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Detection of incidental colorectal pathology on positron emission tomography/computed tomography (PET/CT)

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Running head

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Abstract

Introduction:

Positron emission tomography/computed tomography (PET/CT) is an important modality in cancer imaging. With its increasing availability and use, it is not uncommon to detect incidental focal colorectal ^{18}F -FDG uptake which poses a diagnostic challenge, as they may be associated with malignant or pre-malignant colorectal lesions. The aim of our study is to determine the proportion of these findings which represents true pathology.

Methods and Materials:

Patients with incidental focal colorectal ^{18}F -FDG uptake on PET/CT who subsequently underwent colonoscopy between January 2002 to September 2013 were identified from a prospective database in a tertiary referral centre. PET/CT results were correlated with colonoscopy and pathology results in these patients. Positive predictive values (PPVs) and 95% confidence intervals (CIs) of PET/CT in the detection of incidental colorectal pathology were calculated.

Results:

One hundred and forty-eight patients (92 males and 56 females), with a mean age 73 years (range of 36 to 93 years) were included in the study. A total of 170 foci of colorectal ^{18}F -FDG uptake were detected on PET/CT. Of these, 101 foci corresponded to a malignant or pre-malignant lesion (PPV 59%; 95% CI: 52-67%). On a per-patient analysis, 93 patients had at least one focus of colorectal ^{18}F -FDG uptake which corresponded to a pre-malignant or malignant lesion (PPV 63%; 95% CI: 54-71%).

Conclusion:

Focal colorectal ^{18}F -FDG uptake on PET/CT is associated with a significant proportion of malignant or pre-malignant lesions. Further evaluation with colonoscopy is recommended.

Introduction

For over two decades, positron emission tomography with 18-fluoro-2-deoxyglucose (^{18}F FDG-PET) has been used in the staging and monitoring of various cancers, including non-small cell lung cancers, lymphomas, melanomas, and head and neck cancers (1). Combined with the anatomical data provided by computed tomography (CT), PET/CT has an improved diagnostic accuracy and is now considered an important modality in cancer imaging (2).

With its increasing availability and use in cancer patients, it is not uncommon to detect incidental ^{18}F FDG uptake on PET/CT in sites other than where the primary cancer is known or suspected, posing a diagnostic challenge to clinicians. A common site is the large bowel, where the prevalence of incidental focal colorectal ^{18}F FDG uptake detected by PET or PET/CT is estimated at 3.6% (3). While diffuse and segmental patterns of ^{18}F FDG uptake are attributed to benign or inflammatory causes, focal uptake is associated with a significant risk of neoplasia (4-11). Given that colorectal cancer may be insidious in onset and run a silent course until late, these radiological findings should not be ignored (12). Prompt diagnosis may have a significant impact on patient outcome, particularly in these patients who already has a pre-existing cancer as it may necessitate a management plan that integrates treatment for both cancers within a relatively short period of time.

Previous studies have reported large numbers of patients who had incidental focal colorectal ^{18}F FDG uptake on PET or PET/CT, but few had sufficient numbers who subsequently underwent colonoscopy to investigate the underlying pathology. Therefore, the aim of our study is to determine the proportion of incidental focal colorectal ^{18}F FDG uptake on PET/CT which represents true pathology.

Materials and Methods

Study population

Patients with incidental focal colorectal ^{18}F FDG uptake on PET/CT who subsequently underwent colonoscopy between January 2002 and September 2013 were identified from a prospective database in a tertiary referral centre. Focal colorectal ^{18}F FDG uptake is termed incidental if it is detected in the large bowel on PET/CT in

patients who have a non-colorectal or unknown primary cancer. The institutional review board approved the study and waived the need for individual patient consent for reviewing imaging studies and electronic medical records.

PET/CT protocol

All patients were instructed to fast for at least 6 hours before administration of ^{18}F -FDG (5MBq/kg, up to max. 400MBq). After resting for at least 60 minutes for ^{18}F -FDG uptake to occur, PET/CT scans were performed from the level of skull base to upper thighs using one of the dedicated PET/CT scanners available at our institution (Discovery LS PET/4-slice helical CT, Discovery STE/8-slice helical CT or Discovery 690/64-slice helical CT, General Electric Medical Systems, Milwaukee, WI; Siemens Biograph 64 slice PET/CT, Siemens Healthcare, Erlangen, Germany).

Emission data were processed by iterative reconstruction both with and without attenuation correction using the non-contrast CT scan obtained. All CT, PET and PET/CT images were displayed simultaneously on a Siemens Multimodality Workstation. An experienced nuclear medicine physician generated a clinical report after reviewing these images, previous imaging results and clinical information to reflect routine clinical practice.

Colonoscopy

Colonoscopy was performed by consultant colorectal surgeons who were accredited by Gastroenterological Society of Australia (GESA). All patients received standard bowel preparation on the day before the procedure. Colonoscopy was passed to the caecum as confirmed by the ileocaecal valve. Any abnormalities identified on colonoscopy were recorded, with biopsies taken where appropriate.

Data analysis

In all patients, PET/CT results were correlated with colonoscopy \pm pathology results. Both per-lesion and per-patient analyses were then performed.

On a per-lesion analysis, a PET/CT finding was considered a 'true positive' if a focus of colorectal ^{18}F -FDG uptake on PET/CT corresponded to a structural abnormality identified in the same or adjacent segment on

colonoscopy. A PET/CT finding was considered 'false positive' if a focus of colorectal ^{18}F -FDG uptake on PET/CT did not correspond to a structural abnormality identified in the same or adjacent segment on colonoscopy. On a per-patient analysis, a PET/CT exam was considered 'true positive' if a patient had a positive PET/CT exam and ≥ 1 structural abnormalities identified on colonoscopy. A PET/CT exam was considered 'false positive' if a patient had a positive PET/CT exam but no structural abnormalities identified on colonoscopy.

Statistical Analysis

Positive predictive values (PPVs) of PET/CT in the detection of incidental colorectal pathology were calculated using standard formulas, both on a per-lesion and per-patient level. Results are expressed as percentages where appropriate. A 95% confidence interval (CI) is determined for each parameter.

Results

Patient characteristics

A total of 148 patients with incidental focal colorectal FDG uptake were included in the study. There were 92 males and 56 females with a mean age of 73 years (range of 36 to 93 years). The indications for PET/CT are shown in *Table 1*.

PET/CT results

There were a total of 170 foci of colorectal ^{18}F -FDG uptake detected on PET/CT. One hundred and thirty patients had a single focus of colorectal ^{18}F -FDG uptake, 15 patients had two foci, 2 patients had three foci, and 1 patient had four foci. The distribution of the foci on PET/CT was as follows: ascending colon (n= 31), transverse colon (n= 13), descending colon (n= 21), rectosigmoid colon (n= 102), anorectal region (n= 3).

Colonoscopy results

The mean time interval between the detection of focal colorectal ^{18}F -FDG uptake on PET/CT and subsequent colonoscopy was 52 days (range of 4 to 385 days).

A total of 212 lesions were identified on colonoscopy. The distribution of the colorectal lesions was as follows: ascending colon (n= 44), transverse colon (n= 17), descending colon (n= 16), rectosigmoid colon (n= 134), anorectal region (n= 1). The histology results are shown in *Table 2*.

Per-lesion analysis

Of the 170 foci of colorectal ^{18}F -FDG uptake, 120 corresponded to a structural abnormality identified on colonoscopy (PPV 71%, 95% CI: 63-77%). The distribution of the foci on PET/CT with their corresponding pathology are shown in *Table 3*. Importantly, 101/170 foci corresponded to a pre-malignant or malignant lesion (PPV 59%, 95% CI: 52-67%). These included 20 adenocarcinomas, 20 adenomas with high grade dysplasia, and 61 adenomas with low grade dysplasia.

Three lesions were inflammatory in nature: proctitis (2) and sigmoid diverticulitis (1). Eight lesions were benign: hyperplastic polyps (3), myoglandular polyp (1), fibroepithelial polyp (1), hamartoma (1), polypoid epithelial hyperplasia (1), benign-looking tumour with no biopsy taken (1). Four lesions had normal histology on biopsy. Four lesions were not biopsied on colonoscopy.

The PPVs in the detection of pre-malignant or malignant lesions in the different segments of colon were as follows: 61% (95% CI: 42-78%) in the ascending colon, 31% (95% CI: 10-61%) in the transverse colon, 29% (95% CI: 12-52%) in the descending colon, 70% (95% CI: 60-78%) in the rectosigmoid colon, and 33% (95% CI: 1-87%) in the anorectal region.

Per-patient analysis

Among the 148 patients who underwent colonoscopy, 116 patients had abnormalities identified on colonoscopy (PPV 78%; 95% CI: 71-85%).

One hundred and five patients had at least one focus of colorectal ^{18}F -FDG uptake which corresponded to an abnormality identified on colonoscopy (PPV 71%, 95% CI: 63-78%). Of those, 93 harboured at least one pre-malignant or malignant lesion (PPV 63%, 95% CI: 54-71%), with 12 patients having two or more pathologies.

Discordant findings

On a per-lesion analysis, 50 foci of colorectal ^{18}F -FDG uptake on PET/CT did not correspond to any structural abnormality identified in the same or adjacent segment on colonoscopy and were considered 'false positives'.

On a per-patient analysis, 34 PET/CT exams did not have abnormalities identified on colonoscopy and were considered 'false positives'.

Of the 212 lesions identified on colonoscopy, 92 (43%) did not correspond to any ^{18}F -FDG uptake on PET/CT: adenocarcinomas (2), adenomas (43), benign lesions (18), normal lesions (6), and lesions of unknown histology (23).

Discussion

Our study showed that 120/170 (71%) foci of colorectal ^{18}F -FDG uptake on PET/CT corresponded to a structural abnormality identified on colonoscopy. Of these, 101 (59%) turned out to be pre-malignant or malignant lesions on biopsy. Similar per-patient findings were obtained, with 93/148 patients (63%) having one or more biopsy-proven pre-malignant or malignant lesions. These results are consistent with those of previous studies where the PPV of focal colorectal ^{18}F -FDG uptake on PET/CT in detecting a malignant or pre-malignant colorectal lesion is estimated to be between 50 and 80% (5-7, 9). Therefore, it adds weight to current guidelines that prompt evaluation with colonoscopy is warranted. Early detection of second primary tumour has been shown to improve overall outcome (13), and removal of polyps can result in reduction in incidence and mortality from colorectal cancer (14).

It should be noted that among the 19 foci of colorectal ^{18}F -FDG uptake on PET/CT which were initially classified as non-malignant, 1 was subsequently proven to be adenocarcinoma post-colectomy and 1 was an adenoma with low-grade dysplasia on repeat colonoscopy. The inflammatory lesions were presumably FDG-avid on PET/CT due to the increased metabolism of white cells (15) but it is unclear why benign lesions were FDG-avid as well, although in the case of hyperplastic polyps, it has been suggested that it may be related to their proliferative activity (16). It is also important to consider that some of these structural abnormalities

identified on colonoscopy may have been incidental findings in the context of a 'false positive' PET/CT result, given that there is a margin of error in correlating the exact site between the two.

Few studies have evaluated the likelihood of pathology based on the site of focal ^{18}F -FDG uptake on PET/CT (8, 9). Our study showed that there may be a predilection for the ascending and rectosigmoid colon, although it is unclear why this is the case. A study by Lee et al. has found that focal ^{18}F -FDG uptake in the proximal colon was associated with a high likelihood of pathology (9). However, these findings are in contrast to those reported by Peng et al. where FDG uptake in the ascending colon was an independent negative predictor of finding cancer or polyps (8). Therefore, the site of focal ^{18}F -FDG uptake on PET/CT should not be used as a guide to determine the significance of these findings until further studies are available.

There were a total of 50 foci of colorectal ^{18}F -FDG uptake on PET/CT which did not correspond to an abnormality identified on colonoscopy (FDR 29%, 95% CI: 23-37%). This may be due to several reasons, including physiological uptake by smooth muscle, bowel peristalsis and constipation (17). In addition, inflammation (e.g. inflammatory bowel disease, colitis) had been shown to cause increased colorectal ^{18}F -FDG uptake on PET/CT, although it is usually diffuse or segmental in nature (18, 19). It is also possible that some patients had inflammation which settled prior to colonoscopy. Finally, colonoscopic abnormalities may have been missed due to presence of submucosal lesions, difficult procedure or inadequate bowel preparation.

Conversely, 92 lesions (43%) did not correspond to any ^{18}F -FDG uptake on PET/CT, including 45 pre-malignant and malignant lesions. This is to be expected in the case of benign lesions but is not entirely surprising either in the case of pre-malignant and malignant lesions, given that PET/CT is not a primary screening tool for colorectal cancer due to its poor sensitivity in detecting adenomas (20). A range of factors may be involved, including the spatial resolution of the PET/CT scanner, bowel peristalsis and lesion size. It has been shown that the sensitivity of PET/CT in detecting adenomas improves with increasing size.

Our study included 148 patients with correlation of PET/CT and pathology results in a single institution, making it one of the largest studies to date to establish diagnosis and assess the significance of incidental focal colorectal ^{18}F -FDG uptake on PET/CT. Previous studies have large sample sizes to look at the prevalence of

incidental focal colorectal ^{18}F -FDG uptake on PET/CT, but few had sufficient numbers who subsequently underwent colonoscopy (8, 10, 11). In addition, most patients in our study underwent colonoscopy within the first 2 months of PET/CT findings, hence an accurate histological diagnosis was obtained. Finally, our institution maintained a centralised electronic medical records system since the early 2000s, which allowed us to comprehensively review all patient history, imaging results, colonoscopy reports and pathology results.

There are several limitations to this study. Firstly, our study did not include patients with incidental focal colorectal ^{18}F -FDG uptake on PET/CT who failed to undergo colonoscopy due to various reasons (e.g. patient refusal, palliative intent, multiple co-morbidities), thus affecting the true accuracy of PET/CT. However, it could be argued that this would reflect routine clinical practice. Accordingly, we were unable to determine the specificity and negative predictive values of PET/CT in detecting incidental colorectal pathology. Secondly, some patients may have undergone CT colonography instead, although this number is unlikely to be significant given that it is not the first-line investigation for the detection of colorectal pathology. Thirdly, although colonoscopy remains the gold standard in detecting colorectal pathology, it has a miss rate of 22% for polyps of any size (21). Therefore, misclassification bias may have been introduced.

At present, colonoscopy is still the reference standard to detect true colorectal pathology. Although PET/CT colonography has been proposed to improve accuracy in diagnosing colorectal lesions, it is still in experimental stages and the metabolic information from PET does not appear to increase the accuracy of CT colonography (22). However, it may be valuable in patients who has an obstructing tumour and a complete colonoscopy cannot be performed (23), as well as those who have contraindications or refuse colonoscopy. Further efforts should be made to evaluate the usefulness of PET/CT colonography, as well as develop more sensitive detectors and tumour-specific radiotracers to improve accuracy of PET/CT in detecting pre-malignant or malignant colorectal lesions.

Conclusion

Focal colorectal ^{18}F -FDG uptake on PET/CT is associated with a significant risk of pre-malignant or malignant lesions and may affect subsequent management. Further evaluation with colonoscopy is recommended.

Disclosure statement

The authors declare no potential conflict of interest.

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Tables

Table 1. Types of primary cancer in patient population.

Primary cancer	Number of patients	%
Head & neck cancer	28	18.9
Melanoma	24	16.2
Lymphoma	22	14.9
Lung cancer	19	12.8
Gynaecological cancer	17	11.5
Soft tissue and bone cancer	10	6.8
Upper GI cancer	9	6.1
Cutaneous SCC	6	4.1
Unknown primary	6	4.1
Others	7	4.7
Total	148	100

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Table 2. Distribution and histology results of lesions identified on colonoscopy.

Histology	AC	TC	DC	RS	AJ	Count	%
Adenocarcinoma	3	0	1	18	0	22	10.4
Adenoma						124	58.5
High grade	4	5	0	15	0	24	11.3
Low grade	30	6	9	55	0	100	47.2
Inflammatory	0	0	0	3	0	3	1.4
Benign	4	0	3	18	1	26	12.3
Normal	1	1	1	7	0	10	4.7
Unknown	2	5	2	18	0	27	12.7
Total	44	17	16	134	1	212	100

AC = ascending colon; TC = transverse colon; DC = descending colon; RS = rectosigmoid colon; AJ = anorectal region

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Table 3. Distribution and histology results of focal colorectal ^{18}F -FDG uptake on PET/CT

Histology	AC	TC	DC	RS	AJ	Count	%
Adenocarcinoma	1	1	2	16		20	16.7
Adenoma						81	67.5
High grade	4	1		15		20	16.7
Low grade	14	2	4	40	1	61	50.8
Inflammatory				3		3	2.5
Benign	1		1	4	2	8	6.7
Normal	1	1	2	0		4	3.3
Unknown	1	1		2		4	3.3
Total	22	6	9	80	3	120	100

AC = ascending colon; TC = transverse colon; DC = descending colon; RS = rectosigmoid colon; AJ = anorectal region

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