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Original

Sensitivity of [^{18}F]FDG PET/CT and classification of the primary tumor site in patients with carcinoma of unknown primary

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Abstract

Background: The aim of this study is to find the sensitivity of the [^{18}F]FDG PET/CT and the classification of the primary sites of carcinoma of unknown primary (CUP) as a single-center experience.

Material and methods: Sixty-eight patients with a mean age of 62.43 ± 12.78 years were included in this study retrospectively. Sixty-five patients had biopsy or surgery after PET/CT, which revealed pathological diagnoses of malign primary tumors, while primary tumor site could not be detected in three patients with histopathological examination. We evaluated the primary site of CUP with [^{18}F]FDG PET/CT.

Results: Primary sites of three patients were not determined by histopathological examination. Malign lesions indicating the primary site of tumor were identified in 52 of 68 patients with PET/CT correctly. The primary tumor was lung cancer in 14 patients, cholangiocellular cancer in 9 patients, lymphoma in 9 patients, pancreas cancer in 6 patients, gastric cancer in 4 patients, ovary cancer in 4 patients, colon cancer in 4 patients, breast cancer in 3 patients, hepatocellular cancer in 2 patients, rectal cancer in 2 patients, sarcoma in 2 patients, esophagus, renal cell cancer, squamous cell cancer, endometrium cancer, malign melanoma, and multiple myeloma in 1 patient with histopathological examination. PET/CT was false positive in one patient. There were 13 patients in whom primary tumor could not be localized by PET/CT, but was diagnosed by histopathological evaluation.

Conclusions: PET/CT should be the first-line diagnostic tool for CUP, other diagnostic imaging tools should be applied after a negative whole-body PET/CT.

KEY words: positron emission tomography-computed tomography; unknown primary tumors; ^{18}F-fluorodeoxyglucose

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Introduction

Cancer of unknown primary (CUP) presents with metastasis and the original site of malignancy cannot be identified with a properly standardized diagnostic work-up. CUP is a separate entity because of its different biological properties from other known primary tumors [1]. CUP is one of the ten most frequent cancers and the fourth most common cancer-related death cause [2]. Identification of the primary tumor influences the patient management positively because specific chemotherapy regimens and targeted therapy develop continuously [3].

Detection of the primary tumor in CUP is a diagnostic challenge. Despite many investigations, the primary tumor cannot be identified. The detection rate of the primary tumor varies in a range of 22–73% [2, 4]. Whole-body scanning with fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) may detect the primary tumor. FDG PET/CT

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provides functional and anatomical imaging [4]. The therapeutic impact of PET/CT is not only the localization of the primary tumor but also the result of the identification of additional metastases [5, 6]. FDG PET/CT contributes to patient management by determining the extent of the disease [7]. Despite the identification of the primary tumor, optimal staging, and an opportunity for prognosis, monitoring of chemotherapy response can be evaluated by FDG PET/CT [8].

In this study, we aimed to find the sensitivity of the [^{18}F]FDG PET/CT and the classification of the primary sites of CUP as a single-center experience.

Material and methods

Sixty-eight patients (31 female and 37 male) with a mean age of 62.43 ± 12.78 years (min.: 29, max.: 88) were enrolled in this study retrospectively. Sixty-five patients had biopsy or surgery after PET/CT, which revealed malign pathological diagnoses of the primary tumor, while primary tumor sites of three patients could not be found with histopathological examination. We evaluated the primary site of CUP with [18F]FDG PET/CT. An ethical approval was obtained from Mustafa Kemal University Local Ethics Committee.

[^{18}F]FDG PET/CT imaging

All patients underwent [^{18}F]FDG PET/CT imaging after 6 hours of fasting. Before [^{18}F]FDG injection, the blood glucose of all patients was evaluated and a blood sugar level less than 180 mg/dL was accepted. Oral contrast was given to all patients without intravenous (iv) contrast. After iv injection of F-18 FDG in a dose of ~300–450 mBq according to body weight. Approximately 60 minutes after injection, whole-body scan from vertex to feet was acquired by a PET/CT scanner (Siemens, BioGraph mCT, Germany) with 1–2 minute acquisition for each 6–8 bed positions. The CT scan was used for attenuation correction and anatomical localization. The images were evaluated by two experienced nuclear medicine specialists both visually and semiquantitatively. A lesion with a SUVmax value equal to or greater than 2.5 other than metastatic lesions was considered as the primary site of the tumor.

Data analysis

Age which is a quantitative parameter was represented as mean±standard deviation. Qualitative parameters such as gender and primary sites of CUP were expressed as frequency. Sensitivity, specificity, and accuracy of PET/CT were calculated as the histopathological results accepted as gold standard.

Results

Locations of the metastatic foci were as liver in 29, bone in 13, lymphadenopathy in 10, peritoneal carcinomatosis or omental cake in 5, brain in 6, adrenal in 2, lung in 1, ascites in 1, and pelvic mass in 1 patient. Sixty-five patients had malignancy with histopathological evaluation. The primary sites of three patients were not determined by histopathological examination. Malign lesions indicating the primary site of tumor were identified in 52 of 68 patients with PET/CT correctly. Fifty-two patients detected with PET/CT had malign histopathological results. The primary tumor was lung cancer in 14 patients, cholangiocellular cancer in 9 patients, lymphoma in 9 patients, pancreas cancer in 6 patients, gastric cancer in 4 patients, ovarian cancer in 4 patients, colon cancer in 4 patients, breast cancer in 3 patients, hepatocellular cancer in 2 patients, rectal cancer in 2 patients, sarcoma in 2 patients, esophagus, renal cell cancer, squamous cell cancer, endometrium cancer, malign melanoma and multiple myeloma in 1 patient with histopathological examination. PET/CT could not detect the primary tumor site in 16 patients correctly. PET/CT was false positive in one patient. There were 13 patients that primary tumor could not be localized by PET/CT, but was diagnosed by histopathological evaluation. The diagnosis was lymphoma in four patients, ovary cancer in three patients, lung cancer in three patients, malign melanoma in one patient, sarcoma in one patient, squamous cell cancer in one patient. Sensitivity, specificity, and accuracy values were 80%, 66.7%, and 79.4% respectively (Fig. 1 and 2).

Discussion

CUP is an aggressive disease with early dissemination, accounting for 3–5% of all malignant epithelial tumors [9]. Accurate localization of the primary tumor provides the targeted therapy and maintains better locoregional treatment and survival [10]. The primary site of cancer can be identified as antemortem in less than 20% of patients with CUP despite extensive workup and 70% of cases remained undiagnosed in autopsy series. Half of the patients with CUP are diagnosed as well to moderately differentiated adenocarcinoma, 30% with poorly differentiated or undifferentiated carcinomas, 15% with squamous cell carcinomas, and 5% with undifferentiated carcinomas [11].

FDG PET/CT is a noninvasive and sensitive whole-body imaging modality both allowing for the detection of the primary tumor and tumor staging. FDG PET/CT should be used as a first-line imaging modality rather than using after other imaging procedures that failed to detect primary tumors [12]. If PET/CT is used as an initial workup, it may reduce the cost, save time and guide the other examinations and biopsies [13]. PET/CT-directed biopsy is also more accurate than random biopsies for the detection of the occult primary tumor [14]. High glucose metabolism in cancer cells is exploited in PET/CT scans [15]. FDG PET/CT is not a specific for malign tumors. [^{18}F]FDG is also accumulated in inflammatory or benign tumors and causes false-positive results [7]. Tumors with low or no FDG uptake may be missed with PET/CT [2]. FDG PET/CT also guides biopsy of probable sites of the primary tumor. Intravenous contrast enhancement improves the detection of non-FDG avid tumors like hepatocellular carcinoma, neuroendocrine tumors, and bronchoalveolar carcinoma [16].

Kaya et al. [17] evaluated the primary tumor site with metastatic carcinoma of unknown origin. FDG PET/CT detected the primary tumor in 24 of 43 patients (55.8%), with one false positive benign inflammatory lung lesion. Positive predictive value (PPV) of PET/CT was 96%, whereas in 18 patients (41.8%) scan was negative. Most of the primary (54.2%) tumors were in the lung. In our study, there was only one false-positive result too. In this false positive patient, the primary site was taught ovary with PET/CT, but hypermetabolism in the ovary was physiological as seen in other imaging methods. In another study, the primary tumor was correctly identified in 24% of patients. 31% of patients had metastatic spread without clear identification of a primary tumor. In 4% of patients had a potential

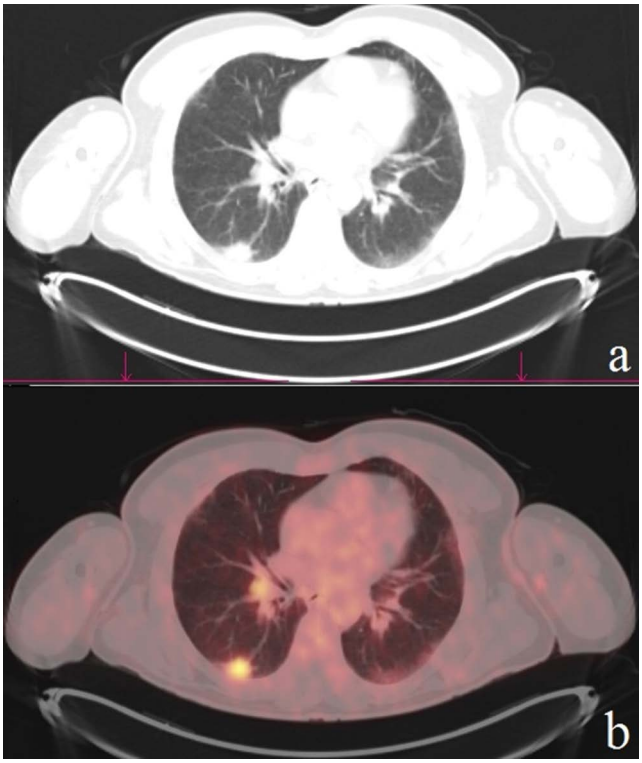

Figure 1. Multiple metastatic lesions on pelvic bones were incidentally detected with bone scintigraphy in a 55-year-old male patient. A lung lesion compatible with the primary tumor was detected in the superior segment of the inferior lobe of the right lung with positron emission tomography/computed tomography

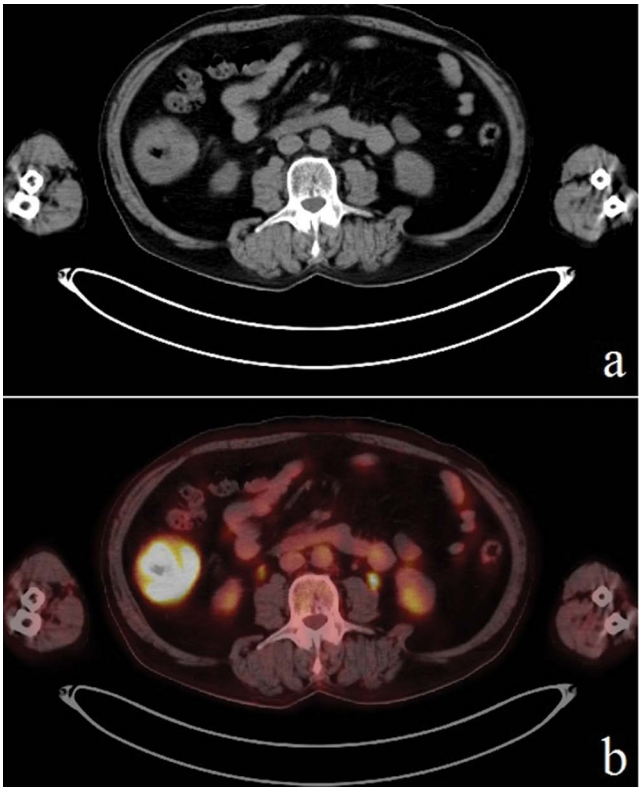

Figure 2. Positron emission tomography/computed tomography was performed for the metastatic lesion in the cerebellum in 62-year-old male patients. The primary tumor was detected in the hepatic flexure of the colon

primary tumor identified turned out to be false positive. The sensitivity, specificity, PPV, and negative predictive value (NPV) were found at 96%, 80%, 95% and 86% when the presence or absence of malignant lesions anywhere in the body were considered [18]. In a study of Deonarine et al. [19], the overall detection rate of primary tumor locations with FDG PET/CT and additional investigations and procedures was 49% with the detection rate of FDG PET/CT being 37.3% and the sensitivity was 79.2%. Lung was the most common primary tumor site and they mentioned that FDG PET/CT should be an early method to improve the accuracy of tumor staging. As in these studies, the most common primary tumor was in the lung. Fencl et al. [20] found the sensitivity and specificity 62.0% and 81.9% for the primary search, 93.6%, and 85.7% for the presence of malignancy search. In our study, the most common primary tumor site was the lung as in these previous studies. In a study of Tamam et al. [21] FDG PET/CT findings correctly diagnosed lesions as the site of the primary true positive in 75% (238 of 316 patients) with the most common was lung cancer (42.4%). Fifty-six cases were false negative with PET/CT. The sensitivity, specificity, accuracy, PPV and NPV of PET/CT were 81%, 45%, 78%, 95% and 15%, respectively [21]. In our study, the sensitivity (80%) and accuracy (79.4%) were similar to the study of Tamam et al. [21].

In some studies identification of the primary tumor was studied in specific metastatic locations. Koç et al. [22] studied the primary tumor which has been admitted with brain metastases. Twenty of 26 patients had positive PET/CT for the primary tumor, 6 lung cancer, 9 primary brain tumor, 2 renal cell carcinoma, 1 skin, 1 breast, and 1 neuroendocrine tumor. They mentioned that PET/CT must be performed in patients with brain metastases to find the primary tumor. Dandekar et al. [23] studied the utility of PET in an unknown primary with cervical metastases. They found the sensitivity and specificity of conventional imaging 92.3% and 50% whereas FDG PET showed 92.8% and 71.4%, respectively. PET had an additional benefit over CT because PET aids in screening infraclavicular primaries and distant metastases. Fan et al. [24] observed patients with malignant ascites of unknown primary sites after conventional imaging methods. 23 of 28 cases had elevated FDG with 20 patients were confirmed by pathology, but 3 were found to be falsely positive due to tuberculosis. In patients with bone metastasis of unknown origin, the primary tumor was identified in 92% of patients, with the most common cause being adenocarcinoma. The most common primary tumor was lung carcinoma (52%) [25].

In a study, the performance of FDG PET/CT was compared with conventional imaging methods, including CT, magnetic resonance imaging, and mammography in cancer of unknown primary. FDG PET/CT detected the primary tumor more than conventional imaging, but not statistically significant. It was considered that FDG PET/CT can be performed as a first-line imaging tool and then adding radiodiagnostic imaging in selective cases [5]. Jain et al. [16] mentioned that tumors that cannot be identified with PET/CT should be subjected to further extensive workup. All patients do not require PET/CT to identify the primary tumor. The decision of PET/CT scan should be made multidisciplinary [14]. But in a few studies, it was found that FDG PET/CT did not have or might be less diagnostic advantage than expected over CT or extensive conventional diagnostic workups for the detection of primary tumor site in CUP patients [26, 27]. Invasive diagnostic procedures or additional imaging were reduced after PET/CT. Additional imaging of selected organs was needed in individual cases after PET/CT [28]. As a limitation, FDG PET/CT had a very low detection rate in locating the primary site in metastatic melanoma and metastatic location in the axilla [29]. We have only one patient diagnosed with malign melanoma, and in this patient PET/CT could not detect the primary tumor site.

As in our study, PET/CT should be the first-line diagnostic tool for CUP, because almost four of five patients' primary tumor sites can be determined with PET/CT. Other diagnostic imaging tools should be applied after a negative whole-body PET/CT.

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