ORIGINAL ARTICLE

ENETS standardized (synoptic) reporting for neuroendocrine tumour pathology

Marie-Louise F. van Velthuysen¹ | Anne Couvelard² | Guido Rindi^{3,4,5} | Nicola Fazio⁶ | Dieter Hörsch⁷ | Els J. Nieveen van Dijkum⁸ | Günter Klöppel⁹ | Aurel Perren¹⁰

¹Department Pathology, Erasmus MC, Rotterdam, The Netherlands

²Service de Pathologie, Hôpital Bichat AP-HP et Université de Paris, Paris, France

³Section of Anatomic Pathology, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Roma, Italia

⁴Unit of Anatomic Pathology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia

⁵Roma European Neuroendocrine Tumor Society (ENETS) Center of Excellence, Roma, Italia

⁶Division of gastrointestinal medical oncology and neuroendocrine tumors, European Institute of Oncology (IEO), IRCCS, Milan, Italy

⁷CA Gastroenterologie, Zentralklinik Bad Berka GmbH, Bad Berka, Germany

⁸Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

⁹Department of Pathology, Consultation Center for Pancreatic and Endocrine Tumors, TU Munich, Munich, Germany

¹⁰Institute of Pathology, University of Bern, Bern, Switzerland

Correspondence

Marie-Louise F. van Velthuysen, Department Pathology, Erasmus MC, Rotterdam, The Netherlands. Email: m.vanvelthuysen@erasmusmc.nl

Abstract

In recent years the WHO classification of neuroendocrine neoplasms (NEN) has evolved. Nomenclature as well as thresholds for grading have changed leading to potential confusion and lack of comparability of tumour reports. Therefore, the European Neuroendocrine Tumour Society (ENETS) has set-up an interdisciplinary working group to develop templates for a pathology data set for standardised reporting of NEN. Experts of various disciplines, members of the ENETS Advisory Board, formed a taskforce that discussed and decided on the structure, content and the number of templates needed for reporting the most common NEN. The selection of the required items was based on the WHO classification of digestive system tumours, the WHO classification of tumours of the lung and mediastinum and on "ENETS standard of care" reports. The final proposal of the working group was approved by the ENETS Advisory Board. Templates for synoptic reporting were created for the seven most common NEN primary sites, that is, stomach, duodenum, jejunum-ileum, appendix, colon-rectum, pancreas, lung and mediastinum. In addition, a general template for reporting biopsies was designed. The templates allow the recording of the essential items on differentiation, proliferation (Ki-67 and mitosis), neuroendocrine features (positivity for chromogranin A and synaptophysin) and stage as well as several optional markers especially helpful for the distinction of neuroendocrine tumours (NET) from neuroendocrine carcinomas (NEC). In summary, this paper presents the content and development of synoptic reports for most sites of NEN by a multidisciplinary team of international experts in the field, which could help to improve unambiguous reporting of NEN.

KEYWORDS

NEC, NET, neuro endocrine neoplasm, pathology report, synoptic report

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1 | INTRODUCTION

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Pathological reports are the basis of diagnosis and treatment in the vast majority of malignancies including neuroendocrine neoplasms (NEN). The information conveyed in these reports changes over time depending on the reigning WHO classification. Traditionally, pathology reports are generated in a free text format. These reports vary from institution to institution and even between pathologists of an individual institution. There is therefore a need for standardised reporting.

The function of pathologists is to collect, process, synthesize and communicate morphological information that guides diagnosis and treatment of NEN. Important quality criteria for this process are accuracy, completeness, adherence to current guidelines and speed. The introduction of synoptic reporting (or structured reporting) has proven in multiple studies and tumour types to improve completeness and adherence to guidelines,¹ with slightly increased workload well tolerated by pathologists due to increased quality.

Synoptic (from Greek, synopsis; overview) reports have been introduced by national pathology societies over the last years including Australian (RCPA), British (RCPath) and American (CAP) societies. Synoptic reports (or structured reports) define both the minimal content (required data elements, RDE) as well as the structure and terminology.² Each required data element is named, followed by the "content", leading to a paired format. The College of American Pathologists (CAP) has been instrumental for implementation of synoptic reports and declared the use of these reports mandatory for CAP-accreditation.

Over the last years, the International Collaboration for Cancer Reporting (ICCR) has been founded, sponsored by increasing numbers of national pathology societies. The ICCR aims to define internationally accepted synoptic reports of the main cancer types, with a well-defined process to ensure broad consensus, reflection of the best evidence available and adaptation to novel WHO classifications.³ In subsequent years, ICCR will provide reports on various tumour types in an increasing number of languages (in 2021 English, Spanish, Portuguese, and French). Templates for reports on NEN from different organs will follow, when templates for the more frequent tumour types have been implemented.

As an interdisciplinary society, ENETS has contributed significantly to development of the classification, and grading of NEN as well as to the definition of content of pathology reports for NEN by issuing consensus- and standard of care guidelines.⁴⁻⁷ To bridge the timespan until publication of ICCR-guidelines for well differentiated NEN (neuroendocrine tumours [NET]), ENETS decided to set up pathology reporting guidelines for NET (well differentiated neuroendocrine tumours) as well as NEC (neuroendocrine carcinomas). Application of ICCR-guidelines of carcinomas of the gastrointestinal tract for NEC is a valid alternative; however, these guidelines cannot be used for NET.

2 | METHOD

An international working group of the ENETS advisory board was initiated in 2018. In a workshop during the ENETS Advisory Board Meeting in Mallorca, the working group decided to develop synoptic/structured reports for the most frequent gastro-enteropancreatic NEN and thoracic NEN, applicable to resection as well as biopsy specimens.

To define required data elements, the respective WHO classifications^{8,9} as well as the requirements defined in the "ENETS standards of care in pathology¹⁰⁴ were used. Only findings based on widely available methods were defined as mandatory, more novel techniques and the use of novel biomarkers were defined as optional. A structure and first draft of the report for pancreatic NET (PanNET) was elaborated in the working group and approved by the interdisciplinary ENETS Advisory Board Meeting in Mallorca.

Consensus was reached for the structure of the ENETS synoptic reports as well as for the following reports to be developed: Gastric NEN, duodenal NEN, jejuno-Ileal NEN, appendiceal NEN, colorectal NEN, pancreatic NEN and thoracic NEN, as well as for a generic report for small biopsies independent from their anatomical site.

For reasons of usability, it was decided to use Microsoft Word templates with dropdown options to generate the reports.

In several iterations the working group has developed these reports and the results were presented to the entire Advisory Board during the 2019 meeting in Vienna. After approval by the Advisory Board, the reports have been made available to all ENETS Centres of Excellence (CoE) for consultation until June 2020, and minor adaptations have been implemented by the working group based on suggestions from this consultation. Final changes have been made by the working group to standardise nomenclature among all documents in 2021.

Updates of the synoptic report templates are planned and will be initiated by the ENETS Executive Committee, if required by changes of the WHO or TNM classifications.

3 | RESULTS

Eight templates for standardised reports were constructed. One general template for biopsies and seven site-specific templates for resection specimens. All templates had the same basic structure starting with a summary including the diagnosis, followed by headings on tumour type, biomarkers, and optional markers, permitting the classification of the NEN. For site-specific templates for resections the pTNM classification was added to the summary, followed by a heading on clinics and macroscopy. Items for local tumour extension were added to the heading of the items needed to classify the tumour type and a heading for vascular invasion, perineural invasion and lymph node status was included in these templates. Furthermore, specific items were added to the site-specific templates.

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In all templates, items on differentiation, necrosis, mitotic count, Ki-67 index and positivity for chromogranin A and synaptophysin were incorporated as a minimal data set, with keratin, SSTR2, P53, RB and hormone expressions as optional markers.

Site specific items were:

- 1. Different tumour nomenclature in thoracic-NEN
- The type of NEN for gastric NET (type 1 in the background of atrophic gastritis, type 2 for NET due to other causes of hypergastrinaemia and type 3 for NET without hypergastrinaemia).
- 3. DAXX and ATRX staining for pancreatic NET
- 4. Size of the biggest lymph node metastasis in small intestinal NET
- 5. Depth of extension into the mesoappendix for appendiceal NET

The immunohistochemical results for biomarkers, if present, are reported as percentage of positive tumour cells except for reporting of p53, RB and SSTR2 where the options in the dropdown menus guide the interpretation of the staining pattern. For example, for P53 staining mutational pattern is to be discriminated from wild-type pattern, 0% or more than 90% staining of tumour cells both suggesting the presence of a *p53* mutation, while all other staining patterns are compatible with wild-type *p53*.¹⁰

The templates are available on the ENETS website (www.enets. org) for all ENETS members.

4 | DISCUSSION

NEN are most frequently found in the lung, mediastinum, gastrointestinal tract, and pancreas. Although many organs are affected, NEN are rare tumours, and also show site specific characteristics. Nomenclature of NEN has been evolving in the last decades, in some instances adding to the confusion of interpretation of pathology reports. However, it has become clear that a limited set of parameters defines clinically relevant patient groups. In 2004 the WHO classification of thoracic NEN, based on mitotic count, was introduced and has not been changed since then.¹¹ In 2010, the WHO classification of gastrointestinal and pancreatic NEN introduced the concept of well and poorly differentiated NEN, that is, NET and NEC, respectively, and also graded these NEN on the basis of the Ki-67 index in NET G1 and G2 and NEC G3.¹¹ The revised WHO classifications in 2017⁹ and 2019⁸ introduced the concept of NET G3 in the pancreas and gastrointestinal tract and exempted the NEC from any grading. These classifications use different nomenclature and different thresholds for separating patient groups, but similar features and biomarkers are used. In a recent publication Zandee et al.¹² showed that if these parameters were present in the report the tumours could be classified according to recent standards irrespective of the nomenclature used in the pathology report, or the reigning WHO classification at the time the report was made, thus demonstrating the relevance of a minimal dataset for these tumours.

The developed templates contain the elements stated in the ENETS pathology consensus guidelines for the standards of care.⁴ The biomarkers define the neuroendocrine nature of the tumour (chromogranin A and synaptophysin), the differentiation of the tumour (well differentiated vs. poorly differentiated) and the proliferative activity (Ki-67 index, mitotic count, and necrosis). Since various grading thresholds for proliferative indices exist in the different WHO-classifications, the templates ask for the raw numbers so that the reports remain usable if threshold values should change in future classifications. For similar reasons, the other biomarkers are scored in percentage of positive cells. This could prove important for the classification of mixed tumours (MiNEN) in the future. There has been some debate for using the H-index for scoring these immunohistochemical staining results,¹³ but this proved to be too cumbersome in daily practice to be incorporated in the templates. A similar strategy is used for the building blocks of TNM classification, for example, numbers of lymph nodes examined and numbers of lymph nodes with metastasis are both registered. Preserving the capacity to generate not only N-stage according to TNM but also lymph node ratio, or minimal numbers of lymph nodes examined at each site.

In view of future developments, some optional biomarkers are included in the templates that at the time of development were not part of the standards of care. P53 and RB are thus incorporated as optional biomarkers as they emerge as helpful in the differential diagnosis of NET G3 versus NEC. The immunohistochemical staining patterns for these proteins reflect the underlying molecular changes that seem to be important in the clinical behaviour as NEC and also predicting therapy response as is suggested for tumours with RB mutations as often seen in small cell carcinoma.¹⁴ ¹⁵

The template for pancreatic NEN also allows, in addition to the above-mentioned biomarkers, to record the staining patterns for DAXX and ATRX as the staining pattern of these two proteins reflects the mutational status of the underlying genes. A mutation in one of these genes is associated with an adverse outcome¹⁶ and can be found in NET G3 but excludes NEC.¹⁷ The dropdown menus for reporting the biomarkers reflecting the mutational status of the genes described guide the user to report the results in this light.

Clinical data are limited to an absolute minimum in the templates, encompassing only the site of origin of the biopsy or the resection. Impending challenges are to see if and how these templates will be implemented in daily practice in different centres and countries, to measure their effect and see if they are indeed an important improvement.

5 | CONCLUSION

As NEN are rare lesions occurring in many sites and as nomenclature and classification of NEN are rapidly evolving, it is especially important that essential pathological parameters are communicated unambiguously. This publication provides synoptic reports for NEN of the most common localisations, and thus meets an urgent need for standardised NEN reporting.

CONFLICT OF INTERESTS

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Marie-Louise van Velthuysen, Anne Couvelard, Els J. Nieveen van Dijkum, Günter Klöppel and Aurel Perrenhave no conflicts of interest. Guido Rindi has received speakers fees from AAA and is consultant for Bracco. Nicola Fazio has received speakers fees from AAA, Hutchinson MediPharma, Merck and Novartis. Dieter Hörsch has received personalfees and grants from Lexicon Pharmaceuticals, Inc., Ipsen Pharmaceuticals, Inc., Novartis Pharmaceuticals, Inc., and Pfizer Pharmaceuticals, Inc., and advisory board honoraria from Advanz Pharma USA.

AUTHOR CONTRIBUTIONS

Marie-Louise van Velthuysen: Conceptualization; Data curation; Methodology; Project administration; Writing – original draft; Writing – review & editing. Anne Couvelard: Conceptualization; Writing – review & editing. Guido Rindi: Conceptualization; Writing – review & editing. Nicola Fazio: Conceptualization; Writing – review & editing. Dieter Hoersch: Writing – review & editing. Els Nieveen van Dijkum: Conceptualization; Writing – review & editing. G. Kloeppel: Conceptualization; Writing – review & editing. Aurel Perren: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

PEER REVIEW

The peer review history for this article is available at https://publo ns.com/publon/10.1111/jne.13100.

DATA AVAILABILITY

The proposed templates of synoptic reports for pathology will be publically available on the ENETS website: www.enets.org.

ORCID

Marie-Louise F. van Velthuysen ^b https://orcid. org/0000-0003-0435-9494 Anne Couvelard ^b https://orcid.org/0000-0002-6316-1210 Guido Rindi ^b https://orcid.org/0000-0003-2996-4404 Nicola Fazio ^b https://orcid.org/0000-0001-6869-0704

Els J. Nieveen van Dijkum ២ https://orcid.

org/0000-0002-3029-6071

Günter Klöppel https://orcid.org/0000-0002-6688-086X Aurel Perren https://orcid.org/0000-0002-6819-6092

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APPENDIX

ENETS ADVISORY BOARD MEETING PARTICIPANTS IN 2018

Arnold, R. (Zentrum für Innere Medizin, Universitätsklinikum Marburg, Marburg, Germany); Bartsch, D. K. (Department of Visceral-, Thoracic- and Vascular Surgery at the Philipps-University Marburg, Marburg, Germany); Belli, S.H. (Instituto Alexander Fleming, Buenos Aires, Argentina); Borbath, I. (Department of Hepato-Gastroenterology, Cliniques universitaires saint-Luc, Bruxelles, Belgium); Caplin, M. (Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free Hospital and University College London, London, United Kingdom); Castaño, J.P. (Maimonides Biomedical Research Institute of Córdoba (IMIBIC), Reina Sofia University Hospital, University of Córdoba, Córdoba, Spain); Chen, J. (Center for Neuroendocrine Tumors, Fudan University Shanghai Cancer Center / Department of Oncology, Shanghai Medical College, Fudan University / Pancreatic Cancer Institute, Fudan University / Shanghai Pancreatic Cancer Institute, Shanghai, China); Costa, F.P. (Centro de Oncologia of Hospital Sírio Libanês, Sao Paulo, Brazil); de Herder W.W. (Department of Internal Medicine, Section of Endocrinology, Erasmus MC, Rotterdam, the Netherlands); Deroose, C.M. (University Hospitals Leuven, Nuclear Medicine and KU Leuven, Department of Imaging and Pathology, Nuclear Medicine & Molecular Imaging, Leuven, Belgium); Dromain, C. (Department of Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland); Faggiano, A. (Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy); Falconi, M. (Department of Surgery, Università Vita-Salute, San Raffaele Hospital IRCCS, Milan, Italy): Falkerby, J. (Department of oncology and endocrine tumors, Uppsala University Hospital, Uppsala, Sweden); Frilling, A. (Imperial College London, Department of Surgery and Cancer, Hammersmith Hospital, London, United Kingdom); Garcia-Carbonero, R. (Department of Oncology, Hospital Universitario Doce de Octubre, Imas12, UCM, Madrid, Spain); Grande, E. (Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain); Grozinsky-Glasberg, S. (Neuroendocrine Tumor Unit, Endocrinology & Metabolism Department, Division of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel); Hand, P. (London North West University Healthcare Trust, London, United Kingdom); Hicks, R.J. (Neuroendocrine Service, the Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia); Howe, J.R. (Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA); Jensen, R.T. (Gastrointestinal Cell Biology Section, Digestive Disease Branch, National Institute of Health, Bethesda, USA); Kolarova, T. (International Neuroendocrine

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Cancer Alliance, Sofia, Bulgaria); Kos-Kudła, B. (Department of Endocrinology and Neuroendocrine Tumors, Medical University of Silesia, Katowice, Poland); Koumarianou A. (National and Kapodistrian University of Athens, Hematology Oncology Unit, 4th Department of Internal Medicine, Athens, Greece); Krejs, G.J. (Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria); Krenning, E.P. (Erasmus MC, Cyclotron Rotterdam BV, Rotterdam, the Netherlands); Krishna, B.A. (Nuclear Medicine department, Lilavati Hospital and Research Centre, Mumbai, India); Leyden, S. (Neuroendocrine Cancer Australia, Blairgowrie, Australia); Masui, T. (Kyoto University, Kyoto, Japan); Niederle, B. (Department of Surgery, Medical University of Vienna, Vienna, Austria); Öberg, K. (Department of Endocrine Oncology, University Hospital Uppsala, Uppsala, Sweden); O'Toole, D. (National Centre for Neuroendocrine Tumours, St. James's and St. Vincent's University Hospitals & Trinity College Dublin, Dublin, Republic of Ireland); Pape, U.-F. (Department of Internal Medicine and Gastroenterology, Asklepios Klinik St. Georg, Asklepios Tumorzentrum Hamburg, Hamburg, Germany); Pavel, M. (Department of Medicine 1, Universitätsklinikum Erlangen, Erlangen, Germany); Prasad, V. (Department of Nuclear Medicine, University Ulm, Ulm, Germany); Ramage, J.K. (Kings Health Partners NET Centre, Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom / Hampshire Hospitals NHS foundation trust, Hampshire, United Kingdom); Reed, N.S. (Beatson Oncology Centre (BOC), Glasgow, United Kingdom); Rinke, A. (Philipps University Marburg and University Hospital Gießen and Marburg (UKGM), Division of Gastroenterology and Endocrinology, Marburg. Germany); Rothmund, М. (Philipps-Universität Marburg, Marburg, Germany); Ruszniewski, P. (Department of Gastroenterology-Pancreatology, Beaujon Hospital and Université de Paris, Clichy, France); Singh, S. (Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Canada); Sundin, A. (Department of Surgical Sciences, Uppsala University, Radiology & Molecular Imaging, Uppsala University Hospital, Uppsala, Sweden); Toumpanakis, C. (Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free Hospital and University College London, London, United Kingdom); Valle, J.W. (Department of Medical Oncology, University of Manchester/The Christie NHS Foundation Trust, Manchester, United Kingdom); Verslype, C. (University Hospitals Leuven and KU Leuven, Leuven, Belgium); Vullierme, M.P. (Department of Radiology, Hôpital Beaujon - Hôpitaux Universitaires Paris Nord Val de Seine, Paris Diderot-Paris 7 University / Université de Paris, Paris, France); Welin, S. (Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden); Wiedenmann, B. (Charité Universitätsmedizin Berlin, Berlin, Germany); Zhao, H. (CNETS, Beijing, China).