Table S8.3 Major clinicopathological features of small cell carcinoma (SmCC) 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 / external auditory canal {32851892}	8041/3	None	Middle ear / temporal bone / mastoid	Purulent discharge, pain, haemorrhage	Extremely rare (few case reports)	Unknown	Unknown
Sinonasal tract {19157501; 19685359; 21794118; 23740425; 24980293; 25457524; 25727332; 26880574; 27392929; 27529044; 27859290; 27938993; 28932042; 29438167; 29734873; 30248495; 30475447; 31161776; 31186531; 31763323; 32358042; 33090899; 33371727; 33433884}	8041/3	None	Ethmoid sinus > nasal cavity > maxillary and sphenoidal sinuses > nasopharynx	Nonspecific symptoms; advanced local and distant disease; rare paraneoplastic syndromes; 70% present at stage IV	3% of sinonasal tumours (< 100 case reports); male predominance; sixth decade of life (mean age: 53 years)	Rare association with HR-HPV and previous irradiation; smoking; EBV in nasopharynx (3 cases)	*TP53* mutation; loss of members of SWI/SNF complex (*ARID1A*, *SMARCA4*, and [less often] *SMARCB1*) and of IDH2; preferentially *ARID1A*-mutated and *IDH2*-proficient; *MAML3* and *GAS6* mutations (case reports)
Oropharynx, oral cavity and salivary glands {18038886; 22430343; 22301491; 23838856; 2421566; 24966986; 27392929; 27496009; 27818885; 29093415; 30475447; 31161776; 31463946; 31523135; 31920384; 33694290}	8041/3	None	Tonsil >>> tongue base, tongue Salivary glands: most frequently in the parotid	Painful mass, nonspecific symptoms; metastases at presentation in 20% of cases Salivary glands: advanced disease at presentation	Oral cavity: M:F ratio: 1.5:1; mean age: 59 years Salivary glands: M:F ratio: 3.4:1; mean age: 73 years	Oropharynx: HPV; previous irradiation Oral cavity: smoking history in 50% of cases Salivary glands: unknown	Some data on p53 and RB1 loss (salivary glands)
Hypopharynx, larynx, trachea, and parapharyngeal space {22430343; 22433139; 23397781; 23397787; 24596175; 24980293; 25351497; 25457524; 25606844; 26173932; 26611246; 27392929; 27859290; 28559027; 29557536; 29909787; 31161776; 31437725}	8041/3	None	Most frequent in the larynx, supraglottis most commonly	Mostly hoarseness and/or dysphagia	Male predominance (80% of patients are male); mean age: 59 years	90% cigarette smokers; HR-HPV association rare	More commonly *TP53* and *RB1* alterations
Thorax							
Lung {27873319; 33209646}	8041/3	None	Most frequently central; peripheral in ~5%	Rapid-onset signs and symptoms due to local growth and/or distant spread and/or paraneoplastic syndromes	13% of all lung cancers; most frequent lung NEN; male predominance; seventh decade of life	Strong association with cigarette smoking; secondary forms due to histological transformation of oncogene-addicted non-small cell cancers treated with tyrosine kinase inhibitors	Most frequently mutations and/or deletions in *TP53*, *RB1*, *LRP1B*, *KMT2D*, and *CSMD3*; copy-number gains of *TERT*, *SDHA*, *RICTOR*, *PIK3CA*, and *MYC*; four major classes based on predominant transcriptional activation of *ASCL1*, *NEUROD1*, *YAP1*, and *POU2F3*
Thymus {31042566; 20485130; 29201448}	8041/3	None	Anterior mediastinum	Weight loss, sweating, chest pain, cough, superior vena cava syndrome	1 case/50 million individuals; < 10% of thymus NENs; no sex bias; median age 58 years	Unknown	High chromosomal instability score (vs carcinoids)
Digestive system							
Oesophagus {33847642; 33686305; 33980813}	8041/3	None	> 50% of cases in the lower third	Nonspecific mass-related symptoms (dysphagia) and weight loss	<1% of all digestive NENs; together with LCNEC, 90% of oesophageal NENs; LCNEC/SCNEC prevalence variable; male predominance; mean age: 56 years	Possible risk factors are tobacco smoking, alcohol drinking (no definitive data)	Most frequently *TP53* and *RB1* (60% and 54%, respectively); *NOTCH1/3*, *PIK3CA*, and *ATM* mutations more frequently than pulmonary SCNEC
Stomach {33686305; 15226341; 28239029; 33359239; 25465415}	8041/3	None	Potentially arise in any part of stomach, usually in antral and cardiac regions	Nonspecific mass-related symptoms (dyspepsia) and weight loss	20.5% of all digestive NECs; 21% of all gastric NENs; male predominance; mean age: 63 years	More frequent in Japanese people; rare gastric primary MCC associated with MCPyV	Most frequently *TP53*; other mutations in *TSHZ3*, *SEMA5A*, *TPH2*, *SDK1*, *PLXNA1*; *RB1* mutations are rare; microsatellite instability in ~10%
Small intestine and ampulla	8041/3	None	Almost exclusively ampullary region	Obstructive effect of mass (mostly obstructive jaundice in ampullary mass)	Rare	Unknown	No studies available
Appendix {18197972}	8041/3	None	No specific localization	Pain, nausea, and vomiting (simulating appendicitis), or nonspecific mass-related symptoms	Very rare (case reports)	Unknown	No studies available
Colorectum {33135938; 28059096; 17063080; 29354876; 25465415}	8041/3	None	Colon and rectum, with similar frequency	Nonspecific mass-related symptoms, bleeding, or metastasis-related symptoms; majority of cases are at an advanced metastatic stage at diagnosis	Increasing incidence; ~10% of all extrapulmonary small cell carcinomas; slight male predominance; sixth or seventh decade of life	Unknown (possibly linked to adenocarcinoma)	Usually mutations in *TP53* and *RB1*; other mutations in *APC*, *KRAS*, *FHIT*, *DCC*, *SMAD4*, *MEN1*, *BRAF*; microsatellite instability in ~10%
Liver {23280574}	8041/3	None	No specific localization	Nonspecific	Very rare; metastatic nature must be excluded in all cases	Unknown; occasional patients have history of viral hepatitis	No studies available

HR-HPV, high-risk HPV; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; MSI-H, high level of microsatellite instability; LCNEC, small cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas.

[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 S8.3 Major clinicopathological features of small cell carcinoma (SmCC) at various anatomical sites[a] (continued)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Gallbladder and bile ducts {29548338; 28040546; 26208508}	8041/3	None	No specific localization	Abdominal pain, jaundice, weight loss, ascites, abdominal distension or mass; distant metastases including in the CNS	4% of all malignant gallbladder neoplasms; female predominance; seventh decade of life	Close to that of adenocarcinoma, frequently associated with gallstones	Few data; whole-genome sequencing in a metastatic case showed alterations in *ERBB4*, *HRAS*, *NRG1*, *HMCN1*, *CDH10*, fusions of *NCAM2*::*SGCZ* and *BTG3*::*CCDC40*, and microsatellite instability
Female genital tract							
Ovary {24875120; 29621125}	8041/3	None	Bilateral disease in 20–50% of cases	Nonspecific (no hypercalcaemia)	Rare; mean age: 39 years (premenopausal)	Unknown; case reports of SCNEC arising in mature teratomas	No studies available
Fallopian tube {10053109}	8041/3	None	No specific localization	Nonspecific	Extremely rare (2 out of 105 cases of fallopian tube cancers in one series)	Unknown	No studies available
Endometrium {24875120; 32773531}	8041/3	None	No specific localization	Abnormal vaginal bleeding, metastasis-related symptoms, paraneoplastic syndromes (retinopathy, Cushing); > 50% are diagnosed at FIGO stages II–IV	Rare, 0.8% of all endometrial carcinomas	Unknown	*TP53* and *RB1* mutations are rare; most frequently represented among the four TCGA groups are microsatellite instability/ hypermutated and no specific molecular profile
Cervix {24875120; 33888337; 30355937; 33830625}	8041/3	None	No specific localization	Vaginal bleeding/discharge and/or detection of cervical mass; stage I in the majority of cases, but as many as 40% have positive nodal status	1–3% of all cervical malignancies; most frequent NEC of the female genital tract; mean age: 45–50 years	HR-HPV (mostly HPV18) in 50–100% of cases	Most frequently involved pathways are RTK/RAS, PI3K/AKT, p53, and MYC; RB1 loss is rare; rare cases with MSI-H / MMR deficiency; inactivation of p53 and RB1 pathways through HPV-mediated oncogenic mechanisms
Vagina {33792412; 24875120}	8041/3	None	No specific localization	Vaginal bleeding, mass-related symptoms; Cushing syndrome in case reports	Very rare (~30 case reports); median age: 55 years	Unknown, HPV detected in some cases	*NF1* or *AR* mutations (2 cases analysed)
Vulva {24875120}	8041/3	SCNEC, classic; MCC	Arise from vulvar skin and rarely from Bartholin gland	Cutaneous nodule(s) with overlying skin erythematous or ulcerated	Rare	MCPyV; higher risk in immunocompromised patients	No studies available
Breast							
Breast {32336623; 33135938; 33584543; 32613538}	8041/3	None	No specific localization	No specific differences in presentation from other high-grade carcinomas	Rare, 0.1% of all breast cancers; 2–10% of all extrapulmonary SCNECs; mean age: < 60 years	Unknown	Frequent mutations in *TP53* but not in *RB1*; *PIK3CA* mutations in 30%
Urinary and male genital tracts							
Kidney {33477429}	8041/3	None	No specific localization	Haematuria and/or abdominal pain; metastatic disease at diagnosis in ~50% of cases	Rare, < 1% of all renal tumours; median age: 69 years; M:F ratio: 1:1	Unknown	No studies available
Urinary tract {21567387; 33561506; 31664527; 27698324}	8041/3	None	Most arise in the bladder	Gross haematuria, dysuria, obstructive symptoms including recurrent infections and weight loss; rare paraneoplastic syndromes (hypercalcaemia, Cushing syndrome); organ-confined disease is present in < 50% of cases	< 0.2 cases/100 000 person-years; < 1% of malignant bladder tumours; M:F ratio: 3:1; median age: ~70 years	No specific etiology; most patients report a history of smoking; additional associated factors are bladder stones and chronic cystitis	Mutations in *TP53*, *RB1*, *CDKN2A*, and *MDM2*, and in chromosome modifiers; *TERT* promoter mutations very frequent
Prostate {33664492; 21336263; 18162772; 24323898; 33847621; 33582100}	8041/3	None	No specific localization	Metastatic disease is present in > 70% of patients at diagnosis in de novo cases; PSA: < 10 ng/mL in > 80%; mean age: 68 years	0.5% of all prostate cancer, but up to 10–20% in autopsies of patients who died from castration-resistant prostate cancer	Unknown; frequently occur in patients with castration-resistant prostate cancer (1–300 months after initial adenocarcinoma diagnosis)	*RB1* inactivation, *PTEN*, *ERG* fusions (50%); increased activity of transcriptional regulators *HOXB5*, *HOXB6*, and *NR1D2*
Testis {25207197}	8041/3	None	No specific localization	Nonspecific; may be distant metastases at diagnosis	Extremely rare	Unknown; case reports of SCNEC arising in mature teratomas	No studies available

HR-HPV, high-risk HPV; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; MSI-H, high level of microsatellite instability; LCNEC, small cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas.

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