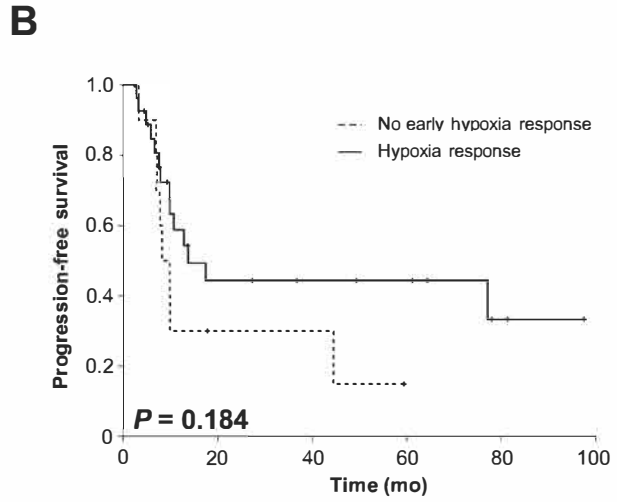
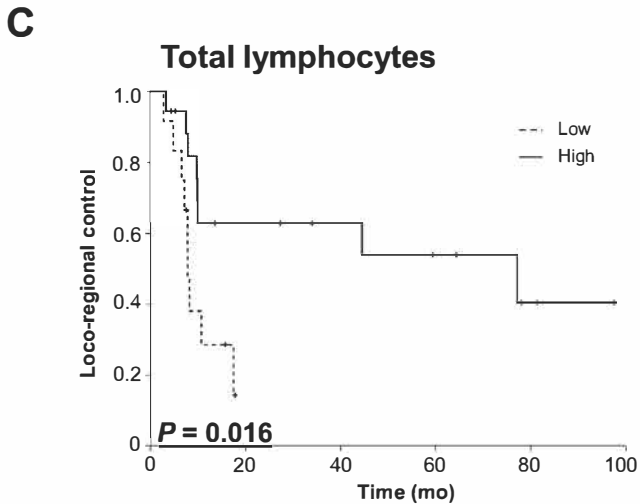


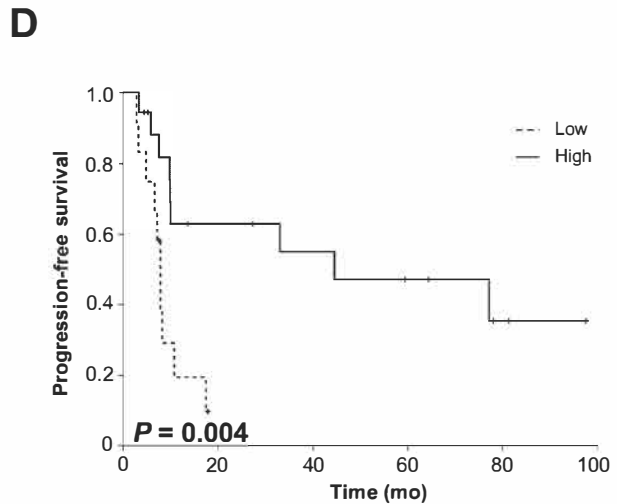
No hypoxia response	10	2	2	0	0	0
Hypoxia response	28	9	7	6	2	0



No hypoxia response	10	2	2	0	0	0
Hypoxia response	28	9	7	6	2	0

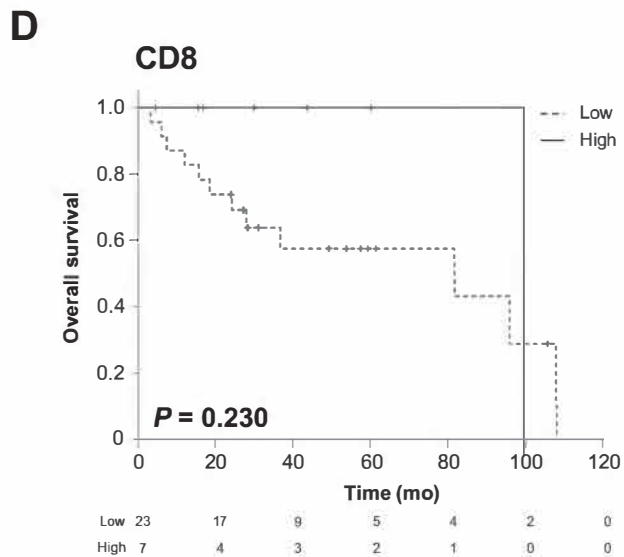
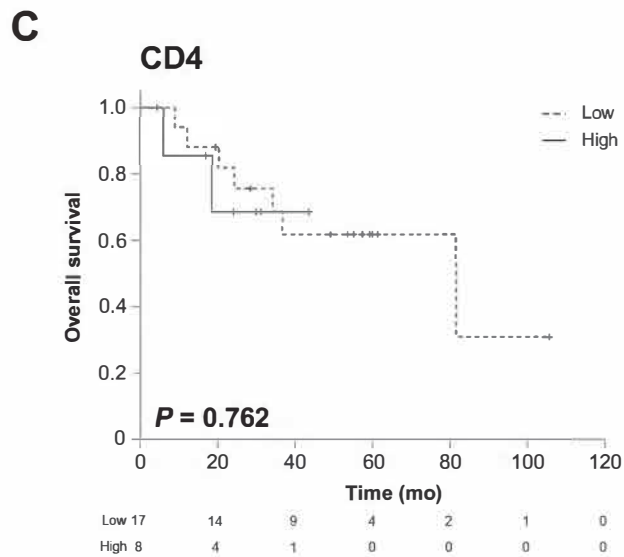
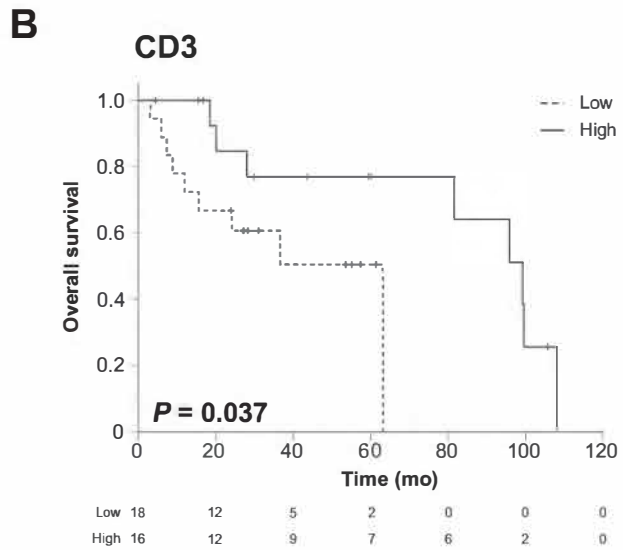
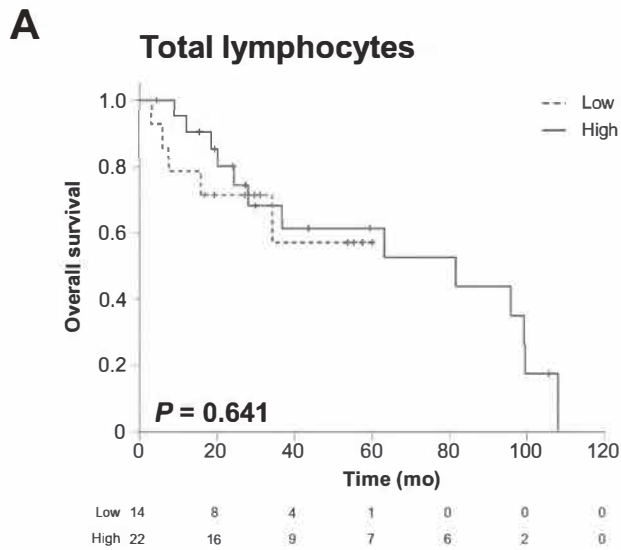


Low	12	0	0	0	0	0
High	18	9	7	5	2	0

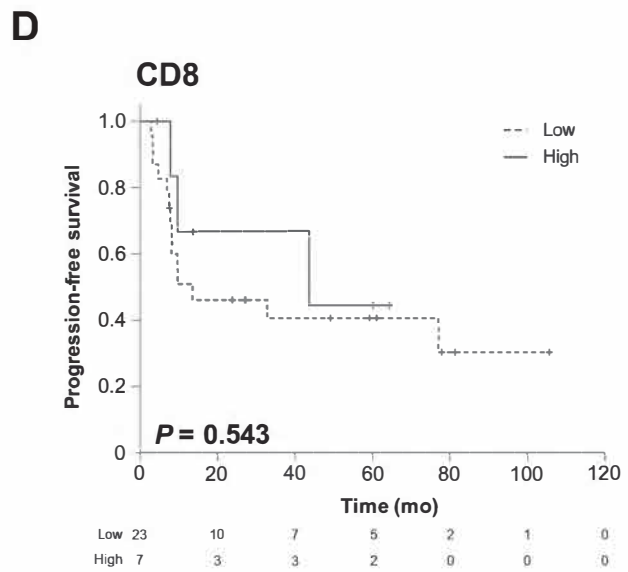
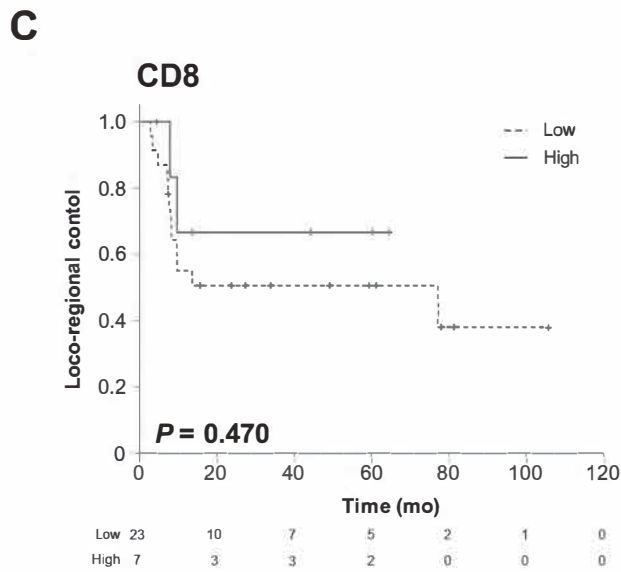
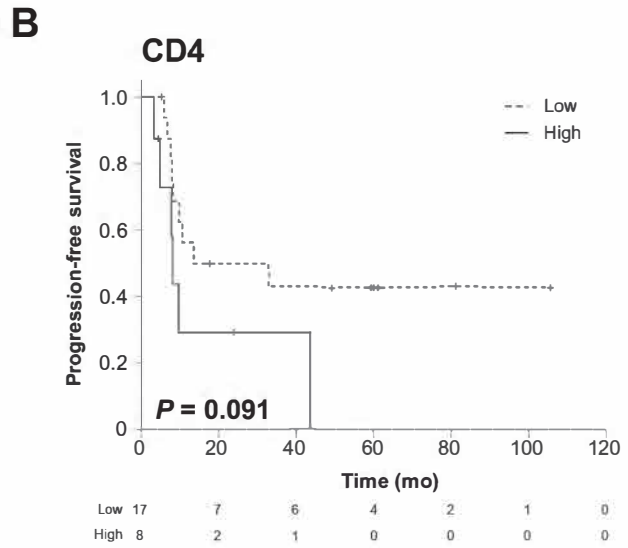
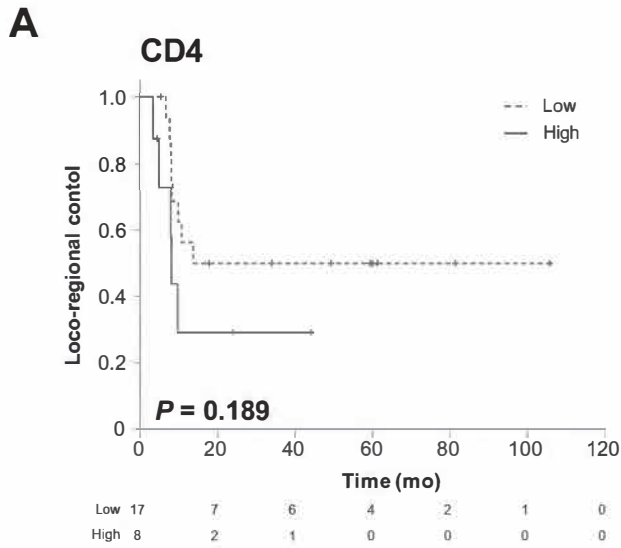


Low	12	0	0	0	0	0
High	18	9	7	5	2	0

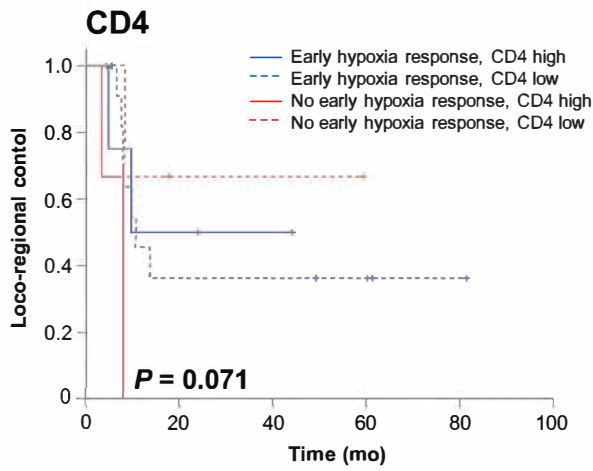
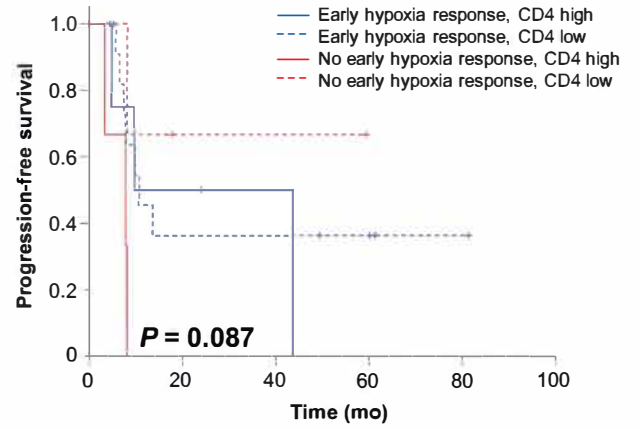
**Supplemental figure 1. LRC and PFS of HPV-negative HNSCC patients depending on early hypoxia response and levels of tumor-infiltrating lymphocytes.** Kaplan-Meier curves showing LRC (A) and PFS (B) depending on hypoxia response in weeks 2 of chemoradiation. LRC (C) and PFS (D) stratified by levels of tumor-infiltrating lymphocytes.



**Supplemental figure 2. OS for HNSCC patients receiving definitive chemoradiation in dependence of their levels of infiltrating lymphocytes.** Kaplan-Meier curves demonstrating OS depending on total lymphocyte (A), CD3-positive (B), CD4-positive (C) and CD8-positive lymphocyte levels in pre-therapeutic tumor biopsies. *P* values are obtained from log-rank tests testing for differences between the Kaplan-Meier curves.

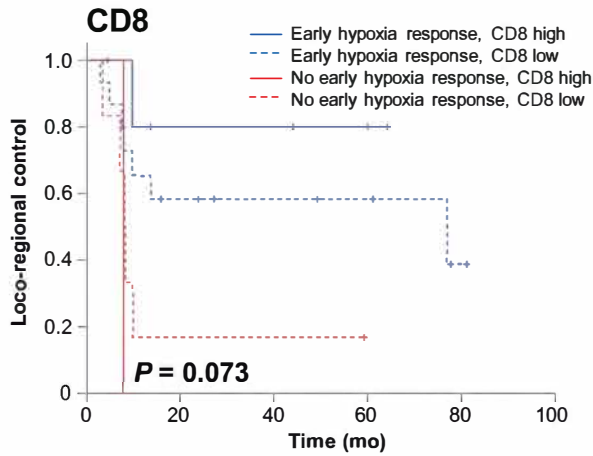
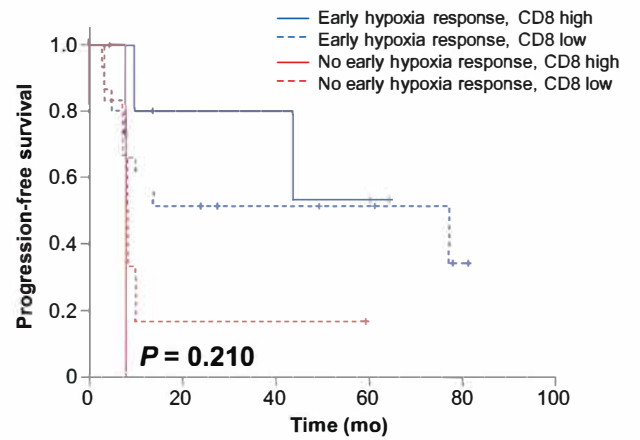


Supplemental figure 3. LRC and PFS as a function of CD4- and CD8-positive T lymphocytes. Kaplan-Meier curves demonstrating LRC and PFS depending on CD4-positive (A and B) and CD8-positive lymphocyte (C and D) levels. P values are obtained from log-rank tests testing for differences between the Kaplan-Meier curves.

**A****B**

Hypoxia response, CD4 high	5	2	1	0	0	0
Hypoxia response, CD4 low	12	4	4	3	1	0
No hypoxia response, CD4 high	3	0	0	0	0	0
No hypoxia response, CD4 low	3	1	1	0	0	0

Hypoxia response, CD4 high	5	2	1	0	0	0
Hypoxia response, CD4 low	12	4	4	3	1	0
No hypoxia response, CD4 high	3	0	0	0	0	0
No hypoxia response, CD4 low	3	1	1	0	0	0

**C****D**

Hypoxia response, CD8 high	6	3	3	2	0	0
Hypoxia response, CD8 low	15	7	5	4	1	0
No hypoxia response, CD8 high	1	0	0	0	0	0
No hypoxia response, CD8 low	6	1	1	0	0	0

Hypoxia response, CD8 high	6	3	3	2	0	0
Hypoxia response, CD8 low	15	7	5	4	1	0
No hypoxia response, CD8 high	1	0	0	0	0	0
No hypoxia response, CD8 low	6	1	1	0	0	0

**Supplemental figure 4. LRC and PFS of HNSCC patients depending on early hypoxia response and levels of CD4- and CD8-positive lymphocytes. Kaplan-Meier curves showing LRC (A) and PFS (B) depending on early hypoxia resolution and CD4-positive lymphocyte levels. LRC (C) and PFS (D) stratified by early hypoxia resolution and levels of CD8-positive lymphocytes.**

Supplemental table 1: Description of antibodies used for immunohistochemical stains and corresponding antigen retrieval.

Antigen	Clone	Company	Dilution	Antigen retrieval
CD3	2GV6	Roche/Ventana	Prediluted	Citrate buffer pH 6,1
CD4	SP35	Roche/Ventana	Prediluted	Citrate buffer pH 9
CD8	SP57	Roche/Ventana	Prediluted	Tris-EDTA buffer pH 9
PD-1	NAT105	Roche/Ventana	Prediluted	Tris-EDTA buffer pH 9
PD-L1	SP263	Roche/Ventana	Prediluted	Tris-EDTA buffer pH 9
CAIX	C48E	Cell Signaling	1:300	pH 6.1 citrate buffer
CD34	QBEnd10 (IR632)	DAKO	Prediluted	pH 6.1 citrate buffer
CD44	156-3C11	Cell Signaling	1:500	pH 6.1 citrate buffer
HIF1 $\alpha$	MAB1935	R&D	1:100	pH 6.1 citrate buffer

Supplemental table 2: Pairwise correlations between immune and hypoxia biomarkers. Pearson correlations were conducted, and Pearson's r and p values are indicated in the table.

		HIF1 $\alpha$ *	CAIX†	CD34
Lymphocytes	r	-0.034	0.074	<b>0.476</b>
	p	0.838	0.656	<b>0.003 (*)</b>
CD3	r	-0.300	0.234	0.313
	p	0.072	0.164	0.059
CD4	r	0.028	-0.048	0.181
	p	0.870	0.777	0.284
CD8	r	-0.323	0.196	0.275
	p	0.052	0.246	0.099

\*HIF1 $\alpha$ =Hypoxia-inducible factor-1 $\alpha$

†CAIX=Carbonic anhydrase IX

Supplemental table 3: Cox proportional hazards analyses of several tumor hypoxia-related parameters regarding their impact on LRC and PFS.

Univariate	LRC		PFS	
	HR	p-value	HR	p-value
Tumor hypoxic subvolume <sub>SUV=1.4</sub> wk0 ≥3.87 mL (median)	0.533	0.152	0.560	0.159
Tumor hypoxic subvolume <sub>SUV=1.4</sub> wk2 ≥0.02 mL (median)	1.502	0.343	1.391	0.421
Tumor hypoxic subvolume <sub>SUV=1.4</sub> wk5 ≥0.00 mL (median)	0.942	0.937	0.783	0.743
SUV index wk0 (tumor-to-muscle) ≥1.89 (median)	1.243	0.612	1.520	0.312
SUV index wk2 (tumor-to-muscle) ≥1.51 (median)	1.883	0.158	1.702	0.213
SUV index wk5 (tumor-to-muscle) ≥1.31 (median)	0.715	0.460	0.450	0.725
SUV index wk0 (tumor-to-muscle) ≥1.4	0.849	0.791	1.058	0.927
SUV index wk0 (tumor-to-muscle) ≥1.6	0.950	0.914	1.169	0.738
<b>SUV index wk2 (tumor-to-muscle) ≥1.4</b>	<b>3.189</b>	<b>0.041</b>	<b>3.661</b>	<b>0.021</b>
SUV index wk2 (tumor-to-muscle) ≥1.6	1.580	0.296	1.463	0.363
SUV index wk5 (tumor-to-muscle) ≥1.4	0.904	0.839	0.752	0.553
SUV index wk5 (tumor-to-muscle) ≥1.6	1.902	0.311	1.685	0.409
<b>ΔSUV index (tumor-to-muscle) wk0-2 ≥0</b>	<b>3.111</b>	<b>0.011</b>	<b>2.487</b>	<b>0.035</b>
ΔSUV index (tumor-to-muscle) wk0-5 ≥0	1.126	0.793	0.863	0.731
ΔSUV index (tumor-to-muscle) wk2-5 ≥0	0.283	0.092	0.242	0.057