74499_Auto_Edited.docx

WORD COUNT	3068	TIME SUBMITTED	11-MAR-2022 03:09PM
		PAPER ID	83521827

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 74499

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Assessment of incidental focal colorectal uptake by analysis of fluorine-18 fluorodeoxyglucose positron emission tomography parameters

Haejun Lee, Kyung-Hoon Hwang, Kwang An Kwon

Abstract

BACKGROUND

Colon and rectal cancers are among the top five cancers worldwide in terms of their incidence and mortality rates. As the treatment options for cure include surgery even in specific advanced-stage cases, the early detection of lesions is important for applying active treatment methods. Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is an established imaging study for many types of cancers; however, physiologic uptake in the gastrointestinal tract is a frequent finding and may interfere with lesion identification. Nevertheless, as unexpectedly observed focal colorectal F-18 FDG uptake may harbor malignant lesions, further examination must not be avoided.

AIM

To assess the clinical implications of unexpected focal colorectal F-18 FDG uptake by analyzing FDG PET parameters.

METHODS

A total of 15,143 F-18 FDG PET/CT scans performed at our hospital between January 2016 and September 2021 were retrospectively reviewed to identify incidentally

observed focal colorectal FDG uptake. Finally, 83 regions showing focal colorectal FDG uptake with final histopathological reports from 80 patients (45 men and 35 women with mean ages of 66.9 ± 10.7 years and 63.7 ± 15.3 years, respectively) were eligible for inclusion in the present study. Each focal hypermetabolic colorectal region was classified as malignant, premalignant, or benign according to the histopathological report. PET parameters such as maximum and peak standardized uptake value (SUVmax and SUVpeak), metabolic tumor volume (MTV), mean SUV of the metabolic tumor volume (mSUVmtv), and total lesion glycolysis (TLG) were measured or calculated for the corresponding hypermetabolic regions. Parametric and non-parametric statistical comparisons of these parameters were performed among the three groups. Receiver operating characteristic (ROC) curves were plotted to identify cut-off values.

RESULTS

The detection rate of incidental focal colorectal uptake was 0.53% (80/15,143). Of the 83 regions with unexpected focal colorectal hypermetabolism, 28.9% (24/83) were malignant, 32.5% (27/83) were premalignant, and 38.6% (32/83) were benign. Overall, 61.4% of the regions had malignant or premalignant lesions. SUVmax, SUVpeak, and mSUVmtv differentiated malignant and/or premalignant lesions from benign lesions with statistical significance ($p < 0.05$). mSUVmtv3.5 differentiated malignant from benign lesions, with the largest area under the curve (AUC) of 0.792 and a cut-off of 4.9. SUVmax showed the largest AUC of 0.758 with a cut-off value of 7.5 for distinguishing between premalignant and benign lesions. Overall, SUVmax with a cut-off value of 7.6 (AUC: 0.770, 95% confidence interval (CI): 0.668–0.872; sensitivity, 0.686; specificity, 0.688) was a superior parameter for distinguishing between malignant/premalignant and benign lesions or physiologic uptake. No parameters differentiated malignant from premalignant lesions. Moderate or weak positive correlations were observed between the long diameter of the malignant lesions and PET parameters such as SUVpeak and some mSUVmtv.

CONCLUSION

Approximately two-thirds (61.4%) of incidental focal hypermetabolic colorectal regions were malignant/premalignant lesions, for which SUVmax was an independent diagnostic parameter. Unexpected suspicious focal colorectal FDG uptake should not be avoided and consideration for further evaluation is strongly recommended not to miss the two-thirds.

INTRODUCTION

According to the Global Cancer Observatory, the worldwide estimated age-standardized incidence and mortality rates of colorectal cancer for both sexes and all ages in 2020 were 19.5 (4^{th}) and 9.0 (3^{rd}), respectively [1, 2], placing the disease among the top five leading cancers.

Like many other cancers, the treatment options for colorectal cancer include local or systemic treatments; however, surgery may be useful for cure in selected colorectal cancer patients with a limited number of small metastatic lesions (stage IV). Even in cases with large or many metastases, surgery may still be considered if the lesions shrink after neoadjuvant chemotherapy. In this way, more active treatment method could be a choice for colorectal cancer than for other cancers, and an improvement in overall survival may be expected through the early detection of lesions.

Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is an established imaging modality used for the diagnosis, treatment response, and follow-up of many types of cancers. Physiologic gastrointestinal FDG uptake is well known, particularly in the colon and rectum, and diffusely or segmentally increased intestinal F-18 FDG uptake (hypermetabolism) is often observed as normal physiologic uptake [3-7]. This may obscure and interfere with the detection of true lesions. Despite this pitfall, FDG PET/CT may help detect lesions that are malignant or harbor a risk of malignancy, which appear as incidentally visualized focal FDG uptake in the intestines [8-10]. This retrospective study aimed to

identify the implications of unexpectedly observed focal colorectal hypermetabolism on F-18 FDG PET/CT performed for purposes other than colorectal concerns by comparing PET parameters among histopathologically confirmed malignant, premalignant, and benign focal hypermetabolism.

MATERIALS AND METHODS

Patients

To identify incidental focal colorectal hypermetabolic lesions, we retrospectively reviewed 15,143 F-18 FDG PET/CT scans performed at our hospital between January 2016 and September 2021. After excluding the scans of patients with current or prior colorectal malignancies or without histopathological reports (gold standard) of the corresponding hypermetabolic regions, 80 patients (45 men and 35 women with mean age 66.9 ± 10.7 years and 63.7 ± 15.3 years, respectively) with 83 regions of focal colorectal FDG uptake and their final histopathological reports were eligible for this study.

F-18 FDG PET/CT imaging

To acquire images of F-18 FDG PET/CT with optimal image quality, all patients fasted for 4–6 h and their blood glucose levels were checked. The examination was rescheduled in cases with blood glucose levels ≥11 mmol/L (200 mg/dL). Scanning was performed 60 min after the intravenous injection of 185 MBq F-18 FDG. Images from the skull base to the upper thigh were acquired using a dedicated PET/CT scanner (Biograph mCT 128, Siemens Healthcare GmbH, Erlangen, Germany). Emission scans were acquired using the step-and-shoot method for 3 min per bed. CT scans were performed using the continuous spiral mode with CareDose4D and CARE kV activated to reduce patient radiation exposure and acquire individually optimized images. No contrast material was used for the CT scans. Both PET and CT images were reconstructed using the iterative reconstruction method and the final fused PET/CT

images were generated on a dedicated image acquisition workstation provided with the PET/CT device.

Analyses of the F-18 FDG PET/CT images and histopathological reports

Two nuclear medicine physicians, one with over 20 years of experience, reviewed the PET/CT images. When a region of focal abnormal FDG uptake by the colon and/or rectum was identified, the patient's medical records were reviewed to obtain a histopathological report of the corresponding location, if available. The hypermetabolic regions revealed by the final histopathological reports, as well as on PET/CT, were categorized as malignant, premalignant, or benign. For these, semi-quantitative standardized uptake value (SUV) was measured as maximum (SUVmax) and peak (SUVpeak). In addition, the metabolic tumor volume (MTV) was measured, which provided information on both the volume and the mean SUV of the volume. When measuring the MTV, different volumes of interest (VOIs) can be applied using different settings of the SUV threshold. This study used several SUV thresholds, ranging from 2 to 5 in increments of 0.5, to obtain multiple MTVs and the mean SUV of each MTV with specific SUV threshold # (MTV# and mSUVmtv#, respectively). Finally, the total lesion glycolysis (TLG) # was calculated by multiplying the volume from the MTV# by the mSUVmtv#. All imaging analyses were performed using a dedicated PET/CT workstation equipped with SyngoMMWP (Siemens Healthcare GmbH, Erlangen, Germany). The measured and calculated PET parameters were compared among the malignant, premalignant, malignant/premalignant, and benign lesions, and receiver operating characteristic (ROC) curve analysis was performed to identify the cut-off values. Additionally, the correlations between PET parameters and tumor size (long diameter) were evaluated.

Statistics

Both parametric (Student's t-test) and non-parametric (such as Mann–Whitney U test) methods were used to compare SUVmax, SUVpeak, MTV#, mSUVmtv#, and TLG#

among the categorized lesions, and to correlate the parameters and size of malignant tumors. ROC curves were plotted and the areas under the curves (AUCs) were calculated to determine the optimal cut-off values to distinguish malignant and/or premalignant from benign lesions. Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Ethics

This retrospective study was approved by the Institutional Review Board of our hospital (IRB no. GAIRB2020-297), and the requirement for informed consent was waived. The study was conducted in accordance with the 1964 Declaration of Helsinki and later amendments.

RESULTS

The demographic and clinical characteristics of the 80 patients classified by histopathological reports are shown in Table 1. The detection rate of incidental focal colorectal uptake was 0.53% (80/15,143). Among the 83 eligible regions of focal colorectal hypermetabolism, 24 were diagnosed as malignant lesions, 27 were premalignant, and the remaining 32 were benign. In terms of malignant lesions, they were 28.9% (24/83) of the focal hypermetabolic regions, consisting of 23 cases of adenocarcinoma and one case of neuroendocrine tumor. Premalignant lesions included tubular (77.8%, 21/27), villous (7.4%, 2/27), and tubulovillous (14.8%, 4/27) adenomas. The benign group comprised patients with inflammation or physiologic uptake with no remarkable mucosal abnormalities on colonoscopy. Overall, 61.4% (51/83) of the regions had malignant or premalignant lesions.

Comparisons of PET parameters and cut-offs

The five PET parameters considered in this study (SUVmax, SUVpeak, MTV#, mSUVmtv#, and TLG#) were compared among malignant, premalignant,

malignant/premalignant, and benign lesions. Table 2 shows representative examples of these comparisons. SUVmax, SUVpeak, and all mSUVmtv# differed significantly between malignant and benign, premalignant and benign, and malignant/premalignant and benign lesions, while no parameters showed significant differences between malignant and premalignant lesions. Figure 1 shows an example of incidental focal ascending colon uptake, which was diagnosed as adenocarcinoma in a patient with a known intrahepatic cholangiocarcinoma. Figure 2 shows a patient with incidental focal rectal uptake (A and B) diagnosed as villous adenoma and a case of proximal ascending colon uptake (C and D) with no remarkable mucosal lesion revealed on colonoscopy.

ROC curves were plotted, and cut-offs were determined for malignant, premalignant, and malignant/premalignant lesions. The AUC, cut-off, 95% confidence interval (CI), sensitivity, and specificity of each parameter are shown in Table 3. An AUC of 0.792 was calculated for mSUVmtv3.5 and a cut-off of 4.9 (CI, 0.671–0.914; sensitivity, 0.667; specificity, 0.656) differentiated malignant from benign lesions. An AUC of 0.758 was calculated for SUVmax, with a cut-off of 7.5 (CI, 0.634–0.882; sensitivity, 0.704; specificity, 0.688) distinguishing between premalignant and benign lesions. Likewise, an AUC 0.770 for SUVmax and a cut-off of 7.6 (CI, 0.668–0.872; sensitivity, 0.686; specificity, 0.688) differentiated malignant/premalignant from benign lesions. Figure 3 shows the ROC curves for SUVmax and mSUVmtv3.5 for malignant/premalignant lesions.

Correlation between PET parameters and tumor size

The long diameters of the malignant lesions were determined histopathologically after surgery, with an average of 32.8 ± 23.3 mm. Using the parametric method (Pearson correlation), SUVpeak was moderately positively correlated with tumor size, with a correlation coefficient (r) of 0.511. The mSUVmtv# (# = 2, 2.5, 3, 3.5, and 4) also showed moderate positive correlations. Using non-parametric methods, mSUVmtv# (# = 2, 2.5, and 3, Spearman's rho, r = 0.457 – 0.522) and mSUVmtv2 (Kendall's tau, r = 0.349) showed moderate or weak positive correlations.

DISCUSSION

Non-malignant intestinal FDG uptake occurs under several conditions, including inflammation [11-14] and the use of medications such as metformin [15-18]. This uptake may be diffuse, intense, and cover a large portion of the intestine. In such cases, it is not easy to identify obscured or hidden lesions. However, the presence of focal FDG uptake in the intestine suggests the need for further evaluation for malignant lesions.

The SUV is a representative semi-quantitative parameter for PET/CT. A high SUV could be more suggestive of malignancy than a benign lesion or physiologic uptake and might be associated with advanced disease or poor prognosis/overall survival in various cancers [19-25]. The present study assessed the clinical significance of incidental focal colorectal uptake by analyzing FDG PET parameters.

The detection rate of unexpected focal colorectal uptake in this study was 0.53% (80/15,143), consistent with the range of 0.5% - 3.3% reported by other studies [26-31]. A meta-analysis reported that a pooled prevalence of focal colorectal incidentalomas of 3.6% [32]. Of the 83 eligible lesions in this study, 51 (61.4%) were malignant (28.9%, 24/83) or premalignant (32.5%, 27/83). The remaining 32 (38.6%) were benign lesions or physiologic uptake. The proportion of premalignant lesions was slightly larger than that of malignant lesions, consistent with other studies [33, 34]. The rate (61.4%, 51/83) of malignant/premalignant lesions was also comparable to that in other studies [32] and colonoscopy was recommended for further evaluation of focal hypermetabolism [35].

SUVmax, SUVpeak, and all mSUVmtv# differentiated malignant and premalignant lesions from benign lesions and physiologic uptake. According to the AUC curves, mSUVmtv3.5, with an AUC of 0.792 and a cut-off of 4.9, showed the best performance in distinguishing between malignant and benign lesions. Other mSUVmtv#s were also useful in identifying malignant lesions; however, as the # of mSUVmtv# approached extreme values (2 or 5, for instance), the boundaries of the visible MTV segmentations tended to be smaller or larger than the actual visible tumor boundaries. Thus, they might not have accurately reflected the MTV and, therefore, mSUVmtv. Practically,

SUVmax, which is the most used among these parameters in the clinical setting, showed a similar AUC (0.784) and higher sensitivity and specificity, suggesting that it could replace mSUVmtv3.5. If the SUVmax is used as a determining factor, 7.6 would be the optimal cut-off. As shown in Table 3, the cut-offs for malignant lesions are similar to those for premalignant lesions, in which the malignant lesions are hardly distinguishable from premalignant lesions using the cut-offs derived in this study. None of the parameters involved in this study could distinguish them by statistical comparisons ($p > 0.05$). Other studies have shown inconsistent results [33, 34], and some studies reported that even the SUVs of malignant lesions were not distinguishable from those of non-pathologic FDG uptake [27, 28]. MTV and TLG were not useful for differentiating malignant and premalignant lesions from benign lesions. Both parameters showed better results than the SUVmax in other studies [36]. By combining malignant and premalignant lesions into one group, SUVmax (AUC 0.770, cut-off 7.6) was superior in distinguishing this group from benign focal colorectal hypermetabolism.

Among the 24 malignant lesions, regardless of the tumor type, 18 (75.0%) were located in the distal colon/rectum, and of the 27 premalignant lesions, 16 (59.3%) were in the proximal colon. Different genetic mechanisms play roles in cancer development in the distal or proximal colon [37-39] and different frequent locations were suggested in various studies [40-42]. Moreover, the distribution of colorectal cancer appears to vary by country, region, race, sex, and age [43-46]. Although the results of these studies are not always consistent, patient characteristics should be taken into account while interpreting PET/CT images. None of the parameters in this study differed significantly between the proximal and distal colon/rectum for malignant, premalignant, and malignant/premalignant lesions.

The long diameter of the malignant lesions was moderately to weakly positively correlated with several PET parameters (SUVpeak and a few mSUVmtv#); however, its clinical significance was unclear. In addition, SUVmax, which significantly

distinguished malignant/premalignant from benign lesions, did not show any statistically significant correlations (p = 0.055).

This study was conducted retrospectively at a single institution. The incidental focal colorectal hypermetabolism discovered with the naked eye may have missed non/Less-FDG-avid pathologic lesions; therefore, there was a selection bias. For the same reason, the incidence of malignancy may be higher than that in the general population. As this study did not include focal hypermetabolism without histopathological reports, the results of this study might not be the same if there were pathological reports for all focal hypermetabolism. Despite these limitations, given the high frequency of malignant/premalignant lesions and statistically significant PET parameters, incidental focal colorectal FDG uptake has clinical significance; thus, the consideration of further assessment such as colonoscopy should not be avoided.

CONCLUSION

Approximately two-thirds (61.4%) of the incidentally observed focal hypermetabolic colorectal regions were malignant or premalignant. Although the role of FDG PET parameters in colorectal cancer remains controversial, the results of this study showed that SUVmax was an independent diagnostic parameter for malignant/premalignant lesions. Therefore, any unexpected suspicious focal colorectal FDG uptake requires attention, and further evaluation is strongly recommended not to miss the two-thirds.

ARTICLE HIGHLIGHTS

Research background

Intestinal fluorine-18 fluorodeoxyglucose (F-18 FDG) uptake is often observed on positron emission tomography/computed tomography (PET/CT). However, unexpectedly observed focal colorectal hypermetabolism might harbor a risk of malignancy; thus, distinguishing malignant from benign tumors is critical.

Research motivation

As with other cancers, early lesion detection is critical in colorectal cancer. As surgery may still be the treatment of choice for cure in selected patients with advanced colorectal cancer, the importance of early detection of lesions is even greater.

Research objectives

To assess the implications of focal colorectal F-18 FDG uptake by analyzing FDG PET parameters.

Research methods

This study included 83 focal colorectal hypermetabolic regions from 80 patients. Each region was classified as malignant, premalignant, or benign according to the histopathological report. PET parameters such as maximum and peak standardized uptake values (SUVmax and SUVpeak), metabolic tumor volume (MTV), mean SUV of metabolic tumor volume (mSUVmtv), and total lesion glycolysis (TLG) of F-18 FDG PET/CT were measured and calculated for the regions, and compared among malignant, premalignant, malignant/premalignant, and benign hypermetabolic regions. Receiver operating characteristic (ROC) curves were plotted to determine the cut-off values for these parameters.

Research results

Of the 83 incidentally observed focal colorectal hypermetabolic regions on F-18 FDG PET-CT, 61.4% (51/83) were malignant/premalignant lesions confirmed by histopathological reports of the corresponding locations. SUVmax, SUVpeak, and mSUVmtv can be used to differentiate malignant and premalignant lesions from benign lesions. SUVmax, with an AUC of 0.770 and a cut-off of 7.6 (confidence interval: 0.668–0.872, sensitivity 0.686, specificity 0.688) was the superior FDG PET parameter in distinguishing malignant and premalignant from benign lesions.

Research conclusions

Approximately two-thirds (61.4%) of the incidental focal hypermetabolic colorectal regions were malignant/premalignant. SUVmax was demonstrated as an independent diagnostic parameter for the lesions. Unexpected suspicious focal colorectal FDG uptake should not be avoided, and further evaluation is required.

Research perspectives

Controversies and debates regarding the parameters assessed in this study remain ongoing. Further studies with larger numbers of subjects are warranted.

74499_Auto_Edited.docx

ORIGINALITY REPORT

3%
SIMILARITY INDEX

PRIMARY SOURCES

1	f6publishing.blob.core.windows.net Internet	18 words — 1%
2	www.ijnm.in Internet	17 words — 1%
3	iranjradiol.com Internet	14 words — < 1%
4	www.dovepress.com Internet	14 words — < 1%
5	worldwidescience.org Internet	13 words — < 1%
6	www.ajronline.org Internet	13 words — < 1%
7	www.scielo.br Internet	12 words — < 1%
8	www.wjgnet.com Internet	12 words — < 1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON
EXCLUDE MATCHES OFF