

THE ROLE OF PET CT IN CANCER OF UNKNOWN PRIMARY

Primeri Bilinmeyen Kanselerde PET BT'nin Rolü

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ABSTRACT

Objective: This study aimed to investigate the diagnostic value of positron emission tomography/computed tomography (PET/CT) in detecting the primary focus and in suspicious foci in patients who underwent PET/CT with a pre-diagnosis of carcinoma of unknown primary.

Material and Methods: In this retrospective study, a total of 49 patients who underwent PET/CT scan with a prediagnosis of carcinoma of the unknown primary between 2015 and 2019, and whose clinical follow-up and histopathological data were available, were included. PET/CT study was performed in 20 (40%) patients after the metastatic lesion was detected as a result of pathology, and in 29 (60%) patients due to clinical findings and imaging methods and suspicion of malignancy. The histopathological and clinical evaluation of the patients before PET/CT and the primary surgery, histopathological examinations and clinical follow-ups after PET/CT were examined. The success of PET/CT in detecting primary lesions and evaluating suspicious lesions in metastatic cases was analyzed.

Results: Seventeen (34.7%) of the patients were female and 32 (65.3%) were male. A primary malignant tumor was detected in 34 (85%) of 40 patients with PET/CT. Regional distribution in patients with primary cancer focus; 9 pancreases, 9 lungs, 4 livers, 3 urothelial, 2 thyroids, 1 vertebra, 1 breast, 1 ovary, 1 esophagus, 1 prostate, 1 iliac bone, 1 skin, 1 stomach and 1 colon. In the follow-up of 6 cases whose primary could not be determined; Cervical cancer was detected in 1, ovarian cancer in 1, and the primary focus could not be detected in the clinical follow-up of 4 metastatic patients.

Conclusion: PET/CT is highly successful in detecting cancers whose primary is unknown. Therefore, PET/CT is a diagnostic imaging method for the detection of the primary in cancer patients whose primary is unknown.

Keywords: Cancer of Unknown Primary; Positron Emission Tomography; Malignant Lesion

ÖZET

Amaç: Bu çalışmanın amacı, primeri bilinmeyen karsinom ön tanısı ile pozitron emisyon tomografisi/bilgisayarlı tomografi PET/BT uygulanan hastalarda, PET/BT'nin primer odak tespiti ve şüpheli odaklardaki tanısallık değerini araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 2015-2019 yılları arasında primeri bilinmeyen karsinom ön tanısı ile PET/BT çekimi yapılmış, klinik takibi ve histopatolojik verileri mevcut toplam 49 hasta dahil edilmiştir. PET/BT çalışması hastaların 20 (%40)'sinde patoloji sonucunda metastatik lezyon tespit edilmesi sonrası, 29 (%60)'unda ise klinik bulgular ve görüntüleme yöntemleri ile malignite şüphesi varlığı nedeniyle uygulandı. Hastaların PET/BT öncesi histopatolojik ve klinik değerlendirilmesi ile PET/BT sonrası primere yönelik cerrahi, histopatolojik incelemeler ve klinik takipleri incelendi. PET/BT'nin metastatik olgularda primer lezyon tespiti ve şüpheli lezyonları değerlendirmesindeki başarısı analiz edildi.

Bulgular: Hastaların 17(%34,7)'si kadın, 32 (%65,3)'si erkekti. PET/BT ile 40 hastadan 34'ünde (%85) primer malign tümör saptandı. Primer kanser odağı tespit edilen hastalarda bölgesel dağılım; 9 pankreas, 9 akciğer, 4 karaciğer, 3 üretelyal, 2 tiroid, 1 vertebra, 1 meme, 1 over, 1 özofagus, 1 prostat, 1 iliac kemik, 1 deri, 1 mide ve 1 kolon idi. Primeri saptanamayan 6 olgunun takiplerinde; 1'inde serviks kanseri, 1'inde over kanseri saptanırken, 4 metastatik hastanın klinik takibinde ise primer odak saptanamamıştır.

Sonuç: Primeri bilinmeyen kanserlerin tespitinde PET/BT oldukça yüksek oranda başarı göstermektedir. Bu nedenle PET/BT primeri bilinmeyen kanserli hastalarda primerin tespiti için, tanıya yardımcı bir görüntüleme metodudur.

Anahtar Kelimeler: Primeri Bilinmeyen Kanseri; Pozitron Emisyon Tomografisi; Malign Lezyon

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INTRODUCTION

Cancers of unknown origin refer to a heterogeneous group of metastatic tumors whose origin of the primary tumor cannot be determined despite extensive research (1,2).

Cancers whose primary is unknown constitute 2-5% of all cancers (3). The median age at diagnosis is 60-65 years, and it is more common in men than women. Sensitivity to treatment is low and the median survival time is 6-10 months (4).

To identify the primary focus in cancers of unknown origin, patients typically undergo a comprehensive physical examination, laboratory tests, and diagnostic procedures, including chest radiographs, computed tomography (CT), and/or magnetic resonance imaging (MRI), ultrasonography, mammography, and endoscopy (5). Even after these extensive tests, the primary site of origin cannot be determined in the majority of patients (6). In cases where a definitive diagnosis cannot be made with all these methods, PET/CT is applied as an auxiliary test.

Patients who underwent PET/CT imaging with a preliminary diagnosis of carcinoma of unknown primary can be divided into two groups. The first of these; is the patient group in whom metastatic focus was detected histologically and the primary focus could not be found by clinical and radiological imaging methods. The second is the group in which a suspicious metastatic lesion was detected by imaging methods, but the biopsy was not performed, and the group with high tumor markers and the tumor focus could not be detected.

PET/CT is among the recommended tests in current guidelines because it can change the management plan in the diagnosis and treatment of patients with tumors of unknown primary, detecting the primary tumor focus, especially in the head and neck region, and detecting possible additional metastases in other regions (6). The study aims to determine the primary focus of PET/CT and to investigate the diagnostic value of suspicious foci in patients who underwent PET/CT with a pre-diagnosis of carcinoma of unknown primary.

MATERIAL AND METHODS

In this retrospective study, a total of 49 patients who underwent PET/CT scan with a prediagnosis

of carcinoma of unknown primary in our clinic between 2015-2019 and whose clinical follow-up and histopathological data were available were included. PET/CT imaging was acquired using Siemens Biograph 2 (Biograph, Siemens, USA) PET/CT device approximately 60 minutes after intravenous injection of 296-407 MBq 18F-fluorodeoxyglucose (18F-FDG). All patients were fasted for at least 6 hours before PET/CT imaging and a blood glucose level of <200 mg/dL was confirmed before 18F-FDG administration. First, a low-dose CT scan was performed for precise anatomic localization and attenuation correction. Next, a three-dimensional PET scan was performed from the skull base to the proximal femur. Images were evaluated visually, lesions were evaluated together with the maximum standardized uptake value (SUV max), which is a semi-quantitative parameter. The histopathological and clinical evaluation of the patients before PET/CT and the primary surgery, histopathological examinations and clinical follow-ups after PET/CT were examined. All analyzes were performed with SPSS 20.0 (IBM corp. Released 2011. IBM SPSS Statistic for Windows, Version 20.0. Armonk, NY: IBM Corp.). The success of PET /CT in detecting primary lesions and evaluating suspicious lesions in metastatic cases was analyzed.

For this study, the approval of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee dated 15.05.2019 and registration number 19-KAEK-110 was obtained.

RESULTS

Of the 49 patients included in the study, 17 (34.7%) were female and 32 (65.3%) were male. The mean age was 64.47±9.92 years. PET/CT was performed to investigate the primary tumor after the metastatic lesion pathology results in 20 (40%) patients, and in 29 (60%) because of imaging methods and clinical findings and suspicion of malignancy. The diagnosis of the primary lesion after PET/CT was by pathology in 29 (60%) patients, and by clinical follow-up-evaluation in 20 patients.

Regional distribution of metastasized or suspicious lesions; they were 18 bones, 8 livers, 6 brains, 6 peritoneal-mesenteric-acid, 4 lymph nodes, 4 lungs and 3 pancreases.

The rate of detecting malignant primary tumors

by PET/CT was 34/42 (80%). In the follow-up of 6 cases whose primary could not be determined; Cervical cancer was detected in 1, ovarian cancer in 1, and the primary focus could not be detected in the clinical follow-up of 4 metastatic patients. PET/CT gave false-positive results in 1 patient. The pathology of the patient was Schwannoma. The percentage of PET/CT benign cases was 5/7 (71.3%) (Table 1). While the pathology results of lesions detected by PET/CT as benign were 1 osteochondroma, 1 giant

cell tumor and 1 para tubal Morgagni hydatid, no malignant finding was found in the follow-ups of 2 cases. Of the 3 cases evaluated as suspicious by PET/CT; 2 of them were malignant (glioblastoma, squamous cell carcinoma), and 1 was a benign lesion (fibrous dysplasia) (Figure 1).

Regional distribution of primary malignancy; 9 pancreas, 9 lungs, 4 liver, 3 urothelial, 2 thyroids, 1 vertebra, 1 breast, 1 ovary, 1 esophagus, 1 prostate, 1 iliac bone, 1 skin, 1 stomach and 1 colon (figure 2).

Table 1. Comparison of PET/CT findings and diagnostic data for the primary lesion

		PET CT			
DIAGNOSIS		Malignant	Benign	Suspicious	Metastasis positive but primary focus undetected
(histological/clinical)	Malignant (primary)	34		2	2
	Benign (primary)	1	5	1	
	Patient with primary undetected malignant metastasis				4

Figure 1. A 50-year-old male patient was diagnosed with FDG-PET/CT imaging after detecting a lesion (met?) in the cerebrum on CT. In FDG-PET/CT, a suspicious lesion with hypometabolic middle and pathologically increased FDG uptake in the periphery was defined in the right part posterior of the cerebrum (primary lesion?). Histopathological confirmation of the lesion was glioblastoma multiforme.

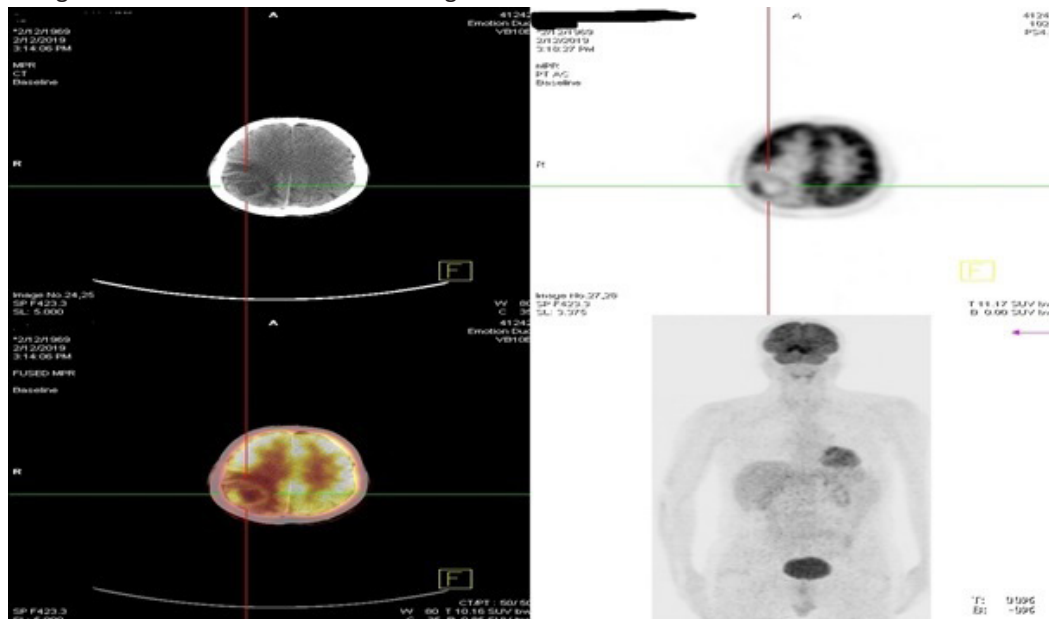
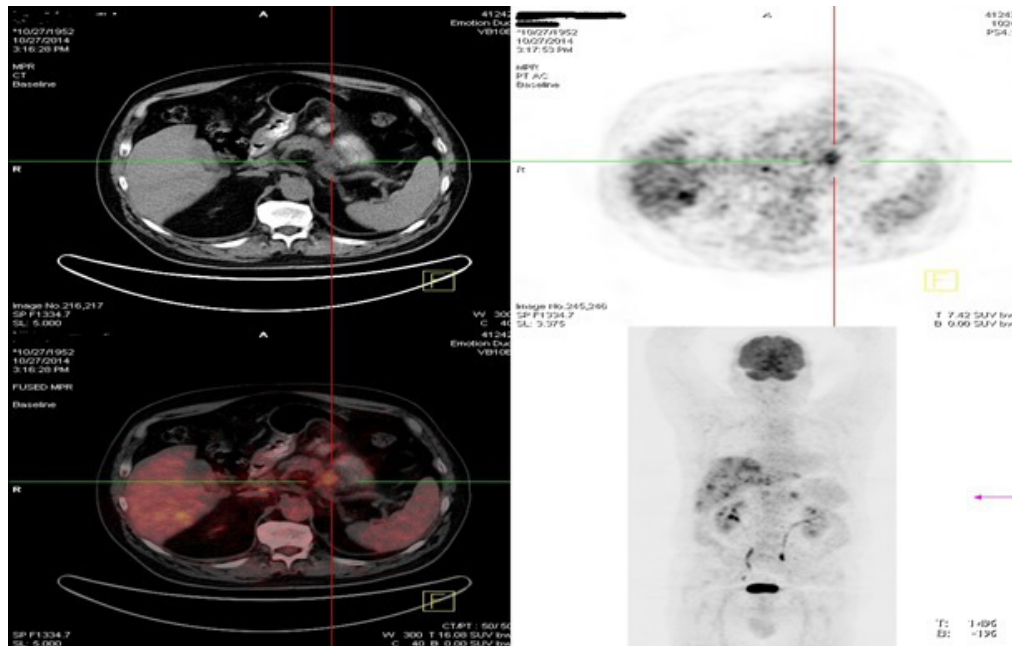


Figure 2. FDG-PET/CT imaging of a 62-year-old male patient was performed to investigate the primary lesion after the liver biopsy was adenocarcinoma metastasis. PET/CT imaging revealed a primary lesion in the pancreas, metastatic lesions in the liver, and metastasis in the hepatic lymph nodes. Histopathological confirmation of the mass in the pancreas was pancreatic adenocarcinoma, one of the most common cancers in our study.



DISCUSSION

In patients with cancer of unknown primary, despite a standard comprehensive diagnostic study according to published guidelines, there is pathological evidence of malignancy, but the primary cancer site could not be identified (7-8). Imaging with FDG PET/CT is more successful than other imaging methods in detecting the primary tumor site and detecting additional metastasis sites (6).

In patients with cancer of unknown primary, the primary tumor is usually small in size. Small tumors with a size below the PET/CT resolution limit can only be detected as long as there is increased FDG uptake (9). Many tumors exhibit maximum FDG uptake 60 minutes after FDG injection, while normal surrounding tissues show a decline in FDG uptake over time. Therefore, in PET/CT late imaging, the primary tumor-background contrast may increase significantly, thereby increasing the detectability of tumors of unknown primary (10-12). Yoo et al., in their study with 74 patients with suspected metastatic foci in the skeletal system, reported that focal increased FDG uptake in areas outside the

skeletal system in PET/CT was an important factor in determining the biopsy site and thus affecting the detection of the primary (13).

Intense FDG uptake other than metastatic foci in PET/CT and guidance of the FDG uptake area to the biopsy site is very useful in detecting the primary tumor.

In our study, PET/CT was performed for patients whose metastatic focus was detected histologically and the primary focus could not be found by clinical and radiological imaging methods, and for patients with suspected malignancy based on imaging methods and clinical findings. We tried to detect the primary focus by detecting areas of intense FDG uptake outside of the metastatic foci, comparing the SUVmax values of the tumoral area in the early late images, and providing guidance for the areas of intense FDG uptake instead of the biopsy. The diagnosis of the primary lesion after PET/CT scan was by pathology in 60% of the patients, and by clinical follow-up-evaluation in 40% of the patients.

In the literature, the success of FDG-PET/CT in detecting primary lesions has been reported at varying rates.

Soni et al. reported that 18F-FDG PET/CT detects the primary in 39% of patients, Thai et al. 40.5%, Ella et al. 44%, in the range of 22-75% reported in other studies in the literature. (14,5,4).

In a comprehensive review of 16 studies and 302 patients, Liu reported that the accuracy rate of FDG-PET in detecting tumors of unknown primary was 78.8% (14).

In our study, we found the rate of detection of malignant primary tumors by PET/CT as 34/42 (80%), slightly higher than the literature. The reason why this rate is slightly higher than in the literature is that the majority of the cases in our study were primarily located in an organ of thoracoabdominal origin as stated in the literature, it was easier to detect compared to those with head and neck cancer, or the widespread use of PET/CT and technological developments in devices may be associated with increased sensitivity (15). In addition, in our study, PET/CT was primarily used in patients with suspected metastasis lesions and was preferred for ease of diagnosis.

In PET/CT studies performed to detect the primary cancers whose primary is unknown in the literature; false positives are also encountered. In the study performed by Soni et al. false positivity was reported histopathologically in 7 of 81 patients whose primary was detected in PET/CT (17). In our study, only 1 patient out of 35 patients who were evaluated as malignant in PET/CT was false positive and 1 was considered suspicious. The causes of these false-positive cases are most commonly various physiological involvement and inflammation (16). In addition, some benign lesions (Schwannoma, fibrous dysplasia, etc.) and cases where the area thought to be primary in PET/CT is histopathologically metastasis of the primary can be counted as causes of false positives. In a meta-analysis by Burglin et al., the mean age of patients with cancers of unknown primary was approximately 60 years for most studies, and 17 of the 20 studies included more men than women (median ratio of men: 57.9%) (17). In our study, the mean age was 64.47 ± 9.92 years, consistent with the literature, and 65.3% of the patients were male.

In our study, the three most common primary tumor sites detected by PET/CT were the digestive system 16 (44.4%) and the respiratory system 9 (25%) and

the excretory system (8.3%) according to pathological examination, which is similar to other studies in the literature (18).

The limitations of our study are that it is a single-center, retrospective study with a limited number of patients.

CONCLUSION

As a result, PET/CT primary shows a very high success rate in detecting cancers unknown primary. For this reason, we recommend PET/CT imaging as a diagnostic test for the detection of the primary in cancer patients whose primary is unknown.

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