SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 12: 4209-4213, 2016

Evaluation of recurrent disease in the re-staging of colorectal cancer by ^{18}F-FDG PET/CT: Use of CEA and CA 19-9 in patient selection

AGOSTINO CHIARAVALLOTI[1], ALESSANDRO FIORENTINI[1], ERIKA PALOMBO[1], DAVIDE RININO[1], ANNAMARIA LACANFORA[1], ROBERTA DANIELI[1], CARMEN DI RUSSO[1], DANIELE DI BIAGIO[1], ETTORE SQUILLACI[1] and ORAZIO SCHILLACI[1,2]

[1]Department of Biomedicine and Prevention, Nuclear Medicine Unit, University Tor Vergata, I-00133 Rome; [2]Institute for Treatment and Research Neuromed, Pozzilli I-86077, Italy

Received November 17, 2015; Accepted June 2, 2016

DOI: 10.3892/ol.2016.5143

Abstract. The aim of the present retrospective study was to evaluate the sensitivity and specificity of fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in assessing the recurrence of colorectal cancer (CRC) with regard to carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). ^{18}F-FDG PET/CT was performed in 100 patients for the re-staging of CRC. Therapy was discontinued prior to the examination. The mean (± standard deviation) CEA value (measured ~30 days prior to PET/CT examination) was 23.71 (±107) ng/ml, whereas the CA 19-9 value was 72 (±190.3) U/ml. Differences in CEA and CA 19-9 values in patients with scans that were positive or negative for recurrence were analyzed by means of a receiver operating characteristic (ROC) curve. ROC curves were used for the calculation of the sensitivity and specificity of ^{18}F-FDG PET/CT for the CEA and CA 19-9 levels. The results of the ^{18}F-FDG PET/CT were found to be associated with the CEA level (P=0.001), but not with the CA 19-9 level (P=0.43). PET/CT was positive for recurrence in 60 patients (60.0%), whose mean CEA and CA 19-9 values were 33.07±136.7 ng/ml and 75.24±192.3 U/ml, respectively. PET/CT was negative for recurrence in 40 patients (40.0%), whose mean CEA and CA 19-9 values were 10.15±30 ng/ml and 67.76±190 U/ml, respectively. On the basis of ROC curve analysis, the best compromise between sensitivity and specificity was achieved for CEA levels of 3.5 ng/ml [sensitivity, 80%; 95% confidence interval (CI), 67-89%; and specificity, 60%; 95% CI, 45-78%]. The study concluded that the detection of recurrence by ^{18}F-FDG PET/CT in patients treated for CRC is associated with CEA, but not CA 19-9 serum levels. Moreover, ^{18}F-FDG PET/CT should be recommended in patients with suspected CRC recurrence even when they present with CEA levels below the normal cut-off.

Correspondence to: Dr Agostino Chiaravalloti, Department of Biomedicine and Prevention, Nuclear Medicine Unit, University Tor Vergata, Viale Oxford 81, I-00133 Rome, Italy
E-mail: agostino.chiaravalloti@gmail.com

Key words: carcinoembryonic antigen, carbohydrate antigen 19-9, positron emission tomography, recurrence, colorectal cancer

Introduction

Colorectal cancer (CRC) survivors are at high risk of cancer recurrence, with recurrent disease being detected in 30-50% of patients undergoing curative resection (1). The primary goal of post-treatment surveillance is to detect recurrences at an early stage when they are potentially curable. It has been demonstrated that although the majority of cases of relapsed CRC are inoperable at the time of diagnosis, one-third of patients with isolated locoregional or distant metastases survive 5 years (2).

Carcinoembryonic antigen (CEA) is a glycoprotein oncofetal antigen that is expressed by a number of epithelial tumors and whose serum levels could also increase in non-malignant conditions such as inflammatory bowel diseases (3). In total, 70% CRC patients will exhibit an elevated CEA level at the time of diagnosis, meaning that it may be a useful marker for curing and monitoring the disease post-surgery (1). Nevertheless, a recent meta-analysis of 20 studies, which included 4,285 patients, revealed controversies regarding the utility of the technique in the detection of recurrent disease (4). An overall sensitivity of 64% and a specificity of 90% was found, which is poor for the use of a biomarker on its own. It was concluded that the optimal balance of sensitivity and specificity occurred at 2.2 ng/ml (4).

Carbohydrate antigen 19-9 (CA 19-9) assays measure a tumor-related mucin (5). The poor performance of this biomarker compared with CEA has been reported, with serum CA 19-9 being greater than normal in only 20-40% of metastatic CRC cases (6). In the post-operative follow-up, additional CA 19-9 measurements do not increase the likelihood of detecting recurrence and monitoring the levels of this sole biomarker during chemotherapy (CHT) is not sufficient (7).

The major limitation of morphological imaging in the assessment of recurrence across all common types of cancer is

the use of size and/or the disappearance of normal features in tissues. Therefore, in common clinical routine, fluorodeoxyglucose (2-deoxy-2-(^{18}F)fluoro-D-glucose; ^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has a major role in the assessment of recurrent CRC (8-12). PET/CT has the ability to detect cancer via the evaluation of tissue metabolism, which is pathologically increased prior to the appearance of morphological changes.

The present study aimed to investigate the potential role of the CEA and CA 19-9 biomarkers in the selection of subjects for imaging, in those individuals with a previous history of CRC, by analyzing ^{18}F-FDG PET/CT results in a population with normal or abnormal serum CEA and CA 19-9 levels (normal range, 0-5 ng/ml and 0-37 U/ml, respectively).

Patients and methods

Patients. A total of 100 consecutive patients (mean age ± standard deviation, 67.7±8 years; range, 35-82 years) undergoing a PET/CT examination for the follow-up of CRC at the Policlinico Tor Vergata (Rome, Italy) between January 2014 and December 2015 were retrospectively evaluated. Of these 100 subjects, 25 were smokers. All patients had suspected recurrence based on elevated CEA or CA 19-9 levels, clinical symptoms and/or other imaging modalities. Patients with a clinical history that was positive for other tumors were excluded from the study. Patients with comorbidities (i.e., Parkinson's disease and cardiovascular disease) were included in the study. All patients underwent whole-body ^{18}F-FDG PET/CT following treatment. A general overview of the population examined is shown in Table I. Of the 100 patients examined, the primitive lesion was located in the colon in 58 subjects and in the sigmoid colon in 17 subjects, while 25 had a lesion detectable in the rectum.

The initial treatment consisted of surgery, CHT and radiotherapy (RT). At the time of the examination all the patients had been subjected to surgery, 3 to RT and 47 to CHT. In particular, 13 patients were subjected to all three treatments (surgery, RT and CHT); 37 to two treatments (surgery and CHT) and 50 to surgery alone. Therapy was discontinued according to standard guidelines, with all the patients having a maximum of 6 months wash out from the various treatments prior to the PET/CT scan (13). The mean time between the measurement of CEA and CA 19-9 and the PET/CT scan was 30 (±12) days.

The level of serum CEA was above the normal range in 61.0% of the patients (61/100), while the level of CA 19-9 was increased in 48 subjects (48.0%). No evidence of paraneoplastic syndrome was found in any of the 100 patients at the time of presentation.

Informed consent was obtained from all patients, in accordance with the Declaration of Helsinki of 1975, as revised in 2008 (14).

PET/CT scanning. The PET/CT system Discovery ST16 (GE Medical Systems, Knoxville, TN, USA) was used to assess ^{18}F-FDG distribution in all patients by three-dimensional (3D) mode standard technique. Reconstruction was performed using the ordered subsets expectation maximization 3D reconstruction method, with 30 subsets and 2 iterations. The system combines a high-speed ultra 16-detector row (912 detectors per row) CT unit and a PET scanner with 10,080 bismuth germanate crystals in 24 rings. The axial full-width at a half-maximum 1-cm radius is 5.2 mm in 3D mode and the axial field of view is 157 mm. All patients fasted for a minimum of 5 h prior to the intravenous (i.v.) injection of ^{18}F-FDG; the level of serum glucose was ≤107 mg/dl in all patients. All patients received 2.5 MBq/kg ±10% (210-410 MBq) of i.v. ^{18}F-FDG and were hydrated with 500 ml of 0.9% i.v. saline sodium chloride. A dedicated room was used for the injection of ^{18}F-FDG for each patient. The lights were turned off and the patients were required to remain resting with their eyes closed prior to the PET/CT scan. A whole-body PET/CT scan was performed 60 min after ^{18}F-FDG injection. A low-amperage whole-body CT scan for attenuation correction (40 mA and 120 kV) was performed prior to image acquisition using PET according to standard guidelines.

Evaluation of PET/CT images. Two nuclear medicine physicians reviewed the PET/CT images at the applicable dedicated PET/CT workstation (Advantage 4.4 and Xeleris 2; GE Healthcare, Fairfield, Connecticut, USA), allowing visualization of PET and CT images separately or in fusion mode in the axial, coronal and sagittal planes. According to our previously reported study in this field (15), pathological uptake was considered when a focal tracer uptake area greater than the background was detected visually. The patients were thereby classified as positive or negative for recurrence. Maximum standardized uptake values were also measured and considered, however, no absolute cut-off value was used for the diagnosis. If a difference in opinion was recorded when assessing the results, the patients were re-examined and a consensus was reached.

Truth standard. A true-positive PET/CT result was defined by the following criteria: Histopathological findings obtained at a subsequent biopsy or a reduced biomarker level following salvage therapy with respect to local recurrence (LR); histopathological findings obtained at subsequent surgical lymphadenectomy or biopsy with respect to lymph node (LN) metastases; histopathological findings that were confirmed by biopsy or subsequent confirmation with dedicated CT or magnetic resonance (MR) imaging with regard to skeletal metastases; and a follow-up time of >6 months (using MR imaging, CT or PET/CT) revealing that the suspected lesions had increased in size. Alternatively, resolution of the lesions or a reduction in the size of the suspected lesions associated with salvage therapy were considered.

Statistical analysis. The mean and standard deviation for CEA and CA 19-9 were calculated (Table I). Associations between the serum levels of CEA and CA 19-9 were evaluated by Spearman's rank correlation (since data were not normally distributed as detectable by means of the D'Agostino and Pearson omnibus normality test).

Differences in CA and CA 19-9 serum values among patients with either negative or positive scans (Table I) were studied by means of a receiver operating characteristics (ROC) curve. A ROC curve was used in order to establish the optimal threshold for CEA and CA 19-9. Since no significant

Table I. General overview of the population examined in the study.

Factor	Whole population (n=100)	Recurrence-positive on PET/CT (n=60)	Recurrence-negative on PET/CT (n=40)	P-value (positive vs. negative)
Age, years	66.75±8.12	69.23±6.33	66.33±5.54	>0.05
CEA, ng/ml	23.78±107.63	33.07±136.74	10.15±30	0.001; AUC=0.70
CA 19-9, U/ml	72.07±190.31	67.76±190.41	75.24±192.33	0.44; AUC=0.55

Data are presented as the mean ± standard deviation. CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; PET/CT, positron emission tomograohy/computed tomography; AUC, are under the curve.

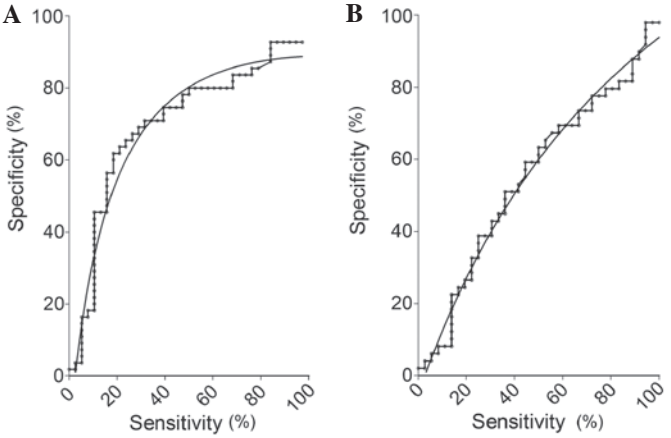

Figure 1. Receiver operating characteristic curve analyses of (A) carcinoembryonic antigen and (B) carbohydrate antigen 19-9 values comparing patients with positron emission tomography/computed tomography scans that were positive or negative for recurrence.

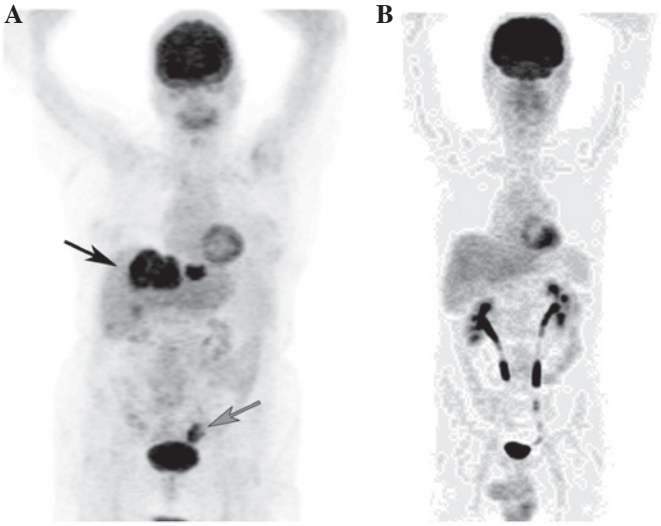

Figure 2. (A) Representative MIP image of a 67-year-old female subject with a previous history of CRC (T3N1M0) treated with surgery and chemotherapy. Pathological fluorodeoxyglucose uptake is detectable in the liver (black arrow) and the iliac lymph nodes (grey arrow). CEA and CA 19-9 levels were 29.38 ng/ml and 7.68 U/ml, respectively. (B) Representative MIP image of a 57-year-old male subject with a previous history of CRC (T2N0M0) treated with surgery, where no pathological findings are detectable. Serum CEA and CA 19-9 levels were 2.8 ng/ml and 35.9 U/ml, respectively. CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; MIP, maximum intensity projection; CRC, colorectal cancer.

difference in CA 19-9 were detected when comparing patients with positive vs. negative PET/CT results, no thresholds for this biomarker were selected. Differences in CEA and CA 19-9 serum levels between smokers and non-smokers were evaluated by Mann-Whitney U test.

In agreement with the values reported in Table I and the ROC curve results, patients were classified into groups depending on a CEA value of ≤3.5 or >3.5 ng/ml.

Fisher's exact test was used in order to investigate the differences in the detection rate (DR) of PET/CT among groups. P≤0.05 was used to indicate a statistically significant difference.

Results

Overall, 59 out of the 100 patients examined showed normal serum CEA levels (<5 ng/ml), while 33 showed abnormal CA 19-9 levels (>37 U/ml). No significant differences were found when comparing CEA and CA 19-9 serum levels between smokers and non-smokers, with serum levels in these subjects being equal to 28.87 (±92.83) ng/ml for CEA and to 82.17 (±188.2) U/ml for CA 19-9 (P>0.05). As shown in Table I, PET/CT was positive for recurrence in 60/100 patients (60.0%) and negative for recurrence in 40/100 patients (40.0%). Patients with a positive scan exhibited higher CEA levels compared with those with negative scans (P<0.05). A CEA value of ≤3.5 ng/ml was associated with a positive scan in 15/43 subjects (34.9%), while 45/57 subjects (78.9%) with a CEA cut-off value of >3.5 ng/ml were positive for recurrence on PET/CT [sensitivity, 80%; 95% confidence interval (CI), 67%-89%; and specificity, 60%; 95% CI, 45-78%). ROC curve analyses for CEA and CA 19-9 are provided in Fig. 1. The DRs were significantly different (P=0.027).

No statistically significant differences were found in the comparison between the CA19.9 levels of patients with positive or negative scans (P>0.05). However, a significant association was found between the serum levels of CEA and CA 19-9 (r=0.316; P=0.006).

At the PET/CT examination, 13 out of the 100 subjects examined were positive for LR only, 7 were positive for LR and LN, 2 presented with LR and liver lesions, 2 with LR and liver and peritoneal lesions, and 2 with LR and lung lesions. Furthermore, 2 patients were positive for LR, LN and adrenal lesions, 4 presented with lesions in the LNs only and 7 with lesions in the LNs and lungs. Lung lesions only were detectable in 5 subjects, liver lesions only were detectable

in 11 subjects, and lung and liver lesions were detectable in 9 subjects. Representative PET images of recurrence-positive and recurrence-negative cases are shown in Fig. 2.

With the exception of 2 subjects that experienced liver recurrence that was not detectable upon ^{18}F-FDG PET/CT (false-negative), all the findings of PET/CT images were confirmed by clinical, imaging and follow-up data.

Discussion

The main finding of the present study in that the DR of PET/CT increases when a cut-off level of 3.5 ng/ml is used for the CEA level. The DR in fact was equal to 79% when a cut-off value of ≥3.5 ng/ml was used for patient selection, which was significantly higher compared with the DR of PET/CT in the whole population examined (60.0%) and in the subjects with CEA serum levels of <3.5 ng/ml (35.0%). On the other hand, no significant differences in CA 19-9 serum levels were detected in the subjects with either a positive or a negative PET/CT scan, suggesting that this biomarker represents a poor parameter for patient selection in the present study.

^{18}F-FDG PET/CT has been proven to be a meaningful diagnostic modality in the management of various cancers, with accuracy in the detection of recurrence and treatment response evaluation in patients with CRC and other types of tumors, such as s ovarian cancer, and Hodgkin and non-Hodgkin lymphomas (15-17). It has been shown that PET has higher sensitivity as compared with CT in the detection of abdominal and extra-abdominal metastatic sites (17). However, PET alone has the limitation of poor localization and thereby increases the number of false-positive results that lead to a lower specificity (18). In a recent meta-analysis that included 11 studies with a total of 510 patients, it was estimated that the sensitivity and specificity of ^{18}F-FDG PET/CT in the detection of tumor recurrence in CRC patients with elevated CEA were 90.3% (95% CI, 67.0-89.6%) and 80.0% (95% CI, 67-89.6%), respectively (19).

To the best of our knowledge, few studies have been performed in order to investigate the performance of ^{18}F-FDG PET/CT in the detection of recurrent CRC in patients with normal CEA and CA 19-9 serum levels. One of the most cited papers aimed at the comparison of PET/CT performance in patients with normal and elevated CEA levels was performed on a pool of 235 patients (11). CRC recurrence was detected in 64.4% of patients with CEA levels <5 ng/ml (sensitivity and specificity of 100 and 84%, respectively) and 88% of patients with levels >5 ng/ml (sensitivity and specificity of 97.1 and 95.7%, respectively) (11).

In past years, several studies have been performed in order to define the ideal parameters in patient selection aimed to decrease the number of patients undergoing ^{18}F-FDG PET/CT (20-25). The main reason for this concern is cost-effectiveness, with this nuclear medicine imaging modality being an expensive examination. Together with the cited study by Sanli *et al* (11), the results of the present study suggested that satisfactory sensitivity and specificities for detecting CRC recurrences can be obtained in patients with a previous history of CRC even at normal CEA levels, ruling out the selection of a patient based on abnormal levels of this biomarker.

The sub-optimal levels of sensitivity and specificity obtained in the present study may be explained by the poor performance of PET/CT due to the tumor response to CHT, which is typically associated with reduced glucose consumption that causes the lesions less detectable on PET (26). While, on one hand, this imaging modality has shown a high sensitivity in the detection of tumor response to therapy in various diseases (18), the absence of pathological metabolism does not mean a complete response to therapy, 85% of lesions that exhibit the disappearance of pathological glucose consumption after CHT showing detectable cancer cells (27). It is possible that the conjunction of PET with contrast-enhanced CT could assist in identifying physiological ^{18}F-FDG in normal tissues and could conversely identify the pathological ^{18}F-FDG uptake in tissues with no pathological abnormalities, increasing the sensitivity and specificity.

As a last aspect, in addition to the absolute CEA and CA 19-9 levels, the pattern of rise of these biomarkers over time appears as a relevant index in patient selection (12). A recent study concluded that patients with a single large increase in CEA may be referred directly for PET, whereas a minor increase led to referral only when the increasing trend had been confirmed in further assays (12). The use of serum biomarkers kinetics indexes such as 'velocity' and 'doubling time' has proven to be a significant advance in the selection of patients undergoing PET/CT in the restaging of other oncological diseases, such as prostate cancer (28). Additional studies are required in order to investigate the performance of ^{18}F-FDG PET/CT with regard to CEA and CA 19-9 kinetic indexes.

In conclusion, the present study indicated that ^{18}F-FDG PET/CT is able to detect recurrent CRC even in patients with normal CEA levels. This imaging modality should be recommended in patients with the suspected recurrence of CRC regardless of the levels of serum biomarkers.

Acknowledgements

The present study was presented as abstract no. P678 at the Annual Congress of the European Association of Nuclear Medicine October 10-14, 2015, Hamburg, Germany. This study was supported by the PICASo project (grant no. 689209).

References

1. van de Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L, Beets-Tan RG, van den Broek CB, Brown G, Van Cutsem E, *et al*: EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum. Eur J Cancer 50: 1.e1-1.e34, 2014.
2. Bowne WB, Lee B, Wong WD, Ben-Porat L, Shia J, Cohen AM, Enker WE, Guillem JG, Paty PB and Weiser MR: Operative salvage for locoregional recurrent colon cancer after curative resection: An analysis of 100 cases. Dis Colon Rectum 48: 897-909, 2005.
3. Chen CH, Hsieh MC, Lai CC, Yeh CY, Chen JS, Hsieh PS, Chiang JM, Tsai WS, Tang R, Changchien CR and Wang JY: Lead time of carcinoembryonic antigen elevation in the postoperative follow-up of colorectal cancer did not affect the survival rate after recurrence. Int J Colorectal Dis 25: 567-571, 2010.
4. Tan E, Gouvas N, Nicholls RJ, Ziprin P, Xynos E and Tekkis PP: Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. Surg Oncol 18: 15-24, 2009.
5. Magnani JL, Steplewski Z, Koprowski H and Ginsburg V: Identification of the gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. Cancer Res 43: 5489-5492, 1983.

6. Filella X, Molina R, Piqué JM, Garcia-Valdecasas JC, Grau JJ, Novell F, Astudillo E, de Lacy A, Daniels M and Ballesta AM: Use of CA 19-9 in the early detection of recurrences in colorectal cancer: Comparison with CEA. Tumour Biol 15: 1-6, 1994.
7. Bast RC Jr, Ravdin P, Hayes DF, Bates S, Fritsche H Jr, Jessup JM, Kemeny N, Locker GY, Mennel RG and Somerfield MR; American Society of Clinical Oncology Tumor Markers Expert Panel: 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 19: 1865-1878, 2001.
8. Panagiotidis E, Datseris IE, Rondogianni P, Vlontzou E, Skilakaki M, Exarhos D and Bamias A: Does CEA and CA 19-9 combined increase the likelihood of 18F-FDG in detecting recurrence in colorectal patients with negative CeCT? Nucl Med Commun 35: 598-605, 2014.
9. Ozkan E, Soydal C, Araz M and Aras G: Serum carcinoembryonic antigen measurement, abdominal contrast-enhanced computed tomography, and fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of colorectal cancer recurrence: A correlative study. Nucl Med Commun 33: 990-994, 2012.
10. Ozkan E, Soydal C, Araz M, Kir KM and Ibis E: The role of 18F-FDG PET/CT in detecting colorectal cancer recurrence in patients with elevated CEA levels. Nucl Med Commun 33: 395-402, 2012.
11. Sanli Y, Kuyumcu S, Ozkan ZG, Kilic L, Balik E, Turkmen C, Has D, Isik G, Asoglu O, Kapran Y and Adalet I: The utility of FDG-PET/CT as an effective tool for detecting recurrent colorectal cancer regardless of serum CEA levels. Ann Nucl Med 26: 551-558, 2012.
12. Gade M, Kubik M, Fisker RV, Thorlacius-Ussing O and Petersen LJ: Diagnostic value of (18)F-FDG PET/CT as first choice in the detection of recurrent colorectal cancer due to rising CEA. Cancer Imaging 15: 11, 2015.
13. Boellaard R, Delgado-Bolton R, Oyen WG, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, *et al*: FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. Eur J Nucl Med Mol Imaging 42: 328-354, 2015.
14. Puri KS, Suresh KR, Gogtay NJ and Thatte UM: Declaration of Helsinki, 2008: Implications for stakeholders in research. J Postgrad Med 55: 131-134, 2009.
15. Chiaravalloti A, Danieli R, Caracciolo CR, Travascio L, Cantonetti M, Gallamini A, Guazzaroni M, Orlacchio A, Simonetti G and Schillaci O: Initial staging of Hodgkin's disease: Role of contrast-enhanced 18F FDG PET/CT. Medicine (Baltimore) 93: e50, 2014.
16. Ogunbiyi OA, Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Birnbaum EH, Fleshman JW, Read TE, Philpott GW and Kodner IJ: Detection of recurrent and metastatic colorectal cancer: Comparison of positron emission tomography and computed tomography. Ann Surg Oncol 4: 613-620, 1997.
17. Caobelli F, Alongi P, Evangelista L, Picchio M, Saladini G, Rensi M, Geatti O, Castello A, Laghai I and Popescu CE: Predictive value of F-FDG PET/CT in restaging patients affected by ovarian carcinoma: A multicentre study. Eur J Nucl Med Mol Imaging 43: 404-413, 2016.
18. Chiaravalloti A, Rubello D, Chondrogiannis S, Giammarile F, Colletti PM and Schillaci O: Low-dose CT and contrast-medium CT in hybrid PET/CT systems for oncologic patients. Nucl Med Commun 36: 867-870, 2015.
19. Lu YY, Chen JH, Chien CR, Chen WT, Tsai SC, Lin WY and Kao CH: Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: A systematic review and meta-analysis. Int J Colorectal Dis 28: 1039-1047, 2013.
20. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, *et al*: Recommendations on the use of F-18-FDG PET in oncology. J Nucl Med 49: 480-508, 2008.
21. Delgado-Bolton RC, Fernández-Pérez C, González-Maté A and Carreras JL: Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. J Nucl Med 44: 1301-1314, 2003.
22. Delgado-Bolton RC, Carreras JL and Pérez-Castejón MJ: A systematic review of the efficacy of F-18-FDG PET in unknown primary tumors. Curr Med Imaging Rev 2: 215-225, 2006.
23. Boellaard R, O'Doherty MJ, Weber WA, *et al*: FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: Version 1.0. Eur J Nucl Med Mol Imaging 37: 181-200, 2010.
24. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, *et al*: Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. J Nucl Med 47: 885-895, 2006.
25. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, *et al*; European Association of Nuclear Medicine (EANM): FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. Eur J Nuclear Med Mol Imaging 42: 328-354, 2015.
26. de Geus-Oei LF, van Laarhoven HW, Visser EP, Hermsen R, van Hoorn BA, Kamm YJ, Krabbe PF, Corstens FH, Punt CJ and Oyen WJ: Chemotherapy response evaluation with FDG-PET inpatients with colorectal cancer. Ann Oncol 19: 348-352, 2008.
27. Tan MC, Linehan DC, Hawkins WG, Siegel BA and Strasberg SM: Chemotherapy-induced normalization of FDG uptake by colorectal liver metastases does not usually indicate complete pathologic response. J Gastrointest Surg 11: 1112-1119, 2007.
28. Calabria F, Rubello D and Schillaci O: The optimal timing to perform 18F/11C-choline PET/CT in patients with suspicion of relapse of prostate cancer: Trigger PSA versus PSA velocity and PSA doubling time. Int J Biol Markers 29: e423-e430, 2014.