EDITORIAL

Gastro-entero-pancreatic neuroendocrine tumors: Is now time for a new approach?

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Abstract

Gastro-entero-pancreatic tumors (GEP-NETs) are rare neoplasms often characterized by an overexpression of somatostatin receptors. Thus, radiolabeled somatostatin analogues have showed an increasing relevance both in diagnosis and treatment, especially in low- and inter-mediate-differentiated GEP-NETs. These evidences have led to a growing development of new functional imaging techniques as 68Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) proved useful in the management of these neoplasms. However these tumors have a heterogeneous behavior also modifying their aggressiveness through time. Therefore sometimes 18F-fluorodeoxyglucose PET/CT appears to be more appropriate to obtain a better assessment of the disease. According to these considerations, the combination of different functional imaging techniques should be considered in the management of GEP-NETs patients allowing clinicians to choose the tailored therapeutic approach among available options.

Key words: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; Gastro-entero-pancreatic neuroendocrine tumor; 68Ga-DOTATATE positron emission tomography/computed tomography; Diagnosis; Imaging

Core tip: Our paper stressed the importance of combined 68Ga-DOTATATE and 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the management of gastro-entero-pancreatic tumors (GEP-NETs). In fact we underlined that the association of these functional imaging techniques showed an important role in redefining the disease after progression, especially in intermediate-grade GEP-NETs, allowing clinicians to choose the tailored therapeutic approach among available options.

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INTRODUCTION

Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) are uncommon neoplasms including a wide range of anatomical, clinical, histological and molecular malignant entities.

Diagnostic approach in this setting is crucial in order to manage the therapeutic strategy.

Development of novel positron emission tomography (PET) tracers (68Ga-DOTApeptides), specifically binding to somatostatin receptors overexpressed on the surface of NET cells, determined the individualization of this kind of neoplasm on 68Ga-DOTA-peptide PET/computed tomography (PET/CT) scans.

Functional imaging of GEP-NETs still plays an important role in the diagnosis and management of this condition, largely due to its ability to provide information for therapy planning.

THE ROLE OF FUNCTIONAL IMAGING

68Ga-DOTATATE PET/CT showed high accuracy in G1-G2 GEP-NETs, especially in bone metastasis and in occult primary tumor detection[1] than other imaging procedures (particularly CT, performed usually as first-line investigation, and other functional assessment [somatostatin receptor scintigraphy (SRS)].

Gabriel *et al*[2] confirmed the diagnostic role of 68Ga-DOTATOC PET, in comparison with SRS, CT, in the detection of unknown primary tumor in the presence of clinical or biochemical suspicion of neuroendocrine malignancy initial tumor staging, and follow-up after therapy for NETs patients, reporting a sensitivity of 97% and specificity of 92%.

Ambrosini *et al*[1] retrospectively studied the sensitivity, specificity and accuracy of 68Ga-DOTA-NOC PET/CT in comparison with CT alone for the evaluation of bone metastasis in patients with neuroendocrine tumor. PET was performed for staging, unknown primary tumor detection, reevaluation of disease, post-therapy assessment and follow-up. In particular PET seems to detect more bone lesions than CT, showing a higher sensitivity (100% *vs* 80%), specificity (100% *vs* 98%), positive predictive value (100% *vs* 92%), and negative predictive value (100% *vs* 95%)[1].

Furthermore, 68Ga PET/CT allows molecular imaging of NETs with very high diagnostic sensitivity and specificity especially to identify earlier occult metastases not manifest with other procedures. It contributes to accuracy of data by facilitating: The selection of patients for a somatostatin analogues therapy with curative/palliative/"neoadjuvant" intent; to assist in finding appropriate surgical option and for evaluation of treatment response [especially to peptide receptor radionuclide therapy (PRRT)] through clinical symptoms improvement or worsening, and prediction of time to progression.

In fact, the greater sensitivity of 68Ga-DOTATOC could provide new clinical information resulting in altered surgical plans in some patients (occasionally preventing unnecessary surgery)[3].

SUV of 68Ga-DOTA-NOC had, also, a prognostic role in patients with NET. A SUVmax ≥ 19.3 was found to be a significant predictor of survival[4], and a SUVmax > 4 seemed to be significantly associated with progression free survival on multivariate analysis[5].

Then the change in tumor-to-spleen SUV ratio appeared an independent predictor of progression free survival after PRRT[3].

The use of 18F-fluorodeoxyglucose (18F-FDG) PET/CT in NETs, instead, is emerging to detect tumors with an increased propensity for invasion and metastasis and with overall poorer prognosis, usually less differentiated neuroendocrine tumors with high Ki67 index (neuroendocrine carcinomas) or G1-G2 NETs developed a de-differentiation[6].

In particular Binderup *et al*[7] found that 18F-FDG-PET positivity was stronger than currently used Ki67 index, representing a different sensitivity depending on grading and proliferation rate: 41% for NETs with Ki67 < 2% and 92% when Ki67 at or above 15%.

Garin *et al*[8] conducted a prospective study of patients with metastatic gastrointestinal and thoracic well-differentiated neuroendocrine tumor to compare principally SRS to 18F-FDG PET imaging. 18F-FDG PET gave excellent negative and positive predictive values for early tumor progression of 91% and 93%, respectively. 18F-FDG PET and SRS resulted associated with progression-free survival (both $P = 0.001$) and overall survival ($P = 0.001$ and $P = 0.03$, respectively). At multivariate analysis, only 18F-FDG PET was predictive for progression-free survival[8].

Then, the use of 18F-FDG PET/CT seems to be auspicious to define prognosis of disease, by directing to a potential more aggressive therapeutic approach.

A routinely use of combined 68Ga and 18FDG PET/CT in patients with GEP-NET still represents matter of research. Many studies are investigating whether those new imaging modalities, alone or in combination, are able to provide more precise information about diagnosis, disease extension, restaging, selection of therapy, patients' response to treatment and disease course, taking into account the heterogeneity of NETs.

Naswa *et al*[9] compared these two molecular imaging technique in a recent retrospective analysis and confirmed that Ga-DOTA-NOC PET-CT is superior to 18FDG PET/CT in the detection of lymph node, liver and skeletal metastases - known to be associated with negative prognostic implication on clinical outcomes, moreover underling their potential complementary role to segregate patients into proper therapeutic groups[9].

A similar study by Has Simsek *et al*[10] compared 68Ga-DOTATATE and 18F-FDG PET/CT in 27 GEP-NET

Table 1 Indirect comparison between studies investigating in the role of dual positron emission tomography/computed tomography							
Ref.	Type of study	Patients enrolled	Sensitivity in detection of liver metastasis	Sensitivity in detection of lympho-node metastasis	Sensitivity in detection of bone metastasis	Relationship between grading and PET/CT positivity	Impact of dual PET/CT on therapeutic decision
Naswa *et al*[9]	Retrospective study	51 GEP-NETs	No statistical differences between 68Ga and 18F-FDG	68Ga was superior to 18F-FDG (*P* < 0.003)	No statistical differences between 68Ga and 18F-FDG	No data	Dual PET/CT helped in selecting therapies
Has Simsek *et al*[10]	Prospective study	27 GEP-NETs: 10 G1 17 G2	68Ga: 95% 18F-FDG: 40%	68Ga: 95% 18F-FDG: 28%	68Ga: 90% 18F-FDG: 28%	In 74% of patients, 68Ga predominated in patients with lower Ki-67 index, while 18F-FDG in higer ki-67 index GEP-NETs	Dual PET/CT influenced treatment decision in 59% of cases
Partelli *et al*[11]	Retrospective, bi-institutional study	49 P-NETs	18F-FDG: Described 1 false negative	No data	18F-FDG: described 1 false negative	Median Ki-67 for 68Ga positive tumors: 7%. Median Ki-67 for both 68Ga and 18F- FDG positive tumors: 10% (*P* = 0.130)	No significant differences

GEP-NETs: Gastroenteropancreatic neuroendocrine tumors; P-NETs: Pancreatic neuroendocrine tumors; 18F-FDG: 18F-fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography.

Table 2 Comparison between 68Ga-DOTATATE and 18F-fluorodeoxyglucose positron emission tomography/computed tomography sensitivity in neuroendocrine neoplasms		
Ref.	68Ga-DOTATATE PET/CT	18F-FDG PET/CT
Kayani *et al*[13]	Sensitivity 82%	Sensitivity 66%
Kayani *et al*[14]	Sensitivity 100%	Sensitivity 54%
Conry *et al*[15]	Sensitivity 72%	Sensitivity 78%

18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography.

patients, investigating the relation between the complementary PET/CT results and histopathological grading; the impact of the combined PET/CT on the therapeutic decision was globally of 59%.

According to these studies, the use of these molecular techniques in combination within clinical practice presents an increasing role in GEP-NETs diagnosis.

Also Partelli *et al*[11] showed that the positivity of both 68Ga PET/CT and 18FDG PET/CT was higher in tumors with median Ki67 index equal to 10% in pancreatic NETs. However this result did not reach statistical significance and the Authors concluded that combined dual tracer PET/CT does not influence the choice of treatment strategy (Table 1).

On the basis of the findings described above, is now time for a new diagnostic approach including the dual tracer PET/CT in GEP-NETs ?

In our opinion, the higher contribution of the combined PET/CT scan can be obtained in the management of intermediate-grade tumors, due to their heterogeneity in response to treatment and prognosis. In particular, in G2 tumor with high Ki-67, near to the 20% cut-off value, the 18F-FDG PET/CT could help to identify patients with a more aggressive disease, who should benefit of conventional chemotherapy.

Furthermore, GEP-NETs' histological grading can change through time. Ki-67 index assessment might show discrepancies between primary tumor and metastatic sites even in more than 35%[12].

There were 3 other studies examining the 68Ga-DOTATATE PET/CT in comparison with 18F-FDG PET/CT in neuroendocrine neoplasms (Table 2). The sensitivity of the 68Ga-DOTATATE PET/CT and 18F-FDG PET/CT described to be 72.2%-100% and 66%-77.8%, respectively[13-15].

In these cases, the real value of combined 68Ga and 18FDG PET CT mainly consists in the possibility to demonstrate areas of different tumor grading or developed de-differentiation and to evaluate post-treatment response assessment, conditioning therapeutic decisions.

CONCLUSION

In conclusion, we believe that combined 68Ga-DOTATATE and 18F-FDG PET/CT at the diagnosis are helpful in the tailored therapeutic approach of GEP-NETs and can overcome the shortcomings of histopathological grading, especially in intermediate-grade GEP-NETs, selecting candidates who would undergo the appropriate mode of treatment, whether SSA analogues, targeted therapies or cytotoxic agents.

In addition, combined dual tracer PET/CT imaging could have an interesting role to redefine the disease after progression, allowing clinicians to choose the most appropriate management after the first line of therapy. Further research is necessary to confirm and validate our hypothesis.

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