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Correlation between serum CEA level and metabolic volume as determined by FDG PET in postoperative patients with recurrent colorectal cancer

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To determine the correlation between serum CEA level and the metabolic volume by FDG PET in postoperative patients with recurrent colorectal cancer, FDG PET was performed in 29 consecutive patients with recurrent or metastatic colorectal cancer whose CEA levels were higher than 5 ng/m*l*. A whole body emission scan was performed 60 minutes after injecting 370–555 MBq of F-18 FDG. "PET volume" and "PET metabolic volume" of tumors were measured on FDG PET images. Based on an isocontour plot of tumor mass at 2.5 SUV (standardized uptake value), the metabolically active tumor "PET volume" was calculated. "PET metabolic volume" was obtained by multiplying the "PET volume" by the mean SUV of the tumor. All recurrent or metastatic lesions were single or multiple lesions of measurable size (axial diameter > 1 cm, minimum "PET volume" 3.5 cm^3), and were verified by operation or by other imaging modalities (CT or MRI). There was a linear associations between "PET volume" and serum CEA level. Further regression analysis by least squares showed a highly significant model with an equation of volume = 41.2 + 0.471•CEA (r^2 = 0.629). However, no such association was found between "PET metabolic volume" and serum CEA level according to the residual normality test. In conclusion, "PET volume" measured by FDG PET and serum CEA level in colorectal cancer are significantly correlated. Tumor volume determined by FDG PET can be used as an effective marker of tumor burden in postoperative patients with colorectal carcinoma.

Key words: FDG PET, colorectal cancer, carcinoembryonic antigen, tumor volume

INTRODUCTION

COLORECTAL CANCER remains the second most common cause of cancer death in the United States and European countries. Advances in treatment strategies include laparoscopic colon resection and the local excision of small tumors, followed by radiation and chemotherapy. However, approximately 40% of patients who undergo first curative surgery for colorectal carcinoma present with suspected recurrence at the first year follow-up.[1,2]

Serum carcinoembryonic antigen (CEA) is a well-established method for the detection of local tumor recurrence and metastases in the postoperative surveillance of colorectal carcinoma patients.[3–8] Circulating CEA levels provide a very sensitive measure of recurrence. In addition, preoperative serum levels of CEA correlate more or less with tumor stage and prognosis.[9,10] Summarizing, the serum level of CEA may reflect tumor burden in colorectal cancer patients.[11,12]

^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) is an advanced imaging technique and allows a highly sensitive whole body search for malignant foci, which are detected by their increased glucose metabolism versus benign tissues, and successful FDG PET

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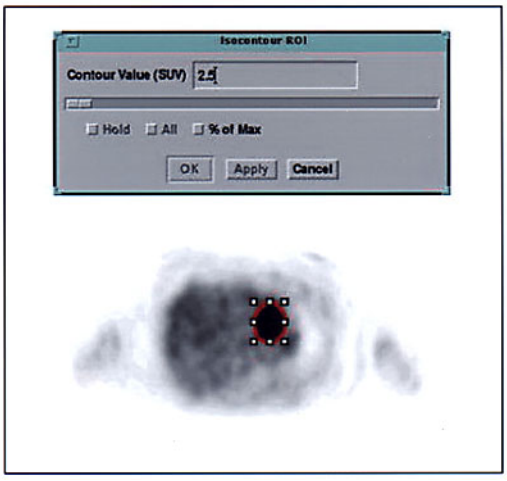


Fig. 1 Selective tumor boundary as determined by isocontour value (SUV) 2.5 in ROI.

scanning has been performed in a wide variety of cancers. Several studies have demonstrated the added value of FDG PET in terms of detecting recurrent colorectal cancer, especially in patients with elevated serum CEA levels.[13–20] However, no investigation has been conducted on the relation between PET findings and serum CEA levels to the best of our knowledge. The purpose of this study was to determine the correlation between serum CEA levels and metabolic volume by FDG PET in postoperative colorectal cancer patients as a basic study for PET use in the detection of recurrent colon cancer.

PATIENTS AND METHODS

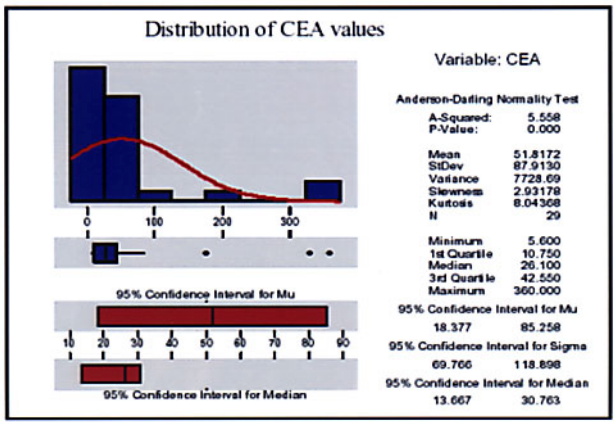
Patients

We retrospectively reviewed the FDG PET images of colorectal cancer patients from February 2000 to October 2003. Patients with preoperative staging were excluded. All patients had previously treated by surgical resection and/or chemotherapy. Twenty-nine consecutive patients with recurrent or metastatic single or multiple lesions of adequate size (axial diameter > 1 cm, minimum volume

Table 1 Lesion characteristics of the included 29 patients

Patient	CEA (ng/m*l*)	SUVmean	PET volume (cm^3)	PET metabolic volume (cm^3)	Lesion sites in PET	Confirmed site by histopathology
1	28.8	10.11	60.5	611.655	3 lesions in Liver	—
2	53.1	2.98	58.4	174.032	Rectum	—
3	41.6	2.54	43.8	111.252	Rectum	—
4	360	19.5	238.8	4656.6	2 lesions in Liver	—
5	29.6	4.95	65.15	322.4925	Liver	Liver
6	5.6	3.63	46.6	169.158	Liver/C-spine	Liver
7	13.5	3.1	34.6	107.26	LLL	LLL
8	30	8.76	68.48	599.8848	Liver	Liver
9	6.6	3.65	80.54	293.971	Liver	Liver
10	16.4	3.19	64.2	204.798	2 lesions in Pelvic cavity	Both ovaries
11	26.8	6.33	78.9	499.437	Liver/RLL	—
12	43.5	4.2	84.6	355.32	Liver	Liver
13	9.2	5.34	96	512.64	Rectum	Rectum
14	83.8	12.75	82.6	1053.15	3 lesions in Liver/spleen	—
15	9.7	6.68	46.86	313.0248	RUL/LLL	RUL
16	11.8	5.43	11.5	62.445	C-spine/Rt pelvic bone	C-spine/Rt pelvic bone
17	27.9	7	66.4	464.8	Liver	Liver
18	13.7	6.42	11.4	73.188	T-spine	T-spine
19	34.6	3.09	104.7	323.523	RLL	RLL
20	331	5.28	139.1	734.448	Liver	Liver
21	15.2	4.66	34.99	163.0534	Liver	Liver
22	8.6	4.4	88.8	390.72	Ascending colon	Ascending colon
23	50.8	3.9	34.68	135.252	Liver	Liver
24	5.9	4	6.8	27.2	Liver	Liver
25	176	3.48	180.3	627.444	Liver	Liver
26	15	4	55.1	220.4	Liver	Liver
27	26.1	2.55	5.1	13.005	Liver	Liver
28	6.2	3.22	23.2	37.03	Liver	Liver
29	21.7	2.5	3.5	8.75	Liver	Liver

Metabolic volume (cm^3) = SUVmean × "PET volume" (cm^3)



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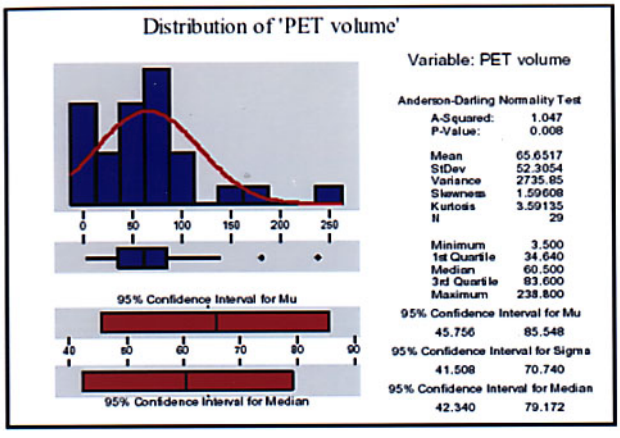

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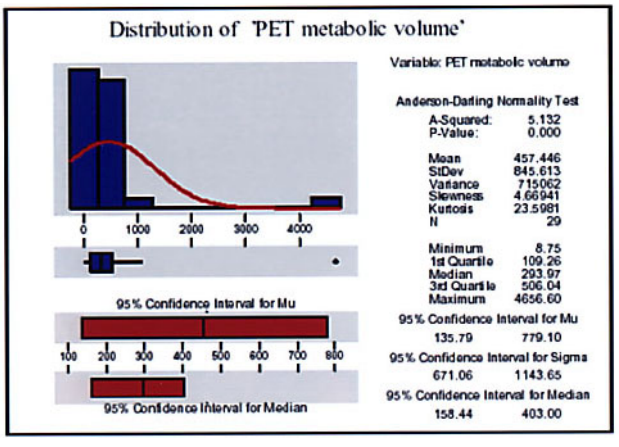

c

Fig. 2 CEA (a), PET volume (b), and PET metabolic volume (c) distribution shown by the 29 patients.

3.5 cm^3) and whose CEA level were higher than 5 ng/m*l* were enrolled. Mean patient age was 55.7 years (range 37–77), and their mean CEA level was 51.81 ± 87.9 ng/m*l* (range 5.6–360). Chemotherapy was discontinued at least 3 months before a PET examination.

Of the 29 patients, the histopathologic findings at the primary operation were moderately differentiated in 20, well differentiated type in one, and poorly differentiated type in one. The histopathologic data on the remaining 7 patients were not available.

Forty lesions of 29 patients were evaluated. Based on lesion site, FDG PET revealed that 19 patients had metastatic liver lesions, 4 patients local recurrence, 4 patients lung lesions, 3 patients bone lesions, one patient spleen lesions, and one patient ovary lesions. All recurrent or metastatic lesions were verified by histological analysis (22 patients) or by other imaging studies, namely, CT, MRI, or bone scintigraphy (7 patients).

FDG-PET imaging protocol

Whole body PET scans were performed using an ECAT EXACT 47 (Siemens-CTI, Knoxville, TN). After fasting for at least 6 hours, 370–555 MBq ^{18}F-FDG was injected intravenously. Sixty minutes later, whole body emission images were obtained for 6 minutes per each bed, and regional emission images were obtained for 30 minutes in the 2D mode. Transmission scanning with three ^{68}Ge ring sources was performed for 2 minutes per each bed in whole body transmission and for 20 minutes in regional transmission to correct attenuation.

Images were visually interpreted by consensus between two experienced nuclear physicians. Standardized uptake values (SUV) were calculated from the amount of FDG injected, body weight and target tissue uptake in regional attenuation corrected images.

"PET volume" and "PET metabolic volume" of tumors

Tumor volume was determined by using a semiautomated attenuation-corrected FDG PET method. Tumor boundaries were outlined with a SUV 2.5 contour using image analysis software in the regional images (Fig. 1). The longest diameter of the isocontour plot of the tumor mass was assessed in coronal, transaxial, and sagittal views, respectively. The metabolically active "PET volume" of the tumor was determined by multiplying the 3 axial diameters. "PET metabolic volume" was obtained by multiplying "PET volume" by mean tumor SUV.

Statistical analysis

Pearson and Spearman's rank correlation analyses were employed since the distribution of CEA data turned out to be non-parametric. Regression analysis was performed using the least squares method after estimating the correlation between the CEA level and the "PET volume" or the "PET metabolic volume." The linear regression model obtained was confirmed by ANOVA (analysis of variance) using the F-test. Finally, the residual analysis was done to verify the following statistical assumptions of the normality of residual left over from the regression model by applying the Anderson-Darling test.

Regression model assumptions:

$\varepsilon \sim \text{NID}(0, \sigma^2)$

where ε is the residual (random) error
NID means normally, independently distributed
0 = zero mean of the random error
σ^2 = constant variance of σ^2 at all levels of x
All data were analyzed using Minitab 13.03 (Mintab, Inc., PA, USA).

RESULTS

FDG uptake within recurrent lesions was variable (Table 1). The metabolic "PET volume" of tumors ranged from 3.5 to 238.8 cm^3 (65.7 ± 52.3 cm^3), and the "PET metabolic volume" of tumors ranged from 8.7 to 4656.6 cm^3 (457.4 ± 845.6 cm^3).

The distribution of CEA and PET volume data was non-parametric (Fig. 2). Pearson and Spearman's rank correlation analyses showed linear associations between "PET volume" and serum CEA level (r = 0.793 p < 0.001 and r = 0.472 p = 0.01, respectively). Further regression analysis using the least squares method resulted in a highly significant model, namely, PET volume = 41.2 + 0.471 • CEA (t = 6.76, p < 0.0001) (Table 2). This statistical regression model (Fig. 3a) was confirmed by ANOVA ($F_{1,28}$ = 45.68, p < 0.0001) (Table 3) and residual analysis by Anderson-Darling normality test (p = 0.651) (Fig. 3b). Based on all the possible residual tests (normality and

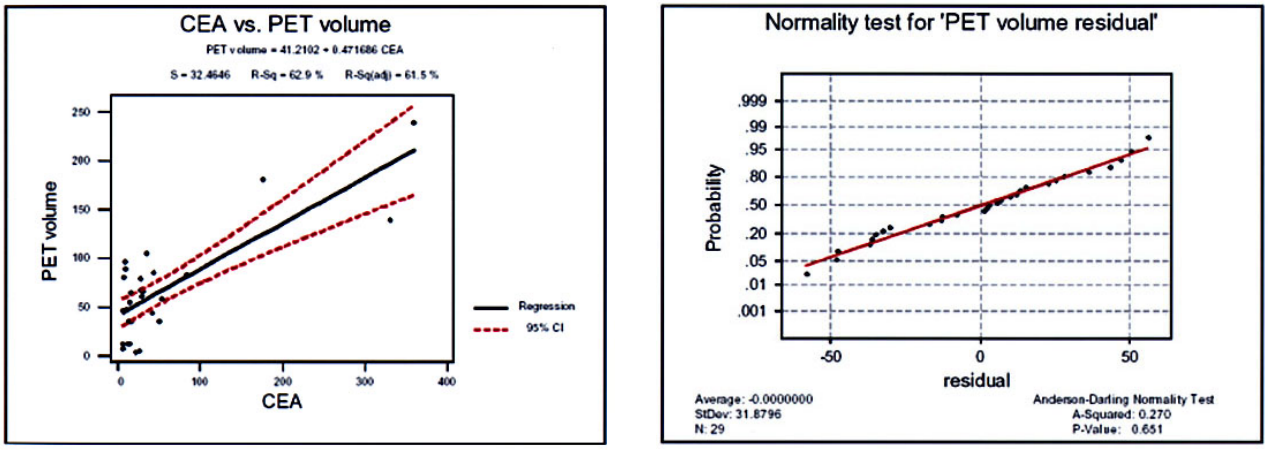

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Fig. 3 Regression model for CEA vs. "PET volume" (a) and normality test for residual from the regression model (b). S; standard deviation, R-sq; coefficient of determination, R-sq (adj); R-sq adjusted by model term. CI; confident interval.

Table 2 Regression analysis of CEA versus tumor "PET volume"

Predictor	Coeff	SE Coeff	T-value	P-value
Constant	41.210	7.030	5.86	0.000
CEA	0.47169	0.06979	6.76	0.000
S = 32.46	R-sq = 62.9%	R-sq (adj) = 61.5%		

Coeff; coefficient, SE Coeff; standard error of coefficient, S; standard deviation, R-sq; coefficient of determination, R-sq (adj); R-sq adjusted by model term

Table 3 ANOVA testing of the regression model of CEA vs. tumor "PET volume"

Source	DF	SS	MS	F-value	P-value
Regression	1	48147	48147	45.68	0.000
Residual error	27	28457	1054		
Total	28	76604			

DF; degrees of freedom, SS; sum of squares, MS; mean of squares

Table 4 Regression analysis of CEA against tumor "PET metabolic volume"

Predictor	Coeff	SE Coeff	T-value	P-value
Constant	79.9	121.7	0.66	0.517
CEA	7.287	1.208	6.03	0.000
S = 562.1	R-sq = 57.4%	R-sq (adj) = 55.8%		

Coeff; coefficient, SE Coeff; standard error of coefficient, S; standard deviation, R-sq; coefficient of determination, R-sq (adj); R-sq adjusted by model term

Table 5 ANOVA test for regression model of CEA vs. "PET metabolic volume" of tumor

Source	DF	SS	MS	F-value	P-value
Regression	1	11490789	11490789	36.37	0.000
Residual error	27	8530952	315961		
Total	28	20021740			

DF; degrees of freedom, SS; sum of squares, MS; mean of squares

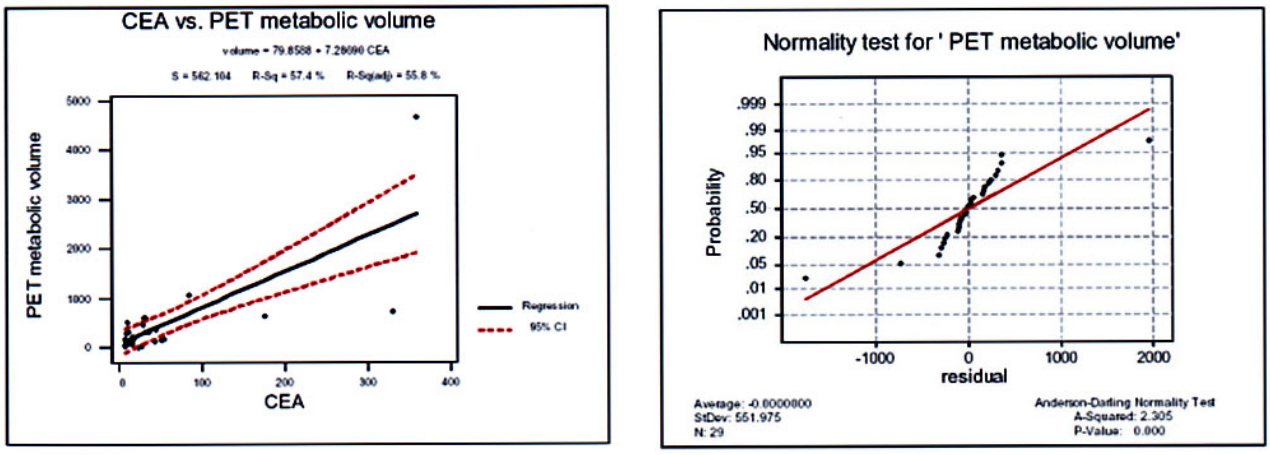

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Fig. 4 Regression model for CEA vs. "PET metabolic volume" (a) and normality test for residual from the regression model (b). S; standard deviation, R-sq; coefficient of determination, R-sq (adj); R-sq adjusted by model term. CI; confident interval.

other residual plots, data not shown), this regression model with CEA as a predictor satisfied all statistical assumptions, and CEA concentration was found to be a significant predictor of "PET volume" obtained from FDG PET.

However, no such linear association was found between the "PET metabolic volume" of a tumor and serum CEA level considering residual normality test ($p < 0.0001$) that violates the statistical assumption of random error (Fig. 4b), in spite of significant regression and ANOVA model (Tables 4, 5, and Fig. 4a).

DISCUSSION

The assessment of tumor burden is important in the management of cancer patients, as prognosis is frequently related to it. In patients with advanced cancer, total tumor burden affects the tumor response to therapy, and has important implications for prognosis.[21–23] Moreover, treatment induced reductions of tumor burden have been shown to be correlated with improvements in survival. Many methods are available for calculating tumor burden, such as the pathologic assessment of resected specimens, serologic markers, and the assessment of tumors by cross-sectional CT imaging.

Since Gold and Freedman[24] first described CEA in 1965, it has proven to be a highly sensitive marker for detecting recurrence, and is widely used in postoperative colorectal cancer.[3–8] Chung et al.[25] found that CEA is expressed homogeneously in adenocarcinoma of the colon by quantitative autoradiography. The fact that the concentration of CEA is uniformly high in colon carcinoma suggests that serum CEA concentration implies tumor volume. However, CEA has several limitations. It is well known that a normal CEA level does not exclude a tumor recurrence, and serum CEA is not proven as a recognized marker for tumor burden in colorectal cancer.

Tumor burden assessment currently depends on cross-sectional imaging modalities such as CT or MRI. Measured CT-derived parameters are reproducible in terms of direct volume measurement and bidimensional measurements.[26,27] However, there are pitfalls in the post-treatment setting, as CT alone cannot distinguish between viable and nonviable mass. In addition, the assessment of small tumors with diameters similar than the slice thickness limits the usefulness of CT imaging. Unfortunately, we could not correlate anatomical tumor volume measured by CT or MRI and serum CEA level, because some lesions were not covered by CT or MRI.

These limitations of CT can be overcome by using FDG PET. ^{18}F-FDG PET detects the glycolytic activities of tumor cells. Higashi et al.[28] reported that FDG uptake *in vitro* and *in vivo* is strongly related with the number of viable cancer cells. A number of investigations have compared tumor volumes by CT and PET. Zasadny et al.[29] and Akhurst et al.[30] reported that CT- and PET-derived volume measures were not identical, but added that PET-derived volumes are strongly correlated with CT volumes. However, large disparities between the two methods may occur due to tumor necrosis in previously treated patients.[29]

In this study, an SUV contour of 2.5 was used for tumor volume determination on FDG PET image. It is generally accepted that FDG PET shows the best sensitivity and specificity in the detection of tumor using the SUV of 2.5 as the cutoff value.[31] We also found that the SUV of 2.5 was a valuable criterion in our PET center, and have used it as a differential marker between tumor uptake and nonspecific uptake of FDG.[32]

The present study shows that the CEA level correlates

with the "PET volume" of a tumor, and not with the "PET metabolic volume" of a tumor. Although some have reported that FDG uptake is related with the number of viable cancer cells, non-neoplastic stroma tissues including inflammatory cells and granulation tissue also show significant FDG uptake in tumor tissue. In particular, high FDG uptake is observed in activated macrophages and young granulation tissue.[33] These might contribute to the lack of a correlation between CEA level and "PET metabolic volume" observed in the present study.

Absolute serum CEA levels are insufficient to detect tumor recurrence. However, serial increases in CEA levels indicate tumor recurrence with high specificity. In addition, local recurrence is associated with slower CEA increases than distant metastatic lesions.[34] For these reasons, the correlation between serum CEA and "PET volume" was only moderate in the present study.

In conclusion, this study demonstrates the existence of a significant correlation between metabolic volume, as measured by FDG PET, and the serum CEA level in postoperative patients with recurrent colorectal cancer. It indicated that "PET tumor volume" can be used as an effective marker of tumor burden in recurrent colorectal cancer.

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