Table S8.7 Major clinicopathological features of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) 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 {12011260; 15053292; 15825200; 16148713; 19303146; 20111612; 22623086; 22935814; 24766278; 25400805; 25992031; 26622884; 27761737; 28611057; 29438167; 30001283; 30069842; 34041698}	8154/3 (MiNEN)	Glandular (adenoma)	Middle ear	Hearing loss, aural fullness, and tonal tinnitus	Rare (< 2% of ear tumours) Fifth decade of life Equal sex distribution	Unknown	Unknown
Sinonasal tract {30001239; 16526967; 29103747; 32138448; 16526967; 19321468; 20961443; 22740238; 23772319; 24944702; 24327102; 24944702}	8154/3 (MiNEN)	IP-SCNEC ITAC-SCNEC SCC-SCNEC AdSC-SCNEC	Nasal cavity, ethmoid sinus, maxillary sinus	Stuffiness, rhinorrhoea, epistaxis, obstruction, pain, mucoid discharge; inappropriate hormone secretion (SIAD) is rare	16% of sinonasal NENs M > F Mean age: 58.8 years (range: 22–85 years)	Unknown; no professional exposure to carcinogens	ITAC-NEC: copy-number changes at *TP53*, *MLH3*, and *KLK3* regions; additional gains and losses at *APC*, *CDK6*, *DAPK1*, *TNFRSF1A*, *CDKN1B*, *BRCA2*, *HIC1*, *BCL2*, *KLK3*, and *TIMP3* regions, and aberrant methylation of *APC* and *DAPK1* in the NEC component; no *KRAS*, *BRAF*, or *TP53* mutations SCC-NEC: *TP53* missense mutation in exon 7, restricted to the NEC component
Oropharynx, oral cavity, and salivary glands {21997688; 26735857; 27496009; 29556964; 31093350; 33709305}	8154/3 (MiNEN)	SCC-SCNEC	Tonsil	Oropharyngeal mass, neck mass (lymph node metastases)	Very rare M > F Mean age: 65.8 years (range: 55–83 years)	High-risk HPV identified in carcinoma History of smoking in some cases	Unknown
Larynx, hypopharynx, trachea, and parapharyngeal space {214939; 6299507; 6295589; 2994505; 3033580; 2838769; 1315242; 11130578; 15504064; 16718502; 19930775; 21228933; 24596175; 28430347; 32335641}	8154/3 (MiNEN)	SCC-SCNEC SCC-NET	More frequently supraglottic	Hoarseness, dysphagia	Very rare M > F Mean age: 65.8 years (range: 55–83 years)	Smoking in most patients	Unknown
Thorax							
Lung {2540288; 12218575; 23010092; 23792008; 28203418; 32592985; 33718010; 31775086; 23792008; 26960398; 27507618; 29535388; 32365350; 23689091; 9792054; 29248665; 26027992; 30429033; 33718010; 14652820; 19179901; 21210145; 17784875; 18829487; 27507618; 26960398; 28884744; 33011388; 22103903; 29101056; 6291745; 3002587; 26273331; 9792054; 21427100; 26027992} [[La Rosa S, Simbolo M, Franzi F, et al. Combined adenocarcinoma–atypical carcinoid of the lung. Targeted next-generation sequencing (NGS) suggests a monoclonal origin of the two components. Diagn Histopathol. 2018 Mar;24(3):120–3. doi:10.1016/j.mpdhp.2018.02.002.]]	8013/3 (combined LCNEC) 8045/3 (combined SCNEC) 8154/3 (MiNEN)	ADC-NEC (SCNEC or LCNEC) SCC-NEC (SCNEC or LCNEC) Large cell carcinoma–NEC (SCNEC or LCNEC) Spindle/giant cell carcinoma–NEC (SCNEC or LCNEC) ADC-NET SCC-NET	Similar to pure non-NE types	ADC or SCC-NEC (LCNEC or SCNEC): similar to pure LCNEC (peripheral or central) or SCNEC Paraneoplastic syndrome described (SIAD, Cushing, etc.) ADC or SCC-NET: similar to pure ADC or SCC	MiNEN with SCNEC component: 2–30% of all SCNECs MiNEN with LCNEC component: 12–37% of all LCNECs MiNEN with NET component: only case reports	Similar to that of pure counterparts, with strong association with smoking history	ADC or SCC-NEC (SCNEC or LCNEC): *RB1*, *TP53*, *KRAS*, *STK11*, *KEAP1*, and (in SCNEC) *EGFR* mutations ADC-NET: *KRAS*, *PAPPA2*, *NF1*, and *SMARCA4* mutations
Thymus [[Travis WD, Brambilla E, Burke AP, et al., editors. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon (France): International Agency for Research on Cancer; 2015. (WHO classification of tumours series, 4th ed.; vol. 7). https://publications.iarc.who.int/17.]] {2222057; 8265883; 18996790}	8013/3 (combined LCNEC) 8045/3 (combined SCNEC)	Thymoma–NEC (SCNEC or LCNEC) Thymic carcinoma–NEC (SCNEC or LCNEC) Thymoma–NET Thymic carcinoma–NET	Similar to pure non-NE types	Thymic epithelial tumour (including thymoma and thymic carcinoma)–NEC (SCNEC or LCNEC) similar to pure LCNEC or SCNEC	Unknown; very rare	Similar to that of pure counterparts, with no established role of smoking in the development	Not properly assessed; probably superimposable to pathogenesis of each counterpart
Digestive system							
Oesophagus {11914632; 28288180; 31963850; 31660035; 31014519; 29050228; 18670347; 29872597; 31134449; 33686305; 32036480}	8154/3	ADC-NEC (SCNEC or LCNEC) SCC-NEC (SCNEC or LCNEC) ADC-NET	ADC-NEC: distal oesophagus SCC-NEC: any location ADC-NET: distal oesophagus	Same as those of ADC and SCC	0.2–4% of all oesophageal malignancies; 6–16% of all digestive MiNENs Mean age: 67 years	Probably the same as that of ADC and SCC	*TP53* and *RB1* mutations, *RB1* deletion or LOH, and amplification of *PIK3CA*, *PTEN*, *KRAS*, *SOX2*, *DVL3*, and *TP63*

ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; CN-H, high copy number; EC, endometrioid carcinoma; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; LOH, loss of heterozygosity; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MSI, microsatellite instability; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SIAD, syndrome of inappropriate antidiuresis; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas; UC, undifferentiated carcinoma; UrC, urothelial carcinoma.

[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 S8.7 Major clinicopathological features of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued from previous page, continued on next page)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Stomach {29592868; 31660035; 16218931; 2776113; 6176315; 2031532; 15792127; 12861036; 11942581; 25342539; 25633872; 9822131; 16167538; 20530158; 21531442; 33142079; 33642833; 32670540}	8140/3	ADC-NEC (SCNEC or LCNEC) ADC-NET	Anywhere in the stomach	Same as those of ADC Paraneoplastic symptoms are uncommon	0.16–1.48% of all gastric malignancies; 6–20% of all digestive MiNENs Mean age: 69 years	Probably the same as that of ADC	ADC-NEC: similar to that of pure ADC ADC-NET: unknown
Small intestine and ampulla {32538468}	8154/3	ADC-NEC (SCNEC or LCNEC) ADC-NET	Most common in duodenum and ampullar region	Same as those of ADC Paraneoplastic hormonal symptoms are uncommon	5.6% of all digestive MiNENs	Probably the same as that of ADC	ADC-NEC: similar to that of pure ADC ADC-NET: similar to that of pure ADC (*KRAS* and *TP53* mutation demonstrated in 1 case)
Appendix (goblet cell adenocarcinoma excluded) {32903647}	8154/3	ADC-NEC (SCNEC or LCNEC)	Anywhere in the appendix	Same as those of ADC, appendicitis	1% of all appendiceal epithelial malignancies Median age: 57 years (range: 10–89 years) M:F ratio: 1:1 Majority (86.7%) of patients are White	Probably the same as that of ADC	ADC-NEC: similar to that of pure ADC
Colorectum {32538468; 25465415; 27586204; 28059096; 25342539; 25633872; 29592868} [[La Rosa S, Simbolo M, Luchini C, et al. MiNENs composed of adenocarcinoma and well differentiated neuroendocrine tumor have a monoclonal origin. Abstracts from USCAP 2020: Endocrine Pathology (565–611). Mod Pathol. 2020;33:720–63.]]	8154/3	ADC-NEC (SCNEC or LCNEC) ADC-NET	Anywhere in the colon	Same as those of adenocarcinoma Paraneoplastic hormonal symptoms are uncommon	30% all digestive MiNENs Median age at diagnosis: 65 years	The same as that of ADC	ADC-NEC: similar to that of pure ADC ADC-NET: similar to that of pure ADC (*KRAS*, *AKT1*, *APC*, *PIK3CA*, *SMAD4*, *RB1*, and *TP53* mutations demonstrated)
Liver {27169712}	8154/3	HCC-NEC HCC-NET CHC-NEC	Anywhere in the liver	Same as those of liver carcinomas	Extremely rare	Unknown	Unclear
Gallbladder and bile ducts {31981075}	8154/3	ADC-NEC (SCNEC or LCNEC) ADC-ICPN-NEC (SCNEC or LCNEC)	Anywhere in the gallbladder or biliary tree	Same as those of ADC Paraneoplastic hormonal symptoms are uncommon	10% of gallbladder carcinomas; 4% of extrahepatic cholangiocarcinomas; 2.4% of all digestive MiNENs Median age at diagnosis: 65 years (range: 34–85 years); M:F ratio: 1:3.3	Unknown	ADC-NEC: similar to that of pure ADC (*TP53* mutation demonstrated)
Female genital tract							
Vulva {32826525}	8154/3	ADC-LCNEC	Labium majus (Bartolini gland)	Vulvar mass	Extremely rare (only 1 case reported)	Unknown	Undefined
Cervix and vagina {15381906; 16730307; 21965825; 22534245; 23722515; 27532149; 28603541; 33241100}	8154/3	ADC-SCNEC ADC-LCNEC SCC-SCNEC SCC-LCNEC AdSC-SCNEC Carcinosarcoma–SCNEC Mesonephric adenocarcinoma–LCNEC Adenoid-cystic adenocarcinoma–SCNEC	Mostly in the uterine cervix	Abnormal vaginal bleeding	Very rare; 12–24% of all cervical NENs	In a subset of cases, HPV is involved	Monoclonal origin for the two components has been demonstrated in a few cases
Endometrium {26945341; 7883422; 3020961; 32773531; 31576694}	8154/3	EC-LCNEC EC-SCNEC HGSC-LCNEC Carcinosarcoma–SCNEC	Everywhere in the endometrial cavity	Abnormal uterine bleeding	Rare in absolute numbers, but about three quarters of endometrial NECs	Unknown	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 MiNENs are not represented in the CN-H group
Ovary {17460463; 19047907; 33194158; 1384368}	8154/3	MC-LCNEC EC-LCNEC EC-SCNEC HGSC-LCNEC UC-LCNEC	Both ovaries may be involved	Abdominal/pelvic pain, abdominal/pelvic mass, ascites	Rare in absolute numbers, but about three quarters of ovarian NECs	Unknown	Monoclonal origin for the two components has been demonstrated in a few cases

ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; CN-H, high copy number; EC, endometrioid carcinoma; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; LOH, loss of heterozygosity; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MSI, microsatellite instability; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SIAD, syndrome of inappropriate antidiuresis; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas; UC, undifferentiated carcinoma; UrC, urothelial carcinoma.

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Table S8.7 Major clinicopathological features of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued)

Site	ICD-O coding	Subtype(s)	Localization	Clinical features	Epidemiology	Etiology	Pathogenesis
Urinary and male genital tracts							
Kidney {27169712}	8154/3	UrC-SCNEC UrC-LCNEC SCC-SCNEC PRCC-SCNEC CCRCC-NET	MiNENs with NEC component are usually located in the renal pelvis MiNENs with NET (carcinoid) component are usually located in the renal parenchyma	Nonspecific symptoms; rarely, flank mass and haematuria	F > M Mean age: 60 years (range: 32–84 years)	Unknown	Unknown
Urinary tract {33454836; 29763719; 29535424}	8154/3	UrC (including subtypes)-SCNEC ADC-SCNEC ADC-LCNEC	Most frequent in urinary bladder (mostly lateral and posterior walls)	Haematuria	Rare in absolute numbers but about two thirds of urinary bladder NECs M > F Mean age: 68 years	Unknown	To be defined; common *TP53* and *RB1* mutations; bladder-specific mutations in the *TERT* promoter
Prostate {30965328; 24705311; 26885643}	8154/3	Acinar ADC-LCNEC Acinar ADC-SCNEC	Anywhere in the prostate	Nonspecific symptoms	Rare in absolute numbers; about two thirds of prostatic NECs; seventh decade of life	Unknown	To be defined; common ETS gene fusions; *AR*, *AURKA*, and *MYCN* amplifications
Skin							
Skin {24729037; 9027628; 9808429; 19609205; 26022453; 26099430; 26433246; 25720654; 31759946; 33533503}	8154/3	SCC-MCC BCC-MCC Trichoblastoma–MCC Sebaceous carcinoma–MCC	Sun-damaged skin	SCC-MCC: M > F; mean age: 76.5 years	Rare, unknown incidence	Unknown; MCPyV usually absent	Suggested origin from precursor stem cells located in the hair follicle; *TP53* and *RB1* mutations

ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; CN-H, high copy number; EC, endometrioid carcinoma; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; LOH, loss of heterozygosity; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MSI, microsatellite instability; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SIAD, syndrome of inappropriate antidiuresis; SCNEC, small cell neuroendocrine carcinoma; TCGA, The Cancer Genome Atlas; UC, undifferentiated carcinoma; UrC, urothelial carcinoma.

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