Table S8.8 Major pathological features and prognosis of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued on next page)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
Head and neck									
Middle ear {30001283; 30069842; 26622884; 22777694; 28547535; 33044790}	Reddish bulging mass	Classic NE patterns intermingled with glandular mucous secretion	Pancytokeratin, chromogranin A, synaptophysin; hindgut NET (including PP, glucagon-related peptides, serotonin, SATB2); luminal PAS and Alcian blue positivity	G1: < 2 mitoses/2 mm^2; no necrosis G2: not defined yet, but 2–10 mitoses/ 2 mm^2 and/or foci of necrosis	Not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A, synaptophysin, and many peptide hormones or two other NE markers *Desirable:* Ki-67 and SSTR2–5	Not performed	5-year survival rate, G1: 80–100%; too few but lower for G2
Sinonasal tract {30001239; 16526967; 29103747; 32138448; 16526967; 19321468; 20961443; 22740238; 23772319; 24944702; 24327102; 24944702}	Polypoid or fungating, friable, sometimes ulcerated or haemorrhagic mass	IP: histological features of IP ITAC: histological features of conventional ITAC SCC: histological features of conventional SCC SCNEC: histological features of conventional SCNEC	ITAC: CK20, CDX2, CEA SCC: CK5/6, p63, p40 SCNEC: synaptophysin, chromogranin A, TTF1	ITAC and SCC components: graded as when present as pure forms NEC component: high-grade by definition	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (CK20, CDX2 or p63, and CK5/6) and ≥ 2 NE markers for the NEC component	Same as for sinonasal cancer	3-year OS rate: 40% 3-year DFS rate: 26.6% 5-year OS and DFS rate: 0%
Oropharynx, oral cavity, and salivary glands {21997688; 27496009}	Ulcerated mass	SCC: histological features of HPV-associated SCC SCNEC: histological features of conventional SCNEC	SCC: CK5/6, p63, p40, p16 SCNEC: synaptophysin, chromogranin A, TTF1, p16	HPV-associated SCC component: histological grading not currently advocated SCNEC component: high-grade by definition	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (p63, p40, CK5/6, p16) and ≥ 2 NE markers for the NEC component	Same as for HPV-positive oropharyngeal cancer	Mean survival time: 8.4 months (range: 2–12 months)
Larynx, hypopharynx, trachea, and parapharyngeal space {214939; 6299507; 6295589; 2994505; 3033580; 2838769; 1315242; 11130578; 15504064; 16718502; 19930775; 21228933; 32335641}	Same as SCC	SCC: histological features of conventional SCC SCNEC: histological features of conventional SCNEC NET: histological features of well-differentiated NET	SCC: CK5/6, p63, p40 SCNEC: synaptophysin, chromogranin A, calcitonin NET: synaptophysin, chromogranin A, INSM1, TTF1 (variable)	SCC component: graded as when present as pure form SCNEC component: high-grade by definition NET component: G2: 2–10 mitoses/2 mm^2 often with foci of necrosis; Ki-67 generally 3–20%	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (p63, p40, CK5/6) and ≥ 2 NE markers for the NEC component	Same as for laryngeal cancer	5-year survival rate: 5–20%
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.]]	Same as in pure counterparts	ADC: histological features of conventional ADC SCC: histological features of conventional SCC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	Same immunophenotype as respective pure ADC (CK7, napsin A, TTF1), SCC (p40, CK5/6), and NEC (synaptophysin, chromogranin, OTP, variable TTF1) counterparts; SCNEC component of MiNEN is more likely to be positive for YAP1 than pure SCNEC	ADC and SCC components: graded as when present as pure forms NEC component: high-grade by definition NET component: TC: < 2 mitoses/2 mm^2; no necrosis; AC: 2–10 mitoses/2 mm^2 and/or foci of necrosis	Same as in pure neoplasm counterparts	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (TTF1. napsin A, p40) and ≥ 2 NE markers for the NEC component	Same as for other primary lung carcinomas	ADC or SCC-SCNEC: clinical outcome is similar to that of pure SCNEC, with some studies suggesting a worse prognosis and/or less chemosensitivity ADC or SCC-LCNEC: appear to have a more favourable prognosis than pure LCNEC, corresponding to a lower Ki-67 proliferation index in the NE component ADC-NET: apparently as that of ADC SCC-NET: apparently as that of SCC
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}	Same as in pure counterparts	Thymic epithelial tumours: histological features of conventional thymic epithelial tumours SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	General NE markers (synaptophysin, chromogranin A) Non-neuroendocrine markers (cytokeratin CAM5.2 or AE1/AE3, CD5, KIT [CD117], p40)	Thymic epithelial tumours: graded as when present as pure forms NEC component: high-grade by definition NET component: TC: < 2 mitoses/2 mm^2 and no necrosis; AC: 2–10 mitoses/2 mm^2 and/or foci of necrosis	Same as in pure neoplasm counterparts	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (cytokeratins CAM5.2 or AE1/AE3, CD5, KIT [CD117], p40) and ≥ 2 NE markers for the NE component	Same as for other primary thymic carcinomas	No specific papers on the clinical outcome of thymus MiNENs are available; poorly differentiated counterparts (LCNEC, SCNEC) could reasonably be considered to drive MiNEN prognosis

AC, atypical carcinoid; ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; DFS, disease-free survival; EC, endometrioid carcinoma; GPC3, glypican-3; GS, glutamine synthetase; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IHC, immunohistochemistry; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; OS, overall survival; OTP, orthopedia homeobox protein; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma; TC, typical carcinoid; TTF1, thyroid transcription factor 1; 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 S8.8 Major pathological features and prognosis of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued from previous page, continued on next page)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
Digestive system									
Oesophagus {11914632; 28288180; 31963850; 31660035; 31014519; 29050228; 18670347; 29872597; 31134449; 33686305; 32036480}	Same as that of SCC or ADC	SCC: histological features of conventional SCC ADC: histological features of conventional ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	SCC: CK5/6, p63, p40 ADC: CK7, CK19 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 NET: synaptophysin, chromogranin A	ADC and SCC components: graded as when present as pure forms NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (p63, p40, CK5/6 or CK7, and CK19) and ≥ 2 NE markers for the NE component	Same as for conventional carcinoma	Median survival about 6 months depending on tumour stage
Stomach {29592868; 31660035; 16218931; 2776113; 6176315; 2031532; 15792127; 12861036; 11942581; 25342539; 25633872; 9822131; 16167538; 20530158; 21531442; 33142079; 33642833; 32670540}	Same as that of ADC	ADC: histological features of conventional or signet-ring cell ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	ADC: CK7, CK19 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1+/– NET: synaptophysin, chromogranin A	ADC component: graded as when present as pure form NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for gastric ADC	ADC-NEC: median survival time: 27 months; 5-year survival rate: 8–11% with advanced-stage disease even after surgical resection ADC-NET: better prognosis than ADC-NEC
Small intestine and ampulla {32538468}	Same as that of ADC	ADC: histological features of conventional or signet-ring cell ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	ADC: CK7, CK19 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1+/– NET: synaptophysin, chromogranin A	ADC component: graded as when present as pure form NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for small intestinal ADC	ADC-NEC: mean survival time: 61 months ADC-NET: better prognosis than ADC-NEC
Appendix (goblet cell adenocarcinoma excluded) {32903647}	Same as that of ADC	ADC: histological features of conventional or signet-ring cell ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	ADC: CK20, CDX2 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1+/– NET: synaptophysin, chromogranin A	ADC component: graded as when present as pure form NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for NE component	Same as for appendiceal ADC	5-year OS rate: 57.4% 5-year disease-specific survival rate: 36.4%; worse than NET, NEC, and goblet cell adenocarcinoma
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.]]	Same as that of ADC	ADC: histological features of conventional or signet-ring cell ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	ADC: CK20, CDX2 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1+/– NET: synaptophysin, chromogranin A	ADC component: graded as when present as pure form NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for colonic ADC	Median OS time: 29.6 months with localized disease Median OS time of 9.6 months with advance disease
Liver {27169712}	Same as that of HCC or CHC	HCC: histological features of conventional HCC CHC: histological features of conventional CHC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of well-differentiated NET	HCC: HepPar1, arginase, GPC3, GS CHC: CK7	HCC and CHC components: graded as when present as pure forms NEC component: high-grade by definition NET component: graded as G1, G2, or G3 according to proliferative index	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for liver cancers	No specific information on OS, but these are aggressive neoplasms

AC, atypical carcinoid; ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; DFS, disease-free survival; EC, endometrioid carcinoma; GPC3, glypican-3; GS, glutamine synthetase; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IHC, immunohistochemistry; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; OS, overall survival; OTP, orthopedia homeobox protein; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma; TC, typical carcinoid; TTF1, thyroid transcription factor 1; 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.]].

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Table S8.8 Major pathological features and prognosis of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued from previous page, continued on next page)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
Gallbladder and bile ducts {31981075}	Same as that of ADC	ADC: histological features of conventional or signet-ring cell ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	ADC: EMA, CK7 ICPN: EMA, MUC5A, CK7 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 +/−	ADC component: graded as when present as pure form NEC component: high-grade by definition	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for ADC	Median OS time of 8.6 months with localized disease Median OS time of 4.4 months with advanced disease
Female genital tract									
Vulva {32826525}	Non-ulcerated nodule, centred in the dermis	LCNEC, classic + G2 ADC with intestinal differentiation	ADC: CK20, SATB2 LCNEC: synaptophysin, chromogranin A, (TTF1−)	High-grade	Not clinically relevant	Not clinically relevant	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers	Same as for conventional carcinoma	Poor (OS time: 9 months)
Cervix and vagina {15381906; 16730307; 21965825; 22534245; 23722515; 27532149; 28603541; 33241100}	Large invasive mass	ADC: histological features of conventional cervical ADC SCC: histological features of conventional cervical HPV-related or unrelated SCC AdSC: histological features of conventional cervical AdSC Carcinosarcoma: histological features of conventional cervical carcinosarcoma SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional SCNEC	ADC: CK7, p16 SCC: CK5/6, p63, p40, p16 (if HPV-related) AdSC: pertinent mixed pattern Carcinosarcoma: mesenchymal markers in sarcomatous cells; cytokeratins in carcinomatous cells SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 (+/−) Mesonephric adenocarcinoma: CD10, GATA3 Adenoid-cystic carcinoma: KIT (CD117), myoepithelial markers	High-grade	Mixed cytology on Pap smear	May be high-risk HPV–related	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers	Same as for conventional carcinoma	Not specifically defined, seems poor and aligned to that of NECs
Endometrium {26945341; 7883422; 3020961; 32773531; 31576694}	Large invasive masses	EC: histological features of conventional EC HGSC: histological features of conventional HGSC Carcinosarcoma: histological features of conventional endometrial carcinosarcoma SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	EC: ER, PR, PAX8 HGSC: WT1, p53, PAX8 Carcinosarcoma: mesenchymal markers in sarcomatous cells; cytokeratins in carcinomatous cells SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 (+/−)	High-grade	Not clinically relevant	Not clinically relevant	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers	Same as for conventional carcinoma	Prognosis reported to be slightly better than that of stage-matched pure NECs
Ovary {17460463; 19047907; 33194158; 1384368}	Large solid-cystic masses with necrosis and haemorrhage; may be bilateral	EC: histological features of conventional EC HGSC: histological features of conventional HGSC MC: histological features of conventional ovarian MC UC: histological features of poorly differentiated carcinoma with no morphologically recognizable differentiation SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	EC: ER, PR, PAX8 HGSC: WT1, p53, PAX8 MC: PAX8−/+, ER−, PR−, SATB2−/+, CDX2−/+, napsin A UC: variable immunophenotype SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 (+/−)	High-grade	Not clinically relevant	Not clinically relevant	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers	Same as for conventional carcinoma	Not specifically defined, seems poor and aligned to that of NECs

AC, atypical carcinoid; ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; DFS, disease-free survival; EC, endometrioid carcinoma; GPC3, glypican-3; GS, glutamine synthetase; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IHC, immunohistochemistry; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; OS, overall survival; OTP, orthopedia homeobox protein; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma; TC, typical carcinoid; TTF1, thyroid transcription factor 1; 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.]].

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Table S8.8 Major pathological features and prognosis of mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) at various anatomical sites[a] (continued)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
Urinary and male genital tracts									
Kidney {27169712}	Large solid masses with necrosis and haemorrhage	UrC: histological features of conventional UrC SCC: histological features of SCC CCRCC: histological features of conventional CCRCC PRCC: histological features of conventional PRCC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC NET: histological features of conventional NET	UrC: GATA3, p63, CK7, CK20 focally +, CDX2 focally + SCC: p63, CK5/6 CCRCC: CD10, vimentin PRCC: CK7 SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 (+/–) NET: synaptophysin, chromogranin A	High-grade (with NEC component) Intermediate-grade (with NET component)	Not clinically relevant	Not clinically relevant	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for conventional carcinoma	Not specifically defined, seems poor and aligned to that of NECs
Urinary tract {33454836; 29763719; 29535424}	Large exophytic and ulcerated masses	UrC: histological features of conventional UrC and its subtypes ADC: histological features of conventional CCRCC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	UrC: GATA3, p63, CK7, CK20 focally +, CDX2 focally + ADC: CDX2, ADC SCNEC and LCNEC: synaptophysin, chromogranin A, TTF1 (+/–), p16	High-grade	Mixed cytology on urinary samples	Not clinically relevant	Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers	Same as for conventional carcinoma	Significantly stage-related; aligned to that of NECs
Prostate {30965328; 24705311; 26885643}	Large, invasive, frequently locally advanced masses	Acinar ADC: histological features of acinar ADC SCNEC: histological features of conventional SCNEC LCNEC: histological features of conventional LCNEC	Acinar ADC: PSA, AR, ERG, AMACR SCNEC and LCNEC: synaptophysin, chromogranin A, INSM1, AR–, PSA–, ERG may be +	High-grade	Not clinically relevant	Not clinically relevant	No previously diagnosed prostatic ADC treated with androgen deprivation therapy Two morphologically identifiable malignant components, NE and non-NE Immunohistochemistry: pertinent non-NE markers for the non-NE component and ≥ 2 NE markers for the NE component	Same as for conventional carcinoma	Patients with prostatic MiNEN may respond to adjuvant therapy and have a better outcome than those with pure de novo or post–adjuvant therapy LCNEC of the prostate
Skin									
Skin {24729037; 9027628; 9808429; 19609205; 26022453; 26099430; 26433246; 25720654; 31759946; 33533503}	Flesh-coloured or violaceous nodule or plaque	SCC: histological features of conventional SCC BCC: histological features of BCC MCC: small to intermediate and large cells with nuclei showing a fine granular salt-and-pepper chromatin pattern without nucleoli	SCC: CK5/6, p63, p40 BCC: CK5/6, p63, BerEP4, BCL2 MCC: synaptophysin, chromogranin A, CK20, p63 (+/–)	High-grade	Not clinically relevant	Not clinically relevant	Mixed tumour morphology Immunohistochemistry: pertinent non-NE markers for the non-NE component (p40, p63, CK5/6, BerEP4) and ≥ 2 NE markers, CK20, and p63 (+/–) for the MCC component	Same as for MCC	

AC, atypical carcinoid; ADC, adenocarcinoma; AdSC, adenosquamous carcinoma; BCC, basal cell carcinoma; CCRCC, clear cell renal cell carcinoma; CHC, cholangiocarcinoma; DFS, disease-free survival; EC, endometrioid carcinoma; GPC3, glypican-3; GS, glutamine synthetase; HCC, hepatocellular carcinoma; HGSC, high-grade serous carcinoma; ICPN, intracholecystic papillary neoplasm; IHC, immunohistochemistry; IP, inverted papilloma; ITAC, intestinal-type adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; MC, mucinous carcinoma; MCC, Merkel cell carcinoma; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; OS, overall survival; OTP, orthopedia homeobox protein; PRCC, papillary renal cell carcinoma; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma; TC, typical carcinoid; TTF1, thyroid transcription factor 1; 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/.