servical, mediastinal, abdominal lymph nodes and severe bone marrow activity accumulations suggesting the infiltration of the disease as well as diminished activity in the soft tissues, physiological uptake in the brain, liver and spleen (Figure 1).

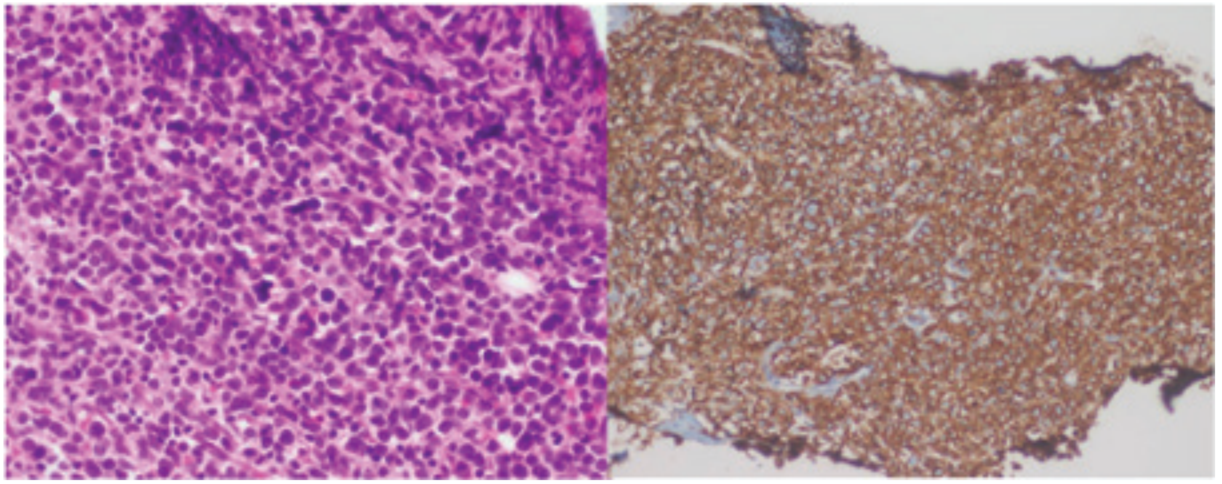

Figure 2. Pathology images of bone marrow biopsy show bone marrow infiltration of lymphoblastic cells with hematoxylene and eosine (left) and CD20 staining (right). The bone marrow biopsy revealed complete blastic (100%) infiltration of the bone marrow (Figure 2) and diagnosis of B cell lymphoma. The superscan imaging examples in the literature were usually due to the malignant tumor infiltration of the bone marrow or hepatic infiltration. According to a review analysis, the possible causes of superscan appearance in the FDG PET/CT imaging of the bone marrow might be due to the benign and malignant pathologies including the colony stimulating factors, pyrexia due to infection, primary or secondary hyperparathyroidism (1). Additionally, diffuse hepatic activity as a consequence of hepatic superscan in the FDG PET/CT was reported in the hepatic lymphoma (2) and hepatic angiosarcoma (3), previously. The superscan appearance obscures some findings and this causes false negative misinterpretation of some of the malignant lesions as well. There were two previously reported cases with diffuse large B cell lymphoma infiltration of the liver (4,5). These cases had significantly decreased physiologic uptake in the brain, cardiac and renal tissues as well. Parida et al. (6) reported a case with superscan acute lymphoblastic lymphoma with slight physiological uptakes in liver and spleen. This present case showed significant increased activity in bone marrow and spleen and superscan appearance as a result of malignant infiltration of "acute lymphoblastic lymphoma" of the tissues which was documented by bone marrow biopsy results.

Ethics

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.P.K., P.Ö.K., A.A., M.Y., Concept: Z.P.K., P.Ö.K., Design: Z.P.K., P.Ö.K., Data Collection or Processing: Z.P.K., P.Ö.K., A.A., M.Y., Analysis or Interpretation: Z.P.K., P.Ö.K., Literature Search: Z.P.K., P.Ö.K., Writing: Z.P.K., P.Ö.K., A.A., M.Y.

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

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References

1. Manov JJ, Roth PJ, Kuker R. Clinical Pearls: Etiologies of Superscan Appearance on Fluorine-18-Fludeoxyglucose Positron Emission Tomography-Computed Tomography. Indian J Nucl Med 2017;32:259-265.
2. Kaneko K, Nishie A, Arima F, Yoshida T, Ono K, Omagari J, Honda H. A case of diffuse-type primary hepatic lymphoma mimicking diffuse hepatocellular carcinoma. Ann Nucl Med 2011;25:303-307.
3. Oe A, Habu D, Kawabe J, Torii K, Kawamura E, Kotani J, Hayashi T, Sakaguchi H, Shiomi S. A case of diffuse hepatic angiosarcoma diagnosed by FDG-PET. Ann Nucl Med 2005;19:519-521.
4. Taneja S, Achong DM. Hepatic superscan on PET/CT due to Richter's transformation of chronic lymphocytic leukemia. Clin Nucl Med 2010;35:644-645.
5. Yang G, Nie P, Wang Z, Xing X. (18)F-FDG hepatic superscan caused by a non-germinal center subtype of diffuse large B-cell lymphoma. Eur J Nucl Med Mol Imaging 2016;43:1928.
6. Parida GK, Soundararajan R, Passah A, Bal C, Kumar R. Metabolic Skeletal Superscan on 18F-FDG PET/CT in a Case of Acute Lymphoblastic Leukemia. Clin Nucl Med 2015;40:567-568.