Value of Dual Assessment of Carcino-embryonic Antigen and Fluorine-18-Fluoro-Deoxyglucose Positron Emission Tomography in Colorectal Cancer Recurrence

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ABSTRACT

Globally, colorectal cancer is a common medical problem and improvement of survival in patients with colorectal carcinoma could be achieved by identifying disease recurrence and progression, as well as by specifying their treatment planning. The use of various biomarkers associated with radio diagnosis techniques is not common in daily clinical practice. The aim of the present study was to evaluate the usefulness of dual assessment of FDG-PET and CEA in detecting recurrence of colorectal carcinoma in patients subsequent to colonic resection or rectal amputation. One hundred sixty patients, 99 males and 61 females, the mean of their age was 55.76 ± 12.25 years with suspected recurrent colonrectal cancer (CRC) after previous colonic resection or rectal amputation for CRC were included in this prospective study from February 2011 to March 2015. The inclusion criteria were: histopathologically confirmed colorectal adenocarcinoma, curative resection of the primary tumor, at least 3 months before and availability for follow-up after 18F-FDG PET/CT and CEA for at least 12 months. The CEA levels were measured within the time of the FDG PET/CT study. Only 132 patients were confirmed by histopathology or 6 month clinical follow up had local recurrence or metastasis (47 patients were confirmed had Intra-abdominal extra-hepatic recurrence , 80 patients had extra-abdominal and/or hepatic recurrence , 30 patients had other form of recurrence (17 patients had metastasis at other sites as the neck, long bones , mediastinal lymph nodes and multiple metastases) .The PET/CT diagnosis of recurrence and metastasis in CRC patients included in the study. Out of 160 patients after CRC resection, 126 patients were diagnosed by PET/CT as true-positive cases (25.62% Stage II /53.13% and I Stage III/IV) and 34 patients as negative cases (21.25 %). The sensitivity of monitoring the recurrence and metastasis of patients with CRC by PET/CT was 95.45 %. However, the diagnostic value of CEA levels for recurrence and metastasis in CRC patients included in the study proved that 102 patients had increased value of CEA (63.8%) and 58 patients (36.2%) had normal CEA value. The sensitivity of the CEA levels for monitoring the recurrence of the patients with CRC was 77.27 %. The sensitivity of the 18F-FDG PET/CT scan is superior to CEA in detection of colorectal cancer recurrence and dual assessment is important in treatment planning.

Key Words: *Carcinoembryonic antigen, Fluorine-18-fluoro-deoxyglucose positron emission tomography, colorectal cancer recurrence*

Kolorektal Kanser Nüksünde Karsinoembriyonik Antijen ve Flor-18-Floro-Deoksiglukoz Pozitron Emisyon Tomografisinin İkili Değerlendirilmesinin Yararı

ÖZET

Küresel olarak, kolorektal kanser genel bir tıbbi problemdir ve kolorektal kanserli hastaların yaşam sürelerinin iyileştirilmesi, tedavi planlarının ortaya konması ile beraber hastalığın nüksü ve progresyonunun tanımlanabilmesi ile başarılabilir. Radyodiagnostik tekniklerle ilişkili çeşitli biyomarkırların kullanımı, günlük klinik uygulamada yaygın değildir. Bu çalışmanın amacı, kolon rezeksiyonu veya rektal ampütasyon sonrası hastalarda kolorektal kanser nüksünün tespitinde FDG-PET ve CEA' nın ikili değerlendirilmesinin yararlılığını değerlendirmektir. Bu prospektif çalışmaya, Şubat 2011 ile Mart 2015 tarihleri arasında kolorektal kanser (KRK) nedeni ile kolonik rezeksiyon veya rektal ampütasyon sonrası KRK nüksü şüphesi bulunan yaşları ortalaması 55.76 ± 12.25 yıl olan, 160 (99 erkek ve 61 kadın) hasta dâhil edildi. Dâhil etme kriterleri: histopatolojik olarak doğrulanmış kolorektal adenokarsinomu, primer tümörün küratif rezeksiyonu, 18F-FDG PET/CT ve CEA öncesi en az 3 ay, sonrası en az 12 ay süre ile takip edilmiş olma. CEA seviyeleri, FDG PET/CT çalışması süresi içerisinde ölçüldü. Sadece 132 hastada lokal nüks veya metastaz varlığı histopatolojik olarak veya 6 aylık klinik takip ile doğrulandı (47 hastada intra-abdominal ekstra-hepatik rekürens, 80 hastada ekstra-abdominal ve/veya hepatik rekürens, 30 hastada diğer rekürens formlarının varlığı doğrulandı, 17 hastada boyun, uzun kemikler ve mediastinal lenf nodları gibi diğer yerlerde metastazlar ile multipl metastaz vardı). Bu çalışmaya, PET/CT ile rekürens ve metastazın tanımlandığı KRK li hastalar dâhil edildi. KRK rezeksiyonu sonrası 160 hastanın 126' sı PET/CT ile doğru pozitif olgu (%25.62 Evre II /%53.13 ve I Evre III/IV) ve 34' ü negatif olgu olarak tanımlandı (%21.25). KRK' li hastalarda metastaz ve rekürensin PET/CT ile gözlemin duyarlılığı %95.45 idi. Bununla beraber, CEA seviyelerinin çalışmaya dahil edilen KRK' li hastalarda rekürens ve metastaz için tanısal değeri, 102 hastada CEA değerinin arttığını (%63.8) ve 58 hastada (%36.2) CEA değerinin normal olduğunu göstermiştir. CEA seviyelerinin KRK' li hastalarda rekürensin gözlemindeki duyarlılığı, %77.27 idi. Kolorektal kanser rekürensinin tespitinde, 18F-FDG PET/CT taramanın duyarlılığı CEA'dan üstündür ve ikili değerlendirme tedavi planlamasında önemlidir.

Anahtar kelimeler: *Karsinoembriyonik antijen, Flor-18-floro-deoksiglukoz pozitron emisyon tomografi, kolorektal kanser rekürens*

INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related mortality in Western countries. It is the third most commonly diagnosed cancer, with an estimated 146, 970 new cases diagnosed in the USA during 2009 (1). Approximately 80% of patients present with local/regional disease and 20% with metastatic disease (2). Given that ~30-50% of patients undergoing a curative resection will ultimately have recurrent disease, optimizing the surveillance strategy is paramount (3). However, one Cochrane update [25] have been completed in the last decade and proved that an intensive follow-up was associated with an overall survival benefit at five years (4).

Colorectal carcinoma represents the third most common malignant tumor in both men and women in developed world and the third leading cause of cancer-related death (5). Despite the advances in surgical treatment and introduction of combined therapeutic modalities, 5 years survival rarely exceeds 60%, varying from 90% in localized disease to 11% in patients with spread to distant organs (6).

Current guidelines after apparently curative resection recommend surveillance with imaging tests and regular serum measurements of carcinoembryogenic antigen (CEA) (7). Despite widespread use of CEA as a marker of early relapse, studies have shown contradictory data, with a large number of false-positive results (8). Moreover, in practice, increased values of CEA signify recurrent disease and necessitate imaging diagnostic procedures, which may not be necessary (9).

Carcinoembryonic antigen (CEA) is a glycoprotein oncofetal antigen that many epithelial tumors express. While CEA is typically considered a tumor marker, levels may also be elevated in a variety of non-malignant conditions including pancreatitis, cigarette smoking, and inflammatory bowel disease. First described by Gold and Freedman in 1965, this relatively inexpensive blood test has been part of the majority of recommended surveillance strategies (10). Seventy percent of patients with colorectal cancer will have an elevation in their CEA level at diagnosis, making it a useful marker for cure and surveillance of disease after surgery (11). Despite this, some controversy still exists regarding its utility. Serum carcinoembryonic antigen (CEA) is a surrogate marker for recurrent colorectal cancer with a value of >5 ng/ml in patients with CRC after treatment suggests recurrent disease (12); however, insufficient sensitivity and specificity of CEA make it inadequate for surveillance (13).

Positron emission tomography with fluorodeoxyglucose (FDG-PET) provides information on the metabolic activity of a lesion, theoretically allowing better discrimination between the hypermetabolic tumor and postoperative changes (14).Fluorine-18-fluoro-deoxyglucose positron

emission tomography/computed tomography (18F-FDG PET/CT) is valuable in the detection of recurrent disease in patients after curative resection of colorectal carcinoma (15). However, Kishimoto stated that CT/PET is a sensitive method of detecting recurrent disease, but noted that its high cost made it a cost ineffective test for general use (16).

The aim of the present study was to evaluate the usefulness of dual assessment of FDG-PET and CEA in detecting recurrence of colorectal carcinoma in patients subsequent to colonic resection or rectal amputation.

MATERIAL AND METHOD

Subjects

One hundred sixty patients, 99 males and 61 females, the mean of their age was 55.76 ± 12.25 years with suspected recurrent colonrectal cancer (CRC) after previous colonic resection or rectal amputation for CRC were included in this prospective study from February 2011 to March 2015. The inclusion criteria were: histopathologically confirmed colorectal adenocarcinoma, curative resection of the primary tumor, at least 3 months before and availability for follow-up after 18F-FDG PET/CT and CEA for at least 12 months. The CEA levels were measured within the time of the FDG PET/CT study. The Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King Abdulaziz University, approved this study. All participants signed the consent form before sharing in the study.

Measurements

A. Fluorine-18-fluoro-deoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) measurements:

All participants were 4-6 hours fasting before they underwent 18F-FDG PET/CT examination on a 64-slice hybrid PET/CT scanner (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA). The serum blood glucose level was <7 mmol/l in all cases prior to the intravenous injection of 5.5MBq/kg of 18FFDG. Blood glucose level over 11mmol/L was considered as exclusion criteria on PET/CT examination. Following injection of 18F-FDG, patients rested in a quiet and darkened room for 60min, after which images of PET/CT were obtained. Low-dose non-enhanced CT scans (120kV with automatic, real-time dose-modulation amperage, slice thickness of 5mm, pitch of 1,5 and a rotation time of 0.5s) and 3-dimensional PET scans (6-7 fields of view, 3min/field) were acquired from the base of the skull to the mid-thigh. Non-corrected and attenuation-corrected CT, PET and fused PET/CT images were displayed for analysis on a Syngo Multimodality workplace (Siemens AG) (17).

B. Carcinoembryonic Antigen (CEA) measurements:

Blood samples were collected from the antecubital vein before and after treatment. Subjects had blood drawn at the same time in the morning on each occasion (between 8 and 10 AM). Subjects were lay supine for 10 min prior to the blood collection. 10 mL of blood was drawn into a tube containing 0.1 M sodium citrate. Blood was centrifuged at 2000 ×g for 10 min at 4 °C and stored at − 80 °C until analysis. Serum Albumin, Hematocrit, Urea, Electrolyte and Carcinoembryonic Antigen (CEA) assays were performed in a single laboratory with using the RIAMAT SR-300 kit (Stratec, Germany).

RESULTS

The demographic and baseline characteristics of patients included in this study revealed that the majority of participants were male patients (61.2%) and about 66.9% were below 55 years old, moreover few patients received

***Table 1**. Demographic and baseline characteristics of patients included in the study.*

Variable		Number	Percentage
Gender	Male	98	61.2%
	Female	62	38.8%
Age	Above 55 years	53	33.1%
	Below 55 years	107	66.9%
Site of primary tumor	Rectum	85	53.1%
	Colon	75	46.9%
Chemotherapy & radiotherapy	Preoperative	14	8.7%
	Postoperative	121	75.6%
	None	25	15.7%

***Table 2**. Final diagnosis of all patients according to the site of recurrence.*

Mode of recurrence	Number	Percentage
Intra-abdominal extra-hepatic recurrence	46	34.8%
Extra-abdominal/ hepatic recurrence	69	52.2%
Oher form of recurrence	17	13%

preoperative chemotherapy & radiotherapy (8.7%) and the majority of participants received postoperative chemotherapy & radiotherapy (75.6%) (Table 1).

All participants enrolled in our study were classified according to the site of recurrence, out of 160 patients after previous colonic resection or rectal amputation for CRC, 132 patients were confirmed by histopathology or 6 month clinical follow up had local recurrence or metastasis (47 patients were confirmed had Intra-abdominal extra-hepatic recurrence, 80 patients had extra-abdominal and/or hepatic recurrence, 30 patients had other form of recurrence (17 patients had metastasis at other sites as the neck, long bones, mediastinal lymph nodes and multiple metastases) (Table 2).

Concerning the PET/CT diagnosis of recurrence and metastasis in CRC patients included in the study. Out of 160 patients after CRC resection, 126 patients were diagnosed by PET/CT as true-positive cases (25.62% Stage II /53.13% and I Stage III/IV) and 34 patients as negative cases (21.25 %). The sensitivity of monitoring the recurrence and metastasis of patients with CRC by PET/CT was 95.45 % (126/132). However, the diagnostic value of CEA levels for recurrence and metastasis in CRC patients included in the study proved that 102 patients had increased value of CEA (63.8%) and 58 patients (36.2%) had normal CEA value. The sensitivity of the CEA levels for monitoring the recurrence of the patients with CRC was 77.27 % (102/132) (Table 3).

DISCUSSION

Colorectal cancer affects about 150,000 patients in the United States and is the cause of almost 50,000 deaths every year (18). Strict postoperative follow up is highly needed to limit cancer recurrence. Although the great advance in surgical resection, radiotherapy and chemotherapy of colon-rectal cancer, about one third of patients develop recurrence (19,20).

The main findings in the present study indicated that the sensitivity of monitoring the recurrence and metastasis of patients with CRC by PET/CT was 95.45 %. However, the sensitivity of the CEA levels for monitoring the recurrence of the patients with CRC was 77.27 % which means that the sensitivity of the 18F-FDG PET/CT scan is superior to CEA in detection of colorectal cancer recurrence and dual assessment is important in treatment planning, these results agreed with many previous studies.

Caglar and colleagues in their follow-up of 155 patients with colorectal cancer (CRC) (87 men, mean age: 61 years) remained for final analysis. Serum CEA and CA 19-9 had a sensitivity of 74 and 35 % for the detection recurrent CRC, respectively. The sensitivities of CT and FDG PET-CT were 79 and 92 % respectively (21). A retrospective study of Votrubova and colleagues for the detection of recurrence of colorectal cancer (CRCR) proved that FDG-PET/CT appears to be a very promising method for distinguishing a viable tumour from fibrous changes as the sensitivity, specificity and overall accuracy of F-fluorodeoxyglucose (FDG) PET/CT were 89%, 92%, and 90% correctly detecting 40 out of 45 patients with recurrent disease (22). Artiko etal. conducted a prosepective study included 75 patients with resected primary colorec-

***Table 3**. PET/CT and CEA diagnosis of recurrence and metastasis in CRC patients included in the study.*

Variable		Number	Percentage
18F-FDG PET/CT	Negative	34	21.25%
	Stage I/II	41	25.62%
	Stage III/IV	85	53.13%
CEA	Normal	58	36.2%
	Increased	102	63.8%

tal adenocarcinoma referred for 18F-FDG PET/CT for detection of recurrent disease 18FFDG PET/CT showed overall sensitivity, specificity and accuracy of 96.6%, 82.4% and 93.3%, respectively, moreover 18F-FDG PET/CT scan induced treatment changes in 30/75 patients, including 12/32 patients in which surgical treatment was previously planned, and progression free survival time was significantly longer in these patients (17). Maas etal. stated in his meta-analysis that PET/CT might be the modality of choice when evaluating patients with a (high) suspicion of recurrent disease, because of its best performance in patient based analyses and confident prediction of disease status and PET/CT shows the highest accuracy in the detection of recurrence (23). Finally, Zhang etal. in their meta-analysis about the diagnostic value of Positron emission tomography (PET) using fluor-18-deoxyglucose (FDG) in recurrent colorectal carcinoma and concluded that FDG-PET is valuable for the assessment of recurrent colorectal carcinoma, which are in accordance with our findings (24).

Tan and colleagues performed a quantitative meta-analysis of 20 studies including 4,285 patients examining the performance characteristics of CEA when used to detect CRC recurrence and found an overall sensitivity of 0.64 with a specificity of 0.90 (25). Also, Chen and colleagues investigated whether CEA elevation provided added value in the detection of postoperative colorectal cancer recurrence and found that 999 patients out of 4,841 patients had elevated CEA (defined at > 5 ng/ml) and recurrence, where about three-quarters of these patients had their recurrence detected via other means at the same time as the first CEA elevation so that they concluded that CEA lacks sufficient sensitivity and specificity to be used in detection of postoperative colorectal cancer recurrence (26). In a study by Metser and colleagues, recurrent disease was found in only 65% of patients with elevated CEA followed by multidetector CT (MDCT) and CT/PET for an average of 18 months after the CEA elevation (27). Moreover, certain tumors that expressed CEA at presentation undergo dedifferentiation and stop expressing CEA when they metastasize, rendering it useless as a surveillance tool in these cases, so that a more sensitive test is need for early detection of recurrence (28). Finally, within the limit of this study dual assessment with 18F-FDG PET/CT and CEA is recommended for detection of colorectal cancer recurrence.

Conclusion

The current study provides evidence that the sensitivity of the 18F-FDG PET/CT scan is superior to CEA in detection of colorectal cancer recurrence and dual assessment is important in treatment planning. In clinical practice, CEA in conjunction with 18F-FDG PET/CT are best to be used as evidence to determine tumor recurrence.

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