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Original Article, PET/CT.

Diagnostic and Prognostic Value of F18 FDG PET/CT in Assessing Nodal Metastasis in High-Risk GIST Patients.

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ABSTRACT:

Aim: In order to diagnose nodal metastases and assess the prognosis and response to Imagine Maculate (Gleevec), this study set out to determine the diagnostic and prognostic utility of F18 FDG PET/CT. **Materials and Methods:** FDG PET/CT scans were retrospectively evaluated in 159 individuals with pathologically confirmed GIST (77 females, 82 males, mean age: 49.2±12.7). A total of 194 PET/CT tests (57 pre-treatment and 137 follow-up) were performed to analyze nodal lesions throughout imatinib therapy. The criteria of reference were pathological and clinical/radiological follow-up for a period of 13-15 months. **Results:** The mean age of the 29 patients (18.2%) with lymph node (LN) metastases was 53.2±12.7. Sixty-two percent of the patients had primary stomach disease, and sixty-nine percent had high-risk spindle cell disease. The size ranged from 1 to 8.7 cm, with a mean SUVmax value of 6.7 ± 4.5 and a size of 2.1 cm. Only six patients had isolated nodal metastases, while the other twenty-three patients had multiple and triple sites of metastases (liver and/or peritoneal deposits). There are 89 lymph nodes seen in all, including 17 with mediastinal deposits and 70 with abdomino-pelvic deposits. Compared to 55% of metastatic patients

without nodal involvement and only 6.5% of non-metastasized patients, 21 patients (72.4%) in the group with nodal metastases suffer disease progression. (P value <0.001). The mortality rate was not statistically significant, with four of the 29 patients with nodal metastases (13.7%) dying, compared to around 10% and 4.9% for the other metastatic and non-metastasized groups, respectively. (p value ~0.841)

Conclusion: With an incidence of 18.2%, lymph node metastases are thought to be a poor prognostic factor for GIST patients, FDG PET/CT appears to be an effective method for detecting lymph nodes and evaluating Imatinib therapy response.

Keywords: prognosis, nodal metastases, GIST, FDG PET/CT, and imatinib therapy.

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INTRODUCTION:

About 0.1% to 3.0% of all gastrointestinal tract malignancy and 6% of all sarcomas are gut stromal tumours (GISTs). Malignant GIST is prone to recurrence or liver and peritoneal metastases. However, lymph node involvement or metastases are uncommon [(1)]. The cornerstone of curative treatment is surgery with good primary tumor excision; however, lymph node (LN) dissection is not frequently carried out because nodal metastases are uncommon [(2)]. For many years, CT was frequently used to stage GIST initially and track how well imatinib therapy was working based on changes in tumor size and density (HU). F-18 FDG The usage of PET/CT in the treatment of cancer is well-established. In a significant proportion of patients, the combination of metabolic and morphologic data in PET/CT was able to improve diagnostic precision, lower risks, and alter treatment approaches [(3)]. The prognosis and pertinent characteristics of GIST patients with lymph node metastases are still poorly understood.

PATIENTS AND METHODS:

This retrospective study included 159 patients with histo-pathologically confirmed gastrointestinal tumors (GIST) referred to the Unit of Nuclear Medicine at the National Cancer Institute Egypt (NCI) from January 2014 to July 2023. The study encompassed the initial diagnosis, assessment of Imatinib Mesylate therapy, and follow-up. Clinical information was obtained from the medical records, encompassing sex, age, pathology data, radiologic findings, and response to therapy. Criteria for inclusion consist of individuals aged 18 years and older with histo-pathologically confirmed malignant gastrointestinal stromal tumors (GIST). Exclusion criteria consist of individuals under 18 years of age, pregnant patients, and those with secondary primary conditions. All participants were provided with information regarding the study's details. The ethical committee of NCI approved the study design.

Imaging*:* 18F-FDG PET/CT: Methodology: All patients underwent a fasting period of 4-6 hours before the examination. Serum glucose levels remained below 180 mg/dL. All patients receive an explanation of the procedure details. Whole body image from the skull to mid-thigh was obtained approximately 60 minutes post-tracer injection (range, 45–110 minutes). Bed position numbers was modified to encompass the entire body during the early acquisition phase, with a duration of 2-3 minutes per bed position, utilizing a specialized PET-CT scanner (GE, PET/CT Discovery). This system combines a PET scanner with a dual-section helical CT scanner, facilitating the simultaneous acquisition of co-registered CT and PET images in a single session. Most patients received an intravenous contrast agent at a dosage of 1.2 ml per kg of body

weight, with exceptions made for individuals with specific contraindications. Patients were examined in the supine position with elevated arms, and a CT scan was performed using 40 mAs and 120 kV. PET scanning of the same region was conducted following the acquisition of CT images. Attenuation correction was performed utilizing reconstructed CT data with 5-mm slice images, employing a standard iterative algorithm known as ordered-subset expectation maximization.

Interpretation:

Images were analyzed using a workstation (Advantage Window AW version 5, GE) as a fusion software, facilitating the display of CT images, PET images, and fused ones. Two nuclear medicine physicians conduct the side-by-side image interpretation. Qualitative visual assessment: The visual (qualitative) interpretation of 18F-FDG PET/CT was determined by the presence of FDG uptake exceeding that of the physiologic hepatic activity in the anatomical locations of lymph nodes or other site of metastases. The maximum standardized uptake values were recorded for each lesion in each patient following the manual application of (volumetric regions of interest), indicating the highest accumulation of 18F-FDG on the trans-axial attenuation-corrected PET slices.

Statistical Analysis*:*

Data were encoded and entered using SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum, and maximum for quantitative data, and frequency (count) and relative frequency (%) for categorical data.

RESULTS:

Patient Characteristics:

A retrospective analysis included 159 pathologically confirmed GIST cancer patients who underwent PET/CT examinations from January 2016 to July 2023 at the National Cancer Institute Egypt (NCI). Seventy-seven females and eighty-two males were included, with patient ages ranging from 20 to 81 years, yielding a mean age of 48 years and 49.2 ± 12.7, respectively. Their clinical and pathological data were evaluated in **Table 1**. The stomach was the predominant site of first occurrence, and the majority of patients exhibited a high-risk classification. All patients received treatment with Imatinib Mesylate. The patients were monitored for a duration of 6 to 24 months using clinical evaluations, radiological imaging, and PET/CT scans.

Table (1): Clinico-pathological characteristics in 159 patients with GIST

CRITERIA		DATA ANALYSIS
AGE	**(mean ± SD)**	**49.2+_12.7SD**
SEX	**(M:F ratio)**	**1.06**
GRADE	**Low Risk** **Intermediate** **Risk** **High Risk**	**35** **15** **109**
SITE OF PRIMARY:	**Stomach** **Bowel** **Esophageal** **Para rectal** **Retro peritoneal** **Liver** **Un-identified**	**89** **57** **1** **5** **3** **2** **2**

Sixty one out of the 159 patients included on our study are non-metastatic, while the remaining 98 patients (61.7%) exhibited metastases during the course of their disease. The liver is the most frequent site for metastases, followed by the peritoneum and, finally, the lymph nodes. The distribution of metastasis sites is summarized in **Table (2)**

Table (2): Distribution of metastatic sites in 159 GIST patients.

	mber of patients	**Percent (%)**
Non-Metastatic	**61**	**38.3**
Metastatic	**98**	**61.7**
Single organ metastases:		
Liver	**39**	**39.7**
Lymph nodes	**6**	**6.1**
Peritoneum	**18**	**18.3**
Lung	**3**	**3.0**
Two organs metastases:		
Liver, Lymph nodes	**8**	**8.1**
Liver, peritoneum	**8**	**8.1**
Lymph nodes, peritoneum	**7**	**7.1**
Three organs metastases:		
Liver, peritoneum, Lymph nodes	**7**	**7.1**
Liver, peritoneum, Bone	**2**	**2.0**
Total	**159**	**100.0**

Per patient analysis:

The 159 patients are classified into 3 groups, patient with no metastases (N=61), patients with nodal metastases (N=29) and metastatic patients with no nodal involvement (N=69). Their clinico-pathological data were analyzed in **Table (3)**. Twenty-nine patients proved to have metastatic nodal deposits represents (18.2%), while 34.4% have metastases without nodal involvement.

Among the 29 patients, predominance of high-risk spindle cell pathological type is present in 20 out of 29 patients (69%) & the stomach is the site of primary in 62% of included patients. There is significant statistical difference regarding the 3 groups in there grading with predominance of nodal metastases in patients with group of high risk. (P value<0.001).

Table (3): Clinico-pathological characteristics in different patient's groups

Criteria		Data Analysis			
		Metastatic with nodal Metastases	Metastatic without nodal metastases	Non-Metastatic	P value
Number		29 (18.2%)	69 (43.4%)	61 (38.4%)	
Age	(mean ± SD)	53.2+_12.7 SD	52.3+-11.3 SD	49.5+-12.1 SD	0.272
Sex	(M:F ratio)	1.63	1.41	1.00	
Grade	High Risk Intermediate Risk Low Risk	20 (69%) 5 (17.2 %) 4 (13.7%)	60 (87%) 4 (5.8%) 5 (7.2%)	29 (47.5%) 6 (9.8%) 26 (42.6%)	<0.001
Site of primary:	Stomach Bowel Esophageal Pelvic (Para rectal) Retro-peritoneal Liver Un-identified	18 (62%) 5 (17.2%) 1 (3.4%) 4 (13.7%) 0 1 (3.4%) 0	40 (57.9%) 23 (23.3%) 0 1 (1.4%) 2 (2.9%) 1(1.4%) 2 (2.9%)	31 (50.8%) 29 (47.5%) 0 0 1 (1.6%) 0 0	0.003

Regarding the 29 patients have lymph node GIST deposits, isolated nodal metastases are seen on only 6 patients, while the presence of multi-organ metastases is presented on 7 patients, the remaining 16 patients have double organ involvement (liver and peritoneal metastases), as illustrated on **Table (4).**

Table (4): distribution of nodal metastases in GIST

Metastases	**Isolated Nodal metastases**	**6**
	Double organ metastases ***Nodal & liver metastases** ***Nodal & peritoneal Metastases**	 **8** **8**
	Triple organ metastases	**7**

Per Nodal lesion analysis:

A total of 89 lymph nodes are detected. 58 lesions in initial staging & 31 lesions in follow up study. The distribution of lymph nodes was 70 abdomino-pelvic and 17 lymph nodes in mediastinum. The median and mean maximum SUV in lymph nodes were 6.3 and 7.6 +_ 4.5 respectively; The mean longest dimension of lymph nodes observed on CT was 2.1 cm, with a range of 1 to 8.7 cm.

It worth mentioning that ~ 72% of the nodal lesions shows progression either on their morphology (number & size) or on their metabolic activity, or both.

Relation of different metastatic patient's status and prognosis.

There were no relations between the incidence of nodal metastases and the age, sex and site of primary, only the high-grade pathology shows statistical significance. (<0.001) Comparing patient`s prognosis among the three groups of the classified patients, 21 out of 29 patient (72.4%) of metastatic patients with nodal metastases experience disease progression compared to 55% in metastatic patient without nodal involvement and for only 6.5% on non-

metastatic patients. **(P value <0.001)** Unfortunately no one on the group of nodal metastases show complete disease remission (CR) & only ~3 % of the metastatic group show CR compared to 54% of the non-metastatic patients. (P value <0.001). The percent of regressed disease is comparable on the three groups. Four out of the 29 patients with nodal metastases died (13.7%) compared to ~10% and 4.9% on other metastatic and non-metastatic groups respectively, which failed to reach a statistical significance. (p value~0.841) **Table (5) and Figure1.**

Table (5): Relation of different metastatic patient's status and prognosis.

Criteria	Data Analysis			
Groups	**Metastatic with nodal Metastases**	**Metastatic without nodal metastases**	**Non-Metastatic**	**P value**
Number/%	**29**	**69**	**61**	
Progression	**21 (72.4%)**	**38 (55%)**	**4 (6.5%)**	**<0.001**
Regression	**6 (20.7%)**	**20 (29.0%)**	**15(24.6%)**	
Stationary	**2 (6.9%)**	**9 (13.0%)**	**9 (14.8%)**	
CR	**0**	**2 (2.9%)**	**33 (54.1%)**	
Died	**4/29 (13.7%)**	**7/69 (10%)**	**6/61(4.9%)**	**0.841**

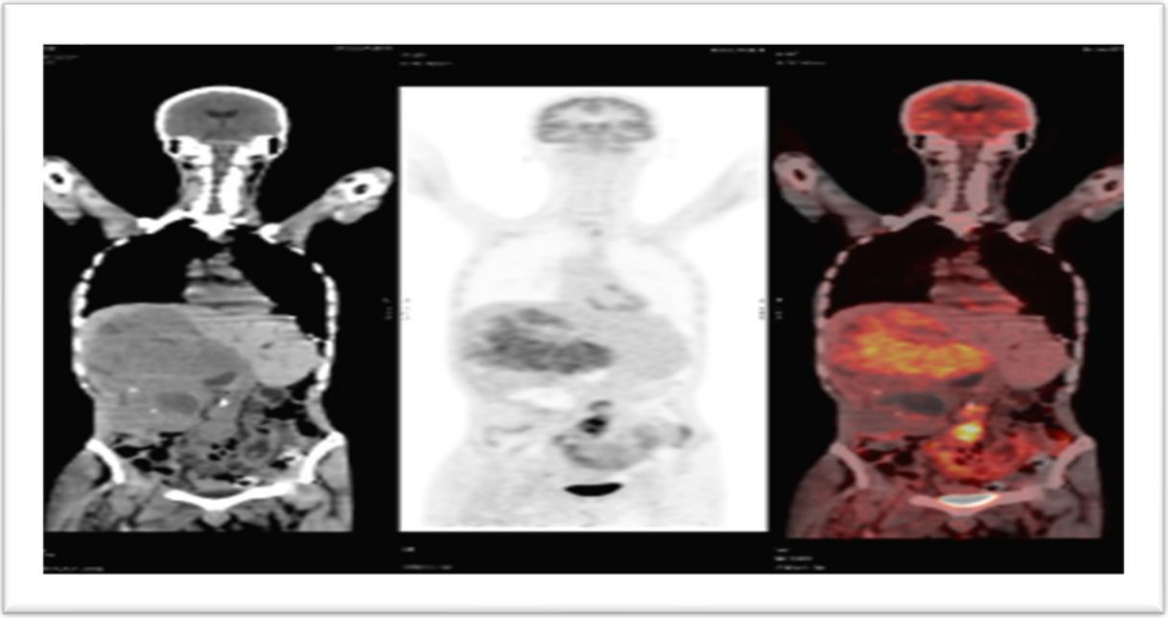

Figure 1: thirty-three-year-old old male, known duodenal GIST- intermediate risk with nodal and liver metastases. The patient received Imatinib Mesylate. The patient was referred to perform PET/CT. PET CT Coronal images revealed Metabolic activity in some of the hepatic focal lesions as well as multiple FDG avid metastatic para-aortic lymph nodes.

DISCUSSION:

Malignant GIST exhibits a propensity for liver and peritoneal metastasis or recurrence; however, primary lymph node involvement or metastasis is uncommon. [(1)]. Surgery involving optimal primary tumor resection constitutes the primary approach for curative treatment; however, lymph node dissection is not routinely conducted due to the infrequency of nodal metastasis [(2)]. For many years, CT has been utilized for the initial staging of GIST and for monitoring the response to Imatinib therapy, depend on tumor size and density (HU) changes. F-18 Fluoro-deoxy-glucose PET/CT plays a recognized role in the management of cancer. The integration of metabolic and

morphologic information in PET/CT enhances diagnostic accuracy, minimizes pitfalls, and significantly alters therapeutic strategies for numerous patients [3]. The characteristics and prognosis of GIST patients with lymph node metastasis remain inadequately understood. This study aimed to assess the diagnostic and prognostic significance of FDG PET/CT in identifying nodal metastases and evaluating the response to Imatinib Mesylate (Gleevec), as well as to determine its prognostic implications. The results indicate that lymph node (LN) metastasis was observed in 29 patients (18.2%), with a mean age of 53.2±12.7 years. Gastric was the site of the primary in 62% of cases, with high-risk spindle cell pathology observed in 69% of patients. Isolated nodal metastases were observed in only 6 patients, while the remaining 23 patients exhibited double and triple metastatic sites, including liver and/or peritoneal deposits. The percent of lymph node metastases in GIST is varying in different studies .Gong, et al described very close results to our study, he investigating total of 29 GIST patients, 6 of them presented with lymph node metastasis, corresponding to (20.7%) [4]. **Zhang et al**. in his study conducted on 16 medical centers on china and including 1109 patients, He reported that nodal metastases ~7.7% on total patients with GIST [5]. **Naguib** et al. reported 19 patients with gastric GIST at the National Cancer Institute of Egypt, where lymph node dissection was performed in 5 cases. Approximately 26% of patients. The dissection was performed due to significant lymph node enlargement [6]. **Agaimy and Wünsch** (2009) identified two instances of lymph node involvement in a cohort of 210 patients. One individual presented with Carney syndrome. A review was conducted on 699 patients, yielding notable conclusions. The incidence of nodal involvement was 1%. Individuals with lymph node involvement were ~20 years younger than others without

nodal metastasis, and the male to female ratio was 1:3. Furthermore, patients exhibiting lymph node metastasis demonstrated a reduced mutation rate in KIT/PDGFR. [7] Regarding the site of the primary, In agreement to our results, **Agaimy and Wünsch** mentioned that high rate of LN spread was present in tumors located in distal stomach and with histology epithelioid [7] In contrary, **Zhang et al.** showed that stomach was not the common site of primary neoplasm [5]. However, their study agreed with ours that high risk spindle cell was the most common pathology [5]. **Ma Maoguang** presented a distinctive perspective regarding the types of metastatic cell types in GIST lymph nodes. He posits that (spindle cells) may undergo (mesenchymal- epithelial transformation) (MET), resulting in the development of epithelial cells with metastatic characteristics via the lymphatic vessels, leading to LN metastasis [8]. On current study, a total of 89 lymph nodes were detected (70 abdomino-pelvic and 17 with mediastinal deposits). The mean size was 2.1 cm in size (range 1-8.7 cm), Regarding the prognosis of the included patients with nodal metastases, there is contra Verica in this issue in literature, Evidence suggests that lymph node metastasis in (soft tissue sarcoma) is associated with an inadequate prognosis. While GIST is classified as a mesenchymal tumor, some researchers argue that lymph node metastasis does not correlate with poor prognosis. On current study, 21 patient (72.4%) of metastatic with nodal metastases group experience disease progression compared to 55% in metastatic patient without nodal involvement and for only 6.5% on non-metastatic patients. (P value <0.001). Four out of the 29 patients with nodal metastases died (13.7%) compared to ~10% and 4.9% on other metastatic and non-metastatic groups respectively, which failed to reach a statistical significance. (P value ~ 0.841) There was no relations between the

incidence of nodal metastases and the age, sex and site of primary, only the high grade pathology shows significant statistical indices. (<0.001). In **Valadao et al.** study involving 29 patients, three cases exhibited lymph node metastasis, which did not negatively affect prognosis [9]. Their findings indicated that the size and grade served as prognostic factors. **Agaimy and Wünsch** contest this notion, asserting that further research is necessary to reach a definitive conclusion [7]. **Prakash et al**. conducted a review of 15 cases of (GIST) in patients under 30 years of age, noting that among those under 18 years, three cases exhibited lymph node metastasis. In one instance, LN metastasis was primary, while in two instances, lymph node involvement was associated with recurrence. The study concluded that GIST in patients under 18 years exhibits distinct clinical and genetic characteristics. While a comparable clinical course is observed in both pediatrics and adult patients, some authors have concluded that gastrointestinal stromal tumours (GIST) exhibit a more indolent nature in the pediatric population. Furthermore, the findings for individuals aged 18 to 30 were not definitive [10,11]

Limitations of the current study:

first, it is selected and retrospective analysis; 2nd, the small sample size is attributable to the rarity of nodal metastases in low-incidence GIST pathology. Third, the current study could not establish a correlation with primary tumor size or mitotic count (per 10 high power fields) (HPF). Finally, the use of SUVmax in PET parameters is not entirely accurate and is influenced by various factors, leading to a lack of proper standardization. Therefore, evaluating other FDG PET-parameters such as MTV and TLG may provide a more accurate assessment.

CONCLUSION:

lymph node metastasis occurs in 18.2% of cases and is believed to be an adverse prognostic factor in patients with GIST. FDG PET/CT appears to be an effective modality for nodal detection and evaluating response to Imatinib therapy.

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