Table S8.5 Major clinicopathological features of large cell neuroendocrine carcinoma (LCNEC) at various anatomical sites[a] (continued on next page)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Head and neck							
Sinonasal tract and nasopharynx {30191506; 31186531; 33433884; 22082601; 30191506; 27392929; 26735857; 25727332; 2208260}	8013/3	None	Paranasal sinuses > nasal cavity > nasopharynx	Nonspecific symptoms; advanced local and distant disease; rare paraneoplastic syndromes; 70% present at stage IV	< 10 cases reported	Smoking; rare association with HR-HPV and previous irradiation; nasopharyngeal cases EBV-associated (3 cases)	*TP53* mutation; loss of various members of SWI/SNF complex (*ARID1A*, *SMARCA4*, and, to a lesser extent, *SMARCB1*) and of *IDH2* have been described; among sinonasal NECs, *IDH2*-mutated cases are LCNECs and *ARID1A*-proficient, whereas SCNECs are preferentially *ARID1A*-mutated and *IDH2*-proficient
Oropharynx, oral cavity, and salivary glands {22082601; 22024350; 26735857; 31463946; 30475447; 27818885; 22718848; 33544384; 22024350; 23953500}	8013/3	None	Most frequent in tonsil and oropharynx; major salivary glands	Nonspecific symptoms; advanced local and distant disease	< 10 cases reported Salivary glands: 13 cases reported, all in the parotid and submandibular glands; M > F; mean age: 68 years	Smoking; rare association with HR-HPV and previous irradiation Salivary glands: unknown	Unknown; salivary glands: some data on p53 and RB1 losses
Hypopharynx, larynx, trachea, and parapharyngeal space {22082601; 31437725; 22024350; 24596175}	8013/3	None	Larynx (supraglottis/ epiglottis); very rare in other sites	Mostly hoarseness and/or dysphagia	< 50 cases reported (far less common than SCNEC); M > F; mean age: 63 years	90% cigarette smokers; questionable HR-HPV association	Not known
Thorax							
Lung	8013/3	None	Most frequent in the peripheral lung	Similar to those of non-small cell lung carcinoma	3% of resected lung carcinomas; M > F; mean age: > 65 years	Highly related to smoking	p53 and RB1 inactivation; mutation of *CREBBP*, *EP300*, *KMT2A* (*MLL*), *FGFR1*, *STK11*, and *KEAP1*
Thymus {33555458; 31042566}	8013/3	None	Anterior mediastinum	Half of patients are asymptomatic; symptoms may be chest pain, dyspnoea, superior vena cava syndrome	1 case/20 million individuals; 14–26% of thymic NENs; M > F; median age: 57 years	Unknown	p53 and RB1 inactivation; intermediate or high copy-number instability score is associated with LCNEC
Digestive system							
Oesophagus {23426118}	8013/3	None	Mostly in lower third	Nonspecific mass-related symptoms (dysphagia) and weight loss	Rare; as many as half of all oesophageal NECs; M > F; mean age: 70 years	Possible risk factors: tobacco smoking, alcohol drinking; specifically LCNEC related: gastroesophageal reflux disease	Common *TP53* and *RB1* mutations
Stomach {32985687; 28239029; 32985687; 23759931; 33142079}	8013/3	None	Anywhere	Nonspecific mass-related symptoms (dyspepsia) and weight loss	Rare; reported to be more frequent than SCNEC; M > F; median age: 70 years	Possible risk factor: *Helicobacter pylori*–related atrophic gastritis	Common *TP53* mutations; *RB1* mutations virtually absent; *TP53*-wildtype cases may have MSI-H; higher frequency of *APC* mutations than pulmonary NECs, and lower frequency of *KRAS* and *BRAF* mutations than colonic NECs; monoclonal origin in cases with a non-NEC component / MiNEN (sharing altered p53 pathway or MMR defect)
Small intestine and ampulla {15832081; 22964952}	8013/3	None	Almost exclusively in the ampullary region	Mostly obstructive jaundice in ampullary mass	Rare; reported to be more frequent than SCNEC; M > F; median age: 70 years	Unknown	To be defined; may be related to non-NE epithelial neoplasms of the same anatomical site
Appendix	8013/3	None	Not specifically investigated	Not specifically investigated	These neoplasms are poorly defined in this location and only anecdotal cases are reported	Unknown	Unknown
Colorectum {18360283; 24763982; 33197299; 27586204; 31672771; 27048246; 30237525; 25465415; 30022911; 30990915}	8013/3	None	Roughly equal distribution between right colon and rectosigmoid, rare in left/descending colon	Nonspecific mass-related symptoms	< 1% of all colorectal cancers; no reported sex differences	Possible risk factors: family history of cancer, tobacco smoking, alcohol consumption, and increased body mass index, with the adjusted summary effect estimate of risk (odds ratio) ranging from 0.67 (increased body mass index) to 1.6 (alcohol consumption)	Common mutations in *KRAS*, *TP53*, and *APC*; compared with CRC: higher rate of *BRAF* p.V600E and distinct methylome; *EGFR* methylated in NECs but not in CRC (different patterns of response and resistance to targeted therapies); possible deregulation of the RB1/p16 pathway and mutations in *FHIT*, *DCC*, *SMAD4*, and *MEN1*; a subset of LCNECs have MSI-H; monoclonal origin in cases with a non-NEC component / MiNEN
Liver {33726764; 27881473; 26184027}	8013/3	None	Anywhere	Nonspecific mass-related symptoms	Extremely rare (0.48% of all hepatic malignancies); metastatic nature must be excluded; almost all occur in association with HCC; combined NEC–intrahepatic cholangiocarcinoma is extremely rare	Unknown; occasional patients have history of viral hepatitis (HCV or HBV)	To be defined
Gallbladder and EHBDs {32739935; 27888490; 19917473}	8013/3	None	Anywhere in gallbladder (44% in fundus); in EHBDs, more common in distal bile duct	Abdominal pain, jaundice, weight loss, ascites, abdominal distension or mass	< 1% of all malignant gallbladder and EHBD neoplasms; F > M; average age in sixth decade of life	Possible risk factors: gallstones, *Clonorchis sinensis* infection	Common *TP53* and *RB1* mutations; other alterations in *ERBB4*, *HRAS*, *NRG1*, *HMCN1*, and *CDH10*, fusions of *NCAM2*::*SGCZ* and *BTG3*::*CCDC40*, and microsatellite instability; no *BRAF* mutations
Female genital tract							
Ovary {33194158}	8013/3	None	Unspecified	Mass	Extremely rare	Unknown	Unknown

CN-H, high copy number; CRC, colorectal carcinoma; EHBD, extrahepatic bile duct; HCC, hepatocellular carcinoma; HR-HPV, high-risk HPV; MCPyV, Merkel cell polyomavirus; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, high level of microsatellite instability; NE, neuroendocrine; NEC, neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas; UV, ultraviolet.

[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 S8.5 Major clinicopathological features of large cell neuroendocrine carcinoma (LCNEC) at various anatomical sites[a] (continued)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Fallopian tube {33194158}	8013/3	None	Unspecified	Mass	Extremely rare	Unknown	Unknown
Endometrium {33194158; 26945341; 32773531}	8013/3	None	Unspecified	Abnormal bleeding	Rare; perimenopausal and postmenopausal women	Unknown	Common defects of MMR; a recent study reported that endometrial NECs may be represented in all four molecular groups defined by TCGA for endometrial carcinomas (*POLE*; MSI; CN-H; no specific molecular profile), but LCNECs are not represented in the CN-H group
Cervix {33194158; 20182342; 32408525; 29728073}	8013/3	None	Unspecified	Mass or abnormal bleeding	Rare; premenopausal women	HR-HPV (mostly HPV18 and HPV16)	Unknown
Vagina {33194158}	8013/3	None	Unspecified	Mass or abnormal bleeding	Extremely rare	Unknown	Unknown
Vulva {33194158; 32826525}	8013/3	None	Unspecified	Cutaneous nodule	Extremely rare	Unknown	Unknown
Breast							
Breast	8013/3	None	Unspecified	No specific differences in presentation from other high-grade carcinomas	Extremely rare	No data on the etiology of NECs; probably the same etiology as other high-grade breast carcinomas	Lack of data
Urinary and male genital tracts							
Kidney {32366387; 29848671}	8013/3	None	Unspecified	Haematuria and/or abdominal pain	Less frequent than SCNEC, < 10 cases reported; M > F; mean age: 52 years	Unknown	Lack of data
Urinary tract {32366387; 28638669; 29180607; 33454836; 20164052; 29763719; 33454836; 26308137}	8013/3	None	Most frequent in urinary bladder (mostly lateral walls); 4 cases reported in the ureter	Gross haematuria, dysuria, and obstructive symptoms	Extremely rare; far less common than SCNEC; 0.5% of primary urinary bladder malignancies, < 40 cases reported; M > F; mostly elderly patients, but wide age range (20–84 years)	Possible risk factors: environmental exposure, smoking, radiation therapy for previous prostatic cancer	Data aggregated with SCNEC: common *TP53* and *RB1* mutations; bladder-specific mutations in the *TERT* promoter
Prostate {16723845; 30965328; 26885643; 30918106}	8013/3	None	Unspecified	Nonspecific; PSA usually low	Extremely rare; 17 cases reported	Possible risk factor: androgen deprivation therapy	May arise de novo or, more frequently, as a transdifferentiation of androgen-resistant prostate carcinomas; interval between initial diagnosis of conventional prostatic adenocarcinoma and subsequent diagnosis of LCNEC: 2–12 years; biallelic loss of *RB1*, elevated expression levels of p16 (CDKN2A) and E2F1, loss of expression of AR and of AR-responsive genes (*TMPRSS2* and *NKX3-1*)
Skin							
Merkel cell carcinoma {19395876; 11486166; 22204708; 30067951; 31233624; 33760021; 33932460; 30349028; 31399473}	8247/3	None	Mostly in sun-exposed areas, but can occur anywhere; primary Merkel cell carcinoma of extracutaneous sites may rarely be encountered	Nodule or plaque	Increasing incidence in the USA (2.7%), Australia (1.8%) and Europe (Scotland, 3.8%); from 0.55 to 1.3/100 000 in males and from 0.28 to 0.45/100 000 in females between 1997 and 2016 in the USA	UV radiation exposure or MCPyV	To be defined; low mutation burden in MCPyV+ cases; high mutation burden in MCPyV− cases, with mutation in *TP53* (97%), *RB1* (80%), NOTCH family (50%), *KMT2D* (26%), *FAT1* (26%), *LRP1B* (23%), *PIK3CA* (21%), *TERT* (15%), and *KMT2C* (13%)

CN-H, high copy number; CRC, colorectal carcinoma; EHBD, extrahepatic bile duct; HCC, hepatocellular carcinoma; HR-HPV, high-risk HPV; MCPyV, Merkel cell polyomavirus; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, high level of microsatellite instability; NE, neuroendocrine; NEC, neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas; UV, ultraviolet.

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