Role of FDG PET-CT in evaluation of Gastrointestinal stromal tumors (GIST)

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By

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ABSTRACT

Imatinib mesylate is a selective, potent, small molecule inhibitor of a family of structurally related tyrosine kinase signaling enzymes . For recurrent or metastatic GIST, the standard of care is treatment with imatinib , the appropriate initial dose is 400 mg/d . Moreover , patients can be treated with neo-adjuvant Imatinib until the optimal time for surgery (when the GIST becomes resectable and the chance of morbidity is acceptable) .

In the present study we attempted to compare the performance of diagnostic CT and F-18 FDG PET/CT in staging and assessment of therapy response of 47 consecutive patients, 18 patients was non metastatic, while the remaining 29 patients had dominating liver, peritoneal and nodal deposits (mean age : 49.2±12.7) with histologically proven GIST. A clinical/radiological CT and PET/CT follow-up of 3-15 months duration served as standards of reference.

Diagnostic CT and PET/CT show comparable results in initial staging , although PET/CT was able to detect more lesions per patient (subcentimetric lymph nodes, few additional peritoneal deposits and marrow based metastases) missed by radiologists, this difference in performance did not had a significant statistical difference. Yet , when planning to assess therapy response with PET CT , a baseline study is essential as approximately 20% of lesions are not FDG avid in initial study .

Keywords

Role of FDG PET-CT in evaluation of Gastrointestinal stromal tumors (GIST)

LIST O ABBREVIATIONS

Abbrev.	*Full Term*
CT	Computed tomography
CMR	Complete metabolic response
EUS	Endoscopic ultrasound
EORTC	The European Organisation for Research and Treatment of Cancer
FNA	Fine needle aspiration
FDG	18F-2-fluoro-2-deoxy-d-glucose
GISTs	Gastrointestinal stromal tumors
GIT	Gastrointestinal tract
68Ga	Galluim-68
HU	Hounsfield unit
HAE	Hepatic arterial embolization
ICCs	Interstitial cells of Cajal
IM	Imatinib Mesylate
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
PERCIST	PET Response Criteria in Solid Tumors
PDGFRA	Platelet-derived growth factor receptor alpha
PET	Positron emission tomography
PMR	Partial metabolic response
PMD	Progressive metabolic disease
ROI	Region of interest
RECIST	Response Evaluation Criteria In Solid Tumors
SEER	Surveillance, Epidemiology, and End Results
SUV	The standardized uptake value
SUL	Standardized uptake value (SUV) normalized by lean body mass
SMD	Stable metabolic disease
TNB	True cut needle biopsy
TKI	Tyrosine Kinase Inhibitors
TLG	Total lesion glycolysis
UICC	The international union against cancer

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract (1).

The first accurate description of mesenchymal neoplasms of the gastrointestinal tract (GIT) was in 1941. Traditionally, these tumors were thought to be derived from smooth muscle cells, based on their resemblance to smooth muscle tumors and they were designated as leiomyomas, bizarre leiomyomas, cellular leiomyomas and leiomyosarcomas. However, with the advent of electron microscopy, it has been shown that many of these neoplasms lacked the immunophenotypical features of smooth muscle differentiation (2) .

With the advent of immunohistochemical analysis a definition of a new entity among the gastrointestinal mesenchymal tumors called the gastrointestinal stromal tumors (GISTs) which particularly express the kit (CD117) protein a growth factor trans-membrane receptor with tyrosine kinase activity (3).

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(4).

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. Patients who become refractory on Imatinib may respond to the multiple tyrosin kinase inhibitor sunitinib (Sutent) (5).

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 (6) .

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 constraints (7).

AIM OF WORK

The aim of this study was to evaluate the feasibility, utility, and efficacy of 18FDG-PET/CT in staging patients affected by GIST , those who were treated by surgery or imatinib mesylate and comparing the results with diagnostic CT for a validation.

Epidemiology of GIST

Incidence of GIST: Gastrointestinal stromal tumors (GISTs) account for less than 1% of gastrointestinal tumors, however, are the most common mesenchymal neoplasms of the gastrointestinal tract. GISTs are usually found in the stomach or small intestine but can occur anywhere along the gastrointestinal tract and rarely have extra-gastrointestinal involvement (7) .

GISTs rank a distant third in prevalence behind adenocarcinomas and lymphomas among the histologic types of gastrointestinal tract tumors (8) .

Age and Sex : predominantly occur in middle aged and older patients (fifth to seventh decades (9) .

SEER (Surveillance, Epidemiology, and End Results) analysis of 1,458 cases from 1992 to 2000 data reported a slightly higher prevalence in males versus females, at 54% and 46%, respectively (10) .

Anatomical Location of GIST: GISTs are usually found in the stomach or small intestine but can occur anywhere along the gastrointestinal tract and rarely have extra-gastrointestinal involvement. The size of the tumor may be smaller than 1 cm or as large as 40 cm in diameter.

Approximately 50-70% of GISTs originate in the stomach. The small intestine is the second most common location, with 20-30% of GISTs arising from the jejuno-ileum. Less frequent sites of occurrence include the colon and rectum (5-15%) and esophagus (< 5%). Primary

pancreatic, omental, or mesenteric GISTs have been reported but are very rare (7) .

The distribution of GISTs in the stomach is as follows: pars media (40%); antrum (25%); pylorus (20%); submucosa (60%); subserosa (30%); and intramural (10%) (11) .

Less than 1 % of GISTs initially occur outside of these organs (12) . These tumors submucosal lesions, which most frequently grow endophytically in parallel with the lumen of the affected structure (10).

Mortality/Morbidity: Outcomes in patients with GISTs are highly dependent on the clinical presentation and the histopathological features of the tumor. The overall 5-year survival rate ranges from 28-60%. This can be stratified for patients presenting with localized primary disease and those presenting with metastatic or recurrent disease. The median survival rate in the former group is 5 years, while the median survival rate in the latter group is approximately 10-20 months (8) .

Pathology of GIST

Cells of Origin of GIST "ICCS":

GISTs have been misclassified as leiomyomas, leiomyosarcomas and leiomyoblastomas. With the advent of immunohistochemistry and electron microscopy, it was discovered that GIST cells of origin are probably related not to smooth muscle cells but to the cells of Cajal (13) .

According to the work of Kindblom (13) , the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal. These are GI pacemaker cells found in the muscularis propria and around the myenteric plexus and are largely responsible for initiating and coordinating GI motility .

Both GIST cells and cells of Cajal 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 (14). In 1998, Hirota et al. reported 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 (15) .

Gross Pathological Features:

GISTs range in size from incidental lesions a few millimeters in diameter to large masses of 35 cm or more; the median size at presentation is about 5 cm. The tumors are generally centered on the bowel wall but may form polypoid serosal- or mucosal-based masses (16). Ulceration of the mucosa is often associated with GI bleeding.