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Prediction of survival and evaluation of diagnostic accuracy whole body 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography in the detection carcinoma of unknown primary origin

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Abstract. – PURPOSE: The aim of the current study was to determine the diagnostic accuracy of whole-body 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in detecting carcinoma of unknown primary (CUP).

MATERIALS AND METHODS: A total of 7,636 patients were investigated by FDG-PET/CT examinations at our Institution. We retrospectively evaluated the file records of 432 patients who were referred to FDG PET/CT imaging with a diagnosis of cancer of unknown primary, and included 316 of the patients with histopathologic verification at the final diagnosis. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. The Kaplan-Meier test was used for survival analysis. Median survival rate was calculated to evaluate the prognostic value of the FDG-PET/CT findings.

RESULTS: In the search for a primary, FDG-PET/CT findings correctly diagnosed lesions as the site of the primary true positive in 238 cases, 10 findings diagnosed no site of a primary and none was subsequently proven true negative, 12 diagnoses were false positive and 56 were false negative. The sensitivity of FDG-PET/CT is 81% and the specificity 45%. Positive predictive value, negative predictive value and diagnostic accuracy were 95%, 15% and 78%, respectively.

CONCLUSIONS: Whole-body FDG-PET/CT imaging is proven to be useful method in the search for the primary focus and metastases in patients with cancer of unknown primary.

Key Words:
Carcinoma of unknown primary, FDG-PET/CT, Survival, inflammatory-granulomatous disease.

Introduction

The definition of carcinoma of unknown primary (CUP) includes patients who have histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography fail to identify the primary site[1,2].

The incidence of carcinoma of unknown primary in oncologic patients is 0.5%-7% at the time of the initial diagnosis[3]. The site of the primary tumor is often detected in only 10-35% of all cases after conventional imaging modalities[3,4].

18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is a macroscopic method[5] that allows noninvasive, single whole-body imaging that is proven to identify the primary tumor in patients with CUP[2] and offers accurate prognostification as additional information[4].

In general, it appears that patients with CUP have a limited life expectancy with a median survival approximately of 4-12 months, the detection of the primary tumor and initiation of therapy can prolong survival to 23 months[1,6-8].

The prognostic and predictive factors were examined in two previous studies, which included age, gender, performance status, weight loss, histopathology, tumour location, number of metastatic sites and serum markers.

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The classification of the different clinicopathological sub-sets in CUP is important in order to guide diagnostic approaches and to be able to offer optimal treatment.

Almost 50% of patients with CUP is diagnosed as metastatic adenocarcinoma of well to moderate differentiation, 30% with undifferentiated or poorly differentiated carcinomas, 15% with squamous cell carcinomas and the remaining 5% as undifferentiated neoplasms[1].

The aim of this study was to determine the diagnostic accuracy of FDG- PET/CT in detecting CUP. Additionally, overall patient survival was calculated to evaluate the prognostic value of FDG PET/CT findings.

Materials and Methods

Patients

A total of 7,636 patients were investigated by FDG-PET/CT at the Okmeydani Training and Research Hospital Nuclear Medicine Department in Istanbul. We retrospectively evaluated the file records of 432 patients who were referred to FDG-PET/CT imaging between December 2008 and May 2011 with a diagnosis of cancer of unknown primary. The CUP attribute was assigned to patients with either metastatic disease or clinical suspicion of malignancy in whom the site of the primary malignancy was not proven by preceding conventional imaging methods. None of the patients had a history of cancer, received chemotherapy and/or radiation therapy prior to the FDG-PET/CT examination.

Histopathologic verification was accepted as a gold standard.

316 of the patients had histopathologic verification at the final diagnosis. The inclusion criteria were the presence of at least one biopsied metastatic lesion and negative results from physical examination, laboratory tests and conventional modalities. None of the patients had a history of cancer, received chemotherapy and/or radiation therapy prior to the FDG-PET/CT imaging.

116 patients were excluded from the study. The exclusion criteria were insufficient clinical data; that is no histopathology of the primary tumor, no clinical and/or radiologic follow-up of at least 6 months.

The reason of reference of the patients were 76 lymph node metastases (32 cervical, 9 supraclavicular, 8 axillary, 12 mediastinal, 9 retroperitoneal, 6 inguinal), 83 skeletal metastases, 62 liver metastases, 28 brain metastases, 2 cerebellum metastases, 1 adrenal metastases, 5 lung metastases, 41 pleural and/or peritoneal malignant effusion and 18 patients with clinical suspicion of the presence of a malignancy (Table I).

Patient Preperations

Patients had fasted for at least 4 hours and their blood glucose levels were controlled before FDG injection. All of the patients had blood glucose levels lower than 200 mg/dl. No intravenous contrast material was used for the CT scans. Water-soluble iodinated contrast material diluted in 1,000 ml of water was given to each patient orally prior to the investigation.

Table I. Localisation of metastases reffered to our clinic.

Metastatic localization	Male	Female	Total	Percent %
Lymph node	40	36	76	24
Cervical	21	11	32	
Axillary	2	6	8	
Mediastinal	5	7	12	
Supraclaviculary	5	4	9	
Intraabdominal	4	5	9	
Inguinal	3	3	6	
Bone	52	31	83	26
Cerebrum	24	4	28	9.8
Cerebellum	1	1	2	0.6
Liver	45	17	62	19.5
Lung	3	2	5	1.5
Adrenal gland	–	1	1	0.4
Peritoneal fluid	9	28	37	11.5
Pleural fluid	2	2	4	1.2
Clinical Suspicion	10	8	18	5.5
Total	186	130	316	

Scanning Procedure

FDG-PET/CT Imaging

Whole body PET/CT imaging was performed on a biograph (Siemens Biograph 6, Chicago, IL, USA) using a full-ring HI-REZ LSO PET and a six-slice CT scanner. Data were acquired 60 minutes following the administration of FDG (296-555 MBq FDG according to body weight). The CT scan was performed first with the following parameters: 40-60 mAs, 140 kV and 5-mm section thickness.

The analysis of malignant involvement was based on qualitative visual interpretation of the images. The criterion for malignancy was FDG hyper metabolism at the site of pathological changes on CT or marked focal hyper metabolism at physiological uptake sites despite absence of signs of pathology on CT. Fused FDG-PET/CT images were analyzed in at least three planes – coronary, sagittal and axial – in the gray scale color table for PET.

Statistical Analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences version 15.0 software (SPSS Inc., Chicago, IL, USA).The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and relative risk were calculated.

To calculate sensitivity and specificity, true-positive (TP) was considered when FDG-PET/CT suggested the location of the primary tumor and was subsequently confirmed, whereas false-positive (FP) was considered when this location was not confirmed. The gold standard was histopathological verification of the site suggested by FDG-PET/CT.

When histological verification could not be done, results of further imaging procedures or clinical follow up were accepted.In those instances when FDG-PET/CT did not suggest the primary tumour location this was considered to be true negative (TN) if the primary remained unknown on follow up even if further lesions or deposits revealed. It was considered false-negative (FN) if the primary tumor was identified subsequently to negative FDG-PET/CT. When possible site of primary diagnosed on FDG-PET/CT, but the actual primary was later found and confirmed in different organs were regarded as both FN and FP.

The Kaplan-Meier test was used for survival analysis. The *p*-values less than 0.05 were considered statistically significant with 95% confidence interval.

Table II. Detail of the 12 FP PET/CT finding in the search for a primary.

Age	Gender	Metastatic localisation	PET/CT	PET/CT other involvement	Patology	Histopatology	Accuracy
37	M	Bone	Lung	Bone, adrenal gland, SID LN,	Bone	Inflammatory-granulomatous disease	FP
62	F	Bone	No	Bone	Bone	Inflammatory-granulomatous disease	FP
23	F	ID LN	ID LN	ID LN	Inguinal LN	Inflammatory-granulomatous disease	FP
78	F	Clinical suspicion	Spleen	No	Spleen	Amiloidosis	FP
44	M	Peritoneal fluid	Liver	No	Liver	Hepatitis	FP
61	M	Liver	Pancreas	Liver	Liver	Hepatitis	FP
66	F	Bone	No	Bone	Bone	Inflammatory-granulomatous disease	FP
71	F	Cervical LN	Cervical LN	Cervical LN		Inflammatory-granulomatous disease	FP
27	M	Supraclavicular LN	Lung	Bone, SD LN	Bone	Inflammatory-granulomatous disease	FP
51	M	Bone	Bone	No	Thorax	Inflammatory-granulomatous disease	FP
60	F	Inguinal LN	SID LN	SID LN	Inguinal LN	Inflammatory-granulomatous disease	FP
49	F	Peritoneal fluid	Peritoneal	No	Peritoneal	Inflammatory-granulomatous disease	FP

Male: M; Female: F; ID: Infradiaphragmatic Lymph node; SID: Supra-Infradiaphragmatic Lymph node.

Table III. Details of the 56 FN FDG-PET/CT findings in the search for a primary.

Age	Gender	Metastatic localisation	PET/CT	PET/CT other involvement	Patology	Histopatology	Accuracy
84	F	Cervical LN	No	No	Breast	Adenocancer	FN
60	M	Liver	No	SID LN, lung, liver	Prostate	Adenocancer	FN
54	M	Brain	No	No	Brain	Brain cancer	FN
55	F	Peritoneal fluid	No	No	Lung	Adenocancer	FN
56	M	Cervical LN	No	Lung, SD LN	Buccal mucosa	Squamous cell	FN
66	F	Bone	No	Bone	NHL	Diffuse B cell	FN
55	F	Peritoneal fluid	No	Peritonitis	Uterus	Adenocancer	FN
30	M	Supraclaviculary LN	No	SID LN, lung	Testis	Germ cell	FN
76	F	ID LN	No	SID LN	Inguinal LN	Signet ring cell ca	FN
49	M	Bone	No	Bone, adrenal gland, SD LN	Lung	Adenocancer	FN
41	F	Bone	No	Bone	Bone	Multiple myeloma	FN
52	F	SD LN	No	Supraklavikuler LN	Lung	Adenocancer	FN
59	F	Peritoneal fluid	No	No	Uterus	Mucinous	FN
54	M	Bone	No	Bone	Bone	Multiple myeloma	FN
45	F	Liver	No	No	Uterus	Adenocancer	FN
32	F	Bone	No	Bone	Gastric	Signet ring cell ca	FN
58	M	Bone	No	Bone, bone marrow	Bone	Multiple myeloma	FN
72	M	Liver	No	Bone, Liver	Lung	Bronchoalveolercancer	FN
61	F	Peritoneal fluid	No	Peritoneal-Omental	Cervix	Squamous cell	FN
68	M	Liver	No	Liver	Colon	Adenocancer	FN
55	M	Cervical LN	No	Cervical LN	Tongue	Squamous cell	FN
50	F	Axillary LN	No	Axillary LN	Breast	Adenocancer	FN
57	M	Cervical LN	No	Cervical LN	Larynx	Squamous cell	FN
36	F	Liver	No	No	Breast	Adenocancer	FN
44	M	Liver	No	No	Colon	Adenocancer	Fn
74	M	Bone	No	No	Lung	Bronchoalveoler cancer	FN
60	M	Brain	No	Bone,SD LN,spleen	Lung	Undifferentiated cancer	FN
38	F	Axillary LN	No	No	Breast	Adenocancer	FN
49	F	SD LN	No	SD LN	Buccal Mucosa	Squamous cell	FN
61	M	Cervical LN	No	No	Nasopharynx	Undifferentiated cancer	FN
55	M	Brain	No	Brain	Lung	Neuroendocrine tumours	FN

Table continued

Table III (*Continued*). Details of the 56 FN FDG-PET/CT findings in the search for a primary.

Age	Gender	Metastatic localisation	PET/CT	PET/CT other involvement	Patology	Histopatology	Accuracy
68	M	Bone	No	SID LN, bone	Prostate	Adenocancer	FN
49	M	Cervical LN	No	SID LN, lung	Gastric	Adenocancer	FN
47	M	Cervical LN	No	No	Cervical LN	Undifferentiated cancer	FN
70	F	Bone	No	ID LN, bone	Bone	Multiple myeloma	FN
81	F	Adrenal gland	No	Adrenal gland	Breast	Adenocancer	FN
71	F	Peritoneal fluid	No	Peritonitis, lung	Ovarian	Mucinous	FN
50	F	Bone	No	Bone	Prostate	Adenocancer	FN
77	F	Cervical LN	No	SID LN, spleen, bone marrow		Negative	FN
61	M	Liver	No	Liver, lung, brain		Negative	FN
50	F	Axillary LN	No	No	Breast	Adenocancer	FN
60	M	Bone	No	SD LN, liver, bone		Negative	FN
60	F	ID LN	Prostate	Lung, ID LN	Lymphoma	Diffuse B cell	FN +FP
74	F	Clinical suspicion	Nasopharynx	Spleen, adnex, SID LN,	Lymphoma	Diffuse B cell	FN +FP
52	F	Brain	Lung	Thyroid, SD LN	Ovarian	Epithelial	FN +FP
58	M	Liver	Liver/gastric	No	Colon	Adenocancer	FN +FP
68	M	Liver	Liver	Liver	Colon	Adenocancer	FN +FP
37	F	Clinical suspicion	Thyroid, over		Breast	Adenocancer	FN +FP
56	F	Cervical LN	Nasopharynx	Cervical LN	Lymphoma	Diffuse B cell	FN +FP
58	M	Bone	Rectum	SD LN	Appendix	Mucinous	FN +FP
61	M	Bone	Lung	SD LN,bone	Gastric	Signet ring cell ca	FN +FP
52	F	Clinical suspicion	Pelvic Mass	Bone	Gastric	Signet ring cell ca	FN +FP
57	M	Cervical LN	Lung	SD LN, brain, muscle	Gastric	Signet ring cell ca	FN +FP
76	M	Cervical LN	Lung	SD LN,liver,bone	Tongue	Squamous cell	FN +FP
55	M	Bone	Lung	SID LN,bone,pleura	Lymphoma	Diffuse B cell	FN +FP

Male: M; Female: F; ID: Infradiaphragmatic Lymph node; SID: Supra-Infradiaphragmatic Lymph; FN: False negative; FP: False positive.

Median survival rate was calculated to evaluate the prognostic value of the FDG-PET/CT findings.

Ethics

The local Ethics Committee of Okmeydani Traning and Resaerch Hospital approved the study and informed consent was obtained from the patients participating in the trial.

Results

In the search for a primary, FDG-PET/CT findings correctly diagnosed lesions as the site of the primary true positive in 238 (75%) cases, 10 (3%) findings diagnosed no site of a primary and none was subsequently proven true negative, 12 (4%) diagnoses were false positive and 56 (18%) were false negative. In 13 out of 56 FN cases, FDG-PET/CT findings diagnosed lesions discordant with the histopathologic diagnosis were accepted as FN+FP.

The localization of primary tumors detected were: 1 aplastic anemia (TP), 1 appendix (FN), 13 skeletal involvement (4 FN, 5FP, 4TP), 4 brain (3 TP, 1FN), 16 breast (9TP, 6FN, 1 FN+ FP), 2 buccal mucosa (2FN), 2 caecum (2TP), 2 cervical LN (1FN, 1FP), 2 cervix (1TP, 1FN), 28 colon (23TP, 3 FN, 2 FN+ FP), 1 duodenal (TP), 10 gastric (5TP, 2FN, 3 FN+ FP), 1 hypopharynx (1 TP), 1 gluteal mass (1TP), 3 inguinal LN (2 FP, 1FN), 2 kidney (2 TP), 5 larynx (4 TP, 1 FN), 10 liver (2 FP, 7 TP, 1 TN), 108 lung (7 FN, 101 TP), 16 lymphoma (12TP, 4 FN+ FP), 1 maxillary (TP), 2 nasal cavity (2 TP), 7 nasopharynx (6 TP, 1 FN), 1 NHL (FN), 12 ovarian (10 TP, 1 FN, 1FN+ FP), 17 pancreas (17 TP), 3 peritoneal (2 TP,1 FP), 5 prostate (3 FN, 2 TP), 6 rectum (6 TP), 1 small bowel (1TP), 2 spleen (1 FP, 1TP), 1 submandibulary (1TP), 2 testis (1 FN, 1TP), 2 thyroid 2 TP), 2 tongue (1FN, 1 FN+ FP), 8 uterine (5TP, 3 FN).

Out of 238 TP patients were detected as; 101 lung cancer, 23 colon cancer, 13 lymphoma, 7 liver cancer, 17 pancreas cancer, 6 gastric cancer, 9 breast cancer, 6 rectum cancer, 5 uterine cancer,6 nasopharnx cancer, 4 larynx cancer, 3 brain cancer, 3 multiple myeloma, 2 nasal cavity cancer, 2 thyroid cancer, 2 prostate cancer, 2 kidney cancer, 2 caecum cancer, 1 bone sarcoma, 1 duodenal, 1 hypopharinx, 1 small bowel, 1 submandibulary, 1 testis, 1 maxillary, 1 aplastic anemia (Figure 2).

The diagnosis of 12 FP patients were; 4 bone inflammatory-granulomatous disease, 1 spleen amiloidosis, 2 liver hepatitis, 1 thorax wall inflammatory disease, 2 inguinal inflammatory-granulomatous disease, 1 cervical abscess, 1 peritoneal inflammatory-granulomatous disease (Figure 3).

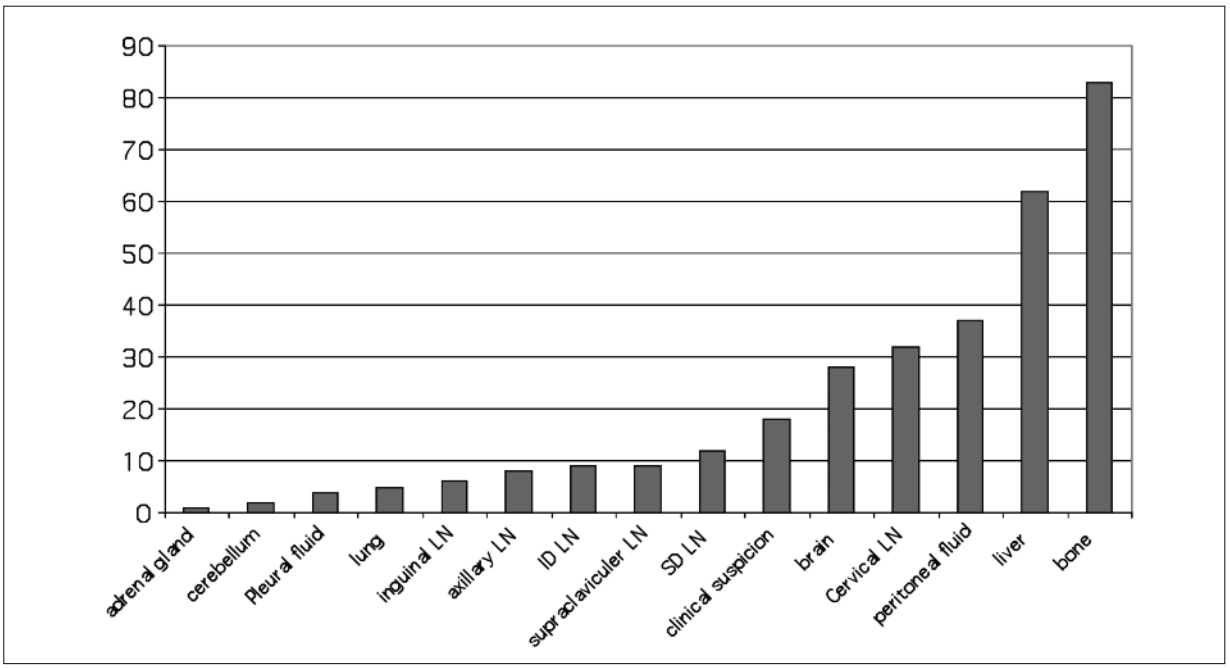

Figure 1. Locations of primary tumors detected by FDG PET/CT.

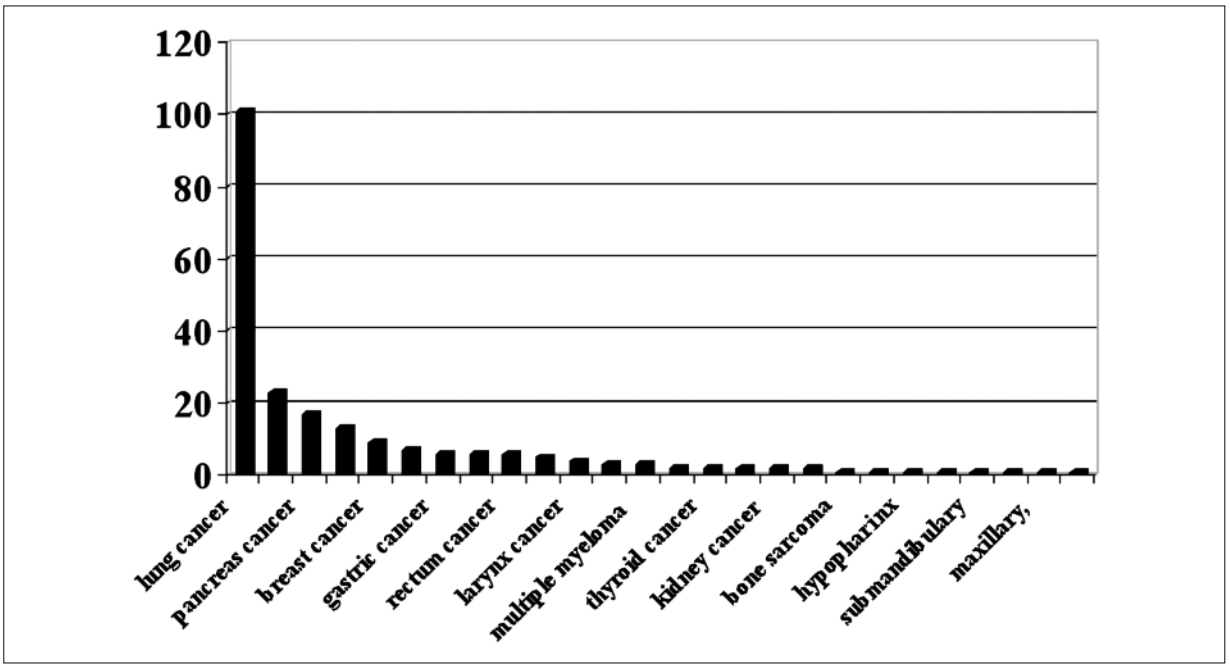

Figure 2. Locations of true-positive (TP) FDG PET/CT results.

40 out of 56 FN patients were identified as; 4 skeletal involvement (multiple myeloma), 1 brain cancer, 6 breast cancer (adenocancer), 2 buccal mucosa (squamous cell cancer), 1 cervix cancer (squamous cell cancer), 3 colon cancer (adenocancer), 2 gastric cancer (1 signet ring cell cancer, 1 adenocancer), 7 lung cancer (3 adenocancer, 2 bronchoalveolary cancer, 1 undifferantiated cancer, 1 Neuroendocrine tumour), 1 NHL (diffuse B cell), 2 ovarian cancer (1 mucinous, 1 epithelial), 1 larynx (squamous cell cancer), 1 nasopharinx (undifferantiated cancer), 3 prostate cancer (adenocancer), 3 uterine cancer (1 mucinous, 2 adenocancer), 1 testis cancer (germ cell), 1 cervical LN (undifferentiated cancer metastases), 1 inguinal LN (1 signet ring cell cancer metastases). 3 FN patients had multiple involvement with no primary detected with FDG-PET/CT and died. In 13 patients accepted as FN+FP, the diagnosis were; 4 lymphoma, 1 appendix, 1 breast, 2 colon, 3 gastric, 1 ovarian, and 1 tongue cancer (Figure 4).

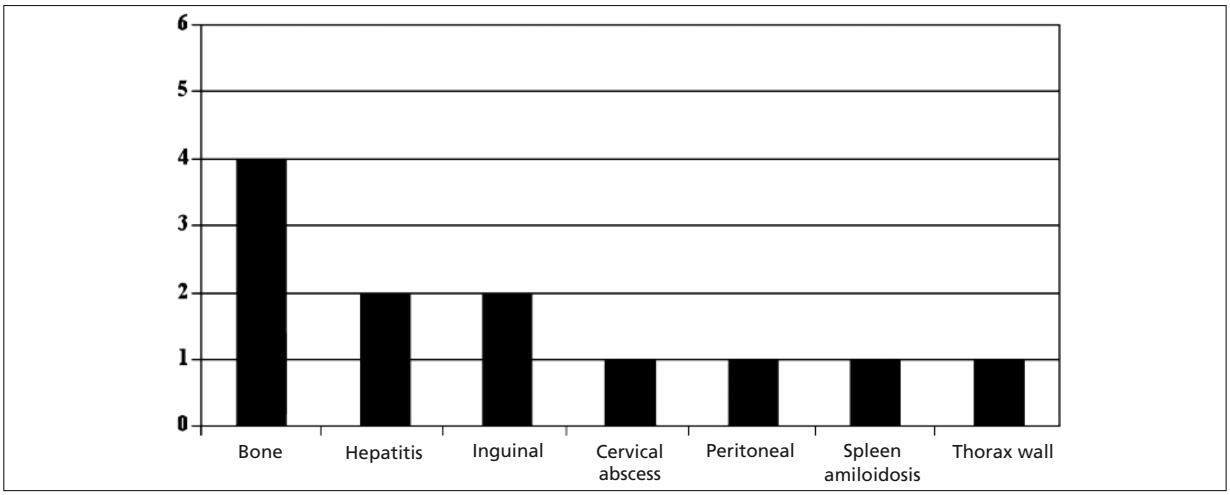

Figure 3. Locations of false-positive (FP) FDG PET/CT results.

Among the 316 patients, we detected multiple lesions in 184 patients (58%), a solitary lesion in 41 (13%), and did not find any malignant lesion in 47 (15%).

The sensitivity of FDG-PET/CT is 81% and the specificity 45%. Positive predictive value (PPV) negative predictive value (NPV) and diagnostic accuracy (Acc) were 95, 15 and 78%, respectively (Table IV).

According to our findings, the mean survival time was 18.637±0.88 [16.9-20.4] months of our all patients (Figure 5) When the survey graphics were evaluated, life expectancy was in between 5 to 25 months.

The mean survival time of the patients with multiple organ involvement and solitary organ involvement on FDG-PET/CT was 18.69±1.13 [16.47-20.91] and 16.01±1.17 [13.71-18.32], respectively. The mean survival times of patients with solitary or no lesion was significantly longer then (p = 0.018), patients with multiple organ involvement (Figure 6).

The mean survival time of the male and female patients on FDG-PET/CT was 17.69±0.94 [15.83-19.54] and 16.54±1.11 [13.35-18.74], respectively. The statistics of survival times of the patients revealed a longer life for female patients (p = 0.004) (Figure 7).

Discussion

It is widely accepted that CUP is a heterogeneous group of metastatic malignancies, in which the primary tumor has not been found and with clinical signs of disease were not seen[2].The early identification of primary tumor may enable a more specific and effective treatment, thus lead a longer mean survival time for CUP patients.

Table IV. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FDG-PET/CT in the search for primary.

Sensitivity	0.81
Specificity	0.45
Positive Predictive Value	0.95
Negative Predictive Value	0.15
Accuracy	0.78

The results of our study indicated that, FDG-PET/CT was able to detect 75% of primary tumors in patients with CUP and diagnostic accuracy (78%), sensitivity (81%), and specificity (45%) of FDG-PET/CT, respectively. The detection rates reported in the literature showed significant variation, ranged from 22% to 73%, with an overall detection rate of 37%[2,9-11]. The metaanalyses on FDG-PET/CT reported primary tumor detection rates ranging between 24.5% and 43%, sensitivities ranging between 87% and 91.9%, and specificities ranging between 71% and 81.9%[2,3,12].

In their study, Fencyl et al[5] stated that the sensitivity and specificity in the search for the CUP were similar in patients with histologically proven metastatic disease and patients with clinical suspicion of the presence of a malignancy. In contrary to their findings our study revealed a lower rate of specificity due to higher rate of false positive results, which may be explained by higher granulomatous disease incidence. In cur-

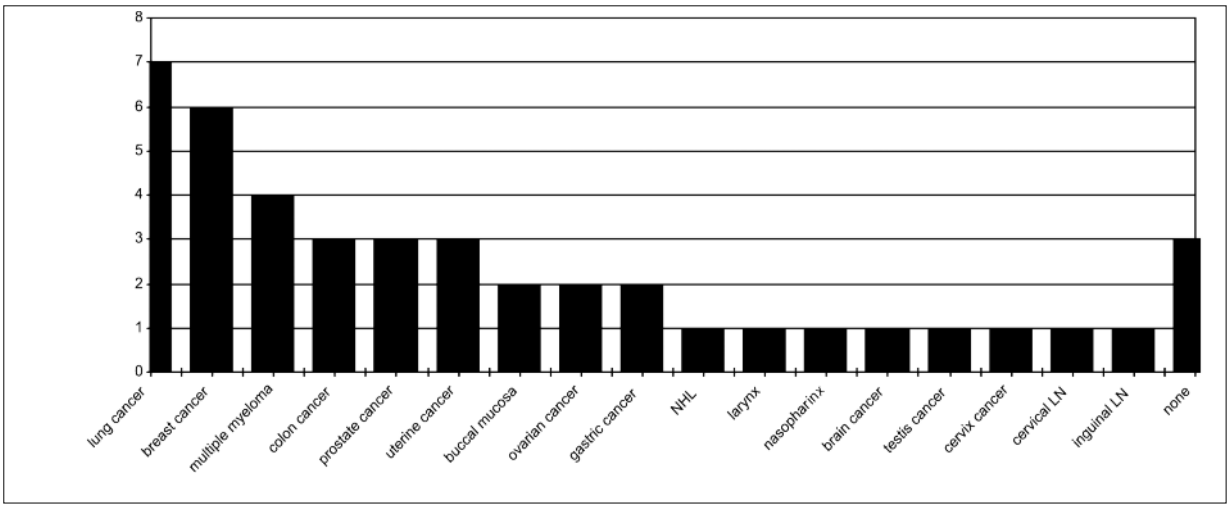

Figure 4. Locations of false-negative FDG PET/CT results.

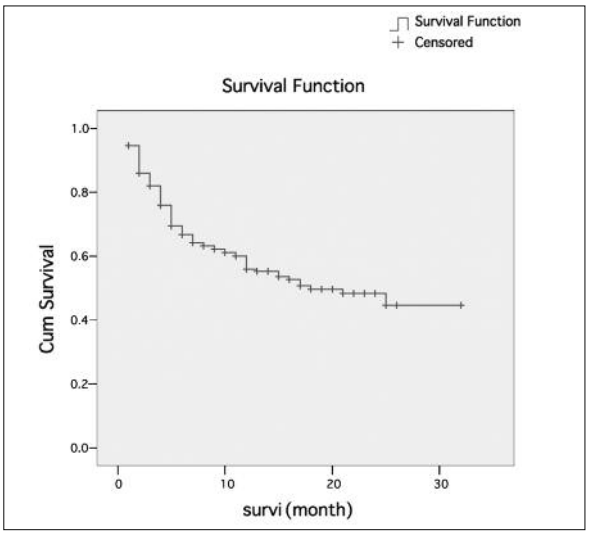

Figure 5. Mean survival time.

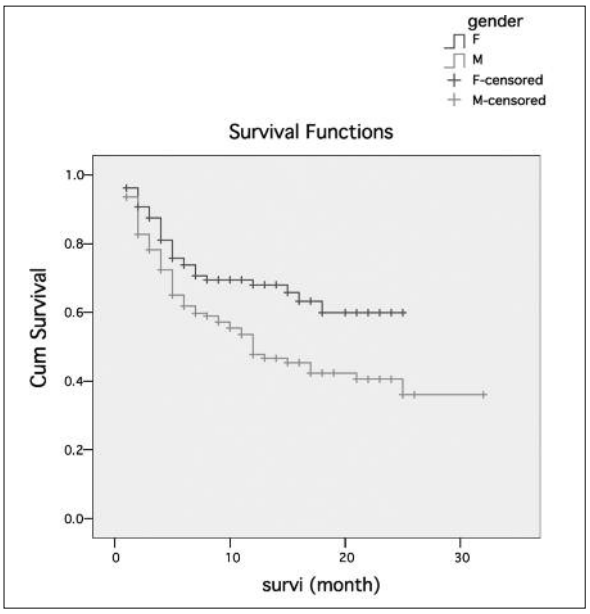

Figure 7. The mean survival time of the male and female patients on FDG PET/CT.

rent study, all results are based on "biopsy-proven malignancy from unidentified anatomical origin following conventional diagnostic evaluation"[7], which makes our investigation unique.

In the current study, the most prevalent location of primary tumors detected by FDG-PET/CT was lung, which is consistent with the literature[2].

Benign processes such as infection (i.e. hepatitis, abscess) inflammation (peritoneal inflammation), and granulomatous diseases (i.e. sarcoidosis, tuberculosis, amiloidosis) are known to cause false-positive results.

The most common site for false-positive FDG-PET/CT results was the vertebral bone tuberculosis. This may be due to increased glucose utilization and FDG uptake caused by increased cellular metabolism in inflammatory lesions[12-14].

In a tuberculosis-endemic country, FDG-PET/CT positive lesions should be cautiously interpreted in terms of granulomatous diseases, because false-positive results may lead to mismanagement. Thus, histopathologic examination of FDG-PET/CT positive lesions should be performed.

The most common sites of false-negative FDG-PET/CT results in the current study were in 7 lung (3 adenocancer, 2 bronchoalveoler cancer, 1 undifferentiated cancer, 1 neuroendocrine tumour), 6 breast cancer (adenocancer), 4 skeletal involvement (multiple myeloma).

The false-negative FDG-PET/CT results may be explained by the facts that; (1) the biological features of the primary tumor may be different from those of the tumor cells in the nodal regions (metastases may uptake higher levels of FDG than in the primary, in low grade epithelial tumors FDG uptake can be low or absent); (2) the size of primary lesion may be smaller than the resolution power of FDG-PET/CT (especially within the abdomen, pelvis, and head and neck, which are anatomically complicated areas)[5,15]; (3) the primary tumor may disappear after seeding the metastasis because its angiogenic incompetence leads to marked apoptosis and cellular turnover[12,16] or because it may have regressed spontaneously[2,8,12,15,16].

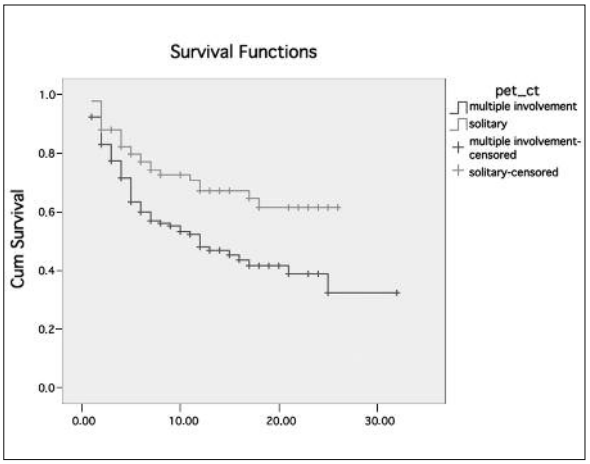

Figure 6. The mean survival time of the patients with multiple organ involvement and solitary or no organ involvement on FDG PET/CT.

Multiple myeloma is another reason for false-negative FDG-PET/CT result. FDG-PET/ CT is a better modality than 99mTc-MIBI and Magnetic Resonance Imaging (MRI) in detection of focal lesions of Multiple Myeloma[17,18] . However, MRI is more capable than with FDG-PET/CT to detect MM lesions in the spine due to an infiltrative pattern[17,18]. On the other hand, FDG-PET/CT fail to differentiate multiple myeloma lesions from multiple lytic bone lesions, unless the patient is referred to our Department with clinical suspicion of multiple myeloma.

In the current study, the number of both FN and FP is 13, which is inconsistent with literature. Additionally to the facts explained above in FN results, the FN & FP FDG-PET/CT results may be due to; (1) a second primary tumor[4,19] (2) inflammation-inflammatory disease. (3) FDG uptake in some cancers mimics benign lesions, d) moderate FDG uptake[12,20,21].

The prognosis of patients with CUP syndrome is generally poor and the median survival is approximately in between 4 and 12 months[2,8,22-26]. According to our results, the mean survival time was 9 months of our all patients and the life expectancy was in between 5 to 25 months.

Conclusions

In current study, the rate of specificity of whole-body FDG-PET/CT was lower than the literature, indicating a higher rate of false positive results, which may be explained by higher granulomatous disease frequency. Although the histopathologic verification is golden standard, by understanding the technical limitations of FDG-PET/CT, false positive and negative results may be decreased and, the diagnostic performance in assessing CUP can be improved.

Finally, whole-body FDG-PET/CT imaging is proven to be useful method in the search for the primary focus and metastases in patients with CUP syndrome.

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