SUPPLEMENTARY MATERIAL

Table S1. Association between clinical features and grading: univariate analysis.

Characteristics	Low grading (G1/G2) N=12 N (%)	High grading (G3) N=19 N (%)	P-value∞
Age at diagnosis^ [years]	55 (45-64)	60 (42-89)	**0.04**
Gender			0.53
Males	9 (86%)	16 (88%)	
Females	3 (14%)	3 (13%)	
Tumor stage (8th ed.) [14]			0.13
I	3 (25%)	0 (0%)	
II	1 (8%)	2 (11%)	
III	1 (8%)	4 (21%)	
IVA/IVB	7 (58%)	13 (68%)	
Tumor site			0.17
Tonsil	5 (42%)	11 (58%)	
Base of tongue	6 (50%)	5 (26%)	
Vallecula	0 (14%)	3 (16%)	
Soft palate	1 (8%)	0 (0%)	
HPV status			0.19
Negative	5 (45%)	4 (22%)	
Positive	6 (55%)	14 (78%)	
Treatment			0.77
Surgery	2 (17%)	4 (21%)	
Surgery+CHT+RT	3 (25%)	2 (11%)	
CHT+RT	6 (50%)	11 (58%)	
Surgery+RT	1 (8%)	2 (11%)	

CHT=chemotherapy; RT=radiotherapy

∞ Fisher Exact test for categorical variables; non-parametric Wilcoxon two-independent samples test for continuous variables

^ Median (range)

Table S2. Association between clinical features and HPV status: univariate analysis.

Characteristics	HPV- N=9 N (%)	HPV+ N=20 N (%)	P-value∞
Age at diagnosis^ [years]	59 (45-75)	60 (42-72)	0.78
Gender			0.07
Males	9 (100%)	14 (70%)	
Females	0 (0%)	6 (30%)	
Tumor stage (8th ed.) [14]			0.18
I	0 (0%)	2 (10%)	
II	1 (11%)	2 (10%)	
III	3 (33%)	1 (5%)	

IVA/IVB	5 (56%)	15 (75%)	
Tumor site			**0.02**
Tonsil	2 (22%)	14 (70%)	
Base of tongue	4 (44%)	6 (21%)	
Vallecula	2 (22%)	0 (8%)	
Soft palate	1 (11%)	0 (0%)	
Grading			0.19
1/2	5 (56%)	6 (30%)	
3	4 (44%)	14 (70%)	
Treatment			0.48
Surgery	1 (11%)	3 (15%)	
Surgery+CHT+RT	3 (33%)	2 (10%)	
CHT+RT	4 (44%)	13 (65%)	
Surgery+RT	1 (11%)	2 (10%)	

CHT=chemotherapy; RT=radiotherapy

∞ Fisher Exact test for categorical variables; non-parametric Wilcoxon two-independent samples test for continuous variables

^ Median (range)

Table S3. Association between clinical features and T stage: univariate analysis.

Characteristics	Tis/T1/T2 N=17 N (%)	T3/T4 N=15 N (%)	P-value∞
Age at diagnosis^ [years]	56 (42-68)	63 (45-89)	0.07
Gender			0.46
Males	13 (76%)	13 (87%)	
Females	4 (24%)	2 (13%)	
Tumor site			**0.04**
Tonsil	13 (76%)	4 (27%)	
Base of tongue	3 (18%)	8 (53%)	
Vallecula	1 (6%)	2 (13%)	
Soft palate	0 (0%)	1 (7%)	
Grading			0.89
1/2	6 (38%)	6 (40%)	
3	10 (63%)	9 (60%)	
HPV status			**0.03**
Negative	2 (13%)	7 (50%)	
Positive	13 (87%)	7 (50%)	
Treatment			0.38
Surgery	5 (29%)	1 (7%)	
Surgery+CHT+RT	2 (12%)	3 (20%)	
CHT+RT	9 (53%)	9 (60%)	
Surgery+RT	1 (6%)	2 (13%)	

CHT=chemotherapy; RT=radiotherapy

∞ Fisher Exact test for categorical variables; non-parametric Wilcoxon two-independent samples test for continuous variables

^ Median (range)

Table S4. Association between representative^ radiomic features from 16 clusters and grading: univariate analysis.

Radiomic features (cluster)	Low grading (G1/G2) N=12 Median (range)	High grading (G3) N=19 Median (range)	P-value	Q-value∞
Shape/Roundness (1)	0.30 (0.11-0.41)	0.25 (0.11-0.45)	0.59	0.63
GLCM3/-333-1SumAverage (2)	134.62 (95.42-164.22)	128.20 (95.27-172.30)	0.41	0.61
GLCM25/180-1InverseVariance (3)	0.16 (0.13-0.20)	0.16 (0.12-0.26)	0.27	0.61
ID/Skewness (4)	-0.33 (-0.89-0.24)	-0.16 (-1.15-0.49)	0.31	0.61
GLCM3/11-7ClusterProminence (5)*	298.73 (131.37-891.70)	235.20 (67.45-571.99)	0.18	0.61
GLCM3/9-1Correlation (6)	0.61 (0.31-0.65)	0.57 (0.37-0.82)	0.35	0.61
GOH/65Percentile (7)	118.45 (106.34-125.36)	115.64 (108.43-124.70)	**0.04**	0.35
GOH/MeanAbsoluteDeviation (8)	46.11 (44.69-49.17)	45.04 (41.93-47.81)	0.07	0.40
GLCM3/10-4Correlation (9)	0.13 (-0.13-0.39)	0.11 (-0.01-0.40)	0.37	0.61
GLCM3/0-4Correlation (10)	0.29 (0.06-0.41)	0.19 (-0.06-0.45)	0.46	0.61
GLCM3/8-7Correlation (11)	0.10 (-0.07-0.36)	0.05 (-0.10-0.38)	0.51	0.63
GLCM3/4-7Correlation (12)	0.12 (-0.1-0.23)	0.10 (-0.03-0.34)	0.46	0.61
GLCM25/180-1InformationMeasureCorr1 (13)	-0.13 (-0.15--0.09)	-0.14 (-0.22--0.09)	0.35	0.61
GLCM3/2-4Correlation (14)	0.34 (0.24-0.50)	0.32 (0.13-0.71)	0.56	0.63
GOH/85Percentile (15)	153.43 (148.39-157.37)	152.10 (145.30-153.43)	**0.01**	0.19
GLCM3/11-7Correlation (16)	0.08 (-0.16-0.26)	0.06 (-0.12-0.31)	0.83	0.83

GLCM=GrayLevelCooccurenceMatrix; GOH=GradientOrientHistogram; ID=IntensityDirect

^ For each cluster, we reported the features with the lowest p-value. For equal p-values, we chose the first calculated feature

∞ False Discovery Rate adjusted P-values for the non-parametric Wilcoxon two-independent samples test

*Values divided by 1000

Table S5. Association between representative^ radiomic features from 16 clusters and HPV status: univariate analysis.

Radiomic features (cluster)	HPV- N=9 Median (range)	HPV+ N=20 Median (range)	P-value	Q-value∞
GLCM25/-333-7InformationMeasureCorr1 (1)	-0.01 (-0.04-0.00)	-0.02 (-0.04--0.01)	0.16	0.34
GLCM3/2-7SumAverage (2)	146.67 (95.60-173.99)	131.67 (96.10-159.05)	0.18	0.34
ND/Busyness (3)*	0.44 (0.31-0.98)	0.60 (0.29-0.85)	0.06	0.22
ID/ Skewness (4)	-0.53 (-1.15-0.16)	-0.15 (-0.89-0.49)	0.06	0.22
GLCM3/12-7MaxProbability (5)*	2.42 (1.43-6.82)	3.25 (1.88-9.84)	0.26	0.34
GLCM3/8-1Correlation (6)	0.72 (0.59-0.75)	0.63 (0.53-0.83)	0.24	0.34
GOH/30Percentile (7)	49.4 (47.23-52.13)	53.13 (45.00-63.43)	0.07	0.22
GOH/10Percentile (8)	14.74 (13.32-16.70)	16.54 (12.99-19.80)	**0.03**	0.22
GLCM3/7-7Correlation (9)	0.06 (-0.08-0.14)	0.11 (-0.08-0.39)	0.14	0.34
GLCM3/-333-7Correlation (10)	0.09 (0.03-0.16)	0.07 (-0.01-0.32)	0.50	0.53
GLCM3/8-4Correlation (11)	0.20 (0.04-0.26)	0.10 (-0.13-0.42)	0.50	0.53
GLCM3/12-7Correlation (12)	0.05 (-0.07-0.15)	0.10 (-0.20-0.37)	0.59	0.59
GLCM3/12-1InformationMeasureCorr1 (13)	-0.08 (-0.15--0.05)	-0.09 (-0.19--0.05)	0.24	0.34
GLCM3/5-7Correlation (14)	0.11 (-0.04-0.17)	0.07 (-0.07-0.36)	0.32	0.39
GOH/90Percentile (15)	161.57 (158.20-164.48)	161.02 (156.37-162.18)	**0.03**	0.22
GLCM3/11-7Correlation (16)	0.11 (-0.09-0.16)	0.06 (-0.16-0.31)	0.24	0.34

GLCM=GrayLevelCooccurenceMatrix; GOH=GradientOrientHistogram; ID=IntensityDirect; ND= NeighborIntensityDifference

^ For each cluster, we reported the features with the lowest p-value. For equal p-values, we chose the first calculated feature

∞ False Discovery Rate adjusted P-values for the non-parametric Wilcoxon two-independent samples test

*Values multiplied by 1000

Table S6. Association between clinical features and local recurrence within two years: univariate analysis*.

Characteristics	No local recurrence N=16 N (%)	Local recurrence N=4 N (%)	P-value[∞]
Age at diagnosis^ [years]	60 (46-72)	54 (42-64)	0.33
Gender			0.20
Males	11 (69%)	4 (100%)	
Females	5 (31%)	0 (0%)	
Tumor stage (8th ed.) [14]			0.55
I	2 (13%)	0 (0%)	
II	2 (13%)	1 (25%)	
III	1 (6%)	1 (25%)	
IVA/IVB	11 (69%)	2 (50%)	
Tumor site			0.05
Tonsil	9 (56%)	3 (75%)	
Base of tongue	7 (44%)	0 (0%)	
Vallecula	0 (0%)	0 (0%)	
Soft palate	0 (0%)	1 (25%)	
Grading			0.57
1/2	2 (18%)	1 (33%)	
3	9 (82%)	2 (67%)	
HPV status			0.17
Negative	1 (10%)	1 (50%)	
Positive	9 (90%)	1 (50%)	
Treatment			0.34
Surgery	3 (19%)	0 (0%)	
Surgery+CHT+RT	4 (25%)	0 (0%)	
CHT+RT	8 (50%)	4 (100%)	
Surgery+RT	1 (6%)	0 (0%)	

CHT=chemotherapy; RT=radiotherapy

* N=20. Twelve patients with less than two years of follow-up were not considered

[∞] Fisher Exact test for categorical variables; non-parametric Wilcoxon two-independent samples test for continuous variables

^ Median (range)

Table S7. Association between representative^ radiomic features from 16 clusters and local recurrence within two years: univariate analysis*.

Radiomic features (cluster)	No local recurrence N=16 Median (range)	Local recurrence N=4 Median (range)	P-value	Q-value∞
Shape/Roundness (1)	0.27 (0.11-0.41)	0.22 (0.11-0.3)	0.33	0.49
GLRLM25/-333LongRunLowGrayLevelEmpha (2)	0.0006 (0.0002-0.004)	0.0004 (0.0002-0.002)	0.43	0.53
GLCM25/-333-1MaxProbability (3)	0.004 (0.002-0.008)	0.003 (0.002-0.004)	0.29	0.47
GLCM3/5-7ClusterShade (4)	-638.93 (-9677.45-3647.36)	28.82 (-2854.32-1222)	0.43	0.53
GLCM3/11-4Variance (5)	256.34 (149.73-631.88)	358.86 (208.81-468)	0.25	0.47
GLCM3/11-1Correlation (6)	0.55 (0.38-0.77)	0.62 (0.52-0.69)	0.14	0.43
Shape/Orientation (7)	-14.66 (-58.07-63.71)	-25.31 (-45.94-16)	0.61	0.68
GOH/InterQuartileRange (8)	90 (80.54-102.63)	92.03 (85.04-97.38)	0.74	0.74
GLCM3/6-4Correlation (9)	0.15 (-0.03-0.49)	0.23 (0.13-0.36)	0.25	0.47
GLCM3/11-4Correlation (10)	0.1 (-0.17-0.38)	0.19 (0.13-0.3)	0.08	0.43
GLCM3/10-7Correlation (11)	0.05 (-0.21-0.31)	0.16 (0.05-0.26)	0.11	0.43
GLCM3/4-7Correlation (12)	0.08 (-0.07-0.23)	0.15 (0.14-0.17)	**0.04**	0.31
GLCM3/2-1InformationMeasureCorr1 (13)	-0.21 (-0.31--0.16)	-0.23 (-0.25--0.23)	**0.04**	0.31
GLCM3/2-1Correlation (14)	0.87 (0.8-0.95)	0.9 (0.86-0.93)	0.19	0.47
GOH/90Percentile (15)	161.33 (156.37-164.48)	161.31 (160.02-162.35)	0.64	0.68
GLCM3/11-7Correlation (16)	0.05 (-0.16-0.26)	0.13 (-0.04-0.2)	0.29	0.47

GLCM=GrayLevelCooccurenceMatrix; GLRLM=GrayLevelRunLengthMatrix; GOH=GradientOrientHistogram
^ For each cluster, we reported the features with the lowest p-value. For equal p-values, we chose the first calculated feature
* N=20. Twelve patients with less than two years of follow-up were not considered
∞ False Discovery Rate adjusted P-values for the non-parametric Wilcoxon two-independent samples test

Table S8. Association between representative^ radiomic features from 16 clusters and T stage: univariate analysis.

Radiomic features (cluster)	Tis/T1/T2 N=17 Median (range)	T3/T4 N=15 Median (range)	P-value	Q-value∞
GLCM25/180-4InformationMeasureCorr2 (1)	0.73 (0.47-0.89)	0.55 (0.39-0.7)	**0.0008**	**0.01**
Shape/MeanBreadth (2)	2.65 (1.58-10.43)	5.14 (2.84-14.66)	**0.01**	**0.03**
GLCM25/90-1InverseDiffMomentNorm (3)*	996.04 (992.53-997.74)	996.89 (995.71-998.46)	**0.01**	**0.03**
GLCM3/9-7ClusterShade (4)	30.76 (-2434.83-2409.44)	-452.46 (-5663.98-1044.45)	0.07	0.09
GLCM3/11-7Dissimilarity (5)	13.23 (10.09-20.2)	10.80 (7.48-15.44)	**0.04**	0.07
GLCM3/0-1Correlation (6)	0.73 (0.62-0.89)	0.80 (0.64-0.85)	0.06	0.09
GOH/30Percentile (7)	53.13 (45.00-63.43)	50.19 (45.00-60.52)	0.24	0.27
GOH/5Percentile (8)	7.35 (5.87-9.46)	6.34 (5.19-7.91)	**0.02**	0.06
GLCM3/6-7Correlation (9)	0.03 (-0.08-0.2)	0.10 (-0.02-0.33)	**0.02**	0.06
GLCM3/0-7Correlation (10)	0.08 (-0.12-0.32)	0.20 (-0.04-0.36)	**0.03**	0.06
GLCM3/8-7Correlation (11)	0.01 (-0.10-0.36)	0.13 (-0.02-0.38)	0.06	0.09
GLCM3/12-7Correlation (12)	0.05 (-0.07-0.37)	0.10 (-0.20-0.25)	0.63	0.67
GLCM3/6-1InformationMeasureCorr1 (13)	-0.12 (-0.21--0.07)	-0.10 (-0.13--0.07)	**0.004**	**0.03**
GLCM3/5-7Correlation (14)	0.09 (-0.07-0.32)	0.10 (-0.04-0.36)	0.82	0.82
GOH/90Percentile (15)	160.35 (156.37-162.35)	161.57 (158.20-164.48)	**0.03**	0.06
GLCM3/11-7Correlation (16)	-0.02 (-0.16-0.26)	0.09 (-0.03-0.31)	0.07	0.09

GLCM=GrayLevelCooccurenceMatrix; GOH=GradientOrientHistogram

^ For each cluster, we reported the features with the lowest p-value. For equal p-values, we chose the first calculated feature

∞ False Discovery Rate adjusted P-values for the non-parametric Wilcoxon two-independent samples test

*Multiplied by 1000