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Advances in the Diagnosis of Neuroendocrine Neoplasms

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Somatostatin receptor PET/CT using ^{68}Ga-labeled somatostatin analogs, is a mainstay for the evaluation of the somatostatin receptor status in neuroendocrine neoplasms. In addition, the assessment of glucose metabolism by ^{18}F-FDG PET/CT at diagnosis can overcome probable shortcomings of histopathologic grading. This offers a systematic theranostic approach for the management of neuroendocrine neoplasms, that is, patient selection for the appropriate treatment—surgery, somatostatin analogs, peptide receptor radionuclide therapy, targeted therapies like everolimus and sunitinib, or chemotherapy—and also for therapy response monitoring. Novel targets, for example, the chemokine receptor CXCR4 in higher-grade tumors and glucagon like peptide-1 receptor in insulinomas, appear promising for imaging. Scandium-44 and Copper-64, especially on account of their longer half-life (for pretherapeutic dosimetry) and cyclotron production (which favors mass production), might be the potential alternatives to ^{68}Ga for PET/CT imaging. The future of molecular imaging lies in Radiomics, that is, qualitative and quantitative characterization of tumor phenotypes in correlation with tumor genomics and proteomics, for a personalized cancer management.
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Introduction

Neuroendocrine neoplasms (NENs) have a low incidence (but relatively high prevalence) and build an extremely heterogeneous group of epithelial neoplasms that are characterized predominantly by neuroendocrine differentiation.[1,2] Gastroenteropancreatic (GEP) NENs are classified according to the World Health Organization (WHO) (new WHO guidelines are going to be published soon) based on proliferation (Ki67 index, mitotic count rate) and differentiation. NENs of the lungs, also referred to as pulmonary carcinoids, are classified according to their mitotic count and the presence of necrosis.[2] The incidence of GEP-NENs has increased in recent years, probably also because of better sensitivity of the imaging modalities used.[3,4] Pulmonary NENs account for 1%-2% of all lung tumors and approximately 30% of all NENs.[5,6] Functional imaging is pivotal in the diagnosis of NENs, principally because of its ability to provide information for therapeutic planning. Particularly, NENs with a Ki67 index $\leq$20% (WHO G1 and G2) have an overexpression of membrane bound somatostatin receptors (SSTRs), which can be targeted with radiolabeled analogs.[7,8]

Positron emission tomography/computed tomography (PET/CT) using ^{68}Ga-labeled somatostatin analogs, which bind specifically to different SSTR subtypes, provides a theranostic approach.[9] ^{68}Ga-SSTR PET/CT allows molecular imaging of NENs with very high diagnostic sensitivity and specificity especially for the early identification of metastases.[10] Thus, PET/CT has a significant effect on the management of disease—for example, to assist in finding the most appropriate surgical strategy, or to prevent unnecessary surgery and opt for a suitable systemic therapy instead. Also in pulmonary NENs (typical and atypical lung carcinoids), SSTR PET/CT has a relevant effect on treatment strategy (in one study in up to 18% of the patients[11]) and enables the selection of patients for peptide receptor radionuclide therapy (PRRT) as well as for accurate evaluation of therapy response (Fig. 1).[12,13]

Radiomics in NENs Using PET/CT

The spatial and temporal heterogeneity of solid tumors restricts the use of molecular assays based on biopsy.[14] Imaging has the ability to capture intratumoral heterogeneity in a noninvasive

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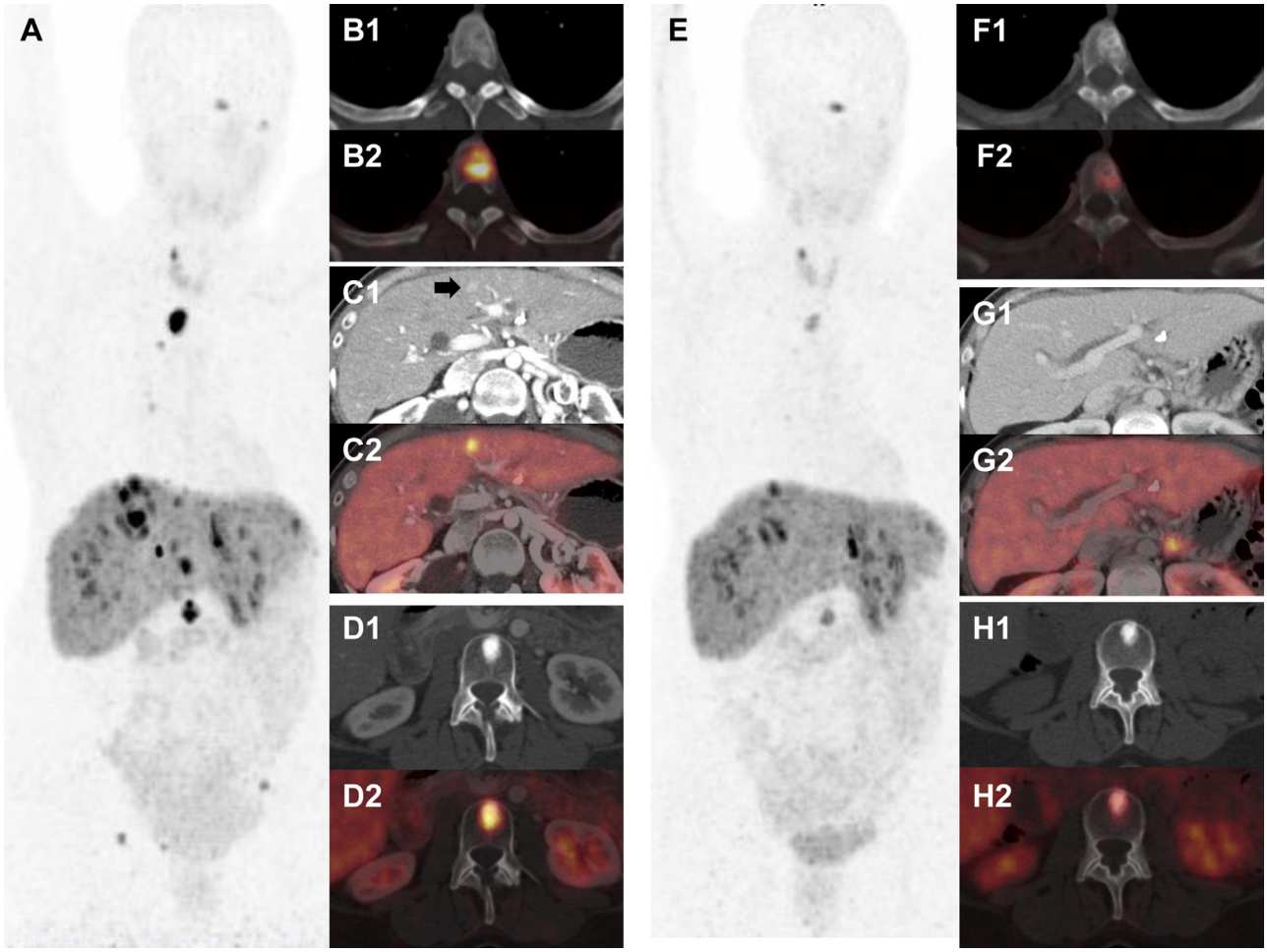

Figure 1 A 67-year-old lady with poorly differentiated functioning neuroendocrine neoplasm (NEN) of the pancreatic tail with metastases to liver, spleen, and bones was referred with progressive disease after a progression-free interval of 19 months status post 3 cycles of peptide receptor radionuclide therapy (PRRT). The fourth PRRT cycle, performed in combination with capecitabine, resulted in partial remission (PR) of disease. (A-D) ^{68}Ga-DOTATOC PET/CT before the fourth PRRT; (E-H) ^{68}Ga-DOTATOC PET/CT after fourth PRRT cycle; (A and E) maximum intensity projection (MIP) images; (B1-D1 and F1-H1), transverse slices of CT and (B2-D2 and F2-H2), corresponding transverse PET/CT slices; (B1 and B2) demonstrate a thoracic vertebral body metastasis before therapy, whereas (F1 and F2) are the corresponding images post-therapy demonstrating a therapy response—increasing sclerosis on CT and decrease of the somatostatin receptor (SSTR) expression; (C1 and C2) represent a small SSTR-positive liver metastasis with response to therapy seen after therapy on CT (G1) and PET/CT (G2); (D1 and D2) represent a metastasis in lumbar vertebral body with significant decrease in uptake seen on PET/CT after therapy (H2), whereas no significant change appreciable on CT (H1).

way. Radiomics is a high throughput approach to extract a large number of qualitative and quantitative features from medical images, which could improve tumor phenotype characterization and treatment outcome prediction.[14,15] PET imaging and assessment of tumor characteristics can reveal the underlying gene expression profiles in many cancer types such as lung and esophageal cancers, and in renal cell carcinoma.[16-18]

SSTR PET/CT and FDG PET/CT imaging may provide better risk stratification of NEN patients, if the findings are complemented with the knowledge of somatic mutations (eg, in genes MEN1, DAXX, or ATRX for the well-differentiated type as against those occurring in the setting of poorly differentiated neuroendocrine carcinomas (NECs) such as TP53, Bcl-2, or RB1).[19] It is known that overexpression of SSTRs is associated with a better prognosis, and overexpression of GLUT and other receptor tyrosine kinases are predictive of poor prognosis and lower survival.[19-21] In a recent study, we studied imaging parameters obtained from ^{68}Ga-SSTR PET/CT and disease-specific molecular data derived from the analysis of gene transcripts in blood and found that the standardized uptake value $(SUV)_{max}$ correlated with a circulating neuroendocrine tumor (NET) transcript signature and that the disease status could be predicted by an elevated quotient of gene expression (MORF4L2) and SUV_{max}.[22]

SSTR PET/CT has also a prognostic role in patients with NENs. A $SUV_{max} \geq 19.3$ on ^{68}Ga-DOTANOC PET/CT was a