

**Table S8.4** Major pathological features and prognosis of small cell neuroendocrine carcinoma (SCNEC) at various anatomical sites<sup>a</sup> (continued on next page)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
<b>Head and neck</b>									
<b>Middle ear / external auditory canal</b> {32851892}	Polypoid mass	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, INSM1	High-grade by definition Mitoses not defined	Not clinically relevant for diagnosis on primary site; for SCNEC classic	No established role	<i>Essential:</i> NE morphology, with high-grade cytology, tumour necrosis, and high mitotic count; expression of cytokeratin(s) and NE markers (> 1) in strong and diffuse pattern <i>Desirable:</i> SSTR2–5; high Ki-67 labelling index	None	Poor prognosis; no large studies available
<b>Sinonasal tract</b> {19157501; 19685359; 21794118; 23740425; 24980293; 25457524; 25727332; 26880574; 27392929; 27529044; 27859290; 27938993; 28932042; 29438167; 29734873; 30248495; 30475447; 31161776; 31186531; 31763323; 32358042; 33090899; 33371727; 33433884}	Large and destructive mass with haemorrhage and necrosis	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, p16 Variable: chromogranin A, synaptophysin, INSM1	High-grade by definition Mitoses not defined	Not clinically relevant for diagnosis on primary site; SCNEC classic	No established role	<i>Essential:</i> NE morphology, with high-grade cytology, tumour necrosis, and high mitotic count; expression of cytokeratin(s) and NE markers (> 1) in strong and diffuse pattern <i>Desirable:</i> SSTR2–5; Ki-67 labelling index	Non-NE carcinoma	5-year survival rates as low as 13%; median survival time: 15 months
<b>Oropharynx, oral cavity, and salivary glands</b> {18038886; 22430343; 22301491; 23838856; 2421566; 24966986; 27392929; 27496009; 27818885; 29093415; 30475447; 31161776; 31463946; 31523135; 31920384; 33694290}	Ulcerated mass, rapid clinical presentation Salivary glands: large, infiltrative nodules with necrosis and haemorrhage	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, p16 Variable chromogranin A, synaptophysin, INSM1 Salivary glands: CK20+, MCPyV–	High-grade by definition Mitoses not defined	Not clinically relevant for diagnosis on primary site Salivary glands and metastasis deposit: SCNEC classic	No established role No UV radiation signature ISH for high-risk HPV is helpful	<i>Essential:</i> NE morphology, with high-grade cytology, tumour necrosis, and high mitotic count; expression of cytokeratin(s) and NE markers (> 1) in strong and diffuse pattern <i>Desirable:</i> SSTR2–5; Ki-67 labelling index	Non-NE carcinoma	Most have a poor prognosis, but few cases reported Oral cavity: median OS time of 21 months; 5-year OS rate of 27% Salivary glands: median OS time of 25 months, 5-year OS rate of 33%
<b>Hypopharynx, larynx, trachea, and parapharyngeal space</b> {22430343; 22433139; 23397781; 23397787; 24596175; 24980293; 25351497; 25457524; 25606844; 26173932; 26611246; 27392929; 27859290; 28559027; 29557536; 29909787; 31161776; 31437725}	Fleshy, ulcerated submucosal mass	SCNEC classic	Positive: p16 in HPV-associated cases	High-grade by definition Mitoses not defined	Not clinically relevant for diagnosis on primary site; for SCNEC classic	No established role	<i>Essential:</i> NE morphology, with high-grade cytology, tumour necrosis, and high mitotic count; expression of cytokeratin(s) and NE markers (> 1) in strong and diffuse pattern <i>Desirable:</i> SSTR2–5; Ki-67 labelling index	Non-NE carcinoma	70% advanced disease; 5-year OS rate of 5–20%
<b>Thorax</b>									
<b>Lung</b> {27873319; 33209646}	Typically perihilar mass but peripheral lesions may occur	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, TTF1, INSM1 Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate > 10 mitoses/2 mm <sup>2</sup> (average: 60 mitoses/2 mm <sup>2</sup> ); Ki-67: > 50% (average: > 80%)	SCNEC classic (FNAB, bronchial aspirates and/or brushing)	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> one/two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	2-year OS rate: 10% in metastatic disease; 5-year OS rate: 25% in non-metastatic disease; median OS time: 12.7 months
<b>Thymus</b> {31042566; 20485130; 29201448}	Grossly invasive with frequent necrosis and haemorrhage	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, TTF1 Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate > 10 mitoses/2 mm <sup>2</sup> (average: 110 mitoses/2 mm <sup>2</sup> )	SCNEC classic (FNAB)	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Epithelial tumours of the thymus	Median survival time: 13.75 months (range: 13–26 months)
<b>Digestive system</b>									
<b>Oesophagus</b> {33847642; 33686305; 33980813}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, TTF1 in 70% Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate: > 20 mitoses/2 mm <sup>2</sup> ; Ki-67: > 20%	SCNEC classic	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median OS time range: 8–15 months; older age, upper third location, advanced stage, and no surgery or radiotherapy or chemotherapy are adverse prognostic factors
<b>Stomach</b> {33686305; 15226341; 28239029; 33359239; 25465415}	Large fungating masses deeply infiltrating the wall	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, TTF1 in 70% Variable: chromogranin A, synaptophysin, CDX2	High-grade by definition Mitotic rate: > 20 mitoses/2 mm <sup>2</sup> ; Ki-67: > 20%	SCNEC classic	Rare MMR-deficient status but potential clinical utility	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Poor prognosis; survival time: a few months (no large studies available)

IHC, immunohistochemistry; ISH, in situ hybridization; LCNEC, large cell neuroendocrine carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1; UV, ultraviolet.

<sup>a</sup>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 S8.4** Major pathological features and prognosis of small cell neuroendocrine carcinoma (SCNEC) at various anatomical sites<sup>a</sup> (continued from previous page, continued on next page)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
<b>Small intestine and ampulla</b>	Large and invasive mass (median size: 25 mm)	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate: > 20 mitoses/ 2 mm <sup>2</sup> ; Ki-67: > 20%	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Poor prognosis; survival time: a few months (no large studies available)
<b>Appendix</b> {18197972}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, TTF1	High-grade by definition Mitotic rate: > 20 mitoses/ 2 mm <sup>2</sup> ; Ki-67: > 20%	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Poor prognosis; no large studies available
<b>Colorectum</b> {33135938; 28059096; 17063080; 29354876; 25465415}	Grossly similar to conventional adenocarcinoma	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, CDX2 (usually) Variable: chromogranin A, synaptophysin, TTF1	High-grade by definition Mitotic rate: > 20 mitoses/ 2 mm <sup>2</sup> ; Ki-67: > 20%	Usually not performed / not clinically relevant	Rare MMR-deficient status but potential clinical utility	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median OS times for patients with extensive and limited disease: 4.04 months and 21.82 months, respectively; administration of chemotherapy and radiotherapy but not surgery are associated with improved survival
<b>Liver</b> {23280574}	Typically a solitary circumscribed mass with gross necrosis	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate: > 20 mitoses/ 2 mm <sup>2</sup> ; Ki-67: > 20%	SCNEC classic	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median survival time: 2 months
<b>Gallbladder and bile ducts</b> {29548338; 28040546; 26208508}	Solid mass with necrotic areas	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition Mitotic rate: > 20 mitoses/ 2 mm <sup>2</sup> ; Ki-67: > 20%	SCNEC classic (brushing)	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median survival time: 3 months
<b>Female genital tract</b>									
<b>Ovary</b> {24875120; 29621125}	Nonspecific; mean size: 130 mm	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, TTF1	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	5-year OS rates of 48.6%, 30.7%, 18%, and 12.3% for stages I, II, III, and IV; earlier disease stage and use of CT are associated with lower mortality
<b>Fallopian tube</b> {10053109}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Unknown
<b>Endometrium</b> {24875120; 32773531}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, p16 MMR abnormalities in 50%	High-grade by definition	SCNEC classic (both on smears and on liquid-based cytology samples)	Rare MMR-deficient status but potential clinical utility	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Mean OS times of 22 and 12 months in early and late stages, respectively
<b>Cervix</b> {24875120; 33888337; 30355937; 33830625}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, p16 (in the majority of cases), TTF1 (often) Variable: chromogranin A, synaptophysin, CDX2, p63	High-grade by definition	SCNEC classic (both on smears and on liquid-based cytology samples)	HPV typing useful	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median OS time of 22–25 months; 5-year OS rate of 35%; adverse prognostic indicators are advanced FIGO stage, larger tumour size, lymph node metastasis, lymphovascular space involvement, parametrial involvement, depth of stromal invasion > 2/3, radiotherapy but not chemotherapy

IHC, immunohistochemistry; ISH, in situ hybridization; LCNEC, large cell neuroendocrine carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1; UV, ultraviolet.

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**Table S8.4** Major pathological features and prognosis of small cell neuroendocrine carcinoma (SCNEC) at various anatomical sites\* (continued)

Site	Macroscopic appearance	Histopathology	IHC	Grading	Cytology	Diagnostic molecular pathology	Diagnostic criteria	Staging	Prognosis
<b>Vagina</b> {33792412; 24875120}	Nonspecific, also submucosal	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition	SCNEC classic (both on smears and on liquid-based cytology samples)	HPV typing useful	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Poor prognosis (mean OS time: 10 months); no large studies available
<b>Vulva</b> {24875120}	Nodules usually predominantly intradermal with areas of haemorrhage, necrosis, and ulceration	SCNEC classic or MCC morphology	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin TTF1+ in SCNEC classic CK20+ and MCPyV+ in MCC	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Unknown for SCNEC classic; see below for MCC
<b>Breast</b>									
<b>Breast</b> {32336623; 33135938; 33584543; 32613538}	No distinctive macroscopic appearance compared with other breast carcinomas	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse, ER, PR, AR, GATA3, GCDPF-15 Variable: chromogranin A, synaptophysin Negative: ERBB2	High-grade by definition	SCNEC classic	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median OS time: 3–5 years; 5-year survival rate: 42%
<b>Urinary and male genital tracts</b>									
<b>Kidney</b> {33477429}	Solid mass with frequent necrosis	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	Median OS time: of 9.3 months
<b>Urinary tract</b> {21567387; 33561506; 31664527; 27698324}	Large, solid, solitary, polypoid, nodular mass with or without ulceration	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, GATA3 (in ~30% of cases), TTF1 (in 40% of cases)	High-grade by definition	SCNEC classic (both on smears and on liquid-based cytology samples)	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	5-year OS rate: 8–25% Organ-confined disease and chemotherapy are favourable prognostic factors
<b>Prostate</b> {33664492; 21336263; 18162772; 24323898; 33847621; 33582100}	Nonspecific (rarely surgically resectable)	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin, TTF1 (in 50% of cases), PSA, AR, NKX3-1 (in a minority of cases)	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE carcinoma	5-year OS rate: 14%; median OS time: 12 months in cases with pure histology
<b>Testis</b> {25207197}	No specific features	SCNEC classic	Positive: AE1/AE3, CAM5.2 dot-like or diffuse Variable: chromogranin A, synaptophysin	High-grade by definition	Usually not performed / not clinically relevant	No established role	<i>Essential:</i> small cell epithelial neoplasm with high-grade features, finely granular nuclear chromatin, and no prominent nucleoli <i>Desirable:</i> two positive NE marker(s); high proliferation index (> 30%, most frequently > 75%); p53 overexpression and/or RB1 loss; SSTR2–5	Non-NE tumours	Poor prognosis

IHC, immunohistochemistry; ISH, in situ hybridization; LCNEC, large cell neuroendocrine carcinoma; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; NE, neuroendocrine; OS, overall survival; TTF1, thyroid transcription factor 1; UV, ultraviolet.

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