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ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Follow-Up and Documentation

Rudolf Arnold[a] Yuan-Jia Chen[b] Frederico Costa[c] Massimo Falconi[d] David Gross[e] Ashley B. Grossman[f] Rudolf Hyrdel[g] Beata Kos-Kudła[h] Ramon Salazar[i] Ursula Plöckinger[j]
and the Mallorca Consensus Conference participants

[a]Department of Internal Medicine, Philipps University Marburg, Marburg, Germany; [b]Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [c]Hopital Sirio Libanes, Centro de Oncologia, São Paulo, Brazil; [d]Department of Medicine and Surgery, General Surgery Section, University of Verona, Verona, Italy; [e]Department of Endocrinology and Metabolism, Hadassah University Hospital, Jerusalem, Israel; [f]Department of Endocrinology, St. Bartholomew's Hospital, London, UK; [g]2nd Internal Medical Department, University Hospital Martin, Martin, Slovakia; [h]Slaska Akademia Medyczna, Klinika Endokrynologii, Zabrze, Poland; [i]Institut Català d'Oncologia, Barcelona, Spain; [j]Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin, Germany

I Introduction

The documentation of patients with neuroendocrine tumors should include the most relevant data characterizing an individual patient from the first contact with their physician/hospital until their 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, tumor histology and biology, disease history, course of the disease, diagnostic tests and therapeutic interventions. 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 organized in Mallorca in 2007, a group of physicians with extensive experience in the clinical care of patients with benign and malignant gastro-entero-pancreatic (GEP) neuroendocrine tumors met to produce proposals for 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 tumor classifications, the individual clinical course of the disease as well as the resource implications relevant to the growing costs of the European healthcare systems. Particular attention was paid to recommend only those investigations which would have a significant impact on further therapeutic strategies.

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Rudolf Arnold
Wittelsbacherstrasse 6
DE–80469 Munich (Germany)
Tel. +49 89 201 6359, Fax +49 892 020 5564
E-Mail arnoldr@mailer.uni-marburg.de

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

The panel agreed that the following 5 categories best define the different tumor entities observed in the clinical setting. The categories follow the recent WHO classification [1, 2] as well as the ENETS recommendations for TNM staging [3, 4] in order to better compare data from different centers.

Insulinomas and small, benign tumors (T1 endocrine tumors of the stomach, rectum and appendix, 'carcinoids') were categorized separately. They belong to the most frequent benign endocrine tumor entities and require a less intensive follow-up compared to malignant variants.

III Categories

III.1 Benign Tumors

- Benign insulinoma (T1 <2 cm)
- Endoscopically resectable benign (T1 <1 cm) neuroendocrine tumor (carcinoid) of the stomach, duodenum and rectum
- Appendiceal carcinoid (T1 <2 cm)

III.2 Resectable Tumors of Probably Benign (Uncertain) (N0, M0) Behavior

- T2 gastric neuroendocrine tumor >1 cm invading muscularis propria or subserosa
- T2 (>1 cm) tumors of the duodenum/ampulla/proximal jejunum; duodenal gastrinomas and midgut carcinoids which are usually <1 cm (T1) and confined to the submucosa are frequently malignant and belong to category III.3
- T2 (>2 cm) tumors limited to the pancreas
- Appendiceal carcinoid 1–2 cm

(a) G1: well-differentiated, Ki-67 <2%

III.3 Resectable Malignant Tumors with/without Regional Nodal Involvement; in This Category Endocrine Tumors of Probably Benign (Uncertain) Behavior but with Ki 67 >2% (G2 and G3) Are Included

- T1–T2 duodenal gastrinomas
- T1–T3 tumors of the lower jejunum, ileum
- T2–T3 tumors of the appendix
- T2–T3 tumors of colon and rectum
- T2–T3 tumors of the stomach, duodenum, pancreas
  (a) G1: well-differentiated, Ki-67 <2%
  (b) G2: well-differentiated, Ki-67 2–20%
  (c) G3: poorly differentiated

III.4 Non-Resectable Tumors with/without Nodal Involvement and/or with/without Liver and Other Metastases

- All localizations
  (a) G1: well-differentiated, Ki-67 <2%
  (b) G2: well-differentiated, Ki-67 2–20%
  (c) G3: poorly differentiated

III.5 Familial Tumors (MEN-1 Syndrome and VHL Disease)

IV Recommendations for Follow-Up Investigations

IV.1 General Recommendations

Documentation of each patient should encompass:

- Patient identification and basic demographic details
- General health score (Karnofsky status)
- Patient's history: onset, extent and severity of tumor-specific symptoms, concomitant diseases, family history for endocrine tumors, metachronous or synchronous malignancies
- Clinical diagnosis
- Preceding biochemical and imaging procedures
- Histopathological diagnosis including WHO and TNM classification and proliferation index Ki-67
- Preceding treatment(s)

IV.2 General Comments

Tumor-specific follow-up investigations are mainly based on imaging procedures 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 global heart function in cases of the carcinoid syndrome and possible carcinoid cardiac disease. However, these items are dif-

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ficult to compare inter- and intra-individually and should be supported where possible by 'objective' procedures such as imaging methods and serum/plasma tumor markers.

IV.2.1 Imaging

Current imaging procedures encompass abdominal ultrasound with or without contrast medium, endoscopy, endoscopic ultrasound, CT, MRI, octreotide scintigraphy (Octreoscan®) and in some centers PET imaging with different tracers. Procedure-specific expertise frequently determines the choice of imaging procedure. Accordingly, abdominal ultrasound may be recommended for follow-up if documentation allows one to compare findings obtained during different follow-up visits, although many would now rely on CT and MRI for their greater sensitivity and resolution. Octreoscan® is currently substituted in some nuclear centers by ^{68}Gallium-DOTA-DOC PET/CT due to its higher sensitivity [5–7]. However, caution is recommended when comparing the number of tumor lesions detected by the Octreoscan and ^{68}Gallium-DOTA-DOC PET/CT. Due to the higher sensitivity of ^{68}Gallium-DOTA-DOC PET more lesions are detected with this technique, so it is essential to use the same technique when assessing for progression or regression. Currently, there are only limited data available which do not permit one to precisely define the significance of ^{68}Gallium-PET for routine follow-up. In most centers and due to their reproducibility and high resolution, CT or MRI are the imaging procedures of choice for follow-up investigations both in the clinical setting as well as in prospective clinical studies. These techniques represent the 'gold standard' to define the tumor burden of a specific patient with a neuroendocrine tumor.

IV.2.2 Tumor Markers

At present, the most common tumor marker is chromogranin A (CgA) for patients with functioning neuroendocrine tumors of the midgut (carcinoid syndrome) and for non-functioning tumors of the midgut and pancreas as CgA reflects tumor mass and hence spread, and may be used to assess the speed of tumor growth [8–10]. Neurospecific enolase may act as additional marker in patients with poorly differentiated tumors. Since several assay kits exist, caution is recommended when comparing values from kits of different manufacturers [9]. 24-Hour urine 5-hydroxy-indol acetic acid (5-HIAA) as an established marker for patients with carcinoid syndrome has a diagnostic sensitivity as plasma CgA but requires 24-hour urine collection.

With functioning pancreatic tumors (insulinoma, gastrinoma, glucagonoma, VIPoma, etc.) the respective hormones can be used as tumor markers as well. In patients with the carcinoid syndrome urinary 5-HIAA and plasma CgA levels are equally useful.

In most metastatic hindgut tumors CgA is negative and no tumor markers are suitable for this tumor entity [8].

Neuron-specific enolase has been shown to act as a valuable tumor marker in patients with poorly differentiated neuroendocrine tumors [9].

Tumor markers should only be estimated in case of positive imaging; otherwise, unnecessary diagnostic procedures might be initiated without any useful impact on the patient's prognosis.

The time intervals for estimation of tumor markers should follow the suggestions given for imaging.

For gastric type 1 endocrine tumors (carcinoids) CgA and gastrin are elevated but are not particularly helpful for follow-up.

Levels of tumor markers like plasma CgA and urine 5-HIAA depend on the underlying diseases, concomitant medications and dietary settings. Plasma CgA is elevated in patients with type A chronic atrophic gastritis, patients with kidney insufficiency and patients taking acid-suppressing agents such as histamine H_2 blockers or proton pump inhibitors. Urine 5-HIAA is influenced by a number of dietary factors, e.g. avocado, banana, tomato and others, and by drugs such as cumarine, paracetamol, phenacetin, aspirin and others.

V Tumor-Specific Recommendations

V.1 Benign Insulinoma

After curative resection of a sporadic insulinoma tumor-specific follow-up investigations are not indicated. Patients with an insulinoma which was not detected intraoperatively and therefore not removed should be referred on to a center with specific experience. The rare event of a relapsing insulinoma cannot be prevented by routine follow-up investigations.

Following surgery, there may also be a place for procedure-specific surgical follow-up.

For malignant insulinomas see: **V.5** and **V.6**.

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V.2 Endoscopically Resectable Benign Neuroendocrine Tumor (Type 1 Endocrine Tumor (Carcinoid)) of the Stomach and Rectum

80% of all gastric neuroendocrine tumors are type 1 tumors in the presence of type A gastritis. They usually occur as multiple lesions and are mostly smaller than 1 cm. They can easily be removed endoscopically by polypectomy. Rectal endocrine tumors (carcinoids) are solitary and rarely relapse.

Follow-up endoscopies for gastric type 1 endocrine tumors should be performed at yearly intervals. Although often massively elevated, estimation of serum gastrin and plasma CgA has no impact on the prognosis and therefore does not influence the interval of follow-up endoscopies. These tumor markers should not be routinely included in routine follow-up programs. Follow-up endoscopy for a T1 rectal endocrine tumors is not indicated if endoscopic polypectomy was curative.

V.3 Appendiceal Endocrine Tumors

Appendicectomy is the curative option for appendiceal endocrine tumors <1 cm (T1). Follow-up investigations are not routinely indicated. The optimal treatment of appendiceal endocrine tumors ≤2 cm (T2) invading the submucosa, muscularis propria and/or minimally (>3 mm) invading subserosa/mesoappendix is a matter of debate. Most surgeons recommend right-sided hemicolectomy. Following this procedure and providing that no metastatic lymph node involvement is present, no routine follow-up investigations are indicated. The beneficial effect of follow-up studies recommended in **IV.4** for patients with a T2 endocrine tumor and simple appendicectomy remains controversial. There is no indication for tumor markers in patients with T1 or T2 appendiceal tumors.

V.4 Resectable Endocrine Tumor of Probably Benign (Uncertain) Behavior

The respective tumors have been defined in **III.2**. In general, their grading is G1. After surgical tumor resection the following investigations are recommended.

V.4.1 Imaging

V.4.1.1 US/CT/MRI

- 6 months postoperatively: US or CT or MRI (depending on availability and experience); if negative:
- Repeat after further 6 months; if negative:
- Repeat at yearly intervals postoperatively; the time intervals can be reconsidered according to (1) the tumor growth characteristics of an individual patient and/or when (2) tumor resection is Nx due to the lack of any nodal sampling at the time of surgery
- In the case of stable disease, longer intervals may be justified

V.4.1.2 Octreotide Scintigraphy (Octreoscan®)

- At baseline, then every 2 years. Reconsider the time intervals according to the tumor growth characteristics of an individual patient. When the disease shows stability or no recurrence, according to US, CT or MRI, the octreotide scan may not be necessary. If a change in the strategy of treatment is considered a new scan may be justified

V.4.1.3 Comments

(a) There was no formal agreement in the panel discussion concerning the duration of follow-up investigations: 4 years – indefinitely

(b) Octreoscan® may be substituted in future by ^{68}Gallium-DOTA-DOC PET due to its higher sensitivity. See **IV.2**.

V.4.2 Tumor Markers

Plasma CgA should only be determined in the presence of a tumor visualized by imaging, except in very occasional patients. In the presence of a tumor repeat every 6 months. For further comments see **IV.2.2**.

V.5 Resectable Malignant Tumor with/without Regional Nodal Involvement; in This Category Endocrine Tumors of Probably Benign (Uncertain) Behavior but with Ki 67 >2% Are Included

The respective tumors have been defined in **III.3**. After surgical resection of a probably malignant tumor according to the WHO classification the following investigations are recommended.

V.5.1 Tumor Grading G1

See recommendations suggested for **V.4**.

V.5.2 Tumor Grading G2 and G3

V.5.2.1 General Comment

Tumors graded as G2 or G3 are much rarer than G1 tumors. In case of doubt with either very slow progres-

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sion of tumors classified as G2 or G3 or very fast progression of tumors classified as G1 or G2 consider re-biopsy.

V.5.2.2 Imaging

V.5.2.2.1 US/CT/MRI. 3 months postoperatively US or CT or MRI (depending on availability and experience); if negative: repeat at 3-month intervals indefinitely.

V.5.2.2.2 Octreoscan®. 3 months postoperatively; if negative: repeat 12 months postoperatively or if new lesions appear during US/CT/MRI imaging.

For further comments see **V.4.1.2**.

V.5.2.2.3 Comment. Octreoscan may be substituted in future by ^{68}Gallium-DOTA-DOC PET due to its higher sensitivity. For further comment see **IV.2**.

V.5.3.3 Tumor Markers

- See **V.4.2**.
- Intervals: 3 months

V.6 Non-Resectable Tumors with/without Nodal Involvement, with/without Liver and Other Metastases: All Localizations

The respective tumors have been defined in **III.3**. Surgical intervention should always be considered as therapeutic option. For follow-up the following investigations are recommended.

V.6.1 Tumor Grading G1

See recommendations suggested for **V.4**.

In patients with carcinoid syndrome echocardiography should be performed at diagnosis. If positive at diagnosis repeat every 6 months; if negative, every 12 months.

V.6.2 Tumor Grading G2 and G3

See recommendations suggested for **V.5.2**.

VI Hereditary Tumors (MEN-I Syndrome, VHL Disease)

VI.1 Genetic Screening

In patients who are not members of a MEN-1 or VHL family but whose clinical spectrum of symptoms and pathohistological findings is suggestive of the MEN-1 or VHL syndromes, mutational analysis of the appropriate genes should be arranged. If positive, predictive genetic testing of family members should be performed according to the country-specific guidelines. Surveillance programs can be stopped in family members who are negative for the identified mutation, but biochemical and clinical surveillance is required for patients at risk. Patients with MEN-1 syndrome and patients with VHL disease should be referred to and followed up in specialized centers.

VI.2 Parathyroid Glands

In non-parathyroidectomized subjects: serum-calcium and plasma PTH levels at 12-month intervals. Most experts agree that in case of confirmed biochemical diagnosis of a primary hyperparathyroidism no further imaging studies are indicated to demonstrate the mostly asymmetric hyperplasia of the parathyroid glands.

In patients with subtotal parathyroidectomy or with total parathyroidectomy and autotransplantation with or without substitution of calcium and 1,25-dihydroxycholecalciferol, the control of serum calcium should be determined according to the individual situation.

Patients with recurrent hyperparathyroidism should be transferred to specialized centers with experience in MIBI scintigraphy and selective vein catheters.

VI.3 Pancreatico-Duodenal Neuroendocrine Tumors

In general, pancreatico-duodenal neuroendocrine tumors are multiple. The resection of an insulinoma (usually pancreatic) should always be actively sought to avoid life-threatening hypoglycemic events.

The resection of a gastrinoma (usually multiple and duodenal) is dependent on factors such as the patient's individual situation (general health status, patient's preference and the policy of the surgical institution). The consequences of hypergastrinemia can usually also be well managed by proton pump inhibitors, although high doses may need to be used.

Most pancreatic neuroendocrine tumors are nonfunctioning and small tumors can be best visualized by endoscopic ultrasound, larger tumors by conventional ultrasound, CT and MRI. However, this will be contingent on the radiological expertise of the center. Follow-up investigations must be individualized and depend on the size and growth behavior of individual tumors. The same

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Table 1. Summary of follow-up recommendations in patients with benign and malignant neuroendocrine tumors

	Follow-up				
	yes/no	endoscopy	US/CT/MRI	Octreoscan	CgA
Benign insulinoma	no				
Type 1 gastric carcinoid	yes	yearly			
Rectal carcinoid	no (if completely resected)				
Appendiceal carcinoid T1	no				
Appendiceal carcinoid T2	? (see text)				
Resectable tumor (uncertain behavior)					
G1	every 6–12 months	yes (gastric carc.)	yes	every 2 years[2]	yes[1]
Resectable malignant tumor with/without nodal involvement					
G1	every 6–12 months		yes	every 2 years[2]	yes[1]
G2	every 6 months		yes	yearly[2]	yes[1]
G3	every 3 months		yes	yearly[2]	yes[3]
Non-resectable malignant tumor with/without nodal involvement and/or liver and other metastases					
G1	every 6–12 months		yes	every 2 years[2]	yes
G2	every 6 months		yes	yearly[2]	yes
G3	every 3 months		yes	yearly[2]	yes[3]

[1] Only in the presence of a visible tumor.
[2] Recommendations regarding the time frames of Octreoscan should be adjusted to the individual situation.
[3] In poorly differentiated tumors and negative CgA NSE may act as a suitable marker.

is true for metastatic tumors. In general, imaging intervals are between 1 and 2 years. Most experts agree that tumors >2 cm should be resected due to a ≈30% probability of metastatic spread.

Tumor markers for pancreatic and duodenal tumors include plasma CgA and serum gastrin for gastrinoma. They can be used to detect a relapsing gastrinoma or tumor growth and should be determined during visits for imaging.

VI.4 Hypophysis

In patients with and without adenomas of the hypophysis screening should be performed in intervals between 1 and 2 years.

VII Summary

The follow-up investigations which should be documented to visualize the specific course of the disease in an individual patient are summarized in table 1.

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

Göran Åkerström, Department of Surgery, University Hospital, Uppsala (Sweden); *Bruno Annibale,* University Sapienza Roma, Rome (Italy); *Emilio Bajetta,* Medical Oncology Unit B, Istituto Nazionale Tumori, Milan (Italy); *Jaroslava Barkmanova,* Department of Oncology, University Hospital, Prague (Czech Republic); *Anne Couvelard,* Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); *Joseph Davar,* Department of Cardiology, Royal Free Hospital, London (UK); *Wouter de Herder,* Department of Internal Medicine, Section of Endocrinology, Erasmus MC, Rotterdam (The Netherlands); *Gianfranco Delle Fave,* Ospedale S. Andrea, Rome (Italy); *Barbro Eriksson,* Medical Department, Endocrine Unit, University Hospital, Uppsala (Sweden); *Diego Ferone,* Departments of Internal Medicine and Endocrinological and Metabolic Sciences, University of Genoa, Genoa (Italy); *Björn Gustafsson,* Medisinsk avd, Gastroseksjon, St Olavs Hospital, Trondheim (Norway); *Diana Ivan,* Endocrinology and Diabetology, Klinikum der Philipps-Universität, Marburg (Germany); *Gregory Kaltsas,* G. Genimatas Hospital, Athens (Greece); *Reza Kianmanesh,* UFR Bichat-Beaujon-Louis Mourier, Service de Chirurgie Digestive, Hôpital Louis Mourier, Colombes (France); *Günter Klöppel,* Institut für Pathologie, TU

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München, Munich (Germany); *Ulrich-Peter Knigge,* Department of Surgery, Rigshospitalet, Copenhagen (Denmark); *Paul Komminoth*, Institute for Pathology, Stadtspital Triemli, Zürich (Switzerland); *Dik Kwekkeboom,* Department of Nuclear Medicine, Erasmus University Medical Center, Rotterdam (The Netherlands); *Rachida Lebtahi,* Nuclear Medicine Department, Bichat Hospital, Paris (France); *Val Lewington,* Royal Marsden, NHS Foundation Trust, Sutton (UK); *Anne Marie McNicol,* Division of Cancer Sciences and Molecular Pathology, Pathology Department, Royal Infirmary, Glasgow (UK); *Emmanuel Mitry,* Hepatogastroenterology and Digestive Oncology, Hôpital Ambroise-Paré, Boulogne (France); *Ola Nilsson,* Department of Pathology, Sahlgrenska sjukhuset, Gothenburg (Sweden); *Kjell Öberg,* Department of Internal Medicine, Endocrine Unit, University Hospital, Uppsala (Sweden); *Juan O'Connor,* Instituto Alexander Fleming, Buenos Aires (Argentina); *Dermot O'Toole,* Department of Gastroenterology and Clinical Medicine, St. James's Hospital and Trinity College Dublin, Dublin (Ireland); *Ulrich-Frank Pape,* Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); *Mauro Papotti,* Department of Biological and Clinical Sciences, University of Turin/St. Luigi Hospital, Turin (Italy); *Marianne Pavel,* Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); *Aurel Perren,* Institut für Allgemeine Pathologie und Pathologische Anatomie der Technischen Universität München, Klinikum r.d. Isar, Munich (Germany); *Marco Platania,* Istituto Nazionale dei Tumori di Milano, Milan (Italy); *Guido Rindi,* Department of Pathology and Laboratory Medicine, Università degli Studi, Parma (Italy); *Philippe Ruszniewski,* Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); *Aldo Scarpa,* Department of Pathology, University of Verona, Verona (Italy); *Klemens Scheidhauer,* Klinikum rechts der Isar, TU München, Munich (Germany); *Jean-Yves Scoazec,* Anatomie Pathologique, Hôpital Edouard-Herriot, Lyon (France); *Anders Sundin,* Department of Radiology, Uppsala University Hospital, Uppsala (Sweden); *Waldemar Szpak,* Westville Hospital, Mayville (South Africa); *Babs Taal,* Netherlands Cancer Centre, Amsterdam (The Netherlands); *Pavel Vitek,* Institute of Radiation Oncology, University Hospital, Prague (Czech Republic); *Marie-Pierre Vullierme,* Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); *Bertram Wiedenmann,* Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany).

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