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Correlation of Ki-67 proliferation index and 18-fluorodeoxyglucose uptake in colorectal incidental lesions detected by positron emission tomography-computed tomography

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Background/aim: To investigate whether focal high maximum standardized uptake value (SUVmax) determined by 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) imaging is correlated with proliferation index in the colorectal region.

Materials and methods: SUVmax values of 31 colorectal neoplasms that were incidentally detected during PET-CT examination were compared to dysplasia degree, histopathologic diagnosis, and immunohistochemical expression of the Ki-67 proliferation marker.

Results: Statistically significant correlations were found between SUVmax and Ki-67 proliferation index, dysplasia degree, and histopathologic diagnosis. Median SUVmax value was found to be significantly higher in high-risk lesions than low-risk lesions.

Conclusion: The Ki-67 proliferation index is an indicator of SUVmax in colorectal tract. SUVmax values can predict malignancy and prognosis in this region. Colonoscopy and biopsy should always be performed whenever a focal high FDG uptake is determined incidentally in a patient.

Key words: Colorectal neoplasm, positron emission tomography, Ki-67 antigen

1. Introduction

18-Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) is a relatively new technique used for tumor imaging, staging, and monitoring. Proliferating activity, glucose transporters, and hexokinase levels can all lead to FDG accumulation in metabolically active cells (1). In routine practice FDG PET-CT is better used for staging and monitoring colorectal carcinoma and rarely for the primary diagnosis, but incidental colorectal lesions can be detected on whole-body images that are applied for many other purposes (2). In this study we evaluated FDG PET-CT of patients with resected colorectal lesions and investigated whether metabolic activity was correlated with proliferating activity, dysplasia degree, and diagnosis.

2. Materials and methods

2.1. Patient selection

This retrospective study was approved by the ethics committee of Keçiören Training and Research Hospital (number: B.10.4.ISM.4.06.68.49, date: 28.11.2012). The medical records of 2521 patients who underwent whole-body imaging by FDG PET-CT for staging of lung carcinoma between January 2010 and December 2012 in the Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital nuclear medicine department were retrospectively reviewed. Ninety-eight subjects followed by colonoscopy within 90 days after FDG PET-CT in the referral gastroenterology department of the Keçiören Training and Research Hospital were identified. Colonoscopic evaluation was generally performed for patients with lung cancer who could benefit from further treatment or in whom a metastatic process to the lungs was excluded. Patients with prior chemo-radiotherapy, inflammatory bowel disease, incomplete colonoscopy because of insufficient bowel cleaning, and negative colonoscopy were excluded. Positive colonoscopic findings corresponding to focal FDG uptake sites were documented. Finally, histopathologic diagnosis of 31 lesions from 22 patients that correlated to incidental focal FDG uptake sites was achieved.

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2.2. FDG PET-CT imaging protocol

All the patients underwent whole-body FDG PET using a Siemens Biograph 6 HI-REZ integrated PET-CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). The patients fasted for at least 6 h and serum glucose levels were confirmed to be less than 180 mg/dL prior to injection. PET-CT images were obtained 60 min after the administration of 370–450 MBq (10–15 mCi) of FDG. Oral contrast material was used in all patients for better visualization of the intestinal lumens. CT scans that were used for attenuation correction were performed just before PET acquisitions. PET data were acquired from the top of the skull to the upper thigh with the arms in an up position. The maximum standardized uptake value for body weight (SUVmax) was calculated by drawing a region of interest (ROI) on the attenuation-corrected transaxial FDG PET images.

2.3. Histopathologic evaluation and immunohistochemical staining

All the slides were reevaluated independently by two pathologists according to the 2010 World Health Organization criteria and if there was a disagreement for the diagnosis or dysplasia degree the decision was made by consensus (3). Age, sex, location, and diameter of the lesions were also recorded. A representative area suitable for the aim of the study was selected for immunohistochemical analysis.

For immunohistochemical staining 4-μm cut sections were prepared on adhesive slides from paraffin blocks. After antigen retrieval by citrate, Ki-67 (Novocastra, NCL-MM1, 1/100) primary antibody was applied by indirect peroxidase method. Positive (nonneoplastic tonsil tissue) and negative controls were used during the process.

The expression of Ki-67 was quantified by two pathologists who were blinded to SUVmax values. Obvious dark-brown staining of cell nuclei was considered positive. One thousand cells were counted in random fields of the mucosal epithelium under 400× magnification. The index of expression was calculated by the following formula:

Ki-67 = [(number of immunostained nuclei × 100) / number of nuclei counted)].

2.4. Statistical analysis

Data are demonstrated as mean ± SD for normally distributed continuous variables, median (minimum–maximum) for skew distributed continuous variables, and frequencies for categorical variables. The Pearson chi-square test was performed for the comparison of categorical variables. Continuous variables were compared by Kruskal–Wallis test. To determine the factors correlated with SUVmax, the Spearman test and Mann–Whitney U test were performed. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of SUVmax when deciding the malignant potential of colon polyps. When a significant cut-off value was observed the sensitivity, specificity, and positive and negative predictive values were calculated. While evaluating the area under the curve (AUC) a 5% type 1 error was used to accept a statistically significant value of the test variables. SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the analysis and $P < 0.05$ was considered significant.

3. Results

The baseline characteristics of the patients are shown in Table 1. Nine of the 22 patients had two separate (at least 5 cm apart) foci of increased FDG PET-CT uptake and corresponding colonoscopic lesions. Histopathologic diagnoses of the lesions were hyperplastic polyp, adenomatous polyp (15 tubular adenoma, 2 tubulovillous adenoma, 2 villous adenoma, 1 traditional serrated adenoma/polyp), and adenocarcinoma not otherwise specified. Sixteen lesions showed low-grade dysplasia and 4 high-grade dysplasia among adenomatous polyps.

Median SUVmax and Ki-67 were 6.96 (range: 2.03–34.37) and 17.2 (range: 4.20–82.6), respectively (Figure 1). Statistical analysis showed significant correlation between SUVmax and Ki-67 ($P < 0.001$). The mean Ki-67 of the adenocarcinoma group was significantly higher than both adenomatous and hyperplastic polyps ($P < 0.001$ and $P < 0.001$). No correlation was found between Ki-67 of adenomatous and hyperplastic polyps ($P = 0.681$). Dysplasia degree and Ki-67 also did not show any correlation ($P = 0.067$).

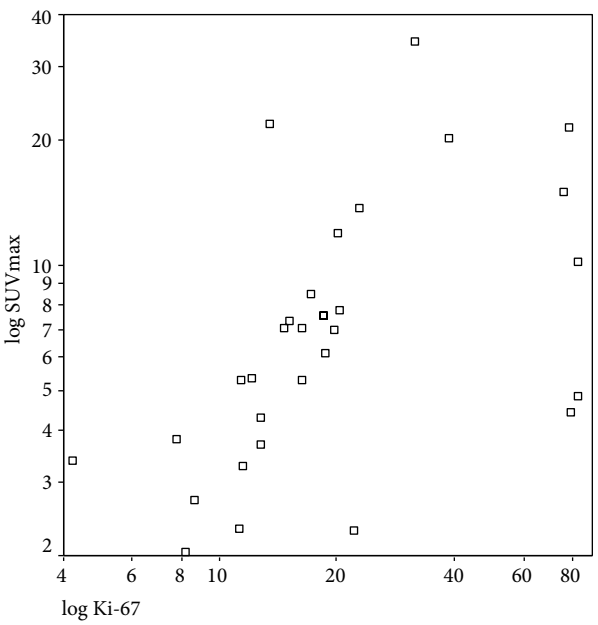

Figure 1. Scattered plot of Ki-67 and SUVmax values of study cohort (n = 31).

Table 1. Baseline characteristics of the patients.

Characteristics	Value
Age, years, median ± SD (range)	68.5 ± 10.6 (46–86)
Male/female, n	18/4
Diameter, median ± SD (range)	1.56 ± 1.3 cm (0.4–6 cm)
Location, n (%)	
Descending-sigmoid colon	19 (61.2%)
Rectum-anal canal	7 (22.6%)
Transverse colon	3 (9.7%)
Ascending colon	2 (6.5%)
Diagnosis, n (%)	
Hyperplastic polyp	4 (12.9%)
Adenomatous polyp	20 (64.5%)
Adenocarcinoma NOS	7 (22.6%)
Dysplasia, n (%)	
No	4 (12.9%)
Low grade	16 (51.6%)
High grade	11 (35.5%)

SUVmax was found to be correlated with diagnosis. The median SUVmax value of adenocarcinoma was significantly higher than the median SUVmax value of both adenomatous and hyperplastic polyps ($P < 0.001$ and $P < 0.001$). The median SUVmax value of adenomatous polyps was significantly higher than hyperplastic polyps' ($P = 0.010$). Dysplasia degree was also correlated with median SUVmax value. Both low- and high-grade dysplasia showed higher median SUVmax values compared to the lacking dysplasia ($P < 0.001$ and $P = 0.020$, respectively). Furthermore, the median SUVmax value of high-grade dysplasia was significantly higher than that of the low-grade dysplasia group ($P < 0.001$) (Table 2).

Finally, median SUVmax value was found to be significantly higher in high-risk lesions (adenocarcinoma and high-grade dysplasia group) than low-risk lesions (hyperplastic polyp and low-grade dysplasia group) (SUVmax value 11.8 (range: 2.7–34.3) and 5.3 (range: 2.0–13.7), respectively, $P = 0.009$). The ROC analysis showed that SUVmax values are diagnostic in predicting the malignant potential of colon polyps. The threshold SUVmax value was found to be 7.05. At this value sensitivity was 80% and specificity was 71.4%. Positive and negative predictive values were 53.3% and 87.5%, respectively (Figure 2).

4. Discussion

The factors that influence the level of metabolic activity in the colon remain a major confounding problem. Glucose transporters and hexokinase levels have shown to lead to FDG accumulation in the colon (4). Even though proliferative activity of cells throughout the gastrointestinal tract is constant, it increases in inflammatory and

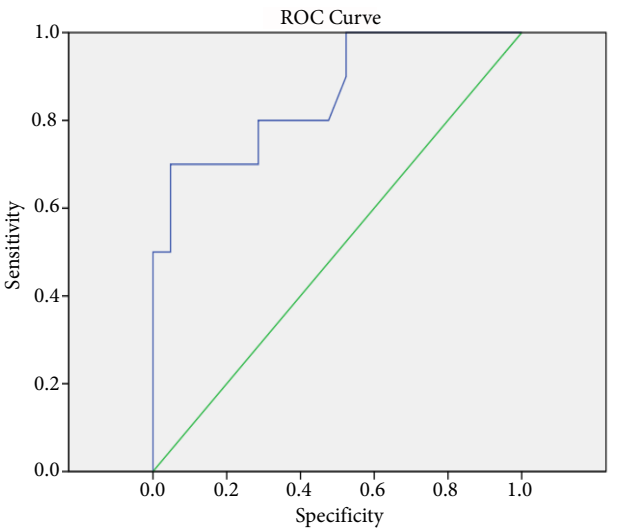

Figure 2. ROC curve showing the sensitivity and specificity of SUVmax value (AUC: 0.86, 95% confidence interval: 0.71–1.00, $P = 0.001$).

Table 2. SUVmax and Ki-67 values according to diagnosis and dysplasia degree.

Characteristics	Median SUVmax (range)	Mean Ki-67 ± SD
Hyperplastic polyp (n = 4) Adenomatous polyp (n = 20) Adenocarcinoma (n = 7)	3.7 (2.0–7.6) 5.3 (2.3–21.9) 14.9 (4.8–34.4)	14.6 ± 5.8 17.9 ± 15.1 58.0 ± 28.2
Dysplasia negative (n = 4) Low-grade dysplasia (n = 16) High-grade dysplasia(n = 11)	3.0 (2.0–7.4) 5.7 (2.3–13.8) 11.9 (2.7–34.4)	14.6 ± 5.8 18.7 ± 16.8 42.2 ± 31.0

neoplastic circumstances. It is reasonable in proliferating cells to have increased glucose metabolism and high FDG accumulation. Ki-67 protein expression appears during the G1 phase of the cell cycle and diminishes after mitosis, and thus it is a good marker of proliferation, demonstrating the large spectrum of the cell cycle (5). Correlation between proliferation markers and FDG uptake have been shown in several other tumors such as breast cancer and non-Hodgkin lymphoma (6,7). To the best of our knowledge there is no literature investigating the correlation between SUVmax and Ki-67 in colorectal neoplasms. In this study we have demonstrated a significant correlation between Ki-67 and SUVmax. Thus, we have proved that proliferation degree is one of the components that leads to FDG accumulation in cells of colorectal neoplasms (Figure 3).

There has been great interest in identifying an association between proliferating markers, such as Ki-67, and tumor behavior in human malignancy. Higher proliferation indexes have shown to be related to worse outcome in colorectal carcinoma in several studies (8,9). We have demonstrated significant correlation between SUVmax and Ki-67 in colorectal neoplasms. The Ki-67 index of carcinomas was also significantly higher than that of adenomatous and hyperplastic polyps. Thus, SUVmax may predict the prognosis of a tumor in the colorectal region. In fact, studies about the prognostic value of SUVmax in colorectal carcinoma are limited. Riedl et al. found that GLUT1, Ki-67, and p53 were all correlated with SUVmax and higher SUVmax levels were correlated with poorer prognosis in metastatic colorectal carcinoma (10). However, Lee et al. did not find a relationship with high FDG uptake and tumor recurrence or disease-free survival in resectable colorectal cancer, but they recognized not providing immunohistochemical information on glucose metabolism (11). Although there are only 7 carcinoma cases in our series, we think that investigation in larger series and long follow-up with correlation between stage, Ki-67, and SUVmax may contribute to better information about this hypothesis.

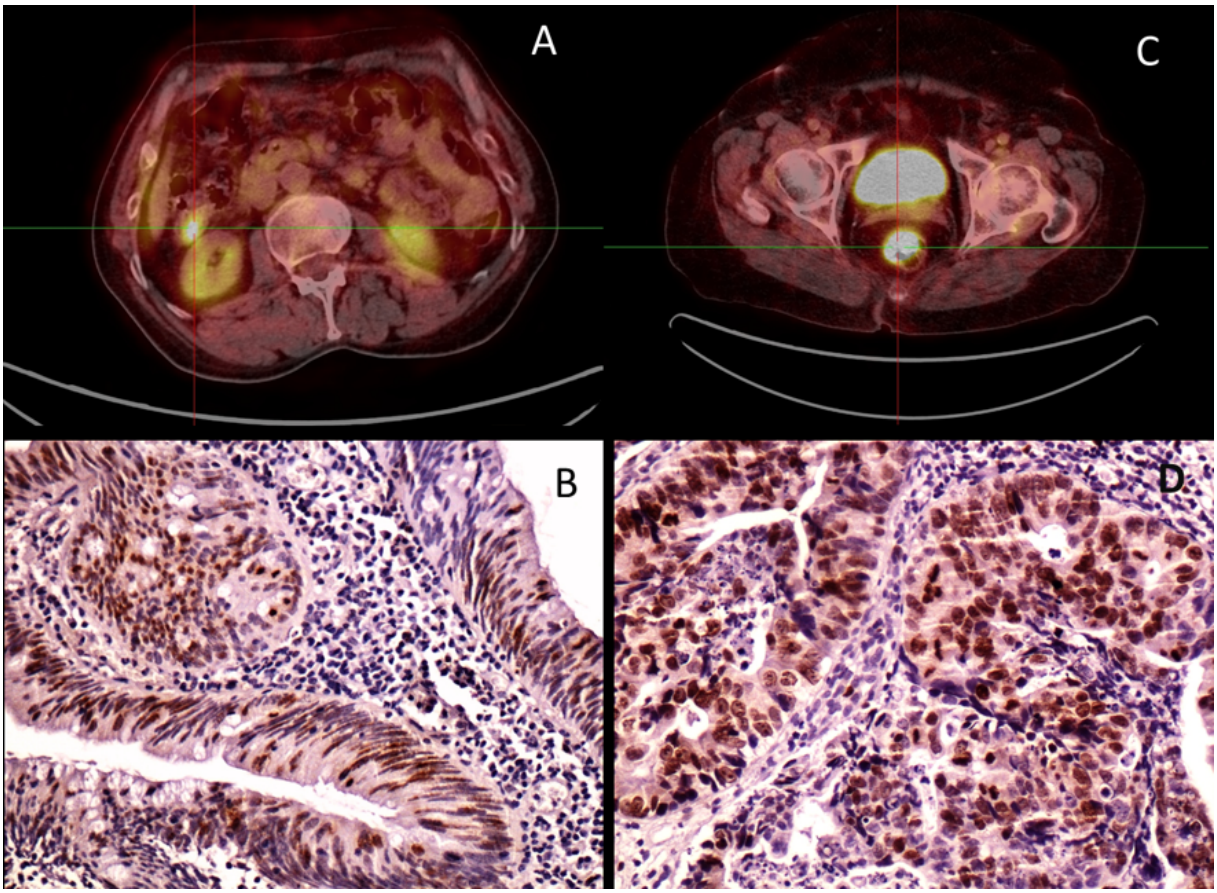

Figure 3. FDG PET-CT image showing focal FDG uptake in ascending colon at the level of the hepatic flexura (SUVmax: 8.1) (A). The histopathologic examination of the same case was consistent with tubular adenoma with a Ki-67 index of 21% (immunoperoxidase, 200×) (B). FDG PET-CT image showing focal FDG uptake in the rectum (SUVmax: 21.47) (C). The histopathologic diagnosis was consistent with adenocarcinoma with a Ki-67 index of 80% (immunoperoxidase 200×) (D)

It is thought that most of the sporadic colorectal carcinomas evolve from adenomatous polyps and severe dysplasia indicates increased risk of carcinoma (12). Early detection of adenomas at a high risk of progression is an effective approach to decrease colon cancer deaths. Current screening methods lack specificity as they detect many adenomas that will never progress to colorectal carcinoma. In this study, although our sample number was low, we have shown that high FDG uptake is significantly correlated with high-risk lesions in the colorectal tract. In this setting, FDG PET-CT may be useful in early identification of colorectal premalignant lesions. In a previous study adenomas with high-grade dysplasia were reported to be more likely to be detected during PET-CT scan, but in that study SUVmax was not compared to dysplasia degree (13). Chen et al. found SUVmax correlation with adenoma and carcinoma, but unlike this study they did not use concomitant CT (14). Gutman et al. succeeded to find a correlation between FDG uptake intensity and severity of the lesion detected by FDG PET-CT. The threshold mean SUVmax values for carcinoma (15 ± 11.6) and low-grade dysplasia (8.84 ± 4.9) in that study are close to this one's (15). In a prospective study SUVmax was found to be a risk factor for predicting carcinoma and polyps (16). A recent study also determined that SUVmax can display malignancy together with metabolic volume (17). Nonetheless, there are several studies that were not able to reach a significant correlation between SUVmax and malignancy but recommended colonoscopy when intense FDG accumulation is determined (18–21).

Even so, our results can indicate that high SUVmax values determined by FDG PET-CT can predict malignancy and prognosis in the colorectal region. Colonoscopy and biopsy should always be performed whenever a focal high FDG uptake is determined incidentally in a patient. We think that the results of our study along with similar further investigations can open a new debate for the use of intriguing PET-CT colonography, at least in selected cases.

References

1. Esteves FP, Schuster DM, Halkar KR. Gastrointestinal tract malignancies and positron emission tomography: an overview. Semin Nucl Med 2006; 36: 169-181.
2. O'Connor OJ, McDermott S, Slattery J, Sahani D, Blake MA. The use of PET-CT in the assesment of patients with colorectal carcinoma. Int J Surg Oncol 2011; 2011: 846512.
3. Odze RD, Riddel RH, Bosman FT. Premalignant lesions of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumors of the Digestive System. 4th ed. Lyon, France: IARC; 2010. pp. 10-12.
4. Hong R, Lim SC. 18-F-fluoro-2-deoxyglucose uptake on PET CT and glucose transporter 1 expression in colorectal adenocarcinoma. World J Gastroenterol 2012; 18: 168-174.
5. Brown DC, Gatter GC. Ki 67 protein: the immaculate deception? Histopathology 2002; 40: 2-11.
6. Tchou J, Sonnad SS, Bergey MR, Basu S, Tomaszewski J, Alavi A, Schnall M. Degree of tumor FDG uptake correlates with proliferation index in triple negative breast cancer. Mol Imag Biol 2010; 12: 657-662.
7. Shou Y, Lu S, Chen T, Ma D, Tong L. Correlation of fluorodeoxyglucose uptake and tumor proliferating antigen Ki-67 in lymphomas. J Can Res Ther 2012; 8: 96-102.
8. Lumachi F, Orlando F, Marino F, Chiara GB, Basso SM. Expression of p53 and Ki-67 as prognostic factors for survival of men with colorectal cancer. Anticancer Res 2012; 32: 3965-3967.
9. He Z, Shi C, Wen H, Li F, Wang B, Wang J. The potential of carcinoembryonic antigen, p53, Ki-67 and glutathione S transferase-π as clinico-histopathological markers for colorectal cancer. J Biomed Res 2010; 24: 51-57.
10. Riedl CC, Akhurst T, Larson S, Stanziale SF, Tuorto S, Bhargava A, Hricak H, Klimstra D, Fong Y. 18-F-FDG PET scanning correlates with tissue markers of poor prognosis and predicts mortality for patients after liver resection for colorectal metastases. J Nucl Med 2007; 48: 771-775.
11. Lee JE, Kim SW, Kim JS, Choi KY, Kang WK, Oh ST, Yoo IR, Kim SH. Prognostic value of 18-fluorodeoxyglucose positron emission tomography-computed tomography in resectable colorectal cancer. World J Gastroenterol 2012; 18: 5072-5077.
12. Konishi K, Morson BC. Pathology of colorectal adenomas: a colonoscopic survey. J Clin Pathol 1982; 35: 830-841.
13. Van Kouwen MC, Nagengast FM, Jansen JB, Oyen WJ, Drenth JP. 2-(18F)-Fluoro-2-deoxy-D-glucose positron emission tomography detects clinical relevant adenomas of the colon: a prospective study. J Clin Oncol 2005; 23: 3713-3717.
14. Chen YK, Kao CH, Liao AC, Shen YY, Su CT. Colorectal cancer screening in asymptomatic adults: the role of FDG PET scan. Anticancer Res 2003; 23: 4357-4361.
15. Gutman F, Alberini JL, Wartski M, Vilian D, Le Stanc E, Sarandi F, Corone C, Tainturier C, Pecking AP. Incidental colonic focal lesions detected by FDG PET/CT. Am J Roentgenol 2005; 185: 495-500.
16. Peng J, He Y, Xu J, Sheng J, Cai S, Zhang Z. Detection of incidental colorectal tumors with 18F-labelled 2-fluoro-2-deoxyglucose positron emission tomography /computed tomography scans: results of a prospective study. Colorectal Dis 2011; 13: 374-378.
17. Oh JR, Min JJ, Song HC, Chong A, Kim GE, Choi C, Seo JH, Bom HS. A stepwise approach using metabolic volume and SUVmax to differentiate malignancy and dysplasia from benign colonic uptakes on 18F-FDG PET/CT. Clin Nuc Med 2012; 37: 134-140.

18. Weston BR, Iyer RB, Qiao W, Lee JH, Bresalier RS, Ross WA. Ability of integrated positron emission and computed tomography to detect significant colonic pathology. Cancer 2010; 116: 1454-1461.

19. Israel O, Yefremov N, Bar-Shalom R, Kagana O, Frenkel A, Keidar Z, Fischer D. PET/CT detection of unexpected gastrointestinal foci of 18F-FDG uptake: incidence, localisation patterns and clinical significance. J Nucl Med 2005; 46: 758-762.

20. Kei PL, Vikram R, Yeung HWD, Stroehlein JR, Macapinlac HA. İncidental finding of focal FDG uptake in bowel during PET/CT: CT features and correlation with histopathologic results. Am J Roentgenol 2010; 194: 401-406.

21. Treglia G, Calcagni ML, Rufini V, Leccisotti L, Meduri GM, Spitilli MG, Dambra DP, De Gaetano AM, Giordano A. Clinical significance of incidental focal colorectal ^{18}F-fluorodeoxyglucose uptake: our experience and a review of the literature. Colorectal Dis 2012; 14: 174-180.