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Neuroendocrine neoplasms – still a challenge despite major advances in clinical care with the development of specialized guidelines

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The term 'neuroendocrine neoplasms' (NEN) covers a wide range of tumors originating from neuroendocrine cells in various organs. Heterogeneity and rarity of NEN have hampered early diagnosis and standardized treatment for years, with many physicians being unaware of the clinical relevance of NEN. Although expanding knowledge of the molecular characteristics of neuroendocrine cells resulted in new diagnostic and therapeutic possibilities, their integration into management algorithms is still ongoing. Furthermore, availability of diagnostic and therapeutic tools varies considerably in different regions of the world.

Confronted with the very specific challenges of NEN, various groups and professional societies developed guidelines to standardize the approach to this fascinating but life-threating disease. Especially the European Neuroendocrine Tumor Society (ENETS) has continuously updated their recommendations, starting 2004 with a summary paper [1], but later developing highly subtype-specific guidelines recognizing the great differences between the various forms of NEN. These guidelines focused on functioning and non-functioning pancreatic NEN ([2–5], revised 2012 [6, 7] and 2016 [8]), gastric and duodenal NEN ([9, 10], revised 2012 [11] and 2016 [12]), jejunal-ileal NEN ([13], revised 2016 [14]), NEN of the appendix ([15], revised 2012 [16] and 2016 [17]), on colorectal NEN ([18], revised 2012 [19] and 2016 [20]), and most recently on pulmonary NEN [21]. Separate guidelines covered metastases from NEN ([22], revised 2012 [23] and 2016 [24]), with a special focus on brain, cardiac and ovarian metastases ([25], bone and lung metastases [26], and on peritoneal carcinomatosis [27]. The importance of adequate grading was acknowledged with specific guidelines for poorly-differentiated NEN [28, 29], and subsequently with guidelines separately for high-grade neuroendocrine tumors and neuroendocrine carcinomas [30]. To allow for a more standardized approach to NEN, ENETS also published consensus proposals on the TNM classification of foregut [31] and midgut/hindgut NEN [32]. In addition, ENETS recognized the need for standards of care when applying various diagnostic and therapeutic techniques, and therefore published specific recommendations on the morphological diagnosis ([33], updated 2017 [34]) and the endocrine evaluation ([35], updated 2017 [36]) of NEN, tumor localization by ultrasound, CT and MRI, and nuclear imaging ([37, 38], updated 2017 [39]), and evaluation of cardiac disease [40]. Standards of therapy were published for surgery [41], with specific recommendations for pre- and perioperative therapy ([42], updated 2017 [43]), for biotherapy ([44], updated 2017 [45]), for peptide receptor radionuclide therapy (PRRT) ([46], updated 2017 [47]), for chemotherapy ([48], updated 2017 [49], and for follow-up ([50], updated 2017 [51]).

Another European Society, the European Society for Medical Oncology (ESMO), published their clinical practice guidelines on NEN ([52, 53], updated 2012 [54, 55] and 2016 [56]) from a slightly different perspective. Furthermore, societies from several countries issued guidelines, e.g. the North American Neuroendocrine Tumor Society [57–68], the Polish Network of Neuroendocrine Tumours ([69–73], updated 2017 [74–78]), the Nordic Neuroendocrine Tumor Group [79–82], the Canadian National Expert Group [54], the Spanish Society of Medical Oncology [83–85], the Brazilian Gastrointestinal Tumour Group [86], and the UK and Ireland Neuroendocrine Tumor Society [87, 88]. Although this list is certainly not complete, it allows recognition of region-specific differences in the handling of NEN, but also underscores the ongoing difficulties in managing patients with NEN.

This and a subsequent issue of *REVIEWS IN ENDOCRINE AND METABOLIC DISORDERS* are devoted to practical

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aspects in the current management of neuroendocrine neoplasms, written from individual experts in their specific field to assist clinicians involved in the daily care of NEN who may be somehow overwhelmed by the large number of published guidelines.

Guido Rindi and his co-authors start with their perspective on histology of NEN in their paper CYTO-HISTOLOGY IN NET: WHAT IS NECESSARY TODAY AND WHAT IS THE FUTURE? [89]. Matthias M. Weber and co-authors discuss the endocrine evaluation of functioning NEN in their paper HORMONE SECRETING GASTRO-ENTERO-PANCREATIC NEUROENDOCRINE NEOPLASIAS (GEP-NEN): WHEN TO CONSIDER, HOW TO DIAGNOSE? [90]. Javier G. Castillo and co-authors give us some insight on diagnostic evaluation of carcinoid heart disease in their paper ECHOCARDIOGRAPHY IN FUNCTIONAL MIDGUT NEUROENDOCRINE TUMORS: WHEN AND HOW OFTEN? [91]. As localization of the primary tumor in patients with proven NEN is sometimes difficult, Gregory A. Kaltsas and his group present an overview on the MANAGEMENT OF NEUROENDOCRINE TUMORS OF UNKNOWN PRIMARY [92]. With many guidelines initially focusing in NEN of the gastrointestinal tract, pulmonary NEN were somehow neglected, but Robert A. Ramirez and co-authors update us on the MANAGEMENT OF PULMONARY NEUROENDOCRINE TUMORS [93]. Moving to new aspects of treatment, Ernst von Dobschuetz and co-authors answer the question IS THERE ANY ROLE FOR MINIMALLY INVASIVE SURGERY IN NET? [94]. With the frequent occurrence of liver metastases, Philippe Ruszniewski and co-authors present their view on LIVER TRANSARTERIAL EMBOLIZATIONS IN METASTATIC NEUROENDOCRINE TUMORS [95], and Vincenzo Mazzaferro and co-authors discuss THE PLACE OF LIVER TRANSPLANTATION IN THE TREATMENT OF HEPATIC METASTASES FROM NEUROENDOCRINE TUMORS: PROS AND CONS [96]. Although the low proliferation rate in the majority of NEN and the possibility of specific treatments such as biotherapy and PRRT leaves a somehow smaller role for chemotherapy, certain types of NEN may require such an approach, and therefore Ashley Grossman and co-authors answer the question CHEMOTHERAPY IN NETs: WHEN AND HOW [97]. As NEN may occur as part of multiple endocrine neoplasia syndromes with important consequences for the patient and family members, Triona O'Shea and Maralyn Druce discuss WHEN SHOULD GENETIC TESTING BE PERFORMED IN PATIENTS WITH NEUROENDOCRINE TUMOURS? [98]. Finally, it is less known, that Merkel cell carcinoma is a skin cancer with a neuroendocrine phenotype, and Claus Garbe and co-authors enlighten us on similarities and differences in their article MERKEL CELL CARCINOMA: EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSIS AND THERAPY [99].

We hope that this first part of 2 issues of this journal devoted to the management of NEN will provide you with the most up-to-date information on key areas in the management of NEN. We are thankful to our colleagues across the world for summarizing their vast experience, and look forward to give you further insight into this orphan disease form which still poses a major challenge to the caring physician.

Compliance with ethical standards

Conflict of interest Prof. Stephan Petersenn declares that he has received fees for serving as a consultant on advisory boards for Ipsen and Novartis, and for presenting at workshops organized by Ipsen, Novartis, and Pfizer. He has no conflict of interest related to this article.

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References

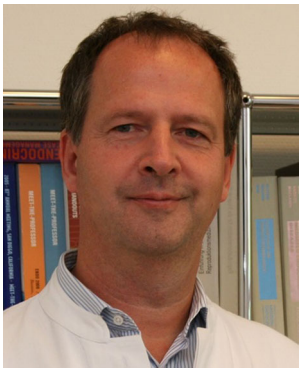
1. Plockinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology. 2004;80(6):394–424. https://doi.org/10.1159/000085237.
2. Jensen RT, Niederle B, Mitry E, Ramage JK, Steinmuller T, Lewington V, et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology. 2006;84(3):173–82. https://doi.org/10.1159/000098009.
3. de Herder WW, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falconi M, et al. Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology. 2006;84(3):183–8. https://doi.org/10.1159/000098010.
4. O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A, de Herder WW, et al. Rare functioning pancreatic endocrine tumors. Neuroendocrinology. 2006;84(3):189–95. https://doi.org/10.1159/000098011.
5. Falconi M, Plockinger U, Kwekkeboom DJ, Manfredi R, Korner M, Kvols L, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology. 2006;84(3):196–211. https://doi.org/10.1159/000098012.
6. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98–119. https://doi.org/10.1159/000335591.
7. Falconi M, Bartsch DK, Eriksson B, Kloppel G, Lopes JM, O'Connor JM, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology. 2012;95(2):120–34. https://doi.org/10.1159/000335587.

8. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103(2):153–71. https://doi.org/10.1159/000443171.
9. Jensen RT, Rindi G, Arnold R, Lopes JM, Brandi ML, Bechstein WO, et al. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). Neuroendocrinology. 2006;84(3):165–72. https://doi.org/10.1159/000098008.
10. Ruszniewski P, Delle Fave G, Cadiot G, Komminoth P, Chung D, Kos-Kudla B, et al. Well-differentiated gastric tumors/carcinomas. Neuroendocrinology. 2006;84(3):158–64. https://doi.org/10.1159/000098007.
11. Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, et al. ENETS consensus guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology. 2012;95(2):74–87. https://doi.org/10.1159/000335595.
12. Delle Fave G, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):119–24. https://doi.org/10.1159/000443168.
13. Eriksson B, Kloppel G, Krenning E, Ahlman H, Plockinger U, Wiedenmann B, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors–well-differentiated jejunal-ileal tumor/carcinoma. Neuroendocrinology. 2008;87(1):8–19. https://doi.org/10.1159/000111034.
14. Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, et al. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. Neuroendocrinology. 2016;103(2):125–38. https://doi.org/10.1159/000443170.
15. Plockinger U, Couvelard A, Falconi M, Sundin A, Salazar R, Christ E, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumours: well-differentiated tumour/carcinoma of the appendix and goblet cell carcinoma. Neuroendocrinology. 2008;87(1):20–30. https://doi.org/10.1159/000109876.
16. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95(2):135–56. https://doi.org/10.1159/000335629.
17. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, et al. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). Neuroendocrinology. 2016;103(2):144–52. https://doi.org/10.1159/000443165.
18. Ramage JK, Goretzki PE, Manfredi R, Komminoth P, Ferone D, Hyrdel R, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumours: well-differentiated colon and rectum tumour/carcinoma. Neuroendocrinology. 2008;87(1):31–9. https://doi.org/10.1159/000111036.
19. Caplin M, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology. 2012;95(2):88–97. https://doi.org/10.1159/000335594.
20. Ramage JK, De Herder WW, Delle Fave G, Ferolla P, Ferone D, Ito T, et al. ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):139–43. https://doi.org/10.1159/000443166.
21. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al. Pulmonary neuroendocrine (carcinoid) tumors: European neuroendocrine tumor society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015;26(8):1604–20. https://doi.org/10.1093/annonc/mdv041.
22. Steinmuller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2008;87(1):47–62. https://doi.org/10.1159/000111037.
23. Pavel M, Baudin E, Couvelard A, Krenning E, Oberg K, Steinmuller T, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2012;95(2):157–76. https://doi.org/10.1159/000335597.
24. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the Management of Distant Metastatic Disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology. 2016;103(2):172–85. https://doi.org/10.1159/000443167.
25. Pavel M, Grossman A, Arnold R, Perren A, Kaltsas G, Steinmuller T, et al. ENETS consensus guidelines for the management of brain, cardiac and ovarian metastases from neuroendocrine tumors. Neuroendocrinology. 2010;91(4):326–32. https://doi.org/10.1159/000287277.
26. Kos-Kudla B, O'Toole D, Falconi M, Gross D, Kloppel G, Sundin A, et al. ENETS consensus guidelines for the management of bone and lung metastases from neuroendocrine tumors. Neuroendocrinology. 2010;91(4):341–50. https://doi.org/10.1159/000287255.
27. Kianmanesh R, Ruszniewski P, Rindi G, Kwekkeboom D, Pape UF, Kulke M, et al. ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. Neuroendocrinology. 2010;91(4):333–40. https://doi.org/10.1159/000286700.
28. Nilsson O, Van Cutsem E, Delle Fave G, Yao JC, Pavel ME, McNicol AM, et al. Poorly differentiated carcinomas of the foregut (gastric, duodenal and pancreatic). Neuroendocrinology. 2006;84(3):212–5. https://doi.org/10.1159/000098013.
29. Ahlman H, Nilsson O, McNicol AM, Ruszniewski P, Niederle B, Ricke J, et al. Poorly-differentiated endocrine carcinomas of midgut and hindgut origin. Neuroendocrinology. 2008;87(1):40–6. https://doi.org/10.1159/000109976.
30. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology. 2016;103(2):186–94. https://doi.org/10.1159/000443172.
31. Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449(4):395–401. https://doi.org/10.1007/s00428-006-0250-1.
32. Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2007;451(4):757–62. https://doi.org/10.1007/s00428-007-0452-1.
33. Kloppel G, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology. 2009;90(2):162–6. https://doi.org/10.1159/000182196.

34. Perren A, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. Neuroendocrinology. 2017;105(3):196–200. https://doi.org/10.1159/000457956.
35. O'Toole D, Grossman A, Gross D, Delle Fave G, Barkmanova J, O'Connor J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biochemical markers. Neuroendocrinology. 2009;90(2):194–202. https://doi.org/10.1159/000225948.
36. Oberg K, Couvelard A, Delle Fave G, Gross D, Grossman A, Jensen RT, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: biochemical markers. Neuroendocrinology. 2017;105(3):201–11. https://doi.org/10.1159/000472254.
37. Sundin A, Vullierme MP, Kaltsas G, Plockinger U, Mallorca Consensus Conference p, European neuroendocrine tumor S. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. Neuroendocrinology. 2009;90(2):167–83. https://doi.org/10.1159/000184855.
38. Kwekkeboom DJ, Krenning EP, Scheidhauer K, Lewington V, Lebtahi R, Grossman A, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with (111)in-pentetreotide. Neuroendocrinology. 2009;90(2):184–9. https://doi.org/10.1159/000225946.
39. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, Nuclear Medicine & Hybrid Imaging. Neuroendocrinology. 2017;105(3):212–44. https://doi.org/10.1159/000471879.
40. Plockinger U, Gustafsson B, Ivan D, Szpak W, Davar J, Conference p MC, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: echocardiography. Neuroendocrinology. 2009;90(2):190–3. https://doi.org/10.1159/000225947.
41. Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. Neuroendocrinology. 2017;105(3):255–65. https://doi.org/10.1159/000464292.
42. Akerstrom G, Falconi M, Kianmanesh R, Ruszniewski P, Plockinger U, Mallorca Consensus Conference p, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pre- and perioperative therapy in patients with neuroendocrine tumors. Neuroendocrinology. 2009;90(2):203–8. https://doi.org/10.1159/000225949.
43. Kaltsas G, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pre- and perioperative therapy in patients with neuroendocrine tumors. Neuroendocrinology. 2017;105(3):245–54. https://doi.org/10.1159/000461583.
44. Oberg K, Ferone D, Kaltsas G, Knigge UP, Taal B, Plockinger U, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biotherapy. Neuroendocrinology. 2009;90(2):209–13. https://doi.org/10.1159/000183751.
45. Pavel M, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: systemic therapy - biotherapy and novel targeted agents. Neuroendocrinology. 2017;105(3):266–80. https://doi.org/10.1159/000471880.
46. Kwekkeboom DJ, Krenning EP, Lebtahi R, Komminoth P, Kos-Kudla B, de Herder WW, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology. 2009;90(2):220–6. https://doi.org/10.1159/000225951.
47. Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology. 2017;105(3):295–309. https://doi.org/10.1159/000475526.
48. Eriksson B, Annibale B, Bajetta E, Mitry E, Pavel M, Platania M, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: chemotherapy in patients with neuroendocrine tumors. Neuroendocrinology. 2009;90(2):214–9. https://doi.org/10.1159/000225950.
49. Garcia-Carbonero R, Rinke A, Valle JW, Fazio N, Caplin M, Gorbounova V, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms. Systemic therapy 2: chemotherapy. Neuroendocrinology. 2017;105(3):281–94. https://doi.org/10.1159/000473892.
50. Arnold R, Chen YJ, Costa F, Falconi M, Gross D, Grossman AB, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: follow-up and documentation. Neuroendocrinology. 2009;90(2):227–33. https://doi.org/10.1159/000225952.
51. Knigge U, Capdevila J, Bartsch DK, Baudin E, Falkerby J, Kianmanesh R, et al. ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms: follow-up and documentation. Neuroendocrinology. 2017;105(3):310–9. https://doi.org/10.1159/000458155.
52. Oberg K, Hellman P, Kwekkeboom D, Jelic S, Group EGW. Neuroendocrine bronchial and thymic tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v220–2. https://doi.org/10.1093/annonc/mdq191.
53. Oberg K, Akerstrom G, Rindi G, Jelic S, Group EGW. Neuroendocrine gastroenteropancreatic tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v223–7. https://doi.org/10.1093/annonc/mdq192.
54. Oberg K, Hellman P, Ferolla P, Papotti M, Group EGW. Neuroendocrine bronchial and thymic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii120–3. https://doi.org/10.1093/annonc/mds267.
55. Oberg K, Knigge U, Kwekkeboom D, Perren A, Group EGW. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii124–30. https://doi.org/10.1093/annonc/mds295.
56. Committee EG. Appendix 3: neuroendocrine tumours: eUpdate published online September 2016 (www.esmo.org/Guidelines/Neuroendocrine-Tumours). Ann Oncol 2016;27(suppl 5):v138-v9. https://doi.org/10.1093/annonc/mdw356.
57. Kvols LK, Brendtro KL; North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society (NANETS) guidelines: mission, goals, and process. Pancreas. 2010;39(6):705–6. https://doi.org/10.1097/MPA.0b013e3181eb7451.
58. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12. https://doi.org/10.1097/MPA.0b013e3181ec124e.
59. Vinik AI, Woltering EA, Warner RR, Caplin M, O'Dorisio TM, Wiseman GA, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. Pancreas. 2010;39(6):713–34. https://doi.org/10.1097/MPA.0b013e3181ebaffd.

60. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39(6):735–52. https://doi.org/10.1097/MPA.0b013e3181ebb168.
61. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753–66. https://doi.org/10.1097/MPA.0b013e3181ebb2a5.
62. Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. Pancreas. 2010;39(6):767–74. https://doi.org/10.1097/MPA.0b013e3181ec1261.
63. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas. 2010;39(6):775–83. https://doi.org/10.1097/MPA.0b013e3181ebb4f0.
64. Phan AT, Oberg K, Choi J, Harrison LH, Jr., Hassan MM, Strosberg JR et al. NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the thorax (includes lung and thymus). Pancreas 2010;39(6):784–798. https://doi.org/10.1097/MPA.0b013e3181ec1380.
65. Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas. 2010;39(6):799–800. https://doi.org/10.1097/MPA.0b013e3181ebb56f.
66. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42(4):557–77. https://doi.org/10.1097/MPA.0b013e31828e34a4.
67. Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2017;46(6):707–14. https://doi.org/10.1097/MPA.0000000000000850.
68. Howe JR, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, et al. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the north American neuroendocrine tumor society. Pancreas. 2017;46(6):715–31. https://doi.org/10.1097/MPA.0000000000000846.
69. Kos-Kudla B, Blicharz-Dorniak J, Handkiewicz-Junak D, Jarzab B, Jarzab M, Kunikowska J, et al. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2013;64(6):418–43. https://doi.org/10.5603/EP.2013.0028.
70. Rydzewska G, Cichocki A, Cwikla JB, Foltyn W, Hubalewska-Dydejczyk A, Kaminski G, et al. Gastroduodenal neuroendocrine neoplasms including gastrinoma - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2013;64(6):444–58. https://doi.org/10.5603/EP.2013.0030.
71. Kos-Kudla B, Hubalewska-Dydejczyk A, Kusnierz K, Lampe P, Marek B, Nasierowska-Guttmejer A, et al. Pancreatic neuroendocrine neoplasms - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2013;64(6):459–79. https://doi.org/10.5603/EP.2013.0031.
72. Bolanowski M, Bednarczuk T, Bobek-Billewicz B, Handkiewicz-Junak D, Jeziorski A, Nowakowska-Dulawa E, et al. Neuroendocrine neoplasms of the small intestine and the appendix - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2013;64(6):480–93. https://doi.org/10.5603/EP.2013.0029.
73. Starzynska T, Deptala A, Krolicki L, Kunikowska J, Londzin-Olesik M, Nasierowska-Guttmejer A, et al. Colorectal neuroendocrine neoplasms - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2013;64(6):494–504. https://doi.org/10.5603/EP.2013.0032.
74. Kos-Kudla B, Blicharz-Dorniak J, Strzelczyk J, Baldys-Waligorska A, Bednarczuk T, Bolanowski M, et al. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2017;68(2):79–110. https://doi.org/10.5603/EP.2017.0015.
75. Lipinski M, Rydzewska G, Foltyn W, Andrysiak-Mamos E, Baldys-Waligorska A, Bednarczuk T, et al. Gastroduodenal neuroendocrine neoplasms, including gastrinoma - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2017;68(2):138–53. https://doi.org/10.5603/EP.2017.0016.
76. Kos-Kudla B, Rosiek V, Borowska M, Baldys-Waligorska A, Bednarczuk T, Blicharz-Dorniak J, et al. Pancreatic neuroendocrine neoplasms - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2017;68(2):169–97. https://doi.org/10.5603/EP.2017.2016.
77. Bednarczuk T, Bolanowski M, Zemczak A, Baldys-Waligorska A, Blicharz-Dorniak J, Boratyn-Nowicka A, et al. Neuroendocrine neoplasms of the small intestine and appendix - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2017;68(2):223–36. https://doi.org/10.5603/EP.2017.0018.
78. Starzynska T, Londzin-Olesik M, Baldys-Waligorska A, Bednarczuk T, Blicharz-Dorniak J, Bolanowski M, et al. Colorectal neuroendocrine neoplasms - management guidelines (recommended by the Polish network of neuroendocrine tumours). Endokrynol Pol. 2017;68(2):250–60. https://doi.org/10.5603/EP.2017.0019.
79. Oberg K, Astrup L, Eriksson B, Falkmer SE, Falkmer UG, Gustafsen J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part I-general overview. Acta Oncol. 2004;43(7):617–25. https://doi.org/10.1080/02841860410018575.
80. Oberg K, Astrup L, Eriksson B, Falkmer SE, Falkmer UG, Gustafsen J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part II-specific NE tumour types. Acta Oncol. 2004;43(7):626–36. https://doi.org/10.1080/02841860410018584.
81. Janson ET, Sorbye H, Welin S, Federspiel B, Gronbaek H, Hellman P, et al. Nordic guidelines 2010 for diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours. Acta Oncol. 2010;49(6):740–56. https://doi.org/10.3109/0284186X.2010.492791.
82. Janson ET, Sorbye H, Welin S, Federspiel B, Gronbaek H, Hellman P, et al. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. Acta Oncol. 2014;53(10):1284–97. https://doi.org/10.3109/0284186X.2014.941999.

83. Garcia-Carbonero R, Salazar R, Sevilla I, Isla D. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETS). Clin Transl Oncol. 2011;13(8):545–51. https://doi.org/10.1007/s12094-011-0695-9.
84. Garcia-Carbonero R, Vilardell F, Jimenez-Fonseca P, Gonzalez-Campora R, Gonzalez E, Cuatrecasas M, et al. Guidelines for biomarker testing in gastroenteropancreatic neuroendocrine neoplasms: a national consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol. 2014;16(3):243–56. https://doi.org/10.1007/s12094-013-1062-9.
85. Garcia-Carbonero R, JI-F P, Teule A, Barriuso J, Sevilla I, Spanish Society for Medical O. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) 2014. Clin Transl Oncol. 2014;16(12):1025–34. https://doi.org/10.1007/s12094-014-1214-6.
86. Riechelmann RP, Weschenfelder RF, Costa FP, Andrade AC, Osvaldt AB, Quidute AR, et al. Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group. Ecancermedicalscience. 2017;11:716. https://doi.org/10.3332/ecancer.2017.716.
87. Ramage JK, Davies AH, Ardill J, Bax N, Caplin M, Grossman A, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut. 2005;54(Suppl 4):iv1–16. https://doi.org/10.1136/gut.2004.053314.
88. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32. https://doi.org/10.1136/gutjnl-2011-300831.
89. Inzani F, Petrone G, Fadda G, Rindi G. Cyto-histology in NET: what is necessary today and what is the future? Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9428-x.
90. Fottner C, Ferrata M, Weber MW. Hormone secreting gastro-entero-pancreatic neuroendocrine neoplasias (GEP-NEN): When to consider, how to diagnose? Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9438-8.
91. Castillo JG, Naib T, Zacks JS, Adams DH. Echocardiography in functional midgut neuroendocrine tumors: When and how often. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9434-z.
92. Alexandraki K, Angelousi A, Boutzios G, Kyriakopoulos G, Rontogianni D, Kaltsas G. Management of neuroendocrine tumors of unknown primary. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9437-9.
93. Ramirez RA, Chauhan A, Gimenez J, Thomas KEH, Kokodis I, Voros BA. Management of pulmonary neuroendocrine tumors. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9429-9.
94. Thomaschewski M, Neeff H, Keck T, Neumann HPH, Strate T, von Dobschuetz E. Is there any role for minimally invasive surgery in NET? Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9436-x.
95. de Mestier L, Zappa M, Hentic O, Vilgrain V, Ruszniewski P. Liver transarterial embolizations in metastatic neuroendocrine tumors. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9431-2.
96. Sposito C, dit Busset MD, Citterio D, Bongini M, Mazzaferro V. The place of liver transplantation in the treatment of hepatic metastases from neuroendocrine tumors: Pros and cons. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9439-7.
97. Angelousi A, Kaltsas G, Koumarianou A, Weickert MO, Grossman A. Chemotherapy in NETs: When and how. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9432-1.
98. O'Shea T, Druce M. When should genetic testing be performed in patients with neuroendocrine tumours? Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9430-3.
99. Amaral T, Leiter U, Garbe C. Merkel cell carcinoma: Epidemiology, pathogenesis, diagnosis and therapy. Rev Endocr Metab Disord. 2017. https://doi.org/10.1007/s11154-017-9433-0.



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