Evaluating digestive neuroendocrine tumor progression and therapeutic responses in the era of targeted therapies: state of the art

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Abstract

Well-differentiated neuroendocrine tumors (NETs) are a group of heterogeneous rare tumors. They are often slow-growing and patients can have very long survival, even at the metastatic stage. The evaluation of tumor progression and therapeutic responses is currently based on Response Evaluation Criteria In Solid Tumors v1.1 (RECIST) criteria. As for other malignancies, RECIST criteria are being reexamined for NETs in the era of targeted therapies because tumor response to targeted therapies is rarely associated with shrinkage, as opposed to prolonged progression-free survival. Therefore, size-based criteria no longer seem to be suitable to the assessment of NET progression and therapeutic responses, especially considering targeted therapies. New imaging criteria, combining morphological and functional techniques, have proven relevant for other malignancies treated with targeted therapies. To date, such studies have rarely been conducted on NETs. Moreover, optimizing the management of NET patients also requires considering clinical, biological, and pathological aspects of tumor evolution. Our objectives herein were to comprehensively review current knowledge on the assessment of tumor progression and early prediction of therapeutic responses and to broaden the outlook on well-differentiated NETs, in the era of targeted therapies.

Key Words
- neuroendocrine tumors
- evaluation
- progression
- response
- prognosis
- targeted therapies
- biomarker
- CT scan
- contrast-enhanced imaging
- ultrasonography
- MRI
- isotopic imaging

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Introduction

Well-differentiated neuroendocrine tumors (NETs) are rare and heterogeneous tumors with specific characteristics in comparison to other malignancies. Well-differentiated NETs have various evolutive profiles; they are often

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slow-growing, associated with long survival even when liver metastases are present (Yao *et al*. 2008, Tsikitis *et al*. 2012). Medical antitumor treatments are mainly based on somatostatin analogs, interferon, chemotherapy, liver (chemo) embolization, peptide receptor radionuclide therapy, and targeted therapies.

NET liver metastases have some particularities that can influence tumor evaluation. Because well-differentiated NETs with low proliferation indexes spontaneously evolve slowly, a long period, sometimes exceeding 1 year, is mandatory to observe a size increase >20% that is required to define progression. Moreover, most NETs are hypervascularized, which underlines the impact of arterial phase acquisition on imaging reproducibility for comparison between examinations. Furthermore, NET responses to the different types of treatments are heterogeneous, depending on the mechanisms of action of those different therapies. Pertinently, targeted therapies do not necessarily yield tumor shrinkage. Thus, methods evaluating NET responses must also take these differences into account.

Currently, the evaluation of NET therapeutic responses is mainly based on Radiological Response Evaluation Criteria In Solid Tumors v1.1 (RECIST; Eisenhauer *et al*. 2009). However, as for other types of tumors, RECIST criteria are being reexamined for NETs in the era of targeted therapies. Preliminary studies have explored alternative or complementary evaluation methods that could be more relevant.

Our objective was to comprehensively review the current knowledge on the evaluation of progression and therapeutic responses of digestive NETs in the era of targeted therapies, excluding poorly differentiated tumors. First, we aimed to analyze and address current evaluation methods and extend the outlook on their optimization. The secondary goal was to establish a multidisciplinary approach to assess NET evolution and predict therapeutic responses to better define the place of targeted therapies in their management.

Challenging the current methods of tumor response assessment of NETs

RECIST criteria were elaborated to evaluate tumor responses to cytotoxic chemotherapies, mainly based on the modifications of the numbers and sizes of measurable target tumors (Table 1). For NETs, as for several malignancies, e.g., imatinib-treated gastrointestinal stromal tumors (GIST) or sorafenib-treated hepatocarcinomas, the continued relevance of RECIST criteria has been questioned for the early evaluation of tumor responses to targeted therapies (Desar *et al*. 2009, Faivre *et al*. 2012, Peungjesada 2013). In patients with NETs, i) discordances have been noted between longer progression-free survival (PFS; doubled vs placebo) and low RECIST-assessed response rates (<10%) (Blanke *et al*. 2008, Llovet *et al*. 2008, Pavel *et al*. 2011, Raymond *et al*. 2011, Yao *et al*. 2011*a*, Faivre *et al*. 2012); ii) because RECIST thresholds are not suited to the spontaneous slow evolution of NETs, they might be misclassified as stable (Yao *et al*. 2010*a*, 2011*a*, Pavel *et al*. 2011, Raymond *et al*. 2011); and iii) the specific type of tumor response to targeted therapies, i.e., decreased tumor density suggestive of their necrosis, is not taken into account (Figs 1 and 2). Moreover, necrosis can render preexisting lesions visible that could be mistaken for new ones (Fig. 1).

Optimizing RECIST criteria is a critical issue to better adapt the management of NET patients. Current thresholds for defining tumor progression (≥20%) or response (≥30%) may not be suitable to the spontaneous slow evolution of most NETs and their low response rates to targeted therapies respectively. However, lowering those thresholds requires validation that the measurement errors are indeed inferior to the cutoffs. It is not certain that computed tomography (CT) and magnetic resonance imaging (MRI) could measure a 10% NET-size modification with sufficient reproducibility. Although that was shown to be feasible in studies with conventional therapies (Suzuki *et al*. 2012), it remains to be confirmed in targeted therapy-treated NET patients.

RECIST criteria provide no specific recommendations about the choice of NET targets, their numbers, or appropriate imaging techniques other than the recommended triphasic CT scan acquisition (including a late arterial phase). However, identifying the most reliable target lesions and their numbers are also necessary. Liver is the main and often unique site of NET metastases. RECIST allows only two target lesions to be considered, which may not be enough because of the possible heterogeneity of responses (Faivre *et al*. 2012). For example, in the case of dissociated evolutions, allowing more target lesions could diminish the impact of dissociation on the global tumor burden evolution. Moreover, determining the progression of extrahepatic non-target lesions is difficult and may be subjective, particularly concerning peritoneal carcinomatosis, which is of major concern for digestive NETs.

Finally, the lymph-node metastases of small-bowel NETs that comprise the typical mesenteric mass are associated with a marked fibrosis, which might explain stability over time, but that possibility has not been specifically investigated (Druce *et al*. 2010). Therefore, a large

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Table 1 Radiological evaluation of target lesions

Criteria	Setting	Response criteria
RECIST	Solid tumors	CR: disappearance of all lesions and no new lesions PR: ≥30% decrease in the sum of diameters SD: no criteria for CR, PR, or PD PD: ≥20% (and ≥5 mm) increase in the sum of diameters, or new lesions
mRECIST	Hepatocarcinomas treated with an antiangiogenic (sorafenib)	CR: disappearance of all arterial contrast enhancement PR: ≥30% decrease in the largest dimension of contrast-enhanced zone SD: no criteria for CR, PR, or PD PD: ≥20% increase in the largest dimension of contrast-enhanced zone or new lesions
Choi	Gastrointestinal stromal tumors treated with imatinib	CR: disappearance of all lesions and no new lesions PR: ≥10% decrease in the sum of diameters, or ≥15% decrease in tumor density during portal venous phase on CT SD: no criteria for CR, PR, or PD and no symptomatic deterioration attributed to tumor progression PD: ≥10% increase in the sum of diameters, increase in size of existing intra-tumoral nodules, new lesion, or intra-tumor nodule
Chun	Colorectal liver metastases treated with bevacizumab-containing chemotherapy regimens	Three groups based on CT tumor characteristics Group 3: heterogeneous attenuation; thick, poorly defined tumor–liver interface or peripheral rim of contrast enhancement Group 2: no criteria for groups 3 and 1 Group 1: homogeneous low attenuation; thin, sharply defined tumor–liver interface, or resolution of a peripheral rim of hyperattenuating contrast enhancement Response criteria Optimal: change from 3/2 to 1 Incomplete: change from 3 to 2 None: no change of group, or increase
MASS	Metastatic clear renal cell cancer treated with sunitinib or sorafenib	Favorable response: no new lesion and ≥20% decrease in tumor size or ≥1 contrast-enhanced lesion(s) with marked central necrosis or decreased attenuation (≥40 HU) Indeterminate response: no criteria of favorable or unfavorable response Unfavorable response: ≥20% increase in tumor size in the absence of central necrosis or decreased attenuation, or new lesions, or new enhancement of a previously homogeneously hypoattenuating non-contrast-enhanced lesion

CR, complete response; CT, computed tomography; HU, Hounsfield units; PD, progressive disease; PR, partial response; SD, stable disease.

mesenteric mass should probably not be considered for optimal evaluation of tumor progression. Pertinently, using RECIST criteria might lead to underestimation of the progression of smaller liver metastases.

CT scan, because it enables exploration of the most common metastatic sites, is the reference technique for initial evaluation and follow-up of NET-associated metastases (Bhosale *et al*. 2013). Because CT is the best currently available and reproducible technique, it was used to define RECIST criteria (Eisenhauer *et al*. 2009). In relationship with the rich NET vascularization, arterial acquisition, performed 20 s after contrast dye injection, increases sensitivity to detect liver metastases by 20% (Paulson *et al*. 1998, Dromain *et al*. 2005). CT scan is sensitive for detecting lung, liver, and brain metastases and may be complemented by somatostatin receptor scintigraphy (SRS), which excels at exploring bones and mediastinum (Panzuto *et al*. 2003). MRI is more sensitive at detecting liver metastases than ultrasonography (US), CT scan, or SRS (Dromain *et al*. 2005). Its sensitivity is similar to that of intra-operative US assessment. However, about half of the liver metastases are not detected by any pre- and intra-operative imaging technique (Elias *et al*. 2010).

In addition to its high sensitivity, MRI has several advantages over CT for evaluating NET progression: i) it is a non-radiant technique that can be repeated over time without any risk of cumulative irradiation; ii) high MRI contrast between metastases and normal liver enables precise measurement of liver metastases on non-contrasted sequences, independently of metastasis enhancement; and iii) MR is the imaging technique with the best interobserver agreement (Dromain *et al*. 2003, 2005). Nonetheless, MRI is less available and more expensive than CT.

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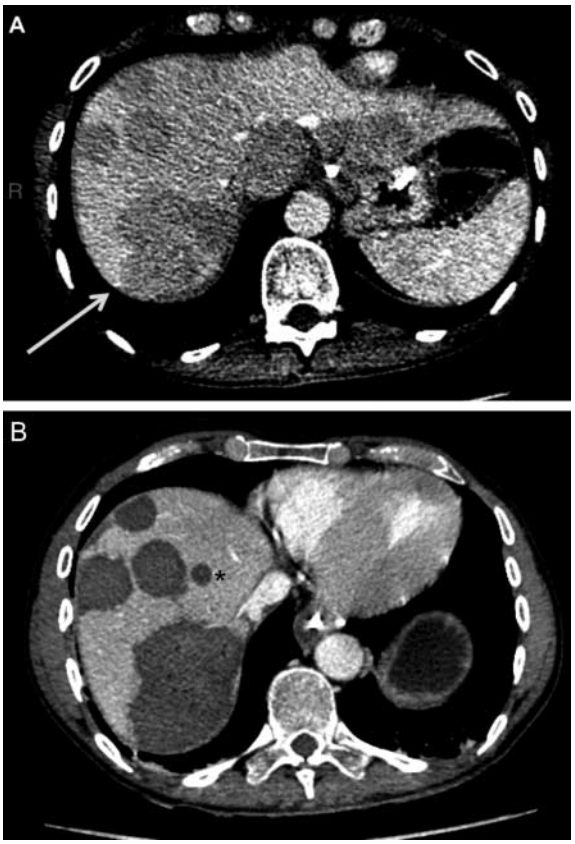

Figure 1
Contrast-enhanced axial CT scans during portal phase, in a 41-year-old man with ileal well-differentiated NET and multiple liver metastases, obtained (A) at baseline and (B) 1 month after hepatic artery embolization (bead blocks; Biocompatible, Farnham, England). The arrow designates the metastasis that served as the target lesion. At 1-month reevaluation, its size had increased by 31%, associated with a 45% decrease in tumor density (100–55 HU). Moreover, a new lesion had appeared (*). This situation corresponded to progressive disease according to RECIST v1.1 criteria and to a partial response according to Choi criteria. The new lesion was considered to be a paradoxical new image due to necrosis of a preexistent small lesion.

Optimizing evaluation of NET progression and therapeutic responses

One major limitation of RECIST criteria is that they are based on the assumption that an antitumor effect is necessarily associated with tumor-size reduction, that is not valid for therapies inducing heterogeneous tumor effects, especially intra-tumor necrosis. Functional modifications of tumors appear soon after starting targeted therapy, unlike decreased tumor size, which takes much longer to be observed.

Therefore, tumor-response evaluation to targeted therapies requires the combined assessment of morphological and functional tumor changes and clear-cut distinction between responding and non-responding tumor areas. Thus, non-size-based morphological criteria and metabolic explorations, e.g., dynamic contrast-enhanced (DCE) modalities and radiopharmaceutical imaging, of NETs are being investigated. Finally, assessing early NET changes would help adjust the treatment strategy, i.e., preventing unnecessarily long regimens with inherent adverse events, and high costs of expensive targeted therapies.

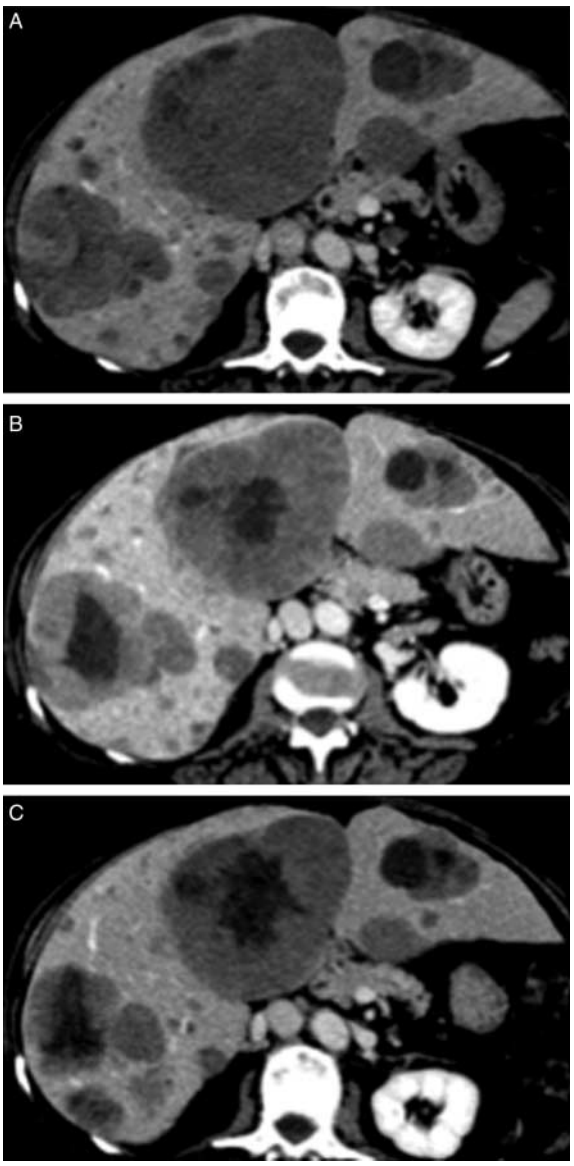

Figure 2
Contrast-enhanced axial CT scans during the portal phase, obtained in a 48-year-old man with a pancreatic well-differentiated neuroendocrine tumor (NET) and multiple liver metastases, at baseline (A) and 1 month (B) and 2 months (C) after starting daily everolimus. Although no size change was observed, the appearance of central necrosis in several lesions suggested a tumor response.

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Morphological imaging with non-size-based criteria

Morphological imaging techniques are reliable, reproducible, and readily available; they remain references for research and clinical settings. In hypervascular tumors, like NETs, contrast dye uptake distinguishes between active and necrotic tumor areas. Criteria based on modified tumor enhancement have been proven relevant for other types of targeted therapy-treated tumors, namely, hepatocarcinoma (mRECIST; Lencioni & Llovet 2010), GIST (Choi criteria; Choi *et al*. 2007), liver metastases from colorectal cancer (Chun criteria; Chun *et al*. 2009), and metastatic renal cell carcinoma (Morphology, Attenuation, Size, and Structure (MASS) criteria; Smith *et al*. 2010; Table 1).

Choi criteria combine density and size features, with a lower size threshold than RECIST (10% for response and progression). In addition to GIST, Choi criteria were recently used to evaluate targeted therapy responses of metastatic renal cell cancers, hepatocarcinomas, and metastatic gastric cancers and better correlated with PFS than RECIST criteria, notably for the early-response assessment (van der Veldt *et al*. 2010, Faivre *et al*. 2011, Wassermann *et al*. 2011, Liu *et al*. 2012). Two preliminary studies evaluated Choi criteria for NET-response assessment. The first included ten patients with metastatic pancreatic NETs after 4 weeks of sunitinib and obtained two responses according to RECIST vs six with Choi criteria (Faivre *et al*. 2012). The second retrospectively compared Choi and RECIST criteria for 23 patients with sunitinib- or everolimus-treated well-differentiated pancreatic NETs (Dreyer *et al*. 2012). Choi criteria correlated significantly with time to progression (i.e., 26.1, 8.7, and 3.5 months respectively for patients with partial responses, stable disease, and progressive disease; $P=0.038$). Moreover, Choi criteria were more relevant than RECIST criteria for identifying patients benefiting from targeted therapies, since 50% of the patients with RECIST-defined stable disease were reassessed as partial responders with Choi criteria (Dreyer *et al*. 2012). However, as underlined before, it is unsure whether CT and MRI can accurately appreciate a 10% tumor-size modification with sufficient reproducibility for NETs, as required by Choi criteria.

Other criteria have not yet been investigated for NETs. Among them, Chun criteria have been proven relevant for patients with bevacizumab-treated metastatic colorectal cancer and should be tested on NETs, especially because bevacizumab seems to be highly effective against NETs (Ducreux *et al*. 2012, Mitry *et al*. 2012).

DCE-based imaging and perfusion parameters

Similar to normal endocrine tissue, NETs commonly possess well-developed capillary networks. This characteristic hypervascularization can be evaluated histologically by microvascular density or radiologically by contrast enhancement, which is routinely used for their diagnosis. DCE methods, which can be used with US, CT or MRI, and contrast dyes specific to each modality, rely on the quantification of perfusion parameters that reflect the vascular characteristics of examined tissues. Thus, they could enable assessing tumor 'deperfusion' under treatment.

DCE-based imaging and perfusion parameters are good candidates for monitoring under treatment. Nevertheless, some NET particularities must be considered. First, compared with other malignancies, the most vascularized NETs have the lowest malignant potential and the best prognoses (Marion-Audibert *et al*. 2003, Couvelard *et al*. 2005, Rodallec *et al*. 2006, d'Assignies *et al*. 2009). Secondly, what has been shown in other models of antiangiogenic-treated tumors is that all the necrosis attributed to therapeutic effects might not be exact for NETs, in which spontaneous necrosis is possible and relatively frequent.

DCE-US enables quantitative assessment of tumor perfusion using injection of an ultrasonic microbubble-based contrast dye. It was recently included in European (Piscaglia *et al*. 2011) and international (Claudon *et al*. 2013) guidelines for monitoring of antiangiogenic treatments and has also been cited in the European Society for Medical Oncology guidelines for GIST management (Casali *et al*. 2010). DCE-US explores microvascularization better than Doppler and enables the evaluation of tumor vascularization changes through the quantification of perfusion parameters (Marcus *et al*. 2009). Among those criteria, the area under the blood–volume curve could be an earlier reliable predictor of therapeutic response (Lassau *et al*. 2011, 2012*a*). In a recent French multicenter series of 539 patients with various malignancies treated with antiangiogenic therapies, including NETs, early (day 30) variations of perfusion parameters of liver metastases were correlated with tumor responses at 6 months, according to RECIST criteria and overall survival (OS; Lassau *et al*. 2012*a*,*b*). Hence, if confirmed by prospective randomized trials, this technique could become an early and specific surrogate marker of tumor response to treatments targeting tumor vascularization.

Only one study was specifically conducted on NET patients to date (Guibal *et al*. 2013). It included 17 patients

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with liver metastases from NETs of various origins that were treated with either transarterial embolization with bead blocks ($n=10$) or transarterial chemoembolization with doxorubicin-eluting beads ($n=7$). DCE-US, using a standardized technique, was performed 1 day before and 2 days, 1 month, and 3 months after the procedure. Those authors elaborated a tumor vitality index, obtained by multiplying the ratio of viable:total tumor dimensions times the relative (tumor/adjacent tissue) blood flow. This new criterion warrants further exploration in NETs and comparison to RECIST criteria for therapeutic evaluation, particularly concerning its relationship with OS.

Similarly, DCE-CT enables examination of tissue enhancement after the injection of a contrast dye bolus and numerous vascularization parameters, including blood flow, blood volume, mean transit time, and permeability area (Fig. 3; Marcus *et al.* 2009). Routine DCE-CT use is limited by the absence of standardization for data interpretation and its high radiant dose. In agreement with earlier qualitative studies (Rodallec *et al.* 2006), DCE-CT parameters correlated significantly with prognostic histological characteristics of pancreatic NETs (d'Assignies *et al.* 2009). Indeed, significant correlations existed between high blood flow and differentiation, proliferation index or microvascular density, and between longer mean transit time and lymph-node or liver metastases. A link between blood flow and OS was also suggested but remains to be confirmed (Rodallec *et al.* 2006, d'Assignies *et al.* 2009).

Subsequently, it was suggested that DCE-CT scan findings could predict early response to targeted therapies. In a preliminary study, 39 patients with metastatic NETs were randomized to receive either bevacizumab or everolimus for 21 days and then the other agent was added. DCE-CT was performed at baseline and after each treatment cycle (Yao *et al.* 2010*b*). Bevacizumab significantly decreased blood flow (21–32%), as did everolimus (15%) that was also associated with increased mean transit time (13–22%) (Yao *et al.* 2010*b*). Notably, these posttreatment perfusion parameters were significantly associated with RECIST-defined partial responses. Similarly, in a randomized phase II study on bevacizumab-treated NET patients, significantly decreased blood flow (41.4%) and blood volume (27.9%) were observed, compared with baseline data (Ng *et al.* 2011). These modifications occurred early (day 2 post-perfusion), were prolonged (18 weeks), and not observed with interferon, used in the control arm (Ng *et al.* 2011). Taken together, these data suggest that DCE-CT-assessed perfusion parameters could be surrogate markers of NET responses to targeted therapies. However, no studies have compared perfusion parameters and RECIST criteria for predicting OS.

DCE-MRI is a noninvasive quantitative method of investigating microvascular structure and function, by tracking the pharmacokinetics of injected low-molecular-weight contrast agents, usually gadolinium pentate based, as they pass through the tumor vasculature. It enables calculation of the area under the curve of gadolinium enhancement, and K_{ep} and K_{trans} parameters, which represent combined physiological processes, e.g., blood flow and volume, vessel permeability, and extracellular–extravascular volume. Early variations of these parameters in patients given antiangiogenic therapy correlated with the responses in various tumors (Desar *et al.* 2009), e.g., sorafenib-treated renal cell cancer (Flaherty *et al.* 2008, Hahn *et al.* 2008). However, high variability of those parameters and their inconstant association with clinical outcome were noted. Moreover, reported studies used

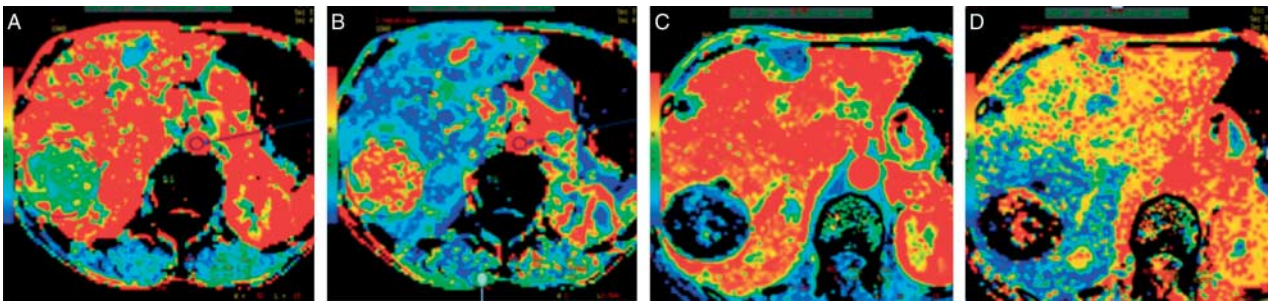

Figure 3

DCE-CT scans of a 43-year-old man with ileal well-differentiated NET and multiple liver metastases, receiving capecitabine and bevacizumab. Parametric images of (A) blood flow and (B) blood volume before treatment showed a highly vascularized lesion. Red, green, and blue correspond to high, medium, and low values respectively. After 4 months of treatment, parametric images showed significantly decreased (C) blood flow and (D) blood volume, suggestive of a response to antiangiogenic therapy.

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different MRI protocols and quantification methods that need to be standardized.

Finally, DCE-based imaging is limited by its assessment of one or only a few targets that has not been proven to be representative of the entire tumor burden, especially in the case of tumor heterogeneity.

Diffusion-weighted MRI

Diffusion-weighted (DW)-MRI indirectly assesses cell density by measuring the apparent diffusion coefficient (Marcus *et al*. 2009). Its diagnostic superiority over morphological techniques, for tumor detection, was reported for different types of malignancies, leading to the implementation of this fast sequence in all MRI examinations in routine clinical practice (Taouli & Koh 2010). A recent study on NET patients showed DW-MRI to be significantly more sensitive (71–72%) than T2-weighted fast spin-echo (48–56%) and dynamic gadolinium-enhanced sequences (48–56%) at assessing liver metastases, including those <1 cm in diameter (d'Assignies *et al*. 2013). Moreover, DW-MRI might be a promising technique to evaluate tumor progression and therapeutic responses (Cui *et al*. 2008, Sun *et al*. 2011). However, to our knowledge, no specific study has so far been conducted on NETs.

Radiopharmaceutical imaging techniques

Isotope-imaging modalities have become increasingly relevant for the management of NET patients. SRS (OctreoScan) uses ^{111}In-pentetreotide, a radiolabeled somatostatin analog emitting gamma camera-detectable radiation, that is injected into the bloodstream. It has good diagnostic performances for somatostatin-2 receptor-expressing tumors (Hofland *et al*. 2003, Asnacios *et al*. 2008). Its positivity, correlated with a favorable prognosis (Asnacios *et al*. 2008, Garin *et al*. 2009), is a strong factor predictive of an antisecretory response to treatment with somatostatin analogs or tumor response to peptide receptor radionuclide therapy (Kwekkeboom *et al*. 2008). Positron-emission tomography (PET)-CT using ^{68}Ga-radiolabeled somatostatin analogs (^{68}Ga-DOTANOC, ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE) demonstrated higher diagnostic sensitivity than SRS (Virgolini *et al*. 2010, Teunissen *et al*. 2011). ^{68}Ga-DOTATOC PET-CT is the most widely used and, for NETs, provides better spatial resolution, higher detection sensitivity, higher tumor-to-normal tissue ratios, and faster examination than SRS (Gabriel *et al*. 2007, Sundin & Rockall 2012).

Figure 4
Coronal views, after multiplanar reconstruction, of (A) computed tomography (CT) scan, (B) SRS (^{111}In-pentetreotide single-photon-emission CT), and (C) ^{18}FDG-PET obtained during the initial evaluation of a woman with a well-differentiated pancreatic NET. Tumor grade was G2 (Ki67: 15%). Although SRS showed no tumor uptake, the ^{18}FDG-PET was positive (maximum standardized uptake value: 7.9), suggesting a highly aggressive tumor.

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However, although isotope imaging using radiolabeled somatostatin analogs is relevant for NET diagnosis, studies exploring their role in therapeutic monitoring have been unconvincing to date, failing to demonstrate a correlation between uptake measurements and tumor responses or clinical outcomes (Gabriel *et al*. 2009, Haug *et al*. 2010). Indeed, because these morphological techniques assess somatostatin receptor density but not tumor viability or metabolism, their relevance for the evaluation of tumor responses is probably limited. Nevertheless, these functional imaging modalities remain an important avenue for further research.

^{18}Fluoro-2-deoxy-D-glucose (^{18}FDG)-PET was shown to have better diagnostic performances than SRS for patients with well-differentiated NETs and high Ki67 indexes (>10%) (Abgral *et al*. 2011) and ^{18}FDG positivity was associated with poor prognosis (Fig. 4; Garin *et al*. 2009). ^{18}FDG uptake quantification with the standardized uptake value could be an early marker of NET response or progression. Although ^{18}FDG-PET has not yet been recommended for the evaluation of NET therapeutic responses, it has been widely and effectively used to this end for numerous other malignancies (Smith *et al*. 2000, Bos *et al*. 2002, Mac Manus *et al*. 2003, Swisher *et al*. 2004, Wieder *et al*. 2004, Dose Schwarz *et al*. 2005, Hawkins *et al*. 2009). Quantification according to European Organization for Research and Treatment of Cancer guidelines could make ^{18}FDG-PET an early marker of an antitumor effect. Recently, PET Response Criteria In Solid Tumors (PERCIST) were proposed as a new standardized quantitative evaluation method of metabolic tumor responses (Wahl *et al*. 2009; Table 2). These criteria have been validated for a variety of malignancies treated in different ways, e.g., chemotherapy, radiation, and/or targeted therapies (Skougaard *et al*. 2013, Ziai *et al*. 2013), but they have not yet been evaluated for NETs.

Other positron-emitting radiotracers are promising. ^{18}Fluoro-dihydroxyphenylalanine (^{18}F-DOPA), which assesses dopamine metabolism, effectively detected small-bowel serotonin-producing NETs with higher sensitivity than SRS but has not been evaluated for tumor evolution assessment (Montravers *et al*. 2009, Ambrosini *et al*. 2012). ^{18}Fluoro-misonidazole (^{18}FMISO-PET) assesses hypoxia metabolism and might be a potential biomarker of response to antiangiogenic therapy, as reported for sunitinib-treated metastatic renal cell carcinoma (Hugonnet *et al*. 2011; Fig. 5).

Do clinical, biological, and histological examinations have a role in the evaluation of NET progression and therapeutic responses?

Clinical symptoms, quality of life, and tumor progression

Assessment of tumor responses requires objective data. Physical examination may provide arguments for tumor progression, in the case of recurrence or worsening functional symptoms. Several signs and symptoms can reflect tumor burden, including palpation of tumor or peripheral lymph nodes that were previously impalpable or had increased in size, along with weight loss, ascites, jaundice, dyspnea, and symptoms of bowel obstruction. However, neither their prior absence nor reproducibility is certain.

Standardizing quality-of-life assessment has been a matter of interest over the past decade (Fröjd *et al*. 2007, Chambers *et al*. 2008, Vinik *et al*. 2011). The QLQ-C30 questionnaire has not been validated as a surrogate marker of tumor progression (Raymond *et al*. 2011). QLQ-GINET21 includes items specific to NET patients

Table 2 PERCIST criteria: positron-emission tomography evaluation of tumor response to anticancer therapy

Tumor evaluation	PERCIST criteria
Complete metabolic response (CMR)	Complete resolution of uptake (less than mean liver activity and indistinguishable from surrounding background blood-pool levels) Disappearance of all other lesions to background blood-pool levels. No new avid lesions in pattern typical of cancer
Partial metabolic response (PMR)	≥30% decrease in SUV peak (and ≥0.8 SUV units) from baseline No SUV increase >30% No increase in lesions size No new lesions
Stable metabolic disease	No criteria for CMR, PMR, or PMD
Progressive metabolic disease (PMD)	≥30% increase in SUV peak (and ≥0.8 SUV units) from baseline Or increase in extent of tumor uptake Or new avid lesions typical of cancer

SUV, standardized uptake value.

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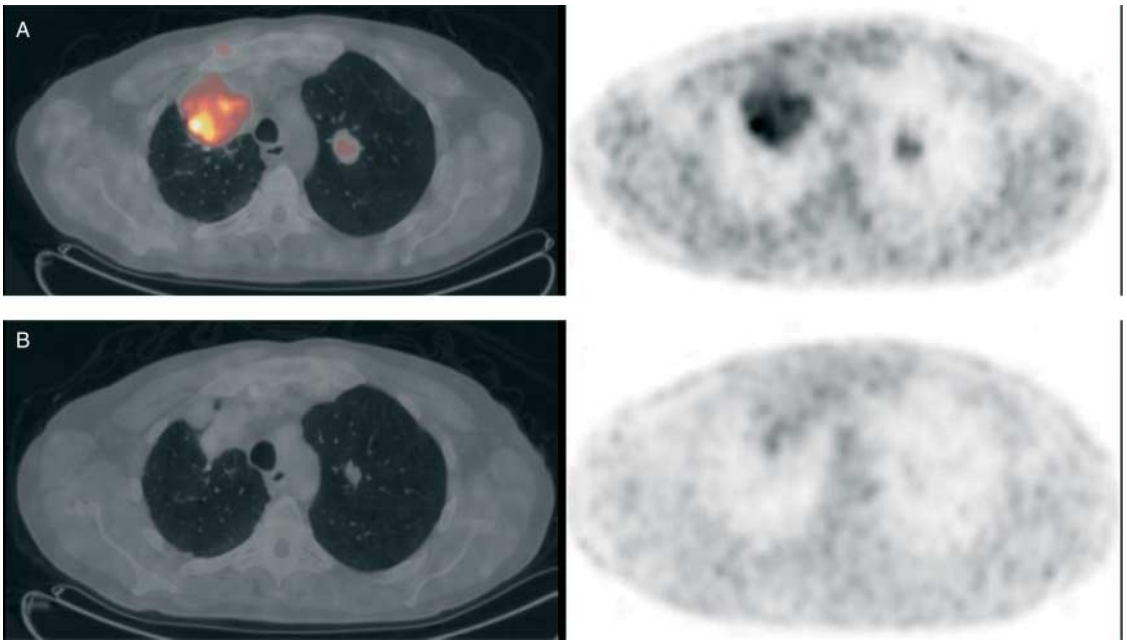

Figure 5
Axial ^{18}FMISO-PET views, obtained in a man with renal cell carcinoma and lung metastases, before (A) and after 4 weeks of sunitinib (B). ^{18}FMISO-PET explores hypoxia metabolism and might be a potential functional biomarker of the metabolic response to antiangiogenic therapy. In this patient, despite residual tumor, ^{18}FMISO-PET detected no uptake, indicating a good therapeutic response. These images were kindly provided by Dr F Hugonnet and Pr M Faraggi, Department of Nuclear Imaging, Princess Grace Hospital, Monaco.

and has been recently shown to change in response to expected clinical evolution after therapy (Davies *et al.* 2006, Vinik *et al.* 2011, Yadegarfar *et al.* 2013). Thus, correlation between variation of the standardized quality-of-life assessment and tumor evolution should be examined for NET patients.

Finally, targeted therapies may cause specific adverse events that might be related to antitumor effect and thus have to be monitored. For example, sunitinib-related hypertension in metastatic renal cell carcinoma patients was reported to be associated with better outcomes, suggesting that the occurrence and intensity of some adverse events could reflect treatment efficacy (Rini *et al.* 2011).

Histology and tumor progression

Whereas tumor progression implies a dynamic and sequential process, the pathologist's viewpoint is essentially static. In rare situations (sequential biopsies, availability of metastatic tissues after resection of a primary tumor), the pathologist is able to compare the same neoplastic tissue at successive times and can assess tumor progression. In those instances, several histological or molecular parameters suggestive of progression can be evaluated, e.g., morphological changes of the neoplastic proliferation's architecture and cytological characteristics, increased proliferative capacities, and accumulation of molecular and genetic changes.

Notably, recent studies showed that the Ki67 index is usually higher in metastatic tumors than their corresponding primary lesions: this may indicate that increased proliferative capacities are likely to occur during progression (Couvelard *et al.* 2009, Hentic *et al.* 2011, Yang *et al.* 2011). Furthermore, additional molecular alterations in metastases, compared with the primary lesion, have been documented (Andersson *et al.* 2009, Nilsson 2013). However, defining predictive factors based on primary tumors (sometimes resected long before) when metastases are the treatment target is not certain. These observations raise important issues. Is it useful to biopsy or re-biopsy NET metastases, especially those occurring long after the initial diagnosis, before deciding the therapeutic strategy? If so, what is the best and most informative biopsy site?

Biological markers, tumor progression, and therapeutic responses

Chromogranin A (CgA) is the only serum marker routinely used for NETs. However, its sensitivity is low, within- and between-subject variations are high, and causes of false

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Table 3 Main studies that reported decreased posttreatment CgA levels to be predictive of disease response and/or improved outcome

Study	Study design	*n*	Main results
Seregni *et al.* (2001)	Various therapies for GEP NETs	46	≥25% decrease in CgA levels was associated with tumor regression in 25% of patients
Abou-Saif *et al.* (2003)	Prospective follow-up of gastrinoma patients	13	≥44% decrease in CgA levels was correlated with 100% of tumor regression (85% sensitivity and 99% specificity)
Kouvaraki *et al.* (2004)	Fluorouracil, doxorubicin and streptozotocin for advanced pancreatic NETs	49	≥30% decrease in CgA levels within 4 months was associated with response to chemotherapy ($P=0.04$)
Nehar *et al.* (2004)	Various therapies for GEP NETs	42	≥25% decrease in CgA levels was associated with tumor regression in 79% of the patients
Jensen *et al.* (2007)	Cytoreductive surgery for hepatic NET metastases (retrospective)	70	≥80% postoperative decrease in CgA levels predicted complete symptom relief ($P=0.007$) and disease stabilization ($P=0.034$)
Yao *et al.* (2010*a*)	Everolimus for advanced pancreatic NETs	115	≥30% decrease in CgA levels at week 4 predicted higher median PFS (13.3 vs 7.5 months; $P=0.00004$)
Baudin *et al.* (2011)	Octreotide LAR plus everolimus or placebo for advanced NETs and carcinoid syndrome	256	≥30% decrease in CgA levels at week 4 predicted higher median PFS (20 vs 10.8 months; $P<0.001$)
Yao *et al.* (2011*b*)	Everolimus for advanced pancreatic NETs	77	≥30% decrease in CgA levels at week 4 predicted higher median PFS (13.31 vs 7.52 months; $P<0.001$), median OS (24.9 vs 12.71 months; $P=0.01$), and RECIST partial response (87.1 vs 50%)
	Everolimus and octreotide LAR for advanced pancreatic NETs	30	≥30% decrease in CgA levels at week 4 predicted higher median PFS (16.7 vs 4.9 months; $P<0.001$) and median OS (not reached vs 24.1 months; $P<0.001$)
Jensen *et al.* (2013)	Various regimens for small-bowel NETs	116	≥25% decrease in CgA levels was correlated with tumor regression (78% sensitivity, 91% specificity, 55% positive, and 97% negative predictive values)
Walter *et al.* (2012)	Various regimens for GEP NETs	15	>50% decrease in CgA levels was associated with tumor regression in 46% of patients

CgA, chromogranin A; GEP, gastroenteropancreatic; NET, neuroendocrine tumor; OS, overall survival; PFS, progression-free survival.

positives are many (Zatelli *et al.* 2007, d'Herbomez *et al.* 2010, Vezzosi *et al.* 2011, Braga *et al.* 2013). After excluding conditions with elevated gastrin levels, the CgA level is highly specific for NET diagnosis (84–98%) and correlated with tumor burden (Campana *et al.* 2007, Zatelli *et al.* 2007, d'Herbomez *et al.* 2010, Modlin *et al.* 2010, Lawrence *et al.* 2011, Schott *et al.* 2011). Moreover, several recent therapeutic trials on NETs demonstrated its prognostic value (Baudin *et al.* 2011, Yao *et al.* 2011*b*, 2012*a*).

Several authors reported correlations between CgA variations during treatment and RECIST-assessed tumor evolution (Bajetta *et al.* 1999, Seregni *et al.* 2001, Abou-Saif *et al.* 2003, Kouvaraki *et al.* 2004, Nehar *et al.* 2004, Jensen *et al.* 2007, 2013, Pavel *et al.* 2011, Yao *et al.* 2011*b*). Early CgA response (≥30% decrease at week 4) was correlated with improved median PFS, median OS, and tumor responses, compared with patients without early CgA responses (Table 3; Yao *et al.* 2010*a*, 2011*b*, Baudin *et al.* 2011). In addition, increased CgA levels, after excluding causes of false-positive rises, seem to be associated with disease progression (Table 4). Although its sensitivity is low in the setting of small NETs, serial CgA measurements have proven useful in monitoring patients with resected NETs to identify early tumor recurrence (Janson *et al.* 1997, Pirker *et al.* 1998, Bajetta *et al.* 1999, Arnold *et al.* 2008, Ekeblad *et al.* 2008, Ahmed *et al.* 2009, Bergestuen *et al.* 2009, Welin *et al.* 2009, d'Herbomez *et al.* 2010, Jensen *et al.* 2013). However, other recent studies failed to demonstrate the interest of CgA for NET monitoring under treatment (Vezzosi *et al.* 2011, Walter *et al.* 2012). Hence, although CgA might be a simple and relevant tool for monitoring treatment efficacy, it urgently needs to be specifically addressed in prospective well-conducted studies.

Other markers of functioning tumors (5-hydroxyindoleacetic acid, insulin, pro-insulin, gastrin, glucagon, vasoactive intestinal peptide, and pancreatic polypeptide) are relevant for diagnosis purposes but their relevance for predicting treatment efficacy has not been demonstrated (O'Toole *et al.* 2009). In one study, the early neuron-specific enolase response

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Table 4 Main studies that reported elevated CgA levels from baseline to be predictive of disease progression and/or poorer outcome

Study	Study design	*n*	Main results
Seregni *et al.* (2001)	Various regimens for GEP NETs	46	≥25% increase in CgA levels was associated with disease progression in 83% of the patients
Abou-Saif *et al.* (2003)	Prospective follow-up of gastrinoma patients	26	≥44% increase in CgA levels was correlated with disease progression in 77% of the patients (62% sensitivity and 53% specificity)
Nehar *et al.* (2004)	Various regimens for GEP NETs	42	≥25% increase in CgA levels was associated with disease progression in 89% of the patients
Welin *et al.* (2009)	Patients with resected small-bowel NETs	33	Increased CgA was the first marker of recurrence in 85% of the patients
Walter *et al.* (2012)	Various regimens for GEP NETs	50	>50% increase in CgA levels was associated with disease progression in 56% of the patients
Jensen *et al.* (2013)	Various regimens for small-bowel NETs	116	≥25% increase in CgA levels was correlated with disease progression (86% sensitivity, 86% specificity, 64% positive, and 85% negative predictive values)

CgA, chromogranin A; GEP, gastroenteropancreatic; NET, neuroendocrine tumor; OS, overall survival; PFS, progression-free survival.

(≥30% decrease at week 4) was predictive of response in everolimus-treated patients with advanced pancreatic NETs (Yao *et al.* 2011*b*).

Recently, new potentially specific biomarkers of tumor responses to antiangiogenic therapies, e.g., plasma levels of placental growth factor, vascular endothelial growth factor (VEGF), or the soluble forms of its receptor (sVEGFR-1 and -2), have been studied in patients with various malignancies. For NETs, those biomarkers were evaluated only in a *post hoc* analysis of the RADIANT-3 trial, in which their baseline levels were not predictive of everolimus efficacy, despite their prognostic value (Yao *et al.* 2012*b*). Further investigation is warranted to determine whether early decreases in those markers during treatment could be predictive of better outcomes, particularly for patients treated with agents targeting the VEGF pathway, like bevacizumab.

Finally, the presence of circulating tumor cells (CTC) was reported to be a significant prognostic factor for NETs (Khan *et al.* 2011, 2012). Indeed, a >33% higher number of CTC, measured after 3–5 weeks of treatment, was associated with poorer PFS and OS (respective HR, 23.1 and 18.9) compared with no increase (Khan *et al.* 2012). Whether serial CTC determinations could be relevant for NET follow-up and a potential surrogate of therapeutic response requires further investigation in specific clinical trials, as shown for other malignancies (Matsusaka *et al.* 2010, Danila *et al.* 2011, Hiltermann *et al.* 2012, Boutrus *et al.* 2013). However, the main limitations of using CTC in routine practice are the limited availability and non-standardization of their measurement technique.

Synthesis and perspectives

Although size-based criteria remain the reference for assessing spontaneous NET evolution or response to conventional chemotherapy, they are not adapted to targeted therapies. Composite criteria, combining morphological and functional explorations, are mandatory because targeted therapies do not necessarily induce tumor shrinkage. Trials evaluating what has been proven for other malignancies treated with targeted therapies are required, namely, assessing whether functional criteria (e.g., Choi, Chun, mRECIST, and PERCIST criteria) and functional techniques (i.e., DCE-based parameters) are better correlated with tumor responses and clinical outcomes than RECIST criteria. This analysis could be done in upcoming large therapeutic trials to validate them as intermediate surrogate judgment criteria.

To be adapted for NET evaluation, these criteria will have to take into account the heterogeneity of liver metastases in terms of prognostic factors, proliferative parameters, histology, biology, and images obtained with the different techniques available. Furthermore, the required percentage decrease in vascularization with DCE-based modalities (and, similarly, DW-MRI-measured apparent diffusion coefficient and PET-measured standardized uptake value) to assess partial response remains an issue; their thresholds could depend on the type of treatment administered. Technique standardization is also an important issue to achieve adaptation from fundamental research to clinical practice. Functional imaging modalities appear to be even more important because no sufficiently relevant clinical, biological, or

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histological method exists to assess tumor progression or response. Notably, CgA might serve as a surrogate marker of PFS, provided that it could be confirmed that early CgA variations after starting targeted therapy predict tumor response. Explorations of alternative possibilities must be pursued, e.g., specific biomarkers of responses to anti-angiogenic therapies and CTC. Moreover, the latter could also constitute samples for repeated histopathological examinations.

Declaration of interest

Drs C Dromain, J-Y Scoazec, G d'Assignies, R Lebtahi, N Lassau, H Brixi, E Mitry, R Guimbaud, F Courbon, M d'Herbomez, and G Cadiot have received honoraria from Novartis Pharmaceuticals Corporation, in relationship with board membership. Dr F Courbon has been a member of a board and has received research grants from Covidien. Drs H Brixi, E Mitry, and G Cadiot have received honoraria from Ipsen Pharma and Novartis Pharmaceuticals Corporation. Dr E Mitry has received honoraria from Pfizer and Keocyt. Dr L de Mestier has no conflicts of interest to declare.

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