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Rathan M. Subramaniam

Neuroendocrine Neoplasms: Epidemiology, Diagnosis, and Management 161

Ajitha Ramesh, Aniruddha Chatterjee, and Rathan M. Subramaniam

Neuroendocrine tumors have variety of biological and clinical characteristics. The classification of neuroendocrine neoplasm has evolved, and the newest 2019 World Health Organization classification outlines a well-differentiated high-grade G3 subtype, recognizing its differences from the poorly differentiated neuroendocrine carcinoma. ⁶⁸Ga-DOTAT PET has largely replaced somatostatin scintigraphy as the diagnostic workup choice for NENs. NETest, a multi-analyte liquid biopsy, is a promising recent development in the biochemical diagnosis. Management includes wait and watch approach, surgical resection, somatostatin analogs, ¹⁷⁷Lu DOTATATE therapy, chemotherapy, radiotherapy or immunotherapy combinations. Further clinical trials are necessary for determining the appropriate sequencing.

Neuroendocrine Neoplasms: Genetics and Epigenetics 169

Jim Smith, Edward Barnett, Euan J. Rodger, Aniruddha Chatterjee, and Rathan M. Subramaniam

Neuroendocrine neoplasms (NENs) are a group of rare, heterogeneous tumors of neuroendocrine cell origin, affecting a range of different organs. The clinical management of NENs poses significant challenges, as tumors are often diagnosed at an advanced stage where overall survival remains poor with current treatment regimens. In addition, a host of complex and often unique molecular changes underpin the pathobiology of each NEN subtype. Exploitation of the unique genetic and epigenetic signatures driving each NEN subtype provides an opportunity to enhance the diagnosis, treatment, and monitoring of NEN in an emerging era of individualized medicine.

Gastroenteropancreatic Neuroendocrine Tumor Diagnosis: DOTATATE PET/CT 189

Asha Kandathil and Rathan M. Subramaniam

Gastroenteropancreatic neuroendocrine tumors (NETs), which arise from the small intestine, rectum, colon, appendix, or pancreas, have variable malignant potential with clinical behavior determined by proliferative activity according to the Ki-67 index and tumor differentiation. Somatostatin receptor (SSTR) expression by NETs allows SSTR imaging using ⁶⁸Ga-DOTATATE PET/computed tomography (CT) and treatment with octreotide or SSTR-targeted peptide receptor radionuclide therapy (PRRT). ⁶⁸Ga-DOTATATE PET/CT is indicated for localization of the primary tumor in select cases, staging patients with known NET, and selecting patients for PRRT. NCCN guidelines consider imaging with ⁶⁸Ga-DOTATATE PET/CT appropriate for staging and receptor status assessment.

Gastro-Enteric-Pancreatic Neuroendocrine Tumor Treatment: ^{177}Lu -DOTATATE 201

Yasemin Sanli, Dilara Denizmen, and Rathan M. Subramaniam

^{177}Lu -DOTA-TATE therapy is a highly effective therapy in metastatic, well-differentiated, somatostatin receptor-positive GEP-neuroendocrine tumors (NETs) with mostly tolerable adverse effects. Guidelines generally refer to peptide receptor radionuclide therapy as a second-line therapy after SSA in gastroenteric and second- or third-line therapy in pancreatic NETs to improve survival rates and quality of life. Although we do not have sufficient data, ^{177}Lu -DOTA-TATE therapy may also have a role in high-grade NET therapy, mostly in combination with other treatments such as chemotherapy.

Gastro-Enteric-Pancreatic Neuroendocrine Tumor Treatment: Actinium-225-DOTATATE and Combined Therapies 215

Swayamjeet Satapathy, Kunal Ramesh Chandekar, and Chandrasekhar Bal

The role of lutetium-177-DOTATATE in advanced well-differentiated gastro-entero-pancreatic neuroendocrine tumors is well established. However, there is a scope for improving treatment outcomes. Actinium-225-DOTATATE is a form of targeted alpha therapy (TAT) that results in more efficient tumor cell killing owing to the substantially higher linear energy transfer of alpha particles. Systemic TAT is also safe given that the shorter path length of the alpha particles spares the surrounding healthy tissue and results in relatively fewer adverse events. Combination therapies with radiosensitizing and other chemotherapeutic agents have also gained popularity, especially in the setting of higher grade and fluorodeoxyglucose-avid tumors.

Diagnosis and Treatment of Lung Neuroendocrine Neoplasms: Somatostatin Receptor PET Imaging and Peptide Receptor Radionuclide Therapy 223

Hyesun Park and Rathan M. Subramaniam

Recently, advancement of somatostatin receptor (SSTR) imaging and theragnostic approach using peptide receptor radionuclide therapy (PRRT) have changed the paradigm of diagnosis and management of neuroendocrine tumor. ^{68}Ga -DOTA-TATE PET/CT can diagnose the lung carcinoids with high SSTR expression. With combination of ^{68}Ga -DOTATATE PET/CT and ^{18}F -FDG PET/CT, tumor heterogeneity of lung carcinoid can be identified, which may guide optimal patient selection for PRRT. PRRT may be an effective and safe treatment of advanced lung carcinoids during progression with first-line somatostatin analog therapy. This review provides updates on the diagnosis and management of lung carcinoids, focusing on SSTR imaging and PRRT.

Paragangliomas and Pheochromocytomas: Positron Emission Tomography/Computed Tomography Diagnosis and Therapy 233

Charles Marcus and Rathan M. Subramaniam

Molecular imaging evaluation of pheochromocytomas and paragangliomas depends on multiple factors, such as localized versus metastatic disease, the genetic, and biochemical profile of tumors. Positron emission tomography/computed tomography (PET/CT) imaging of these tumors outperforms Meta-Iodo-Benzyl-Guanidine (MIBG) scintigraphy in most cases. A few PET radiotracers have been studied in evaluating these patients with somatostatin receptor PET imaging and have shown superior performance compared with other agents in most of these patients. ^{18}F -fluorodeoxyglucose PET/CT imaging is useful in select patients, such as those with succinate dehydrogenase complex subunit B-associated disease. Treatment strategy depends on multiple factors and necessitates a multidisciplinary approach.

Gastro-Entero-Pancreatic Tumors: FDG Positron Emission Tomography/Computed Tomography 243

Wajahat Khatri, Ergi Spiro, Amanda Henderson, Steven P. Rowe, and Lilja B. Solnes

Gastro-entero-pancreatic tumors comprise a group of heterogenous neoplasms, with medical imaging being paramount in the diagnosis, staging, and treatment planning of these tumors. Moreover, with the advent of newer radiopharmaceuticals, such as ^{68}Ga -labeled and ^{64}Cu -labeled somatostatin analogs (eg, ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE, ^{68}Ga -DOTANOC, and ^{64}Cu -DOTATATE) that bind to the somatostatin receptor (SSTR), molecular imaging plays an increasing and critical role in the diagnosis, staging, and treatment planning of these neoplasms. Dual-tracer imaging with ^{18}F -FDG PET/CT and SSTR agents may play a significant role in treatment planning and predicting patient outcomes in the setting of high-grade or poorly differentiated neuroendocrine tumors.

Neuroendocrine Neoplasms: Total-body PET/Computed Tomography 251

Guobing Liu, Chi Qi, and Hongcheng Shi

Total-body PET/computed tomography (CT) (uExplorer) static and dynamic scan using low-dose (48.1 to 73.6 MBq) gallium-68 (^{68}Ga) DOTATATE combined with low-dose (1.55 MBq/kg) or ultra-low-dose (0.37 MBq/kg) ^{18}F -fluorodeoxyglucose (^{18}F -FDG) were used as a routine in patients with neuroendocrine neoplasms (NENs). ^{68}Ga DOTATATE and ^{18}F -FDG PET/CT static imaging play complementary roles in diagnosis, staging, and therapy-response evaluation in a patient with NENs. Kinetic parameters and time activity curve derived from the dynamic scan is helpful for understanding tumors biological characteristics and differential diagnosis of NENs.

Neuroendocrine Tumor Diagnosis: PET/MR Imaging 259

Heying Duan and Andrei Iagaru

Imaging plays a critical role in the diagnosis and management of neuroendocrine tumors (NETs). The initial workup of the primary tumor, including its characterization, local and distant staging, defines subsequent treatment decisions. Functional imaging using hybrid systems, such as PET combined with computed tomography, has become the gold standard. As NETs majorly arise from the gastrointestinal system and metastasize primarily to the liver, simultaneous PET and MR imaging with its high soft tissue contrast might be a valuable clinical one-stop-shop whole-body imaging tool. This review presents the current status and challenges of PET/MR imaging for diagnosis of NETs.

Neuroendocrine Tumor Therapy Response Assessment 267

Vetri Sudar Jayaprakasam and Lisa Bodei

Peptide receptor radionuclide therapy has become an integral part of management of neuroendocrine neoplasms. Gallium-68- and lutetium-177-labeled somatostatin receptor analogues have replaced yttrium-90- and ^{111}In -based tracers. Several newer targeted therapies are also being used in clinical and research settings. It is imperative to accurately evaluate the response to these agents. The characteristics of NENs and the response patterns of the targeted therapies make response assessment in this group challenging. This article provides an overview of the strengths and weaknesses of the various biomarkers available for response assessment.