**Table S8.6** Major pathological features and prognosis of large cell neuroendocrine carcinoma (LCNEC) 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** | | | | | | | | | |
| **Sinonasal tract and nasopharynx** {30191506; 31186531; 33433884; 22082601; 30191506; 27392929; 26735857; 25727332; 2208260} | Large and destructive mass with haemorrhage and necrosis | LCNEC classic | AE1/AE3, CAM5.2 dot-like or diffuse; variable chromogranin A, synaptophysin, INSM1; p16+ | High-grade by definition<br>Mitotic count not determined | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | To be defined; reported 5-year DFS rate: 50–65% |
| **Oropharynx, oral cavity, salivary glands** {22082601; 22024350; 26735857; 31463946; 30475447; 27818885; 22718848; 33544384; 23953500} | Large and ulcerated mass<br>Salivary glands: large infiltrative nodules with necrosis and haemorrhage | LCNEC classic | AE1/AE3, CAM5.2 dot-like or diffuse; variable chromogranin A, synaptophysin; p16+<br>Salivary glands: AE1/AE3, CAM5.2 dot-like or diffuse, high-molecular-weight cytokeratins negative; variable chromogranin A, synaptophysin; p16+, p63−; may be focally CK20+ but always MCPyV− | High-grade by definition<br>Mitotic count not determined | ISH for high-risk HPV is helpful in the oropharynx and oral cavity<br>Salivary glands: LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor prognosis<br>Salivary glands: 5-year DFS rate: 5–20% |
| **Hypopharynx, larynx, trachea, and parapharyngeal space** {22082601; 31437725; 22024350; 24596175; 26611246; 22718848; 22433139; 22430343; 20679623; 20589486} | Fleshy, ulcerated submucosal mass | LCNEC classic | AE1/AE3, CAM5.2 dot-like or diffuse; variable chromogranin A, synaptophysin; p16+ | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | 5-year DFS rate: 15% |
| **Thorax** | | | | | | | | | |
| **Lung** | Large (average: 30–40 mm) masses, well circumscribed, with necrotic areas | LCNEC classic; combined forms with small cell carcinoma | AE1/AE3, CAM5.2 dot-like or diffuse; variable chromogranin A, synaptophysin; TTF1+ (50% of cases); KIT (CD117) (70%); INSM1 | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | 2-year OS rate: 10% in metastatic disease; 5-year OS rate: 25% in non-metastatic disease; median OS time: 10 months |
| **Thymus** {33555458; 31042566} | Grossly invasive with frequent necrosis and haemorrhage | LCNEC classic; combined forms with small cell carcinoma | AE1/AE3, CAM5.2 dot-like or diffuse; variable chromogranin A, synaptophysin; TTF1 and CD5 generally negative | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ (average: 110 mitoses/2 $mm^2$) | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | 5-year OS rate: 0–66% |
| **Digestive system** | | | | | | | | | |
| **Oesophagus** {23426118} | Exophytic/polypoid or ulcerated | LCNEC classic; may be associated with a non-NE component (squamous cell carcinoma or adenocarcinoma) | AE1/AE3, CAM5.2 dot-like or diffuse; synaptophysin (100%), chromogranin A (60%), p63 (40%), TTF1 (40%), CK8/18 (100%), KIT (CD117) (60%), and p16 (60%) | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Median OS time: 8–15 months |
| **Stomach** {32985687; 28239029; 32985687; 23759931; 33142079} | Large fungating masses deeply infiltrating the wall | LCNEC classic; frequently associated with adenocarcinoma; may be associated with an SCNEC component | AE1/AE3, CAM5.2 dot-like or diffuse; synaptophysin (90%); chromogranin A (85%); ASH1L (32%); TTF1 (35%) | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor prognosis, overlapping with SCNEC; 5-year OS rate: 8–66% |
| **Small intestine and ampulla** {15832081; 22964952} | Large and invasive mass (median size: 25 mm) | LCNEC classic; may be associated with an adenoma or adenocarcinoma | Cytokeratins and general NE markers (no systematic study) | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Median OS time: 11.8 months |
| **Appendix** | Not specifically investigated | Not specifically investigated | Not specifically investigated | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Not specifically investigated |
| **Colorectum** {18360283; 24763982; 33197299; 27586204; 31672771; 27048246; 30237525; 25465415; 30022911; 30990915} | Large and invasive mass | LCNEC classic; about half associated with an adenoma and/or adenocarcinoma, rare cases with a squamous cell carcinoma component | 91–100% of cases positive for chromogranin and/or synaptophysin | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Ominous outcome related to Ki-67 PI: < 55%, median OS 25.4 months; > 55%, median OS 5.3 months; LCNECs with MSI-H may have better OS than non–MSI-H counterparts |
| **Liver** {33726764; 27881473; 26184027} | Typically solitary circumscribed mass with gross necrosis (mean size: 58 mm) | LCNEC classic; typically mixed with non-NEC components (HCC) | Synaptophysin+, chromogranin+/−, hepatocyte markers −, albumin (ISH) −, Ki-67 PI > 80% | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Worse than pure HCC; analysis of a small number of reported cases revealed a 1-year cumulative survival rate of 53% |

AT, adjuvant therapy; DFS, disease-free survival; EHBD, extrahepatic bile duct; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; ISH, in situ hybridization; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; MSI-H, high level of microsatellite instability; NE, neuroendocrine; NEC, neuroendocrine carcinoma; OS, overall survival; PI, proliferation index; SCNEC, small cell neuroendocrine carcinoma; 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.]].

References: The in-text citations provided within curly brackets are PubMed reference numbers (PMIDs), searchable at https://pubmed.ncbi.nlm.nih.gov/.

**Table S8.6** Major pathological features and prognosis of large cell neuroendocrine carcinoma (LCNEC) at various anatomical sites[a] (continued)

| Site | Macroscopic appearance | Histopathology | IHC | Grading | Cytology | Diagnostic molecular pathology | Diagnostic criteria | Staging | Prognosis |
|---|---|---|---|---|---|---|---|---|---|
| **Gallbladder and EHBDs** {32739935; 27888490; 19917473} | Solid mass with necrotic areas; diameter: 2.2–30 mm in EHBDs, 35–56 mm in gallbladder NENs | LCNEC classic; one third of cases mixed with adenocarcinoma or SCNEC | AE1/AE3, CAM5.2 dot-like or diffuse; synaptophysin (100%), chromogranin A (53%) | High-grade by definition<br>Mitotic count > 20 mitoses/2 $mm^2$; Ki-67 PI > 20% | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Median survival time: < 1 year; 5-year OS rate: 20%; 10-year OS rate: 0% |
| **Female genital tract** | | | | | | | | | |
| **Ovary** {33194158} | No distinctive macroscopic appearance vs other ovarian carcinomas | LCNEC classic; usually associated with surface epithelial tumours, rarely with teratoma | Variable expression of NE markers and pancytokeratin; PAX8 and WT1 may be positive; ER and PR usually negative | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ and frequent necrosis; Ki-67: no cut-off point defined | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor; median OS time: 10 months |
| **Fallopian tube** {33194158} | No distinctive macroscopic appearance vs other carcinomas | LCNEC classic | Variable expression of NE markers and pancytokeratin; PAX8, WT1, ER, and PR usually negative | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ and frequent necrosis; Ki-67: no cut-off point defined | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor |
| **Endometrium** {33194158; 26945341; 32773531} | No distinctive macroscopic appearance vs other endometrial carcinomas | LCNEC classic; frequent association with other endometrial cancers (endometrioid, serous) | Variable expression of NE markers and pancytokeratin; p16+/−; MMR abnormalities in 50% | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ and frequent necrosis; Ki-67: no cut-off point defined | Pap smear: large cells with prominent nucleoli dispersed as single cells or arranged as loosely cohesive sheets | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor |
| **Cervix** {33194158; 20182342; 32408525; 29728073} | No distinctive macroscopic appearance vs other cervical neoplasms | LCNEC classic; in situ or invasive minor glandular or squamous component | Variable expression of NE markers and pancytokeratin; p16+; CDX2, TTF1, p63, SSTR2A, and SSTR5 may be expressed | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ and frequent necrosis; Ki-67: no cut-off point defined | Pap smear: large cells with prominent nucleoli dispersed as single cells or arranged as loosely cohesive sheets | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | 5-year survival rate: 14–39%; mean OS time: 40 months |
| **Vagina** {33194158} | No distinctive macroscopic appearance vs other vaginal carcinomas | LCNEC classic | Variable expression of NE markers and pancytokeratin; p16+ | High-grade by definition<br>Mitotic count > 10 mitoses/2 $mm^2$ and frequent necrosis; Ki-67: no cut-off point defined | Pap smear: large cells with prominent nucleoli dispersed as single cells or arranged as loosely cohesive sheets | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor |
| **Vulva** {33194158; 32826525} | Nodules with areas of haemorrhage, necrosis, and ulceration | LCNEC classic; MCC | Variable expression of NE markers; TTF1+; CK20− | High-grade by definition | Not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor |
| **Breast** | | | | | | | | | |
| **Breast** | No distinctive macroscopic appearance vs other breast carcinomas | LCNEC classic | Variable expression of NE markers; GATA3+; variable expression of ER and PR; ERBB2− | High-grade by definition | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Not specifically investigated |
| **Urinary and male genital tracts** | | | | | | | | | |
| **Kidney** {32366387; 29848671} | Large, solid mass with frequent necrosis | LCNEC classic | Not specifically investigated | High-grade by definition | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Aggressive with frequent distant metastases |
| **Urinary tract** {32366387; 28638669; 29180607; 33454836; 20164052; 29763719; 33454836; 26308137} | Large, solid, solitary, polypoid, nodular mass with or without ulceration | LCNEC classic; frequently associated with urothelial-derived components | Synaptophysin (92%), chromogranin A (85%), epithelial markers (pancytokeratin, CAM5.2, EMA), p16; TTF1 (< 70%); negative for p63 and GATA3 | High-grade by definition | LCNEC classic | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Dismal prognosis, similar to stage-matched urothelial carcinoma |
| **Prostate** {16723845; 30965328; 26885643; 30918106} | Nonspecific | LCNEC classic; sometimes in association with squamous cell carcinoma and adenocarcinoma | Synaptophysin, chromogranin A, epithelial markers (pancytokeratin, CAM5.2, EMA), p16; negative for PSA and AR; AMACR may be positive | High-grade by definition | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; large cells; expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* high Ki-67 PI (> 55%), SSTR2–5 | As epithelial malignancies of the site | Poor prognosis; patients with de novo LCNEC mixed with prostatic adenocarcinoma may respond to AT and have a better outcome than those with pure de novo or post-AT LCNEC |
| **Skin** | | | | | | | | | |
| **Merkel cell carcinoma** {19395876; 11486166; 30067951; 31233624; 33760021; 33932460; 30349028; 31399473} | Nodule in dermis and/or subcutis with haemorrhage, necrosis, and ulceration | A spectrum of cytological features from small to intermediate and large cells has been described; fine granular salt-and-pepper chromatin pattern; nuclear moulding is uncommon but may be observed; nucleoli are inconspicuous; rosette-like structures may be seen; mitotic figures and apoptotic bodies are numerous | Positive for CK20, AE1/AE3, CAM5.2; negative for CK7; frequently positive for NFP, INSM1; variable expression of other NE markers; positive for CM2B4, if positive for MCPyV; consistently positive for SATB2 and negative for TTF1; may express PAX5 | High-grade by definition | Usually not performed / not clinically relevant | No | *Essential:* poorly differentiated NE morphology; diffuse and intense expression of cytokeratin(s) and chromogranin A or two other NE markers<br>*Desirable:* CK20+, NFP+, TTF1−, CK7−; MCPyV+/− | In the skin, specific staging for MCC according to the size of the neoplasm | 5-year OS: 51% localized; 35% regional; 14% distant; 5-year disease-specific survival: 30% |

AT, adjuvant therapy; DFS, disease-free survival; EHBD, extrahepatic bile duct; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; ISH, in situ hybridization; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, mismatch repair; MSI-H, high level of microsatellite instability; NE, neuroendocrine; NEC, neuroendocrine carcinoma; OS, overall survival; PI, proliferation index; SCNEC, small cell neuroendocrine carcinoma; TTF1, thyroid transcription factor 1.

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