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REVIEW

Unexpected focal fluorodeoxyglucose uptake in main organs; pass through or pass by?

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Abstract

Since the inception of fluorine-18 fluorodeoxyglucose (F-18 FDG), positron emission tomography/computed tomography (PET/CT) utilizing F-18 FDG has become widely accepted as a valuable imaging modality in the field of oncology, with global prevalence in clinical practice. Given that a single Torso PET/CT scan encompasses the anatomical region from the skull base to the upper thigh, the detection of incidental abnormal focal hypermetabolism in areas of limited clinical interest is both feasible and not uncommon. Numerous investigations have been undertaken to delineate the distinctive features of these findings, yet the outcomes have proven inconclusive. The incongruent results of these studies present a challenge for physicians, leaving them uncertain about the appropriate course of action. This article provides a succinct overview of the characteristics of fluorodeoxyglucose, followed by a comprehensive discussion of the imaging findings and clinical significance associated with incidental focal abnormal F-18 FDG activity in several representative organs. In conclusion, while the prevalence of unrecognized malignancy varies across organs, malignancies account for a substantial proportion, ranging from approximately one-third to over half, of incidental focal uptake. In light of these rates, physicians are urged to exercise vigilance in not disregarding unexpected uptake, facilitating more assured clinical decisions, and advocating for further active evaluation.

Key Words: Incidental; Focal; Incidentaloma; Fluorodeoxyglucose; Positron emission tomography; Hypermetabolism

Core Tip: Unexpected incidental focal fluorine-18 fluorodeoxyglucose uptake on positron emission tomography/computed tomography is not an uncommon finding. The nature of this uptake has been the subject of various studies, with outcomes varying depending on the organ in which it manifests. A noteworthy finding from these investigations reveals that over one-third of such uptakes were determined to be malignant. This observation underscores the importance of conducting further examinations in cases where incidental uptake is identified, as it could potentially serve as a crucial indicator for malignancy.

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INTRODUCTION

The role of fluorine-18 fluorodeoxyglucose (F-18 FDG) is pivotal in establishing positron emission tomography/computed tomography (PET/CT) as a preeminent imaging modality within the realm of oncology. This radiopharmaceutical is readily available and routinely employed worldwide on a daily basis. Unlike conventional radiological images such as those obtained through computed tomography (CT) or magnetic resonance imaging, nuclear medicine images offer a functional perspective, enabling the assessment of molecular-level changes. Given that biochemical alterations precede observable physical changes such as alterations in size[1,2], PET/CT assumes a crucial role in the early detection of disease states. Presently, this imaging technique serves various purposes, including diagnosis, treatment planning, post-treatment evaluation, and follow-up.

Torso PET/CT scans encompass a range extending from the skull base to the upper thigh, with the possibility of conducting whole-body PET/CT scans contingent upon the capabilities of the scanner. The extensive scan range introduces the potential inclusion of regions with diminished clinical interest, leading to the observation of increased fluorodeoxyglucose (FDG) uptake (hypermetabolism) at unexpected sites. Such incidental uptake can pose a challenge for physicians in their interpretation. Studies have been undertaken to investigate incidental hypermetabolic regions, yielding diverse outcomes. This article delves into the distinctive characteristics of F-18 FDG, elucidates imaging findings, and explores the clinical significance of incidental hypermetabolism in several organs where unexpected uptake is relatively commonplace.

F-18 FDG INTO CELLS

The initial synthesis of F-18 FDG was accomplished by Pacák *et al*[3] in 1968, followed by the successful preparation of F-18 FDG by Ido *et al*[4] in 1978, thereby facilitating its utilization as a radiopharmaceutical for positron emission tomography (PET) imaging[3-6]. FDG has found extensive applications in diverse fields such as oncology, neurology, and cardiology. Structurally, FDG closely resembles glucose, with the key distinction being the substitution of the hydroxyl group on the 2-carbon of a glucose molecule with a fluorine-18 radionuclide[7,8]. This glucose analogue is actively transported into cells through glucose transporters, primarily GLUT1 and GLUT3, mirroring the cellular uptake of glucose[7-9]. However, owing to its structural dissimilarity, FDG cannot complete the glucose metabolic pathway and becomes trapped within cells[10]. Despite this metabolic divergence, the initial stages of FDG uptake closely parallel those of glucose, enabling FDG to assess and depict cellular glucose metabolism due to their shared metabolic behavior.

Living cells rely on glucose as a primary energy source. Notably, cancer cells exhibit a heightened uptake of glucose, a phenomenon well-described by the Warburg effect[11]. In terms of energy production, cancer cells predominantly favor glycolysis over oxidative phosphorylation, despite its lower efficiency in adenosine triphosphate yields when compared to the latter. The preference for glycolysis, despite its lower efficiency, is attributed to its faster rate, effectively meeting the energy demands of cancer cells[12-15]. This accelerated glycolytic activity contributes to the increased uptake of both glucose and FDG in cancer cells, visualized through PET[16]. However, it is essential to note that FDG, while commonly used as a marker, lacks specificity for cancer cells. Organs with naturally high glucose metabolism, such as the brain or liver, exhibit elevated FDG uptake. Moreover, benign conditions characterized by increased glycolysis also result in the accumulation of FDG in cells[17-21]. Consequently, FDG cannot be considered a selective agent for distinguishing between malignant and benign cells.

The assessment of accumulated FDG in PET images involves both visual interpretation and quantitative analysis. One widely used semi-quantitative index is the standardized uptake value (SUV), a representative dimensionless ratio indicating the relative concentration of FDG in a region of interest[22]. The calculation of SUV is outlined as follows:

$$\text{SUV} = \frac{\text{Tissue radioactivity concentration (decay-corrected) mCi/mL}}{\text{Injected tracer dose mCi/body weight (g)}}$$

The popular application of SUV is evident in the differentiation between malignant and benign lesions. A cutoff value is investigated for specific cancers; subsequently, this determined cutoff serves as a reference value. Furthermore, SUV finds frequent use in the evaluation of treatment efficacy, involving a comparison of values obtained from pre- and post-therapy images. SUV can be quantified in various ways. Noteworthy methods include the determination of the highest

SUV for a single pixel (maximum SUV or SUV_{max}), the average SUV for a freely drawn region (mean SUV or SUV_{mean}), and the average SUV for a small fixed-sized region centered on a highly uptake area (peak SUV or SUV_{peak}). While SUV_{max} remains consistent regardless of the evaluator, it is susceptible to noise interference[23,24]. Conversely, SUV_{mean} is prone to alterations based on the delineated area[25,26]. SUV_{peak} encompasses a relatively larger volume, making it less influenced by noise; however, its application becomes challenging for small or tiny lesions that do not attain a certain size [27-29]. In addition to these parameters, various SUV-derived metrics such as SUV corrected for lean body mass, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are employed. Acknowledging the imperfections inherent in each parameter, it becomes apparent that no single parameter can entirely substitute others.

F-18 FDG AVIDITY TO CANCER CELLS

The elevated glycolytic activity observed in cancer cells contributes to an increased uptake of FDG, resulting in pronounced visualization on PET imaging[30-32]. This uptake can be quantified, with SUV serving as a widely used metric in clinical settings. While SUV has inherent limitations, a generally accepted threshold is an SUV of 2.5 or higher, indicating a potential malignancy. It is crucial to acknowledge that non-specific FDG uptake can lead to elevated SUV values in normal physiological or benign inflammatory/infectious conditions[33-37].

The degree of FDG uptake varies depending on several factors. In solid tumors, low cellularity or reduced glucose metabolism may result in diminished FDG uptake, as observed in well-differentiated thyroid cancers, low-grade lung adenocarcinomas, low-grade lymphomas, well-differentiated neuroendocrine tumors, renal cell carcinoma, clear cell carcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, low-grade hepatocellular carcinoma, pancreatic cancer, prostate cancer, and so on[38-45]. However, these tumors may exhibit heightened FDG uptake during progression, marked by dedifferentiation or transformation[46-51]. Factors such as the cell cycle phase, oxygen levels, and the surrounding environment, particularly acidity, are implicated in influencing FDG uptake[52-57]. The level of FDG uptake also varies based on cancer cell type and degree of differentiation. Complementary to FDG, other PET radiopharmaceuticals structurally derived from amino acids or choline can be employed for a more comprehensive assessment of cancer avidity[58-61].

F-18 FDG UPTAKE IN BENIGN/NORMAL CONDITIONS

The transport of both glucose and FDG across cell membranes is facilitated by common plasma membrane proteins. Consequently, blood glucose concentration plays a pivotal role in influencing FDG transport dynamics. Numerous studies have elucidated that elevated blood sugar levels adversely affect image quality, attributing this phenomenon to the competitive inhibition of FDG transport by blood glucose across cell membranes[62-65]. Recognizing the significance of this relationship, guidelines outlined by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine recommend conducting F-18 FDG PET/CT scans under stringent blood glucose control, specifically targeting concentrations lower than 11 mmol/L (approximately 200 mg/dL)[16,66]. Although a subset of recent literature suggests a limited impact of blood glucose levels on imaging outcomes[67-73], it is noteworthy that adherence to the established guidelines remains prevalent in the field.

The non-specific uptake mechanism of FDG renders it susceptible to uptake in both malignant and non-malignant cells, with a particular affinity for those exhibiting elevated glycolysis. Non-malignant cells, akin to their malignant counterparts, may avidly seek out glucose. Notably, active infectious or inflammatory lesions, as well as benign polyps, can manifest high FDG uptake, thereby mimicking the metabolic patterns observed in malignant lesions[74-78]. Consequently, relying solely on heightened FDG uptake poses challenges in accurately differentiating between malignant and non-malignant lesions. FDG, in this context, remains impartial, lacking discriminatory specificity.

The human body harbors several tissues and organs exhibiting noteworthy physiological FDG uptake. The brain, characterized by its elevated glucose metabolism, typically manifests robust FDG uptake, constituting approximately 6% of the administered dose[36]. The liver, too, engages in active facilitated glucose transport, resulting in a discernible FDG uptake. Hepatic FDG uptake generally surpasses that of the blood pool, and owing to the relatively stable metabolic activity of the liver, it frequently serves as a reference for FDG uptake[36,79]. Physiological uptake of FDG in the gastrointestinal tract is a commonly observed phenomenon, and there is a well-documented association between metformin use and heightened FDG uptake in the colon[80-85]. The excretion of FDG predominantly occurs through the urinary system, leading to discernible radioactivity in the kidneys, renal pelvis, ureters, urinary bladder, and urethra[86,87]. Additional biodistribution sites encompass skeletal muscles, the heart (with a notable concentration in the left ventricle), brown adipose tissue, and various other tissues.

Studies noted the usefulness of SUV in differentiation between primary and metastatic lesions[88-90], however, challenges persist when confronted with intense FDG uptake.

F-18 FDG UPTAKE PATTERN, FOCAL VS DIFFUSE

When elevated FDG metabolism is evident in imaging, the observed uptake manifests as either focal or diffuse[91-94]. In certain organs, diffuse uptake is more likely to be benign or physiological when compared to focal uptake[34,36,95-100].

Conversely, focal uptake holds greater clinical significance; it necessitates careful consideration, as it may indicate the presence of a malignant lesion[101-104]. The pattern of uptake becomes crucial in evaluating the potential pathology.

INCIDENTAL FOCAL F-18 FDG UPTAKE BY ORGANS

F-18 FDG PET/CT is a widely performed imaging modality encompassing various anatomical regions, not rarely revealing incidental focal FDG uptake outside the primary area of interest. However, it is imperative to acknowledge that non-FDG-avid or diminutive malignant lesions may be inherently excluded due to the inherent limitations of F-18 FDG PET/CT. The degree of FDG uptake serves as a crucial parameter, with higher uptake correlating with an elevated likelihood of malignancy or advanced disease[105-107]. Consequently, these incidentally observed uptakes should not be casually disregarded. The subsequent discussion delves into the clinical implications of incidentally observed focal F-18 FDG uptake within several organs that are frequently affected[108].

Thyroid

Approximately 85% of thyroid cancer is composed of well-differentiated cancer including papillary and follicular carcinomas[109,110]. They are relatively indolent than other subtypes such as poorly differentiated carcinoma or Hürthle cell cancer. F-18 FDG PET/CT is not routinely engaged in diagnosis and follow-up evaluation of well-differentiated cancer, unless the situation with elevated serum thyroglobulin (generally > 10 ng/mL) and negative radioiodine-131 whole body scan[111]. The prevalence of incidental FDG uptake, including both diffuse and focal, is up to 8%[112], and that of focal uptake is around 2%-4%[113-116]. Diffuse FDG uptake has more chance to be benign diseases such as thyroiditis than cancer[96,117], while approximately up to 60% of focal uptake proved to be malignant[112,116,118-120]. Noticeably, benign Hürthle cell adenoma show focal high FDG uptake as well mimicking a malignant lesion[121-123].

In healthy men with a mean age 55.5 ± 13 (min 28, max 75), the SUV of thyroid ranges from a minimum of 1.2 to a maximum of 2.2 with a mean of 1.5 ± 0.2. In healthy women with a mean age 49 ± 17 (min 18, max 73), it is from 1.1 to 2.4 with a mean of 1.5 ± 0.3[124]. Although studies show some differences in findings, most focal thyroid uptake had SUV greater than 3, and it was able to differentiate malignant from benign lesions in many instances. Other PET parameters such as MTV or TLG are under discussion for differentiation.

Of those malignant lesions, well-differentiated cancers accounted for a large part[102]. These FDG-avid well-differentiated cancers are possibly related to the dedifferentiation or mutation. The upregulation of glucose transporters is one of the possible mechanisms of increased FDG avidity[125,126]. BRAF V600E mutation is also the possible cause of elevated expression of glucose transporters and glycolysis, resulting in high FDG uptake[127-130]. Therefore, incidentally visualized focal thyroid uptake on FDG PET possibly has more aggressive features than non-visualized occult lesions. Also, the fact that more than half (from one-third to two-thirds) of incidental focal uptake turned out to be malignant suggests that further evaluation should be weighted to identify the nature of the uptake.

Breast

The incidence of breast cancer in the year 2020 is the overwhelming number one in women, and the mortality rate is the highest among the types of malignant tumors[131,132]. Breast cancer is classified into many subtypes. The two main histological subtypes are invasive and preinvasive[133-135]. Invasive breast cancer is about three times more common than preinvasive one. Ductal carcinoma no special type of invasive breast cancer (also known as invasive ductal carcinoma) makes up close to 80% of all breast cancers. Invasive lobular carcinoma is the other subtype of invasive breast cancer. Preinvasive breast cancer includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS accounts for about 80% of preinvasive breast cancer and may develop into invasive breast cancer, whereas LCIS rarely exhibits invasive features. Many molecular subtypes area known including triple-negative, human epidermal growth factor receptor 2 positive, luminal B, luminal A.

The prevalence and incidence of breast cancer is obviously much higher in woman than in man[136-138]. The prevalence of incidental focal breast FDG uptake in woman is varying in some extent, several studies documented it around 1.0%[103,139-143] and the highest was about 23% in a study[144]. Possibly over 50% of the focal uptake proved to be malignant and common histologic type was invasive ductal carcinoma[103,145-148].

As expected, homogeneously diffuse and low breast FDG uptake appears to be a normal finding, and SUV_{max} is less than 2.5. A study reported that in the age group of 50.9 ± 9.70 (range 32-77), the average SUV_{max} of normal dense breasts was 1.243, while that of normal nondense breasts was 0.997. Similar results have been reported in other studies[149-151]. Due to low SUV in normal breast, focal uptake can be observed without great difficulty. However, DCIS was reported to have an average SUV_{max} between 2.0 and 2.4[152,153], which may not be visually distinguishable on images. Moreover, the SUV may be affected by physiological states (density change) such as pregnancy, breastfeeding, menstrual cycle[154, 155], and age. Enlarged breast during pregnancy may show SUV similar to liver which has the value from 2 to 5[124]. Suckling of the lactating breast may be associated with increase in expression of glucose transporters resulting in high FDG uptake[156]. SUV decreases as age increases (with diminished breast density).

Breast cancers with lobular feature or small size limit the role of FDG PET/CT in evaluation[157-160]. F-18 FDG PET/CT is not indicated for the routine use except when standard studies bring equivocal results or in advanced disease[161]. In evaluation of breast, axillary lymph node uptake may be a challenge too. Focal FDG uptake in the breast and/or axilla may be observed in the situations such as infection/inflammation[37], primary/metastatic disease[162-164], benign neoplasm (fibroadenoma, intraductal papilloma, ductal epithelial hyperplasia, sclerosing adenosis, and so on)[165], gynecomastia[166], and artefacts[167]. These should be included in differential diagnosis. The most common benign

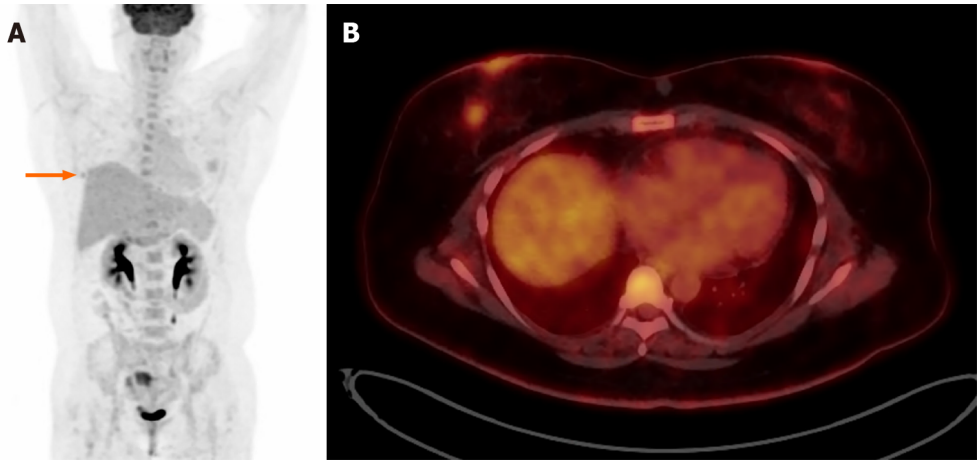

Figure 1 Incidental focal right breast fluorine-18 fluorodeoxyglucose uptake. A: Focal mild to moderate uptake (arrow) is observed in the right chest on the maximum intensity projection image of a 32-year-old woman diagnosed with endometrial cancer; B: Axial image of fused positron emission tomography/computed tomography showing hypermetabolism (maximum standardized uptake value 3.3) in her right breast and the uptake was histopathologically confirmed as a ductal carcinoma in situ.

breast tumor, fibroadenoma, often shows low FDG uptake, but it may have high uptake mimicking a malignant lesion [168,169]. Asymmetrical or nodular appearance of gynecomastia also can mimic malignancy. SUV failed in differentiation between malignant and benign lesions in a study[139]. Nevertheless, incidental focal breast FDG uptake has up to more than 50% of malignancy, therefore, a thorough appropriate evaluation is needed.

Figure 1 shows incidental right breast uptake in a 32-year-old woman who was diagnosed with endometrial cancer. Increased uptake in the right pelvic cavity indicates primary cancer lesion, and another focal moderate uptake is observed in her right breast unexpectedly (SUV_{max} 3.29). The uptake turned out to be a coincident malignant lesion which was confirmed as DCIS histopathologically.

Colon and rectum

Incidental colorectal FDG uptake is up to around 5%[170-172]. Focal uptake has more chance to be malignant[173]. Diffuse and segmental uptake may be due to inflammation, physiological uptake, or FDG excretion[174,175]; and considered to have a low risk of malignancy. The prevalence of focal uptake is up to around 16%[176]. The malignant and premalignant lesions were up to 68% of focal uptake[101,176,177]. Premalignant lesions are not yet malignant; however, they have more chance to develop into malignant lesions. Adenomas (tubular adenomas, villous adenomas, tubulovillous adenomas) are the most frequent premalignant lesions and others include chronic inflammatory bowel diseases, hereditary syndromes (familial adenomatous polyposis, Peutz-Jeghers syndrome, and juvenile polyposis). Colorectal adenomatous polyps are known to develop in up to 40% of people over the age of 60[178].

Different genetic mechanisms are suggested for cancer development by the location (distal or proximal)[179-181]. Proximal colon cancer (up to splenic flexure) accounted for 41%; distal colon cancer 22%; and rectal cancer 28% in the United States from 2009 to 2013[182]. Other paper observed that the most frequent site (42%) of malignant and premalignant lesions was the ascending colon[173], while another reported it as the rectum (60.0%), followed by the sigmoid colon (17.4%)[183]. The distribution of colorectal cancer appears to vary by country, region, race, and age[184-186]. It also varies with sex. Women are more likely to experience proximal colon cancer compared with men[187,188]. Because specific colorectal regions are more likely to involve malignancy than others, consideration of patient characteristics is recommended in reading FDG PET/CT.

Often, mixed single/multiple focal and diffuse uptake is observed together in colorectal region. In this case, diffuse uptake may not preclude further evaluation including colonoscopy and histopathological confirmation. The role of SUV to differentiate malignant/premalignant from benign lesions is still in debate[170,189-193]. Again, more than 50% of malignancy is observed in the incidental focal FDG colorectal uptake.

Figure 2 shows F-18 FDG PET/CT images of a 79-year-old woman who was diagnosed with pancreatic body cancer. Suspicious focal uptake is observed in the right lower abdomen. With an aid of CT, it was revealed as urine radioactivity at the right ureter. Another interesting thing is the multiple foci of hypermetabolism along the descending and sigmoid colon. Colonoscopy was conducted and it found no significant abnormal lesion. The uptake is probably due to normal physiological uptake.

Figure 3 shows a maximum intensity projection image of a 76-year-old woman diagnosed with cecal cancer and multiple metastases/seeding nodules. The primary cecal cancer is observed in the right lower abdomen and diffuse intestinal uptake is also shown. The diffuse uptake may be physiological; however, the possibility of hidden pathological lesions, which may be obscured by the intense intestinal uptake, cannot be ruled out.

Prostate

With the recent advent of United States Food and Drug Administration-approved prostate-specific membrane antigen-targeted PET imaging radiopharmaceuticals, PET/CT has become actively used in the evaluation of prostate cancer. In

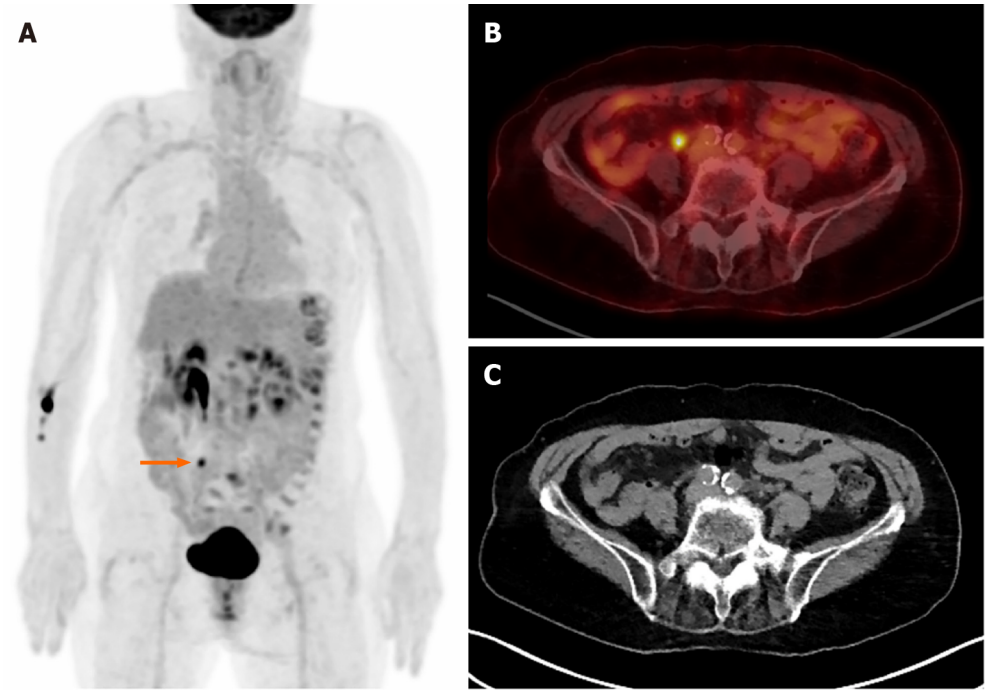

Figure 2 Multiple foci of physiological fluorine-18 fluorodeoxyglucose uptake. Images of a 79-year-old woman diagnosed with pancreatic body cancer. A: Focal uptake is observed in the right lower abdomen (arrow); B: Suspicious uptake as a lesion; C: No lesion but right ureter. Multiple hypermetabolic areas are observed along the descending and sigmoid colon in image A. Colonoscopy found nothing abnormal, and the uptake is probably due to normal physiological uptake.

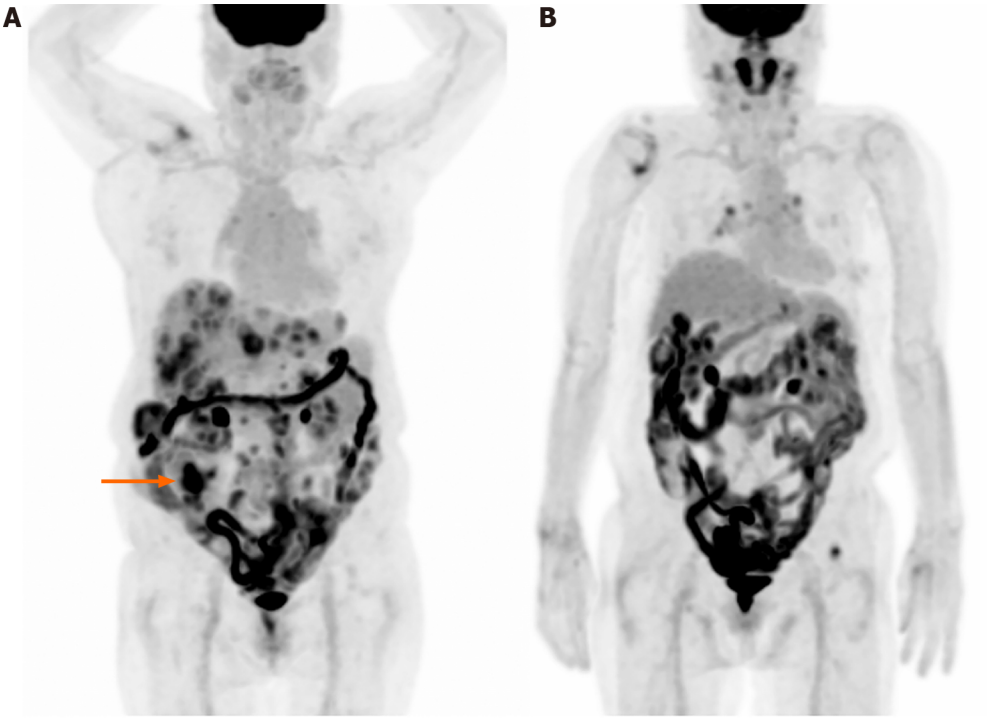

Figure 3 Diffuse intestinal fluorine-18 fluorodeoxyglucose uptake. A: 76-year-old woman diagnosed with cecal cancer and multiple metastases/seeding nodules. Primary cecal cancer is observed in the right lower abdomen (arrow) and diffuse intestinal uptake is also shown. The diffuse uptake may be physiological; however, pathological lesions may be obscured by the intense intestinal uptake; B: 79-year-old woman diagnosed with mantle cell lymphoma, and also had a history of colon cancer about three decades ago. Mixed focal and diffuse intestinal uptake is challenging.

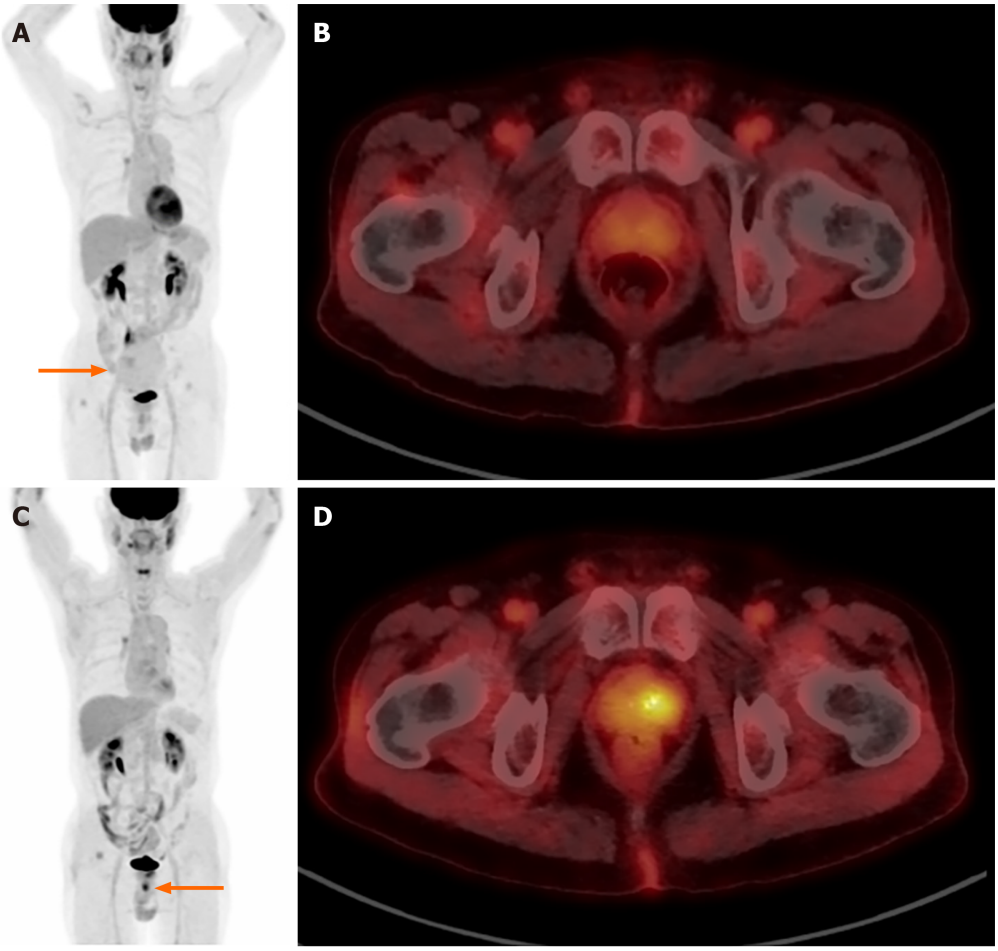

Figure 4 Incidental prostate fluorine-18 fluorodeoxyglucose uptake. A 74-year-old man diagnosed with small bowel gastrointestinal stromal tumor. A: On the initial image, known small bowel gastrointestinal stromal tumor with low uptake is observed (arrow); B: Also, nearly symmetrical low prostate uptake is shown; C: An incidental focal uptake is observed beneath urinary bladder (arrow) on the five-year follow-up image; D: The uptake is at the left side of prostate (maximum standardized uptake value 5.6) and it was proved histopathologically as an adenocarcinoma of prostate.

terms of FDG, prostate is one of the organs that shows low FDG uptake even if it is cancerous. In a group of men with a mean age of 63.6 years (range 22-97), SUV_{mean} and SUV_{max} in normal prostate were reported as 1.3 ± 0.4 (range 0.1-2.7) and 1.6 ± 0.4 (range 1.1-3.7), respectively[194]. The degree of uptake may overlap among prostate cancer, benign prostate hyperplasia, and normal prostate. SUV showed questionable or suboptimal performance in differentiation between malignant and benign lesions. As a result, F-18 FDG PET/CT is not routinely recommended and performed in detection or initial staging of primary prostate cancer[195,196]. However, incidentally observed focal uptake may have clinical implications[100,104,197,198], particularly in the peripheral zone[199,200]. The prevalence of uptake is up to around 2% [200,201] and malignant rate is up to over 60%[197,201-203]. Multifocal uptake is not a significant differential diagnostic criterion between malignant and benign lesions[204]. The location of focal uptake may be the key in differentiation, that is, focal uptake in the peripheral zone is possibly related with malignancy[204,205]. Although with low FDG uptake in both malignant and benign prostate diseases, focal and peripheral uptake should be noted and lead to further evaluation.

Figure 4 shows F-18 FDG PET/CT images of a 74-year-old man who was diagnosed with small bowel gastrointestinal stromal tumor. Initial maximum intensity projection image Figure 4A shows a large pelvic mass with low FDG uptake (arrow). Also, nearly symmetrical low prostate FDG uptake is observed (Figure 4B). F-18 FDG PET/CT conducted in five years for a suspicious recurrent pelvic mass noticed on CT show an incidental focal FDG uptake (SUV_{max} 5.6) in the left side of prostate (Figure 4C and D). The uptake was proved as an adenocarcinoma of prostate histopathologically.

CONCLUSION

This article comprehensively addresses the characteristics of FDG, discusses imaging findings, and outlines the clinical implications of incidental focal FDG uptake across various organs. Existing literature consistently reports that a significant proportion, ranging from approximately one-third to over a half, of incidental focal FDG uptake is indicative of yet unrecognized malignancy. Considering the malignancy rate associated with incidental focal uptake in diverse organs, it is imperative for healthcare professionals not to disregard such unexpected findings. By doing so, they can make more informed and confident clinical decisions, prompting a proactive approach towards further comprehensive

evaluation.

FOOTNOTES

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