Table S8.2 Major pathological features and prognosis of neuroendocrine tumour (NET) 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 {30069842; 22964339; 27166275}	Reddish bulging mass	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1: < 2 mitoses/2 mm^2; no necrosis G2: 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 or two other NE markers *Desirable:* Ki-67 and SSTR2–5	Not performed	Few cases
Sinonasal tract, nasopharynx {17481837; 29103747; 26830400; 26622884; 30332658; 33474978; 33770323}	n/a	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin, S100 Negative: TTF1	n/a	n/a	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	Not performed	Not sufficiently reported
Oropharynx, oral cavity, and salivary glands {14720139; 21493041; 27840746; 28116178; 22614165; 23456649}	Bulging/palpable mass, 10–50 mm	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	n/a	n/a	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinomas	Not sufficiently reported
Hypopharynx, larynx, trachea, and parapharyngeal space {12071530; 15053292; 15098009; 15995505; 18617341; 19172557; 20580173; 20961285; 23397781; 24220389; 24596175; 26622884; 26854777; 26886629; 30974468; 31012344; 33167723}	Submucosal polypoid or sessile mass	Classic NE patterns for G1 G2: epithelioid; nested, moulded in some cases; surface involvement; focal necrosis may be seen; mitoses are not defined; spotty necrosis for atypical carcinoid	Positive: pancytokeratin, chromogranin A, synaptophysin, INSM1, various hormones (calcitonin, serotonin, bombesin [GRP], somatostatin) Negative: TTF1	Mitoses not used at present; tumour necrosis places in G2	n/a	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinomas	5-year survival rates: 80% for G1 typical carcinoid, 50% for G2 atypical carcinoid
Thorax									
Lung	Well-circumscribed round to ovoid lesion	Classic NE patterns; spotty necrosis for atypical carcinoid	Positive: pancytokeratin, chromogranin A, synaptophysin, INSM1 TTF1+ in peripheral tumours, TTF1− in central tumours	Typical carcinoid: < 2 mitoses/2 mm^2; no necrosis Atypical carcinoid: 2–10 mitoses/2 mm^2 and/or foci of necrosis	Tumour cells are discohesive and small, with round, oval, or spindle-shaped nuclei with finely granular chromatin and inconspicuous nucleoli; background is clean	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE lung carcinomas	5-year survival rates: > 90% for typical carcinoid, 60% for atypical carcinoid
Thymus	Most are unencapsulated and either circumscribed or grossly invasive; mean size: 80–100 mm; calcifications are frequent	Classic NE patterns; spotty necrosis for atypical carcinoid	Positive: pancytokeratin, chromogranin A, synaptophysin Negative: often TTF1 Hormones can be detected	Typical carcinoid: < 2 mitoses/2 mm^2; no necrosis Atypical carcinoid: 2–10 mitoses/2 mm^2 and/or foci of necrosis	Loose clusters or small strands of tumour cells with indistinct cell borders; cells are uniformly small and round to oval, with scant cytoplasm	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for other non-NE thymic carcinomas	5-year survival rates: 50–70% for typical carcinoid, 20–70% for atypical carcinoid
Digestive system									
Oesophagus	Polypoid or nodular submucosal mass; mean size: 24 mm	Classic NE patterns; spotty necrosis rare	Positive: cytokeratin, chromogranin A, synaptophysin, hormones (serotonin, PP, gastrin, enteroglucagon), VMAT2	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Usually not performed / not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	The same as for non-NE carcinoma	Good prognosis (few reports)
Stomach	Polypoid or nodular lesions; type I and type II ECL-cell NETs are mostly multiple; type III are single	Classic NE patterns; spotty necrosis rare	Positive: pancytokeratin, chromogranin A, synaptophysin, CDX2, SSTR2 ECL-cell NET: VMAT2+ and ghrelin G-cell NET: gastrin EC-cell NET: serotonin D-cell NET: somatostatin	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Usually not performed / not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	Gastric NET–specific	Largely depends on stage and grade; variable according to type: type I, excellent prognosis; type III, worst; type II, intermediate
Small intestine and ampulla	Submucosal nodules; often multiple; small in the duodenum; larger in the ileum, with muscular wall invasion	Classic NE patterns; usually solid islets; spotty necrosis rare; glandular pattern with psammoma bodies in duodenum (D-cell NETs)	Positive: pancytokeratin, chromogranin A, synaptophysin, CDX2, and SSTR2–5 G-cell NET: gastrin EC-cell NET: VMAT1 and serotonin D-cell NET: somatostatin	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Usually not performed / not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	Duodenal-ileal NET–specific	Largely depends on stage and grade Ampullary NET: 10-year survival rate of 71% Benign NET of ileum: 5-year survival rates of 70–100% when localized, 35–60% with distant metastases

EC, enterochromaffin; ECL, enterochromaffin-like; IHC, immunohistochemistry; n/a, not available; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1.

[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 S8.2 Major pathological features and prognosis of neuroendocrine tumour (NET) 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
Appendix	Well-demarcated yellowish nodules, mostly < 20 mm	Classic NE patterns; usually solid islets (EC-cell NET); trabeculae/ glands (L-cell NET)	Positive: pancytokeratin, chromogranin A, synaptophysin, CDX2, and SSTR2 EC-cell NET: serotonin+ L-cell NET: chromogranin A− and enteroglucagon/PYY+	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Usually not performed / not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	Appendiceal NET–specific	Largely depends on stage and grade; excellent outcome (10-year survival rate of 92%)
Colorectum	Well-demarcated submucosal nodules	Classic NE patterns; usually solid islets (EC-cell NET); trabeculae/ glands (L-cell NET)	Positive: pancytokeratin, chromogranin A, synaptophysin, CDX2, and SSTR2 EC-cell NET: serotonin+ L-cell NET: chromogranin A− and enteroglucagon/PYY+ and PAP	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Usually not performed / not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	Colorectal NET–specific	Largely depends on stage and grade; for low-stage G1–G2, median OS is 30 years (rectum) or 12 years (colon); G3 NET has poor OS (12 months)
Liver	Well-demarcated nodules	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Loose clusters or small strands of tumour cells with indistinct cell borders; cells are uniformly small and round to oval, with scant cytoplasm	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	The same as for non-NE carcinoma	Long survival when amenable for surgery; 18–47% metastatic disease (G2)
Gallbladder and bile ducts	Submucosal nodules	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1: < 2 mitoses/2 mm^2 and Ki-67 < 3% G2: 2–20 mitoses/2 mm^2 and/or Ki-67 3–20% G3: > 20 mitoses/2 mm^2 and/or Ki-67 > 20%	Lesions are seldom aspirated	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers; Ki-67 *Desirable:* SSTR2, SSTR5	The same as for non-NE carcinoma	Limited data; depends on size (larger tumours extend into the liver); 36% OS at 10 years
Female genital tract									
Ovary {28735441}	Usually a unilateral and small nodule within a dermoid cyst	Classic NE patterns admixed with thyroid follicles (strumal), associated with mucin pools with goblet cells (mucinous)	Positive: pancytokeratin, chromogranin A, synaptophysin Strumal carcinoids: TTF1+ and thyroglobulin+ Insular carcinoids: CDX2+	Well-differentiated; grade not defined	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Generally excellent
Fallopian tube	Polypoid/nodular lesion	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1 tumours show rare mitotic figures, whereas G2 tumours can show 2–20 mitoses/2 mm^2 (10 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) and foci of necrosis	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Very few studies
Endometrium {28735441}	Mass	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1 tumours show rare mitotic figures, whereas G2 tumours can show 2–20 mitoses/2 mm^2 (10 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) and foci of necrosis	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Very few studies
Cervix {28735441}	Polypoid/nodular lesion	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1 tumours show rare mitotic figures, whereas G2 tumours can show 2–20 mitoses/2 mm^2 (10 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) and foci of necrosis	Pap smear: cuboidal/columnar/ polygonal cells with variable amounts of pale, granular cytoplasm and monotonous nuclei	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Very few studies
Vagina {28735441}	Mass	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1 tumours show rare mitotic figures, whereas G2 tumours can show 2–20 mitoses/2 mm^2 (10 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) and foci of necrosis	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Very few studies

EC, enterochromaffin; ECL, enterochromaffin-like; IHC, immunohistochemistry; n/a, not available; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1.

[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 S8.2 Major pathological features and prognosis of neuroendocrine tumour (NET) at various anatomical sites[a] (continued)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
Vulva {28735441}	Mass	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	G1 tumours show rare mitotic figures, whereas G2 tumours can show 2–20 mitoses/2 mm^2 (10 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) and foci of necrosis	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67	The same as for non-NE carcinoma	Very few studies
Breast									
Breast	Infiltrating or expansile tumour	Densely cellular, solid nests and trabeculae of spindle to plasmacytoid cells	Positive: pancytokeratin, chromogranin A, synaptophysin, ER (> 90%) Negative: ERBB2	Nottingham grading G1 or G2	Cell clusters with rigid borders; plasmacytoid aspect; peripheral cytoplasmic granules on Giemsa stain; synaptophysin, chromogranin A, and ER are positive	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinoma	Variable according to grade and stage
Urinary and male genital tracts									
Kidney {33613455; 30732641}	Yellow nodule usually < 80 mm with possible haemorrhage	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin Negative: TTF1	Grade not defined	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinoma	Variable, depends on stage
Urinary tract {27334654; 33301750}	Small polypoid masses in the bladder neck or trigone	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin Negative: WT1	Grade not defined	Not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinoma	Rarely muscle-invasive
Prostate {33301750; 31415779}	Not defined	Not defined	Positive: pancytokeratin, chromogranin A, synaptophysin Negative: PSA Immunohistochemistry with chromogranin A or synaptophysin is not recommended in usual prostatic adenocarcinomas	Grade not defined	Seldom undertaken	No	A combination of an NE component (characterized by synaptophysin or chromogranin A immunostaining) and a significant non-NE component	The same as for non-NE carcinoma	Undefined
Testis {28559773; 26027014; 18316560; 22347748}	Mass; average size: 46 mm	Classic NE patterns	Positive: pancytokeratin, chromogranin A, synaptophysin	Grade not defined	Seldom undertaken	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinoma	Usually excellent; depends on tumour size and stage, and presence of syndrome
Skin									
Skin {28169866}	10–40 mm lesion	Classic NE patterns; evident mitoses; Ki-67: < 20%	Positive: pancytokeratin, chromogranin A, synaptophysin, ER, AR, GCDFP-15, GATA3 Positive/negative: mammaglobin	Grade not defined; considered low-grade	Not clinically relevant	No	*Essential:* NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers *Desirable:* Ki-67, SSTR2, and SSTR5	The same as for non-NE carcinoma	Depends on stage (2 of 11 reported cases had metastases/recurrence)

EC, enterochromaffin; ECL, enterochromaffin-like; IHC, immunohistochemistry; n/a, not available; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1.

[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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