^{18}F-FDG PET/CT. Its correlation with carcinoembryonic antigen in patients with colorectal carcinoma

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Abstract

Background: *^{18}F-FDG PET scan has been shown to be highly accurate for recurrent and metastasic disease, as well as in restaging. Carcinoembryonic antigen (CEA) can be used as a prognostic and recurrence marker.* **Objective:** *To determine the correlation between the presence of lesions detected with ^{18}F-FDG PET and the determination of CEA in patients with colorectal carcinoma.* **Material and Methods:** *Two thousand and fifty-one patient records were reviewed. One hundred and one colorectal carcinoma patients with CEA results were included.* **Results:** *One-hundred and one patients (51 women and 50 men) were included, with a mean age of 60.21 years. The prevailing clinical stage was IIA, with moderately differentiated adenocarcinoma histology (88.12%). There was an adequate correlation between CEA elevation and the presence of lesions in the positron emission tomography computed tomography scan (PET/CT) in 73.9% of the cases. In those patients with CEA within normal ranges, the PET/CT scan was positive to tumor recurrence and/or metastases in 42%.* **Conclusion:** *Our study revealed that the PET/CT scan with ^{18}FDG can provide additional information in 42% of patients with CEA normal levels and detect recurrences and/or metastases earlier.* (Gac Med Mex. 2014;150:503-10)

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Introduction

The frequency of colorectal carcinoma has increased both in Mexico and in the rest of the world, largely due to people's lifestyle. The colorectal carcinoma precursor lesions are aberrant crypt foci and adenomas; advanced adenomas are more likely to present neoplastic progression. According to Morson, 100% of carcinomas originate in adenomas. These can be classified by macroscopic presentation, histologic type, level of invasion and hereditary pattern. Treatment and prognosis depend largely on a comprehensive diagnosis and accurate staging. Eighty-five percent of the patients with a neoplasm limited to the intestinal wall have a survival of 5 years, whereas when nodal metasteses are present, the figure is reduced to less than 50%. Poorly differentiated, non-differentiated and mucinous adenocarcinomas are biologically more aggressive than those well and moderately differentiated[1].

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Colorectal cancer (CRC) is the second cause of death in Mexico and the third most common type of metastatic tumor in the general population[2]. This malignancy occurs with the same frequency in men than in women[3]. In spite of being a neoplasm that occurs in older patients, with a mean of 50.8 years at diagnosis, cases in younger people are being increasingly detected[2]. Up to 90% of cancer cases appear after 50 years of age. CRC is one of the most commonly occurring neoplasms. The high incidence of CRC is due to environmental-type factors, such as a diet that is fundamentally rich in fat and protein and poor in fiber and vegetables, as well as to a progressively aging population[4].

The etiology of CRC is complex, since it includes environmental and genetic factors. Approximately 75% colon and rectum malignant tumors occur in patients without known risk factors. Individuals with ulcerative colitis, familial polyposis and hereditary nonpolyposis colon cancer are at higher risk of developing the disease; however, they account for less than 10% of all CRCs[5]. Case-control and cohort studies suggest that obesity, physical inactivity, alcohol abuse, smoking

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and a diet high in fat and/or poor in fruits, vegetables and fiber are associated with an increased risk for adenomas and CRC[2]. However, preventing obesity, practicing exercise regularly and eating a healthy diet over a period of 3 to 8 years does not significantly reduce the risk of adenoma or CRC[5,6].

Surgery is the main therapeutic approach for colon cancer. It involves en-bloc resection of the tumor and regional lymph nodes, and it must include high ligation of the primary vessel of the segment and resection of at least 12 lymph nodes in the specimen to be considered an adequate procedure since, presently, lymph nodes remain the most important prognostic factor for adjuvant treatment decisions[7].

Surgery will cure approximately 50% of patients; however, in 30-40% stage II or III cases, recurrent disease will be restricted to a single organ, such as the liver, or anatomical zone, such as the pelvis.

There is no clear consensus about the factors that can predict surgical success for recurrent metastases to the liver and lung. However, for patients with liver-limited recurrence there is an agreement that multiple metastases and the presence of extra-hepatic lesions confer an adverse prognosis[8].

Positron emission tomography-computed tomography with ^{18}F-FDG has been shown to be highly accurate in the detection of recurrent and metastatic disease, since, most of all, it helps to restage in case of recurrence (primarily in the liver), to look for distant metastases and to monitor the response to treatment, as well as in the change of therapeutic management[8,9].

Positron emission tomography-computed tomography with ^{18}F-FDG seems to have a role in the assessment of the extent of distant metastatic disease prior to metastasectomy, since this technique is more sensitive than contrasted CT. The potential of the standardized uptake value (SUV_{max}) of the PET as a prognostic and predictive biomarker has been reported.

There is strongly circumstantial evidence that tumor hypoxia, with high glucose metabolism, represents a particularly aggressive neoplastic type. Given the high avalability of CT-integrated PET scans, the combination of anatomical with metabolic neoplastic phenotype assessment is now possible[10].

In medicine, there are complementary methods for the prognosis of neoplasms at the moment of diagnosis, usually found at advanced stages, which complicates the selection of a specific therapy that provides the patient better survival, as well as improved quality of life[11].

The carcinoembryonic antigen is a glycoprotein located in the apical pole of enterocytes. Genes encoding for CEA are located at chromosome 19q13.2. The entire group is comprised by 29 genes, divided into three sub-groups, out of which only 18 are expressed. In healthy individuals, there are multiple functions of the CEA that have been extensively studied; its function as an adhesion molecule has been the most diffused. In healthy patients, in addittion to being expressed at the colonic level, CEA is expressed in tongue, esophagus, stomach, cervix and prostate cells. Patients who derive most clinical usefulness are those with CRC, and it is used as a prognostic marker, for staging, as a marker of recurrence and response to treatment, as well as an indicator of metastases to the liver[12,13].

PET/CT, in addition to multiple indications in CRC (initial staging, assessment of recurrences, restaging and evaluation of potentially resectable liver or lung metastatic lesions), is also highly useful in cases where there is a CEA elevation without any known cause to differentiate cancer from scarring in the presacral mass after surgery or radiotherapy and to assess the response to treatment.

Positron emission tomography-computed tomography is more useful in distant metastases, with very high sensitivity and specificity; in 11-23% of cases there is extra-hepatic metastasis. With regard to liver metastases, these are very common and it is important to have anatomical and metabolic information on them. When we want to assess recurrence by elevated CEA, we should consider that it is increased in two thirds of patientes with recurrence and has 70-84% specificity, with 80%sensitivity.

One of the PET/CT indications is for tumor markers elevation with negative conventional imaging. In such cases, PET/CT with ^{18}FDG has been shown to have high sensitivity and positive and negative predictive values that could reach up to 100%[14].

The purpose of this study was to determine the correlation between the presence of lesions detected with ^{18}F-FDG PET and the measurement of CEA in patients with colorectal carcinoma.

Material and methods

Patient selection

An ambispective, observational, descriptive, open-label study was carried out in the Cyclotron PET/CT Unit of the Universidad Nacional Autónoma de México (UNAM) during the first semester of 2012. Clinical records of 2051 patients were reviewed, out of which 101 patients diagnosed with colorectal cancer who also had CEA

Table 1. Frequency by sex

Value	Frequency	Percentage
Women	51	50.50
Men	50	49.50
Total	101	100.00

results were found. All patients had CEA results, which were considered to be abnormal when levels exceeded 5 ng/ml.

PET/CT scan

All patients underwent the PET/CT acquisition protocol established at the unit, which indicated fasting for at least 6 h with previous glucose measurement. Non-ionic iodinated contrast was administered intravenously (except to those who were allergic to the contrast medium), as well as oral contrast and 370 MBq (10 mCi) of ^{18}F-FDG, a radiopharmaceutical that is synthesized in the unit itself. Patients were left to rest for 60 min.

A multislice Biograph 64 True Point PET/CT equipment (Siemens Medical Solutions), with high-resolution lutetium oxyorthosilicate (LSO) crystal and 64-slice CT was used. Reconstructions from the base of the skull to the proximal third of the tighs were carried out and obtained with a time of 2.5 min/bed position.

Study analysis

The ^{18}F-FDG images were assessed by two different nuclear physicians and a radiologist physician. ^{18}F-FDG uptake by the lesions was evaluated semi-quantitatively using the SUV_{max}.

Statistical analysis

The analysis was performed with central tendency measures, besides of using the statistical package for the social sciences (SPSS) Statistics 21 and EPIDAT 4.0. Chi-square (χ^2) test with a statistically significant value lower than 0.05 ($p = 0.05$).

Results

A total of 101 CRC-diagnosed patients were included, with ages ranging from 26 to 90 years and a mean age of 60.21 years; out of them, 51 were women and 50 were men (Table 1) (Fig. 1).

Of the 101 studied patients, 89 (88.12%) had a moderately differentiated adenocarcinoma histopathological report; 6 (5.94%), well differentiated adenocarcinoma; 3 (2.97%), poorly differentiated adenocarcinoma; and 3 (2.97%), mucinous-type adenocarcinoma.

Distribution according to location and laterality of the neoplasm is specified in tables 2 and 3.

Taking into account the colorectal adenocarcinoma staging according to the National Comprehensive Cancer

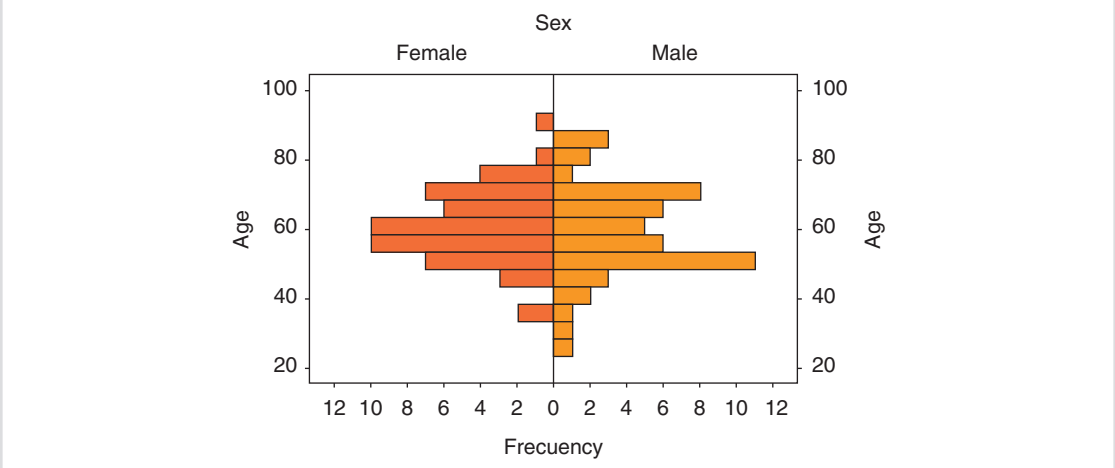

Figure 1. *Frequency by sex.*

Table 2. Frequency of location

Location	Frequency	Percentage
Ascending	22	21.78
Cecum	10	9.90
Descending	14	13.86
Rectum	23	22.77
Rectosigmoid	14	13.86
Sigmoid	15	14.85
Transverse	1	0.99
Ileocecal valve	2	1.98
Total	101	100.00

Table 3. Laterality

Laterality	Frequency	Percentage
Right	33	32.67
Left	67	66.34
Transversal	1	0.99
Total	101	100.00

Table 4. Staging

Clinical stage	Frequency	Percentage
I	4	3.96
IIA	20	19.80
IIB	10	9.90
IIIA	8	7.92
IIIB	19	18.81
IIIC	16	15.84
IVA	19	18.81
IVB	5	4.95
Total	101	100.00

Network (NCCN) guidelines, version 3.2013, with the obtained data, a higher percentage of stage IIA patients were observed, followed by stages IIIB and IVA (Table 4). With regard to response criteria, using the response evaluation criteria in solid tumors (RECIST) 1.1 and PERCIST[16-18], seven patients were found to have stable disease, two with complete response, and in the 17 remaining cases, progression of the disease was observed.

The association was sought between the presence of ^{18}F-FDG PET/CT-detected lesions and CEA elevation (Table 5), with an increase exceeding 5 ng/ml considered to be elevated and with lower values regarded as normal. Sixty-nine patients were reported with a positive PET/CT scan, and 32 patients with negative scan (Table 6). Overall, 58 patients had elevated CEA levels and 43 showed normal CEA values (Fig. 2). In those patients with elevated CEA, the PET/CT scan was reported to be positive in 87.9% (n = 51) of the cases. Since the obtained chi-square value (8.298) was higher than the critical value (p = 0.05; critical value: 3.841), an association between the presence of ^{18}F-FDG PET/CT-detected lesions and CEA increase was found to exist. However, in 12.1% (n = 7) of the patients with CEA elevation the PET/CT scan was negative.

On the other hand, 58.1% of the patients with negative PET/CT had normal CEA levels. Noteworthy, in 41.9% of the cases (n = 18) with negative CEA, the ^{18}FDG PET/CT scan was reported to be positive. There was no correlation between the SUV_{max} units and the level of CEA.

Of the 101 studied cases, 26 had follow-up and control ^{18}F-FDG PET/CT scans performed; the remaining 75 scans were first-time scans.

With regard to metastatic sites, they were divided into solid organs, lymph nodes, bone and local relapse (Table 7) (Fig. 3).

Table 5. Association of PET/CT with CEA

		CEA		Total
		Elevated	Normal	
PET/CT	Negative	7	25	32
	Positive	51	18	69
Total		58	43	101

Table 6. Report PET/CT study

PET	Frequency	Percentage
Negative	32	31.7
Positive	69	68.3
Total	101	100.00

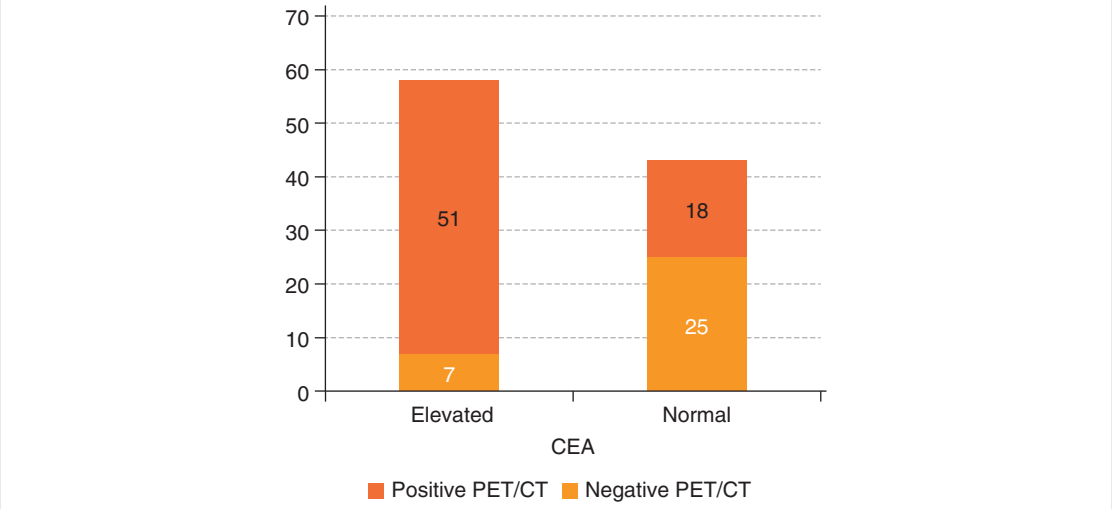

Figure 2. *PET/CT as related to CEA.*

The different lymph node levels are depicted in figure 4, and the frequency of local invasion and/or colon metastases is shown in table 8 and figure 5.

With regard to the standardized uptake value, the sites where the highest metabolism increases were observed were the liver and the lung, where a SUV_{max} of 25 was obtained for the liver and 16 for the lung. For the remaining sites with enhanced ^{18}FDG uptake, the SUV_{max} ranged from 2 to 14; this last value was obtained at the level of the colon (cecum).

Of the reviewed cases, the number of metastases detected per patient was observed to range from 1 to 12, with an average of 5 per patient and a total of 890 metastatic lesions (Figs. 6-8).

Table 7. Solid organ metastases

Liver	25
Spleen	1
Pancreas	1
Lung/Pleura	24
Bone	1
Abdominal muscle	1
Psoas muscle	2
Other	10

Discussion

Colorectal cancer accounts for approximately 9% of malignancies in the human being. In Mexico, it is the most common gastrointestinal tract cancer[6]. A simultaneous increase in tumor markers, such as CEA, is frequently observed. Patients that derive greater clinical usefulness are those with a CRC diagnosis, since it is used as a diagnostic, staging and recurrence marker, as well as an indicator of response to treatment and metastases to the liver[12,13].

During the course of the investigation, we observed that, in line with previous reports, this disease occurs with the same frequency in women than in men[3], since we found a frequency of 50 and 49%, respectively. Compared with the findings of Erazo et al.[2], who report a mean age of 50.8 years at diagnosis[2], in the case of the present study, a mean of 60.21 years was found.

Carcinoembryonic antigen is the most important indicator of recurrence in symptomatic patients[13]. PET/CT with ^{18}F-FDG has a role in the assessment of the extension of distant metastatic disease, in staging and in the assessment of recurrences, as well as in restaging and evaluation of liver or lung lesions; it is also very useful in cases where there is CEA elevation[10,14]. This was demonstrated when a significant frequency of association between CEA and ^{18}F-FDG PET/CT was found, with 73.9%.

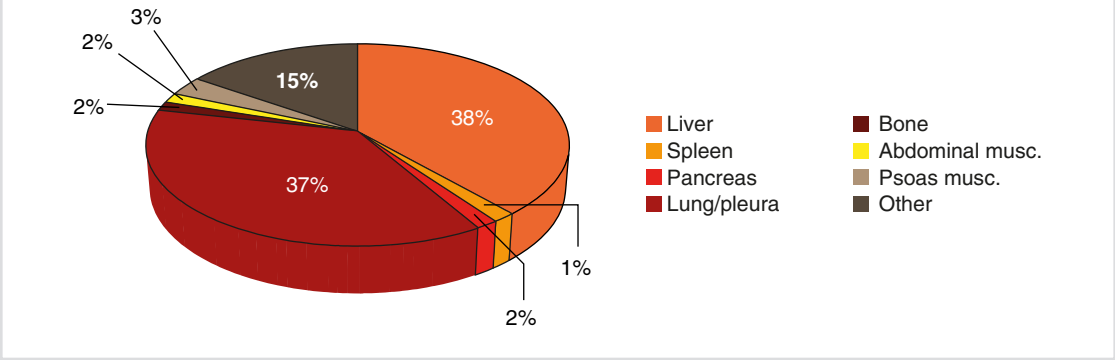

Figure 3. *Metastases to solid organs.*

The new NCCN classification, which includes clinical staging up to IVB, was taken into account[15]. One of the findings over the course of the study was that, out of the total number of patients, there was a higher percentage at clinical stage IIA, followed by IIIB and IVA.

According to reports by Medwave[14], it is agreed that the liver is the organ most affected by metastasis, followed by the lung.

One of the PET/CT indications is for elevated tumor markers with negative conventional imaging; in these cases, ^{18}F-FDG PET/CT has been shown to have high sensitivity and positive and negative predictive values that could reach up to 100%[14]. This is most helpful for the treating physician, since thanks to the role these methods play, the patient can be offered a better prognosis by being able to modify or continue the established treatment.

In spite of CEA being considered a factor to assess CRC recurrence, in our study we found that 41.9% of the patients showing CEA within normal ranges had a

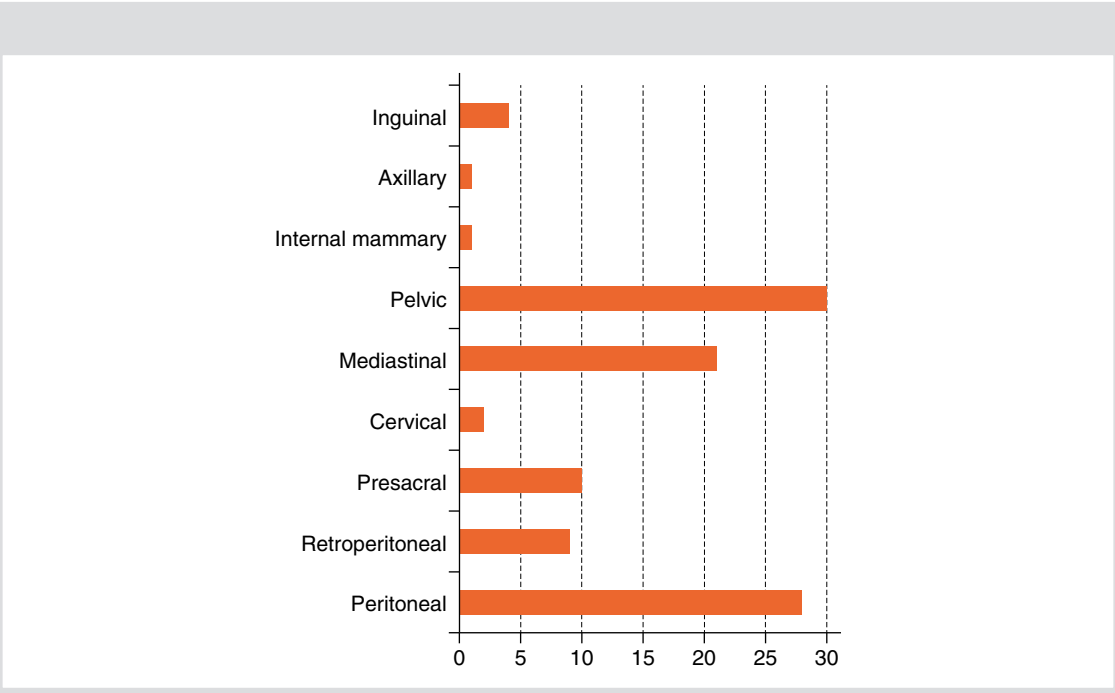

Figure 4. *Metastases to lymph nodes.*

Table 8. Local invasion

Cecum	1
Ascending colon	2
Transverse	2
Rectosigmoid	18

positive PET/CT scan, similar to the findings of Lee et al.[19], who report 63.3% of patients with positive PET/CT scan and CEA within normal values.

Our findings show that even in those patients with normal CEA levels, the PET/CT scan with ^{18}FDG may play a role in the assessment and follow-up of patients with colorectal cancer, especially in those at high risk of recurrence.

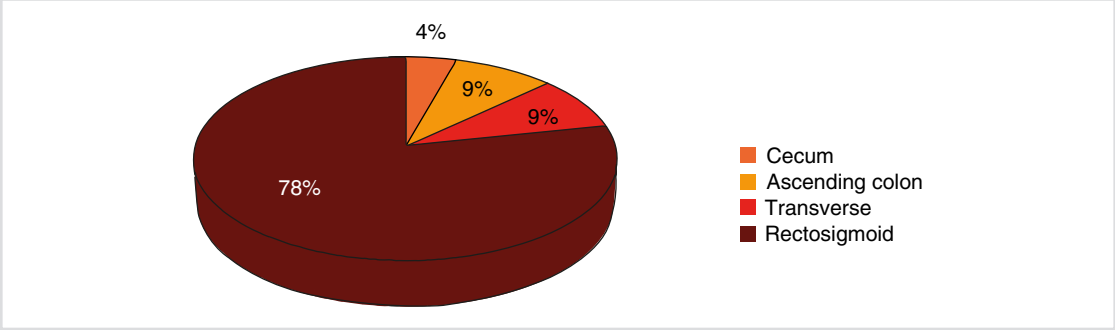

Figure 5. *Local relapse.*

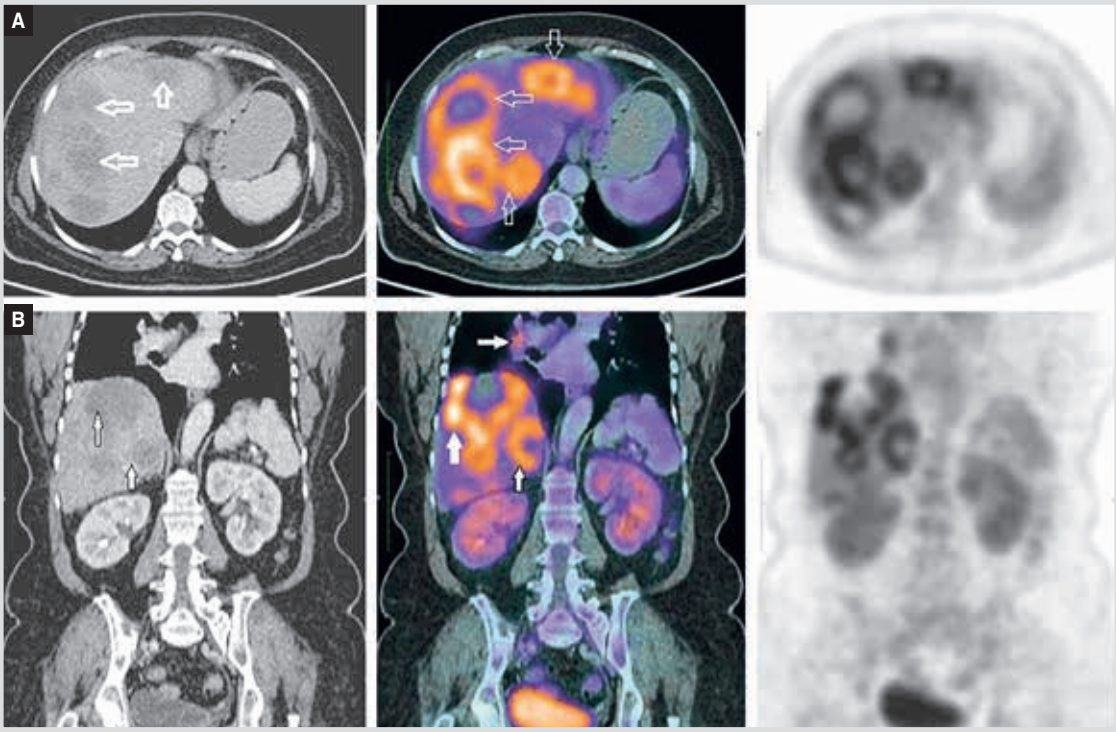

Figure 6. *63-year old women diagnosed with ascending colon invasive, moderately differentiated adenocarcinoma, clinical stage IVA, treated with surgery and chemotherapy. The patient presents CEA elevation to 434 ng/ml. PET/CT scan with ^{18}FDG was performed and multiple hypodense, hypermetabolic lesions at the liver parenchyma were observed **(A)**, with SUV_{max} of 9.2 (white arrows) and mediastinal lymph nodes **(B)**.*

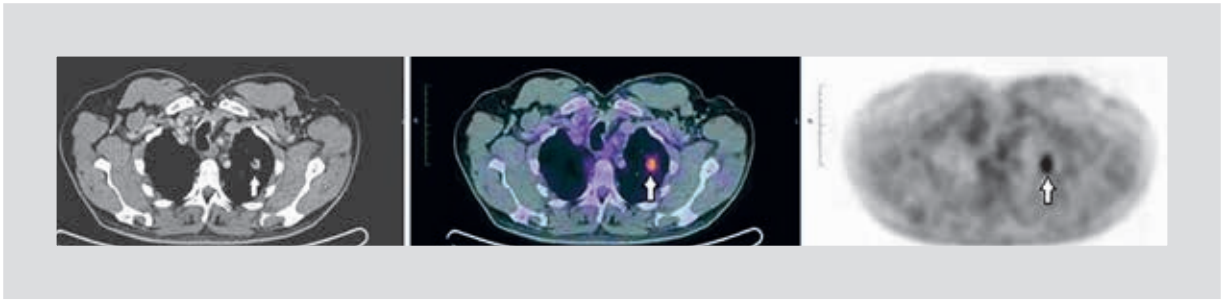

Figure 7. *60-year old male diagnosed with rectosigmoid moderately differentiated adenocarcinoma, clinical stage IVA; surgery and chemotherapy were performed, with CEA elevation (60.6 ng/ml). ^{18}FDG PET/CT scan showing highly uptaking lung parenchyma lymph nodes, with a SUV_{max} of 3.8 (white arrows).*

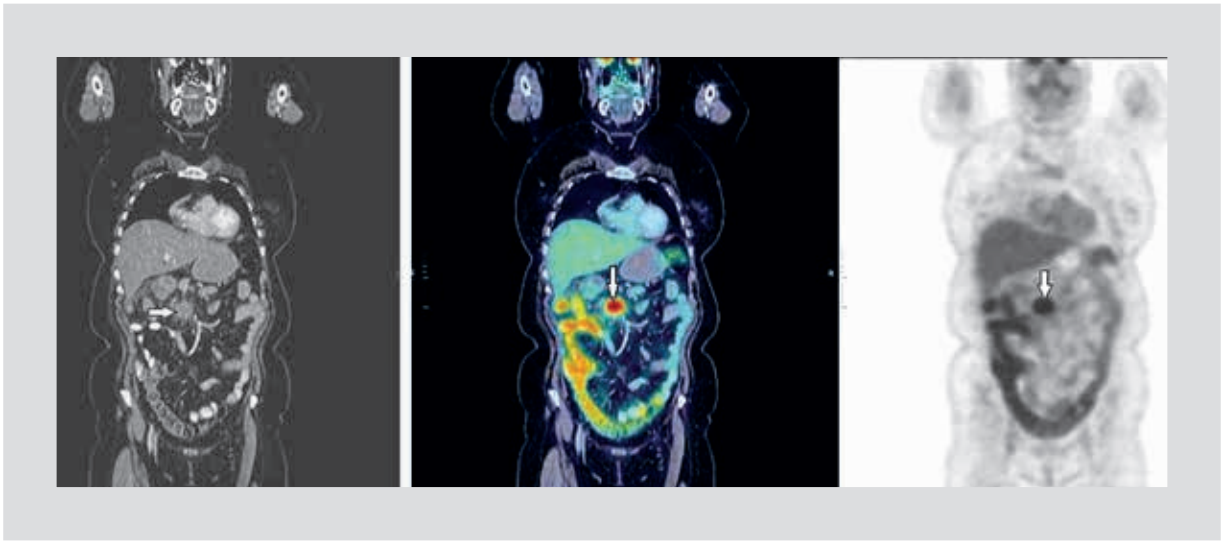

Figure 8. *62-year old women diagnosed with moderately differentiated adenocarcinoma of the ascending colon, clinical stage IVA, managed with surgery and chemotherapy. CEA of 18.4 ng/ml. The PET/CT scan with ^{18}FDG shows a hypermetabolic lesion in the mesentery, with a SUV_{max} of 11 (white arrows).*

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