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A Population Based Pathology Analysis on Application of World Health Organization Nomenclature in Pulmonary Neuroendocrine Tumors

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Background

The WHO 2015 classification for pulmonary carcinoids, large cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC) is in essence unchanged compared to the previous one (1999 and 2004)[1].

This despite known limitations in the diagnostic process, such as:

- Infrequent exposure in daily pathology practice (carcinoids/LCNEC)
- Impossibility to classify carcinoids/LCNEC on limited material (biopsies)
- Different nomenclature systems (gastrointestinal vs. pulmonary)[2]

Study aims

1) **To analyze if the nomenclature used in daily practice to describe the diagnosis of pulmonary carcinoids, LCNEC and (non-small cell) carcinomas with immunohistochemical differentiation, is in line with the recommended WHO 1999/2004 classification terminology.**
2) **To examine differences between physicians and pathologists in interpretation of retrieved non-WHO nomenclature diagnoses.**

Methods:

Retrospective analysis of conclusions of pathology reports selected from PALGA (the Dutch Pathology Registry) from 01-2003 to 12-2012

Inclusion criteria for PALGA search:

- Anatomic location: lung/bronchus/pleura/mediastinum
- Primary tumor/metastasis: NET grade 1-3, LCNEC, (atypical/typical) carcinoid and all carcinomas with text keyword "endocrine".

Exclusion criteria used while screening conclusions:

- Non-pulmonary or undefined origin
- Without final conclusion (i.e. differential diagnosis)
- SCLC diagnosis
- Cases were selected for final revision (if applicable) or largest tissue specimen

Retrieved diagnoses were scored and clustered for the following variables:

- Diagnostic cluster: carcinoid, high-grade neuroendocrine carcinoma, carcinoma with neuroendocrine features/differentiation and neuroendocrine tumor n.o.s.
- Non-WHO nomenclature (i.e. is the terminology in accordance with the recommended WHO 2004 classification yes/no?). For recommended nomenclature all diagnoses were strictly compared with the WHO 2004 manual[1]

Online questionnaire non-WHO nomenclature:

- Non-WHO nomenclature diagnoses retrieved through the screening were presented to N=35 physicians and N=19 pathologists.
- Participants were requested to cluster the non-WHO nomenclature diagnoses into one of the WHO 2004 classification categories or as unknown[1].

Results

7989 conclusions were screened, after applying the exclusion criteria conclusions from 3216 unique patients were selected for analyses. This included N=3052 patients with a conclusive diagnosis.

15% of retrieved diagnoses had applied non-WHO nomenclature

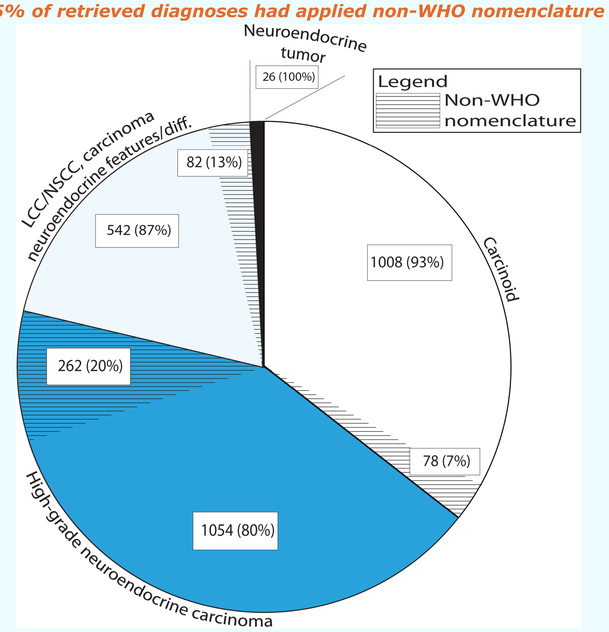

Figure 1: Overview of retrieved diagnoses from PALGA between 2003-2012, clustered by diagnoses category and assessment of (non)-WHO nomenclature.

Non-WHO nomenclature diagnoses retrieved from pathology report conclusions

Table 1a. Diagnoses selected by screener as non-WHO nomenclature

Retrieved diagnosis	Number
Low grade/well diff. neuroendocrine tumor/ca. (carcinoid)	34
Low grade neuroendocrine tumor/ca.	10
Neuroendocrine tumor/carcinoid	6
Well diff. neuroendocrine tumor/ca.	4
Neuroendocrine tumor grade I	6
Neuroendocrine tumor grade II	7
Intermediate diff. neuroendocrine ca.	5
Neuroendocrine tumor (n.o.s.)	26

Abbreviations:
Ca., carcinoma; n.o.s., not otherwise specified;
Diff, differentiation

Table 1b. Diagnoses selected by screener as non-WHO nomenclature

Retrieved diagnosis	Number
Non-small cell neuroendocrine ca.	47
Poorly diff. neuroendocrine non-small cell ca.	11
High-grade neuroendocrine ca, non-small cell	6
Neuroendocrine ca.(n.o.s.)	102
High-grade neuroendocrine tumor/ca.	42
Poorly diff. neuroendocrine ca.	36
Neuroendocrine ca., intermediate cell type	18
Ca. neuroendocrine features	25
Poorly diff. carcinoma neuroendocrine features	27
Ca. neuroendocrine diff.	11
Poorly diff. ca. neuroendocrine diff.	13
Ca. with AdC, SqCC and neuroendocrine component	4

Non-WHO nomenclature is more often established on small tissue specimens

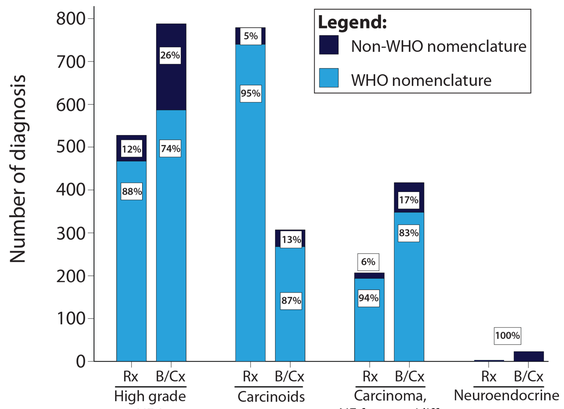

Figure 2: Overview of retrieved diagnoses clustered for diagnosis category and type of sampling method.

Abbreviations:
Rx, resection; B/Cx, biopsy/cytology specimen; NE, neuroendocrine; NEC, neuroendocrine carcinoma;
Diff, differentiation; n.o.s., not otherwise specified.

Uniform interpretation among physicians and pathologists is lacking in diagnoses described by non-WHO nomenclature

	Non-WHO nomenclature diagnoses that had ≥50% agreement	
Clustered cohorts	**Physicians**	**Pathologists**
Carcinoids (and neuroendocrine tumor)	1/8	2/8
High-grade neuroendocrine carcinomas	1/7	4/7
(LCC/NSCC) Carcinoma neuroendocrine features/diff.	2/4	3/4

- Physicians were unable to interpreted "neuroendocrine tumors grade I-II" whereas these diagnoses had >50% agreement among pathologists.
- Physicians were unable to interpreted neuroendocrine non-small cell carcinomas and high grade neuroendocrine tumors/carcinomas whereas pathologists had more than 50% agreement.

Conclusions

- **In 15% of pulmonary neuroendocrine tumors other than SCLC, a non-WHO nomenclature diagnoses was given, this occurred more frequently on smaller tissue specimens**
- **Usage of non-WHO nomenclature may lead to misunderstanding among physicians and pathologists**
- **Whether nomenclature deviates from the WHO is due to pathologist's preferences or to difficulties fitting the current classification (on small tissue samples), remains to be examined.**

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References:
1. William D. Travis, Elizabeth Brambilla, H. Konrad Müller-Hermelink, Harris CC. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC press 2004.
2. Klimstra DS, Modlin IR, Coppola D et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010; 39: 707-712.