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ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation

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Keywords

Neuroendocrine neoplasm · Neuroendocrine tumor · Neuroendocrine carcinoma · Follow-up · TNM staging · Chromogranin A · Neuron-specific enolase · 5-Hydroxyindoleacetic acid · NT-pro-brain natriuretic peptide · Functional imaging · Somatostatin receptor imaging

Abstract

ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms (NEN) concerning follow-up and documentation are considered in this review. The documentation of patients with NEN should include the most relevant data characterizing an individual patient from the first contact with his/her physician/hospital until his/her last presentation during follow-up. It is advocated that follow-up occurs in specialized NEN centers with regular NEN tumor boards with expert panels. The follow-up should be in accordance with the ENETS consensus guidelines from 2011 and 2016, the present and coming WHO classification and ENETS/UICC recommendations for TNM staging. The recommendations for follow-up in patients with thymic, bronchopulmonary and gastroenteropancreatic NEN are given in Table 1. However, it should be stressed that evidence-based studies for follow-up are largely missing.

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Introduction

The documentation of patients with neuroendocrine neoplasms (NEN) should include the most relevant data characterizing an individual patient from the first contact with his/her physician/hospital until his/her last presentation during follow-up. The documentation should be both simple but nevertheless as complete as possible and should include basic demographic details to identify a specific patient, family history, tumor histology and biology, course of the disease, tumor board evaluations, diagnostic tests, and therapeutic interventions. Additional data about biological samples, such as tumor specimens preserved in paraffin-embedded or fresh frozen samples and the patient's samples like blood or serum, would be of high interest for current and future translational research. This information is essential for treatment and follow-up strategies adjusted to the specific features of the tumor of the patient. Furthermore, standardized documentation acts as a key precondition to learn more about patients with specific tumor subtypes and regarding the impact of treatment modalities on the course of the disease. In the present clinical setting, the timing of data collection and content of documented data vary considerably. Therefore, comparison of data from different centers is frequently hampered by lack of data uniformity.

During the ENETS Standards of Care Conference Advisory Board meeting organized in Antibes, France in 2015, a group of physicians with extensive experience in the clinical care of patients with gastroenteropancreatic (GEP), bronchopulmonary (BP) and thymic NEN met to write recommendations on the unified collection of data and suggested time intervals for follow-up investigations. These guidelines recognize the diversity of tumor subtypes, the actual WHO and TNM classifications, the individual clinical course of the disease as well as the resource implications relevant to the growing costs of the European health care systems. Particular attention was paid to recommend only those investigations that would have a significant impact on further therapeutic strategies.

It is advocated that follow-up occurs in specialized NEN centers or at least in hospitals with close collaboration with specialized NEN centers. It is of minor importance which specialty (e.g., oncology, gastroenterology, endocrinology, pulmonology or surgery) follows the patient as long as experienced NEN specialists are present. Regularly NEN tumor boards with expert panels are essential for follow-up. Besides all new patients, patients with recurrence or progression as well as patients with other relevant problems during follow-up should be presented at the multidisciplinary tumor board.

Documentation at Follow-Up Should Adhere to the Present WHO Classification and Recognize the ENETS Consensus Guidelines and Recommendations for TNM Staging

The panel agreed that the following categories best define the different tumor entities observed in the clinical setting. The categories follow the WHO 2010 classification [1] as well as the ENETS consensus guidelines from 2011 [2] and 2016 [3] and the recommendations for TNM staging [4, 5] in order to better compare data from different centers. We are aware that a revised WHO classification will be published within the next few years, also considering G3 neuroendocrine carcinomas (NEC G3, poorly differentiated) versus G3 neuroendocrine tumors (NET G3, well differentiated) as different entities based upon differentiation. This may refine the current classifications, if an objective definition of differentiation is achieved. This subclassification may have an impact on treatment, but may not change the general follow-up procedures and recommendations. It should be stressed that evidence-based studies for follow-up are largely missing.

In this article, we have revised the previous recommendations [6] and introduced a new set-up, which we find easier to apply on the daily routine for follow-up on patients with GEP, BP and thymic NEN (Table 1). For BP NEN, typical and atypical carcinoids as well as large-cell neuroendocrine carcinomas have been included as per ENETS guidelines [7] and Danish guidelines [8]. Small-cell lung cancer is not included in the article as it is beyond the scope of these recommendations and as it is dealt with in several other guidelines. We have included a suggested follow-up regime for thymic NEN, although evidence for follow-up in these tumor types is lacking.

Firstly, the different NEN are divided according to the organ of the primary tumor, including cancer of unknown primary. Secondly, the tumors are recorded according to their grading (GEP NEN), differentiation (thymic and BP NEN), status, and operative outcome, respectively (Table 1). Data on stage (TNM – including size of the primary but also tumor burden), tumor aggressiveness (stable vs. progressive disease), functionality, chromogranin A (CgA) levels, and hereditary disease, which all may have an impact and thus may affect the follow-up

Table 1. Tumor-specific recommendations for follow-up (in most cases life-long)

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Bronchopulmonary										
Typical	resected	yes	6–12 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 5–10 y	6–12 m	12–36 m[e]		EBUS may be required if recurrence is suspected
Typical	residual tumor or metastases	yes	3–6 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 5–10 y	3–6 m	12–36 m[e]	12–24 m[l]	EBUS may be required if progression is suspected
Atypical	resected	yes	3–6 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 1–3 y	(3)–6 m	12–24 m[e,f]	12–24 m[l]	EBUS may be required if recurrence is suspected
Atypical	residual tumor or metastases	yes	3 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 1–3 y	3–6 m	12–24 m[e,f]	12–24 m[l]	EBUS may be required if progression is suspected
LCNEC poorly diff.	resected/ nonresected	yes	2–3 m	yes[d]	NSE[d] relevant tumor hormones[d]	bronchoscopy[m] if symptoms	2–3 m	12–24 m[e,f]	12–24 m[l]	bronchoscopy indicated if rebiopsy, argon-beam or bronchial stent is required; EBUS may be required if recurrence or progression is suspected
Thymic										
Typical	resected/ residual tumor or metastases	yes	6–12 m	yes	relevant tumor hormones[d]		6–12 m	12–36 m[e,f]	12–36 m[e,f]	
Atypical	resected/ residual tumor or metastases	yes	3–6 m	yes	relevant tumor hormones[d]		3–6 m	12–24 m[e,f]	6–24 m[e,f]	
Poorly diff.	resected/ nonresected	yes	2–3 m	yes[d]	relevant tumor hormones[d]		3–6 m	12–24 m[e,6]	6–24 m[e,f]	
Esophagus										
G1–G2 NET	resected/ nonresected	yes	3 m	yes[d]	none	12 m or symptoms	3–6 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
G3 NEC	resected/ nonresected	yes	3 m	yes[d]	none	12 m, or symptoms	2–3 m	12–24 m[e,6]	6–24 m[l]	EUS may be required if recurrence or progression is suspected
Stomach										
Type 1 G1–G2 NET	resected/ nonresected	yes	6–12 m	yes[g]	gastrin[g] B_{12} vitamin	12 m, or symptoms	no[h]	no[h]	no	EUS may be required if recurrence or progression is suspected
Type 2 G1–G2	resected/ nonresected	yes	6–12 m	yes	gastrin Ca^{2+}, PTH	6–12 m, or symptoms	12 m	12–24 [me,f]	no	EUS may be required if recurrence or progression is suspected
Type 3 G1–G3 NEC/NET	resected/ nonresected	yes	2–3 m	yes[d]	none	6–12 m, or symptoms	2–6 m	12–24 m[e,f]	12–24 m[l]	EUS may be required if recurrence or progression is suspected
Duodenum										
Gastrinoma G1–G2	resected	yes	6–12 m	yes	gastrin, Ca^{2+}, PTH	12 m, or symptoms	12 m	12–24 m[e]		Gastric pH measurement or secretin test may be performed if symptoms recur; EUS may be required if recurrence is suspected
Gastrinoma G1-G2	nonresected	yes	3–6 m	yes	gastrin, Ca^{2+}, PTH	6–12 m, or symptoms	6–12 m	12–24 m[e]		EUS may be required if progression is suspected
Other G1–G2 NET[n]	resected/ nonresected	yes	3–6 m	yes[d]	relevant tumor hormones[d]	12 m, or symptoms	6–12 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
G3 NEC/NET[n]	resected/ nonresected	yes	3 m	yes[d]	none	12 m, or symptoms	3 m	12–24 m[e,f]	12–24 m[l]	EUS may be required if recurrence or progression is suspected

Table 1 (continued)

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Pancreas										
Insulinoma solitary G1–G2 NET[n]	resected	yes	once 3–6 m	yes[d]	fasting BS insulin C-peptide pro-insulin	no	no	no		fasting test performed if symptoms recur; EUS may be required if recurrence is suspected
Insulinoma localized or metastases G1–G2 NET[n]	nonresected	yes	3–6 m	yes[d]	fasting BS insulin C-peptide pro-insulin	no	3–6 m	12 m[e]		EBUS may be required if progression is suspected
Gastrinoma G1–G2	resected	yes	3–6 m	yes	gastrin, B_{12}, Ca^{2+}, PTH		6–12 m	12–24 m[e]		gastric pH measurement or secretin test may be performed if symptoms recur; EUS may be required if recurrence is suspected
Gastrinoma G1–G2	nonresected	yes	3–6 m	yes	gastrin, B_{12}, Ca^{2+}, PTH		3–6 m	12–24 m[e]		EUS may be required if progression is suspected
Functional pNET G1–G2 localized or metastases[n]	resected/ nonresected	yes	3–6 m	yes	relevant tumor hormones[d]	no	3–6 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
Nonfunctional pNET G1–G2[n]	resected/ nonresected	yes	3–6 m	yes	none	no	3–6 m	12–24 m[e]		EBUS may be required if recurrence or progression is suspected
pNET G3 NEC/ NET[n]	resected/ nonresected	yes	3 m	yes[d]	if functioning relevant tumor hormones[i]	no	2–3 m	12–24 m[e,f]	12–24 m[l]	EBUS may be required if recurrence or progression is suspected
Small intestine										
G1–G2	curatively resected	yes	6–12 m	yes	5-HIAA	no	6–12 m	24 m[e]		
G1–G2	residual tumor or metastases	yes	3–6 m	yes	5-HIAA	no	3–6 m	12 m[e]		in patients with carcinoid syndrome: NT-pro-BNP and echocardiography at least yearly
G3 NEC/ NET	resected/ nonresected	yes	3 m	yes[d]	relevant tumor hormones[i]	no	2–3 m	12–24 m[e,f]	12–24 m[l]	in patients with carcinoid syndrome: NT-pro-BNP and echocardiography at least yearly
Appendix										
G1–G2 <2 cm[j]	curatively resected	no	no	no	no	no	no	no		appendectomy
G1–G2 >2 cm[k]	curatively resected/ nonresected	yes	3–6 m	yes	5-HIAA[d]	no	3–12 m	24 m[e]		right hemicolectomy
G3 NEC/ NET	resected/ nonresected	yes	3 m	yes[d]	relevant tumor hormones[i]	no	2–3 m	12–24 m[e,f]	12–24 m[l]	in patients with carcinoid syndrome: NT-pro-BNP and echocardiography at least yearly
Colon										
G1–G2	curatively resected	yes	6–12 m	yes[d]	5-HIAA[d]	yes 12–24 m	6–12 m	24 m[e]		serotonin-producing tumors of the cecum or if 5-HIAA is elevated at diagnosis
G1–G2	residual tumor or metastases	yes	3–6 m	yes[d]	5-HIAA[d]	yes, if symptoms	3–6 m	12 m[e]		serotonin-producing tumors of the cecum or if 5-HIAA is elevated at diagnosis
G3 NEC/ NET	resected/ nonresected	yes	3 m	yes[d]	none	yes, if symptoms	2–3 m	12–24 m[e,f]	12–24 m[l]	
Rectum										
G1–G2 <1 cm	curatively resected	yes	once	no	none	once and if symptoms	no	no		EUS may be required if recurrence is suspected
G1–G2 1–2 cm	curatively/ noncuratively resected	yes	12 m	yes[d]	none	12 m or if symptoms	3–12 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
G1–G2 >2 cm	curatively/ noncuratively resected	yes	3–12 m	yes[d]	none	6–12 m or if symptoms	3–12 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
G3 NEC/NET	curatively/ noncuratively resected	yes	3 m	yes[d]	none	6–12 m or if symptoms	3 m	12 m[e,f]	12–24 m[l]	EUS may be required if recurrence or progression is suspected

Table 1 (continued)

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Cancer – unknown primary										
G1–G2	noncuratively resected	yes	3–6 m	yes[d]	5-HIAA[d]	no	3–6 m	12 m[e]		
G3 NEC/ NET	noncuratively resected	yes	3 m	yes[d]	5-HIAA[d]	no	3 m	12 m[e,f]	12–24 m[l]	

LNEC, large-cell neuroendocrine carcinomas; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; pNET, pancreatic neuroendocrine tumor; F-U, follow-up; m, months; NSE, neuron-specific enolase; PTH, parathyroid hormone; BS, blood sugar; y, years; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

[a] Other tumor markers and hormones in blood and urine. [b] CT is preferred for routine control. [c] Somatostatin receptor imaging (^{68}Ga-DOTA PET; octreotide scintigraphy). [d] Only if elevated at diagnosis. [e] Only if positive at diagnosis. [f] In G3 NEC or atypical pulmonary NET, ^{18}FDG-PET may be used instead. [g] Are usually elevated, but have no implement on F-U. [h] Only if metastasized; for CT/MRI/US every 6 months, for SRI every 12–24 months. [i] Rarely functioning. [j] No metastases, no angioinvasion, mesoappendiceal invasion <3 mm. [k] Or metastases, angioinvasion, mesoappendiceal invasion >3 mm, localized at the base, uncertain resection margins. [l] FDG-PET-CT may be used instead of SRI if positive at diagnosis. [m] Only if tumor is visible by bronchoscopy at diagnosis. [n] Hereditary diseases (MEN-1, VHL and neurofibromatosis type 1 is included).

intervals, are too comprehensive to be included in Table 1, but are mentioned in Table 2.

Functioning tumors (the specific secreted hormone being their tumor marker) should be followed up with hormone analyses and imaging every 3–12 months depending on hormone-related symptoms and tumor aggressiveness. If recurrence or persistence is highly suspected, functional tests, for example fasting test for insulinomas and secretin test for gastrinomas, may be required.

Table 2. Shorter intervals between follow-ups in patients with NEN

High-grade tumors
Large tumor burden (e.g., liver burden >30% and lung/bone metastases)
Extensive disease
Aggressive behavior (progression within few months)
Severe (uncontrolled) endocrine symptoms
Weight loss and clinical aggravation
High chromogranin A levels >10 UNL

UNL, upper normal level.

Recommendations for Follow-Up Investigations

It is recommended that follow-up should be performed in specialized NEN centers to obtain specific biochemistry and high-quality imaging.

General Recommendations

Documentation of each patient should encompass:

- Patient identification and basic demographic details
- General health score (Karnofsky status/WHO score/ECOG performance status)
- Patient's history: onset, extent, and severity of tumor-specific symptoms, hormone-related syndromes, family history, inherited syndromes, metachronous or synchronous malignancies
- Comorbidity including concomitant diseases, including kidney and liver disease
- Plasma CgA and relevant hormone levels with reference to previous levels considering the current unspecific medical treatment of the patient (e.g., proton pump inhibitors may induce elevation of plasma CgA and gastrin levels)
- Presence of carcinoid heart disease
- Availability of tumor and/or patient samples, including characteristics of the samples and location
- Pathological diagnosis including TNM stage (ENETS and UICC) and WHO grade (mitotic count or preferred Ki-67 proliferation index) from resected tumor specimens or from biopsies from targeted organs
- Development of tumor and metastases and changes in tumor burden based on computerized tomography/magnetic resonance imaging (CT/MRI) and somatostatin receptor imaging (SRI); for SRI, up-take grade should be recorded
- Preceding and actual treatment(s)
- Consider referral to curative or debulking surgery
- Consider referral to medical treatment
- Consider referral to peptide receptor radionuclide treatment
- Consider referral to liver-directed interventional treatment
- Consider referral to palliative unit for supportive care

If relevant from the above, the patient documentation should be presented at the multidisciplinary tumor board for further planning.

General Comments

Tumor-specific follow-up investigations are mainly based on clinical symptoms, imaging procedures such as functional and cross-sectional imaging, and tumor markers. However, an expert physician who is in charge of an individual patient is able to judge the patient's general health and even prognosis by a careful history and examination, assessment of weight loss, muscular mass and symptoms, for example heart function in cases of the carcinoid syndrome and possible carcinoid cardiac disease. However, these items are difficult to compare inter- and intraindividually and should be supported where possible by "objective" procedures such as imaging methods and serum/plasma tumor markers.

Tumor Markers

Chromogranin A

At present, the most common and reliable tumor marker is plasma CgA for patients with G1 and G2 NEN. However, plasma CgA is generally normal in patients with nonfunctioning duodenal NEN, appendiceal NEN, small rectal NEN and insulinomas and is often normal in patients with localized G1 and G2 NEN and in patients with G3 NEN (some G3 NET can have increased CgA plasma levels). Plasma CgA may reflect tumor mass and changes in tumor burden but also secretory activity of the tumor [9–13]. In addition, plasma CgA may be an indicator for prognosis mainly in small intestinal NEN [9, 11, 14]. Furthermore, an increase in the CgA level has been suggested as the first indicator of recurrence [15]. However, fluctuations in plasma CgA are frequently seen and in case of more than 25% increase from the previous level, determination of CgA should be repeated. If still increased, imaging with CT/MRI or SRI is recommended. Plasma CgA may also be elevated without the presence of NEN, for example due to the use of proton pump inhibitors, chronic atrophic gastritis, or decreased kidney and liver function [16, 17].

In some clinical trials with new targeted agents, significant reductions in CgA have been associated with better outcomes [14]. However, variations in plasma CgA without changes in imaging or symptoms compared to baseline levels should not be considered for treatment modification. Since several assay kits exist, but with no international standard, caution is recommended when comparing values from kits of different manufacturers [10]. Furthermore, each CgA kit has to be evaluated concerning sensitivity and specificity. CgA levels and normal ranges differ in the literature and from laboratory to laboratory and from assay to assay because they are measured by different methods. Therefore, "cutoff levels" recommended for decision-making should be applied with caution, and each institution has to define its own "cutoff levels."

Chromogranin B

Plasma chromogranin B (CgB) may be of value in the follow-up of BP and rectal NEN [18]. However, the availability for CgB is limited.

Neuron-Specific Enolase

Plasma neuron-specific enolase may act as an additional marker in patients with G3 NEN [19] and has been shown to be a prognostic marker in GEP NEN [14, 20].

5-Hydroxyindoleacetic Acid

Twenty-four-hour urine 5-hydroxyindoleacetic acid (5-HIAA) is an established marker for patients with serotonin-producing small intestinal/appendiceal and BP NEN, in particular in the presence of the "carcinoid syndrome." However, the sensitivity is less than that of plasma CgA [21]. Recently, analyses for serum 5-HIAA have been introduced [22]. Urine 5-HIAA is influenced by a number of dietary factors, for example avocado, banana, tomato and others, and by drugs such as coumarin, paracetamol, phenacetin, aspirin and others.

Serotonin

Measurement of serum serotonin is not recommended for follow-up [23].

Gastrointestinal Hormones

In patients with functioning pancreaticoduodenal tumors (insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma, etc.), the respective hormones are used as diagnostic markers. However, the prognostic value of change in hormone values is uncertain.

NT-pro-Brain Natriuretic Peptide

Measurement of NT-pro-brain natriuretic peptide (NT-pro-BNP) once yearly or at least every 2nd year is recommended in the follow-up of patients with carcinoid syndrome to reveal development and to control carcinoid heart disease [24]. It is supplemented by echocardiography or eventually MRI of the heart [25–27].

Imaging

For G1 and G2 neuroendocrine tumors, which are generally slow growing, follow-up imaging is usually between 6 and 12 months but some patients may require imaging evaluation earlier. Better determination of the

timing of morphological evaluation is required in studies either retrospectively or prospectively.

Cross-Sectional Imaging

Current imaging procedures encompass CT, MRI, abdominal ultrasound (US), with or without contrast enhancement, and SRI. Primarily CT is used because of its standardized imaging planes that facilitate comparison between examinations and since the tissue resolution is better in cases of extended tumor load. Additionally, MRI may be preferable in younger patients having several imaging procedures, to reduce radiation dose. In addition, MRI is superior to CT to evaluate liver metastases, pancreatic and rectal NEN. Abdominal US may, however, be used for follow-up if documentation allows one to compare findings obtained during different follow-up visits. US is also valuable for the occasional patients in whom liver metastases are better visualized by US than by CT and for biopsy of new or rapidly growing lesions.

Thoracoabdominal CT, including three-phase examination of the liver, is the preferred imaging for follow-up as it is widely available and has relatively low cost. However, in many centers, abdominal MRI is preferred and if resection of liver metastases is considered during follow-up, it is generally recommended to perform MRI to reveal small liver metastases not visualized by CT [28].

Functional Imaging

Somatostatin receptor scintigraphy (SRS) with ^{111}In-pentetreotide (octreotide scintigraphy), including planar imaging and SPECT, has been the mainstay for SRI although most NEN centers currently perform PET-CT with ^{68}Ga-DOTA-conjugated peptide (e.g., TOC/NOC/TATE) as this PET imaging technique is superior to SRS showing higher sensitivity, spatial resolution, identification of more lesions, less radiation, and a shorter investigation time [29–32] and is therefore preferred in follow-up. Other PET tracers, such as ^{64}Cu-DOTATATE-PET-CT [30, 31],^{18}F-DOPA-PET-CT [33–35] and ^{11}C-5-HTP-PET [36] as well as GLP-1 receptor imaging with ^{111}In-DTPA-exendin-4 SPECT-CT [37], may be used in follow-up if positive at baseline and if available at the center. Currently, there are only limited data available of PET-based imaging for routine follow-up, and its significance in this respect is currently not possible to define. However, PET may reveal metastases not seen on SRS or CT, particularly in bone and lymph nodes [30, 31, 33–35]. Grade uptake at SRI as well as homogeneity of uptake should be specified [38], also to evaluate the eligibility for peptide receptor radionuclide treatment.

^{18}FDG-PET-CT has a higher sensitivity than SRS in patients with G3 NEN and should instead be utilized for follow-up in this group of patients [39]. Furthermore, ^{18}FDG-PET-CT is frequently positive in G2 NEN with a high Ki-67 index and in aggressive and rapidly growing NEN [39, 40]. In addition, ^{18}FDG-PET is an important prognostic factor in NEN, as patients with a positive PET have a significantly poorer prognosis than patients with a negative one [39, 41]. Additionally, evidence of different uptake in ^{18}FDG-PET and SRI in the same patient reflects the tumor heterogeneity and could have an impact in decision-making criteria [42]. However, ^{18}FDG-PET-CT is not commonly used for follow-up and in general only when SRI is negative, in patients with G3 NEN or in other selected subgroups of patients.

Endoscopy

Upper endoscopy should be utilized in the follow-up and control of gastric NEN and colonoscopy and sigmoidoscopy should be used for the follow-up of patients with colorectal NEN. National follow-up strategies should be followed to early diagnose metachronously appearing secondary gastrointestinal malignancy. Follow-up bronchoscopy for recurrence is indicated in patients with BP neuroendocrine tumors localized preoperatively by bronchoscopy.

Endoscopic ultrasonography, eventually with biopsy, of the stomach, duodenum, pancreas, and rectum could be useful for follow-up in selected patients (T and N staging) and also in patients with MEN-1. Capsule endoscopy (jejunum/ileum) is rarely indicated in the follow-up. Endoscopic bronchial ultrasonography may be indicated in follow-up if biopsy of pathologic peribronchial lymph nodes is required.

Histopathology

In patients with tumor or metastatic recurrence and/or rapid or unexpected progression imaging-guided biopsy should be considered to re-evaluate the Ki-67 proliferation index. An increase may change the treatment strategy or may rule out secondary malignances. Biopsies should be taken from new or rapidly growing metastases.

Echocardiography

"Carcinoid heart disease" with involvement of the tricuspid and pulmonary valves is observed in up to 10–20% of patients with the carcinoid syndrome [43]. In all patients with carcinoid syndrome and in patients with G1/G2 GEP NEN or BP NEN with high 24-h urine, 5-HIAA level echocardiography should be performed at diagnosis

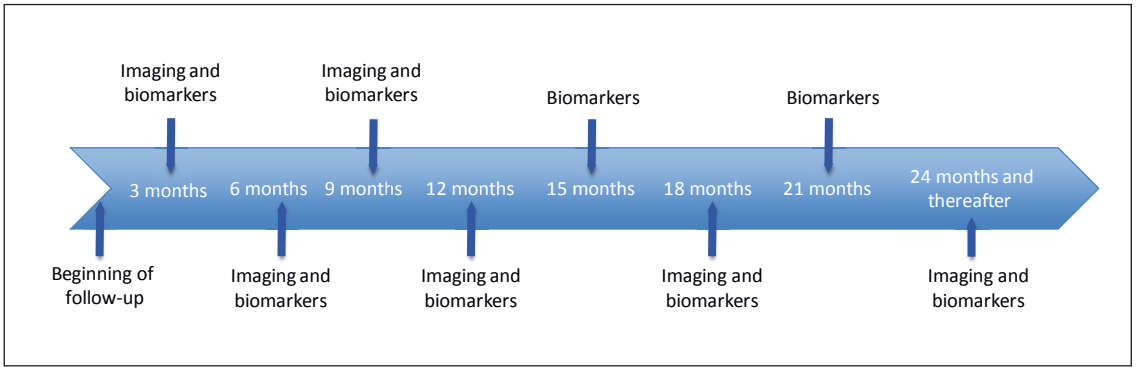

Fig. 1. Proposed timeline schedule for the follow-up of patients with G1/G2 gastroenteropancreatic neuroendocrine neoplasms and bronchopulmonary (typical and atypical) carcinoids regarding tumor progression rate. Initial follow-up every 3 months with clinical assessment, imaging and biomarkers is suggested to define progression rate. If stable disease has been confirmed after 15 months, imaging control could be performed every 6–12 months and clinical and biomarker evaluation every 3–6 months.

and thereafter annually or shorter if clinically indicated [25–27]. The measurement of NT-pro-BNP should be performed as well [24].

Progression Rate

Progression disease rates within G1/G2 GEP NEN and BP NEN are not always well defined only using the grading system. Stable and slowly growing tumors should be differentiated from more aggressive tumors in follow-up schedules, i.e., patients with aggressive and rapidly growing tumors should have a follow-up with imaging every 3 months while patients with stable or slowly growing tumors may have imaging every 6–12 months (Tables 1, 2). Efforts to quantify the rate of progression should be performed. Furthermore, if stable disease is seen over longer time, the interval between follow-up visits and imaging may be further extended. Trying to define the progression rate and the influence in follow-up for metastatic disease, a proposed timeline for follow-up regarding tumor progression is given in Figure 1.

Hereditary Diseases

Patients with hereditary diseases such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindaus syndrome (VHL), or neurofibromatosis type 1 should be followed according to the organ of the primary tumor, for example the pancreas and duodenum. Guidelines for the follow-up of non-GEP disease or manifestations, for example parathyroid or pituitary adenomas in MEN-1, brain and kidney manifestations in VHL and GIST in neurofibromatosis type 1, are not described in these recommendations as they are beyond the scope of this review and are dealt with in several other guidelines.

Tumor-Specific Recommendations

The recommended follow-up for NEN, including GEP NEN, BP (typical and atypical) carcinoids, large-cell neuroendocrine carcinomas as well as thymic NEN, is given in Table 1. The panel agrees that the level of evidence for follow-up recommendations is low. The recommendations are in accordance with those given in the WHO 2010 classification of GEP NEN, the ENETS 2016 guidelines for GEP NEN [3] and the recent guidelines for BP NEN [7].

Follow-up is life-long for most patients, with the exceptions mentioned in Table 1. The comprehensive Table 1 on follow-up is based on the organ of the primary tumor and is intended to give a simple overview or catalog for the clinician. Therefore, some of the schemes are repeated from one organ to the other. The panel did not distinguish in the follow-up between patients with G1 and G2 GEP NEN, whereas patients with G3 GEP NEN were considered as a separate group.

In general, follow-up for resected or nonresected tumors are placed in the same group, but the intervals between follow-ups are in general shorter in patients with

residual tumor or metastases compared to patients with curatively resected tumor or metastases as well as in patients with aggressive disease (Table 2).

The follow-up investigations that should be documented to visualize the specific course of the disease in an individual patient are summarized in Tables 1 and 2 and in Figure 1.

Disclosure Statement

The authors have no conflicts of interest.

Appendix

Antibes Consensus Conference Participants

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