ROLE OF FDG PET-CT IN COMPARISON WITH ENHANCED CT IN DETECTION OF POST THERAPEUTIC COLORECTAL CANCER RECURRENCE AND METASTASIS

INTRODUCTION
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Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidence. It is the third most common cancer worldwide and the fourth most common cause of death. It affects men and women almost equally (Fatima and Robin, 2009).

Despite optimal primary treatment, with adequate surgery with or without adjuvant chemotherapy, 30%–50% of patients with colon cancer will relapse and die of their disease. The principal aim of follow-up programmes after curative resection of colorectal cancer is to improve survival (Gan et al., 2007).

Early detection of recurrence is clinically important and can improve the prognosis and survival of patients with cancer. CT is considered the primary method of investigation because of its low cost, widespread availability, and high-resolution of anatomic details, but may under-estimate the actual tumor burden by overlooking small tumor clusters in areas of distorted anatomy after treatment. (Israel and Kuten, 2007).

Cancer-related metabolic abnormalities usually precede structural changes and are readily detected by PET. PET is a highly sensitive imaging test for the detection of occult recurrences, such as those seen in colorectal cancer (Israel et al., 2011).

Accurate imaging of patients with possible recurrent colorectal cancer (CRC) is vital, as it is now clear that curative surgery is still possible for a proportion of patients with metastatic disease. Follow-up is usually performed with carcinoembryonic antigen (CEA) level, computerized tomography (CT) and other conventional imaging techniques, but in the last few years, functional imaging using integrated positron emission tomography and CT (PET/CT) is being used increasingly to identify recurrent disease (Mittal et al., 2011).

AIM OF THE WORK
The goal of this study is to elucidate the role of 18F-FDG PET-CT in comparison with enhanced CT for detection of post therapeutic colo-rectal cancer recurrence and metastasis

Review of literature
COLORECTAL ANATOMY
The large intestine is a long muscular tube which starts from the caecum down to the rectum with approximately 1.5 m in length. The colon has three longitudinal muscle layers (taenia coli) that converge on the appendix proximally and the rectum distally, both of which have a complete muscular coat. The taenia coli are about 30 cm shorter than the colon, giving sacculations (haustra) (Khan, 2012).

Gross anatomy:
Fig.1: Anatomy and relations of colonic segments
(Quoted from Bharwani and Reznek, 2011).
The Cecum
Fig.2: The extension and relations of the cecum (Quoted from Netter, 2014)
It is an intraperitoneal blind ended “pouch-like” structure situated in the right iliac fossa bounded to the abdominal wall by the cecal peritoneal folds. The cecum measures about 7.5 cm and connects the ileum to the large intestine by an invagination known as the ileocecal valve. The vermiform appendix arises from the posteromedial aspect of cecum about 3.5 cm from the ileocecal valve (Netter, 2014).
The ileum ends in the posteromedial aspect of the cecum. The superior and inferior ileocecal ligaments give support to the ileum and, in addition to mesentery of the appendix, they form three pericecal fossae (superior ileocecal, inferior ileocecal and retrocecal) (Jorge and Habr-Gama, 2011).
The Ascending Colon
It is a retroperitoneal colonic segment which appears on the right side of the posterior abdominal wall between the cecum and the hepatic flexure. The hepatic flexure appears as curvature just below the liver till it reaches the transverse colon (Netter, 2014).
Fig.3: (a) the extension of the ascending colon (green coded) between the cecum and the hepatic flexure (b) the relation of the ascending colon (Quoted from Netter 2014).
Its length is approximately 15 cm long. It lies lateral to the psoas muscle and anterior to the iliacus, the quadratus lumborum and the lower pole of the right kidney. It is covered with peritoneum anteriorly and on
both sides. Jackson’s membrane is an attachment between the right abdominal wall and the anterior aspect of the ascending colon. The hepatic flexure is attached to the nephrocolic ligament and lies immediately anterior to the lower part of the right kidney and also the descending duodenum (Jorge and Habr-Gama, 2011).

The Transverse Colon
It is an intraperitoneal colonic part which appears within the peritoneum sheaths and it starts from the hepatic flexure to the splenic flexure. It is the largest segment of the large intestine and the most mobile, despite of its attachment to the posterior abdominal wall by its own mesentery (Netter, 2014). Fig.4: the extension of the transverse colon (green coded) between both hepatic and splenic flexure (Quoted from Netter, 2014).

The transverse colon is approximately 45 cm in length. It traverses the abdomen immediately below to the greater curvature of the stomach. It appears fixed at each flexure and mobile at its middle portion which may reach the hypogastrium. The splenic flexure is situated below the lower angle of the spleen and is attached to the diaphragm by the phrenocolic ligament forming a shelf giving support the spleen. It is more acute, higher, and more deeply situated when compared with the hepatic flexure (Jorge and Habr-Gama, 2011).

Fig.5: Sagittal right paramedian diagram showing transverse mesocolon and its extension (Quoted from Bharwani and Reznek, 2011).

Transverse mesocolon is formed of two layers and connects the transverse colon to the posterior abdominal wall, passing anterior to the anterior surface of the head and the anterior border of the body of the pancreas. The upper layer is adherent to and separable from the greater omentum. It also carries the middle colic vessels, autonomic nerves, and lymphatics which supply the transverse colon and become in confluence with the root of the small bowel mesentery near the uncinate process of the pancreas (Bharwani and Reznek, 2011).

The Descending Colon
Fig.6: the extension of the descending colon (green coded) between the splenic and sigmoid colon (Quoted from Netter, 2014).

It is a retroperitoneal colonic part in posterior left side extending from the splenic curvature to the sigmoid colon (Netter, 2014).

Its length is approximately 25 cm, almost equal to the ascending colon. The descending colon is covered by peritoneum on its anterior and lateral walls. Posteriorly, it rests directly against the quadratus lumborum, transversus abdominis muscles and the left kidney. The descending colon is narrower and more dorsally situated compared to the ascending colon (Jorge and Habr-Gama, 2011).

The Sigmoid Colon
Fig.7: (a) the extension of the sigmoid colon between the descending colon and rectum (green coded), (b) the sigmoid mesocolon and the inter sigmoid recess (Quoted from Netter, 2014).

It is intraperitoneal in location and suspended by the sigmoid mesocolon giving an S-shaped loop, connecting the descending colon and the rectum (Netter, 2014).

The sigmoid colon is mobile with length about 35 to 40cm, showing great variations in length and configuration. Mesosigmoid is attached to the pelvic walls, giving inverted V shape. Its apex is anterior to the left ureter and left common iliac vessels, resting in a recess known as the inter sigmoid recess. The left ureter is situated underneath this recess where it is crossed by the left colic, sigmoid vessels and spermatic cord (Jorge and Habr-Gama, 2011).

The Rectum and Anal Canal
The rectum lies in the sacral concavity; it starts at to level of the 3rd sacral vertebra and ends 2–3 cm from the tip of the coccyx where it angulates backward to pass through the levators then continues as the anal. The rectum measuring about 12–15 cm in length. The upper two third of the rectum is covered by peritoneum while its lower third is extraperitoneal. The peritoneal reflection occurs about 8cm from the anal verge in males and 6cm in females. In women, the rectum is posterior to the cervix and posterior vaginal wall while in men, it is posterior to the bladder, seminal vesicles, vas deferens, and prostate. Posterior to the rectum lie the sacral vessels and the roots of the sacral nerve plexus (Jorge and Habr-Gama, 2011).

Fig.8: (a) Rectal relations in both female and (b) male pelvis (Quoted from Netter, 2014).

Lymphatic drainage:
• Ascending colon and caecum drain via epiploic nodes (lie along the ascending colon) and via paracolic nodes along the mesenteric arteries to the superior mesenteric group of nodes.
• Transverse colon drains via superior mesenteric and inferior mesenteric group of nodes along the middle and left colic vessels. The inferior mesenteric nodes lie around the inferior mesenteric origin.
• Descending colon drains via inferior mesenteric nodes along the left colic and sigmoid vessels.
• Rectum drains via mesorectal lymph nodes:
  Upper third drains to nodes along the IMV
  Mid and lower rectum drain to internal iliac nodes. (Khan, 2012).
Fig.9: Diagram of the abdominal LNs: right colic (dark green), superior mesenteric (aqua), middle colic (light green), Para colic (red), left colic (pink), sigmoid (purple) and inferior mesenteric (orange) (Quoted from Moron and Szklaruk, 2007).
Arterial supply:
The caecum, ascending colon and proximal two-thirds of the transverse colon receive a blood supply from the superior mesenteric artery by the following branches:
• Ileocolic artery supplies the caecum and proximal part of the ascending colon.
• Right colic artery supplies distal ascending colon.
• Middle colic artery supplies proximal two-thirds of the transverse colon.
The remaining distal transverse colon, descending colon, sigmoid and the upper two-third of the rectum receive blood supply from the inferior mesenteric artery through following branches:
• Ascending branch of the left colic (marginal artery) supplies the distal third of the transverse colon.
• Descending branch of the left colic supplies proximal part of the descending colon.
• Sigmoid arteries supply sigmoid colon and distal descending colon.
• Superior rectal artery supplies proximal two-thirds of the rectum.
The distal rectum receives blood supply from the internal iliac artery (anterior division) by the following branches:
• Middle rectal artery.
• Terminal branch of the internal pudendal artery. (Khan, 2012).
Fig.10: Distal aorta and its branches supplying the colon.
(Quoted from Netter,2014)
Venous drainage:
Drainage is according to corresponding arteries.
• Superior mesenteric vein tributaries drain to the portal vein.
• Inferior mesenteric vein tributaries drain to the splenic vein.
• Mid and lower rectum drain to the internal iliac veins via the middle rectal and internal pudendal vein. (Khan, 2012).
Fig.11: Veins draining different colonic segments
(Quoted from Netter,2014).
Radiological Anatomy of The Colon:
The following are axial CT images showing colonic segments and lymph node stations:
Imaging of the Colonic Arterial Supply:
Fig.20: CT angiography with volume rendered reconstructions of the abdominal aorta and its branches (Quoted from Khan, 2012).
Imaging of the Colonic Venous drainage:
Fig.21: CT venogram with maximum intensity projection (MIP) of the visceral veins (Quoted from Khan, 2012).
EPIDEMIOLOGY
Colorectal adenocarcinoma is the third most common cancer. Over 90% of cases occur after the age of 50 years. Most of the cases arise from adenomatous polyps. Personal or family history of colorectal cancer, polyps or inflammatory bowel disease, low fiber diet / high fat and animal protein content, obesity and asbestos workers are contributing risk factors. The treatment for colorectal cancer is surgical resection, usually, radiation precede therapy and sometimes chemotherapy. The prognosis depends on the tumor stage. The 5-year survival for stage I colorectal cancer is over 90% and is 0% for stage IV rectal cancer (Moron
About 65% of colon cancers discovered distal to the splenic flexure and potentially detectable by sigmoidoscopy, while the remaining 35% are not easily detectable by flexible sigmoidoscopy (Cappell, 2005).

Early carcinomas which appear limited to the submucosa are mostly in the following morphologic appearance:
- polypoid
- pedunculated
- semi pedunculated
- sessile (broad base)
- flat lesions
- flat with slight elevation or slight central depression

Advanced carcinomas which appear extending beyond the submucosa are four types:
- Polypoid
- Ulcerated showing sharply demarcated margins
- Ulcerated showing no definite borders
- Diffusely infiltrating (Wittekind ,2007)

Pathology
Histologic type of colorectal cancer:
According to the WHO classification, the histologic types of colorectal cancer include:
- Adenocarcinoma
- Signet-ring cell carcinoma
- Mucinous adenocarcinoma
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Small cell carcinoma
- Medullary carcinoma
- Undifferentiated carcinoma (Lanza et al ., 2011).

Nearly 85% of colorectal carcinomas are usually adenocarcinomas, and 10 to 15% are mucinous adenocarcinomas. The remaining tumor histologic types (such as clear cell carcinoma, sarcomatoid carcinoma, and choriocarcinoma) are extremely rare (Redston ,2009).

Recently discovered subtypes of large bowel adenocarcinoma named micropapillary, serrated, and villous adenocarcinoma (Lanza et al ., 2011).

Adenocarcinomas and mucinous tumors have a tendency to send peritoneal deposits and extensive lymph node metastases as well as invading the adjacent organs (Redston, 2009).

Signet-ring carcinoma is about 1% of all colorectal carcinomas and frequently occurs in individuals younger than 50 years and in patients complaining from ulcerative colitis. Signet-ring cell carcinomas are diagnosed at advanced stage giving a worse prognosis than adenocarcinomas. Peritoneal deposits develop in the majority of patients who die of the disease (Lanza et al., 2011).

Small cell carcinomas are histologically similar to the same histologic type arising in the lungs. They often appear to develop within an adenoma and usually secrete neuroendocrine markers. Distant metastases at diagnosis and the very poor prognosis are common features.

Medullary carcinomas are characterized by a solid growth pattern and marked intratumoral and peritumoral lymphocytic infiltration.

Undifferentiated carcinomas show no morphological evidence of differentiation beyond that of an epithelial tumor, with quite an unpredictable clinical outcome (Lanza et al., 2011).

Histological grading:
Choice of treatment and prognosis dependes on the grades and aggressiveness. Union of international Cancer Control (UICC ) distinguishes four grades :
Grade I: well differentiated tumor
Grade II: moderately differentiated tumor
Grade III: poorly differentiated tumor
Grade IV: undifferentiated tumor
The WHO classifies colorectal cancer into:
Low-grade, combining Grade I and II
High-grade, combining Grade III and IV (Wittekind, 2007).

Staging:
The UICC TNM / pTNM Classification of Tumors of the Colon and Rectum (Lanza et al., 2011).
Primary tumor (pT)
pTX: – Cannot be evaluated
pT0: – No evidence of primary tumor
pTis: – Carcinoma in situ, intra epithelial or invasion of lamina propria
pT1: Tumor extends to submucosa
pT2: Tumor extends to muscularis propria
pT3: Tumor extends through the muscularis propria reaching pericolorectal tissues
pT4a: Tumor invades the visceral peritoneum
pT4b: Tumor directly extends to other organs or structures
Regional lymph nodes (pN)
pNX: Cannot be evaluated
pN0: No regional lymph node metastasis
pN1a: Metastasis are found in 1 regional lymph node
pN1b: Metastasis are found in 2 to 3 regional lymph nodes
pN1c: Tumor is found in the subserosa or non peritonealized pericolic or perirectal tissues without regional lymph node metastasis.
pN2a: Metastasis are found in 4 to 6 regional lymph nodes.
pN2b: Metastasis are found in 7 or more regional lymph nodes.
Distant metastasis (pM)
pM1a: Metastasis to single site/organ (e.g., liver, lung, ovary, non regional lymph node).
pM1b: Metastasis to more than one site/organ or to the peritoneum.

TECHNIQUE OF PET-CT
Positron emission tomography (PET) is considered a tomographic imaging technique, which gives a non-invasive assessment of biochemical and functional processes. Multiple positron emitters are available for use, but 18F (combined with FDG – fluorodeoxyglucose) is the most commonly used. PET-CT has a growing role in cancer diagnosis and management (Hogg and Testanera, 2010).
Computed tomography (CT) uses an x-ray beam to generate high-resolution images in demonstrating anatomy (Hogg and Testanera, 2010).
Integration between PET and CT in a single unit (PET/CT) has become an established and useful imaging modality in clinical routine. PET-CT is more accurate for lesion localization and characterization than either PET or CT alone (Hogg and Testanera, 2010).
Fig.22: A schematic illustration of a PET/CT system and a real unit (Quoted from Saha, 2010).
The Physical Principles of PET:
PET is based on two independent factors, the first factor is related to positron-emitting radionuclides chemistry, and the second factor is related to their radioactive decay. Positron-emitting isotopes exist for a number of elements that are found in organic molecules in the body. Carbon, nitrogen, and oxygen all have corresponding isotopes that decay by positron emission (11C, 13N and 15O), and these can be substituted directly into bio- molecules of interest with very little effect on the molecule’s behavior. The half-lives of these isotopes are only a few minutes, making them suitable for administration to patients. This means that patients do not receive high radiation exposure for extended periods after the imaging procedure is complete. In addition to natural substrates, analogue such as FDG can be labeled with positron emitters. 18F-labeled FDG is a glucose analogue that has the advantage that phosphorylated FDG in cells cannot be further metabolized and is effectively trapped, allowing its distribution in the body to be conveniently measured with.
PET. It also has a relatively long half-life of 110 minutes, which allows it to be practical to use and particularly well suited to the clinical application. FDG is by far the most popular tracer used for current clinical applications because malignant tumors have an elevated glucose metabolism compared with normal tissue (Lodge, 2008).

Radioisotope production for PET

A cyclotron is used to accelerate charged particles. These accelerated particles then interact with a target to produce radioisotopes for use in PET imaging. Fluorine-18 is produced by proton bombardment of oxygen-18-enriched water. The proton interacts with the oxygen-18 and produces a neutron and Fluorine -18 (Szczepura, 2010).

Positron (β+) Decay

A radionuclide is proton-rich and it decays by the emission of a positron (β+) along with a neutrino (ν). The proton in the nucleus is converted to a neutron in the process.

\[ p \rightarrow n + \beta^+ + \nu \]  
(Saha, 2010).

PET is a molecular imaging technique, which measures the distribution of a radioactive tracer in vivo. Upon administration of very small amounts of a radiotracer to the patient, it distributes among and within the organs. The radioactive atom of the radiotracer emits positrons. The emitted positron combines with an electron after travelling a distance up to several millimeters in tissue. The positron and electron are then converted into two photons, each having the energy of 511 keV, which are emitted in nearly opposite directions. PET image acquisition is based on the simultaneous (coincidence) detection of these two photons. A PET scanner consists of many photon detectors surrounding the patient. During a PET scan, millions of coincidence detections are collected, providing information about the distribution of the radiotracer in tissue (Boellaard, 2010).

Figure (23): a schematic illustration of the annihilation of a positron and an electron in the medium (Quoted from Boellaard, 2010)

In fact, not all coincidences contribute to the signal, i.e. the ‘true’ 3D distribution of the tracer. Background noise is added to the signal due to scattered photons before detection or by coincidence detection of two uncorrelated photons, i.e. so-called random coincidences (Boellaard, 2010).

Figure (24) illustrates the differences between true, random, scatter and multiple coincidences. True coincidences are the result of simultaneous (coincident) detection of two annihilation photons generated by one positron emission. Only true counts are detected, and a large fraction of the emitted photons (up to 50%) is scattered before leaving the patient. When one of the photons has been scattered, it will result in a dislocation of the ‘true’ coincidence detection. Moreover, when two photons from two different positron emissions are accidentally (randomly) detected simultaneously (while the others are undetected), the PET camera will notice a random coincidence detection. It may be clear that these random coincidences result in image distortions (appearing as the addition of a smooth background). Finally, multiple detections can occur when three or more photons are detected at the same time. These multiples are usually discarded. Moreover, due to attenuation (scatter and absorption) of photons in the patient, a large fraction of the emitted photons is not detected (Boellaard, 2010).

Figure 24: Illustrations of true (top, left), random (top, right), scatter (bottom, left) and multiple (bottom, right) coincidences (Quoted from Boellaard, 2010)

Photon Attenuation

The tissue attenuates the 511-keV annihilation photons originating from different locations in the body, as they cut out different body thicknesses to reach the detector pair in coincidence. If (μ) is considered the linear attenuation coefficient of photons in the tissue, (a) and (b) are considered the tissue thicknesses cut out by the two 511-keV photons along the line of response (LOR) connecting the two relevant detectors then the probability (P) of a coincidence detection is given by where (D) is the total body thickness. The equation is applicable to organs or tissues of uniform density. All coincidence along the same LOR will have the attenuation effect.

Figure 25: Two 511-keV photons detected by two detectors after passing through two different tissue thicknesses, a and b. The sum of a and b is equal to D. Attenuation is independent of the location of annihilation and depends on the total dimension of the body (Quoted from Saha, 2010).

When photons travel through different organs or tissues with different μ values, then Equation $P = e^{-\mu D}$.
\[ \sum_{t=0}^{n} \mu_i D_i \], where \( \mu_i \) and \( D_i \) are the linear attenuation coefficient and the thickness of the i organ or tissue, and \( n \) is the number of tissues or organs the photon passes through. Photon attenuation causes non-uniformities in the images because the two photons may pass through different organs along the LOR. Therefore, corrections must be done for this attenuation of photons in the body tissue. The probability \( P \) is the factor of attenuation correction and it is independent of the location of positron annihilation and depends on the total thickness of the tissue (Saha, 2010).

The attenuation of external radiation passes through the body will be determined by an effective attenuation coefficient \( \mu \) (tissues of different \( \mu_i \)) and the thickness of the body, as expressed by Equation. This introduces the application of an external source of radiation as a transmission method of attenuation correction instead of using the patient as the emission source (Saha, 2010).

Attenuation Correction Methods

CT Transmission Method: in PET/CT scanning, in addition to its use in fusion of PET and CT images for better anatomical localization and better diagnostic accuracy, the CT transmission scan can be used to make attenuation correction of PET data. A blank CT scan is done without the patient in the scanner. The CT scan takes a minute at the most and is then stored for subsequent calculation of attenuation correction factors for patients’ emission scans for the entire day. The CT transmission scan of each examined patient is obtained and the attenuation correction map factors are generated from this scan in addition to the blank CT scan and then applied to correct each patient’s scan.

The basic principle of CT transmission method for attenuation correction depends on that correction factors derived from 70 keV CT X-ray scans are scaled to the 511-keV photons of the PET by applying a scaling factor defined by the ratio of the mass attenuation coefficient of the 511-keV photons to mass attenuation coefficient of the 70-keV X-ray in a given tissue. Calculated attenuation correction factors for each pixel are applied to PET emission data. The CT transmission method is essentially noiseless attenuation correction factors (Saha, 2010).

Fig.26: Difference between attenuated and non-attenuated images (Quoted from Heathcote et al., 2010).

The Principles of CT:

Geoffrey Hounsfield invented CT scanning in 1970. In the beginning, only one image was produced per rotation of the x-ray tube and image quality was consequently very poor compared with the detail and resolution achievable today. CT technology has developed significantly over the last 20 years, with the advent of spiral CT in the 1990 and the subsequent introduction of dual-slice CT scanners and then multi-slice scanners with the capability of generating up to 128 slices per rotation. To understand the fundamental principles of CT, knowledge of the basic CT imaging system configuration is required.

The gantry is a rotating framework that the patient moves through on the patient table during data acquisition. It holds the x-ray tube, x-ray generator, slip rings, detectors, collimators and digital acquisition system (DAS) (Heathcote et al., 2010).

The x-ray tube is responsible for the production of x-ray photons. The filters are responsible for removing low-energy x-ray photons, thereby reducing patient dose. The collimators are used to define the slice thickness and localise the x-ray field to the area of interest. The detectors capture the x-ray photons after they have passed through the patient and convert them ultimately into digital information via the (DAS).

Fig.27: Basic system components of the CT scanner (Quoted from Ulzheimer and Flohr, 2009).

As the x-ray tube rotates around the patient, the detectors measure the radiation transmitted through the patient from various locations. The attenuation measurements are calculated by the computer and stored as raw data files (also called projections). Modern scanners collect projections from 360° and typically measure 800-1500 projections per image. Attenuation is the reduction of the intensity of a beam of radiation when it passes through an object, some photons are absorbed and others are scattered. The computer system receives the digital data from the DAS and then processes it to reconstruct the cross-sectional image. The computer system also enables general imaging techniques such as windowing, multi-planar reconstructions, and 3D imaging. Reconstruction of the differential attenuation information is acquired by the detectors and converted to a digital signal (Heathcote et al., 2010).

The CT image is the measurement of the linear attenuation coefficients \( \mu \) of the structures that the x-ray beam passes through during the examination. The value \( \mu \) is converted into a CT value relative to the
attenuation of water; this is to make the value more user-friendly. The CT value/number is displayed in Hounsfield units (HU) (Heathcote et al., 2010).

Factors affecting the quality of PET-CT images:

Patient preparation:
Fasting: complete fasting is recommended for a minimum of 6 h before the scan to minimize glucose-related competitive inhibition of 18F-FDG uptake and to decrease serum insulin. Fasting includes a complete cessation of tube feeding, parenteral hyperalimentation, and dextrose-containing intravenous fluids. (Unflavored) water is permitted during this time (Surasi et al., 2014).

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