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Etiology and significance of incidentally detected focal colonic uptake on FDG PET/CT

Nilendu C Purandare, Sachin K Gawade, Ameya D Puranik, Archi Agrawal, Sneha Shah, Venkatesh Rangarajan

Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Parel, Mumbai, India

Correspondence: Dr. Venkatesh Rangarajan, Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Parel, Mumbai - 400 012, Maharashtra, India. E-mail: drvrangarajan@gmail.com

Abstract

Background: Incidental colonic uptake of 18F-flurodeoxyglucose (FDG) is not an infrequent finding encountered during whole body positron emission tomography (PET) imaging. Almost all studies on this topic are in Western populations, which have a markedly different epidemiological profile for colorectal premalignant and malignant conditions as compared to that of the Indian subcontinent. **Aim:** The purpose of this study was to assess the etiology of incidentally detected focal FDG uptake in the colon by comparing it with colonoscopy and histopathology. **Materials and Methods**: Electronic medical records of patients who underwent FDG PET/computed tomography (CT) at our institution for a 2½-year period from January 2009 to July 2011 were reviewed. There were 32 out of 9000 (0.35%) patients whose PET/CT reports mentioned incidental focal colonic FDG uptake, of which 24 patients subsequently underwent colonoscopy. Lesions which appeared neoplastic on colonoscopy were confirmed with histopathology obtained after biopsy or surgery. Colonoscopy and pathology findings were considered as gold standard. **Results:** Among the 24 patients who underwent a colonoscopy, 3 patients had normal findings (12.5%). A positive colonoscopy was noted in 21 patients (87.5%) with the lesion coinciding with the location described in the PET/CT report. Adenomatous polyps were detected in 12 patients (37.5%), whereas in 8 patients (25%) malignant lesions were confirmed [adenocarcinoma $n = 5$, non-Hodgkin's lymphoma (NHL) $n = 2$, malignant melanoma $n = 1$]. In one patient, colonic uptake was diagnosed as inflammatory. The mean standardized uptake value $_{max}$ (SUV_{max}) for the 12 premalignant lesions was 16.9 ± 9.6 (range 7.5-37.4) and the mean SUV_{max} for the 8 malignant lesions was 12.9 ± 5.5 (range 6.7-21.6). The difference in SUV_{max} between the premalignant adenomatous polyps and the malignant lesions was not statistically significant ($P = 0.316$). **Conclusions:** Our study shows that a significant proportion of patients (62.5%, 20/32) showing an incidental focal FDG uptake will harbor premalignant (adenomatous polyps) or malignant lesions, and further evaluation with colonoscopy and biopsy is warranted in such cases.

Key words: 18F-flurodeoxyglucose; positron emission tomography; colon cancer; colonoscopy; incidental colonic lesions; polyps

Introduction

Positron emission tomography (PET) using 18F-flurodeoxyglucose (FDG) is used commonly for staging and restaging of several cancers.[1] With the introduction of combined PET/computed tomography (CT), the accuracy of the technique has improved further due to combination of anatomical and functional data in a single study.[2] The past few years have seen such a rapid growth of PET/CT that it is now being recommended as the initial imaging modality for staging, restaging, and treatment response assessment of several malignancies.[3] However, increased FDG uptake due to various physiological and inflammatory conditions in the body can lead to false-positive (FP) FDG PET results.[4] The advent of integrated PET/CT has to an extent reduced the FPs due to excellent anatomical correlation available in the combined study. In spite of the correlative imaging capabilities of the hybrid scanner, one of the common occurrences in PET/CT acquisitions is the incidental or

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unexpected FDG uptake in regions which are beyond the commonly known disease patterns. The clinical value of incidental tracer uptake has been studied and has been attributed to various physiological phenomena, clinically significant pathologic processes, metastatic spread, and synchronous or metachronous second malignancies.[5] The colon is one region where incidental FDG uptake is not infrequently encountered. There are studies in literature which have analyzed incidental colorectal FDG uptake. However, almost all of them are in Western populations, which have a markedly different epidemiological profile for colorectal premalignant and malignant conditions as compared to that of the Indian subcontinent. The aim of our study was to assess the relevance of an incidentally detected focal FDG PET finding in the colon by comparing it with colonoscopy in the context of detecting pre-cancerous lesions and synchronous malignancies.

Materials and Methods

Study design

The electronic medical records of patients who underwent FDG PET/CT at our institution for a 2½-year period from January 2009 to July 2011 were reviewed for PET/CT indication – findings, demographic data, colonoscopy results, and histopathologic correlation. Our institutional review board waives the approval or individual informed consent for retrospective review of imaging studies and electronic medical records. Patients whose PET/CT reports read incidental focal colonic/rectal FDG uptake were considered for analysis. Patients imaged for metastatic staging of primary colorectal cancer whose reports showed a focus of incidental FDG uptake elsewhere in the large bowel other than the primary site were also included. There were 32 out of 9000 (0.35%) patients whose PET/CT reports mentioned incidental focal colonic FDG uptake with a recommendation to obtain a colonoscopic confirmation of a pre-neoplastic or neoplastic pathology. Twenty-four (15 men and 9 women, age range 46-80 years) out of the 32 patients underwent a colonoscopy within a month of the PET/CT study. Lesions which appeared neoplastic on colonoscopy were confirmed with histopathology obtained after biopsy or polypectomy/surgery. Colonoscopy and pathology findings were considered as gold standard. The primary malignancies in these patients were non-Hodgkin's lymphoma (NHL) (n = 7), lung cancer (n = 3), esophageal cancer (n = 3), rectal cancer (n = 3), cervix cancer (n = 1), breast cancer (n = 1), endometrial cancer (n = 1), sarcoma (n = 1), tongue (n = 1), hepatoma (n = 1), cancer of unknown primary (n = 1), and nasopharyngeal cancer (n = 1). In eight patients colonoscopy was not performed and their follow-up data were not available.

Patient preparation and PET/CT imaging protocol

All patients were asked to fast for 4-6 h prior to the study, and blood glucose levels were checked and confirmed to be less than 150 mg/dl. The studies were performed 60-90 min following intravenous administration of 5 MBq/kg of ^{18}F-FDG with delayed images acquired in the region of the focal colonic uptake. Patients were positioned supine with their arms to their sides and were asked to breathe normally during image acquisition

Imaging was performed on a Discovery ST PET/CT system (GE Medical Systems, Milwaukee, Wisconsin, USA).

It combines a 16-slice CT scanner with a dedicated PET (BGO plus crystal, dimensions 3.8 mm × 3.8 mm × 3.8 cm).

A CT was performed over five to eight bed positions from the skull base to the level of the knee joint (location of the lesion determined the inferior extent of the coverage) using multislice (16-slice) CT component of the system. CT parameters included 120 kV, 110 mA, 0.8 s/rotation, pitch of 1.75:1, Field of view (FOV) 50 cm, length of scan 1.0-1.6 m, 0.625 spatial resolution, and slice thickness of 3.75 mm. Intravenous and oral contrast was not routinely administered in all patients unless there was a specific indication and request to do so. This was followed immediately by acquisition of PET data in the same anatomic locations with 15.4 cm axial FOV acquired in 3D mode with 3 min/bed position.

Image reconstruction and interpretation

CT data obtained were used for attenuation correction of PET images, and images were reconstructed using a standard vendor provided reconstruction algorithm which incorporated ordered subset expectation maximization (OSEM). Image fusion was performed using co-ordinate based fusion software and subsequently reviewed at a workstation that provided multiplanar reformatted images and displayed PET images, CT images, and PET/CT fusion images.

Studies were interpreted by trained Nuclear Radiologists. The CT data was used for anatomical localization and corroboration of the PET findings. The maximum standardized uptake values (SUVs) were automatically generated according to the following equation: $SUV_{max\ (bw)} = C_{tis}/D_{inj}/bw$, where $SUV_{max\ (bw)}$ is the maximum SUV normalized for the body weight, C_{tis} is tissue concentration expressed as megabecquerels per milliliter, D_{inj} is injected dose expressed as megabecquerels, and bw is bodyweight expressed as kilograms. The SUV_{max} for each area of focal colonic uptake obtained from the attenuated corrected PET data was noted.

The large bowel was divided into the following regions: Cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. Focal FDG uptake in the colon which was considered as abnormal was localized to any of the above

segments. The corresponding morphological abnormality like focal wall thickening, mass, or polypoidal lesion seen on the CT component of the study was also noted.

PET/CT finding was considered as true positive (TP) if colonoscopy confirmed the presence of a pathology in that particular segment of the large bowel. If the focus of FDG uptake did not show a matching corresponding abnormality on colonoscopy, then the PET/CT finding was considered to be FP. The positive predictive value (PPV) of an incidental focal colonic uptake to detect a pathology was calculated. We used the unpaired *t* test to compare if there was a statistically significant difference between the SUV_{max} in the premalignant and malignant groups.

Results

The PET/CT and colonoscopic findings are summarized in Table 1.

Among the 24 patients who underwent a colonoscopy, 3 patients showed normal findings (12.5%). A positive colonoscopy was noted in 21 patients (87.5%) with the lesion coinciding with the location described in the PET/CT report. Each of the 21 patients had a solitary focus of FDG detected on PET/CT, with no patient showing multiple lesions. Adenomatous polyps (tubular adenoma $n = 7$, tubulo-villous adenoma $n = 3$, villous adenoma $n = 2$) were detected in 12 patients (12/32, 37.5%), which are considered to be premalignant lesions and showed varying degrees of dysplasia (low grade $n = 8$, moderate grade $n = 3$, high grade $n = 1$), [Figure 1]. Histopathologic confirmation was obtained after surgical excision (polypectomy) or a colonoscopic biopsy. In 8 patients (8/32, 25%), malignant lesions were confirmed (adenocarcinoma $n = 5$, NHL $n = 2$, malignant melanoma $n = 1$) [Figure 2]. One patient after colonoscopy was diagnosed with inflammatory colitis of the sigmoid colon (pt #18). Thus, 62.5% (20/32) patients with an incidental focal colonic uptake were diagnosed as either premalignant lesions in the form of adenomatous polyps or malignant pathologies with a PPV of 86.9%. Morphological abnormality either in the form of soft tissue opacity or focal bowel wall thickening was seen in majority of the patients (19/24). The mean SUV_{max} for TP lesions was 15.1 ± 8.1 (range 6.7-37.4), whereas the mean SUV_{max} for the three FP cases was 7.4 ± 0.8 (range 6.5-8.3). One of the TP cases showing high FDG uptake with SUV_{max} of 11.3 was diagnosed an infective colitis on colonoscopy. The mean SUV_{max} for the 12 premalignant lesions was 16.9 ± 9.6 (range 7.5-37.4) and the mean SUV_{max} for the 8

Table 1: Positron emission tomography indication and findings, colonoscopy results, and final histopathology of the 24 patients who underwent colonoscopy

Pt #	Indication for PET/primary	Location of FDG uptake	SUV_{max}	Colonoscopy	Histopathology	TP/FP
1	NHL (nodal)	Rectum	13	Sessile polyp	Tubular adenoma with low-grade dysplasia	TP
2	NHL (nodal)	Descending colon	17.6	Pedunculated polyp	Tubular adenoma with low-grade dysplasia	TP
3	Breast	Rectum	21.6	Ulcerated lesion	Adenocarcinoma	TP
4	Esophagus	Ascending colon	17.5	Pedunculated polyp	Tubular adenoma with low-grade dysplasia	TP
5	Esophagus	Splenic flexure	19.4	Ulcero-proliferative	Adenocarcinoma	TP
6	Lung	Sigmoid	8.8	Ulcero-proliferative	Adenocarcinoma	TP
7	CUP	Rectum	19.5	Pedunculated polyp	Villous adenoma with high-grade dysplasia	TP
8	NHL nasopharynx	Rectum	14	Polypoidal lesion	NHL	TP
9	Rectum	Sigmoid	13.6	Pedunculated polyp	Tubulo-villous adenoma with low-grade dysplasia	TP
10	Lung	Descending colon	6.5	Normal melanosis coli	NA	FP
11	Lung	Transverse colon	7.5	Pedunculated polyp	Tubulo-villous adenoma with moderate dysplasia	TP
12	NHL (nodal)	Rectum	8.5	Polypoidal lesion	Malignant melanoma	TP
13	Endometrium	Ascending colon	6.7	Ulcerated growth	Adenocarcinoma	TP
14	NHL (nodal)	Sigmoid	9.3	Ulcerated growth	NHL	TP
15	Tongue	Sigmoid	12.6	Pedunculated polyp	Tubular adenoma with low-grade dysplasia	TP
16	Hepatic SOL	Sigmoid	37.4	Pedunculated polyp	Tubulo-villous adenoma with moderate dysplasia	TP
17	NHL (nodal)	Hepatic flexure	34.5	Pedunculated polyp	Tubulo-villous adenoma with moderate dysplasia	TP
18	Esophagus	Sigmoid	11.3	Inflammatory lesion	Inflammatory colitis	TP
19	Rectum	Ascending colon	8.3	Sessile polyp	Tubular adenoma with low-grade dysplasia	TP
20	Sarcoma	Ascending colon	7.2	Normal	NA	FP
21	NHL (nodal)	Transverse colon	8.4	Normal	NA	FP
22	Rectum	Sigmoid	8.9	Pedunculated polyp	Tubular adenoma with low-grade dysplasia	TP
23	Cervix	Cecum	15.6	Ulcerated lesion	Adenocarcinoma	TP
24	Nasopharynx	Transverse colon	12.4	Pedunculated Polyp	Tubular adenoma with low-grade dysplasia	TP

TP: True positive, FP: False positive, NA: Not applicable, NHL: Non-Hodgkin's lymphoma, FDG: 18F-flurodeoxyglucose, PET: Positron emission tomography, SUV_{max}: Standardized uptake value max

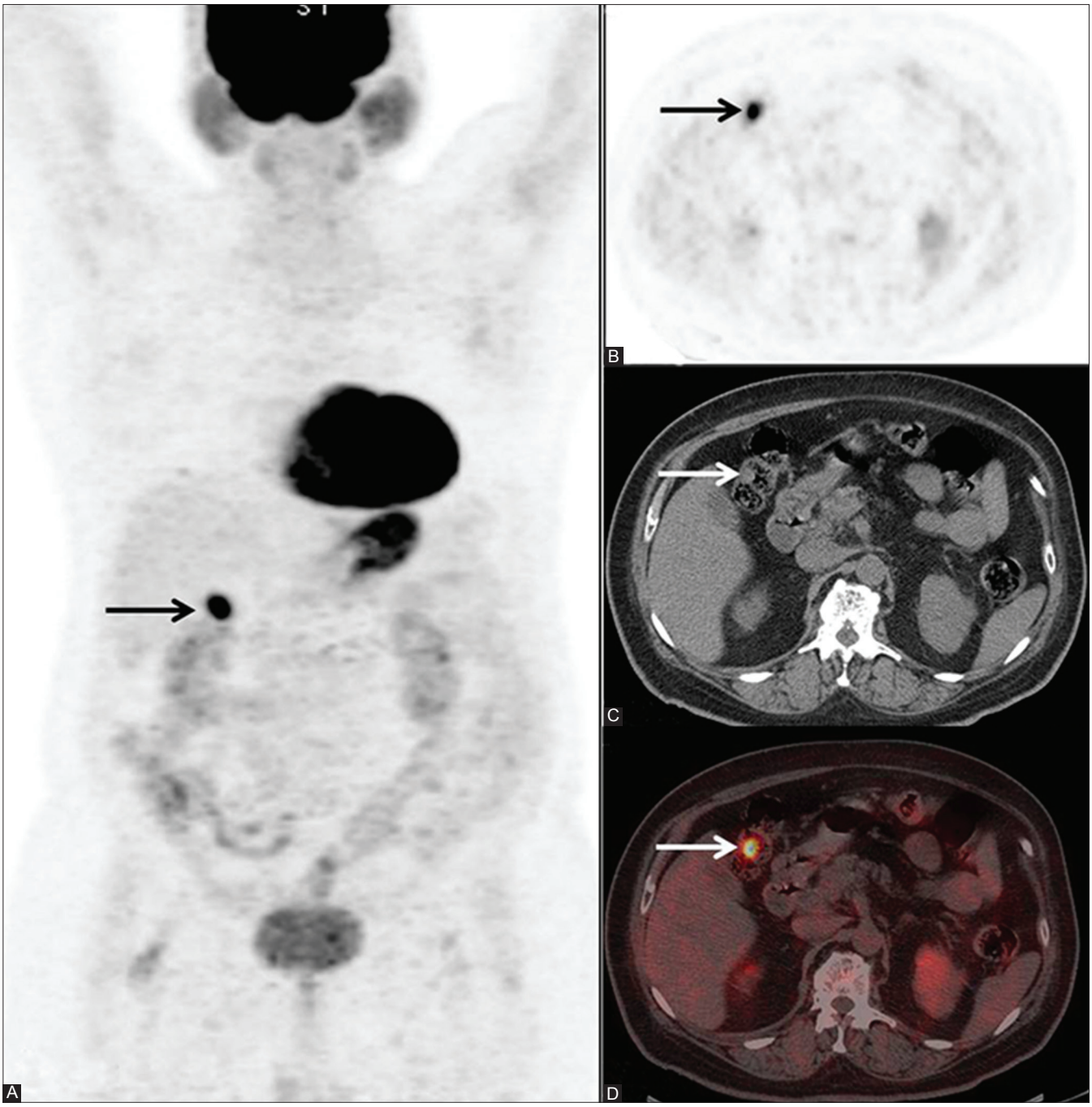

Figure 1 (A-D): A 74-year-old man treated for NHL referred for a restaging FDG PET/CT (pt # 17). Focus of intense FDG uptake (SUV_{max} 34.5) is seen in the abdomen on the whole body maximum intensity projection (MIP) and axial PET images (arrows in A and B). The focus of uptake seen on the MIP and the axial PET correlates with a small soft tissue density in the hepatic flexure seen on the CT image (arrow in C) and is confirmed on fusion image (arrow in D). Colonoscopy revealed a pedunculated polyp and pathology confirmed the diagnosis of an adenomatous polyp with moderate-grade dysplasia

malignant lesions was 12.9 ± 5.5 (range 6.7-21.6). There was no statistically significant difference in SUV_{max} between the premalignant adenomatous polyps and the malignant lesions (P = 0.316). This suggested a clear overlap in the intensity of tracer uptake between the precancerous and malignant lesions. In three patients, no corresponding abnormality was noted on colonoscopy and they were considered as FP findings attributed to the physiological uptake of FDG in the colon.

Discussion

The gastrointestinal tract (GIT) is one of the common sites of physiological and incidental uptake of FDG. Focal FDG

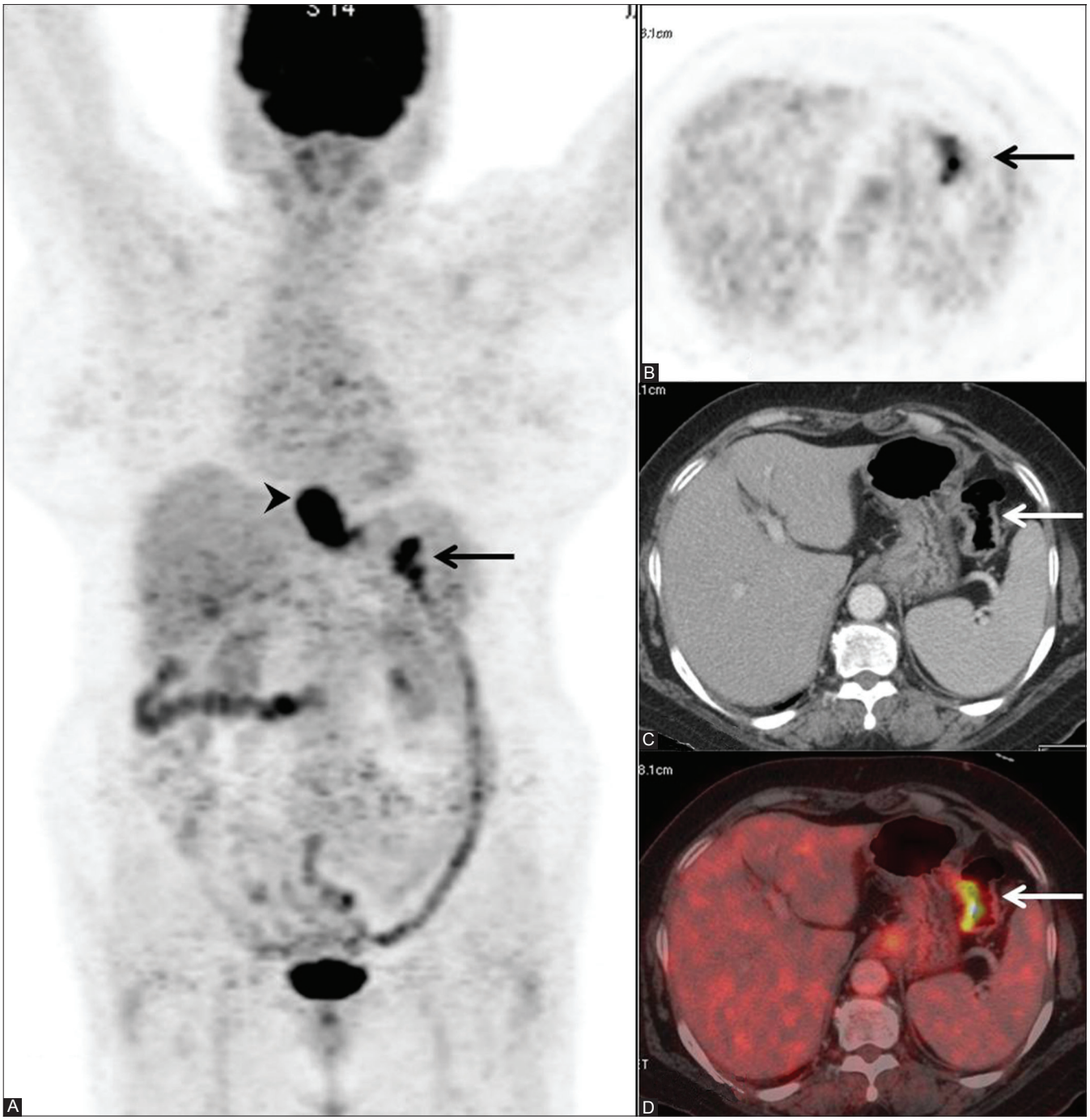

Figure 2 (A-D): A 59-year-old lady referred for a staging FDG PET/CT for gastro-esophageal (GE) junction (pt # 5) cancer. Intense focus of FDG uptake is seen on the MIP image at the site of the primary tumor (arrow head in A). Another focus of uptake (SUV_{max} 19.4) is seen in the abdomen on the MIP and axial PET images (arrows in A and B) corresponding to focal eccentric wall thickening of the splenic flexure seen on axial CT image (arrow in C) and on fusion image (arrow in D). Colonoscopy revealed an ulcero-proliferative lesion and pathology confirmed the diagnosis of colonic adenocarcinoma

uptake is often seen at the gastro-esophageal junction, stomach, small bowel, and the colon.[6] Physiological concentration of tracer in the GIT has been attributed to several mechanisms like uptake by smooth muscles, swallowed secretions, and luminal secretion[7,8] During analysis of gastrointestinal tracer uptake, a diffuse pattern regardless of the intensity is always interpreted as physiological or sometimes inflammatory,[9] whereas a focal uptake is viewed with caution and correlative imaging or further investigation is recommended. Investigators have studied the etiology, distribution pattern, and clinical significance of FDG uptake in the GIT.[10-13] It has been shown in these studies that vast majority of the foci of incidental FDG uptake in the GIT, which subsequently

were confirmed to be due to a significant pathology, were localized to the colon–rectum (82-89%), whereas only a small number was attributed to rest of the GIT including esophagus, stomach, and the small bowel put together. This emphasizes the preponderance of co-existing significant pathology (inflammation, premalignant conditions, malignancies) in the colon–rectum, which can be detected on FDG PET studies. There have been several reports and studies that have investigated the clinical relevance of incidental focal uptake of FDG localized specifically to the colon–rectum.[14-19] Though our study is on similar lines, the epidemiological profile of our patients as regards colorectal lesions was different from other patient populations, particularly their Western counterparts.[20,21]

62.5% patients with focal FDG uptake in our study showed a premalignant (adenomatous polyps) or a malignant lesion after colonoscopy and biopsy. Similar results were seen in a few recent studies where 44%, 56%, and 64% of the colonic pathologies detected on FDG PET were premalignant or malignant lesions.[17-19] These findings concur with most of the studies in literature, thus emphasizing the need to confirm focal colonic FDG uptake with colonoscopy. In one patient (pt # 18), focal uptake ($SUV_{ma} \times 11.3$) in the sigmoid colon was diagnosed as inflammatory after colonoscopy. There were three patients (pts # 10, 20, and 21) in whom the focal uptake was considered to be FP where colonoscopy did not reveal any abnormality. The possible mechanisms for these FPs could be physiological uptake by smooth muscle activity or FDG excretion in the lumen.[7] The mean SUV_{max} in these patients was 7.3 ± 0.9 (range 6.5-8.3). The solitary case of inflammatory uptake and relatively small number of FP cases in our study differs from the published literature. One of the possible reasons could be the strict inclusion criteria of cases showing only focal FDG uptake which have a higher possibility of a neoplastic etiology as compared to segmental or diffuse uptake which are more likely to be seen in inflammation or physiological processes.[9] Also, attention to the CT component of the PET/CT study can help detect a corresponding morphological abnormality in the bowel and increase the confidence in diagnosing significant pathologies. We found a very broad overlap in SUV_{max} values between premalignant lesions and cancer. The mean SUV_{max} of adenomatous polyps was slightly higher (16.9 ± 9.6) than that of malignant lesions (12.9 ± 5.5) in our study. Though several studies have reported a marginally higher mean SUV for malignant lesions as compared to premalignant ones, there was a broad overlap in the SUV range in these two groups.[14,16-18] Our study also shows a similar overlap in uptake characteristics of the lesions with no statistically significant difference in the SUV values between the premalignant and malignant lesions ($P = 0.316$). It is important to note that differentiation between inflammatory, premalignant, and malignant lesions solely on the basis of FDG uptake is difficult as shown in few studies.[16,18] Our study proves that the difference in FDG uptake between premalignant and malignant lesions did not reach statistical significance; however, similar inference could not be drawn for inflammatory lesions and physiological uptakes due to their small number (1 inflammatory and 3 physiological), though their uptake shows an obvious overlap with that of the malignant lesions. Likewise, we did not find any significant correlation between the SUV values and progressive grades of dysplasia. This is in accordance with findings of Israel, *et al*.[11] who did not observe rising SUV values with progressive histological dysplasia. Gutman, *et al*.[14] and van Kouwen, *et al*.,[21] however, showed higher SUV value and increased sensitivity of FDG PET for higher grades of dysplasia. The importance of detecting a premalignant lesion (adenomatous polyp) in the colon cannot be overemphasized as it has been shown that early detection and removal of polyps can result in reduction in the incidence and mortality form colorectal cancer.[22] The ability of FDG PET to detect colonic adenomas has been harnessed and used as a screening tool in high-risk populations to detect significant premalignant adenomas and colon cance.[21,23] Incidental malignant lesions in the colon, either synchronous or metachronous, can have a bearing on the overall approach to the management strategy, as it could alter the therapeutic regime for the known primary disease as well as add a new treatment protocol for the incidentally discovered malignancy.

The prevalence of incidental focal uptake in our study was 0.35%, which is much below the published rate in the literature, i.e., 1.1-2.7%.[11,13,14,18] We feel that one of the important reasons for this could be the low incidence of large bowel adenomas and cancers in our patient subpopulation, which has been attributed to differences in diet and environmental risk factors.[20] We found incidentally detected colorectal cancer in 5 out of 9000 (0.055%) and premalignant adenomatous polyps in 12 out of 9000 (0.13%) patients, which is expectedly lower (0.2%) as compared to the various cancer screening studies performed using FDG PET.[23,24] Another reason of the lower prevalence could be non-availability of colonoscopic correlation or follow-up in a quarter of the patients, which possibly could have led to detection of few more significant colonic pathologies. We attribute this to the retrospective nature of the study with its inherent limitations and biases where clinical follow-up and subsequent investigations cannot be strictly monitored and adhered to.

Despite these limitations, our study shows that a significant proportion of patients (62.5%) showing an incidental focal pattern of FDG uptake will harbor premalignant or malignant lesions in the colon–rectum (PPV 86.9%). Though focal colonic FDG uptake could be due to inflammatory conditions and there could be FPs due to physiological processes, the high risk of a neoplastic etiology certainly warrants further evaluation with colonoscopy and biopsy.

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