Original Article

Is SUVmax of ^{18}F-FDG PET/CT Predictive Factor for Malignancy in Gastrointestinal Tract?

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Abstract

Background: Increasing use of ^{18}F-FDG PET/CT in cancer patients, has led to more common detection of ^{18}F- FDG uptake in the gastrointestinal tract (GIT). **Aims:** The objective of this study was to assess ^{18}F-FDG uptake in incidental and known GIT malignancy. **Methods:** A total of 6500 patients followed-up in a single and tertiary center between January 2010 and September 2016 were retrospectively reviewed. Of 2850 patients assessed with ^{18}FDG-PET/CT, known GIT malignancy and ^{18}F-FDG uptake cases during follow-up were included in the study. **Results:** Of 658 patients with ^{18}F-FDG uptake, 150 patients who underwent endoscopy were included in the study. Seventy-seven of these patients had known GIT malignancy and 73 had incidental ^{18}F-FDG uptake. Among these 73 patients; 7 (9.6%) had malignancy, 20 (27,2%) adenoma and 24 (32.9%) inflammation that were confirmed. Endoscopy was normal in 22 (30.2%) patients. One hundred forty-three (95.3%) patients had focal and 7 (4.7%) had diffuse uptake. While no malignancy was detected in patients with diffuse uptake, 58.7% (84/143) of the patients with focal uptake presented malignancy. Mean the standardized uptake value (SUV) max values were found as 15.0 ± 10.6 (range, 3.8–56.5) in malignant disease, 10.2 ± 4.3 (range, 2.4-19.7) in adenoma, 7.3 ± 3.6 (range, 3.6–18.7) in inflammation, and 9.8 ± 4.2 (range, 3.8–19.9) in normal endoscopy groups ($p < 0.001$, rho = 0.378). **Conclusion:** Although this study demonstrated high probability of malignant disease with increased ^{18}F-FDG uptake in the GIT, it would be a more appropriate approach to confirm all patients with ^{18}F-FDG uptake through endoscopy as SUVmax values vary in a wide range.

Keywords: *SUVmax, Gastrointestinal Tract, Fluorodeoxyglucose F18, Positron Emission Tomography, PET/CT*

Introduction

Positron emission tomography (PET) scan is a nuclear medicine imaging technique, frequently used in clinical oncology to detect neoplasia.[1] ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG-PET/CT) is the most commonly used radiolabeled tracer in PET medical imaging modality. As a glucose analog, ^{18}F-FDG PET/CT is intracellularly taken up by and accumulates in various tissues that use glucose, and this activity occurs at a relatively higher rate in various cancer cells. However, increased accumulation of ^{18}F-FDG PET/CT occurs not only in cancer cells, but also in several metabolically hyperactive conditions including infection, inflammation, and other non-neoplastic conditions such as adenomas and hyperplastyc polyps.[2]

Therefore, PET/CT method has a low specificity, but a high sensitivity for the gastrointestinal tract (GIT).[2,3] The most common sections of physiologic ^{18}F-FDG uptake throughout body include the distal esophagus, stomach, and colon.[4]

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Two distinct patterns of ^{18}F-FDG uptake in the GIT have been defined on PET/CT examination as diffuse and focal patterns. Whereas diffuse ^{18}F-FDG uptake usually indicates a physiological uptake, focal ^{18}F-FDG uptake may be associated with serious diseases such as primary tumors, premalignant lesions or unusual metastatic radiation sites. Herein, the key point is to rule out or confirm malignancy.[5]

The maximum standardized uptake value (SUVmax) is a quantitative index of glucose metabolism obtained from the ^{18}F-FDG PET/CT data. It represents the ratio of ^{18}F-FDG uptake by the related site to the average uptake by whole body. The SUVmax values are the most commonly used method in assesment of FDG uptake. High values of SUVmax which are estimated based on the uptake intensity on PET/CT indicate tumoral activity and probability of malignant lesions, and also may function as a prognostic factor.[6,7] Incidental GIT uptake is being increasingly detected as the use of ^{18}F-FDG PET/CT becomes widespread in the field of oncology.[8,9] Several previous studies have evaluated the incidence and clinical significance of FDG uptake in the gastrointestinal tract and reported that the findings point to the need for further investigations on this issue.[8,10] The objective of this retrospective study was to evaluate incidental FDG uptake in the GIT, the rates of confirmed malignancy in patients showing FDG uptake, rates of malignancy in patients with focal and diffuse FDG uptake and specifically the relationship between the SUVmax values and the rates of malignancy in the GIT.

Patients and Methods

Patients

A total of 6500 patients aged over 18, followed-up in the oncology department between January 2010 and September 2016 were retrospectively screened in a single center. Of these patients, 2850 were assessed with ^{18}F-FDG PET/CT. FDG uptake in the GIT was reported in 658 (23%) of these patients. Of these, patients diagnosed on gastroscopy and colonoscopy through biopsy taken from the region of ^{18}F-FDG uptake were enrolled in the study. Patients who had not been assessed with gastroscopy and colonoscopy were excluded. The study included patients who were newly diagnosed with GIT malignancy, yet were not operated and undergone PET/CT for the first staging; patients with malignancy other than the GIT who were incidentally found to have FDG uptake in the GIT during follow-up and those with GIT malignancy who were incidentally found to have FDG uptake in another region of the GIT. Patients with FDG involvement in the anastomosis line after surgery for GIT malignancy were excluded from the study. Ethics committee approval and informed consent were received (ethics committee approval number: 2017/003).

^{18}F-FDG PET/CT protocol

PET/CT scans were performed with a Philips Gemini TF model PET/CT scanner system using an integrated 16-slice multidetector CT (Philips Medical Systems, Cleveland, Ohio, USA). All patients were appropriately hidrated by intravenous%0.9 NaCl solution or drinking water before FDG injection. Blood glucose levels were measured before fluorodeoxyglucose injection of 296–555 MBq (8-15 mCi) in patients after fasting for at least 4-6 h. Fluorodeoxyglucose was intravenously injected to patients with a blood sugar level <200 mg/dL. After 45 to 50 minutes of the injection, a whole-body scan was carried out from the base of the skull to the superior portion of the thighs in patients with arms crossed above head at 6-7 bed positions with 2 minutes in each position. Evaluation of PET/CT images was visually and semi-quantitatively made by two experienced nuclear medicine physicians. PET scans that revealed increased single or multiple well-circumscribed focal or diffuse ^{18}F-FDG uptakes in the stomach, small intestine or colon, were evaluated. Patients who were on anti-diabetic therapy were not included in the evaluation. Semi-quantitative analysis was performed by drawing the region of interest around any site of suspicious FDG uptake which had or not been visualized on CT images and the SUVmax value of each lesion was used in calculation.

GIT

The GIT was divided into six anatomical sections as the oesophagus, stomach, small bowel, colon, rectum and anal margin. In this study, the final diagnoses were classified as confirmed malignancy, confirmed premalignant lesions (dysplasia and adenomas), confirmed inflammation, confirmed hyperplastyc polyp and normal endoscopy. The diagnoses were confirmed by gastroscopy/colonoscopy and histopathology.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (IBM, USA). Quantitative variables are expressed as mean ± standard deviation (SD) and qualitative variables as number and percentage. Comparison of SUVmax values between malignant and benign diagnosis groups was made with Spearman correlation test (Spearman's rho) and Mann– Whitney tests. A value of $P < 0.05$ was considered statistically significant.

Results

GIT findings and diagnosis

Out of 658 patients with GIT uptake on ^{18}F-FDG PET/CT, 150 patients whom diagnosis was established

through gastroscopy and colonoscopy and/or biopsy were included in the study. Out of these 150 patients, 77 had been diagnosed with GIT cancer just before PET/CT (2 oesophagus cancer, 2 gastric stromal tumor, 23 gastric cancer, 50 colorectal cancer), while the remaining 73 patients had incidental GIT uptake. In 7 (9.6%) of these 73 patients, malignancy was incidentally identified in the GIT (5 adenocarcinoma and 2 adenocarcinoma metastasis) [Figure 1]. Majority of the final diagnoses associated with GIT uptake was confirmed malignant disease (n = 84, 56%).

Seventy-three of the 150 patients with incidental GIT findings were investigated by endoscopy. Among these 73 patients; 7 (9.6%) had confirmed malignancy, 20 (27.2%) confirmed adenoma and 24 (32.9%) confirmed inflammation. In addition, gastroscopy and colonoscopy was strictly normal in 22 (30.2%) of these 73 patients. Therefore, positive predictive value was found as 69% (51/73) in the incidental group and 85% (128/150) in general study population.

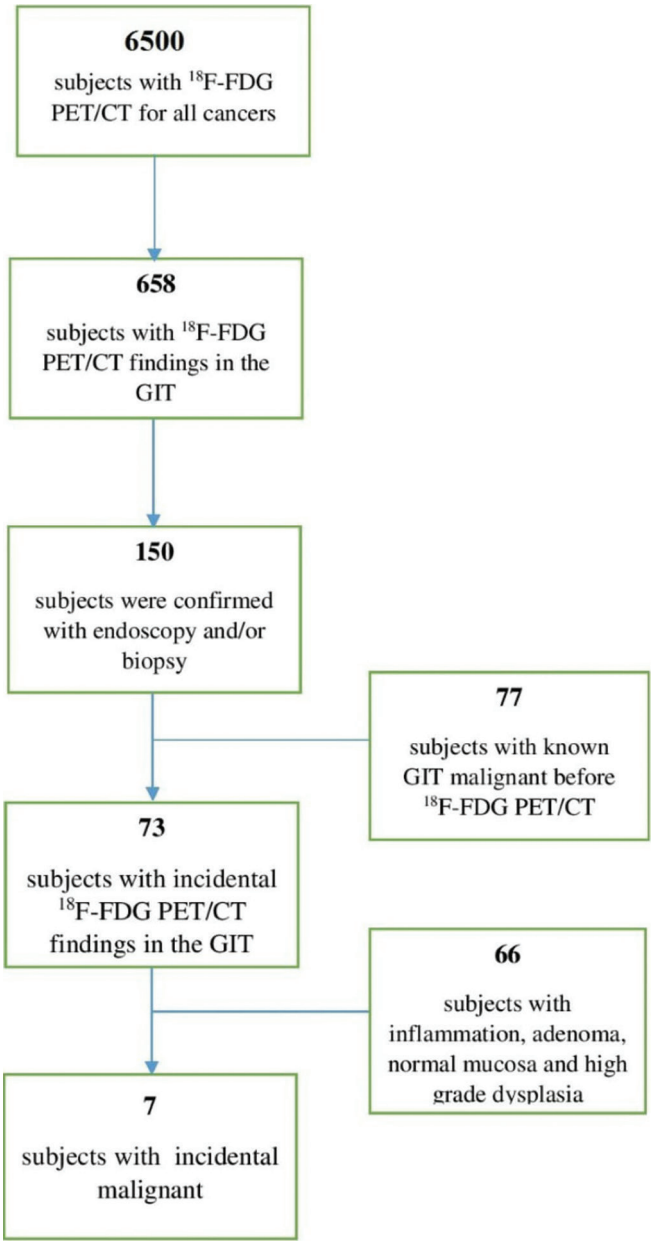

Figure 1: Flow chart of patients performed FDG PET/CT

Incidental colon uptake was observed in 49 patients and incidental stomach uptake in 24 patients. On the other hand, incidental malignancy was found in the colon in 6 patients (12%) and in the stomach in only 1 patient (4%). Of the patients with incidental colon malignancy; localization of primary cancer was the breast in two patients, lungs in one patient, ovary in one patient, cervix in one patient and pancreas in one patient. In one patient with incidental stomach malignancy, primary cancer region was the colon.

In the two patients with incidentally identified high-grade dysplasia adenoma, primer cancer localization was the lungs. One of the high-grade dysplasia localizations was in the stomach and the other was in the descending colon. Malignant/premalignant lesions in the colon sections are shown in Table 1.

The characteristics and sites of incidental and known FDG uptake in the PET/CT GIT positive group were described according to two patterns as focal and diffuse uptake. One hundred forty-three (95.3%) of these patients had focal and 7 (4.7%) had diffuse uptake. Among the 143 patients with focal FDG-uptake, sites of uptake were found as various sections of the colon in 90 cases (ascending colon in 17 cases, transverse colon in 5 cases, descending colon in 11 cases, sigmoid colon in 16 cases and rectum in 41 cases), stomach in 49 cases, oesophagus in 2 cases and small intestine in 2 cases. While none of the subjects with diffuse uptake showed malignancy, 58.7% (84/143) patients with focal uptake had malignancy. Among these, all of the 7 patients with incidental malignancy had focal uptake. In the cases of FDG uptake, focal patterns seen in colonic lesion were confirmed as malignant, premalignant and non-neoplastic lesions by 100% (84/84), 89% (16/18) and 89% (43/48); respectively [Table 2]. In addition, FDG uptake was seen in the rectum, which was not revealed on CT and interestingly, the pathology was not malignant in both patients.

SUVmax

The mean SUVmax values were 10.7 ± 2.8 for diffuse FDG uptake, and 12.4 ± 9.1 for focal FDG uptake (p = 0.686). The mean SUVmax values were found as 15.0 ± 10.6 (range, 3.8 – 56.5) in the confirmed malignant disease group, 9.4 ± 2.5

(range, 7.6 – 11.2) in the confirmed high grade dysplasia adenoma group, 10.2 ± 4.3 (2.4-19.7) in the confirmed adenoma group, 7.3 ± 3.6 (range, 3.6 – 18.7) in the confirmed inflammation group, 8.3 ± 1.9 (range, 7.0 – 9.7) in the confirmed hyperplastyc polyp group and 9.8 ± 4.2 (3.8 – 19.9) in the normal endoscopy group (p < 0.001, rho = 0.378) [Figure 2a and 2b]. SUVmax values were found as 20.5 ± 18.2 (range, 7.4 – 56.5) in patients with incidentally found malignancy and 9.0 ± 4.1 (range, 2.4 – 19.9) in patients with incidentally identified benign lesions (p = 0.023, rho = 0.266). Looking at the SUVmax values, the higest value was found as 19.9 in benign lesions. Of note, all patients with a SUVmax ≥20 were diagnosed with malignancy. While specificity was 100% for the diagnosis of malignancy in the uptakes with a SUVmax of 20 and over, sensitivity was very low (20.2%).

SUVmax values were not correlated with grade of tumor, stage of disease and serum levels of tumor markers such as CEA and CA 19-9 in patients diagnosed with malignancy in the GIT (p = 0.79, *P* = 0.92, *P* = 0.62 and *P* = 0.98; respectively). SUVmax value was increased with the size of the lesion with FDG uptake in the GIT, but this was not statistically significant (p = 0.067). In addition, SUVmax was not correlated with the wall thickness and segment length of the lesion with FDG uptake in the GIT (p = 0.38 and *P* = 0.11). No significant correlation was found between SUVmax and the region with FDG uptake in the stomach (p = 0.74). FDG uptake was higher in the lesions found in the left colon than in those localized in the right colon (p = 0.014).

Table 1: Incidental FDG uptake findings, incidental malignancy and dysplasia according to the colon sections

Primary tumor sites	Incidental FDG uptake	Incidental malignant lesion	Incidental premalignant lesion
	n	*n* (%)*	*n* (%)*
Cecum	5	1 (20%)	-
Ascending colon	9	1 (11%)	3 (33%)
Transverse colon	7	-	1 (14%)
Descending colon	6	3 (50%)	2 (33%)
Sigmoid colon	7	1 (14%)	4 (57%)
Rectum	15	-	5 (33%)
Total	49	6 (12%)	16 (2%)

*percentage of their colon section

Table 2: The relationship between FDG uptake and diagnosis of gastrointestinal tract findings

Diagnosis	Focal uptake (*n*=143)	Diffuse uptake (*n*=7)	Total (*n*=150)
Malignancy confirmed	84	-	84 (56%)
High grade dysplasia confirmed	2	-	2 (1.3%)
Adenoma confirmed	14	2	16 (11%)
Inflammation confirmed	22	2	24 (16%)
Hyperplastyc polyp confirmed	2	-	2 (1.3%)
Normal endoscopy confirmed	19	3	22 (15%)

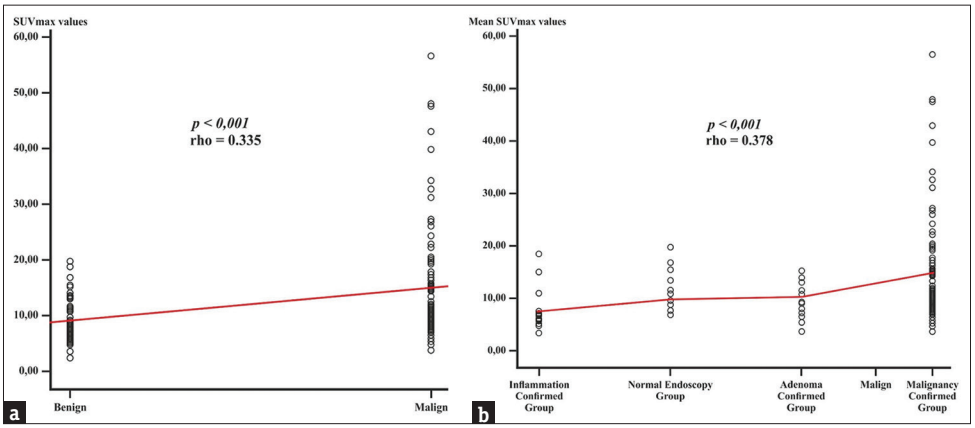

Figure 2: (a) Comparison of SUVmax values of bengn and malign lesions. (b) Comparison of SUVmax values for each groups of lesions

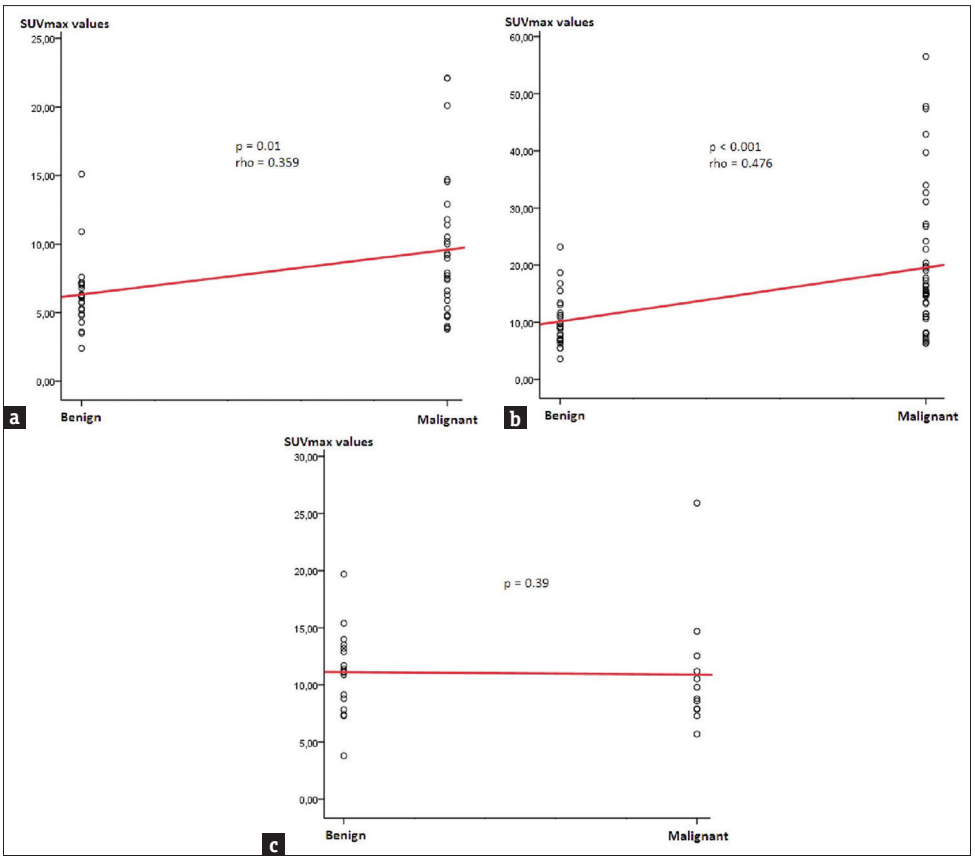

Figure 3: (a) SUV_{max} values of benign and malign lesions detected in stomach. (b) SUV_{max} values of benign and malign lesions detected in left colon. (c) SUV_{max} values of benign and malign lesions detected in right colon

SUVmax values were found as 9.5 ± 5.1 (range, 3.8-22.1) in patients with malignancy (n = 27) and 6.3 ± 2.5 (range, 2.4-15.1) in patients with benign lesions (n = 22) detected in the stomach (p = 0.01, rho = 0.359). The mean SUVmax values were found as 19.5 ± 12.1 (range, 5.7-56.5) in the patients (n = 44) with malignant and 10.1 ± 4.4 (range, 3.6-19.9) in the patients (n = 26) with benign lesions detected in the left colon (p < 0.001, rho = 0.476). Whereas the SUVmax values were 10.9 ± 5.3 (range, 5.7-25.9) in the patients (n = 12) with malignant and 11.1 ± 3.6 (range, 3.8-19.7) in those with benign lesions found in the right colon (p = 0.39) [Figure 3a, 3b and 3c].

On colonoscopy; 14 of 17 (82%) ulcerated lesions, 26 of 39 (67%) of polypoid lesions and 1 of 5 (20%) the lesions with erythematous mucosa were found to be malignant. The mean SUVmax values were 21.5 ± 13.8 in the ulcerated lesions, 14.9 ± 9.2 in the polypoid lesions, 8.5 ± 5.8 in the lesions with erythematous mucosa and 10.4 ± 4.3 in the lesions with normal mucosa (p = 0.039, rho = 0.229). Whereas on gastroscopy; 11 of 14 (79%) ulcerated lesions, 5 of 7 (71%) of polypoid lesions and 1 of 11 (9%) lesions with erythematous mucosa were found to be malignany. The SUVmax values were 10.5 ± 6.2 in the ulcerated lesions, 7.9 ± 5.7 in the polypoid lesions, 6.1 ± 1.2 in the lesions with erythematous mucosa and 5.7 ± 0.7 in the lesions with normal mucosa 5.7 ± 0.7 (p = 0.567).

Discussion

With the widespread use of PET/CT imaging technique in clinical oncology, incidental ^{18}F- FDG uptake is being frequently detected in the GIT. In our study, 16.5% of cases showed incidental FDG uptake in the GIT. This prevalence is higher than that reported by the other studies in the literature about all types of cancer with GIT or colorectal FDG uptake, with rates of uptake varying between 0,7 and 1,35%.[11-13] However, another study has found a much higher rate of FDG uptake at 23%.[14]

In a study by Schmidt *et al*.,[11] 232 (96.6%) of patients had focal and 8 (3.3%) had diffuse uptake. None of the patients with diffuse uptake had malignancy and only one patient had premalignant lesion. Similarly, in our study 143 of 150 (95.3%) of patients had focal and 7 (4.6%) diffuse uptake. Consistently with the literature,[11,14-16] in our study also none of the patients with diffuse uptake showed malignancy. Very high

rates of focal uptake in the present and the previous studies may be resulted from that, diffuse uptakes might be considered as a physiological activity and thus, further investigations were not made. Although exact mechanisms of this physiological activity are unclear, several mechanisms have been proposed such as the lymphoid tissue presented in the cecum, peristaltic muscular activity, high WBC concentrations in the intestinal wall and/or existence of the cells releasing FDG within the intestinal wall, particularly in the case of a distended cecum.[17] Supporting this, in several studies histopathological verification have been made only in patients with focal uptake on ^{18}F-FDG PET/CT.[4,18]

There is no a clear consensus among the studies performed about the colon sections where malignant and premalignant lesions are common in patients showing incidental FDG uptake in the colon. While some studies[16,17] have shown that incidental malignant and premalignant lesions are more commonly seen in the distal colon and rectum, ascending colon was shown in one study[17] and descending colon in our study as more common regions of uptake. Of note, in our study no malignancy was seen in the rectum where is the most common colon section of FDG uptake in our study.

Tumor size is one the most important factors affecting prognosis and survival in all cancers; however, so far no SUVmax value could be determined associated with size, type and stage of the tumor.[19,20] Supporting these studies, in our study also we could not find a significant correlation between tumor size and SUVmax value.

Although numerous previous studies have shown differences between malignant and benign lesions in terms of SUVmax values obtained on ^{18}F-FDG PET/CT, this difference could not be statistically demonstrated.[4,17,18] Kei *et al*.[4] found the mean SUVmax as 15.8 ± 7.5 (range, 5–25.8) in seven malignant lesions, 20.7 ± 11.3 (range, 11.3–45) in 13 premalignant lesions, 12 in solitary benign (hyperplastic polyp) lesions and 10.2 ± 1.1 (range, 8–10.5) in four sites of physiologic activity. In that study, no statistically significant difference was found in terms of SUVmax values between the malignant and benign–physiologic lesion groups ($p = 0.17$). In addition, no statistically significant difference was found in the mentioned study in terms of SUVmax values between the premalignant lesions with and without high-grade dysplasia ($p = 0.76$). Similarly, in a study performed by Choi *et al*.,[18] the SUVmax values were found to be higher in true positive foci compared to false-positive foci for advanced colorectal carcinoma on ^{18}F-FDG PET/CT, but the difference did not reach to statistical significance (12.9 ± 8.7 vs 7.8 ± 2.7, $P = 0.116$). In another study by Gutman *et al*.[17] SUVmax differed between 3.1 and 25 (mean value 10.5 ± 6.6). SUVmax values were found as 15 ± 11.6 in carcinomas (n = 3), 12 ± 3.7 in high-grade dysplasia adenomas (n = 4), 8.8 ± 4.9 in mild-to-moderate-grade dysplasia adenomas (n = 6), 25 in benign hyperplastic polyps (n = 1), and 7.1 ± 3.3 in negative colonoscopy group (n = 7). SUVmax values showed no statistical significance ($p = 0.14$).

The most important result obtained in our study is that, unlike previous studies, SUVmax values were higher in both all subjects and those with incidentally detected malignant lesions than in the patients with benign lesions, and the difference was statistically significant ($p < 0.001$, $P = 0.023$; respectively). Another important point is that all of the 17 cases with a SUVmax value ≥20.0 were malignant. Therefore, we can conclude that SUVmax value of lesions found in the GIT on FDG-PET/CT could be directing in malignant and benign distinction, but since our study SUVmax values of the malignant subjects were in a wide range (3.8-56.5) and we could not find a cut-off value for SUVmax in benign-malignant distinction, further studies with greater number of patients are warranted.

Several studies with large sample sizes have demonstrated effectiveness of FDG PET/CT for identification of malignant lesions and premalignant adenomas.[4,18-21] In a series of PET/CT scans in 4,390 patients, Israel *et al*.[21] found 58 foci of intense FDG uptake in the gastrointestinal tract. Among 34 patients followed-up, 24 (71%) had GIT abnormalities, including premalignant and malignant progression. In another study[4] 20 true positive and 4 false-positive cases detected yielded a positive predictive value of 20 ⁄ 24 (83%). Sixteen of these 20 patients had premalignant or malignant lesions. Positive predictive values vary between 67% and 96% in the current literature, and in this study, this rate was found as 69% (51/73) in the incidental group and 85% (128/150) in general study population, consistently with the literature.[4,17,18,22,23] Number of incidental lesions is likely to increase as PET-CT becomes more widespread.

Similar to the earlier reported publications, the rate of unexpected incidental malignant lesions was 9.6% (7/73) and premalignant adenoma 27.4% (20/73) in our study population. Özkol *et al*.[24] studied the malignant potential of unexpected ^{18}F-FDG-avid PET/CT foci in 2,370 patients with all body uptakes. They demonstrated that 22 of 116 biopsied PET foci were either premalignant or malignant lesions in the GIT, while the rate of unexpected malignant lesions was found as 18.1% (4/22) and premalignant lesions as 13.6% (3/22) in their study population. In a study by Vella-Boucaud

et al.,[14] 12 of 52 patients with metastatic lung cancer who had incidental FDG uptake were assessed with endoscopy and malignancy was found in 4 (36.3%) of these patients. Endoscopy was not performed in the remaining patients, because they had a poor performance status and probably were considered as benign. This might be the reason of high incidental malignancy rate.

Limitation of our study includes its retrospective design; however, almost all previous studies conducted on this topic are retrospective. Furthermore, our study has several positive aspects such as being conducted in a single and tertiary referral center by 2 nuclear medicine specialist, and number of the patients confirmed by biopsy in our study is higher than the other studies, published in the literature.

In conclusion, according to our study and previous studies we can say that there may no need for further investigations about malignancy in patients with diffuse FDG uptake in the GIT. This study is the first in the literature to show that mean SUVmax value is significantly higher in patients with malignancy identified in the GIT. Another remarkable point this study is that all patients with a SUVmax value over 20.0 were diagnosed with malignancy. We can predict that probability of malignancy increases with FDG uptake in the GIT on PET/CT. Further studies with a larger number of patients are needed on this topic to find a SUVmax cut-off value with high specificity and sensitivity. However; it can be said that currently endoscopic confirmation of all cases with FDG uptake would be a more reasonable approach, because although the likelihood of malignancy may be reduced by this means, it would not be fully eliminated.

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Conflicts of interest

There are no conflicts of interest.

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