Endoscopic findings in case of incidental colonic uptake in PET-CT How to improve PET-CT specificity ?

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Abstract

Unexpected colonic ^{18}FDG focal uptakes (UCFU) in PET CT occur in 1.3–3.3% of cases in retrospective study and are often associated with significant colorectal findings in endoscopy, especially neoplastic lesions. The purpose of our prospective study was to evaluate the significance of UCFU and to assess criteria improving PET CT specificity for advanced adenoma and neoplasia. This study was conducted in a single institution from April 2012 to September 2013. In the 2904 patients who benefit from PET CT, 52 had an UCFU and 43 were referred for colonoscopy. After endoscopy, 8 examinations showed no colonic abnormality (18.6%), 7 showed benign lesion (16.3%), 18 showed advanced adenoma (42.9%) and 10 showed carcinoma (23.3%).

There were more false positives results in the proximal colon compared to distal colon. Eighteen patients had UCFU and tomodensitometric abnormalities in the same colonic area. This pathological combination was strongly associated to the diagnosis of malignancy.

Comparing standardized uptake values (SUV), we showed statistically significant difference between the adenocarcinoma and advanced adenoma groups and a difference at the margin of statistical significance between adenocarcinoma and benign lesion groups. Any cut off value could be determined.

In conclusion, we confirmed that UCFU are often associated to endoscopic findings and neoplastic lesions and justify systematic endoscopic exploration. Considering the fragility of oncologic patients, criteria improving PET CT specificity are needed to select endoscopies which should be performed quickly from those who could be delayed. We showed that associated tomodensitometric abnormality and high focal FDG activity are more predictive of a neoplastic lesion. (Acta gastroenterol. belg., **2014**, 77, **413-417**).

Key words : PET CT, Coloscopy, advanced adenoma, neoplasia, and focal uptake.

Introduction

^{18}F-fluorodesoxyglucose (FDG) positron emission tomography combined with computed tomography scanner (PET-CT) base on the uptake of radiolabelled glucose by hyper metabolic malignant cells, is a highly sensitive tool, commonly used for staging, restaging and post therapeutic surveillance in general oncology (1). This ability of ^{18}FDG to mark cells and organs with increased glycolysis also leads to unexpected detection of uptakes which could be secondary neoplasia, benign lesions, inflammatory or infectious processes or normal physiological uptakes (2). According to the literature, unexpected colonic ^{18}FDG focal uptakes (UCFU) occur in about 1.3-3.3% of cases (3). If endoscopy is performed, UCFU are often associated with significant colorectal findings and especially neoplastic lesions. For this reason, the usual recommendation in case of UCFU is to perform endoscopy to detect the presence of colorectal cancer or advanced adenoma. However, considering the weakness caused by their disease and treatments, not all oncologic patients who benefit from PET CT are able to undergo colonoscopy. Therefore, the first endpoint was to evaluate the significance of UCFU encountered during PET CT in a prospective study. The secondary endpoint was to assess criteria in PET CT that are able to discriminate between endoscopies which should be performed quickly from those which could be delayed.

Method

Study protocol

After approval by the Liege Centre Hospitalier Chretien ethics committee, a prospective study was conducted in the institution from April 2012 to September 2013. In patients who underwent ^{18}FDG PET-CT for oncologic, infectious or inflammatory disease, total colonoscopy was proposed to each presenting UCFU after agreement of his physician and signature of informed consent. Endoscopy was performed within 45 days after PET-CT in our institution. Exclusion criteria were a history of colorectal cancer, evidence for acute diverticulitis or active inflammatory bowel disease. All detected lesions during endoscopy were resected if possible or biopsied and sent for pathology analyses. The colonoscopic and the pathological findings, clinical data, the UCFU location, the ratio SUVmax lesion/SUVmean liver value and tomodensitometric imaging in PET CT were evaluated. Standardized uptake value (SUV) is a semi quantitative analysis of FDG activity for each focal FDG uptakes. We chose to study the ratio : colonic lesion maximum standardized uptake value (SUVmax) / liver mean SUV, arbitrarily called normalized SUV (nSUV) to avoid bias due to differences of the metabolic status, kinetics of ^{18}FDG uptake among patients and limit the bias due to differences in the way data were acquired and processed during the study (4-5). We assessed nSUV in three

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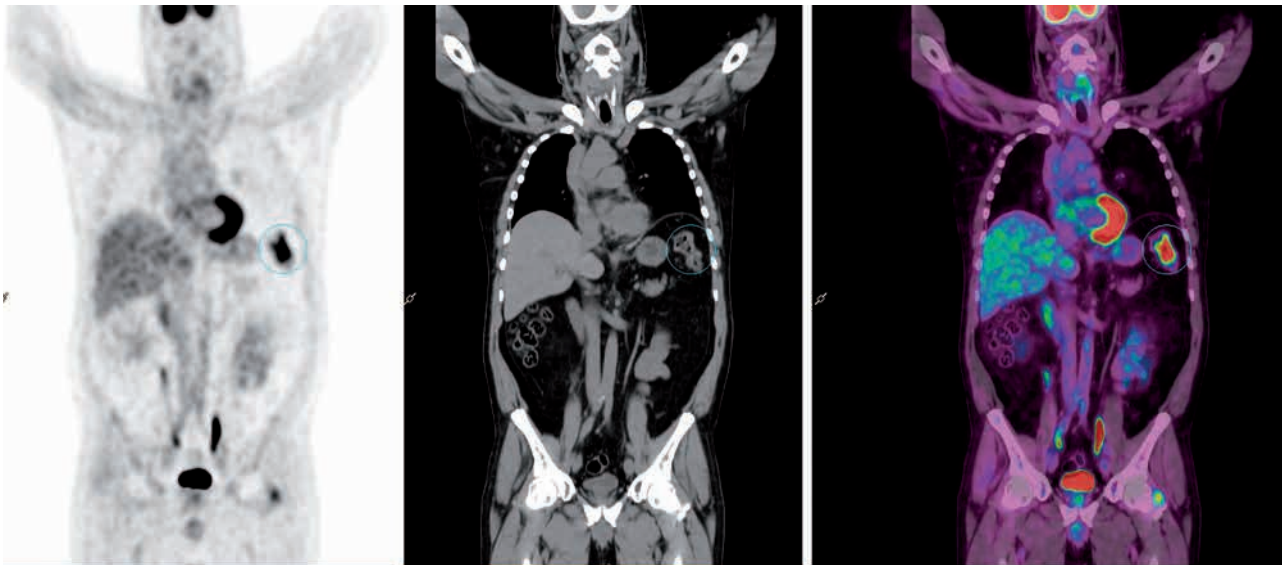

Fig. 1. — UCFU of left colic flexure corresponding to neoplasic endoscopic finding

groups : normal colonoscopy and benign lesions (hyperplasic polyps, adenoma without villous or high grade dysplasia component or < 10 mm in size), advanced adenoma (adenoma with villous histology or high grade dysplasia or ≥ 10 mm in size) and neoplasia to determine a cut-off value for each one. Benign lesions were associated with normal endoscopies considering their lower risk to progress into neoplastic lesion in short term (6-7). Tomodensitometric imaging in PET CT is the colon CT appearance in the region of the focal uptake. Focal colonic wall thickening, intraluminal mass or pericolonic infiltration were considered as abnormal. All parts of the colon starting with the caecum up to the rectum were separately analysed.

PET-CT imaging protocol

PET/CT studies were acquired using either a Discovery LS device (4-slice CT, GE Healthcare, Liège, Belgium) before September 2012 or, from September 2012 onwards, a Gemini TF machine (16-slice CT, Philips, Liège, Belgium). All patients fasted for at least 6 hours and plasma blood glucose levels were measured before administering the tracer. FDG (3.3 MBq/kg body weight) was injected through an indwelling catheter. The uptake time was 60 minutes. When indicated, oral CT contrast agent was administered during the uptake time and considered non relevant in term of correction of artefacts in PET images (8). The acquisition protocol varied slightly during the time of the study. With the Discovery LS, a CT with the following parameters (5 mm collimation, 50 × 50 cm field-of-view, 120 kVp, pitch of 1.5:1, gantry rotation cycle of 0.8 s, and automatic adaptation of the amperage at each tube rotation, optimized with indications provided by the scout view) with or without intravenous contrast agent (120 ml of Omnipaque 350 mg of I/ml, GE Healthcare) was first acquired and followed by the PET emission scan from the skull to the upper thighs (4 minutes per bed position). Data were corrected for decay, scatter, random, attenuation and reconstructed using an iterative algorithm. CT data were used for attenuation correction of PET images. Due to a risk of correction artefacts with overestimation of FDG uptake into colonic foci, the patients who received intravenous CT contrast agent were not included for semi-quantitative analyses (Standardized Uptake Values, SUV). With the Gemini TF, before may 2013, either a low-dose CT (thickness 5mm, increment 5 mm, voltage 120 kV, current 30 mAs/slice) or a diagnostic contrast-enhanced full-dose *CT* (thickness 3 mm, increment 1.5 mm, 120 kV, 150-250 mAs/slice with dose modulation) was first acquired, followed by the PET emission scan (80 seconds per bed position). If a contrast-enhanced CT was used for attenuation correction, a special protocol was adopted, wherein all regions with densities greater than a standard tissue density were considered as having this tissue density, eliminating by this way the risk of overestimation of FDG uptake into colonic foci. After May 2013, a low-dose CT was always first acquired (and used for attenuation correction) and followed by the PET emission scan, with a full-dose contrast-enhanced CT between those two acquisitions if indicated. UCFU was defined as a focal FDG accumulation (hot spot) visually distinct from the surrounding colonic background activity.

Statistical analyses

We performed a Chi square test (χ^2) to analyse nominal data (clinical data and PET CT characteristics) and compare their relationships with endoscopic diagnoses and a Mann Whitney U test to compare ^{18}FDG values between groups (SPSS 17.0). The best cut off nSUV point for each group was determined by using a ROC (receiver operating characteristic) curve. Correlation

Table 1. — **Indications of the PET CT**

Reason	Patients (n)
Initial staging of :	26
Lung cancer/solitary pulmonary nodule	14
Oesophageal cancer	4
Hepatocarcinoma	3
Nasopharyngeal cancer	1
Prostatic cancer	1
Melanoma	1
Gallbladder cancer	1
Breast cancer	1
Follow up of :	11
Lung cancer	1
Lymphoma	2
Bladder cancer	1
Oesophageal cancer	1
Prostatic cancer	1
Pancreatic cancer	1
Breast cancer	1
Gastric cancer	1
Ovarian cancer	1
Renal cancer	1
Non-neoplastic disorders :	6
Aortic anevrysma staging	1
Unknown origin fever	2
Neurologic paraneoplastic syndrom	3

between SUVmax and nSUV was assessed using Spearman Correlation Test. P-value < 0.05 was considered statistically significant.

Results

During the study period, 2904 patients underwent ^{18}FDG PET-CT. Fifty two (1.8%) had an UCFU and were referred for a colonoscopy. Among them, eight refused or were not able to undergo endoscopy and one was explored by virtual colonoscopy. These nine patients were excluded of the study. Of the 43 patients who underwent endoscopy, 32 were men. The median age was 69 years (range 34-86) and 7 had diabetes mellitus. Indications for PET CT are illustrated in table 1 : Initial staging of cancer in 26 patients, cancer follow ups in 11 patients, and non-neoplastic diseases in 6 patients.

After endoscopy and pathological analysis, eight examinations (18.6%) showed no colonic abnormality and thirty five examinations (81.4%) showed endoscopic findings in the expected colonic segment : benign lesions in 7 patients (16.3%), 18 patients with advanced adenoma (41.9%) and 10 patients with neoplasia (23.2%). All neoplasia were enteric adenocarcinoma. The positive predictive value of PET CT for endoscopic findings was 81.4%.

Fifteen UCFU were located in the proximal colon and twenty-eight in the distal colon. Endoscopic analyses showed more false positives results in the proximal colon compared to distal colon with 33.3% versus 10.7% ($p < 0.05$), respectively. Considering the well known colonoscopy miss rate of lesions in the right colon (9), extra-time was taken for endoscopic exploration in case of UCFU in the proximal colon, including retroflexion. UCFU location was not discriminatory for neoplastic diagnosis.

Among the 43 patients of the cohort, 18 had tomodensitometric abnormalities in the same colonic area than UCFU. On endoscopy, 3 had a normal examination, 1 had a benign lesion, 5 had advanced adenoma and 9 had neoplasia (50%). The combination pathological images on CT and focal colonic uptakes were significantly associated with diagnosis of neoplasia. It was not discriminatory for advanced adenoma diagnosis.

Sensitivity and specificity in case of associated pathological images (PET and tomodensitometry) were 90% and 72.7%, respectively, for colonic neoplasia and 27.8% and 48.0%, respectively, for advanced adenoma. The negative predictive value of associated pathological images for colonic neoplasia was 96%.

SUVmax and nSUV values were highly correlated in our series ($R = 0.8656$; $p < 0.00001$). Comparing nSUV between the three groups, normal colonoscopy/benign lesion, advanced adenoma and neoplasia with median values of 2.6 (range 1.2-5.2), 2.6 (range 1.5-4.4) and 4.4 (range 1.7-7.5) respectively, no significant difference was found comparing normal colonoscopy group/benign lesion and advanced adenoma groups. Comparing normal colonoscopy/benign lesion and neoplasia groups, we found a difference at the margin of statistical significance ($p = 0.05$). Comparing advanced adenoma and neoplasia groups, significant statistical difference was showed ($p = 0.023$). No cut-off value could be determined between each group due to the broad overlap of nSUV values among each group. Analyses of gender, age and metabolic status did not show significant differences between the three groups.

All these results are listed in table 2.

Discussion

PET CT has been widely used in general oncology for many years. Providing anatomical and functional data, this exam became the gold standard for staging and follow-up of many neoplastic diseases, allowing the choice of the best treatment for patients (10-11). The benefit of the PET CT has also been demonstrated in colorectal pathology, in the context of patients' follow up for the detection of metastatic lesions and local recurrences (12). In Belgium, colorectal cancer is the second and third most frequent cancer in women and men, respectively, with a total of 8500 new diagnoses in 2011. It represents the second cause of cancer death in men and third in women (Belgium, 2008) (13). In most cases, these cancers develop from adenomatous lesions. The prevalence of these pre- neoplastic lesions in the general population is difficult to define. Studies of large cohorts show rates of 17-45 %. This incidence is higher in men and after the age of 60 (14-16). Considering these incidences, it is not

Table 2. — **Correlations between clinical characteristics, pathological analyses and PET CT results**
(Relationshhips between gender, age, metabolic status, foci location and colonoscopic diagnosis were analysed using χ^2 test. Mann Whitney U was used to compare ^{18}FDG values between groups. Normal colonoscopy and benign lesion groups were analysed together))

	Normal colonoscopy	Benign lesion	Advanced adenoma	Neoplasia
Number of patients (n = 43)	8 (18.6%)	7 (16.3%)		
	15 (34.9%)		18 (41.9%)	10 (23.2%)
Gender				
Male (n = 32)	3 (9.3%)	7 (22.9%)		
	10 (32.2%)		15 (46.9%)	7 (21.9%)
Female (n = 11)	5 (45.4%)	0		
	5 (45.4%)		3 (27.3%)	3 (27.3%)
Age				
> = 60 years (n = 32)	6 (18.7%)	6 (18.7%)		
	12 (37.4%)		13 (40.7%)	7 (21.9%)
< 60 years (n = 11)	2 (18.2%)	1 (9.1%)		
	3 (27.3%)		5 (45.5%)	3 (27.3%)
Diabetes (n = 7)	1 (14%)	2 (29%)		
	3 (43%)		1 (14%)	3 (43%)
FDG foci location				
Proximal colon (n = 15)	5 (33.3%)	4 (26.7%)		
	9 (60%)		3 (20%)	3 (20%)
Distal colon (n = 28)	3 (10.7%)	3 (10.7%)		
	6 (21.4%)		15 (53.6%)	7 (25%)
Associated foci with tomographic abnormalities (n = 18)	3 (16.7%)	1 (5.5%)		
	4 (22.2%)		5 (27.8%)	9 (50%)
Normalized SUV median values	2.7 (1.2-5.2)	2.3 (1.7-4)		
	2.5 (1.2-5.2)		2,4 (1,5-4,4)	4,5 (1,7-7,5)

surprising to detect neoplastic or pre-neoplastic colonic lesions in patients treated for extra-colonic oncologic disease.

Since the publications by Israel *et al*. and Gutman *et al*. in 2005 (17-18), many studies have been conducted to analyze the significance of these hypermetabolic foci (4,19,20,21). The frequency of UCFU was 0.3-3.9% in retrospective studies and 1.34% in the only prospective study from Peng *et al*. (3) in 2011. Positive predictive value (PPV) of PET CT for endoscopic finding was 44-91% in retrospective studies and 44.1% in the prospective study. The PPV of PET CT for the diagnosis of neoplastic lesions was 10-40% in retrospective analyzes and 23.5% in the prospective analysis. The results of our study are similar to the literature and confirm the necessity of endoscopic exploration after UCFU detection given the risk of detection of malignant lesions or advanced adenoma, in 23.2% and 41.9% of the patients, respectively. Moreover, several studies assessed PET CT criteria for predicting the nature of the endoscopic findings. In some series, the analysis of SUVmax values showed significant differences between patients with normal examination, advanced adenoma or neoplasia. However, no cutoff values have been determined between different groups (3,18). Tessonnier *et al*. analyzed the ratio colonic lesion SUVmax/liver mean SUV value (4) and despite of a high correlation between nSUV and SUVmax values, no significant difference was found between their diagnostic groups.

The study of scanner images obtained during the PET CT was also evaluated to improve the specificity of the test. Gutman *et al*. (18) already showed in 2005 that the combination of pathological scannographic images such as pericolonic infiltration or endoluminal mass was suggestive of significant endoscopy findings. The benefit of optimal analysis of scanner images from PET CT to refine diagnoses has also been described by K. Miles *et al*. in 2008 (22). Finally, studies have shown a significantly higher rate of false positives (normal colonoscopy) in the proximal colon compared to the distal colon (3,20). The hypotheses to explain this difference were lymphoid tissue accumulation in the caecum, a greater peristaltic activity or metabolically active mucosa in the proximal colon.

Limitations of this study

PET CT imaging was acquired by two different equipments and the acquisition protocol was not strictly standardized considering variable oral or intra-venous contrast agent administrations. The change of PET CT device during the study could affect the SUV in a random way but the use of colonic lesion maximum standardized uptake value/liver mean SUV ratio limited this bias. The use of contrast agent could induce overestimation of FDG uptake into colonic foci. All measures possible were applied to fix to these potential bias.

Conlcusion

Our study confirms the necessity of endoscopic exploration in case of unexpected colonic focal uptakes in PET CT considering the high rates of neoplasia and advanced adenoma detection associated with the UCFU. Although high nSUV values and scannographic abnormalities combined to focal uptake suggest malignancy, we could not determine strong criteria predicting the presence and the nature of endoscopic findings. For this reason, the only restriction for colonic exploration in case of UCFU should be disease related and post therapeutic deterioration of the general status.

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