Open Access Maced J Med Sci **electronic publication ahead of print, published on July 27, 2019 as https://doi.org/10.3889/oamjms.2019.640**

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.640
eISSN: 1857-9655
Clinical Science

Reliability of Contrast CT and Positron Emission Tomography in Post-Surgical Colorectal Cancer and Its Association with Obesity

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Citation: El Sherity SY, Shalaby SA, Hassan NE, El-Masry SA, El-Banna RA. Reliability of Contrast CT and Positron Emission Tomography in Post-Surgical Colorectal Cancer and Its Association with Obesity. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.640

Keywords: Post-surgical; PET/CT and colorectal cancer

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Received: 25-Jun-2019; **Revised:** 06-Jul-2019; **Accepted:** 07-Jul-2019; **Online first:** 27-Jul-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Post-surgical recurrence of cancer colon occurs in one-third of patients within the first two years, so early detection is important. The assessment of the therapeutic response is important to change protocol strategy. Positron emission tomography/computed tomography PET/CT, a valuable tool gives both metabolic and anatomic information for whole-body regions. Obesity is an important risk factor for colorectal cancer.

AIM: To evaluate post-surgical and therapeutic colorectal cancer by PET/CT and study obesity association to its prognosis.

METHODS: This was a prospective study involved 93 patients with, post-surgical colorectal cancer examined by PET/CT, then follow up after 4-6 months.

RESULTS: There was a statistically significant difference between PET/CT and contrast CT. The sensitivity& the specificity were (96.4%-100% & 92.3%-98.2%) for PET/CT and (84.2%-90.2% & 76.5%-85.4%) for contrast CT respectively. Post-therapeutic follow up showed; progressive course (24.5%), stationary course (26.4%), partial regression (28.3%) and complete regression course (20.8%). Obesity is a risk factor for progression with highly statistically significant to treatment response. Obese patients had a progressive or stationary course of the disease. Also, there was a highly statistically significant association between total abdominal fat & visceral abdominal fat areas with good response of treatment.

CONCLUSION: PET/CT is the most appropriate imaging technique to detect any recurrence or metastases in post-surgical colorectal cancer with high sensitivity and specificity comparing to CT. Obesity is a predictor risk factor for prognosis of the disease, as generally and abdominally (total & visceral fat) had an association with therapeutic response.

Introduction

Worldwide more than one million people get colorectal cancer yearly [1]. Also, it is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018, according to GLOBOCAN database. The highest incidence rates are in Europe, North America, Australia, and New Zealand, while the lowest rates are in South-Central Asia and Africa [2]. Colorectal cancer is the 7th commonest cancer in Egypt; it represents 3.5% of male cancers and 3% of female cancers [3]. The estimated numbers of colon cancer patients were more than three thousand in 2015 [3].

Post-surgical recurrence of cancer colon occurs within the first two years. It can recur loco-regionally or at distant sites [4]. In therapy, resection of one metastasis is associated with good survival rate while multifocal metastatic lesions give a less favourable prognosis [5]. Also, the assessment of the therapeutic response (chemo-radiotherapy) is important for change protocol strategy of ineffective and toxic chemotherapy [6]. So, early detection helps design the clinical therapeutic guidelines; secondary operation, radiotherapy or chemotherapy.

Serum carcinoembryonic antigen (CEA) and contrast computed tomography (CT) are conventional methods. As serum CEA levels are used for recurrence monitoring, with its high-level imaging modality will be necessary to localise the site of recurrence and metastases [7]. Regarding changes of

anatomical structures and fibrous tissue in the operative region, contrast CT is likely unable to differentiate postsurgical changes from recurrence and may miss metastatic deposits. While the functional imaging; Fluorine-18 fluoro-D-glucose positron emission tomography / computed tomography (18F-FDG PET/CT) scan can be greatly used to recognise the metabolic characteristics of the lesions and detect any active cells [8]. The integrated PET/CT gives both metabolic and anatomic information with a single device at one diagnostic session for the whole-body regions to detect any recurrence and metastases [9].

Several studies reported that obesity is an important risk factor for colorectal cancer [10], [11], [12], [13], while Scarpa et al., showed the role of obesity in postoperative recurrence and multifocal disease [14].

The aims of this study; to evaluate post-surgical and therapeutic colorectal cancer by PET/CT for proper management, also predict the effect of obesity as a risk factor in prognosis among a sample of Egyptian patients.

Sample size estimation

The sample size was calculated using PASS 11 (USA), regarding the proportional of PET/CT sensitivity at the previous study; 90 subjects were adequate with power 90.0%, α = 0.05, and B = 0.1

Patients and Methods

Design: A prospective study

Ethics: This study was approved by the research ethics committee, faculty of medicine, Helwan University (FMHU 1-2019) and informed written consent were signed by each patient.

Participants: Ninety-four Egyptian's patients with post-surgical cancer colon, examined for follow up after 4-6 months by PET/CT, both genders were included in this study (55 males and 39 females); their ages were ranged from 38 to 75 years. They were referred from clinical oncology and surgery departments due to elevated CEA or follow up to assess the effect of treatment. The inclusion criteria: pathologically proven colorectal carcinoma and underwent appropriate therapy for 4-6 months. Exclusion criteria included those who had a bad general condition, impaired renal function, allergy to intravenous contrast material and a blood glucose level > 200 mg/dl at the time of the study.

The duration of the study: January 2019- June 2019.

Location: Misr Radiology center (MRC), Cairo, Egypt.

Methods

Patient preparation: allow low carbohydrate and high protein diets with liquids (24 hours before), then fasting 6 hours before the examination.

The day of examination: complete history was taken and indication (High tumour marker CEA and previous PET/CT scan for follow up), then measurements were taken before starting the examination: Fasting blood sugar, body height and weight (using a Seca scale balance and anthropometer with light clothes and no shoes, the measure was taken to nearest 0.1 cm and 0.01 kg respectively) [15]. The Body mass index (BMI) was calculated as; the weight (kg)/ height (m^2) and classified into; (18.5 ≥ normal weight < 25), (≥ 25 overweight < 30) and obese (≥ 30) [16].

Examinations: Intravenous injection of 5 – 10 mCi as an average dose of ^{18}F-FDG (0.1 mCi/Kg) one hour before starting the scan. Each patient was examined by PET/CT using Phillips Ingenuity TF, 128 slice machines (Cleveland, OH, USA) as the following A low-dose non-contrast CT for attenuation correction followed by PET scan from the skull to the mid-thigh, then a diagnostic post-contrast CT using nonionic contrast medium. Those PET images were assessed by both visually & semi-quantitatively for the regions with pathologic tracer accumulation using maximum standardized uptake value (SUV_{max}); loco-regional lesion (recurrent) was identified by presence of metabolically active tumour tissue with high FDG accumulation and correlated this activity to its anatomical site in the combined PET/CT images, the lymph nodes and distant metastases (lung, liver, bone, brain, and others) were evaluated as well. The comparison between the recent scan and the previous one in follow up cases was made to evaluate the response of treatment (Fig. 1).

The assessment of therapeutic response evaluated by PET/CT according to RECIST criteria [17]:

- Complete response (CR): The disappearance of FDG uptake at the target tumour lesion.no new FDG avid lesion.

- Partial response (PR): reduction at least a 30% in target measurable tumour FDG uptake, taking the baseline lesion as a reference.

- Progressive disease (PD): at least a 25% increase in tumour SUVmax peak uptake, taking a reference the baseline lesion from starting of treatment or an appearance of a new lesion or more.

- Stationary disease (SD): no sufficient

changes, almost same as reference baseline lesion from starting of treatment; less than 25% increase (not PD) and 30% decrease (not PR). No new lesion.

Regarding abdominal fat assessment, no extra-scan was required, the analysis was processed by special software at an advanced workstation (AW Volumeshare2- version 4.4 Software), assessed total, visceral and subcutaneous abdominal fat compartments at the L4-L5 level by drawing then a calculation of area was done.

Statistical Analysis

SPSS version 22 software was used to analyse the data; mean ± standard deviations (SD) for parametric data, numbers (percentage) for the frequency distribution of non-parametric data, crosstabs for sensitivity and specificity, Chi-square, Pearson´s correlation test, and odds ratio. A significance was set at P = 0.05

Results

This study included 94 patients: 55 male (58.5%) and 39 female (41.5%), their age ranged from 38 to 75 years (mean ± SD: 58.3 ± 4.1 years), weight; 61-109 kg (90.9 ± 5.8 kg), height; 153-169 cm (162.8 ± 3.7 cm), BMI; 22.6-39.8 kg/m2 (34.4 ± 5.4 kg/m2) and fasting blood sugar; 70-197 mg/dl (101.2 ± 2.4 mg/dl). Regarding BMI; 31 (33%) were of normal weight (20 males and 11 females), 12 (12.8 %) were overweight (7 males and 5 females) and 51 (54.3%) were obese (28 males and 23 females), then classified into two groups; the first one included normal weight patients and the second one included both; overweight & obese to involve 63 patients (67%)(35 males and 28 females).

Regarding indications; 41 patients underwent PET-CT post-surgical, while 53 patients follow up post-therapeutic (chemo and radiotherapy) to assess the response of treatment, as well, 62 patients (66%) had elevated tumour marker CEA, and 32 had a negative marker (34%). The CEA was (0.9-116 ng/ml).

The frequency distribution of local recurrence lesions and metastatic deposits detected by contrast CT and PET/CT imaging for a total of 94 patients (Table 1), revealed; lymph nodes metastasis were the most frequent site (36.2% and 46.8%) for CT and PET/CT respectively followed by local recurrence & hepatic deposits (25.5%) by CT, while local recurrence represents (34%) by PET/CT then peritoneal deposits (18.1% and 28.7%), pulmonary deposits (14.9% and 17%) and osseous deposits (11.7% and 23.4%) by CT and PET/CT respectively. Although PET/CT gives additional information about active tumour cell by measuring its avidity to ^{18}F-FDG uptake and measuring the maximum standardised uptake values (SUVmax). Its ranges were; 9-29.4 (mean 17.2 ± 5.4 SD) for local recurrence, 4.5-29.7 (mean 13.3 ± 6.9 SD) for LN metastasis, 5.7-23 (mean 10.7 ± 5.2SD) for hepatic deposits, 7.7-15.3 (mean 11.9 ± 2.5SD) for peritoneal deposits, 7.7-15.3 (mean 10.8 ± 6.1SD) for pulmonary deposits and 4.5-11.8 (mean 9.1 ± 1.7SD) for osseous deposits.

Table 1: Frequency distribution of local recurrence and metastatic lesions detected by Contrast CT and PET/CT

	Contrast CT	PET/CT		p-value
	No. &frequency	No. &frequency	SUVmax value Mean ± SD	
Local Recurrence	24 (25.5%)	32 (34%)	17.2 ± 5.4	0.000
LN Metastasis	34 (36.2%)	44 (46.8%)	13.3 ± 6.9	0.000
Peritoneal Deposits	17 (18.1%)	27 (28.7%)	11.9 ± 2.5	0.000
Pulmonary Deposits	14 (14.9%)	16 (17%)	10.8 ± 6.1	0.000
Hepatic Deposits	24 (25.5%)	24 (25.5%)	10.7 ± 5.2	0.000
Osseous Deposits	11 (11.7%)	22 (23.4%)	9.1 ± 1.7	0.000

There were statistically significant differences between contrast CT and PET/CT (P = 0.000); 8 cases of local recurrence were missed by CT and detected by PET/CT, 10 cases of metastatic LNs and peritoneal deposits detected only PET/CT may be due smaller in size to localize by CT, as well extra 11 osseous lesions were detected by PET/CT (bone marrow affection) compared to CT, while two pulmonary nodules couldn't be detected by CT as it surrounded by consolidation area and pleural effusion.

Then, the sensitivity and the specificity of PET/CT was done related to elevated tumour markers, measuring (96.4%-100% & 92.3%-98.2% respectively) compared to contrast CT (84.2%-90.2% & 76.5%-85.4% respectively), the positive and negative predictive values were 94% and 84% for PET/CT, and 81% and 76.3% for CT.

Regarding obesity, all patients were classified according to BMI categories; normal weight and (overweight & obese) with PET/CT findings to detect frequency of local recurrence and metastatic deposits on each group (Table 2), There was an insignificantly statistical association between obesity and PET/CT findings (no significant differences regarding sex), however, the most frequent local recurrence and metastatic deposits were detected at obese patients (71.9%-81.2%).

Table 2: Comparison between BMI categories (normal weight and overweight &obese) with PET/CT findings

PET/CT	Normal Weight No.&%	Overweight & Obese No.&%	p-value
Local Recurrence	9 (28.1%)	23 (71.9%)	0.312
LN Metastasis	12 (27.3%)	32 (72.7%)	0.074
Peritoneal Deposits	9 (33.3%)	18 (66.7%)	0.865
Pulmonary Deposits	3 (18.8%)	13 (81.2%)	0.410
Hepatic Deposits	5 (20.8%)	19 (79.2%)	0.314
Osseous Deposits	6 (27.3%)	16 (72.7%)	0.786

Then frequency distribution between obesity and response of treatment (post-therapeutic follow up) was done (Table 3). Fifty-three patients were classified; normal weight and (overweight and obese),

The assessment depends on the avidity of the lesion to 18 F-FDG uptakes, quantitative analysis by measuring (SUVmax) value and compared with the previously PET/CT scan from 4-6 months. Thirteen patients (24.5%) had a progressive course of the disease, all were obese, while good response of treatment was recorded at 40 patients (75.5%) as the following; stationary course (26.4%) (57.1% of them were obese), partial regression (28.3%) (60.0% of them were within normal weight) and complete regression course (20.8%) (54.5% of them were within normal weight).

Table 3: Frequency distribution between obesity and response of treatment (Post-therapeutic follow up)

	Total No. &Frequency	Non obese No.&%	Obese No.&%
Progression	13 (24.5%)	0 (42.9%)	13 (100%)
Good response to treatment:	40	20	20
Stationary	14 (26.4%)	6 (42.9%)	8 (57.1%)
Partial Regression	15 (28.3%)	9 (60.0%)	6 (40.0%)
Complete Regression	11 (20.8%)	6 (54.5%)	5 (45.5%)

The odds ratio was done to know the effect of obesity as a risk factor on the progression of cancer colon (Table 4). There was highly statistical significance with a response of treatment (p = 0.001, odd value > 2 and CI = 1.46-2.72), also hepatic and pulmonary deposits had high precision by odd value and 95% confidence interval (CI), followed by LN metastasis and local recurrence, while peritoneal and osseous deposits had a low association with obesity.

Table 4: Odds ratio to predict if obesity a risk factor for the progression of the cancer colon

	Odd Value	95% Confidence Interval	P-Value
Response of treatment	2.0	1.46-2.72	0.001**
Local Recurrence	1.4	0.555- 3.56	0.472
LN Metastasis	1.5	0.622-3.61	0.365
Peritoneal Deposits	0.9	0.352-2.366	0.851
Pulmonary Deposits	2.3	0.601-8.755	0.215
Hepatic Deposits	2.1	0.703-6.341	0.177
Osseous Deposits	1.3	0.463-3.843	0.594

** Highly Significant at P ≤ 0.001.

For more specification of obesity, the abdominal obesity assessed by CT and measured; total abdominal fat, subcutaneous fat and visceral abdominal fat areas (cm^2), their range (100.4-998.7 cm^2), (80-789.6 cm^2) and (16.27-267 cm^2) respectively. Then a comparison between abdominal obesity and response of treatment (post-therapeutic follow up) regarding sex was made (Table 5).

Table 5: Comparison between abdominal obesity and the response of treatment (Post-therapeutic follow up) regarding sex

	Sex	Progressive course No. (13)	Good response to treatment No. (40)	p-value
		Mean ± SD	Mean ± SD	
Total abdominal fat (cm^2)	Male	837.72 ± 60.5	618.20 ± 25.5	0.008
	Female	834.74 ±10.2	463.04 ± 24.9	0.054
Subcutaneous abdominal fat (cm^2)	Male	412.11 ± 36.0	349.16 ± 44.8	0.203
	Female	203.54 ± 53.5	334.70 ± 45.5	0.370
Visceral abdominal fat (cm^2)	Male	217.50 ± 38.3	138.02 ± 35.7	0.000
	Female	229.50 ± 53.5	100.75 ± 42.5	0.004

It was revealed that; 31 males and 9 females had a good response of treatment, while 11 males and 2 females had progressive course after treatment. There was a highly statistically significant difference between total abdominal fat & visceral abdominal fat areas with good response of treatment at both sexes (P ≤ 0.001). However, no statistically significant difference was detected with a subcutaneous fat area.

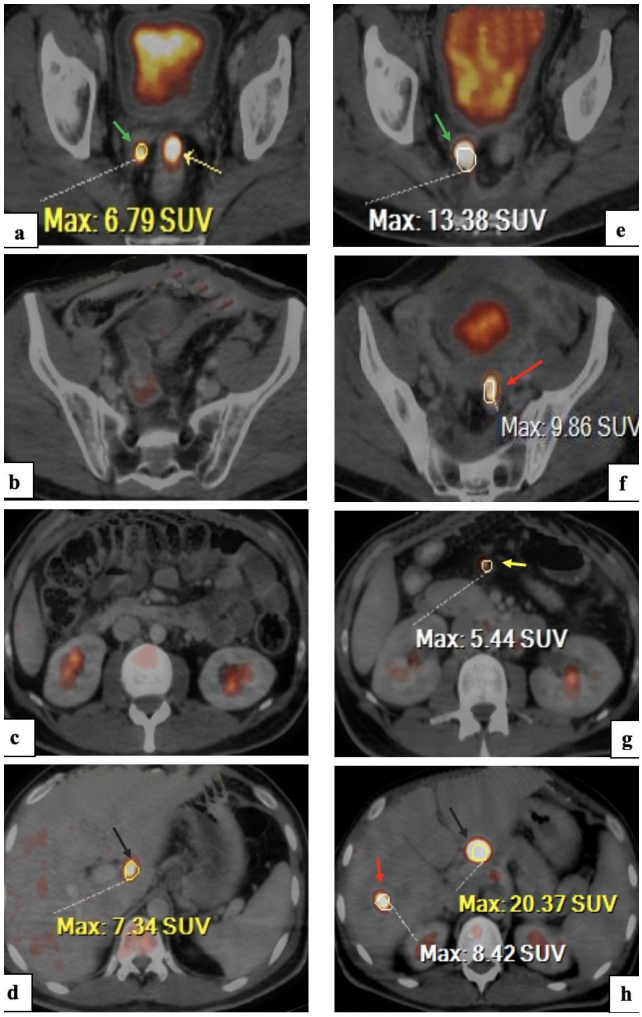

Figure 2: A 72-years old obese male patient, referred after resection of the recto-sigmoid mass and chemo-radiotherapy for follow up. Axial PET/CT images for two examinations; the first (a-d images) and the second examination (e, f, g, h images) after 4 months of treatment for comparison revealed; (a and e) progression of hyper-metabolic peri-rectal soft tissue nodule achieving 13.38 SUVmax (6.79 SUVmax previously) (green arrow), while another lesion (yellow arrow image a) can't be detected in newly one (b and f) a small active hypermetabolic lesion (recurrent) is seen at the distal sigmoid colon, achieving 9.86 SUVmax (red arrow image f) (c and g) Newly developed a small hyper-metabolic peritoneal nodule is noted achieving 5.44 SUVmax (yellow arrow image g) (d and h). Metabolically and morphologically progression of porta-hepatis lymph node, achieves 20.37 SUVmax (7.34 SUVmax previously) (back arrow) and newly developed active right hepatic lobe focal lesion is seen (segment VI) achieves 8.42 SUVmax (red arrow)

Discussion

The most serious problem of colorectal cancer is a recurrence, as it represents around 10% -

50% within 5 years after the surgery in the form of local or distant. So, the key to diminishing postoperative recurrence is early detection for fast proper management to improve the survive [9].

Postoperative monitoring was done by CEA serum level when elevated suspected of recurrence and imaging modality is necessary to detect any metastasis [18]. Contrast CT could be detected only sizable morphological changes, however, its inability to discriminate inflammatory lesions from recurrence or metastases [7], while ^{18}F-FDG PET/CT shows early metabolic changes to detect any recurrence or metastases for choosing an adequate plan of therapy [8].

Several studies and meta-analysis studies reported a strong positive association between obesity and colorectal cancer. It estimated 30%-50% of new diagnosed colorectal cancer cases [14, [19], [20], [21]. Also, obesity had an effective role in recurrence and prognosis of treatment, as those patients were obese had a higher incidence of recurrence than those had normal or over-weight [13]. Obesity was assessed by BMI, while abdominal obesity was evaluated by CT scan cut at L4 – L5 level [22].

In this Egyptian study, the first purpose was evaluating the role of PET/CT in post-surgical cancer colon comparing to contrast CT, revealed that sensitivity of CT was 84.2%-90.2% and for PET/CT was 96.4%-100%, whereas the specificity of CT was 76.5%-85.4% and for PET/CT was 92.3%-98.2%. These were in agreement with the previous studies; that had approved PET/CT was the technique of choice for postoperative assessment of colorectal cancer to detect recurrence with sensitivity (93%-100%) and specificity (74%-96%) [5], [6]. While, Stuckle et al., reported the sensitivity of CT was 38% – 82% in the detection of the recurrence [23].

In this study, more lesions were detected by PET/CT compared to CT, in spite of the same number of hepatic and almost pulmonary deposits were found in both imaging modalities. This, in agreement with Choi et al. as well had added abdominal LN [24].

Additionally, lymph nodes were the most frequent site of recurrence (46.8%) in the current study by PET/CT, followed by local recurrence (34%), peritoneal deposits (28.7%), hepatic deposits (25.5%), osseous deposits (23.4%) and pulmonary deposits (17%).

Many studies reported that lymph nodes were the most frequent site of recurrence [25], [26]. However, Owen et al. found the liver metastasis was the most frequent site (50%) [27] and Chiewvit et al., reported, the pulmonary metastatic was the second site [28]. Regarding osseous lesions more lesions detected by PET/CT due to bone marrow affection, this is by Bar-Shalom et al., study, as no corresponding CT findings (osteolytic lesions or destruction of bone) at the same detected site by PET/CT [29].

The second purpose of this research was to assess the association between obesity and colorectal cancer recurrence. Our findings revealed that the most frequent local recurrence and metastatic deposits were detected at obese patients (71.9%-81.2%). Several studies concluded the association between obesity and colorectal cancer, as well obese patients had higher recurrence and mortality rates than normal and overweight patients [14], [30], [31], [32], the incidence of obese patients had colorectal cancer was 11.9%-40% in Italian study [33]. The commonest mechanism could be clarified this association; effect of high leptin level at obese persons, which induce pre-neoplastic epithelial cells of the colon [34].

Our results regarding post-therapeutic follow up and prognosis of the disease showed that obesity was highly statistically significant with response of treatment ($p = 0.001$, odds value > 2 and CI = 1.46-2.72), as obese patients had progressive or stationary course (100% and 57.1% respectively), while normal-weight patients had partial and complete regression course (60.0% and 54.5% respectively). Also, there was a highly statistically significant difference between total abdominal fat & visceral abdominal fat areas with good response of treatment at both sexes. This agreement with Jochem and Leitzmann, they found general obesity (BMI) and abdominal obesity had increased risk of colorectal cancer in both sexes [32]. Increased visceral fat area, not subcutaneous or total body fat, was established as the metabolic risk factors for colon cancer, those patients had 1.5 times of the visceral fat area compared to patients without that [35].

Finally, this research has an important recommendation to add at the therapeutic strategy plan of colorectal cancer; reduce body weight and preserve it within normal to improve the response of the treatment.

In conclusion, positron Emission Tomography (PET/CT) is the most appropriate imaging technique to detect any recurrence or metastases in post-surgical& therapeutic follow up colorectal cancer patients with high sensitivity and specificity compared to computed tomography (CT). General obesity is a predictor risk factor for prognosis of the disease, although abdominal obesity (total & visceral fat) had an association with a therapeutic response; as the progressive and stationary courses of the disease were noticed at obese patients with high visceral and total abdominal fat.

Acknowledgements

Authors are grateful to all participated in this study, patients and staff members of the Misr

radiology centre (MRC), Cairo, Egypt.

Author Contribution

Safenaz Y. El Sherity (corresponding author): designed the study, statistical analysis, interpretation of the data and wrote the manuscript. Shymaa A. Shalaby: collected the data and shared in manuscript writing. Nayera E. Hassan, Sahar A. El-Masry, and Rokia A. El-Banna: gave conceptual advice and manipulation of the data. All authors share in references collection, drafting the article and approval the final version.

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