RESEARCH COMMUNICATION

Whole Body 18F-FDG PET/CT Imaging in the Detection of Primary Tumours in Patients with a Metastatic Carcinoma of Unknown Origin

Ali Osman Kaya[1], Ugur Coskun[1], Mustafa Unlu[1], Umit Ozgur Akdemir[1], Nuriye Yildirim Ozdemir[1], Nurullah Zengin[1], Mustafa Benekli[1], Ramazan Yildiz[1], Emel Yaman[1], Banu Ozturk[1], Mahmut Gumus[1], Aytug Uner[1], Deniz Yamac[1], Emel Ucgul[1], Suleyman Buyukberber[1], for the Anatolian Society of Medical Oncology

Abstract

Purpose: The aim of this study was to evaluate the role of whole body 18F-FDG PET/CT imaging in the detection of primary tumors in patients with a metastatic cancer from an unknown primary site. Methods: The study population consisted of 43 patients with a biopsy proven metastatic disease, negative conventional diagnostic procedures (including CT/MRI/endoscopic procedures) and a whole body 18F-FDG PET/CT examination. Patients' records were retrospectively analyzed. According to the final pathologic diagnoses, rate of detection of the primary tumor site was determined. Additionally, overall patient survival was calculated to evaluate the prognostic value of 18F-FDG PET/CT findings. Results: A primary tumor site was shown by 18F-FDG PET/CT in 24 patients (24/43; 55.8%). In 18 patients 18F-FDG PET/CT scans were negative (18/43; 41.8%). In a patient with an adenocarcinoma metastasis 18F-FDG PET/CT was falsely positive for an inflammatory lesion in the lung. Among the 18F-FDG PET/CT positive and negative groups median overall survival was not significantly different (log-rank p=0.573). Conclusion: Whole body 18F-FDG PET/CT imaging has a high rate of detection of a primary tumor in patients with a carcinoma of unknown origin.

Key Words: Carcinoma of unknown primary, CUP, 18F-FDG PET/CT, survival

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Introduction

Metastatic cancer of unknown primary origin (CUP) is a syndrome consisting of a biopsy-proven malignancy with an unidentified primary lesion after careful review of the patient's medical history, thorough physical examination, relevant laboratory (including prostate-specific antigen) and imaging tests (abdominal-pelvic-thoracic computed tomography (CT) and/or magnetic resonance imaging (MRI) and mammography in women) (Abbruzzese et al., 1995). In CUP, only 20-27 % of primary tumor sites are identified by conventional methods, and even at autopsy series the primary tumor site is detected in only 30-82 % of patients (Le Chevalier et al.,1988; Steckel et al.,1980). The low detection rate of the primary tumor may be due to several reasons: A primary tumor either remains microscopic and escapes clinical detection, or due to an angiogenetic incompetence that leads to marked apoptosis disappears after seeding the metastasis (Naresh,2002). In addition, the sensitivity of conventional diagnostic procedures may not be satisfactory. Although the median survival in patients with CUP is approximately 4-12 months, the detection of the primary tumor and initiation of therapy can prolong survival to 23 months (Raber et al.,1991; Lenzi et al.,1997).

Whole body positron emission computerized tomography (PET) and PET/CT hybrid imaging with 18F-fluorodeoxyglucose (18F-FDG) have gained wide application in the diagnosis, staging and follow-up of cancer patients. The degree and amount of 18F-FDG uptake in tumor tissues are also valuable indicators in the prognostic stratification of cancer patients. Therefore, we aimed to study the role of whole body 18F-FDG PET/CT imaging in the detection of the primary site and prognostic stratification in patients presenting with a histologically proven metastasis from an unknown primary tumor.

Materials and Methods

Patients

We retrospectively evaluated the file records of 43

*[1]Gazi University, School of Medicine, Department of Medical Oncology and Department of Nuclear Medicine, Ankara Numune Education and Research Hospital, Department of Medical Oncology, Istanbul Kartal Education and Research Hospital, Department of Medical Oncology, Istanbul, Turkey *For correspondence: ugurcos@hotmail.com*

patients who were referred to 18F-FDG PET/CT imaging between August 2004 and March 2008 with a diagnosis of cancer of unknown primary. Thirty-two patients (74.4 %) were males and 11 patients (25.6 %) were females. The median age was 50 years (range: 37-76). The inclusion criteria were the presence of at least one biopsied metastatic lesion and negative results from physical examination, laboratory tests and conventional diagnostic procedures (thoracic-abdominal-pelvic CT and/or MRI, mammography in women, prostate-specific antigen in men, and endoscopic procedures). None of the patients had a history of cancer, received chemotherapy and/or radiation therapy prior to the 18F-FDG PET/CT examination. Median follow up duration of total 43 patients was 9 months (range:2 – 34 months).

18F-FDG PET-CT Imaging

Whole body PET-CT data were acquired 45 minutes following the administration of 18F-FDG (0.14 mCi/kg of body weight) using a Discovery ST PET-CT scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). Patients had fasted for at least 4 hours and their blood glucose levels were controlled before 18F-FDG injection. All of the patients had blood glucose levels lower than 200 mg/dl. No iv contrast material was used for the CT scans. During the uptake phase of 18F-FDG patients laid still in a warm room. Each patient underwent a low dose (140 kV, 80 mA) whole body CT scan and subsequently a 2D whole body PET scan with an acquisition time of 4 minutes per bed position. The resulting axial, coronal and sagittal slices were visually evaluated by two nuclear medicine physicians experienced in whole body PET/CT imaging.

Statistical analysis

According to the results of 18F-FDG PET/CT and histopathologic examinations the rate of detection of the primary tumor was determined. Overall survival times were estimated by the Kaplan-Meier method and survival curves were compared with the log-rank test using SPSS 12.0 program. The p-values less than 0.05 were considered statistically significant.

Results

A lesion with an increased 18F-FDG uptake that indicated the primary tumor, was detected in 25 patients. However, in one of these patients, the biopsy of the 18F-FDG avid lung lesion revealed benign inflammatory changes. In the remaining 24 patients (24/43, 55.8%) the primary tumors were correctly shown by whole body 18F-FDG PET/CT scan. The false positive rate and positive predictive value were calculated as 1/43 (2.3 %) and 24/25 (96 %), respectively. In 18 patients 18F-FDG PET/CT scans were negative (18/43; 41.8%).

The primary tumors detected were: in 13 patients lung

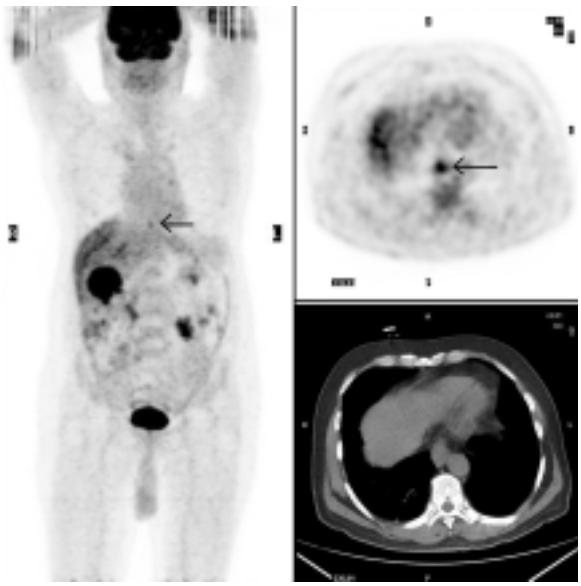

Figure 2. 18F-FDG PET/CT Showing Focal Increase of 18F-FDG Uptake in the Gastroesophageal Junction. See arrows on maximum intensity projection image on the left and transaxial PET image on the upper right. Liver and mesenteric metastatic lesions have intense 18F-FDG uptake

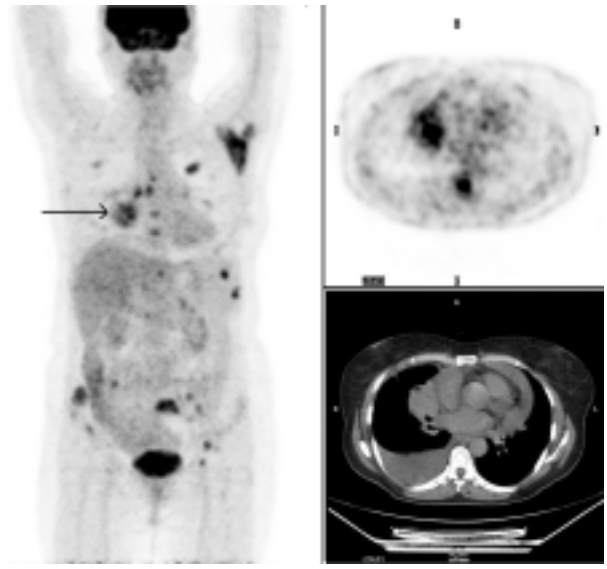

Figure 1. 18F-FDG PET/CT Showing a Hypermetabolic Lesion in the Right Lung. See arrow on maximum intensity projection image on the left, transaxial PET and corresponding CT images on the right) in addition to multiple hypermetabolic bone metastases

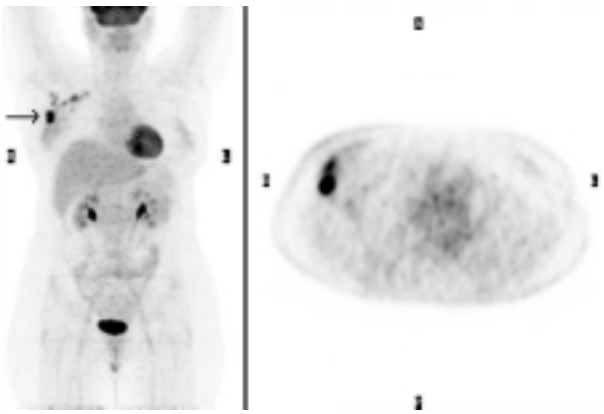

Figure 3. 18F-FDG PET Showing a Hypermetabolic Lesion in the Right Breast. See arrow on maximum intensity projection image on the left and several focal hypermetabolic lesions in the right axillary and pectoral regions corresponding to metastatic lymph nodes

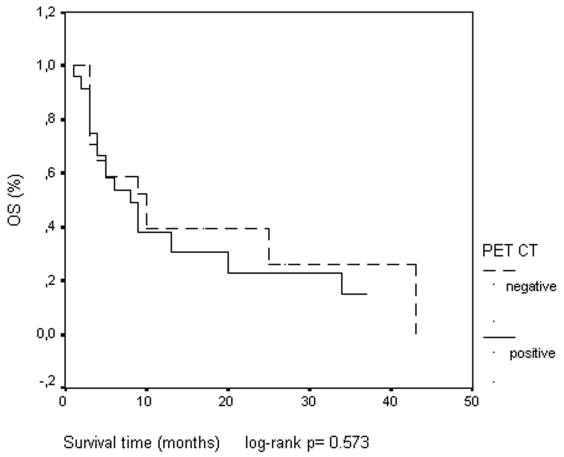

Figure 4. Overall Survival in the 18 F-FDG-PET/CT Negative and Positive Groups. Median values were 10 months (95%CI: 3.9-16.1) and 8 months (95%CI: 4-12) patients, not statistically significant (log-rank p= 0.573)

adenocarcinomas (54.2%) (Figure 1), in two patients pancreas adenocarcinomas (8.32%), in two patients gastric adenocarcinomas (8.3%) (Figure 2), in one patient a rectum adenocarcinoma (4.2%), in two patients invasive ductal adenocarcinomas of breast (8.3%) (Figure 3), in one patient a uterine leiomyosarcoma (4.16%), in one patient a rhabdomyosarcoma (4.2%), in one patient a malignant melanoma (4.2%), and in one patient a tongue squamous cell carcinoma (4.2%).

Median overall survival in the 18F-FDG PET/CT positive and negative groups were eight (95% CI: 4-12) and ten (95% CI: 1-11) months, respectively. However, this difference was not statistically significant (log-rank p= 0.573) (Figure 4).

Discussion

The CUP syndrome covers a heterogeneous group of metastatic malignant tumors. The prognosis of patients with CUP syndrome still remains poor and the median duration of survival is between 4 and 12 months (Raber et al.,1991; Lenzi et al., 1997). The low rate of detection of the primary tumor site has two main causes: The size of the primary lesion may be smaller than the resolution power of conventional imaging procedures (such as CT and MRI) (Abbruzzese et al.,1995). Secondly, the primary tumor might disappear after giving rise to a metastasis because of its angiogenetic incompetence which leads to marked apoptosis (Naresh, 2002).

In our study, we found a higher rate of detection of the primary tumor origin by 18F-FDG PET/CT imaging (55.8 %) in comparison to the some studies in literature (Kole et al.,1998; Bohuslavizki et al., 2000; Gutzeit et al.,2005; Pelosi et al.,2006). However, it was similar to two important studies (Alberini et al., 2003; Nanni et al.,2005). The recent clinical introduction of hybrid PET/CT imaging, which allows simultaneous acquisition of accurately aligned whole body anatomical and functional images, seems to be more accurate than PET alone in assessing the presence and location of tumor foci, and therefore in tumor staging (Hany et al.,2002; Pelosi et al.,2004). Gutzeit et al (2005) studied 45 patients with tumor metastasis from unknown primary site by 18F-FDG PET/CT, obtaining an identification rate of the primary cancer in 33% of cases Nanni et al (2005) detected a primary tumor site in 12 out of 21 (57%) patients by 18F-FDG PET/CT scan and Pelosi et al (2006) identified the primary tumor site in 24 of 68 (35.3%) patients with CUP syndrome. The reported detection rates are similar for the 18F-FDG PET imaging. Kole et al (1998) studied 29 patients with CUP syndrome and identified the primary tumor in 7 (24 %). In a series of 44 patients, Alberini et al (2003) reported 59% (26/44) rate of detection. Bohuslavizki et al (2000) studied 53 CUP patients with 18F-FDG PET imaging before conventional diagnostics tests, and rate of primary tumor detection found as 37.8%. Therefore, in contrast to the superiority of PET/CT imaging in cancer staging, in the detection of primary tumor in CUP syndrome 18F-FDG PET alone and PET/CT imagings gave similar results.

The detection rates reported in the literature showed significant variation (from 24% to 59%) (Kole et al.,1998; Alberini et al., 2003). Despite the high rate of identification of the presence of a malignancy by 18F-FDG PET/CT imaging, the precise diagnosis of the primary site is not possible in certain types of neoplasm (Fencl P et al.,2007). High grade epithelial tumors show an elevated glucose consumption with a high 18F-FDG uptake, while in low grade epithelial tumors, such as in tumors with neuroendocrine differentiation, 18F-FDG uptake can be low or absent (Alberini JL et al.,2003).

We tested overall survival rates between the PET/CT positive and negative groups. Although the difference was not statistically different we found a better median overall survival in the 18F-FDG PET/CT negative group (10 versus 8 months). In the literature, in accordance with our result, it was reported that life expectancy was significantly shorter in patients with a positive 18F-FDG PET/CT finding in comparison to 18F-FDG PET/CT negative patients (Fencl et al., 2007). The presence of a 18F-FDG avid lesion was a sensitive prognostic indicator of a shorter life expectancy in patients with CUP syndrome, when different prognostic factors, such as age, histology, the site of metastatic involvement, performance status, the site of lymph node metastasis and histologically versus clinically proven metastatic disease were also considered (Maiche,1993; Hess et al.,1999; Levi et al.,2002; van de Wouw et al., 2002; Pavlidis et al., 2003). However, it might be expected that once the primary tumor was identified by 18F-FDG PET/CT imaging, patient would be given a more targeted therapy and have a better outcome. This expectation is supported by the observation that in patients with CUP syndrome the detection of the primary tumor can prolong survival from 4-12 months to 23 months (Raber et al.,1991; Lenzi et al.,1997).

In conclusion, 18F-FDG PET/CT imaging showed a high detection rate for the primary tumor origin in patients with the CUP syndrome. This contribution of 18F-FDG PET/CT imaging might be expected to prolong survival in these patients. However, in this study we did not observe any significant difference between PET/CT positive and negative patient groups in respect to median overall survival.

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