Original Article, Oncology

PET/CT in Evaluation of Gastrointestinal Stromal Tumors (GISTs) Tumors

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Objective: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract with 70% of all GISTs are found in the stomach. The management of gastrointestinal stromal tumors (GISTs) has been revolutionized with the introduction of Imatinib mysylate as a targeted therapeutic agent and the dramatic change in the tumor metabolic activity following successful therapy with follow up using (FDG)-PET/CT.

Patients and Methods: 47 consecutive patients (mean age: 49.2±12.7) with histologically proven GIST underwent whole-body FDG-PET/CT.

A clinical/radiological CT and PET/CT follow-up for 3-15 months duration served as standards of reference. **Results:** There was no difference between CT and PET/CT in the initial staging of GIST or in detection of primary /recurrent lesions. A higher PET CT value in assessment of target therapy response was found in 11 patients (28%) compared to CT. Regarding patients prognosis 66.7 % of patients with lymph nodes metastases showed disease progression. In addition, 92.3% of patients who had complete metabolic remission or stable disease on follow up PET CT and did not had any newly developed metastases, while 55.5 % of patients who died or progressed on follow up PET/CT had double/triple organ metastases (5 patients), with statistically significant difference (P <0.001). No statistically significant relation was found between prognosis and patient`s age, sex, site of primary GIST.

Conclusion: Combined PET/CT can provide additional functional information as compared with diagnostic CT in GIST, especially in therapy assessment.

Key Words: FDG PET/CT, GIST, Imatinib mysylate, therapy response.

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INTRODUCTION:

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors and account for less than 1% of all gastrointestinal tumors. Approximately 90% of cases originate in the stomach and small intestine[1]. They have a wide clinical spectrum ranging from benign incidentally detected nodules to large malignant tumors and must be distinguished from other mesenchymal tumors[2]. Their origin was initially attributed to Cajal's cells but it has recently been supposed that they originate from multi potential mesenchymal stem cells, which could explain their resistance to chemotherapy.[3]. These cells have been shown to express the cell surface receptor C-kit, which is identified by CD117. C-kit functions as a tyrosine kinase, which is activated as a ligand in the presence of a stem cell factor. (4) A mutation of the C-kit proto-oncogene that activates tyrosine kinase in the absence of a stem cell factor, leading to uncontrolled cell proliferation. So therapy with a tyrosine kinase inhibitor (TKI) shows an impressive response.[4]. It usually occurs in middle aged and older patients (fifth to seventh decades, with no specific sex predominance.[5]. Surgery is the mainstay of therapy for non-metastatic GISTs. Laparoscopic surgery has been shown to be effective for removal of these tumors without the need of large incisions[6]. Tumors are usually resistant to conventional cytotoxic-chemotherapy and radiation[7]. The c-kit tyrosine kinase inhibitor Imatinib (Glivec/Gleevec), a drug initially marked for chronic myelogenous leukemia, was found to be useful in treating GISTs, leading to a 40-70% response rate in metastatic or inoperable cases.[8].The current response evaluation criteria in solid tumors are based on uni-dimensional tumor size, and do not take into account changes in responding GISTs such as a decrease in tumor density and decrease in the number of intratumoral vessels with computed tomography (CT). Modified CT criteria using a combination of tumor density and tumor size are promising in early response evaluation, and have excellent prognostic value[9]. Positron emission tomography (PET) has been found to be highly sensitive in assessment early response to Imatinib mesylate. Also, it is useful in predicting long-term response to imatinib in patients with metastatic GIST; however, widespread use of PET is limited because of cost constrains[10]. We retrospectively compared the performance and prognostic impact of 18F-FDG PET/CT and diagnostic CT in staging and evaluating

response to therapy with Imatinib mesylate in patients with GIST.

MATERIALS AND ETHODS:

Patients: A retrospective study included 47 patients from the National Cancer Institute (NCI), Children's Cancer Hospital Egypt and Nasser Institute, between January 2011 and October 2015. All patients were referred to Nuclear Medicine departments in different clinical phases of disease (initial, assessment of therapy or follow up). All patients were histo-pathologically proven malignant gastro intestinal stromal tumors. Clinical information were extracted from the medical records, including age, sex, methods of diagnosis, detailed pathology, imaging findings, response to treatment and survival data.

Inclusion criteria includes age above 18 years old, histo-pathologically proved malignant GIST (high, intermediate & low risk) and patient referred initially or during Imatinib mesylate therapy.

Exclusion criteria include age below 18 years, pregnancy, patients having double primary. The ethical committee of NEMROCK and the radiation safety committee at NCI had given approval for study design.

Imaging: FDG PET/CT: Procedure: All patients fasted for at least 4 h before the exam. Blood glucose levels did not exceed 160 mg/dl. FDG PET/CT was performed in the patients without stoppage Imatinib mesylate unless physician instructed differently. FDG PET/CT study was done using a dedicated PET/CT scanner was integrated with a dual-section helical CT scanner and allows the acquisition of co-registered CT and PET images in one session. Scanning started 60-90 min after tracer injection of 370-555 MBq of 18F-FDG. Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started at the level of the cervico-thoracic region with the following parameters: 400 mAs; 120 kV; slice thickness, 3 mm; pitch, 1.5. The CT scans were acquired during normal respiration; reached caudally to the mid thighs. PET was performed immediately after acquisition of the CT images (5–7 bed positions; acquisition time, 2-3 min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 5-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization).

Processing: Images were interpreted at a workstation equipped with fusion software that provides multi-planar reformatted

images and enables display of the PET images, CT images, and fused PET/CT images was interpreted by 2 experienced nuclear medicine physicians. The analysis was conducted on per patient and per lesion based analysis.

Imaging Interpretation:

Qualitative (Visual) assessment: For 18F-FDG PET/CT interpretation, any focal uptake, superior-to hepatic reference in the primary site, lymph nodes or metastases (liver, peritoneal, lung.) was interpreted as abnormal FDG uptake.

Quantitative assessment: The maximum standardized uptake values were recorded for each lesion in each patient after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity. Another sizable ROI was drawn over the normal liver where its max SUV was considered reference activity for further quantitative analysis.

Data Analysis was performed depending on RECIST criteria: **True positive PET/CT results:** 18F FDG PET/CT and CT agreed, evidence of progression on follow-up CT and / or PET CT scans, metabolically active FDG avid primary or metastatic lesion of SUVmax higher than the reference hepatic activity. **True negative PET/CT results:** CT and PET/CT results within one month agreed with clinical follow up after 4-6 months from radiological investigations were free i.e no newly developed relevant symptoms or signs, no appreciable FDG uptake in metastatic deposits in cross sectional PET/CT with follow up CT results of six months or more duration revealed stationary course, mass of low metabolic activity of SUVmax less than the reference hepatic activity that does not show significant increase in FDG uptake on the delayed images and a CT detected primary / recurrence mass and pathology after surgical excision was benign GIST. **False positive PET/CT results:** Metabolically active FDG avid lesion proved to be benign using pathological analysis after excision or follow-up studies. **False negative PET/CT results:** Mass of low metabolic activity of SUVmax less than the reference hepatic activity that does not show significant increase in FDG uptake on the delayed images, pathology after excision was malignant GIST or follow up CT revealed disease progression. ***Follow up:*** data for patients were retrieved from their medical records at the hospital where clinical and radiological data were obtained to evaluate patients' response to therapy till the last visit. Follow up PET CT was performed for some of the patients at

different time scales ranging from 3 to 15 months. ***Statistical Analysis:*** The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of CT alone and PET/CT were calculated on the basis of the true-positive and true-negative findings as described in the same anatomic region with a lesion-based and a patient-based analysis. The McNemar test (x^2 test) was used for comparison of the sensitivity and specificity of CT alone with those of fused PET/CT (and for calculation of localizing accuracy comparing diagnostic CT with fused PET/CT) with a confidence level of 95% ($P<0.05$ was considered significant all through).

RESULTS:

Consecutive patients with histologically proven CD117-positive GIST referred to perform PET/CT examination in the period between January 2011 to October 2015 at the 3 institutions included were analyzed in the present study. A total number of 47 patients (23 female, 24 male) were included in this study. The age of patients ranged from 20 to 74 years with 49.2 ±12.7. Male to female ratio was 1.04. Majority of patients were in high risk group in 23 patients. Stomach and bowel was main site of GIST in 22 and 14 patients as seen in Table (1).

Table (1): Clinico-pathological characteristics in 47 patients with GIST.

Criteria		**Data Analysis**
Age	(mean ± SD) y. s	49.2+_12.7SD
Sex	(M:F ratio)	1.04
Grade*	High Risk Intermediate Risk Low Risk Not available	23 3 5 15
Site of primary:	Stomach Bowel Para rectal Retro peritoneal Liver Un-identified	22 14 4 1 2 4

*One patient`s pathology after excision proved to be a benign GIST

The liver was the most common site for metastases, followed by the lymph nodes and lastly the peritoneum.

The distribution of site/organ metastases are summarized at table (2).

Table (2): Distribution of site/organ metastases in 47 patients with GIST.

	Number of patients	**Percent (%)**
Non Metastatic	18	38.3
Single organ metastases:		
Liver	12	25.5
Lymph nodes	5	10.6
Peritoneum	3	6.4
Lung	1	2.1
Two organs metastases:		
Liver, LNs	3	6.4
Liver, peritoneum	2	4.3
LNs, peritoneum	1	2.1
Three organs metastases:		
Liver, peritoneum ,LNs	1	2.1
Liver, peritoneum, Bone	1	2.1
Total	47	100.0

All patients were treated with Imatinib mesylate. patients were followed up for a period between 2-15 months by clinical examinations, radiological imaging and PET/CT. Patients were classified into 2 subgroups: (A) with single PET/CT study in 23 patients. (B) With pre-therapy and follow up PET/CT studies in 24 patients.

Subgroup (A): Patients with single PET/CT study: *23* patients (12 male, 11 female) underwent single PET/CT study are included. The findings on PET/CT scans were correlated with patients' symptoms, pathology and CT scan at 3-6 months interval.14 out of 23 patients were metastatic. 18 patients were on Imatinib mesylate treatment at the time of the scan.

Correlation between the PET/CT findings with patients' symptoms, pathology and CT scan results of 3-6 months interval were conducted. 21 patients PET/CT results were compared to clinical and CT results. PET/CT had superior results in 8 patients of 23 (34.8%) compared to diagnostic CT in assessment of response to therapy in GIST, as seen in **table (3).** 11 patients had similar findings PET/CT, and follow up diagnostic CT results. 8 patients of them had only the primary neoplasm, and 3 patients had peritoneal /lymph nodes and liver metastases. Stationary lesions in CT detected in follow up of 8 patients, 6 of them had complete metabolic response by FDG PET/CT (5 with liver metastases,

1 had liver and peritoneum deposits), and 2 shows residual viable lesions. A single false negative PET/CT result regarding the site of primary tumor (i.e. no metabolic activity), pathology shows positive malignant GIST.

Table (3): Results of PET/CT and follow-up in 23 patients with GIST underwent single PET/CT study.

	No. of patients (Total=23)	**PET CT results**	**Follow up**
Comparable PET/CT and Diagnostic CT	8	CMR of primary lesion	Free on CT
	3	CMR of metastatic lesions	Free on CT
	2	Positive for liver/LNs, Liver/bone	PD on CT
Negative PET/CTpositive CT	6	CMR of metastatic lesions	SD on CT
Positive PET/CT false negative CT	2	Positive for residual viable tumor tissue	SD on CT
False Negative PET/CT positive CT	1	No metabolic activity	Pathology revealed malignant GIST.
True Negative PET/CT false positive CT	1	Low grade metabolic activity (less than the reference hepatic activity)	Pathology proved benign GIST.

CMR = complete metabolic remission. PD = Progressive disease. SD = Stable disease.

Subgroup (B): 18 patients with pre-therapy & follow up PET/CT for assessment of therapy response:

Initial PET/CT: 18 patients (8 male, 10 female) underwent pre-therapy scan. 14 patients had undergone previous resection of their primary tumors and 4 patients had undergone only biopsy. All FDG-PET/CT results were compared with diagnostic computed tomography (CT) ***Table (4).*** A difference between CT and PET/CT were detected in 2 patients having metastatic lymph nodes and intra medullary bone lesions. Also, PET/CT showed metabolically inactive small liver deposits (around 1 cm) in 3 patients that were not detected by CT. ***Table (4).*** Regarding the site of primary tumor / residual / operative bed, PET/CT and CT results were comparable except for a single higher value of PET/ CT in detection of liver lesions. There was no significant statistical

difference between CT and PET/CT on the initial staging for GIST.

Table (4): Frequency of metastatic sites by PET CT and CT Scans in initial staging**.**

Site or organ	PET/CT	CT
Liver	6	9
Peritoneum	5	5
Lymph nodes	6	5
Lung	2	2
Bone	1	0
Total	**20**	**21**

Follow up PET/CT: A total number 16 patients out of 18 patients had repeated PET/CT scan after initiation of Imatinib mesylate. 2 patients of them had 3 sites metastases were died within one month after being diagnosed. The results of diagnostic CT scan and PET/ CT were comparable (7 patients had CMR, 5 patients had PMD and one patient had SMD in PET/CT). The other 3 patients PET/CT was better in assessment of therapy response as compared to that of diagnostic CT results (p=0.7). In 2 patients, it showed PMD while diagnostic CT revealed SD ***Table (5).***

Table (5): Results of 18F-FDG PET/CT and CT scan in 16 patients with GIST on follow up.

Number of Patients	PET/CT	CT
Comparable Results		
7	CMR	CR
5	PMD	PD
1	SMD	SD
Discrepant Results		
2	PMD	SD
1	CMR	SD
Total	**16**	**16**

CMR = complete metabolic remission. PD = Progressive disease. SD = Stable disease.

Prognosis in GIST tumors: No statistically significant relation was found between prognosis and patient`s age, sex, site of primary GIST in 41 patients (6 patients skipped follow up) (P value are 0.18, 0.15 and 0.34 respectively), While there was significant difference with single or multiple sites of metastases ***Table (6).***

Table (6): Relation of prognosis with age, sex & site of primary and site of metastases.

Relation	Statistical Significance	P-value
Age	**No**	**0.18**
Sex	**No**	**0.15**
Site of primary	**No**	**0.34**
Multiple organ involvement	**Yes**	**<0.001**
Nodal metastases	**Yes**	**0.026**
Liver metastases	**No**	**0.65**
Peritoneal metastases	**No**	**0.27**

DISCUSSION:

Gastrointestinal stromal tumors (GISTs) management has been revolutionized in last few years by two major developments: the introduction of imatinib mesylate as a targeted therapeutic agent that dramatically change the tumor metabolic activity and the use of fluorodeoxyglucose (FDG)-PET as a functional image in monitoring therapeutic response making in[11]. There is now convincing evidence that serial PET study is more sensitive and reliable for determining treatment response to Imatinib mesylate in patients of GIST, when compared with only conventional CT monitoring.[11]. Traditional tumor response criteria such as RECIST are based on uni-dimensional tumor size and do not take into account changes in tumor metabolism, tumor density, and decrease in the number of intra-tumoral vessels. All of these changes indicate response to TKI therapy in patients with GIST. Hence, response assessment according to RECIST is known to be insensitive in evaluating response to TKI therapy[11].

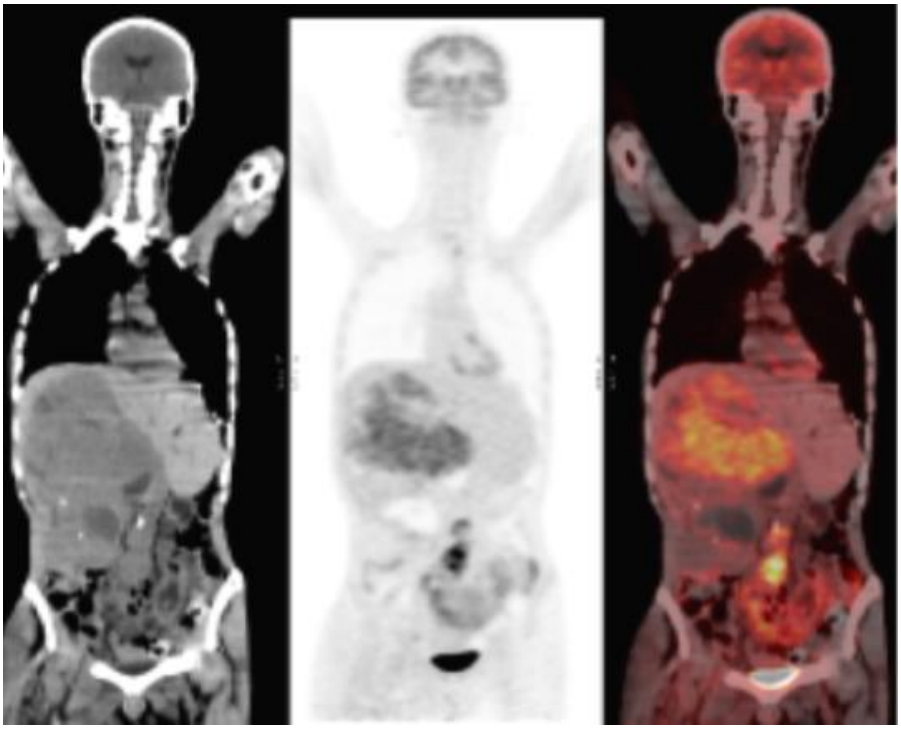

Figure (1):33 years old male, with duodenal GIST with metastases to liver and lymph nodes on Imatinib mesylate starting from 2009. PET CT Coronal fused images revealed partial remission with residual FDG avid metastatic hepatic focal lesions with multiple FDG avid para aortic lymph nodes.

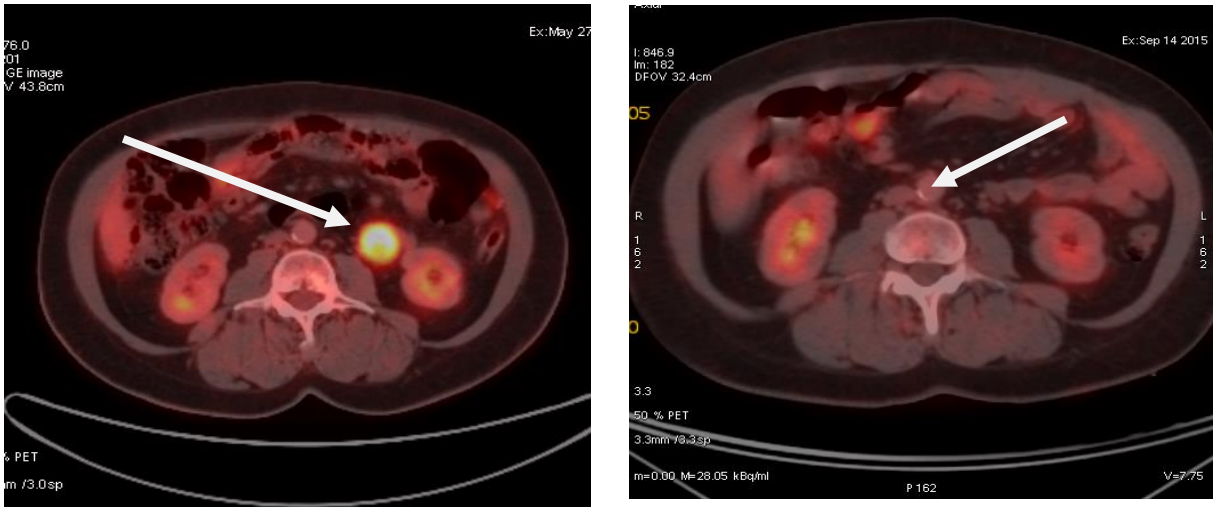

Figure (2): 65 years old female patient with intestinal GIST on Imatinib mesylate. A baseline PET/CT (the right image) shows multiple peritoneal deposits. Follow up PET/CT (the left image): showed complete metabolic remission (CMR).

In the present study it was found that F-18 FDG PET/CT had superior results in 11 patients (out of 39 patients) (28%) rather than diagnostic CT in assessment of therapy response. In all of patients with discrepant results, follow up CT scans showed a stationary course regarding the size of metastatic lesions, while PET/CT showed either complete metabolic remission, progressive metabolic disease of the same sized metastatic lesions i.e. the size of metastatic deposits did not increase compared to SUVmax that showed an increasing difference. Also, Gayed et al.[12] reported agreement between 18-F-FDG PET and diagnostic CT scans in 71.4% of patients and discrepant results between 18-F-FDG PET and diagnostic CT were recorded for 28.6% of the patients. Moreover, Antoch et al.[13] compared the value of diagnostic CT and PET/CT imaging for assessing response to Imatinib mesylate therapy in 20 patients using (RECIST) and (EORTC) criteria for therapy response. They comparable results in 60%, 57% of patients and discrepant results in 40% and 43 % of patients after 3 and 6 months of target therapy for diagnostic CT and PET/CT results respectively .These findings suggest that FDG PET/CT is superior to diagnostic CT in assessment of response to therapy in recurrent or metastatic GIST patients. Concluding that tumor response to imatinib should be assessed with a combination of morphologic and functional imaging using F18-FDG PET/CT has been judged a better guide for Imatinib mesylate therapy.

In the present study; 18 patients were involved on pre-therapy staging that showed a comparable performance between PET/CT and diagnostic CT. The sensitivity and positive predictive values for PET/CT were 90% and 100% as compared to 90% and 90% respectively for diagnostic CT. Although PET/CT was able to detect more lesions per patient (sub-centmetric lymph nodes, few additional peritoneal deposits and marrow based metastases) missed by radiologists, however this difference in performance has significant statistical difference. Similar results were performed by Gayed et al[12]; in their study of 54 patients who underwent FDG PET and diagnostic CT scans. In contrary to our results, Antoch et al.[13] showed a higher PET/CT value in initial staging of 20 patients compared to diagnostic CT alone ($P < 0.001$). Although GIST showed usually high FDG uptake in primary and metastatic lesions, we found that small sub-cent metric liver deposits was not FDG avid initially in contrary to

lymph nodes and peritoneal lesions of the same size. The liver is the most common site of metastases in GIST, both at the time of presentation and during relapse. It is seen in 49−65% of the cases[14] .On the current study, hepatic metastases is reported in 19 patient (~40%). A separate analysis of liver deposits using PET/CT was performed ; as it was noticed in pre-therapy PET/CT that liver deposits measures ~1 cm do not have significant FDG uptake to fulfill the PET/CT criteria for true positive lesions, while a significant decrease of SUVmax in FDG avid liver lesions was observed after treatment. Although no significant statistical difference in sensitivity and PPV values at initial staging, yet a significant difference was found (P value = 0.03) with higher PPV for PET/CT in assessment of therapy response compared to diagnostic CT (97% versus 57%) respectively. The relative lower sensitivity of PET/CT after treatment (83%) as compared to diagnostic CT (86.5%) is not interpreted in favor of diagnostic CT but likely attributed to relative low true positive lesions in PET/CT as compared to total number of lesions with remarkable decrease in SUV max while the size of the lesions did not show a significant reduction in size in diagnostic CT. Response to imatinib is associated with change in the density of GIST tumor masses, which become more cystic and therefore more visible against the surrounding dense hepatic parenchyma and 18FDG-PET will be negative, which confirms the patient's response to treatment. 18FDG-PET is also helpful when CT findings may suggest tumor growth while the increase in size is actually related to intratumoral bleeding or to tumor swelling unrelated to progressive disease. In both cases, 18FDG-PET will be negative due to absence of viable tumor tissue. It is worth mentioning that some patients may present with new lesions in the liver during imatinib treatment. Traditional response criteria, such as WHO, or RECIST, would label the appearance of these lesions as disease progression rather than as response to therapy. However, these patients are most likely responding to the treatment [15]. This phenomenon was observed by Joensuu et al.[16], they stated that some lesions can be isodense to the hepatic parenchyma prior to therapy and may not be seen on CT at that time. It is important to recognize this pattern of response, because it may potentially lead to misinterpretation of progressive disease on CT in a patient who is actually responding to the treatment. Nodal metastases were found in 9 out of 47 patients (21.3%) usually in combination

with liver or peritoneal metastases (multi-site metastases). It is usually considered as a morphological feature associated with malignancy and poor prognosis. Our results support this opinion, it showed that 66.7 % of patients with lymph nodes metastases showed disease progression (P=0.026) .This agreed with Bucher et al.[17] that considered the presence of LN invasion one of the two major criteria that affect patient prognosis. Tumors having four or five minor criteria or one major criterion were classified as high grade GIST. Wang et al. (2014) [18] do not support this opinion , three out of the 5 patients with lymph node metastases in their study achieved longer than 2 years' disease free survival . One of them, though untreated with Imatinib mesylate was still disease-free at the latest follow-up, over 8 years after surgery. Also, ***Valadao et al (2008)*** [19].Their results showed that nodal metastasis had no prognostic significance for overall and disease free survival (p = 0.65 and p = 0.57, respectively). ***Prakash et al.***[20,21] in a review on 15 patients with GIST found 3 cases with lymph node metastasis and they were all <18 years old. They concluded that the GIST in patients who are <18 years old may have different clinical and genetic aspects, concluding GIST is more indolent in pediatric population. It has been widely accepted that the risk of progression for a newly diagnosed primary GIST rely on three parameters; mitotic index, tumor size and tumor location. These factors form the basis for consensus risk classification[22,23,24]. Our results showed no significant relations between patient`s age, sex, site of primary and risk of progression (P value are 0.18, 0.15 and 0.34 respectively). Moreover, comparing patient`s prognosis to metastatic status , we found that all 9 patients who died or progressed were metastatic while 17 out of 20 patients (85%) who were free on follow up; were not metastatic on initial staging. This agreed with ***Wang et al.***[18] as regard age and metastatic status but not in patient`s sex. They reviewed clinical and pathological data of 497 GIST patients in the period between 1997 and 2012, their results of univariate analysis revealed that male gender, non-gastric origin, larger tumor size, higher mitotic rate, higher risk grade, CD34 negative expression, and adjacent organ involvement contributed to poorer outcome (lower OS and RFS), whereas age and expression of CD117, SMA, and S-100 were not associated with prognosis. It is also reported that males had lower survival rate than females (5-yaer OS, 80.2% vs. 90.6%, P = 0.010; 5-year RFS, 71.6% vs. 84.4%, P = 0.003). This finding was inconsistent with other

retrospective studies. However, no relationship between sex and survival was found in the multivariate analysis. In another study of 920 patients with GIST, Joensuu et al (2012)[25] results showed that large tumor size, high mitosis count, non-gastric location, presence of rupture, and male sex were independent adverse prognostic factors.

Study limitations: Although, we could acceptably assess the role of F18-FDG-PET/CT in GIST evaluation and in monitoring therapy response. Most notably, the criteria depending on change in tumor size only on CT scans using RECIST criteria in assessment of therapy response to Imatinib mesylate therapy was not satisfactory as change in tumor densities, cystic and necrotic variations in these tumors are proved to be additional parameters for assessment of response. Fortunately FDG PET/CT with its accurate detection of metabolic activity was present. Moreover, this retrospective of five years at 3 different institutions may have different imaging techniques; however this was done because of the rarity of this type of tumor. But a larger number of patients are essential in future study for better statistical analysis. Also, we did not have access to all soft-copy scans, with the added benefits of electronic measurement and attenuation assessment. In clinical practice some patients do not have an initial staging study before therapy, because of waiting lists, department workloads and clinical necessities, could draw the referring physician to start therapy in the absence of initial evaluation. Finally, as it is a retrospective study, the possibility of early therapy response assessment was not feasible, yet, according to our results, differentiating responder from non-responder is clearly analyzed.

Conclusion: Despite diagnostic CT and PET/CT may be performed for pre-therapy staging of patients with GIST, yet, tumor response to imatinib is better assessed with a combination of morphologic and functional imaging, hence PET/CT can provide additional information in individual cases. It is preferred to perform PET/CT before starting target therapy in metastatic patients as a baseline study and after 2-3 cycles to assess early therapy response. And finally patient`s prognosis in GIST is significantly correlated to the presence of lymph node metastases and number of organs involved with metastases.

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