Clinical significance of incidental focal bowel uptake on ^{18}F-FDG PET/CT as related to colorectal cancer

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Abstract

Objective: Increased focal colorectal uptake of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is reported to occur in 1%-3% of patients undergoing ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) for disease outside the bowel. However, there is no consensus on how to deal with this finding in the clinic. Due to the non-specific appearance of such lesions and a certain rate of false positive findings, patients may by subjected to unnecessary invasive procedures or, conversely, cancers may be overlooked if the risk of malignancy is downplayed. The purpose of this study was to examine the incidence and clinical significance of focal colorectal incidentalomas (FCI) at our institution and to assess the potential benefit of using semi-quantitative measures instead of visual interpretation to discern malignant from benign lesions. **Subjects and Methods:** We identified all patients in 2011 with a report of FCI. We reviewed patient charts with regard to basic characteristics, indications for and results of ^{18}F-FDG-PET/CT and subsequent workup including colonoscopy and histopathological analyses, and applied post hoc semi-quantitative analysis. Out of 4,829 patients, twenty-five met the inclusion criteria (mean age 71 years, 13 females, 12 males). **Results:** Of the 25 included patients, eight presented with no pathologic or non-malignant findings (e.g. inflammation), while ten had polyps/adenomas and seven a hitherto undiagnosed colorectal cancer. Semi-quantitative SUVmax values and ROC analysis based cut-off values could not reliably discriminate benign from premalignant or malignant disease. **Conclusion:** It is the opinion of the authors that ^{18}F-FDG PET/CT scan may identify incidentally sites of colorectal carcinoma but cannot discriminate them from polyps/adenomas. Nevertheless, incidental focal bowel uptake should always be reported and/or further evaluated.

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Introduction

Increased colorectal uptake is a fairly common incidental finding in patients undergoing fluorine-18-fluorodeoxyglucose photon emission tomography/computed tomography (^{18}F-FDG PET/CT) for diseases outside the bowel, usually reported in the range of 1%-3% of all ^{18}F-FDG PET/CT scans [1-14]. The increased uptake may be nonspecific or represent physiologic bowel activity, but the literature reports a substantial proportion to represent colorectal cancers or premalignant lesions, especially if focal in appearance [6, 15]. However, at present there is no established way of discriminating benign lesions from malignant or premalignant ones based on visual appearance alone, and at our institution there is no consensus on the management of these "focal colorectal incidentalomas" (FCI); this is left at the discretion of the referring physician. Due to the nonspecific appearance of the lesions and a number of false positives, some patients are subjected to unnecessary invasive endoscopies, and, conversely, some cancers may be overlooked if not followed up properly, and this could lead to delayed diagnosis of bowel malignancies with negative impact on patient outcome [16, 17]. Some studies have reported favorable results by using semi-quantitative PET-parameters to help differentiate benign from malignant or pre-malignant lesions [4, 5, 18-20]. The purpose of this study was to examine the incidence and clinical significance of FCI detected by ^{18}F-FDG PET/CT at our institution, including assessment of any benefit of using semi-quantitative measures besides visual characterization of lesion etiology.

Subjects and Methods

All ^{18}F-FDG-PET/CT studies performed at our institution were entered into a comprehensive and searchable database with basic and clinical data on every patient. We identified all patients in 2011 with a report of FCI, defined as focal uptake of ^{18}F-FDG in the bowel recognized by a physician specialised in nuclear medicine and based on visual interpretation of scans.

We reviewed patient charts with regard to basic characteristics, indications for and results of ^{18}F-FDG PET/CT and subsequent work up including colonoscopy and histopathological analyses. All patients with negative findings at colonoscopy or without colonoscopy were followed-up, and events during follow-up were recorded. We applied post hoc semiquantitative analysis.

Focal colorectal incidentalomas were reported in 52 (1.1 %) of 4,829 patients (Figure 1). Excluded patients can be seen in Figure 1. After exclusion, 36 patients (20 females and 16 males; mean age 69 years [range 33-93]) were available for data analysis. Of these, 25 underwent colonoscopy with biopsies (13 females and 12 males; mean age 71 year [range 33-90]). We found no correlation between age or gender and cancer/pre-cancerous FCI. The patients were very heterogeneous in terms of what led to their PET/CT scan (Table 1) and out of 25, who underwent colonoscopy, eight presented with no pathologic or non-malignant findings (e.g. inflammation), while ten had polyps/adenomas, and seven a hitherto undiagnosed colorectal cancer (Table 2). Out of the 25 FCIs, five were rectal (one benign, one polyp and three malignant) and twenty were colonic, but all calculations were made using the pooled data of both colonic and rectal findings. The colonic and the rectal FCIs are described in Table 2.

All PET/CT scans were performed according to the department's standard protocol in line with guidelines of the European Association of Nuclear Medicine [21] and depending on indication with CT without or with contrast enhancement. All patients fasted for at least six hours prior to tracer injection, and water was used as oral contrast in all patients. Scans were performed approximately one hour after administration of a weight-adjusted dose of ^{18}F-FDG of 4MBq/kg ^{18}F-FDG (minimum 200MBq and maximum 400MBq). The ^{18}F-FDG PET/CT examinations were performed on a GE Discovery VCT or Discovery 690 PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin, USA). Data were reconstructed with a standard filter into transaxial slices with a field of view of 50cm, matrix size of 512x512 and a slice thickness of 3.75 mm. Scans were originally assessed visually. The CT scan was followed immediately by a PET scan performed using a standard whole-body acquisition protocol with five, six or seven bed positions and an acquisition time of 2,5min/bed position. The scan field of view was 70cm. Attenuation correction was performed from the CT scan. The PET data were reconstructed into transaxial slices with a matrix size of 128x 128 and a slice thickness of 3.3mm using iterative three-dimensional OS-EM (two iterations, 28 subsets) and displayed in coronal, transverse and sagittal planes. Corrections for attenuation, randoms, dead time and normalization were carried out inside the iterative loop. Analysis of the PET and fused PET/CT data as well as post hoc analysis with regard to semiquantitative measurements was carried out using a GE Advantage Server 2.0 (GE Healthcare, Milwaukee, Wisconsin, USA). A fixed circle encompassing the region of analysis was placed around all areas with focally increased ^{18}F-FDG uptake in the bowel and the maximum standardized uptake value (SUVmax) was recorded for each lesion. Exploratory receiver operating characteristic (ROC) analyses were performed for differentiating cancers from other findings on subsequent colonoscopy (i.e. polyps/adenomas, non-malignant findings, and normal colonoscopies). The area under the ROC curve (AUC-ROC) was estimated and supplemented by its 95% confidence interval (95% CI). An optimal threshold for maximizing classification was found by using the point on the ROC curve closest to the (0,1) point in the ROC graph [22]. Sensitivity and specificity were assessed at that point, and the precision of these estimates was evaluated by 95% CIs, based on Wilson scores [23]. Ad hoc comparisons of groups were done by Kruskal-Wallis test and Fisher's exact test, when investigating continuous and categorical outcomes, respectively. The level of statistical significance was 5%. All analyses were performed with STATA/MP 14 (StataCorp LP, College Station, Texas 77845 USA).

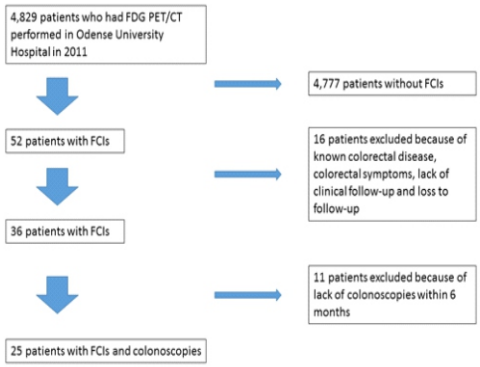

Figure 1. Flowchart for patients selection.

Results

Exploratory ROC analyses identified the optimal cut-off at an SUVmax value of 11g/mL BW, and this cut-off yielded a sensitivity of 85.7% (95% CI: 48.7% to 97.4%) and a specificity of 66.7% (95% CI: 43.7% to 83.7%) for differentiating manifest cancers from other findings. The area under the ROC curve was 0.68 (95% CI: 0.42 to 0.94) (Figure 2). SUVmax values in non-malignant lesions (mean 10.3g/mL; range 7.2-19.0), premalignancies (mean 14.4g/mL; range 5.0-26.0), and cancers (mean 16.2; range 6.4-23.6) overlapped (Figure 3) and were not statistically significant different across groups (P=0.27). Patients who did not undergo colonoscopy and patients without colorectal cancer were followed for an average of 29 months (range 9-36). None of these developed colorectal cancer during this period.

Table 1. *Indications for ^{18}F-FDG PET/CT in patients with focal colonic incidentalomas (FCI) and subsequent colonoscopy (n=25).*

Histologic diagnosis/findings related to FCI	Indications for PET/CT
Colon cancer (n=7)	Suspected cancer (n=3) Brain lesions and aphasia Lung infiltrates High CA-125 value Suspicion of severe illness/ fever of unknown origin
Polyps/adenomas (n=10)	Suspected cancer (n=6) Rheumatoid arthritis and bacteremia of unknown origin Myelomatosis Suspected spondylitis Suspicion of severe illness/ kidney failure
Normal/benign findings (n=8)	Suspected cancer (n=6) Cervical cancer (post-therapy control) Fever of unknown origin

Table 2. *Histopathologic findings related to focal colonic incidentalomas.*

Cancer (n=7)	Tubulovillous adenocarcinoma (n=1) Mucinous adenocarcinoma (n=1) Adenocarcinomas with intermediate grade differentiation (n=2) Adenocarcinomas without specification (n=3)
Polyps/adeno -mas (n=10)	Tubulovillous adenomas (n=4) moderate dysplasia (n=2) mild dysplasia (n=1) unspecified dysplasia (n=1) Tubular adenomas (n=3) high grade dysplasia (n=1) moderate dysplasia (n=1) mild dysplasia (n=1) Villous adenoma with mild dysplasia (n=1) Hyper-/metaplastic polyp (n=1) Benign polyp (n=1)

Discussion

Focal colorectal incidentalomas are a relatively common finding that requires attention from the referring physicians: the proportion of novel cancers and potentially premalignant polyps underlying FCI is high. A pooled incidence of 68% was found both in our study and in another meta-study and semi-quantitative SUVmax cannot discriminate reliably between benign and malign etiology (Figure 4) [15]. The strength of our study is the representability of our population; all patients who underwent an ^{18}F-FDG PET/CT scan at Odense University Hospital in 2011 were included. Limitations adhere to the retrospective design. Thus, patients may have been lost due to missing data or recall bias. Furthermore, the number of FCI were limited (n=36) and the number of subsequent colonoscopies even fewer (n=25). Also, semi-quantitative values and ROC-curves were derived from only 25 observations without any validation (analysis performed by only one experienced physician specialized in nuclear medicine).

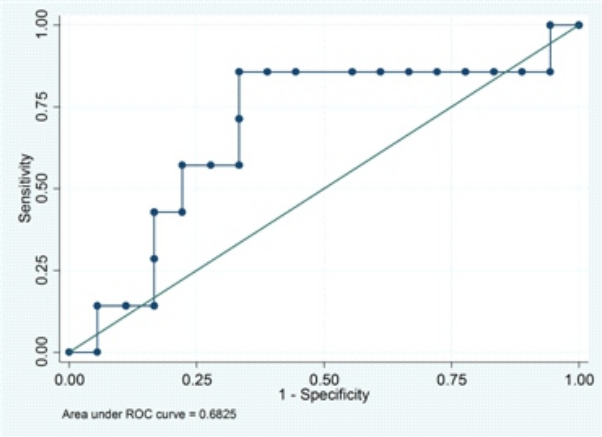

Figure 2. Results from ROC analysis: ROC curve and respective area under the ROC curve of 0.68.

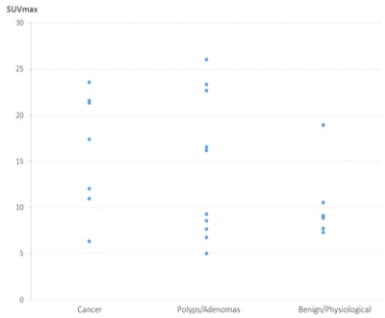

Figure 3. Distribution of SUVmax values across groups.

Our results were in general consistent with the literature. The incidence of FCI in our study was 1.1% compared to 3.6% found by Treglia et al. (2014). The reported incidence of FCI varies mostly from 1% to 3% [1-14], albeit that some studies found much higher percentages [24-27]. Similarly, the pooled proportion of malignant and potentially malignant findings at our institution were in agreagreement with meta-

Table 3. *Studies on focal colonic incidentalomas (FCI) including SUVmax measurements.*

Study	Patients	Patients with FCI	Cut-offs for FCI	Mean SUVmax
Kei et al. (2010)	Non-GI cancer patients	16/2,250 (0.7%)	> liver uptake	C: 15.8±7.5* A: 20.7±11.3 B/P: 12/10.2±1.1
Weston et al. (2010)	Patients with ^{18}F-FDG PET/CT and CS	58/10,031 (0.6%)	SUV > 3.5	C: 10.1±3.4/18.7/ 22.7±13.2** A: 14.2±7.2 and 11.8±3.5 B/P: 11.7±8.3
Peng et al. (2011)	Patients with ^{18}F-FDG PET/CT and CS and no GI symptoms	136/10,978 (1.2%)	SUV > 2.5	C: 9.7 A: 7.8 B/P: 6.1
Oh et al. (2012)	Patients with ^{18}F-FDG PET/CT and CS and no GI symptoms	99/21,317 (0.5%)	Visual	C: 13.6±4.9 A: 8.4±4.5 B/P: 6.7±2.3
Van Hoeij et al. (2014)	Patients with ^{18}F-FDG PET/CT and CS	203/7,318 (2.8%)	Visual	C: 16.6 A: 8.3 and 9.7 B/P: 8.2

GI = Gastrointestinal; CS = colonoscopy; C = cancer; A = adenomas; B/P = benign/physiologic processes
**Results were calculated from 25 GI regions with increased FDG uptake; 16 of these were colorectal.*
*** The three SUVmax values represent lymphomas, metastatic cancer and colon cancers, respectively.*

analysis result of Treglia et al. (2014) who comprised results of 31 studies (95% CI 60%-75%) [15].

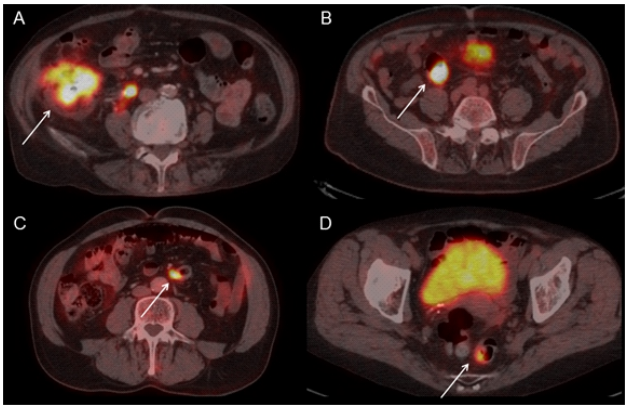

Figure 4. Variations in colon uptake appearance and semi-quantitative values

In five of the studies included in the meta-analysis, SUVmax managed to differentiate benign from malignant or premalig-nant lesions to some degree, but its discriminatory value was at best equivocal [4,5,18-20] (Table 3). In four of five studies, SUVmax was able to discriminate cancer from adenomas/ dysplasia [4, 18-20], whereas it was able to differentiate ade-nomas/dysplasia from benign processes in only a single study by Kei et al. (2010) [5]. Others took an interesting, stepwise approach and included metabolic volume (MV) in their diagnostic approach along with SUVmax, resul-ting in increased sensitivity and specificity compared to using SUVmax alone [19]. However, all five studies agreed that, even though they found some significant results, SUVmax as a single determining parameter was not a reli-able diagnostic tool allowing differentiation of cancer from benign processes.

The cut-off value obtained by our ROC analysis was also in line with a previously derived cut-off by other researchers, who had 203 observations [1]. Other studies found different cut-offs (SUVmax values of 4.5, 5.0, and 9.1, respectively) and different areas under the ROC curve and sensitivity and specificity of ^{18}F-FDG-PET/CT at the cut-off point were in all studies clinically in-sufficient [19, 28, 29]. Consequently, we cannot recommend SUVmax in ^{18}F-FDG-PET/CT scans as a single tool to differentiate reliably between malignant/pre-malignant and benign/normal FCI.

Potential future developments include PET/MRI [30], bow-el segment analysis [31, 32] or dual time point imaging (DTPI) [33], but unfortunately these approaches have not yet been studied in relevant prospective materials. Theoretically, DTPI may show better sensitivity and specificity in this setting than ordinary 1-hour ^{18}F-FDG-PET/CT scans and thus may be able to better differentiate benign from malignant findings. How-ever, from a logistic point of view, DTPI is a challenge and the need of an additional 3-hour acquisition is seldom realized in the daily routine before the patient has left the scanner room and is no longer available for delayed imaging. Still, other

severity of disease might improve the diagnostic accuracy. These include calculation of the summed lesion SUV mean and the total lesional glycolysis as has been proposed for quantifying malignant lymphomas [34]. However, this requires proper segmentation with mandatory partial volume corrections, i.e. procedures that are still under investigation. Although promising, there is limited data on their application in a variety of bowel diseases.

In conclusion, it is the opinion of the authors that ^{18}F-FDG PET/CT scan may identify incidentally sites of colorectal carcinoma but cannot discriminate them from polyps/adenomas. Nevertheless, incidental focal bowel uptake should always be reported and/or further evaluated.

The authors declare that they have no conflicts of interest

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