Table S8.1 Major clinicopathological features of neuroendocrine tumour (NET) at various anatomical sites[a] (continued on next page)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Head and neck							
Middle ear {30069842; 22964339; 27166275}	8240/3 8249/3	Well-differentiated (G1) and moderately differentiated (G2)	Middle ear and external auditory canal	Hearing loss, aural fullness, tonal tinnitus {30001283}	Exceedingly rare (few reported cases); middle ear tumours account for < 2% of ear tumours; fifth decade of life; M:F ratio: 2:1	Unknown	Unknown
Sinonasal tract, nasopharynx {17481837; 29103747; 26830400; 26622884; 30332658; 33474978; 33770323}	8240/3 8249/3	Well-differentiated (G1) and moderately differentiated (G2) (not recognized reproducibly)	n/a	n/a	Rare to extremely rare; metastasis from gastroenteropancreatic system or lung must be excluded	Unknown	Unknown
Oropharynx, oral cavity, and salivary glands {14720139; 21493041; 27840746; 28116178; 22614165; 23456649}	8240/3 8249/3	Well-differentiated (G1) and moderately differentiated (G2)	Base of the tongue; tonsil; uvula; floor of the mouth; retromolar region; sublingual, submandibular, and parotid glands	n/a	Exceedingly rare; 1–2% of salivary gland tumours	Unknown	Unknown
Hypopharynx, larynx, trachea, and parapharyngeal space {12071530; 15053292; 15098009; 15995505; 18617341; 19172557; 20580173; 20961285; 23397781; 24220389; 24596175; 26622884; 26854777; 26886629; 30974468; 31012344; 33167723}	8240/3 8249/3	Grade 1: typical carcinoid Grade 2: atypical carcinoid Grade 3: not recognized by any criteria presently	Supraglottic larynx most commonly	Hoarseness, dysphagia, sore throat, voice changes, haemoptysis, airway obstruction	Rare (< 1% of laryngeal tumours); grade 1, 5%; grade 2, majority; male > female; fifth to seventh decade of life	Association with tobacco smoking	Unknown
Thorax							
Lung	8240/3 8249/3	Typical carcinoid, atypical carcinoid	Central or peripheral airways	Asymptomatic or symptoms due to local growth; endocrine hyperfunction syndromes uncommon	< 0.1–1.5 cases/100 000 person-years; < 1% of all lung cancers; mostly typical carcinoid (70–90%); sixth decade of life; female prevalence	Not clear; some arising in DIPNECH and tumourlets; no clear association with smoking	Mutations of *MEN1*, *CBX6* of polycomb repressive complex 1 and *EZH2* of polycomb repressive complex 2; alterations of chromatin-remodelling genes
Thymus	8240/3 8249/3	Typical carcinoid, atypical carcinoid	Anterior mediastinum	Local mass symptoms: chest pain, cough, dyspnoea; Cushing syndrome and hypercalcaemia/ hypophosphataemia when functioning	2–5% of thymic neoplasms; fifth to sixth decade of life; male prevalence	25% in MEN1	Chromosomal recurrent aberrations occur especially in atypical carcinoids; *ATRX*/*DAXX* mutations
Digestive system							
Oesophagus	8240/3 8249/3	NET	Lower oesophagus	Incidental at endoscopy	Extremely rare (0.04–1% of all GEP-NENs); sixth to seventh decade of life; no sex bias	Unknown	Unknown
Stomach	8240/3 8249/3 8242/3 8156/3 8153/3 8241/3	ECL-cell NET (type 1 associated with CAG, type 2 associated with ZES/MEN1, type 3 sporadic), D-cell NET, G-cell NET, EC-cell NET	Corpus/fundus (ECL-cell and EC-cell NETs), antrum (G-cell and D-cell NETs)	No specific symptoms; rare ZES due to antral gastrinoma; hypergastrinaemia and low BAO and MAO	0.4 cases/100 000 person-years; seventh decade of life; female predominance; type 1 ECL-cell NETs are the most frequent	Type 1 ECL-cell NET: hypergastrinaemia due to CAG; type 2 ECL-cell NET: ZES-MEN1; type 3 ECL-cell NET: unknown	MEN1 LOH in sporadic ECL-cell NET; *MEN1* mutation in type 2 ECL-cell NET
Small intestine and ampulla	8240/3 8249/3 8156/3 8153/3 8241/3	D-cell NET, G-cell NET, EC-cell NET	Duodenum/ampulla (D-cell NET, G-cell NET), ileum (EC-cell NET)	No specific mass-related symptoms; possible transit obstruction and occlusion; vague persisting pain Hormonal syndromes: ZES by gastrinoma; somatostatinoma syndrome; carcinoid syndrome	1.2 cases/100 000 person-years; sixth to seventh decade of life; no sex bias	Unknown; a minority arise in the setting of hereditary cancer predisposition syndrome, e.g. MEN1, NF1	Duodenum and ampulla: *MEN1* mutation; small intestine: chromosome 18 deletion; CpG island methylation; *CDKN1B* mutation; whole-arm copy-number variations
Appendix	8240/3 8249/3 8241/3 8152/3	EC-cell NET, L-cell NET	Corpus to tip	Nonspecific symptoms; identified incidentally after surgery for appendicitis	0.5–0.6 cases/100 000 person-years; fifth most frequent GEP-NET; third to fourth decade of life, and in children; female prevalence	Unknown	Rare chromosome 18 deletions
Colorectum	8240/3 8249/3 8241/3 8152/3	L-cell NET, EC-cell NET	Anywhere	Nonspecific mass-related symptoms	1.2 cases/100 000 person-years in rectum; 0.2 cases/100 000 person-years in colon; sixth to seventh decade of life; no sex bias	Unknown	Unknown
Liver	8240/3 8249/3	NET	Anywhere	Nonspecific mass-related symptoms	Extremely rare; metastatic nature must be excluded; 0.4% of all resected hepatic primaries	Unknown; occasional patients have history of viral hepatitis	Unknown
Gallbladder and bile ducts	8240/3	NET	Gallbladder > bile ducts	Nonspecific mass-related symptoms	Extremely rare (0.21% of all NETs)	Unknown; some associated with VHL and MEN1	Unknown

BAO, basal acid output; CAG, chronic atrophic gastritis; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; EC, enterochromaffin; ECL, enterochromaffin-like; GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; GEP-NET, gastroenteropancreatic neuroendocrine tumour; LOH, loss of heterozygosity; MAO, maximal acid output; MEN1, multiple endocrine neoplasia type 1; n/a, not available; NF1, neurofibromatosis type 1; VHL, von Hippel–Lindau syndrome; ZES, Zollinger–Ellison syndrome.

[a]See also the relevant site-specific volumes of the WHO Classification of Tumours series: *Head and neck tumours* [[WHO Classification of Tumours Editorial Board. Head and neck tumours. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series, 5th ed.; vol. 9). https://publications.iarc.who.int/629.]], *Thoracic tumours* [[WHO Classification of Tumours Editorial Board. Thoracic tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.who.int/595.]], *Digestive system tumours* [[WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1). https://publications.iarc.who.int/579.]], *Female genital tumours* [[WHO Classification of Tumours Editorial Board. Female genital tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 4). https://publications.iarc.who.int/592.]], *Breast tumours* [[WHO Classification of Tumours Editorial Board. Breast tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 2). https://publications.iarc.who.int/581.]], *Urinary and male genital tumours* [[WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8). https://publications.iarc.who.int/610.]], and Skin tumours [[WHO Classification of Tumours Editorial Board. *Skin tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2023. (WHO classification of tumours series, 5th ed.; vol. 12). https://tumourclassification.iarc.who.int/chapters/64.]].

References: The in-text citations provided within curly brackets are PubMed reference numbers (PMIDs), searchable at https://pubmed.ncbi.nlm.nih.gov/.

Table S8.1 Major clinicopathological features of neuroendocrine tumour (NET) at various anatomical sites[a] (continued)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Female genital tract							
Ovary {28735441}	9091/1	Carcinoid (insular, trabecular, strumal, mucinous)	Anywhere	Usually an incidental finding in a dermoid cyst	Most common site for NETs in female genital tract; account for approximately 1% of ovarian neoplasms; fifth to sixth decade of life	Usually arise within teratomas; when pure they are considered monodermal teratomas; occasionally arise within other ovarian neoplasms, such as Sertoli–Leydig cell tumour, Brenner tumour, mucinous tumour, yolk sac tumour	Unknown
Fallopian tube	8240/3 8249/3	G1 NET, G2 NET	Anywhere	Usually an incidental finding	Extremely rare	Unknown	Unknown
Endometrium {28735441}	8240/3 8249/3	G1 NET, G2 NET	Anywhere	Abnormal vaginal bleeding	Extremely rare	Unknown	Unknown
Cervix {28735441}	8240/3 8249/3	G1 NET, G2 NET	Anywhere	Mass or abnormal vaginal bleeding	Extremely rare	Rare cases associated with HPV infection	Occasionally associated with persistent HPV infection
Vagina {28735441}	8240/3 8249/3	G1 NET, G2 NET	Anywhere	Mass or abnormal vaginal bleeding	Extremely rare	Unknown	Unknown
Vulva {28735441}	8240/3 8249/3	G1 NET, G2 NET	Anywhere	Vulvar mass	Extremely rare	Unknown	Unknown
Breast							
Breast	8240/3 8249/3	NET; Nottingham grading G1 or G2	Anywhere	Not different from invasive carcinoma NOS; possible ectopic hormone production	Rare (< 1% of breast carcinomas); sixth to seventh decade of life	Probably the same etiology as other ER-positive breast carcinomas	Frequent mutation of *FOXA1*, *TBX3*, *GATA3*, and *ARID1A*
Urinary and male genital tracts							
Kidney {33613455; 30732641}	8240/3 8249/3	NET	Anywhere in the kidney, with overrepresentation in horseshoe kidneys	Nonspecific mass-related symptoms	Extremely rare	Unknown	Chromosome 3p21 LOH in subsets
Urinary tract {27334654; 33301750}	8240/3 8249/3	NET	Bladder	Haematuria, irritative voiding symptoms	Few cases described	Unknown	Unknown
Prostate {33301750; 31415779}	8240/3 8249/3	Not defined	Prostate	Neuroendocrine differentiation frequent in prostate adenocarcinomas	Existence of pure prostate NET is debated	Unknown	Unknown
Testis {28559773; 26027014; 18316560; 22347748}	8240/3 8249/3	Carcinoid (EC-cell NET)	Left testis; rarely bilateral	Occurs in mature teratoma; enlargement, pain, hydrocoele, and (rarely) cryptorchidism; rare carcinoid syndrome	Rare (1% of testicular tumours); third to fifth decade of life	Unknown	Isochromosome 12p overrepresentation
Skin							
Skin {28169866}	8240/3 8249/3	Carcinoid, NET	Anterior body (chest, abdomen)	Metastasis from gastroenteropancreatic system or lung must be excluded	Extremely rare; sixth to seventh decade of life (range: 40–79 years); no sex bias	Unknown	Unknown

BAO, basal acid output; CAG, chronic atrophic gastritis; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; EC, enterochromaffin; ECL, enterochromaffin-like; GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; GEP-NET, gastroenteropancreatic neuroendocrine tumour; LOH, loss of heterozygosity; MAO, maximal acid output; MEN1, multiple endocrine neoplasia type 1; n/a, not available; NF1, neurofibromatosis type 1; VHL, von Hippel–Lindau syndrome; ZES, Zollinger–Ellison syndrome.

[a]See also the relevant site-specific volumes of the WHO Classification of Tumours series: *Head and neck tumours* [[WHO Classification of Tumours Editorial Board. Head and neck tumours. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series, 5th ed.; vol. 9). https://publications.iarc.who.int/629.]], *Thoracic tumours* [[WHO Classification of Tumours Editorial Board. Thoracic tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.who.int/595.]], *Digestive system tumours* [[WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1). https://publications.iarc.who.int/579.]], *Female genital tumours* [[WHO Classification of Tumours Editorial Board. Female genital tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 4). https://publications.iarc.who.int/592.]], *Breast tumours* [[WHO Classification of Tumours Editorial Board. Breast tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 2). https://publications.iarc.who.int/581.]], *Urinary and male genital tumours* [[WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8). https://publications.iarc.who.int/610.]], and Skin tumours [[WHO Classification of Tumours Editorial Board. *Skin tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2023. (WHO classification of tumours series, 5th ed.; vol. 12). https://tumourclassification.iarc.who.int/chapters/64.]].

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