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CLINICAL—PANCREAS

Prognostic Utility of Total ^{68}Ga-DOTATATE-Avid Tumor Volume in Patients With Neuroendocrine Tumors

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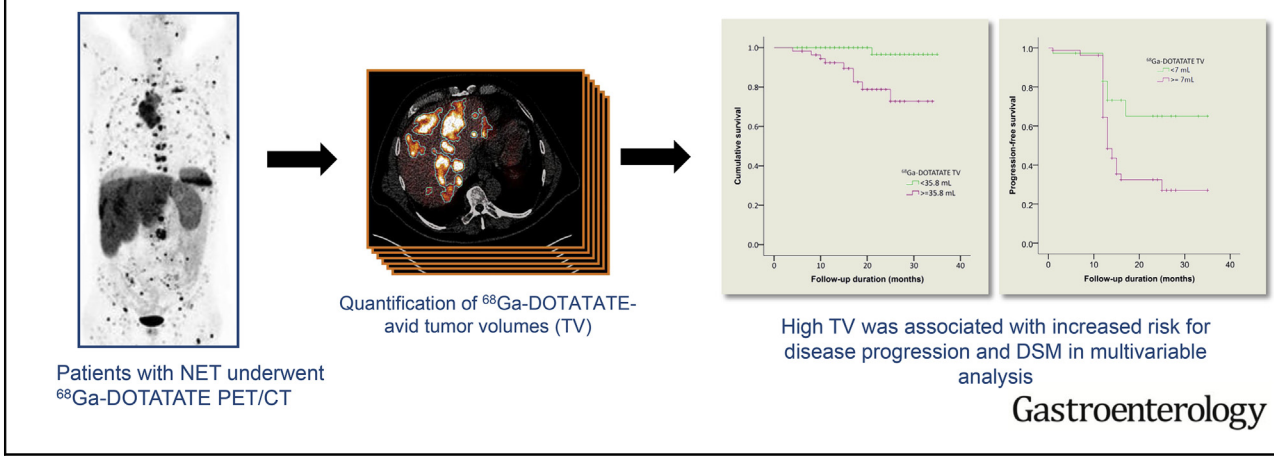

BACKGROUND & AIMS: Survival times vary among patients with neuroendocrine tumors (NETs) – even among those with the same site, stage, and grade of primary tumor. This makes it difficult to select treatment for patients with unresectable NETs because some patients can survive decades without treatment. ^{68}Gallium-DOTATATE positron emission tomography with computed tomography (^{68}Ga-DOTATATE PET/CT) is a sensitive imaging technique for detection of NETs. We investigated the prognostic accuracy of ^{68}Ga-DOTATATE PET/CT-based analysis of tumor volume in patients with NETs. **METHODS:** We performed a prospective study of 184 patients with NETs (128 [69.6%] with metastases and 11 patients [6.0%] with locally advanced disease) at the National Institutes of Health Clinical Center (Bethesda, MD) from 2013 through 2017. All patients underwent ^{68}Ga-DOTATATE PET/CT image analysis and total ^{68}Ga-DOTATATE-Avid tumor volume (^{68}Ga-DOTATATE TV) was determined. We also measured fasting serum chromogranin A, neuron-specific enolase, gastrin, glucagon, vasoactive intestinal peptide, pancreatic polypeptide, and 24-hour urinary 5-hydroxyindoleacetic acid levels in all patients. Disease progression was defined as a new lesion or a growth of a known lesion during the interval between baseline ^{68}Ga-DOTATATE PET/CT scan and follow-up imaging (14.0 ± 6.1 months; range, 1–35 months). The primary outcomes were progression-free survival (PFS) and disease-specific mortality during a median follow-up time of 18 months (range, 4–35 months). **RESULTS:** We found an inverse correlation between quartiles of ^{68}Ga-DOTATATE TV and PFS ($P = .001$) and disease-specific survival ($P = .002$). A ^{68}Ga-DOTATATE TV of 7.0 mL or more was associated with higher odds of disease progression (hazard ratio, 3.0; $P = .04$). A ^{68}Ga-DOTATATE TV of 35.8 mL or more was associated with increased risk of disease-specific death (hazard ratio, 10.6) in multivariable analysis ($P = .01$), as well as in subgroup analysis of patients with pancreatic NETs. **CONCLUSIONS:** In a prospective study, we demonstrated the prognostic utility of ^{68}Ga-DOTATATE TV in a large cohort of patients with NETs, in terms of PFS and disease-specific mortality.

Keywords: Survival; Radiology; Tumor Size; Pancreas.

EDITOR'S NOTES

BACKGROUND AND CONTEXT

^{68}Gallium-DOTATATE positron emission tomography with computed tomography (^{68}Ga-DOTATATE PET/CT) is a sensitive imaging technique for detection of neuroendocrine tumors (NETs).

NEW FINDINGS

A prospective study demonstrated the prognostic utility of ^{68}Ga-DOTATATE TV in a large cohort of patients with NETs, in terms of PFS and disease-specific mortality.

LIMITATIONS

The heterogenous study cohort consisted of patients with various primary NET locations, and of different disease stages and grades. These results need to be validated in future studies.

IMPACT

This new data could be used to determine the need for treatment intervention, frequency of follow up and ultimately lead to precision medicine in patients with NET.

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies arising from neuroendocrine cells that are dispersed throughout the human body. About two thirds of NETs originate from the gastrointestinal tract and pancreas, 25% from the bronchopulmonary tract, and the remaining are from other sites.[1] The incidence of NETs is increasing and is estimated to exceed 6 cases per 100,000 people per year.[2] Although most NETs have an indolent course, a subset of patients with NETs have aggressive disease, and a substantial number of patients with NETs present with distant metastases at initial diagnosis.[3–5]

Many treatment options have been developed over the last decade for patients with locally advanced and metastatic NETs. Such new treatments include medical therapy with somatostatin analogs,[6,7] everolimus,[8,9] sunitinib,[10,11] liver-directed therapies,[12] and peptide receptor radionuclide therapy.[13] However, the optimal timing of treatment interventions for NETs is unknown because the disease course of patients with locally advanced and metastatic NETs is highly variable, even when patients have the same tumor stage and grade. Thus, new clinical prognostic tools are required to select the population of patients that are at risk of disease-progression and disease-specific mortality. Such prognostic tools could determine which patients with NETs would benefit from treatment intervention, the type and timing of treatment, and whether the treatment-associated side effects are justified in light of the estimated life expectancy and their impact on quality of life.

Positron emission tomography (PET)/computed tomography (CT) imaging has been shown to improve the management of patients with both solid and hematologic malignancies. For example, in patients with non–small-cell lung cancer, preoperative ^{18}Fluoro-deoxy-glucose (^{18}FDG) PET/CT scanning reduced the number of thoracotomies,[14] and its use for surveillance of advanced head and neck cancer reduced the intervention rate.[15] In patients with Hodgkin's lymphoma, the use of ^{18}FDG-PET/CT might avert further radiotherapy in patients with early disease[16] and lead to reduced treatment toxicity among those with advanced disease.[17] The clinical utility of measuring total ligand-avid tumor volume (TV) based on PET/CT scanning has been evaluated in patients with cancer in small-cohort and/or retrospective studies. For example, ^{18}FDG-PET/CT-based volume measurements predicted shorter progression-free survival (PFS) in follicular lymphoma[18] and breast cancer,[19] and total ^{11}C-Methionine-avid volume predicted PFS in high-grade glioma.[20] Furthermore, ^{18}FDG-PET/CT TV in multiple myeloma,[21] adrenocortical carcinoma,[22] and non–small-cell lung cancer[23] were associated with patient survival, as was ^{18}F-fluoroethyl-tyrosine (^{18}F-FET) PET/CT in patients with gliomas.[24] A large prospective study has shown that a high SUVmax (>3) derived from ^{18}F-FDG PET/CT was independently associated with shorter PFS in patients with NETs.[25] Furthermore, the combined use of ^{68}Gallium-DOTATATE (^{68}Ga-DOTATATE) and ^{18}F-FDG PET/CT scans was found to be beneficial in the clinical management of patients with poorly differentiated NET.[26]

Radiolabeled somatostatin receptor (SSR)-binding molecules with PET/CT imaging are commonly used to stage patients with NETs.[27] This imaging approach is highly sensitive for detecting sites of NETs because these tumors express SSR. Among the new-generation radiolabeled high-affinity SSR ligands (DOTATATE, DOTATOC, DOTANOC) developed and evaluated in studies, ^{68}Ga-DOTATATE PET/CT imaging is one of the more sensitive and specific imaging modalities for detecting NETs.[28] To our knowledge, no study has utilized this quantitative imaging measurement approach in patients with NETs who had ^{68}Ga-DOTATATE PET/CT imaging to determine if it has any prognostic utility.

In this prospective study, we evaluated the prognostic utility of ^{68}Ga-DOTATATE TV as a marker for PFS and disease-specific mortality in a large cohort of patients with NETs. In addition, we performed multivariable analyses of other clinical and biochemical variables associated with PFS and disease-specific mortality.

Methods

Study Population

Patients known to have NETs based on imaging (CT, magnetic resonance imaging [MRI], and ^{18}F-FDG PET) and biochemical evidence, and/or a pathologically confirmed NET,

Abbreviations used in this paper: **^{18}FDG, ^{18}Fluoro-deoxy-glucose; ^{68}Ga-DOTATATE, ^{68}Gallium-DOTATATE; CT, computed tomography; HR, hazard ratio; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PFS, progression-free survival; PNET, pancreatic neuroendocrine tumor; SINET, small intestine neuroendocrine tumor; SSR, somatostatin receptor; TV, tumor volume; WHO, World Health Organization.**

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