Commonwealth Neuroendocrine Tumour Research Collaboration and the North American Neuroendocrine Tumor Society Guidelines for the Diagnosis and Management of Patients With Lung Neuroendocrine Tumors: An International Collaborative Endorsement and Update of the 2015 European Neuroendocrine Tumor Society Expert Consensus Guidelines

Simron Singh, MD, MPH,[a],* Emily K. Bergsland, MD,[b] Cynthia M. Card, MD, MSc,[c]
Thomas A. Hope, MD,[d] Pamela L. Kunz, MD,[e] David T. Laidley, MD, MSc, FRCPC,[f]
Ben Lawrence, MbChB, MSc, FRACP,[g] Simone Leyden, BBM,[h] David C. Metz, MBBCh,[i]
Michael Michael, M.B.B.S., DM, FRACP,[j] Lucy E. Modahl, MD, PhD,[k]
Sten Myrehaug, MD, FRCPC,[a] Sukhmani K. Padda, MD,[l] Rodney F. Pommier, MD,[m]
Robert A. Ramirez, DO,[n] Michael Soulen, MD,[o] Jonathan Strosberg, MD,[p]
Arthur Sung, MD,[q] Alia Thawer, HBSc, PharmD,[a] Benjamin Wei, MD,[r]
Bin Xu, MD, PhD,[a] Eva Segelov, M.B.B.S., PhD, FRACP[s]

[a]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[b]Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco, San Francisco, California
[c]Tom Baker Cancer Centre, Calgary, Alberta, Canada
[d]Department of Radiology and Biomedical Imaging, Division of Hematology/Oncology, University of California, San Francisco, San Francisco, California
[e]Department of Medicine, Yale University, New Haven, Connecticut
[f]Department of Medical Imaging, Division of Nuclear Medicine, London Health Sciences Centre, London, Ontario, Canada
[g]Discipline of Oncology, University of Auckland, Auckland, New Zealand
[h]Unicorn Foundation, Blairgowrie, Victoria, Australia
[i]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
[j]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Victoria, Australia
[k]Auckland Radiology Group, Auckland City Hospital, Auckland, New Zealand
[l]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California

[m]Oregon Health & Science University, Portland, Oregon
[n]Department of Medical Oncology, Ochsner Medical Center, New Orleans, Louisiana
[o]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania
[p]Moffitt Cancer Center, Tampa, Florida
[q]Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University, Stanford, California
[r]Department of Surgery, Birmingham Medical Center, University of Alabama, Birmingham, Alabama
[s]Department of Oncology, Monash Health, Monash University, Melbourne, Victoria, Australia

*Corresponding author.
Disclosure: Dr. Singh reports receiving grants and personal fees from Novartis; grants from End Serono; personal fees from Ipsen outside of the submitted work. Dr. Bergsland reports receiving personal fees from UpToDate; grants from Merck and Novartis; and other fees from Hutchison MediPharma outside of the submitted work. Dr. Hope reports receiving other fees from Ipsen; personal fees and other fees from Curium outside of the submitted work. Dr. Kunz reports receiving grants and other fees from Advanced Accelerator Applications and Lexicon Pharmaceuticals; grants from Thermo Fisher Scientific, Ipsen, and Xencor outside of the submitted work. Dr. Laidley reports receiving grants and other fees from Ipsen and Novartis; other fees from Progenics and Nordic Nanovector outside of the submitted work. Dr. Metz reports receiving grants and personal fees from Ipsen and Advanced Accelerator Applications; nonfinancial support from Lexicon; grants from Medtronic outside of the submitted work. Dr. Myrehaug reports receiving grants from Ipsen, Novartis, and Advanced Accelerator Applications outside of the submitted work. Dr. Padda reports receiving grants from EpicentRx, Bayer, Boehringer Ingelheim, and Forty Seven Inc.; personal fees and other fees from Pfizer, AstraZeneca, G1 therapeutics, and AbbVie outside of the submitted work.

Dr. Pommier reports receiving personal fees and other fees from Novartis; personal fees from Advanced Accelerator Applications and Lexicon outside of the submitted work. Dr. Ramirez reports receiving grants from Aadi Bioscience; grants and personal fees from Merck; personal fees from Curium, Advanced Accelerator Applications, AstraZeneca, Ipsen, Genetech, and Guardant outside of the submitted work. Dr. Soulen reports receiving grants and personal fees from Guerbet LLC and Sirtex Medical; grants from BTG International outside of the submitted work. Dr. Strosberg reports receiving personal fees from Novartis, Ipsen, and Lexicon outside of the submitted work. Dr. Thawer reports receiving personal fees from Novartis outside of the submitted work. The remaining authors declare no conflict of interest.
Address for correspondence: Simron Singh, MD, MPH, Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Room T2-047, Toronto, ON M4N 3M5, Canada. E-mail: Simron.singh@ sunnybrook.ca

ABSTRACT

Lung neuroendocrine tumors (LNETs) are uncommon cancers, and there is a paucity of randomized evidence to guide practice. As a result, current guidelines from different neuroendocrine tumor societies vary considerably. There is a need to update and harmonize global consensus guidelines. This article reports the best practice guidelines produced by a collaboration between the Commonwealth Neuroendocrine Tumour Research Collaboration and the North American Neuroendocrine Tumor Society. We performed a formal endorsement and updating process of the 2015 European Neuroendocrine Tumor Society expert consensus article on LNET. A systematic review from January 2013 to October 2017 was conducted to procure the most recent evidence. The stepwise endorsement process involved experts from all major subspecialties, patients, and advocates. Guided by discussion of the most recent evidence, each statement from the European Neuroendocrine Tumor Society was either endorsed, modified, or removed. New consensus statements were added if appropriate. The search yielded 1109 new publications, of which 230 met the inclusion criteria. A total of 12 statements were endorsed, 22 statements were modified or updated, one was removed, and two were added. Critical answered questions for each topic in LNET were identified. Through the consensus process, guidelines for the management of patients with local and metastatic neuroendocrine tumors have been updated to include both recent evidence and practice changes relating to technological and definitional advances. The guidelines provide clear, evidence-based statements aimed at harmonizing the global approach to patients with LNETs,

on the basis of the principles of person-centered and LNET-specific care. The importance of LNET-directed research and person-centered care throughout the diagnosis, treatment, and follow-up journey is emphasized along with directions for future collaborative research.

Keywords: Guidelines; Lung neuroendocrine tumors/tumours; Consensus statements; Lung carcinoids; Bronchial neuroendocrine tumors/tumours

INTRODUCTION

Lung neuroendocrine tumors (LNETs), also referred to as bronchial neuroendocrine tumors (NETs) and lung carcinoids, though uncommon cancers are increasing in incidence and prevalence.[1-3] There is a paucity of randomized evidence to guide diagnosis and treatment, which not surprisingly has led to diverse patterns of practice. Current guidelines regarding the care of patients with LNETs from different NET societies vary substantially owing to different interpretations and varying thresholds of data extrapolation from non-LNET studies, such as NSCLC and SCLC. In addition, the primary treating physicians of patients with LNET vary depending on the center and can include respiratory physicians (i.e., pulmonologists), lung (i.e., thoracic) medical oncologists, or other NET specialists.

To update and harmonize global consensus guidelines, the Commonwealth Neuroendocrine Tumour Research Collaboration (CommNETs), a tri-nation research enterprise among Canada, Australia, and New Zealand, partnered with the North American Neuroendocrine Tumor Society (NANETS). Rather than producing de novo guidelines, a formal endorsement and updating process was undertaken based on the 2015 European Neuroendocrine Tumor Society (ENETS) expert consensus article "Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoid."[4] The lead authors of the 2015 ENETS expert consensus article were consulted before embarking on this updated CommNETs and NANETS guidelines. A formal consensus methodology was used by an expert panel to integrate the published evidence based on the ENETS guidelines, and incorporate paradigm shifts in clinical practice toward a person-centered care model.

MATERIALS AND METHODS
Nomenclature
Reflecting on the recent proposals to change the nomenclature to harmonize with NETs of other sites of origin, the terms typical carcinoids (TC) and atypical pulmonary carcinoids (AC) were only specified where this distinction was reported on the basis of histology; otherwise, the term "LNET" was used.

Endorsement Process
Based on the methodology of the American Society of Clinical Oncology for the endorsement of existing guidelines, which is informed by ADAPTE,[5,6] a five-step project was undertaken. First, the ENETS consensus article was assessed by an endorsement panel (two members: SS, ES) for quality of development using the Rigor of Development subscale of the Appraisal of Guidelines for Research and Evaluation II instrument (Appendix A).[5] The endorsement panel members are medical oncologists specializing in NETs and are both cofounders of CommNETs. Second, a review of the content and quality of ENETS recommendations was assessed by the endorsement panel. Third, a comprehensive systematic literature review was performed to identify publications subsequent to those considered for the 2015 ENETS article. Fourth, a 22-member expert panel was convened with experts from CommNETs and NANETS, covering clinicians specializing in all major subspecialties involved in NET care, including patient advocates who provided perspectives on person-centered care. Each member reviewed the entirety of the new data in their area of expertise to prepare discussion points and propose a new or modified consensus statement or a recommendation to endorse without any changes. Prospective data from NETs of other sites were included if they were considered to be applicable to LNETs. In addition, the members were asked to nominate a research question regarding LNETs that should be prioritized for investigation in their field. Finally, the expert panel met face-to-face for one day to review the new evidence presented by each topic expert and to make a group decision to endorse, modify, remove, or add a consensus statement. Patient advocates led discussions on how each statement can affect the experiences of patients.

Literature Review
The ENETS consensus search strategy was current as of 2013, so for this project the search time frame spanned from January 2013 to October 2017. This time frame was chosen to ensure that sufficient follow-up time elapsed for prospective studies to report out comes so that the most up-to-date and comprehensive data were available to the expert panel. Published literature and conference databases, including PubMed, American Society of Clinical Oncology, European Society for Medical Oncology and the European Cancer Organisation, World Conference on Lung Cancer, ENETS, and NANETs, were searched using

the following terms: "pulmonary neuroendocrine tumors," "bronchial neuroendocrine tumors," "bronchial carcinoid tumors," "pulmonary carcinoid," "pulmonary typical carcinoid," "pulmonary atypical, carcinoid," "pulmonary carcinoid and diagnosis," "pulmonary, carcinoid and treatment," "pulmonary carcinoid and epidemiology," and "pulmonary carcinoid and prognosis." Filters were applied for publication type (Clinical Trial, Phase IV, Clinical Trial, Phase III; Randomized Controlled Trial [RCT]; Clinical Trial, Phase II; Clinical Trial, Phase I; meta-analyses), and the Medical Subject Headings terms "case-control studies" and "cohort studies" were used. PubMed records not yet indexed to MEDLINE and recent presentations at major lung and NET conferences were also reviewed. The records were screened at the abstract level, and then inclusion was confirmed using the full text. Studies were included if at least one patient with LNET was included and excluded if they only addressed thymic NETs, poorly differentiated LNETs (SCLC and large cell lung cancers), were nonoriginal, preclinical, phase 1 trials in mixed tumor sites, or case reports. Meta-analyses and RCTs were prioritized. If updated published versions of the original data were published during manuscript writing, the most recent reference was cited.

Level of Evidence Assignment and Statement Grading
The level of evidence and grade of recommendation of the Oxford Centre for Evidence-Based Medicine,[7] with minor modifications designed by the endorsement panel (Appendix B), were assigned at the face-to-face panel discussion. For epidemiology-related statements, this classification system was deemed not appropriate and not applied.

RESULTS
ENETs Guideline Methodology and Recent Literature Review
The endorsement panel found the methods for developing the 2015 ENETS recommendations to be rigorous and well described with support for recommendations appropriately indicated. The Methods, Results, and Recommendations sections were clear and well referenced. A review of the content found that the recommendations were comprehensive and widely applicable (Appendix A). This justified commencing an endorsement and update process, rather than developing a de novo set of recommendations. The panel believed that this was also preferable to provide a consistent global approach for practitioners and patients.

The literature search yielded 1109 publications since the previous publication, of which 230 studies met the inclusion criteria (Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram; Fig. 1).

Consensus Statements
The endorsed and updated consensus statements are presented alongside the original 2015 ENETS statements in Table 1.[8-80] A total of 12 statements were endorsed, 22 statements were modified or updated, one was removed, and two were added. A summary of discussions regarding the impact of the new data is presented in Table 1.

Diagnosis
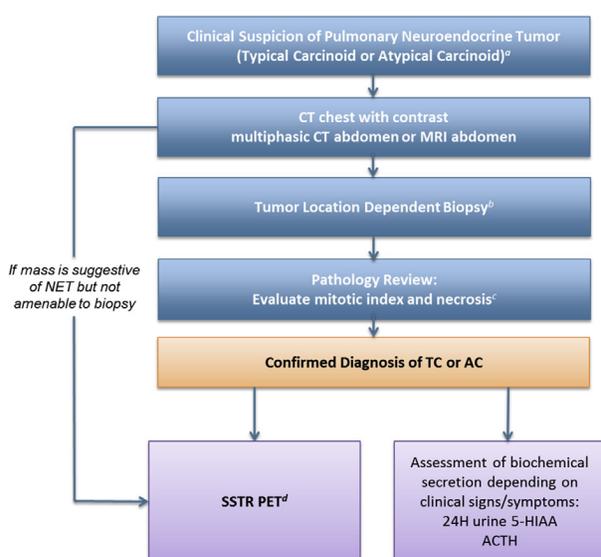A diagnostic algorithm was developed, based on the discussions outlined in the sections in Figure 2.

Figure 2. CommNETs and NANETS diagnostic algorithm. [a]Multidisciplinary care is critical in diagnosis and management of LNETs. [b]Consider the following biopsy approaches: central tumor: bronchoscopic; peripheral tumor: trans- bronchial or transthoracic; metastatic: most accessible site (endobronchial ultrasound-guided biopsy in selected cases of suspected mediastinal lymph node involvement). [c]Cytopathology specimen may not differentiate typical versus atypical carcinoid. Ki-67 is used mainly to separate the high-grade SCLC and large cell neuroendocrine carcinoma from the carcinoid tumors, especially in small biopsies with crushed or necrotic tumor cell sampling. Ki-67 is not validated in separating typical from atypical carcinoid tumors. Include differentiation as well. [d]SSTR-PET should replace 111- pentetreotide scintigraphy (Octreoscan) in all indications in which SSTR scintigraphy is currently being used. If mass is suggestive of NET but not amenable to biopsy,

proceeding to functional SSTR imaging or perhaps FDG-PET may be appropriate. 5-HIAA, 5-hydroxyindoleacetic acid; AC, atypical pulmonary carcinoid; ACTH, adrenocorticotropic hormone; CommNETs, Commonwealth Neuroendocrine Tumour Research Collaboration; CT, computed tomography; FDG, fluorodeoxyglucose; H, hour; LNET, Lung neuroendocrine tumors; NANETS, North American Neuroendocrine Tumor Society; NET, neuroendocrine tumor; PET, positron emission tomography; SSTR, somatostatin receptor; TC, typical pulmonary carcinoid.

Epidemiology

Three very large patient cohort studies have described a rising incidence of LNET, with two also documenting increased prevalence.[1-3] The report from the Surveillance, Epidemiology and End Results population database encompassing 64,971 patients diagnosed with NETs between 1973 and 2012 revealed a 4.63-fold increase in the incidence of LNETs, from 0.35 to 1.62 per 100,000 persons, over a 39-year period. An increase in prevalence from approximately 0.001% to 0.01% was reported, based on the period between 1993 and 2012.[1]

A population-based retrospective cohort study of patients diagnosed with NETs in the province of Ontario, Canada, reported 5619 NET diagnoses in a population that grew from 8 million in 1994 to more than 10 million in 2009. A rise in LNET incidence from 0.83 to 1.28 per 100,000 persons was reported, representing a 1.54-fold increase over the 15-year period.[2]
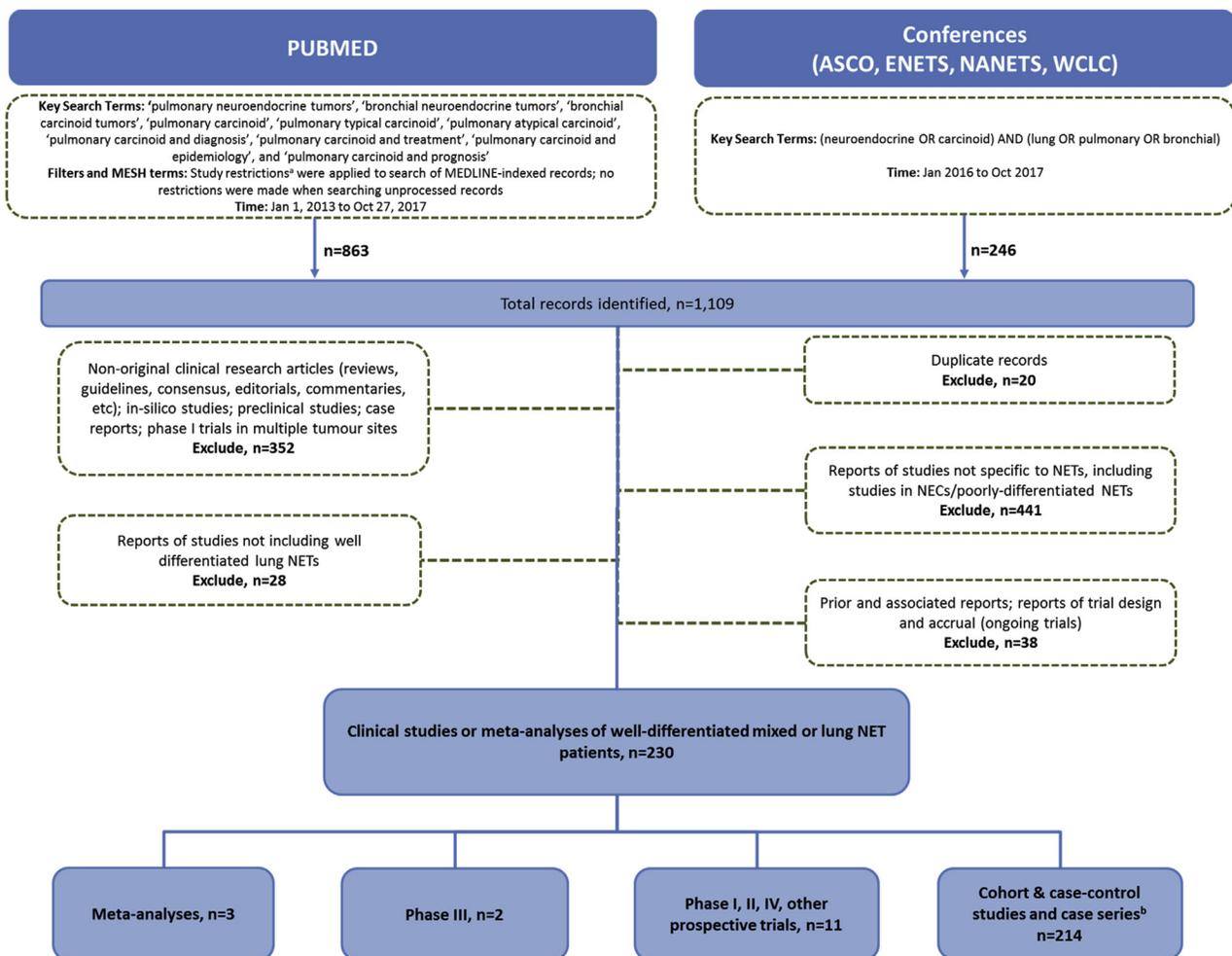

Figure 1. PRISMA diagram. [a]PubMed filters: meta-analyses, clinical trials (RCTs and phases I-IV); MeSH terms: cohort studies; [b]Prospective or retrospective: includes database reviews, registry analyses, and other observational, comparative, and noncomparative studies. ASCO, American Society of Clinical Oncology; ENETS, European Neuroendocrine Tumor Society; MeSH, medical subject headings; NANETS, North American Neuroendocrine Tumor Society; NET, neuroendocrine tumor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; WCLC, World Conference on Lung Cancer.

Table 1. CommNETs and NANETS Consensus Statements

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
Epidemiology		
No ENETS statement.	Added to highlight the increase of incidence and prevalence in LNETs.	The incidence and prevalence of LNETs has markedly increased in recent years.
Pathology—classification, grading, and Ki-67		
Original ENETS statement endorsed without modification.		Pathology is the criterion standard in the assessment of any LNET diagnosis. Difficult cases may benefit from review by expert pathologists (level of evidence 3; grade of recommendation B).
Current standard for classification and nomenclature is the 2004 WHO classification. Relevant information also derives from the UICC and AJCC seventh edition TNM staging. Other classifications are not recommended (level of evidence 3; grade of recommendation B).	Updated to reflect the new WHO classification system and the staging component of the statement was separated out for additional clarity.	Current standard for classification and nomenclature is the 2015 WHO classification.[8] Other classifications are not recommended (level of evidence 3; grade of recommendation B).
Original ENETS statement endorsed without modification.		Pathology report on LNETs should be shared by the multidisciplinary team along with oncologists, radiologists, nuclear medicine physicians, surgeons, pneumologists, and endocrinologists, in which pathologists contribute to the clinical decision-making process (level of evidence 5; grade of recommendation C).
LNETs as a whole are well-differentiated NETs as opposed to poorly differentiated SCLC and LCNEC and include low-grade malignant tumors, that is, TC, and intermediate-grade malignant tumors, that is, AC. TC is closest to the G1 GEP-NETs, and AC is closest to the G2 GEP-NETs. SCLC and LCNEC generally correspond to the NEC category of the gastrointestinal tract according to the current WHO classification. Diagnostic criteria, however, still rely primarily on histology (level of evidence 3; grade of recommendation B).	Removed, as LNETs and GEP-NETs have separate grading and classification schemes that do not always allow for direct comparison.	
Original ENETS statement endorsed without modification.		Mitotic count, necrosis, and Ki-67 labeling index should be indicated in the pathology reports of surgical specimens or biopsy samples for at least of the following two reasons: (1) mitoses and necrosis are part of the classification criteria and permit cross-study comparisons; (2) since the mitotic rate and Ki-67 proliferation index impact on survival even within AC (level of evidence 3; grade of recommendation C).
Original ENETS statement endorsed without modification.		There are at least the following four major issues regarding Ki-67 labeling index assessment in LNETs: (1) Ki-67 is useful in biopsy for distinguishing TC and AC from SCLC cytology (level of evidence 4; grade of recommendation C); (2) Ki-67 does not reliably distinguish TC from AC in any material (level of evidence 4; grade of recommendation C); (3) Ki-67 has been revealed to predict prognosis of TC and AC (level of evidence 4; grade of recommendation C); and (4) the optimal procedure for performing Ki-67 IHC and the criteria for performing the relevant labeling index (digital image analysis, manual counting, eyeball evaluation, hotspot areas vs. randomly selected field vs. entire tumor area, and number of cells) remains to be settled (level of evidence 4/5; grade of recommendation C).

Table 1. Continued

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
Tumor staging and other		
Current standard for classification and nomenclature is the 2004 WHO classification. Relevant information also derives from the UICC and AJCC seventh edition TNM staging. Other classifications are not recommended (level of evidence 3; grade of recommendation B).	Modified to reflect new standards for the staging of lung tumors.	Current standard for staging is the UICC and AJCC eighth edition for TNM staging[9] (level of evidence 3; grade of recommendation B).
Separation of TC from AC requires a surgical specimen. TC and AC cannot be reliably distinguished from each other in small biopsy and cytology (level of evidence 3; grade of recommendation C).	Modified to clarify that there is potential for sufficient sampling through either endobronchial biopsy or surgical resection.	Distinguishing TC from AC requires a sufficient tissue sample,[4,8] therefore surgery or endobronchial resection are preferred sampling methods over cytology or small biopsies.[10,11] (level of evidence 3; grade of recommendation C).
Original ENETS statement endorsed without modification.		A few NE immunomarkers (chromogranin A, synaptophysin, and CD56 and NCAM) may be used to confirm NE nature of tumors especially in biopsy or cytology specimens or surgical specimens, if needed. In case of metastatic LNETs presentation, positive TTF1 staining is suggestive of a lung or thyroid origin (level of evidence 3; grade of recommendation C).
Original ENETS statement endorsed without modification.		NE cell hyperplasia, tumorlets, DIPNECH, and multiple tumors should be carefully documented and most often pertain to LNETs. DIPNECH is a preinvasive lesion able to progress to TC or AC. Histologic evaluation may provide information to decide if multiple LNETs are intrapulmonary seeding or multiple primaries, as an association with NE cell hyperplasia, tumorlets, or DIPNECH favors multiple NETs (level of evidence 4; grade of recommendation C).
Original ENETS statement endorsed without modification.		No proof has been provided that different histologic tumor cell features may have clinical significance, although they may seriously affect differential diagnosis. Cell atypia or pleomorphism is not useful to classify LNETs (level of evidence 4; grade of recommendation C).
Original ENETS statement endorsed without modification.		No molecular tests should currently be routinely carried out in LNETs, (level of evidence 4; grade of recommendation C).
Biochemical assessment and functional syndromes		
Biochemical baseline tests should be limited to renal function, liver function, calcium, glucose, and plasma chromogranin A measurements (level of evidence 4, grade of recommendation D).	Modified to reflect the lack of supporting evidence for limiting biochemical baseline tests, and the emerging evidence indicating the limited clinical value of chromogranin A in the diagnosis and determination of disease state of LNETs.	Baseline and routine use of plasma chromogranin A is of limited clinical value in LNETs[12,13] (level of evidence 4, grade of recommendation C).
Paraneoplastic syndrome might occur in the setting of LNETs. Biochemical testing should be carried out in consideration of clinical symptoms and features including as appropriate 24-h urine 5-hydroxy-indole-acetic acid, ACTH, and GHRH (level of evidence 4, grade of recommendation A).	Modified to reflect the two most common functional syndromes associated with LNETs, carcinoid, and Cushing syndromes. The grade of recommendation was changed from A to C to better reflect the level of supporting evidence.	Functional syndromes might occur in the setting of LNETs. Biochemical testing should be carried out in consideration of clinical symptoms and features including 24-h urine 5-hydroxy-indole-acetic acid and ACTH, as appropriate[14,15] (level of evidence 4, grade of recommendation C).

(continued)

Table 1. Continued

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
MEN1-associated forms		
LNETs may be associated with MEN1 syndrome in <5% of patients. MEN1 is investigated by family history, clinical examination, and minimal laboratory screening (level of evidence 4, grade of recommendation C). If the familial history is suggestive of a MEN1 syndrome or a second MEN1 feature is present, screening for MEN1 gene mutation should be carried out (level of evidence 5, grade of recommendation C).	The qualifier "approximately" was added to more closely align with recent data regarding incidence of MEN1 disease in LNET populations.	LNETs may be associated with MEN1 syndrome in approximately 5% of patients.[16,17] MEN1 is investigated by family history, clinical examination, and minimal laboratory screening[18] (level of evidence 4, grade of recommendation C). If the familial history is suggestive of a MEN1 syndrome or a second MEN1 feature is present, screening for MEN1 gene mutation should be carried out[19] (level of evidence 5, grade of recommendation C).
Diagnosis—radiological imaging		
More than 40% of the cases may be incidentally detectable on a standard chest radiograph (level of evidence 3/4, grade of recommendation C). The accepted standard is contrast CT (level of evidence 3, grade of recommendation B). In patients in whom contrast is contraindicated, high-resolution CT may be used (level of evidence 4, grade of recommendation C). Multiphase CT, including arterial and portal phase or MRI with dynamic acquisition and diffusion-weighted sequences of the liver should be used for the detection of liver metastases (level of evidence 4, grade of recommendation C). A CT chest and abdomen should be undertaken for preoperative staging (level of evidence 4, grade of recommendation A). Echocardiography is always indicated in patients with carcinoid syndrome before surgery (level of evidence 4, grade of recommendation B). In LNETs, left-side and right-side valves should be screened (level of evidence 4, grade of recommendation B).	Modified to simplify guidance and clarify differences in requirements for diagnostic compared with liver imaging.	At initial diagnosis, imaging should include a contrast enhanced CT of the chest[4,20] with multiphase CT or MRI of the liver[21] (level of evidence 3, grade of recommendation C). Hepatobiliary-phase liver MRI is more sensitive than CT or SSTR-PET and should be used for detection of small hepatic metastases[21-23] (level of evidence 3, grade of recommendation C).
Functional imaging		
Most TCs have low or no uptake on FDG-PET, whereas ACs may have higher uptake. FDG-PET is most useful for poorly differentiated forms (SCLC and LCLC) (level of evidence 4, grade of recommendation C). Whole-body SRS with thorax SPECT CT may be useful to visualize nearly 80% of the primary tumors (level of evidence 4, grade of recommendation B). Gallium-68-DOTA SSA PET is more sensitive and preferable to SRS if available (level of evidence 4, grade of recommendation C). SRS and SSTR-PET imaging may have a higher grade of sensitivity for bone metastases (level of evidence 4, grade of recommendation D).	Modified to better direct application of various nuclear imaging techniques.	SSTR-PET can be used in patients to detect metastatic disease[24] (level of evidence 2 and grade of recommendation C). FDG-PET may be useful in addition to SSTR-PET in heterogeneous disease (level of evidence 4, grade of recommendation C). The clinical utility in small primary LNETs without evidence of metastatic disease on contrast imaging is limited[25] (level of evidence 4, grade of recommendation C).

<div align="right">(continued)</div>

Table 1. Continued

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
Bronchoscopy		
Bronchoscopy may be required for the staging and assessment of central airway tumors preoperatively (level of evidence 4, grade of recommendation A). Flexible bronchoscopy is preferable; however, in patients at high risk for bleeding, rigid bronchoscopy may be preferred for obtaining biopsy specimens (level of evidence 4, grade of recommendation B). There is currently limited evidence regarding the added value of new bronchoscopic techniques to increase the sensitivity of detection of primary tumors or recurrence (level of evidence 4, grade of recommendation D).	Simplified as new technological advancements have made both flexible and rigid bronchoscopy effective and safe.	Bronchoscopy is a safe and effective method for diagnosing LNETs and may be considered as the initial diagnostic modality for these tumors[26] (level of evidence 3; grade of recommendation C).
Functional respiratory tests		
Patients with LNETs, who are candidates for lung resection should undergo pulmonary function testing to help determine surgical risk[27] (level of evidence 3, grade of recommendation C). The presence of a central obstruction should be taken into account when evaluating outcomes (level of evidence 5, grade of recommendation D).	Modified as nonsurgical candidates do not routinely require pulmonary function tests, and to account for the possibility of nonobstructive lung disease.	For surgical candidates, functional respiratory tests should always be carried out to assess the surgical risk and the association with chronic obstructive airways disease and to screen for bronchostenosis. Nonsurgical candidates should not undergo routine functional respiratory testing (level of evidence 4, grade of recommendation A).
Surgery		
In the case of localized disease, the surgical techniques of choice are lobectomy or sleeve resection (level of evidence 5, grade of recommendation A).	Revised to update the level of evidence supporting surgical techniques for localized disease, and reflect increasing evidence that patients undergoing sublobar resection have equivalent survival to patients undergoing lobectomy, especially for TC tumors.	In the case of localized disease, the surgical techniques of choice are lobectomy or sleeve resection[28-30] (level of evidence 3, grade of recommendation B). Sublobar resection is a possible acceptable alternative if complete (R0) resection can be achieved in peripheral <2 cm typical LNETs[31-34] (level of evidence 3, grade of recommendation B).
Complete anatomical resection and systematic nodal dissection are recommended as the resection extent of choice of patients with peripheral tumors (level of evidence 5, grade of recommendation D).	Designation updated based on current level of evidence.	Complete anatomical resection and systematic nodal dissection are recommended as the resection extent of choice of patients with peripheral tumors[29,31] (level of evidence 3, grade of recommendation B).
Lung parenchymal-sparing surgery should be preferred over pneumonectomy (level of evidence 5, grade of recommendation C).	Designation updated based on current level of evidence.	Lung parenchymal-sparing surgery should be preferred over pneumonectomy[31,35-38] (level of evidence 3, grade of recommendation B).
Local resection should be reserved for patients who are considered unacceptably high risk for bronchopulmonary surgery (level of evidence 5, grade of recommendation D). Endoluminal bronchoscopic surgery, more appropriately for TC, should be reserved for patients who are considered unacceptably high risk for bronchopulmonary surgery or occasionally as a possible bridge to surgery (level of evidence 5, grade of recommendation D).	Revised to combine aspects related to endobronchial resection, reflect new data, and align with current terminology used in this context.	Endobronchial resection[11,39,40] should be reserved for patients who are considered unacceptably high risk for surgical resection or occasionally as a possible bridge to surgery (level of evidence 5; grade of recommendation D).
Resection of liver metastases should be carried out whenever possible if curative intent is considered and in syndromic patients when >90% of tumor burden can be removed. The minimal requirements for curative intent include resectable TC and low-grade AC; <5% mortality; absence of right heart insufficiency; absence of unresectable lymph node and extraabdominal metastases; and absence of unresectable peritoneal carcinomatosis (level of evidence 4, grade of recommendation C).	Modified to expand the indication for cytoreductive surgery of the liver based on recent NET data.	In patients with nonaggressive tumors, even with limited extrahepatic disease, palliative cytoreductive surgery of the liver should be considered[41-43] (level of evidence 4, grade of recommendation C).

(continued)

Table 1. Continued

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
Locoregional therapy		
Locoregional options, including surgery (for primary and metastases), TAE, and RF should always be considered for slow-progressive LNETs (level of evidence 4, grade of recommendation C).	Modified as group felt that there was insufficient evidence to support recommendation for always considering TAE and RF in slow-progressive LNETs.	Local ablative radiation and thermal therapies can be used for local tumor control of primary LNETs and for palliation of symptoms in patients unfit for or declining surgery[44-49] (level of evidence 3; grade of recommendation B). Locoregional therapies including surgery should be considered for progressive or symptomatic metastases in the liver[50,51] or other solid organs and the skeleton[52] (level of evidence 3, grade of recommendation C).
Adjuvant therapy		
There is no consensus on adjuvant therapy in LNETs after complete resection. There might be consideration in patient with AC of high proliferative index (level of evidence 4, grade of recommendation D).	Modified to be definitive, reflecting lack of data.	Adjuvant therapy with SSAs, chemotherapy or radiation, is not recommended in LNETs after complete resection[53-55] (level of evidence 4, grade of recommendation C).
Therapy for unresectable locally advanced or metastatic LNET		
Original ENETS statement endorsed without modification.		A watch-and-see policy may be considered in a subgroup of asymptomatic patients mainly with TC or AC of low proliferative index (level of evidence 5, grade of recommendation D).
Original ENETS statement endorsed without modification.		SSAs are the first-line treatment of carcinoid syndrome (level of evidence 3, grade of recommendation B).
Original ENETS statement endorsed without modification.		In patients with Cushing syndrome, control of cortisol secretion is needed (level of evidence 3, grade of recommendation B).
Original ENETS statement endorsed without modification.		SSA may be considered as first-line systemic antiproliferative treatment of patients with advanced unresectable LNETs of good prognosis particularly TC and AC with low proliferative index, and slowly progressive provided that somatostatin receptor imaging is positive (level of evidence 3, grade of recommendation B).
PRRT is an option in patients with tumors that reveal strong expression of SSTRs (level of evidence 3, grade of recommendation C).	The need for strong expression of SSTRs was removed as it is unclear what cutoff should be used with somatostatin receptor PET. The grade of recommendation was augmented to reflect consistent benefits seen in LNET cohort studies and those seen in the NETTER-1 RCT in small bowel NETs.	PRRT may be an option in patients with somatostatin receptor-positive tumors[56-60] (level of evidence 3, grade of recommendation B).
No ENETS statement.	Statement was added to better define the role of this modality.	External beam radiation is an effective palliative therapy for patients with symptomatic locally advanced[61,62] or metastatic disease[62-64] (level of evidence 4, grade of recommendation B).
There is evidence of preliminary efficacy for everolimus in the treatment of progressive LNETs. The ongoing randomized phase II LUNA study will determine future management (level of evidence 4, grade of recommendation D).	The statement was revised to reflect significant improvements in median PFS arising from addition of everolimus to standard therapy in progressive nonfunctional LNETs and emerging evidence indicating benefit in functional LNETs.	Everolimus should be considered for routine use in progressive nonfunctional LNETs[65,66] (level of evidence 1, grade of recommendation A) and may be considered in functional LNETs[67] (level of evidence 3, grade of recommendation B).

(continued)

Table 1. Continued

2015 ENETS Statement	Endorsements and Modifications	Final CommNETs and NANETS Statement
Cytotoxic treatment has been the standard for aggressive metastatic LNETs, although the available chemotherapy regimens reveal a limited effect (level of evidence 3, grade of recommendation B). A combination of cisplatinum and etoposide is mainly used in high proliferating LNETs (level of evidence 3 grade of recommendation B). TMZ alone has revealed clinical benefit (level of evidence 3, grade of recommendation B).	Revised to better reflect current body of data regarding use of cytotoxic therapy in advanced LNETs.	Use of streptozocin-based[68,69] (level of evidence 4, grade of recommendation B), oxaliplatin-based[70-72] etoposide-based[68,69] or temolizomide-based[68,73-75] chemotherapy may be considered in advanced LNETs, with particular consideration in atypical carcinoids[68,69,76] (level of evidence 4, grade of recommendation C).
No ENETS statement.	The statement was added to reflect new data indicating unknown benefit for antiangiogenic agents in LNET compared with other patients with NET (pancreas).	There remains insufficient data to suggest the routine use of antiangiogenics in LNETs[77-79] (level of evidence 4, grade of recommendation C).
Follow-up		
After primary surgery, patients with TC and AC should be followed long term (level of evidence 4, grade of recommendation B).	Revised and recommendation augmented to better define and direct use of imaging for follow-up and reflect recent data revealing a lack of benefit for postoperative surveillance in patients with node-negative TC.	For lymph node–negative TC, recurrence rate is sufficiently low as to not warrant surveillance.[80] Exceptions can be made if there are concerning features such as tumor size (>3 cm), close margins, multifocality, etc. (level of evidence 3, grade of recommendation B). Long-term follow-up is recommended for lymph node-positive TC and for AC of any size[80] (level of evidence 3, grade of recommendation B). When surveillance is warranted, patients should be followed with conventional imaging (CT) of the thorax/abdomen (including liver)[25] (level of evidence 4, grade of recommendation C). SSTR-PET should be limited to patients with suspicion of progression or in patients whom metastatic disease is seen primarily on SSTR-PET[25] (level of evidence 4, grade of recommendation C).

AC, atypical carcinoid; ACTH, adrenocorticotropic hormone; AJCC, American Joint Committee on Cancer; CD56/NCAM, neural cell adhesion molecule; CommNETs, Commonwealth Neuroendocrine Tumour Research Collaboration; CT, computed tomography; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; ENETS, European Neuroendocrine Tumor Society; FDG-PET, fluorodeoxyglucose positron emission tomography; GEP, gastroenteropancreatic; GHRH, growth hormone-releasing hormone; GX, grade X; IHC, immunohistochemistry; LCLC, large cell lung cancer; LCNEC, large cell neuroendocrine carcinoma; LNET, lung neuroendocrine tumor; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NANETS, North American Neuroendocrine Tumor Society; NE, neuroendocrine; NET, neuroendocrine tumor; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; R0, complete resection; RCT, randomized controlled trial; RF, radiofrequency; SPECT/CT, single-photon emission computed tomography/computed tomography; SRS, somatostatin receptor scintigraphy; SSA, somatostatin analog; SSTR-PET, somatostatin receptor-positron emission tomography; TAE, transarterial embolization; TC, typical carcinoid; TMZ, temozolomide; TNM, tumor nodes metastasis; TTF1, thyroid transcription factor 1; UICC, Union for International Cancer Control.

A third source of new data comprised a retrospective, cross-sectional study from two US medical insurance claims databases from 2010 to 2014. During that period, the LNET incidence increased from 15.2 to 19.2 per million person-years in one database and 13.1 to 16.0 per million person-years in the other. A rise of 39% to 60% in the prevalence of cases per million per year was also observed.[3]

Therefore, a new statement was added to highlight the increase in incidence and prevalence of LNET.

Pathology and Staging
The ENETS statement was updated to reflect new standards for classification and clarified staging

recommendations. A preference for endobronchial biopsy or surgical resection over cytology was stated to ensure sufficient sampling to differentiate TC from AC.[10,11] The WHO classification system was updated from 2004 to 2015, although the classification of LNETs was unchanged.[8] These tumors are primarily classified based on the mitotic index (defined as the number of mitotic figures per 2 mm^2) and tumor necrosis. TC has a mitotic index of fewer than two mitoses per 2 mm2 and absence of necrosis, whereas AC has a mitotic index of 2 to 10 per mm^2 and necrosis.

No new data on the use of Ki-67 in the classification of LNETs were determined to be practice changing at this time.[81-84] Several studies revealed that Ki-67 carries independent prognostic value on univariant but not

multivariant analysis; moreover, no reliable cutoff value has been established in distinguishing AC from TC.[10,11,85]

Staging of LNETs has always been in line with staging of NSCLC; thus, the current (eighth) edition of the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (Union for International Cancer Control and American Joint Committee on Cancer) of the lung cancer TNM was determined as the best classification system.[9] It was noted that LNETs and gastrointestinal or pancreatic-NETs currently still have separate grading and classification schemes, hindering direct comparison. There is movement toward unifying all NET classification schemes for exactly this reason.[86]

It was recognized that molecular studies being undertaken in NET comparing tumors of various sites of origin with regard to genomics, transcriptomics, proteomics, and epigenetic changes may yield significant clinical correlations that would allow better diagnostics and streamlining of therapy.[87] At this time, however, there is insufficient evidence to advocate for routine molecular classification of LNETs.

Biochemical Assessment and Functional Syndromes
The major change to the previous statements resulted from discussion of new data indicating the limited clinical value of chromogranin A (CgA) in diagnosis, disease state characterization, and determination of prognosis.

In one study of 118 patients with LNETs, elevated levels of CgA were observed in only 37% of the patients, and CgA was poor at distinguishing LNETs from healthy controls (area under receiver operating characteristic curve 0.68, 95% confidence interval [CI]: 0.61–0.76; p < 0.0001), translating into a sensitivity of 36% and negative predictive value of 55%. Furthermore, CgA was unable to differentiate stable disease from progressive disease (area under receiver operating characteristic curve 0.52, 95% CI: 0.40–0.64; p 0.75).[12]

A 2017 NANETS conference abstract reported a meta analysis of 27 publications and three case reports of CgA in LNETs, with the majority being retrospective studies.[13] The diagnostic sensitivity with nine different assays was 62% (range 25%–93%). No study provided data on specificity. Only two studies revealed correlation of elevated CgA levels with overall survival, and no study reported the utility of CgA in differentiating disease state.

Given the growing data revealing poor sensitivity and lack of predictive value of CgA, and the variability in assays used and the lack of prospective data, the ENETS statement was revised to emphasize the limited clinical value of CgA in LNETs.

Recent data confirm that functional syndromes are uncommon in LNETs, with the two most encountered syndromes being carcinoid and Cushing syndrome.[14,15] In an analysis from the Surveillance, Epidemiology and End Results database of patients older than 65 yearswith NETs of all grades, only 229 of 1786 patients (13%) with carcinoid syndrome had lung as the primary site of origin. Conversely, lung was the most common site for patients who did not have carcinoid syndrome (2773 of 7726 patients; 35%).[14]

Therefore, the CommNETs and NANETS statement limited recommending biochemical testing to those patients deemed appropriate after consideration of clinical symptoms and signs. The nomenclature was changed from "paraneoplastic syndromes" to "functional syndromes," and the grade of recommendation was adjusted given the additional evidence.

Multiple Endocrine Neoplasia 1–Associated Forms
Previously, a few studies of LNETs in patients with multiple endocrine neoplasia 1 estimated an association ranging from 3% to 13%, with some very small series reporting even higher rates.[16] A report from the Groupe d'Etude des Tumeurs Endocrines network for multiple endocrine neoplasia 1 in France and Belgium followed 1023 patients for a median of 48.7 years and documented that 51 patients (4.8%, [95% CI: 3.6%–6.2%]) developed a LNET.[17] The wordings of the 2015 ENETS statement was, therefore, modified to reflect the new data.

Radiological Imaging
The 2015 ENETS statements were simplified, and an explicit requirement for adequate assessment of the liver was added as a result of data suggesting the hepatobiliary-phase liver magnetic resonance imaging is more sensitive than computed tomography (CT) for detection of metastases.[21,22] Moreover, it may be more sensitive than somatostatin receptor-positron emission tomography (SSTR-PET) for small hepatic metastasis.[22,23]

Functional Imaging
It was discussed that the clinical utility of SSTR-PET in detecting small primary LNETs remains limited and that differences have been found in the sensitivity of radioactive

tracers used in PET CT for diagnosis of NETs, which guide both disease classification and patient selection for subsequent therapy.[25] In gastroenteropancreatic (GEP)-NETs, a study of 68Ga- DOTATATE PET CT imaging revealed greater sensitivity of detection (95.1% of lesions detected; 95% CI: 92.4%– 96.8%]; p < 0.001) than either anatomical imaging (45.3%) or 111In-pentetreotide single-photon emission CT (30.9%).[24]

The expert panel modified the ENETS statements to clarify the role of SSTR-PET in detection of metastatic disease while noting its limited utility in small primary LNETs without evidence of metastatic disease on contrast anatomical imaging.[24,25] The importance of having a positive SSTR-PET as a selection criterion for patients who are being considered for peptide receptor radionuclide therapy (PRRT) was added; however, it was seen that there was a lack of approval by many health authorities for the use of PRRT in LNETs.[25,88]

Bronchoscopy
As LNETs are usually situated in the central airways, bronchoscopy can play an important role in the diagnosis. A series published in 2016 from the University of Maryland School of Medicine in Baltimore, MD, reported that 30 of 49 patients with LNET diagnosed between 2003 and 2013 had undergone diagnostic bronchoscopy.[26] The bronchoscopic yield was 65.7%, with 76.7% of patients subsequently diagnosed through analysis of the resulting biopsy. Only two complications of moderate-to-severe bleeding and no emergent thoracotomies, transfusions, or deaths were reported.

Hence, the 2015 ENETS statements in this domain were simplified to highlight the utility and safety of bronchoscopy and to remove the previous preference for rigid over flexible scopes.

Functional Respiratory Tests
Data from studies on lobectomies were used to inform LNET recommendations regarding pulmonary function tests (PFTs). A prospective database analysis revealed that postoperative predicted forced expiratory volume in the first second and diffusing capacity of the lung are independent predictors of postoperative pulmonary complications after minimally invasive lobectomy,[27] consistent with previous data from open lobectomy.[89] When central airway obstruction is present and a pneumonectomy is being considered, a quantitative perfusion scan combined with PFTs to calculate postresection forced expiratory volume in the first second is helpful. For patients who have marginal PFTs, pulmonary

exercise testing to calculate maximum rate of oxygen consumption can further assist in calculating the surgical risk.[89]

The 2015 ENETS statement was modified to exclude nonsurgical candidates from routinely requiring PFTs.

Surgery for Primary Tumors
New analyses of databases involving more than 1000 patients with TC reported equal 5-year overall survival between sublobar resection and lobectomy, with overall survival rates of 80% to 93%.[31,33] These studies add weight to the option of lung parenchymal-sparing operation as an acceptable option if complete resection of the LNET can be achieved in patients with peripheral typical carcinoids less than 2 cm.

Recent studies have revealed that endobronchial TC or AC without an extraluminal component can be treated through endobronchial resection, resulting in an excellent long-term outcome and more tissue-sparing than surgical resection.[11,39] Endobronchial resection may also reduce the risk of postobstructive infection and result in increased residual pulmonary reserve.[39]

The panel concluded that current evidence supports endobronchial resection for patients with LNET for whom surgery would be high risk, or occasionally as a bridge to future operation. However, there were insufficient data to promote this as a standard of care. In summary, statements regarding surgery were revised to update the level of evidence supporting surgical techniques for localized disease and to reflect growing evidence. Statements were also updated to align with current surgical terminology for the newer techniques

Surgery for Metastatic Disease
Cytoreductive or tumor-debulking surgery has an increasing role in the palliation of unresectable NET liver metastases.[42,43] Nonrandomized data from liver resection for metastatic NET from various primaries support lowering the threshold for cytoreduction to greater than or equal to 70% from 90% of tumor that can be removed. Even in the presence of some extrahepatic disease, debulking may be associated with improved outcomes.[41-43] The ENETS 2015 statement was expanded so that consideration of cytoreductive surgery of the liver included patients with nonaggressive tumors and even with limited extrahepatic disease. The prescriptive criteria for resection were removed.

Locoregional Therapy

Systematic analyses and multiple large phase II multicenter trials have established the role of locoregional therapy in NSCLC, including stereotactic ablative radiotherapy and radiofrequency ablation.[47] However, data supporting the use of locoregional therapy in LNETs are limited. The panel felt it was reasonable to expect that control rates in this setting would be similar to those seen in other lung histologies. In addition, ablative therapies may be particularly suitable for localized LNET lesions in patients unfit for or declining surgery.[90]

There are no data specific to metastatic LNETs regarding the role of ablative techniques, such as stereotactic ablative radiotherapy and stereotactic body radiotherapy, microwave ablation, and cryoablation, for low-volume metastases in solid organs and the skeleton. The panel felt it appropriate to consider their use on an individualized basis, extrapolating from studies in other cancer histologies.[45,50-52]

Therefore, the expert panel modified the ENETS statement as it was felt that there was insufficient evidence to support the previous recommendation for "always" considering transarterial embolization and radiofrequency ablation in slow-progressive LNETs.[50]

Adjuvant Therapies

Adjuvant Chemotherapy. The 2015 ENETS recommendations stated that there was "no consensus" on adjuvant therapy in LNETs after complete resection and that this might be considered in patients with AC of high proliferative index. Our expert panel felt strongly that this should be modified to reflect the fact that there are no data to support adjuvant chemotherapy, including in the high-risk AC group.

Although no randomized trials have been undertaken (and are unlikely ever to be), findings from two large retrospective LNET series from different time periods of data from the National Cancer Database, USA,[54,55] did not reveal a benefit in overall survival for patients positive with node treated with chemotherapy after lobectomy for TC and AC.

Nussbaum et al.[54] analyzed 629 patients with LNET (typical histology) resected between 1998 and 2006 with positive lymph nodes (13.6% of the total cohort). A total of 37 patients (5.9%) received adjuvant chemotherapy and, of concern, this group was associated with an inferior survival at 5 years compared with those with no chemotherapy (69.7% versus 82.8%; p 0.026).[54] After propensity matching

to adjust for confounding variables, a trend toward inferior 5-year survival for patients who received adjuvant chemotherapy persisted but did not retain statistical significance (69.7% versus 80.9%; p 0.096). The type of chemotherapy was not described.

A 2017 conference abstract reported 1682 patients positive with node who underwent lobectomy between 2004 and 2012, including 651 patients with TC and 239 with AC. Adjuvant chemotherapy was administered to 6% and 40%, respectively. Once again there was an association with inferior overall survival in patients with TC (hazard ratio [HR]: 3.8; 95% CI: 1.9–7.0; p 0.004). There was no overall survival benefit revealed for patients with AC (HR 1.1; 95% CI: 0.68–1.78; p ¼ 0.6).[55]

Adjuvant Somatostatin Analogs and Adjuvant Radiotherapy. There are no data to support use of adjuvant somatostatin analog (SSA) therapy for NETs f rom any site of origin. There is similarly a paucity of data for radiation therapy in this setting.[53] The updated statement specified a lack of supporting data for these adjuvant therapies.

Therapy for Unresectable Locally Advanced or Metastatic LNET

Somatostatin Analogs. The SSAs are the first line of treatment for carcinoid syndrome, regardless of the primary site, although this is rare in LNET.[4] For nonfunctioning GEP-NET, there are robust data supporting the antiproliferative effects of SSA, but LNET- specific data are lacking. The 2015 ENETS guideline discussion of SSAs was based on the inclusion of some patients with LNET in older series.

Since 2015, several more retrospective series in LNET populations have been published. An analysis of 30 patients with SSTR-positive LNET registered in an Italian rare tumor database concluded that outcomes with use of first-line SSA appeared to support benefit in disease control.[91] In a retrospective series of 61 patients with progressive, metastatic LNET reported from the Gustave Roussy Cancer Campus, Villejuif, France, of which almost half had functioning tumors, the association between SSA use and increased median progression-free survival (PFS) was described as "encouraging."[92]

The consensus group recognized the results from the double-blind, placebo-controlled phase III SPINET trial as pending. The trial planned to randomize 216 well-differentiated, SSTR-positive patients with first-line or second-line advanced LNET to either lanreotide

or placebo.[93] However, the subsequent early closure of recruitment at 77 patients, owing to the slow pace of accrual, will significantly restrict the amount of information that this key trial will provide.

Peptide Receptor Radionuclide Therapy. *The Peptide receptor radionuclide therapy* (PRRT) has been used for many years in a few large-volume centers globally as treatment for NETs, which reveals expression of SSTR by imaging, despite the absence of randomized trial data. With the large benefit of PRRT revealed in the NETTER-1 trial in well-differentiated midgut of the patients with NET, the question again arises about the degree to which this can be extrapolated to all SSTR- positive NETs.[60]

New data since the ENETS guidelines include a series of patients treated with PRRT from the Erasmus Centre, Rotterdam, Netherlands. Of 443 patients, 23 had LNET, with no grade stated. Response to PRRT was reported as stable disease (SD) or partial response for seven patients each, progressive disease for six patients, and nonassessable. for three patients. The median overall survival was 52 months (95% CI: 49–55 mo) with median PFS of 20 months.[56]

In a phase II study undertaken in Italy, 34 patients with radiologically documented progressive LNET received 177Lu-DOTATATE (Lu-PRRT).[57] The response in the 15 patients with TC was 6% complete response, 27% partial response, and 47% SD, with median PFS remarkably similar to that of the Erasmus Centre series at 20.1 months (95% CI: 11.8–26.8 mo). Of the 19 patients with AC, SD was achieved in 47% with median PFS of 15.7 months (95% CI: 10.6–25.9 mo).[57]

Two small retrospective series of patients with PRRT-treated metastatic LNET, were reported in 2017, each with 22 patients.[59] Patients from these two German centers were reported to have a disease control rate of 68.1%.[59]

Therefore, although randomized data supporting use of PRRT in LNETs are not available, the panel felt it appropriate to recommend this modality as a possible option in patients with SSTR-positive tumors by imaging. However, the previous ENET qualification requiring strong SSTR expression was removed, as the link between the level of expression and response to PRRT has not been firmly established in LNETs.

Systemic Chemotherapy. There were no new data relating to chemotherapy in LNET with the older agents still used for metastatic GEP-NETs, such as streptozocin. However, there was a retrospective analysis on platinumetoposide

based regimens for LNETs revealing an overall response rate of 23%, disease control rate of 69%, and median PFS of 7 months.[68,69]

Patients with LNET were included in small retrospective series reporting responses to oxaliplatin-based regimens, including 8 of 31 patients treated with modified FOLFOX at four French centers and 24 of 78 patients treated with FOLFOX, Capeox, or gemcitabine-oxaliplatin at five sites in Italy.[70,72]

Several conference abstracts reported on temozolomide (TMZ). The combination of TMZ plus capecitabine at a single UK center revealed antitumor activity in eight patients with TC and 15 patients with AC, and singleagent TMZ revealed activity as second-line therapy.[94,95] Results from an ongoing phase II study examining the use of TMZ in combination with lanreotide in patients with lung and thymic NETs were not available at the time of the consensus generation (trial number NCT02698410).

The new consensus statement clarified the types of chemotherapy to be considered in the use of metastatic LNETs.

Radiation. Data supporting a benefit for external beam radiation for management of metastatic disease for LNET are limited, but its use is empirically supported for symptom control. A 2015 series presented 29 patients with LNET from 1998 to 2013 treated for brain metastasis: 16 patients with whole-brain radiation therapy (WBRT), five with WBRT with a stereotactic radiosurgery (SRS) boost, and eight who underwent primary SRS alone. The conclusion was that either WBRT or SRS was effective and that the pattern of failure more resembled NSCLC than SCLC.[62,63]

A consensus statement was added to address the palliative use of radiation for locally advanced and metastatic LNET.

Targeted Therapy

Mammalian Target of Rapamycin Inhibitors. Everolimus is the only systemic treatment for which there is high-quality RCT evidence in LNETs. The phase III RADIANT-4 trial included 302 patients with advanced, progressive, well-differentiated (grade 1 or grade 2) nonfunctional NETs from multiple primary sites, stratified for site of origin into two prognostic groups, with lung in the worse prognosis stratum.[66] A posthoc exploratory analysis of the lung cohort (n ¼ 90) revealed that the median PFS by central review in the everolimus group was 9.2 months (95% CI: 6.8–10.9 mo) versus 3.6 months (95% CI: 1.9–5.1 mo) for placebo

(HR, 0.50; 95% CI: 0.28–0.88).65 Toxicity was similar in the entire cohort.

For functional NETs, both trials evaluating everolimus alone or in combination with SSA therapy included LNETs. The phase III RADIANT-2 study (n 429; 44 with LNETs) was published at the time of the 2015 ENETS consensus. However, the randomized phase II LUNA study, the first international randomized study enrolling only lung and thymic NETs comparing everolimus alone, everolimus in association with pasireotide, and pasireotide alone, was not reported at the time of consensus. The results, published in 2017, revealed that long-acting pasireotide (n ¼ 41) or everolimus (n ¼ 42) as single agents or in combination (n ¼ 41) are active in well-differentiated functional and nonfunctional lung and thymic NET.[67] All three treatment groups met the prespecified threshold of 9 months PFS, with 39%, 33%, and 59% of patients receiving pasireotide, everolimus, or combination therapy, respectively.

With these additional data and relatively high-quality evidence, our expert panel recommends that everolimus should be considered for routine use in progressive nonfunctional LNET. Everolimus appears safe, with toxicities manageable through dose interruption or modification. It may also be considered in functional LNET, albeit with a lesser evidence base.

Antiangiogenics. Antiangiogenics are considered modestly effective in NETs. Data in LNET involve small numbers with nonstatistically significant inferior outcomes in the five patients with NET receiving pazopanib in the open-label phase II PAZONET study, compared with patients with 39 NETs from other sites; this is similar to previous data with sunitinib.[77,78] Other agents with antiangiogenic activity are also being tested.

As the 2015 ENETS guidelines did not have a recommendation regarding antiangiogenic agents, a new consensus statement was added stating the current lack of evidence.

Immunotherapy. Although the phase IB KEYNOTE 028 study assessing the programmed cell death-protein 1 blocker pembrolizumab in solid tumors included nine pulmonary carcinoids, only one responded (for 7 mo) based on the Response Evaluation Criteria in Solid Tumors criteria.[96]

Follow-Up
The long duration until recurrence after curative resection in GEP-NET has been recognized.[97,98] and many members of this consensus article had participated in forming the CommNETs and NANETS guidelines for routine surveillance after curative surgery in this population.[99] For LNET, a retrospective study evaluating rates of recurrence in 337 patients (86% TC,14% AC) who underwent resection at Memorial Sloan- Kettering Cancer Center, New York City, NY, reported that only nine of 291 TC (3%) recurred, with a median time to recurrence of 50 months (range 9–141).[80] Among the 268 patients with node-negative TC, only six (2%) recurred; of the 23 node-positive TC, there were three recurrences. For AC, 12 of 46 patients (26%) recurred, with a median time of 22 months (range 2–83). Most relapses involved distant metastases. The authors state that routine surveillance imaging failed to detect a significant proportion of recurrences but recognize that this practice is recommended in many guidelines.

These findings suggest introduction of risk-stratified follow-up, with patients with node-negative TC least likely to benefit. The consensus of our expert panel was to modify the ENETS guidelines to reflect the risk conferred by stage and histology.

Person-Centered Care
The expert panel, led by patient advocates, discussed the paradigm shift in clinical practice whereby person-centered care should be at the core of LNET practice. Patients with NETs face many challenges, as do their clinicians in delivering best practice care. Despite being the single largest site, LNETs are perhaps the least well studied.[100] The barriers faced in diagnosis and management for patients with a rare tumor are especially difficult for patients with LNET, in which the care pathway differs widely around the world. In particular, the primary physician managing these patients is variably a respiratory physician (i.e., pulmonologist/ respirologist), lung/thoracic oncologist, or NET oncologist. Rural-urban disparities in incidence and outcomes of NETS have also been revealed.[101] Variation of practice is a source of great concern to patients.[102]

Common to patients with NETs of all sites are the issues of delayed diagnosis, geographic isolation, access to care provided by NET experts, and a heavy burden of disease over a protracted time, including physical, psychological, social, and financial strains.[102,103] Access to clinical trials has been a particular problem for both patients with LNETs and researchers, with extreme difficulty in sourcing funding and slow recruitment as common barriers.[103] Government funding, even for well-established medication, such as everolimus, is also difficult owing to the rarity of the condition.

Although there are no NET specific data, it is particularly reasonable to suggest that for a rare tumor, such as LNET, individualized care plans should be created by multidisciplinary teams at NET centers[104,105] in collaboration with patients. These plans, which address prognosis and available clinical trials, should be shared with primary care providers to help alleviate psychological and symptom strain.[106-109] Survivorship planning is also an area of major need.[108]

Critical Unanswered Questions for Future Direction
The panel discussed key questions for the care of patients with LNET. These centered on the key themes of understanding risk factors in development of LNETs, the role of modern imaging, and better understanding the optimal treatment options and care delivery pathways in these patients.

DISCUSSION
The heterogeneity of LNET, with clinical behavior ranging from indolent cancers with long-life expectancy to aggressive tumors,[87] makes standardization of care for patients diagnosed with having this rare tumor difficult. Comprehensive, practical, and evidence-based guidelines are important to aid multidisciplinary health care providers to deliver consistent care for all cancers but have a particular role for rare cancers, in which patients often encounter nonexperts, particularly at diagnosis. This raises the challenge of formulating recommendations in the absence of evidence, and for LNET in particular, decisions regarding how much to extrapolate from evidence generated in NETs originating inother primary sites. The formation of international, multidisciplinary expert groups, as has been undertaken for this project, is an acceptable way to provide comprehensive and representative consensus.

Improving person-centered care remains a primary goal for patients with NETs. Particularly for rare tumors, guidelines should address areas outside of traditional diagnosis and therapy, including access to health services and optimal care pathways. For LNETs, this would include defining the role of NET experts and local expert centers' access to clinical trials and access to all proven therapies. Optimizing clinical pathways for LNETs will require continued engagement from organizations, such as CommNETs and NANETS, that aim to aggregate and disseminate NETs expertise. Our group felt strongly that patients with LNET should have access to NET expert centers for best possible outcomes. Involvement of patients and advocates has been a key part of CommNETs' mission; input from patient

from the advocate members of CommNETs and NANETS was highly valuable in the current consensus process.

These guidelines are unique in several aspects. First, we intentionally brought together two major global neuroendocrine groups—CommNETs and NANETS. This cooperation was undertaken to enhance robust consideration of the data and harness experience from the geographic variation of practices around the world. PRRT is an excellent example of this, in which the various member countries had diverse experience with this therapy. Second, combining forces to produce guidelines saves repetition of effort and publication, including potential "one-upmanship." Having a single set of guidelines across Australia, Canada, New Zealand, and the United States should increase harmonization and reduce variation of practice, which is a source of great concern to patients. Increasing uniformity of care was also the rationale behind endorsement of existing ENETs guidelines rather than publishing new guidelines. As significant data had been published since the 2015 ENETS document was produced, an update was warranted but without the duplication of a "start-from- scratch" process. Our panel could therefore concentrate efforts on synthesizing information from more recent studies.

Most studies of localized LNET have been based on data from non-LNET lung cancers. Similarly, most reports of therapy for metastatic disease involve extrapolation from GEP-NETs, with studies including none or very small numbers of patients with LNET within a larger cohort of NETs from multiple other sites of origin. However, since the 2015 ENETS guidelines, we have seen the first clinical trials focused on LNETs and attention to stratification in mixed NET studies to allow conclusions to be drawn for individual diagnoses andclassifications. The difficulties of recruitment, as revealed by the early stoppage of the seminal SSA trial in LNET, only furthers the argument for global involvement of NET experts, which can be facilitated best through research collaborations and societies, such as Comm- NETs, NANETS, and ENETS working together. The next steps include harmonizing recommendations through active collaboration between these organizations.

Some major themes emerged from our evidence review and endorsement process. We were able to simplify the diagnostic algorithm to increase its usability and applicability in clinical practice. We discussed the low incidence of carcinoid syndrome and the low probability of LNET being part of the multiple endocrine neoplasia syndromes. In addition to updating the pathology

and staging standards, our group was able to make a strong statement on the limited use of CgA testing in this population. Unnecessary testing not only results in excessive use of valuable health care resources but also adds to patient and clinician anxiety. This is in keeping with current global campaigns, such as Choosing Wisely.[110]

On the basis of new data, we were able to make concrete recommendations for the use of more conventional cross-sectional imaging and functional imaging with SSTR-PET. We made an unequivocal statement regarding the lack of evidence supporting any adjuvant therapy for resected LNETs, despite this still being presented for consideration in the current National Comprehensive Cancer Network guidelines. We included four new statements covering the rising incidence and prevalence of LNET, use of external beam radiotherapy for palliation, and lack of evidence for antiangiogenic agents. Updated recommendations also clarified the role of PRRT and various classes of systemic agents in the treatment of metastatic disease.

During the evidence review, grading, and endorsement process, it was apparent that a number of clinical questions remained unanswered. Our group felt it imperative to include these issues, so it is clear that no conclusive data, or often no data at all, exist in this area. These areas should guide research planning, and it is our quest that data be available in these important domains for future consensus papers.

The recommendations in this guideline should be understood in the light of its limitations. Although the expert panel used their clinical experience to interpret the published data to endorse and/or create recommendations, they were limited by the paucity of LNET- specific data, which is likely owing to the rarity and heterogeneity of LNETs. Nonetheless, we were explicit when heterogeneous or low-quality data were used to guide the recommendations. Second, the practicality of applying these recommendations will likely be influenced by geographic, socioeconomic, and other disparities in access to care. Although the expert panel recognized practice variations and barriers to care for patients with LNETs, each recommendation will have to be interpreted in the individual context of the patient, clinician, and health system. Finally, we recognize that as new data emerge, guidelines such as this will need ongoing updating.

CONCLUSIONS

Through the consensus process, guidelines for the management of patients with local and metastatic LNETs have been updated to include both recent evidence and practice changes relating to technological and definitional advances. The guidelines provide clear evidence-based statements aimed at harmonizing the global approach to patients with LNETs based on the principles of person-centered and LNET-specific care. The importance of LNET-directed research and person-centered care throughout the diagnosis, treatment, and follow- up journey is emphasized along with directions for future collaborative research.

ACKNOWLEDGMENTS

References

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335–1342.

2. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121:589–597.

3. Cai B, Broder MS, Chang E, Burk C, Grzegorzewski KJ, Neary MP. PS01. 23: Epidemiology of neuroendocrine tumors (NET) of the lung in the US: analysis of 2 large insurance claims databases. J Thorac Oncol. 2016;11(suppl):S282–S283.

4. Caplin ME, Baudin E, Ferolla P, 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;26:1604–1620.

5. Fervers B, Burgers JS, Voellinger R, et al. Guideline adaptation: an approach to enhance efficiency in guideline development and improve utilisation. BMJ Qual Saf. 2011;20:228–236.

6. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol. 2014;32:1605–1619.

7. Oxford Centre for Evidence-Based Medicine. OCEBM Levels of Evidence Working Group. "The Oxford 2011 levels of evidence.". http://www.cebm.net/index. aspx?o 5653. Accessed December 12, 2017.

8. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10:1243–1260.

9. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest. 2017;151:193–203.

10. Barnes J, Johnson S, French J. Correlation of Ki-67 indices from biopsy and resection specimens of neuroendocrine tumours. Ann R Coll Surg Engl. 2017;99:193– 197.

11. Brokx HA, Paul MA, Postmus PE, Sutedja TG. Long-term follow-up after first-line bronchoscopic therapy in patients with bronchial carcinoids. Thorax. 2015;70:468– 472.

12. Filosso PL, Kidd M, Roffinella M, et al. The utility of blood neuroendocrine gene transcript measurement in the diagnosis of bronchopulmonary neuroendocrine tumours and as a tool to evaluate surgical resection and disease progression. Eur J Cardio Thorac Surg. 2018;53:631–639.

13. Malczewska A, Kidd M, Matar S, Kos-Kudla B, Modlin I. The failure of circulating chromogranin A as a biomarker of bronchopulmonary neuroendocrine neoplasia: a meta-analysis. Paper presented at: NANETS 2017 Symposium. October 19–21, 2017; Philadelphia, PA.

14. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18:525–534.

15. Lococo F, Margaritora S, Cardillo G, et al. Bronchopulmonary carcinoids causing Cushing syndrome: results from a multicentric study suggesting a more aggressive behavior. Thorac Cardiovasc Surg. 2016;64:172–181.

16. de Laat JM, Pieterman CR, van den Broek MF, et al. Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients. J Clin Endocrinol Metab. 2014;99:3325–3333.

17. Lecomte P, Binquet C, Le Bras M, et al. Histologically proven bronchial neuroendocrine tumors in MEN1: a GTE 51-case cohort study. World J Surg. 2018;42:143–152.

18. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97:2990–3011.

19. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86:5658–5671.

20. Oberg KE. The management of neuroendocrine tumours: current and future medical therapy options. Clin Oncol (R Coll Radiol). 2012;24:282–293.

21. Dromain C, de Baere T, Lumbroso J, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol. 2004;23:70–78.

22. Morse B, Jeong D, Thomas K, Diallo D, Strosberg JR. Magnetic resonance imaging of neuroendocrine tumor hepatic metastases: does hepatobiliary phase imaging improve lesion conspicuity and interobserver agreement of lesion measurements? Pancreas. 2017;46:1219– 1224.

23. Tirumani SH, Jagannathan JP, Braschi-Amirfarzan M, et al. Value of hepatocellular phase imaging after intravenous gadoxetate disodium for assessing hepatic metastases from gastroenteropancreatic neuroendocrine tumors: comparison with other MRI pulse sequences and with extracellular agent. Abdom Radiol (NY). 2018;43:2329–2339.

24. Sadowski SM, Neychev V, Millo C, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/ computed tomography for detecting gastro-enteropancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol. 2016;34:588–596.

25. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. J Nucl Med. 2018;59:66–74.

26. Dixon RK, Britt EJ, Netzer GA, et al. Ten-year single center experience of pulmonary carcinoid tumors and diagnostic yield of bronchoscopic biopsy. Lung. 2016;194:905–910.

27. Zhang R, Lee SM, Wigfield C, Vigneswaran WT, Ferguson MK. Lung function predicts pulmonary complications regardless of the surgical approach. Ann Thorac Surg. 2015;99:1761–1767.

28. Aydin E, Yazici U, Gulgosteren M, et al. Long-term outcomes and prognostic factors of patients with surgically treated pulmonary carcinoid: our institutional experience with 104 patients. Eur J Cardiothorac Surg. 2011;39:549–554.

29. Daddi N, Ferolla P, Urbani M, et al. Surgical treatment of neuroendocrine tumors of the lung. Eur J Cardiothorac Surg. 2004;26:813–817.

30. Filosso PL, Rena O, Donati G, et al. Bronchial carcinoid tumors: surgical management and long-term outcome. J Thorac Cardiovasc Surg. 2002;123:303–309.

31. Brown LM, Cooke DT, Jett JR, David EA. Extent of resection and lymph node assessment for clinical stage T1aN0M0 typical carcinoid tumors. Ann Thorac Surg. 2018;105:207–213.

32. Fox M, Van Berkel V, Bousamra M 2nd, Sloan S, Martin RC 2nd. Surgical management of pulmonary carcinoid tumors: sublobar resection versus lobectomy. Am J Surg. 2013;205:200–208.

33. Raz DJ, Nelson RA, Grannis FW, Kim JY. Natural history of typical pulmonary carcinoid tumors: a comparison of non-surgical and surgical treatment. Chest. 2015;147:1111–1117.

34. Yendamuri S, Gold D, Jayaprakash V, Dexter E, Nwogu C, Demmy T. Is sublobar resection sufficient for carcinoid tumors? Ann Thorac Surg. 2011;92:1774–1778 [discussion: 1778–1779].Barbe C, Murat A, Dupas B, et al Magnetic resonance imaging versus endoscopic ultrasonography for the detection of pancreatic tumours in multiple endocrine neoplasia type 1. *Dig Liver Dis*. 2012;44:228-234.

35. Ducrocq X, Thomas P, Massard G, et al. Operative risk and prognostic factors of typical bronchial carcinoid tumors. Ann Thorac Surg. 1998;65:1410–1414.

36. Mezzetti M, Raveglia F, Panigalli T, et al. Assessment of outcomes in typical and atypical carcinoids according to latest WHO classification. Ann Thorac Surg. 2003;76:1838–1842.

37. Okike N, Bernatz PE, Woolner LB. Carcinoid tumors of the lung. Ann Thorac Surg. 1976;22:270–277.

38. Schreurs AJ, Westermann CJ, van den Bosch JM, Vanderschueren RG, Brutel de la Riviere A, Knaepen PJ. A twenty-five-year follow-up of ninety-three resected typical carcinoid tumors of the lung. J Thorac Car diovasc Surg. 1992;104:1470–1475.

39. Guarino C, Mazzarella G, De Rosa N, et al. Pre-surgical bronchoscopic treatment for typical endobronchial carcinoids. Int J Surg. 2016;33(suppl 1):S30–S35.

40. Luckraz H, Amer K, Thomas L, Gibbs A, Butchart EG. Long-term outcome of bronchoscopically resected endobronchial typical carcinoid tumors. J Thorac Cardiovasc Surg. 2006;132:113–115.

41. Graff-Baker AN, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: maintaining survival and increasing the number of eligible patients. Surgery. 2014;156:1369–1377.

42. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? Surgery. 2016;159:320–333.

43. Morgan RE, Pommier SJ, Pommier RF. Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. Surgery. 2018;163:218–225.

44. Bi N, Shedden K, Zheng X, Kong FS. Comparison of the effectiveness of radiofrequency ablation with stereotactic body radiation therapy in inoperable stage I non-small cell lung cancer: a systemic review and pooled analysis. Int J Radiat Oncol Biol Phys. 2016;95:1378– 1390.

45. de Baere T, Tselikas L, Woodrum D, et al. Evaluating cryoablation of metastatic lung tumors in patients— safety and efficacy: the ECLIPSE Trial—interim analysis at 1 year. J Thorac Oncol. 2015;10:1468–1474.

46. Gobara H, Arai Y, Kobayashi T, et al. Percutaneous radiofrequency ablation for patients with malignant lung tumors: a phase II prospective multicenter study (JIVROSG-0702). Jpn J Rad. 2016;34:556–563.

47. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol. 2008;9:621– 628.

48. Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. Br J Radiol. 2017;90:20160732.

49. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: results of a phase 2 clinical trial. Cancer. 2017;123:3031–3039.

50. Chen JX, Rose S, White SB, et al. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. Cardiovasc Intervent Rad. 2017;40:69– 80.

51. Yang TX, Chua TC, Morris DL. Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases—a systematic review. Surg Oncol. 2012;21:299–308.

52. Kim E, Jeans E, Shinohara ET, Stavas MJ. Stereotactic body radiotherapy (SBRT) for metastatic and recurrent soft tissue and bone sarcomas. Int J Radiat Oncol Biol Phys. 2017;99:E754.

53. Herde RF, Kokeny KE, Reddy CB, et al. Primary pulmonary carcinoid tumor: a long-term single institution experience. Am J Clin Oncol. 2018;41:24–29.

54. Nussbaum DP, Speicher PJ, Gulack BC, et al. Defining the role of adjuvant chemotherapy after lobectomy for typical bronchopulmonary carcinoid tumors. Ann Thorac Surg. 2015;99:428–434.

55. Westin GFM, Alsidawi S, Leventakos K, Halfdanarson TR, Molina JR. Impact of adjuvant chemotherapy in non-metastatic node positive bronchial neuroendocrine tumors (BNET). J Clin Oncol. 2017;35(suppl 15):8533–8533.

56. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA, Tyr3] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res. 2017;23:4617–4624.

57. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur J Nucl Med Mol Imaging. 2016;43:1040–1046.

58. Parghane RV, Talole S, Prabhash K, Basu S. Clinical response profile of metastatic/advanced pulmonary neuroendocrine tumors to peptide receptor radionuclide therapy with 177Lu-DOTATATE. Clin Nucl Med. 2017;42:428–435.

59. Sabet A, Haug AR, Eiden C, et al. Efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in metastatic pulmonary neuroendocrine tumors: a dualcentre analysis. Am J Nucl Med Mol Imaging. 2017;7:74–83.

60. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125–135.

61. Bezjak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). Int J Radiat Oncol Biol Phys. 2002;54:719–728.

62. Chakravarthy A, Abrams RA. Radiation therapy in the management of patients with malignant carcinoid tumors. Cancer. 1995;75:1386–1390.

63. Kotecha R, Zimmerman A, Murphy ES, et al. Management of brain metastasis in patients with pulmonary neuroendocrine carcinomas. Technol Cancer Res Treat. 2016;15:566–572.

64. McDonald R, Ding K, Brundage M, et al. Effect of radiotherapy on painful bone metastases: a secondary analysis of the NCIC clinical trials group symptom control trial SC.23. JAMA Oncol. 2017;3:953–959.Bartsch DK, Waldmann J, Fendrich V, et al Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. *Br J Surg*. 2012;99:1234-1240.

65. Fazio N, Buzzoni R, Delle Fave G, et al. Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. Cancer Sci. 2018;109:174–181.

66. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT- 4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–977.

67. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 2017;18:1652–1664.

68. Chong CR, Wirth LJ, Nishino M, et al. Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. Lung Cancer. 2014;86:241–246.

69. Forde PM, Hooker CM, Boikos SA, et al. Systemic therapy, clinical outcomes, and overall survival in locally advanced or metastatic pulmonary carcinoid: a brief report. J Thorac Oncol. 2014;9:414–418.

70. Faure M, Niccoli P, Autret A, Cavaglione G, Mineur L, Raoul J. Systemic chemotherapy with FOLFOX in metastatic grade 1/2 neuroendocrine cancer. Mol Clin Oncol. 2017;6:44–48.

71. Ferrarotto R, Testa L, Riechelmann RP, et al. Combination of capecitabine and oxaliplatin is an effective treatment option for advanced neuroendocrine tumors. Rare Tumors. 2013;5:e35.

72. Spada F, Antonuzzo L, Marconcini R, et al. Oxaliplatin- based chemotherapy in advanced neuroendocrine tumors: clinical outcomes and preliminary correlation with biological factors. Neuroendocrinology. 2016;103:806–814.

73. Bello Roufai D, Planchard D, Walter T, et al. Antitumor efficacy of temozolomide in patients with metastatic pulmonary carcinoids. Paper presented at: 13th Annual European Neuroendocrine Tumor Society Conference. March 9–11, 2016; Barcelona, Spain.

74. Crona J, Fanola I, Lindholm DP, et al. Effect of temozolomide in patients with metastatic bronchial carcinoids. Neuroendocrinology. 2013;98:151–155.

75. Papaxoinis G, Syrigos K, Saif MW. New concepts in the treatment strategy of neuroendocrine tumors: the role of biotherapy. Discov Med. 2016;21:381–389.

76. Walter T, Planchard D, Bouledrak K, et al. Evaluation of the combination of oxaliplatin and 5-fluorouracil or gemcitabine in patients with sporadic metastatic pulmonary carcinoid tumors. Lung Cancer. 2016;96:68– 73.

77. Grande E, Capdevila J, Castellano D, et al. Pazopanib in pretreated advanced neuroendocrine tumors: a phase II, open-label trial of the Spanish Task Force Group for Neuroendocrine Tumors (GETNE). Ann Oncol. 2015;26:1987–1993.

78. Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008;26:3403–3410.

79. Xu J, Li J, Bai C, et al. An open-label phase Ib/II study of sulfatinib in patients with advanced neuroendocrine tumors (NCT02267967). Paper presented at: 14th Annual European Neuroendocrine Tumor Society Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. March 8–10, 2017; Barcelona, Spain.

80. Lou F, Sarkaria I, Pietanza C, et al. Recurrence of pulmonary carcinoid tumors after resection: implications for postoperative surveillance. Ann Thorac Surg. 2013;96:1156–1162.

81. Marchiò C, Gatti G, Massa F, et al. Distinctive pathological and clinical features of lung carcinoids with high proliferation index. Virchows Arch. 2017;471:713–720.

82. Swarts DR, Rudelius M, Claessen SM, et al. Limited additive value of the Ki-67 proliferative index on patient survival in World Health Organization-classified pulmonary carcinoids. Histopathology. 2017;70:412–442.

83. Joseph MG, Shibani A, Panjwani N, et al. Usefulness of Ki-67, mitoses, and tumor size for predicting metastasis in carcinoid tumors of the lung: a study of 48 cases at a tertiary care centre in Canada. Lung Cancer Int. 2015;2015:545601.

84. Wang H, Li Z, Sun W, et al. PUB034 automated quantification of Ki-67 index associates with pathologic grade and prognosis of pulmonary neuroendocrine tumors. J Thorac Oncol. 2017;12:S2376.

85. Fabbri A, Cossa M, Sonzogni A, et al. Ki-67 labeling index of neuroendocrine tumors of the lung has a high level of correspondence between biopsy samples and surgical specimens when strict counting guidelines are applied. Virchows Arch. 2017;470:153–164.

86. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018;31:1770–1786.

87. Pelosi G, Sonzogni A, Harari S, et al. Classification of pulmonary neuroendocrine tumors: new insights. Transl Lung Cancer Res. 2017;6:513–529.

88. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer. 2008;112:2447–2455.

89. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(suppl 5): e166S–e190S.

90. Alexander ES, Dupuy DE. Lung cancer ablation: technologies and techniques. Semin Intervent Radiol. 2013;30:141–150.

91. Bongiovanni A, Recine F, Riva N, et al. Outcome analysis of first-line somatostatin analog treatment in metastatic pulmonary neuroendocrine tumors and prognostic significance of 18FDG-PET/CT. Clin Lung Cancer. 2017;18:415–420.

92. Sullivan I, Le Teuff G, Guigay J, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. Eur J Cancer. 2017;75:259–267.

93. Reidy-Lagunes D, Kulke M, Wolin E, et al. PUB119 lanreotide in patients with lung neuroendocrine tumors: the randomized double-blind placebo-controlled international phase 3 SPINET study. J Thorac Oncol. 2017;12:S1516–S1517.

94. Kordatou Z, Papaxoinis G, McCallum L, et al. Efficacy of the combination of capecitabine and temozolamide in patients with advanced pulmonary carcinoid tumors: a single institution experience. Paper presented at: UKI NETS 14th National Conference. December 5, 2016; London, United Kingdom.

95. Tabaksblat E, Ladekarl M. Temozolomide-based second-line chemotherapy in patients with advanced bronchopulmonary neuroendocrine tumours. Paper presented at: 13th Annual ENETS conference. March 9–11; Barcelona, Spain.

96. Mehnert J, Rugo H, O'Neil B, et al. Pembrolizumab for patients with PD-L1–positive advanced carcinoid or pancreatic neuroendocrine tumors: results from the KEYNOTE-028 study. Ann Oncol. 2017;28(suppl 5): v142–v157.

97. Singh S, Chan D, Moody L, et al. Recurrence in resected gastroenteropancreatic neuroendocrine tumors. JAMA Oncol. 2018;3:583–585.

98. Chi W, Warner RR, Chan DL, et al. Long-term outcomes of gastroenteropancreatic neuroendocrine tumors. Pancreas. 2018;47:321–325.

99. Singh S, Chan D, M D, Chan DL, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours. JAMA Oncol. 2018;4:1597–1604.

100. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated disease. J Thorac Oncol. 2017;12:425–436.

101. Hallet J, Law CH, Karanicolas PJ, Saskin R, Liu N, Singh S. Rural-urban disparities in incidence and outcomes of neuroendocrine tumors: a population-based analysis of 6271 cases. Cancer. 2015;121:2214–2221.

102. Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2017;3:43–53.

103. Kolarova T, Bouvier C, Caplin M, et al. Unmet needs in the global NETs patient community from the perspectives of patients, patient advocates, and NET health professionals. Paper presented at: 6th Annual Asia Pacific Neuroendocrine Tumour Society. November 9–11, 2018; Melbourne, Australia.

104. Feinberg Y, Law C, Singh S, Wright FC. Patient experiences of having a neuroendocrine tumour: a qualitative study. Eur J Oncol Nurs. 2013;17:541–545.

105. Singh S, Law C. Multidisciplinary reference centers: the care of neuroendocrine tumors. J Oncol Pract. 2010;6:e11–e16.

106. Gilligan T, Coyle N, Frankel RM, et al. Patient-clinician communication: American Society of Clinical Oncology consensus guideline. Obstet Gynecol Surv. 2018;73:96– 97.

107. Gilligan T, Bohlke K, Baile WF. Patient-clinician communication: American Society of Clinical Oncology consensus guideline summary. J Oncol Pract. 2018;14:42–46.

108. Mayer DK, Nekhlyudov L, Snyder CF, Merrill JK, Wollins DS, Shulman LN. American Society of Clinical Oncology clinical expert statement on cancer survivorship care planning. J Oncol Pract. 2014;10:345– 351.

109. Peppercorn JM, Smith TJ, Helft PR, et al. American Society of Clinical Oncology statement: toward individualized care for patients with advanced cancer. J Clin Oncol. 2011;29:755–760.

110. Levinson W, Kallewaard M, Bhatia RS, et al. 'Choosing wisely': a growing international campaign. BMJ Qual Saf. 2015;24:167–174.

Appendix A. Ratings (Low = 0, High = 10) for Rigor of Development of ENETs Recommendations by Two Endorsement Panel Members[5]

	Rater 1	Rater 2	Total
Systematic methods were used to search for evidence	6	7	13
The criteria for selecting the evidence are clearly described	7	7	14
The strengths and limitations of the body of evidence are clearly described	7	7	14
The methods used for formulating the recommendations are clearly described	7	7	14
The health benefits, side effects, and risks have been considered in formulating the recommendations	5	6	11
There is an explicit link between the recommendations and the supporting evidence	7	6	13
The guideline has been externally reviewed by experts before its publication	7	7	14
A procedure for updating the guideline is provided	5	5	10
Total	51	52	103 (91%)

ENETS, European Neuroendocrine Tumor Society.

Appendix B. Oxford Center for Evidence-Based Medicine Level of Evidence and Grade of Recommendation[7] Adaptation

Levels of Evidence

Question	Step 1 (Level 1[a])	Step 2 (Level 2[a])	Step 3 (Level 3[a])	Step 4 (Level 4[a])	Step 5 (Level 5[a])
Adaptation of Oxford 2011 for LNETs Consensus[b]	Systematic review of randomized trials or n-of-1 trials[c] or single homogeneous RCT with good treatment effect (through upgrading[c])	Randomized trial or observational study with dramatic effect[c] or single comparative prospective cohort study or low-quality RCT (Rd Phase II)	Nonrandomized controlled cohort follow-up study[c,d] or single case-control study, phase II, or single cohort study (>20 pts) with dramatic effect (through upgrading[c])	Case-series, case-control studies, or historically controlled studies[c,d] or prospective and retrospective cohort studies (<20 pts)	Mechanism-based reasoning[c] or clinical opinion

Grades of Recommendation

A	Consistent level 1 studies in target population
B	Consistent level 2 or 3 studies or extrapolations[a] from level 1 studies in other settings
C	Level 4 studies or extrapolations[a] from level 2 or 3 studies in another treatment area in other settings
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

[a]Consistent level 2 or 3 studies or extrapolations from level 1 studies in other settings.
[b]Based on categories for "Does this intervention help? (treatment benefits)."
[c]Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small or level may be graded up if there is a large or very large effect size.
[d]A systematic review is generally better than an individual study.
LNET, lung neuroendocrine tumor; PICO, patient, intervention, control, outcome (evidence-based technique to frame and answer a clinical question); pts, patients; RCT, randomized controlled trial.