

# Neuroendocrine neoplasms in gynaecological malignancies

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## 1. What has changed?

Neuroendocrine neoplasms (NENs) can develop in most organs, including the female genital tract [1], due to the diffuse localisation of neuroendocrine cells throughout the body [2]. The classification of NENs has been based on various organ-specific terminologies and criteria. Therefore, it was difficult for physicians, patients, and pathologists to understand the bigger picture regarding NENs. Furthermore, it was almost impossible to extrapolate the findings obtained from one organ to another. However, in 2010, the World Health Organization (WHO) introduced a revolutionary universal classification system for the gastro-entero-pancreatic (GEP) tract [3]. This revision initially used NENs to describe both neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs). GEP-NENs can be classified into three types: (1) NETs, for well-differentiated NENs, (2) NECs, for poorly differentiated NENs, and (3) mixed adeno-NECs. This paved the way to the tumour-agnostic diagnosis of NENs. The principles of the common classification framework for NENs were also utilised in the WHO 2017 classification of pancreatic NENs [4] and the WHO 2019 classification for digestive system tumours [5] with some revisions.

The WHO modified the NEN categories for the female genital tract (Table 1). In the WHO 2014 classification for female reproductive organs [6], NENs of the uterine corpus, cervix, vagina, and vulva are divided into two tumour types: (1) low-grade NETs and (2) high-grade NECs. However, ovarian NENs are classified into four types: (1) carcinoid, (2) small-cell carcinoma of the ovary, pulmonary type (SCCOPT), (3) small-cell carcinoma of the ovary, hypercalcaemic type (SCCOHT), and (4) paraganglioma. In the latest WHO 2020 classification for female genital tumours [7], NENs are separated from sections on individual organs and are covered in an independent chapter. Except for ovarian carcinoids, four tumour types of NENs are proposed. Similar to that in the previous revision, the categorization for ovarian NENs did not follow pre-existing principles of classification. Although SCCOHT is not subcategorised as an NEN, an SWI/SNF-deficient malignancy due to inactivating somatic or germline *SMARCA4* mutations is found in almost all cases [8].

## 2. What is the problem?

There are three unsolved problems related to NENs in gynaecological malignancies: (1) non-categorisation of ovarian carcinoids as NETs, (2) difficulty in establishing a pathologic diagnosis, and (3) limited information regarding the treatment options for NENs.

In the WHO 2020 classification for female genital tumours, ovarian NETs are not introduced because of the excellent prognosis of low-grade NETs and limited evidence for tumour grading [7]. However, a study from the Kansai Clinical Oncology Group in Japan found that retrospective adaption of the GEP-NEN classification for ovarian NENs is feasible and well correlated with the prognosis of ovarian NENs [9]. The study examined 64 ovarian NENs through a central pathologic review using a common slide set (hematoxylin-eosin, Ki67, chromogranin A, synaptophysin, and/or NCAM1). Forty-eight of 64 samples were available for final data analysis (34 NETs, 14 NECs), excluding 13 cases (20%) of diagnostic discrepancy between two independent pathologic reviewers and three cases (5%) of SCCOHT. This study showed that ovarian NETs tended to behave in a benign fashion with metastatic and/or invasive potential. Therefore, it is desirable to categorise ovarian carcinoids into ovarian NETs in the next WHO revision.

The difficulty in establishing a pathologic diagnosis is applicable not only to ovarian NENs but also to tumours of the uterine cervix and corpus. Kuji *et al.* examined 71 cervical small-cell NECs through a central pathologic review and found that 19 cases (27%) did not involve small-cell NECs [10]. Matsumoto *et al.* studied 65 endometrial NECs through a central pathological review and found that 23 of 65 (35%) cases did not involve NECs [11]. These diagnostic discrepancies suggest that a new diagnostic marker is required for NENs.

To date, treatment strategies have been only established for cervical small-cell NECs based on the National Comprehensive Cancer Network guideline [12]; however, due to their rarity, the exact treatment for ovarian and endometrial NENs has not yet been identified. The Surveillance, Epidemiology, and End Results database lacks data on chemotherapy for SCCOHT and SCCOPT [13]. For endometrial NENs, the

**Table 1. Modifications of the WHO classification for tumours of the female genital tract from 2014 to 2020.**

Site	WHO 2014	WHO 2020
Ovary	Carcinoid	Ovarian carcinoid
	Small-cell carcinoma, hypercalcaemic type	Non-NEN*
	Small-cell carcinoma, pulmonary type	
	Paranglioma†	
Uterine corpus	Low-grade NET	
	High-grade NEC	NET
	Low-grade NET	Small-cell NEC
Uterine cervix	High-grade NEC	Large-cell NEC
	Adenocarcinoma admixed with NEC	Carcinoma admixed with NEC
	Small-cell NEC	
Vagina	Large-cell NEC	
	High-grade NEC	
Vulva	High-grade NEC	
	Merkel cell tumour‡	

\*Small-cell carcinoma, hypercalcaemic type was re-categorised into miscellaneous tumours of the ovary. †Paranglioma was re-categorised from miscellaneous tumours in ovarian tumours to Von Hippel-Lindau syndrome in genetic tumour syndromes of the female genital tract. ‡Merkel cell tumour was deleted from the subject index.

NEN, neuroendocrine tumour; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.

study by Schlechtweg *et al.* examining 364 cases of small-/large-cell NECs and NECs with carcinoma components using the National Cancer Database revealed data on only first-line adjuvant therapy (chemotherapy or radiation) without details of chemotherapeutic agents [14].

### 3. What do we need?

Achaete-scute family bHLH transcription factor 1 (ASCL1) and INSM transcriptional repressor 1 (INSM1) are promising diagnostic markers for lung NENs [15]. In lung tumours, the NOTCH1-HES1 signalling pathway represses neuroendocrine differentiation by inactivating INSM1 and ASCL1. The inactivation of INSM1 and ASCL1 promotes the expression of three neuroendocrine molecules: chromogranin A, synaptophysin, and NCAM1. In other words, the present immunohistochemical diagnostic markers are not a cause but a consequence of neuroendocrine differentiation. If we apply these upstream molecules for the diagnosis of gynaecological NENs, diagnostic accuracy is expected to be high.

Data on the diagnostic molecular pathology of NENs are needed. Historically, breakthroughs in molecular pathology for gynaecological neoplasms have changed the methods of diagnosis. In the past, DNA polymorphisms in hydatidiform moles and *FOXL2* mutation in adult-type granulosa cell tumours have been evaluated. Recently, *SMARCA4* mutation has been reported for SCCOHT. The combination of morphological and molecular approaches is a powerful tool to diagnose gynaecological NENs.

Generally, NETs respond well to surgical resection alone, whereas NECs have a short response duration to existing primary therapies and an extremely poor prognosis. Therefore, established adjuvant therapies and promising second-line treatments are needed. Due to the low incidence of gy-

naecological NENs, it is difficult to obtain new evidence. To change this situation, a paradigm shift from organ-specific to tumour-agnostic diagnosis and treatment is needed. In this way, promising targeted therapies traditionally used for tumours of other organs (such as octreotide for midgut NENs and sunitinib and everolimus for pancreatic NENs) may be utilised for gynaecological NENs.

### Author contributions

KK conceived and wrote an original draft. KN conceived, supervised review and edited the draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

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### Conflict of interest

The authors declare no conflict of interest.

### References

- [1] Kloppel G. Neuroendocrine neoplasms: dichotomy, origin and classifications. *Visceral Medicine*. 2017; 33: 324–330.
- [2] Montuenga LM, Guembe L, Burrell MA, Bodegas ME, Calvo A, Sola JJ, *et al.* The diffuse endocrine system: from embryogenesis to carcinogenesis. *Progress in Histochemistry and Cytochemistry*. 2003; 38: 155–272.

- [3] Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. Vol. 3. Lyon, France: IARC Press. 2010.
- [4] Lioyd RV, Osamura RY, Kloppel G, Rosai J. WHO classification of tumours of endocrine organs. Vol. 10. Lyon, France: IARC Press. 2017.
- [5] WHO Classification of Tumours Editorial Board. WHO classification of tumours. Digestive system tumours. Lyon, France: IARC Press. 2019.
- [6] Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. Vol. 6. Lyon, France: IARC Press. 2014.
- [7] WHO Classification of Tumours Editorial Board. WHO classification of tumors. Female genital tumours. Lyon, France: IARC Press. 2020.
- [8] Wang Y, Hoang L, Ji JX, Huntsman DG. SWI/SNF complex mutations in gynecologic cancers: molecular mechanisms and models. *Annual Review of Pathology*. 2020; 15: 467–492.
- [9] Kai K, Nasu K, Nishida H, Daa T, Shikama A, Shiozaki T, *et al*. Correlation of World Health Organization 2010 classification for gastroenteropancreatic neuroendocrine neoplasms with the prognosis of ovarian neuroendocrine neoplasms: Kansai Clinical Oncology Group-Protocol Review Committee/Intergroup Study. *Neuroendocrinology*. 2020; 111: 320–329.
- [10] Kuji S, Hirashima Y, Nakayama H, Nishio S, Otsuki T, Nagamitsu Y, *et al*. Diagnosis, clinicopathologic features, treatment, and prognosis of small cell carcinoma of the uterine cervix; Kansai Clinical Oncology Group/Intergroup study in Japan. *Gynecologic Oncology*. 2013; 129: 522–527.
- [11] Matsumoto H, Shimokawa M, Nasu K, Shikama A, Shiozaki T, Futagami M, *et al*. Clinicopathologic features, treatment, prognosis and prognostic factors of neuroendocrine carcinoma of the endometrium: a retrospective analysis of 42 cases from the Kansai Clinical Oncology Group/Intergroup study in Japan. *Journal of Gynecologic Oncology*. 2019; 30: e103.
- [12] Network NCC. Cervical cancer. 2021. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/cervical.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf) (Accessed: 28 March 2021).
- [13] Jamy O, Yaghmour G, Hare F, Martin MG. Population-based analysis of the clinical features of primary small cell carcinoma of the ovary. *Anticancer Research*. 2015; 35: 3091–3095.
- [14] Schlechtweg K, Chen L, St Clair CM, Tergas AI, Khoury-Collado F, Hou JY, *et al*. Neuroendocrine carcinoma of the endometrium: Disease course, treatment, and outcomes. *Gynecologic Oncology*. 2019; 155: 254–261.
- [15] Inamura K. Update on immunohistochemistry for the diagnosis of lung cancer. *Cancers*. 2018; 10: 72.