PET/Computed Tomography and Precision Medicine: Gastric Cancer

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KEYWORDS

• Gastric cancer • Gastric carcinoma • Gastric lymphoma • PET • PET/CT

KEY POINTS

- National Comprehensive Cancer Network guidelines for the management of gastric cancer workup algorithm for patients with newly diagnosed gastric cancer includes fluorine-18 fluoro-2-deoxy-D-glucose PET/computed tomography (^{18}F-FDG PET/CT) evaluation, especially when metastatic cancer is not evident and in the use of ^{18}F-FDG PET/CT in the posttreatment assessment and re-staging of these patients.
- The metabolic activity of the primary tumor in the staging ^{18}F-FDG PET/CT may help in surgical planning and identifying different gastric cancer histopathologies.
- ^{18}F-FDG PET/CT provides value in detecting metastases, especially distant metastases and synchronous second malignancies, treatment response assessment and modifying therapy for individual patients.
- ^{18}F-FDG PET/CT has good performance in the detection or recurrent disease and follow-up of these patients.
- The metabolic tumor markers measured in an ^{18}F-FDG PET/CT study can provide valuable prognostic information.

INTRODUCTION

There are about 7.4 new cases of gastric cancer per 100,000 men and women per year in the United States. It is the fifteenth leading cause of cancer death. The number of deaths estimated is 3.3 per 100,000 men and women per year, between 2009 and 2013. The lifetime risk of developing gastric cancer is approximately 0.9%. The estimated number of new cases in 2016 is 26,370, and the estimated number of deaths due to gastric cancer is 10,730. Gastric cancer is more common in men than women and other

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ethnicities than non-Hispanic whites. Age, diet, and stomach disease, including infection with *Helicobacter pylori*, can affect the risk of developing gastric cancer. The overall 5-year survival for gastric cancer is only 30.4%. The 5-year survival decreases with the stage of the disease, ranging from 66.9% in patients with localized disease to 30.9% in regional disease and 5.0% in distant disease, respectively.[1] The treatment algorithm of gastric cancer ranges from surgical resection to palliative systemic therapy depending on the clinical stage of the disease and warrants accurate staging of the disease and appropriate treatment planning to improve the survival in these patients. Imaging plays a vital role in accurate and rapid staging of these patients. According to the National Comprehensive Cancer Network (NCCN) guidelines for the management of gastric cancer, the workup algorithm for patients with newly diagnosed gastric cancer includes fluorine-18 fluoro-2-deoxy-D-glucose PET/computed tomography (^{18}F-FDG PET/CT) evaluation, if clinically indicated and if metastatic cancer is not evident. It also recommends the use of ^{18}F-FDG PET/CT in the post-treatment assessment and restaging of these patients.[2] The histopathology of gastric tumors varies depending on which layer of the stomach they arise from. Most gastric cancers arise from the glands of the gastric mucosa and are classified as adenocarcinomas. Gastric cancers can also originate from other components of the stomach, such as the lymphoid tissue, neuroendocrine cells, or the muscular layers of the stomach wall. The behavior of gastric tumors varies based on their histopathology, and hence, the treatment plan is also tailored to the type of gastric cancer.[3,4]

Although most gastric cancers have been found to be sporadic, true hereditary gastric cancers contribute to a very small proportion of patients. It has been found that nearly 40% of hereditary gastric cancers exhibit mutated CDH1, leading to defective or loss of expression of E-cadherin, which in turn results in activation of epidermal growth factor receptor (EGFR). Genetic susceptibility to gastric cancer may also be conferred by several single nucleotide polymorphisms, particularly in the genes coding for inflammatory cytokines, such as interleukin-1, tumor necrosis factor-α, and so forth, and carbone metabolism methylenetetrahydrofolate reductase, which play a critical role in regulation of DNA methylation and epigenetic modulation. Several signaling pathways are known to be altered during gastric carcinogenesis, and the precise cause-and-effect relationship for these changes is not clear. The altered pathways include EGFR, c-MET oncogene overexpression, vascular endothelial growth factor receptor, mammalian target of rapamycin, fibroblast growth factor, Hedgehog PATCH1 smoothened pathway, mitogen-activated protein kinase, and kinase-extracellular signal-regulated kinase pathway. Many of these altered pathways are involved in cell proliferation, angiogenesis, apoptosis, and cell cycle and can result in cancer. An important target in human malignancy is the EGFR family. This family includes EGFR/HER1, HER2/neu, HER3, and HER4. Stimulation of pathways involving these receptors influences cell proliferation, differentiation, migration, and apoptosis. HER2/new oncogene amplification results in HER2-receptor overexpression and can enhance and prolong signals that lead to uncontrolled cell growth and tumorigenesis. The incidence of HER2-positive gastric cancer has been reported to be as high as 22%. These targets are also being used for directed therapies.[5–7]

^{18}F-FDG PET/CT has been shown to provide valuable information in the staging, treatment response evaluation, detecting recurrence, follow-up, and prognosis in patients with gastric cancer. Some studies have also shown that the imaging of gastric cancers is also possible with the proliferation marker ^{18}F Fluorothymidine, and that it can be more sensitive in gastric tumors without or with low FDG activity. It has also shown good performance in the evaluation of the primary tumor and regional lymph nodes.[8–10] The aim of this review article is to provide a concise summary of the available literature on ^{18}F-FDG PET/CT and its role in the evaluation and management of gastric cancer.

DIAGNOSIS AND STAGING OF GASTRIC CANCER

The role of ^{18}F-FDG PET/CT in the evaluation of the primary tumor, locoregional and distant lymph node involvement, and distant metastases has been described in the following few sections. The final importance of these findings is that ^{18}F-FDG PET/CT plays an important role in accurately staging these patients and thereby having an impact on the management and prognosis of these patients: tailoring the therapy for these patients and influencing the outcomes. In a study involving 608 patients with biopsy-proven gastric adenocarcinoma, FDG-PET changed the stage in 28.9% patients. Of those who were upstaged, 64.5% developed progressive disease.[11] Similarly, in gastric lymphoma, ^{18}F-FDG PET/CT changed the stage in up to 35% of patients with a primary gastric lymphoma.[12]