

Table SI. Treatments received for the initial tumor by patients in the irradiated area cohort.

Characteristics	Data
Surgery	28 (56.0)
Tumor surgery	27 (96.4)
Neck dissection	27 (96.4)
Ipsilateral	10 (37.0)
Bilateral	16 (59.3)
Unknown	1 (3.7)
Surgery T/N + RT	22 (44.0)
Type of RT	
3D	13 (59.1)
IMRT	9 (40.9)
Dose on tumor site recurrence (T and/or N) (Gy)	55.0; 56.3±8.8
Number of fractions	27.0; 28.1±4.5
Overall treatment time (days)	37.5; 55.8±86.6
Mean dose on tumor site recurrence (T and/or N) <sup>a</sup> (Gy)	50.0; 53.8±13.0
Surgery T/N + RTCT	6 (12.0)
RT	
Type of RT	
3D	2 (33.3)
IMRT	4 (66.7)
Dose on tumor site recurrence (T and/or N) (Gy)	66.0; 63.6±7.0
Number of fractions	33.0; 32.2±4.6
Overall treatment time (days)	44.0; 45.2±9.9
Mean dose on tumor site recurrence (T and/or N) <sup>a</sup> (Gy)	64.6; 60.3±7.9
CT	
Cisplatin Q3w	6 (100)
Duration of CT (days)	32.5; 32.5±11.9
Number of cycles	
2	3 (50)
3	3 (50)
Definitive RTCT <sup>b</sup>	10 (20.0)
RT	
Type of RT	
3D	3 (30.0)
IMRT	7 (70.0)
Dose on tumor site recurrence (T and/or N) (Gy)	70.0; 67.5±6.3
Number of fractions	34.0; 33.1±3.1
Overall treatment time (days)	51.5; 49.0±16.1
Mean dose on tumor site recurrence (T and/or N) <sup>a</sup> (Gy)	70.0; 67.5±6.3
CT	
Type of CT	
Cisplatin Q3w	2 (20.0)
Carboplatin 5-FU	1 (10.0)
Cetuximab	4 (40.0)
Other	3 (30.0)
Duration of CT (days)	43.5; 45.5±11.6
Number of cycles	5.0; 5.2±2.6
RT only	5 (10.0)
Type of RT	
3D	4 (80.0)
IMRT	1 (20.0)
Dose on tumor site recurrence (T and/or N)(Gy)	50.0; 57.2±10.0
Number of fractions	25.0; 28.6±5.0
Overall treatment time (days)	35.0; 37.0±4.5

Table SI. Continued.

Characteristics	Data
Mean dose on tumor site recurrence (T and/or N) <sup>a</sup> (Gy)	50.0; 57.2±10.0
Induction chemotherapy + RTCT	7 (14.0)
TPF	7 (100)
Number of cycles of TPF	50.0; 57.2±10.0

Data are expressed as frequency and percentage [n, (%)] or as median; mean ± standard deviation. CT, chemotherapy; Gy, Gray; IMRT, intensity-modulated radiation therapy; Q3w, every three weeks; RT, radiotherapy; RTCT, chemoradiotherapy; T/N Tumor/Node; TPF, docetaxel, cisplatin and fluorouracil; 3D, three-dimensional; 5-FU, 5-fluorouracil. <sup>a</sup>Comprising tumor progression. <sup>b</sup>Comprising cetuximab.

Table SII. Prognostic factors of PFS for the irradiated area cohort in univariate and multivariate analyses.

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age >60 years	0.87 (0.43-1.75)	0.699		
Sex, male	1.24 (0.58-2.63)	0.581		
Smoking		0.405		
Current smoker	1			
Former smoker	0.80 (0.40-1.62)			
Never smoker	1.67 (0.54-5.20)			
Alcohol	0.74 (0.37-1.47)	0.387		
Tumor location hypopharynx	1.03 (0.37-2.91)	0.953		
Oropharynx p16 <sup>-</sup>	0.81 (0.18-3.71)	0.785		
Tumor well differentiated	0.95 (0.49-1.83)	0.885		
pT3-pT4	1.32 (0.71-2.48)	0.379		
pN3-pN4	0.84 (0.40-1.78)	0.653		
AJCC disease stage (8th edition)		0.730		
I/II	1			
III	1.38 (0.62-3.06)			
IV	1.13 (0.54-2.35)			
Smoking history (pack*year) ≥40	0.71 (0.37-1.33)	0.281		
Former drinker	0.59 (0.23-1.55)	0.289		
Positive resection margins (R1 or R2)	1.12 (0.60-2.07)	0.729		
Lymphovascular invasion	1.33 (0.62-2.85)	0.471		
Perineural invasion	1.42 (0.60-3.33)	0.425		
Number of lymphadenopathies >1	0.70 (0.31-1.55)	0.3759		
Number of nodes removed ≥30	0.22 (0.03-1.68)	0.145		
Extranodal spread	1.85 (0.38-9.03) <sup>1</sup>	0.447		
P16 negative (<70%)	0.41 (0.12-1.40)	0.156		
TPS ≥1%	0.92 (0.49-1.73)	0.799		
PD-L1 IC Intratumoral low expression	0.84 (0.45-1.56)	0.584		
PD-L1 IC Stromal low expression	0.87 (0.46-1.64)	0.668		
TPS <1% and PD-L1 IC Intratumoral = 0	0.69 (0.35-1.37)	0.291		
CD3 Intratumoral low counts	1.31 (0.68-2.50)	0.420		
CD3 Stromal low counts	0.98 (0.51-1.90)	0.957		
CD3 Intratumoral low counts and CD3 stromal low counts	1.22 (0.63-2.35)	0.559		
CD8 Intratumoral low counts	1.25 (0.67-2.33)	0.487		
CD8 Stromal low counts	0.90 (0.48-1.68)	0.730		
CD8 Intratumoral low counts AND CD8 stromal low counts	1.30 (0.67-2.53)	0.434		
Treatment of the initial tumor		0.849		
Surgery T/N + RT	0.62 (0.24-1.60)			
Surgery T/N + RTCT	1			
Definitive RTCT	0.55 (0.19-1.62)			
RT only	0.65 (0.18-1.62)			
Induction chemotherapy + RTCT	0.57 (0.16-1.62)			
Surgery T/N of the initial tumor	1.19 (0.63-2.22)	0.589		
Type of RT received for the initial tumor <sup>a</sup>		0.058		0.002
IMRT vs. 3D	1.89 (0.97-3.66)		3.30 (1.53-7.14)	
Dose on tumor site recurrence (Gy) <sup>a</sup>	0.54 (0.28-1.07)	0.076	0.31 (0.14-0.67)	0.003
Mean dose on tumor site recurrence (Gy) <sup>a</sup>	0.51 (0.26-1.02)	0.057		
Overall treatment time (days) >6 weeks <sup>a</sup>	1.42 (0.74-2.72)	0.295		
Locoregional recurrence ≤6 months <sup>b</sup>	1.18 (0.48-2.94)	0.131		

HR, hazard ratio; 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; CT, chemotherapy; Gy, Gray; IC, immune cells; IMRT, intensity-modulated radiation therapy; PD-L1, programmed death-ligand 1; RT, radiotherapy; RTCT, chemoradiotherapy; TCs, tumor cells; TILs, tumor-infiltrating lymphocytes; TPS, tumor proportion score; Tum, tumoral; T/N Tumor/Node; Stro, stromal; WHO, World Health Organization; 3D, three-dimensional. For CD3<sup>+</sup> and CD8<sup>+</sup> TIL counts, values were dichotomized (low/high) according to the median cell number calculated from all samples and considered high if >40 CD3<sup>+</sup> cells and >30 CD8<sup>+</sup> cells were observed in intratumoral regions and if >160 CD3<sup>+</sup> cells and >90 CD8<sup>+</sup> cells were observed in stromal regions. Expression of PD-L1 by tumor cells was considered positive if TPS ≥1%. The expression of PD-L1 by immune cells was considered high with a score of 1-2 in intratumoral components and 2-5 in stromal components. <sup>a</sup>Computed on the 43 patients with radiotherapy (T and/or N). <sup>b</sup>Calculated for the 29 patients that had locoregional recurrence.