## Supplemental material

### **Supplemental table 1:** Genes included in the NanoString panel.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| SMTN | UBE2J1 | UBA7 | ALDH3A1 | KCTD12 | SLC2A1 |
| IGF2BP2 | CD2 | OSMR | IL33 | SLA | RPA2 |
| HRAS | ARL6IP5 | PTPRC | CIITA | DPT | GCHFR |
| COL13A1 | COL17A1 | SLAMF7 | YIF1A | TNFRSF1A | CD247 |
| PECAM1 | F2RL1 | SASH1 | PPP1R16B | ZDHHC11 | CXCL12 |
| LAMC2 | TLR7 | MAD1L1 | ZAK | FADS3 | IL11 |
| C16ORF57 | SPRR3 | IL17A | MT2A | PANX1 | MFAP4 |
| TUBB3 | GALNT6 | GPR171 | TRAF3IP3 | TGFBI | PCDH7 |
| NCF4 | PDPN | CA9 | SEMA4D | CDC7 | CBS |
| FKBP14 | FLNA | KCNS3 | MCM2 | GZMK | PLEK2 |
| GIMAP6 | CDKN2A | FBLN1 | ZBED2 | LRIG1 | SPARCL1 |
| CD74 | IFNG | MMP10 | EVI2B | AREG | TNFAIP2 |
| KRT1 | HLADPB1 | STAT1 | PIM2 | KRT17 | ICOS |
| PLAU | MYC | S100A4 | TGFBR2 | IL10RA | ECHDC2 |
| PYGL | VEGFC | PPAP2B | ITGB1 | MEF2C | ACTN1 |
| ALDH1A1 | HIF1A | MAN1C1 | HLADMA | E6 (HPV16) | VNN2 |
| DBI | SLC2A9 | GIMAP5 | CXCL10 | ST6GAL1 | MCCC1 |
| SUSD4 | ITGA3 | NTRK2 | F3 | CAMK2N1 | KRT13 |
| SELL | FBXO2 | ACTL6A | REPIN1 | TSPAN5 | FUCA1 |
| EYA2 | CTSL2 | EGFR | CD8A | PROCR | POSB(32) |
| FST | PXN | KRT16 | HK2 | SEMA3C | POSC(8) |
| SLC16A1 | HOMER3 | CAV2 | NRG1 | CYORF15B | POSE(0.5) |
| PAPPA | AKR1C3 | TPBG | AMMECR1L | HLADPA1 | POSD(2) |
| TNFRSF12A | E2F2 | IL1B | LMO4 | CYP27B1 | POSF(0.125) |
| HLADOB | KRT9 | CECR1 | BPGM | GIMAP4 | POSA(128) |
| CAV1 | CCR7 | SNAI2 | ITGA5 | LIMA1 | NEGC(0) |
| KRT19 | CDA | HLADRA | CSPG4 | CD79A | NEGD(0) |
| AKR1C1 | ITGAL | CYBB | MMP9 | IRS1 | NEGB(0) |
| CD3G | MCM10 | C20ORF20 | P4HA2 | C19ORF21 | NEGF(0) |
| CSF1R | TMUB2 | LAG3 | GATM | TACC1 | NEGE(0) |
| VIM | NME7 | GLTSCR2 | FOSL1 | VEGF | NEGA(0) |
| IRF8 | PRPF38A | SELENBP1 | PTGDS | PBX1 |  |
| PTGS1 | TNFRSF17 | ITGB7 | CCL19 | PPFIBP2 |  |
| LRMP | CORO1A | TMEM176A | CDH3 | ARTN |  |
| MYO5C | EHD2 | FAM46C | IGJ | FCGRT |  |
| GZMH | NKG7 | SLAMF6 | STAB1 | IDO1 |  |
| RGS20 | ABCC5 | NT5E | RASSF2 | RRAS2 |  |
| KRT75 | CD69 | HLADMB | ICAM3 | KLRB1 |  |
| PTHLH | ICAM2 | DOCK10 | ACSL5 | MYO1B |  |
| ITM2A | FHL2 | CXCL9 | LAMA3 | DDX50 |  |

### 

### **Supplemental table 2:** Clinicopathologic characteristics of all histologically analyzed samples.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient Number | Used for survival analysis | Subtype | Histotype | Grading (WHO) | Tumor cell budding (2 tier) | Cell nest size (2 tier) | Mitotic count (2 tier) | Nuclear size (2 tier) | Stroma content (2 tier) | Necrosis (2 tier) | Inflammatory infiltrate (2 tier) | Lymphvessel invasion | Perineural invasion | Sex | Age at randomisation | Localization sample | Tumor stadium |
| 2 | yes | CL | non-keratinizing | G2 | high | small | high | big | low | low | low | present | absent | male | 64 | Oropharynx | 4 |
| 3 | yes | BA | keratinizing | G2 | high | small | high | small | low | low | high | absent | absent | male | 62 | Hypopharynx | 4 |
| 4 | yes | BA | keratinizing | G3 | high | small | high | small | low | low | low | absent | absent | male | 57 | Oropharynx | 4 |
| 5 | yes | MS | keratinizing | G3 | high | small | low | small | high | high | low | absent | present | male | 62 | Hypopharynx | 4 |
| 5 | no | MS | non-keratinizing | G2 | high | small | low | big | low | low | low | absent | absent | male | 62 | Hypopharynx | 4 |
| 5 | no | BA | non-keratinizing | G3 | high | small | high | big | low | low | high | absent | absent | male | 62 | Hypopharynx | 4 |
| 6 | yes | BA | keratinizing | G2 | high | small | low | big | low | high | high | absent | absent | male | 52 | Hypopharynx | 3 |
| 6 | no | MS | non-keratinizing | G2 | high | small | high | small | low | high | low | present | absent | male | 52 | Hypopharynx | 3 |
| 7 | yes | MS | non-keratinizing | G3 | high | small | low | big | low | low | high | absent | absent | male | 66 | Oropharynx | 4 |
| 8 | yes | MS | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 62 | NA | NA |
| 11 | yes | CL | non-keratinizing | G3 | high | small | low | small | low | high | low | absent | absent | female | 64 | Hypopharynx | 4 |
| 16 | yes | BA | keratinizing | G2 | high | small | low | small | low | low | high | absent | absent | male | 58 | Tongue | 4 |
| 17 | yes | BA | non-keratinizing | G2 | high | small | low | small | high | low | low | absent | absent | male | 40 | Hypopharynx | 4 |
| 18 | yes | BA | keratinizing | G2 | high | small | low | small | high | low | high | absent | absent | male | 67 | Larynx | 4 |
| 18 | no | BA | non-keratinizing | G2 | high | small | low | small | low | low | low | absent | absent | male | 67 | Larynx | 4 |
| 18 | no | BA | keratinizing | G3 | high | small | low | small | low | high | low | present | present | male | 67 | Larynx | 4 |
| 18 | no | BA | non-keratinizing | G2 | high | small | low | small | low | low | high | absent | absent | male | 67 | Larynx | 4 |
| 19 | yes | MS | basaloid | G3 | high | small | high | small | high | high | low | absent | absent | male | 72 | Hypopharynx | 4 |
| 19 | no | CL | keratinizing | G2 | low | big | low | small | low | low | high | absent | absent | male | 72 | Hypopharynx | 4 |
| 21 | no | BA | non-keratinizing | G2 | high | small | low | small | low | low | high | absent | absent | male | 69 | Tongue | 4 |
| 22 | yes | CL | keratinizing | G3 | high | small | high | small | low | high | low | absent | absent | male | 61 | Tonsil | 3 |
| 22 | no | MS | keratinizing | G2 | high | small | high | big | low | high | high | absent | absent | male | 61 | Tonsil | 3 |
| 22 | no | MS | keratinizing | G2 | high | small | high | small | low | high | high | absent | present | male | 61 | Tonsil | 3 |
| 22 | no | MS | basaloid | G3 | high | small | low | small | low | high | high | present | absent | male | 61 | Tonsil | 3 |
| 23 | yes | BA | keratinizing | G3 | high | small | low | small | low | high | low | absent | absent | male | 57 | Tongue | 4 |
| 25 | yes | CL | basaloid | G3 | high | small | high | small | low | high | low | present | absent | male | 55 | Oropharynx | 4 |
| 26 | yes | BA | keratinizing | G2 | high | small | high | big | low | high | high | present | absent | male | 58 | Hypopharynx | 4 |
| 30 | yes | MS | non-keratinizing | G2 | high | big | low | small | low | low | high | present | absent | male | 70 | Tonsil | 3 |
| 145 | yes | CL | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 146 | yes | MS | non-keratinizing | G2 | high | small | high | big | low | high | high | absent | absent | male | 54 | Tongue | 4 |
| 147 | yes | CL | non-keratinizing | G2 | low | big | low | small | low | low | high | absent | absent | male | 63 | Tongue | 4 |
| 217 | yes | BA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | female | NA | NA | NA |
| 218 | yes | CL | keratinizing | G2 | high | big | low | small | high | low | high | present | absent | male | 58 | Oropharynx | 4 |
| 219 | yes | CL | non-keratinizing | G2 | low | big | low | small | low | low | low | absent | absent | male | 59 | Oropharynx | 4 |
| 253 | yes | BA | non-keratinizing | G2 | low | big | high | small | low | low | low | absent | absent | female | 46 | Oral cavity | 4 |
| 254 | yes | MS | non-keratinizing | G2 | low | big | low | small | low | low | high | absent | absent | male | 65 | Larynx | 4 |
| 255 | yes | MS | basaloid | G3 | high | big | high | small | low | high | high | absent | absent | male | 61 | Oropharynx | 4 |
| 256 | no | CL | basaloid | G3 | high | small | high | small | low | high | high | present | absent | male | 59 | Oral cavity | 4 |
| 256 | yes | CL | keratinizing | G2 | high | small | high | small | low | low | high | absent | absent | male | 59 | Oral cavity | 4 |
| 265 | yes | MS | keratinizing | G2 | high | small | high | small | high | high | high | absent | absent | male | 59 | Larynx | 4 |
| 268 | yes | MS | non-keratinizing | G3 | high | big | low | small | low | low | high | absent | absent | male | 67 | Hypopharynx | 4 |
| 362 | yes | BA | keratinizing | G2 | high | small | low | small | low | low | low | absent | absent | male | 57 | Tongue | 4 |
| 363 | yes | BA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | female | 42 | Oral cavity | 3 |
| 364 | yes | BA | keratinizing | G2 | low | big | high | small | low | low | low | absent | absent | female | 54 | Tonsil | 4 |
| 365 | yes | BA | keratinizing | G2 | high | small | high | small | low | low | high | present | absent | male | 60 | Larynx | 3 |
| 369 | yes | CL | keratinizing | G2 | low | big | low | small | high | high | high | absent | absent | male | 52 | Oropharynx | 4 |
| 372 | yes | BA | keratinizing | G3 | high | small | low | small | high | low | low | absent | absent | male | 56 | Larynx | 3 |
| 373 | yes | MS | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | male | 66 | Oropharynx | 4 |
| 375 | yes | MS | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | male | 69 | Hypopharynx | 4 |
| 383 | yes | MS | non-keratinizing | G2 | high | small | high | small | high | high | high | absent | absent | male | 62 | Oropharynx | 4 |
| 384 | yes | BA | keratinizing | G2 | high | big | high | big | low | high | high | absent | present | female | 53 | Hypopharynx | 4 |
| 387 | yes | CL | non-keratinizing | G3 | high | small | low | big | low | high | high | absent | absent | male | 67 | Larynx | 4 |
| 397 | no | CL | keratinizing | G2 | high | small | high | small | high | low | high | absent | absent | male | 47 | Oral cavity | 4 |
| 397 | yes | CL | keratinizing | G2 | high | small | high | small | high | low | high | absent | absent | male | 47 | Oral cavity | 4 |
| 399 | yes | BA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | male | 61 | Hypopharynx | 4 |
| 578 | yes | MS | non-keratinizing | G2 | low | big | high | small | high | high | high | absent | absent | male | 74 | Tongue | 4 |
| 615 | yes | CL | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | female | 52 | Tongue | 4 |
| 617 | yes | BA | non-keratinizing | G2 | low | small | low | small | low | low | high | present | absent | male | 46 | Hypopharynx | 4 |
| 619 | yes | BA | non-keratinizing | G2 | low | big | low | small | low | low | high | present | absent | male | 58 | Larynx | 4 |
| 620 | yes | MS | keratinizing | G2 | high | small | low | small | high | low | high | absent | absent | female | 72 | Oropharynx | 4 |
| 621 | yes | BA | keratinizing | G2 | high | small | low | small | low | high | low | absent | absent | male | 59 | Oral cavity | 4 |
| 624 | yes | BA | keratinizing | G2 | high | small | low | small | low | high | high | absent | present | male | 76 | Larynx | 4 |
| 632 | yes | CL | keratinizing | G3 | high | small | low | small | low | low | high | present | absent | male | 53 | Hypopharynx | 3 |
| 633 | yes | BA | keratinizing | G2 | high | big | low | small | low | high | high | absent | absent | male | 53 | Oropharynx | 4 |
| 634 | yes | CL | non-keratinizing | G2 | high | small | low | small | low | low | high | absent | absent | male | 59 | Oropharynx | 4 |
| 635 | yes | BA | non-keratinizing | G3 | high | small | low | small | low | low | low | absent | absent | male | 56 | Oral cavity | 4 |
| 636 | yes | MS | non-keratinizing | G2 | high | small | low | small | high | low | high | present | absent | male | 62 | Larynx | 4 |
| 637 | yes | MS | basaloid | G3 | high | small | low | big | low | high | low | absent | absent | male | 66 | Hypopharynx | 4 |
| 638 | yes | CL | keratinizing | G2 | high | small | high | small | high | low | high | absent | absent | male | 47 | Hypopharynx | 4 |
| 641 | yes | BA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | male | 58 | Tonsil | 4 |
| 642 | yes | CL | non-keratinizing | G2 | low | big | low | small | low | high | high | absent | absent | male | 68 | Oral cavity | 4 |
| 643 | yes | BA | non-keratinizing | G3 | high | small | low | big | high | low | high | absent | absent | male | 53 | Larynx | 4 |
| 644 | yes | BA | keratinizing | G2 | high | small | low | big | low | low | high | absent | absent | male | 63 | Larynx | 4 |
| 652 | yes | CL | non-keratinizing | G2 | low | big | low | big | low | low | high | absent | absent | male | 57 | Tonsil | 4 |
| 652 | no | CL | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 655 | yes | MS | keratinizing | G2 | low | big | low | big | high | high | high | absent | absent | male | 54 | Oropharynx | 4 |
| 685 | yes | BA | keratinizing | G2 | high | small | high | small | low | low | high | absent | absent | male | 46 | Tongue | 4 |
| 686 | yes | BA | keratinizing | G1 | high | small | low | small | high | low | high | absent | absent | female | 73 | Oral cavity | 4 |
| 687 | yes | BA | non-keratinizing | G2 | high | small | high | small | low | high | high | absent | absent | male | 62 | Oropharynx | 4 |
| 688 | yes | MS | non-keratinizing | G2 | high | small | low | big | low | low | low | absent | absent | male | 60 | Oral cavity | 4 |

### **Supplemental table 3:** Metrics of the histological parameters.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | median | interquartile range | mean | standard deviation | min | max |
| Tumor budding | 3.0 | 4.0 | 4.7 | 4.7 | 0 | 25 |
| Mitotic activity | 2.0 | 3.8 | 3.1 | 2.4 | 1 | 12 |
| Stroma content | 20.0 | 23.8 | 24.4 | 16.7 | 1 | 65 |
| Necrosis | 0.0 | 7.8 | 7.4 | 14.0 | 0 | 50 |
| Lymphocytic infiltrate | 3.0 | 7.0 | 5.0 | 5.3 | 0.5 | 30 |
| Minimal cell nest size | 1.0 | 0.8 | 5.6 | 13.3 | 1 | 60 |
| Nuclear size | 2.0 | 1.0 | 1.8 | 0.8 | 1 | 3 |

### **Supplemental table 4:** Distribution of the samples according to the cutoffs identified by “Cutoff Finder”.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | TB low | TB high | Mitotic activity low | Mitotic activity high | Stroma content low | Stroma content high | Necrosis low | Necrosis high | Lymphocytic infiltrate low | Lymphocytic infiltrate high |
| Cutoffs | 0-1 | ≥ 2 | 0-3 | ≥ 4 | 0-32 | ≥ 33 | 0 | ≥ 1 | 0-1 | ≥ 2 |
| Number of samples with available data | 57 | 13 | 27 | 43 | 18 | 52 | 29 | 41 | 48 | 22 |
| % | 81.4 | 18.6 | 38.6 | 61.4 | 25.7 | 74.3 | 41.4 | 58.6 | 68.6 | 31.4 |
|  | Minimal cell nest size small | Minimal cell nest size big | Nuclear size small | Nuclear size big | Lymphovascular invasion | Lymphovascular invasion | Perineural invasion | Perineural invasion | Keratinization | Keratinization |
| Cutoffs | 1 | ≥ 2 | 1-2 | ≥ 3 | absent | present | absent | present | absent | present |
| Number of samples with available data | 18 | 52 | 16 | 54 | 56 | 14 | 65 | 5 | 33 | 37 |
| % | 25.7 | 74.3 | 22.9 | 77.1 | 80.0 | 20.0 | 92.9 | 7.1 | 47.1 | 52.9 |

### **Supplemental table 5:** Clinical and histological correlations of the CeFCiD cohort.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number of samples with available data** | **Minimal cell nest size** | |  | **Mitoses** | |  | **Nuclear size** | |  | **Stroma content** | |  | **Necrosis** | |  | **Inflammation** | |  |
|  |  | small | big | p | low | high | p | small | high | p | low | high | p | low | high | p | low | high | p |
| **Age (median; IQR)** | 70 | 60.5 (8) | 58.5 (12.5) | 0.984 | 62 (10) | 59 (8) | 0.052 | 59.5 (10.5) | 60.5 (9.25) | 0.785 | 60.5 (7.25) | 58.5 (13.5) | 0.572 | 59 (9) | 61 (9) | 0.672 | 59 (7.5) | 61 (12.25) | 0.455 |
| **Sex** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **male** | 64 | 49 (94.2) | 15 (83.3) | 0.172 | 40 (93.0) | 24 (88.9) | 0.670 | 49 (90.7) | 15 (93.8) | >0.999 | 48 (92.3) | 16 (88.9) | 0.643 | 37 (90.2) | 27 (93.1) | >0.999 | 19 (86.4) | 45 (93.8) | 0.370 |
| **female** | 6 | 3 (5.8) | 3 (16.7) |  | 3 (7.0) | 3 (11.1) |  | 5 (9.3) | 1 (6.2) |  | 4 (7.7) | 2 (11.1) |  | 4 (9.8) | 2 (6.9) |  | 3 (13.6) | 3 (6.2) |  |
| **Tumor stage** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **3** | 10 | 9 (17.3) | 1 (5.6) | 0.435 | 5 (11.6) | 5 (18.5) | 0.493 | 8 (14.8) | 2 (12.5) | >0.999 | 9 (17.3) | 1 (5.6) | 0.435 | 4 (9.8) | 6 (20.7) | 0.299 | 3 (13.6) | 7 (14.6) | >0.999 |
| **4** | 60 | 43 (82.7) | 17 (94.4) |  | 38 (88.4) | 22 (81.5) |  | 46 (85.2) | 14 (87.5) |  | 43 (82.7) | 17 (94.4) |  | 37 (90.2) | 23 (79.3) |  | 19 (86.4) | 41 (85.4) |  |
| **Grading** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **G1/G2** | 50 | 34 (65.4) | 16 (88.9) | 0.073 | 30 (69.8) | 20 (74.1) | 0.790 | 39 (72.2) | 11 (68.8) | 0.763 | 36 (69.2) | 14 (77.8) | 0.560 | 33 (80.5) | 17 (58.6) | 0.062 | 11 (50.0) | 39 (81.2) | **0.011** |
| **G3** | 20 | 18 (34.6) | 2 (11.1) |  | 13 (30.2) | 7 (25.9) |  | 15 (27.8) | 5 (31.2) |  | 16 (30.8) | 4 (22.2) |  | 8 (19.5) | 12 (41.4) |  | 11 (50.0) | 9 (18.8) |  |
| **Histotype** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **basaloid** | 6 | 5 (9.6) | 1 (5.6) | 0.503 | 2 (4.7) | 4 (14.8) | 0.137 | 5 (9.3) | 1 (6.2) | 0.580 | 5 (9.6) | 1 (5.6) | 0.208 | 0 (0.0) | 6 (20.7) | **0.002** | 3 (13.6) | 3 (6.2) | 0.468 |
| **conventional (keratinizing)** | 34 | 27 (51.9) | 7 (38.9) |  | 19 (44.2) | 15 (55.6) |  | 28 (51.9) | 6 (37.5) |  | 22 (42.3) | 12 (66.7) |  | 19 (46.3) | 15 (51.7) |  | 9 (40.9) | 25 (52.1) |  |
| **conventional (non-keratinizing)** | 30 | 20 (38.5) | 10 (55.6) |  | 22 (51.2) | 8 (29.6) |  | 21 (38.9) | 9 (56.2) |  | 25 (48.1) | 5 (27.8) |  | 22 (53.7) | 8 (27.6) |  | 10 (45.5) | 20 (41.7) |  |
| **Localization** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Hypopharynx** | 17 | 14 (26.9) | 3 (16.7) | 0.458 | 10 (23.3) | 7 (25.9) | 0.366 | 11 (20.4) | 6 (37.5) | 0.748 | 13 (25.0) | 4 (22.2) | 0.486 | 9 (22.0) | 8 (27.6) | 0.733 | 7 (31.8) | 10 (20.8) | 0.871 |
| **Larynx** | 14 | 12 (23.1) | 2 (11.1) |  | 12 (27.9) | 2 (7.4) |  | 11 (20.4) | 3 (18.8) |  | 9 (17.3) | 5 (27.8) |  | 10 (24.4) | 4 (13.8) |  | 3 (13.6) | 11 (22.9) |  |
| **Oral cavity** | 10 | 8 (15.4) | 2 (11.1) |  | 5 (11.6) | 5 (18.5) |  | 9 (16.7) | 1 (6.2) |  | 7 (13.5) | 3 (16.7) |  | 7 (17.1) | 3 (10.3) |  | 4 (18.2) | 6 (12.5) |  |
| **Oropharynx** | 14 | 8 (15.4) | 6 (33.3) |  | 8 (18.6) | 6 (22.2) |  | 11 (20.4) | 3 (18.8) |  | 9 (17.3) | 5 (27.8) |  | 7 (17.1) | 7 (24.1) |  | 4 (18.2) | 10 (20.8) |  |
| **Tongue** | 8 | 6 (11.5) | 2 (11.1) |  | 5 (11.6) | 3 (11.1) |  | 7 (13.0) | 1 (6.2) |  | 7 (13.5) | 1 (5.6) |  | 5 (12.2) | 3 (10.3) |  | 2 (9.1) | 6 (12.5) |  |
| **Tonsil** | 7 | 4 (7.7) | 3 (16.7) |  | 3 (7.0) | 4 (14.8) |  | 5 (9.3) | 2 (12.5) |  | 7 (13.5) | 0 (0.0) |  | 3 (7.3) | 4 (13.8) |  | 2 (9.1) | 5 (10.4) |  |
| **Lymphangiosis** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **absent** | 56 | 41 (78.8) | 15 (83.3) | >0.999 | 35 (81.4) | 21 (77.8) | 0.764 | 42 (77.8) | 14 (87.5) | 0.497 | 40 (76.9) | 16 (88.9) | 0.494 | 33 (80.5) | 23 (79.3) | >0.999 | 18 (81.8) | 38 (79.2) | >0.999 |
| **present** | 14 | 11 (21.2) | 3 (16.7) |  | 8 (18.6) | 6 (22.2) |  | 12 (22.2) | 2 (12.5) |  | 12 (23.1) | 2 (11.1) |  | 8 (19.5) | 6 (20.7) |  | 4 (18.2) | 10 (20.8) |  |
| **Perineural invasion** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **absent** | 65 | 48 (92.3) | 17 (94.4) | >0.999 | 40 (93.0) | 25 (92.6) | >0.999 | 50 (92.6) | 15 (93.8) | >0.999 | 48 (92.3) | 17 (94.4) | >0.999 | 41 (100.0) | 24 (82.8) | **0.010** | 20 (90.9) | 45 (93.8) | 0.646 |
| **present** | 5 | 4 (7.7) | 1 (5.6) |  | 3 (7.0) | 2 (7.4) |  | 4 (7.4) | 1 (6.2) |  | 4 (7.7) | 1 (5.6) |  | 0 (0.0) | 5 (17.2) |  | 2 (9.1) | 3 (6.2) |  |
| **Subtype** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **basal** | 30 | 25 (48.1) | 5 (27.8) | 0.254 | 20 (46.5) | 10 (37.0) | 0.743 | 24 (44.4) | 6 (37.5) | 0.391 | 25 (48.1) | 5 (27.8) | 0.237 | 21 (51.2) | 9 (31.0) | 0.066 | 11 (50.0) | 19 (39.6) | 0.803 |
| **classical** | 19 | 12 (23.1) | 7 (38.9) |  | 11 (25.6) | 8 (29.6) |  | 16 (29.6) | 3 (18.8) |  | 14 (26.9) | 5 (27.8) |  | 12 (29.3) | 7 (24.1) |  | 5 (22.7) | 14 (29.2) |  |
| **mesenchymal/ inflamed** | 21 | 15 (28.8) | 6 (33.3) |  | 12 (27.9) | 9 (33.3) |  | 14 (25.9) | 7 (43.8) |  | 13 (25.0) | 8 (44.4) |  | 8 (19.5) | 13 (44.8) |  | 6 (27.3) | 15 (31.2) |  |

### 

### **Supplemental figure 1:** Photomicrographs of histological parameters. Tumors show high (A, arrows) and low (B) tumor budding, high (C) and low (D) lymphocytic infiltrate, high (E) and low (F) stroma content and lymphovascular invasion (G, arrow)

### **Supplemental figure 2:** Clinicopathological correlations of the study cohort. For continuous variables, the Pearson-correlation was applied to obtain p-values.