

Supplementary material:

Supplementary Table S1: Details of patient positioning and planning CT, high and low dose clinical target volume delineation, dose prescription and planning objectives.

Patient positioning and CT	Patients were immobilized with a 5-point thermoplastic mask and positioned with a knee support and head rest. Each patient had a contrast enhanced planning CT with 1 x 1 x 3mm ³ voxel size (Somatom Sensation Open, Siemens AG, Erlangen, Germany).
Target volume delineation	The primary tumor and pathological nodes (GTV) were delineated based on clinical and imaging information available. A high risk CTV (CTV1) was created by expansion of GTV with 10 mm, allowing adjustment for anatomical borders. A low risk CTV (CTV2) was created around CTV1 by another expansion of 5 mm. Additionally, bilateral elective neck nodes were delineated and included in CTV2. A planning target volume (PTV) margin was constructed around all CTVs, 5 mm margin was used in patients treated before the 1 st of April 2015 (90 patients), thereafter, a PTV margin of 3mm was applied (98 patients).
Dose prescription	The prescribed dose was 54.25 Gy in 35 fractions to low risk PTV (PTV2) and 70 Gy in 35 fractions to high risk PTV (PTV1), delivered using a simultaneous integrated boost technique.
Planning requirements	Planning objectives for optimization of PTVs were: dose to 99% of the volume (D_{99}) > 95% and D_1 < 107% of prescribed dose. Dose calculation in the first 4 mm from the external contour was considered unreliable and ignored for the target volume during plan optimization and analysis.

Supplementary Table S2: Threshold violation of 1 and 2 Gy difference of accumulated versus planned dose

		ETV to PTV		CTV to PTV		PTV to PTV		CTV to CTV	
		1 Gy	2 Gy	1 Gy	2 Gy	1 Gy	2 Gy	1 Gy	2 Gy
Target 1 (n = 188)	D ₉₉	15 (8%)	4 (2%)	3 (2%)	2 (1%)	79 (42%)	39 (21%)	26 (14%)	8 (4%)
	D ₁	7 (4%)	4 (2%)	9 (5%)	4 (2%)	7 (4%)	3(2%)	6 (3%)	4 (2%)
		ETV to PTV		CTV to PTV		PTV to PTV		CTV to CTV	
		1 Gy	2 Gy	1 Gy	2 Gy	1 Gy	2 Gy	1 Gy	2 Gy
Target 2 (n = 177)	D ₉₉	23 (13%)	7 (4%)	3 (2%)	1 (1%)	56 (32%)	14 (8%)	15 (8%)	5 (3%)
	D ₁	7 (4%)	2 (1%)	10 (6%)	2 (1%)	5 (3%)	2 (1%)	5 (3%)	2 (1%)

Supplementary Table S3a: Association of characteristics with deterioration over 1 and 2 Gy of the accumulated D₉₉_ETV1 dose versus the planned D₉₉_PTV1 dose.

Target Volume 1	D ₉₉ (Threshold 1 Gy Deterioration)			D ₉₉ (Threshold 2 Gy Deterioration)		
N	<1 Gy: 173	>1 Gy: 15	<i>p</i>	<2 Gy:184	>2 Gy:4	<i>P</i>
Age (years, (SD))	61.0 (10.5)	62.2 (14.4)	0.681	61.0 (10.9)	64.0 (5.5)	0.588
Gender (n, (%))						
Male	121 (70)	12 (80)	0.559	131 (71)	2 (40)	0.582
Female	52 (30)	3 (20)		53 (29)	3 (60)	
Weight (kg, (SD))	76.1 (71.6)	77.5 (22.0)	0.774	76.3 (17.7)	74.5 (30.1)	0.843
BMI (kg/m ² , (SD))	24.9 (5.2)	24.9 (8.0)	0.958	24.8 (5.3)	26.2 (13.4)	0.852
Location (n, (%))						
Nasopharynx	30 (17)	1 (7)	0.623	31 (17)	0 (0)	0.561
Oroph/oral cavity	79 (48)	7 (47)		83 (45)	3 (75)	
Larynx/Hypoph	38 (22)	5 (33)		42 (23)	1 (25)	
Other	26 (15)	2 (13)		28 (15)	0 (0)	
Pathology (n, (%))						
Squamous cell	159 (92)	15 (100)	0.608	170 (92)	4 (100)	1.000
Other	14 (8)	0 (0)		14 (8)	0 (0)	
T stage (n, (%))						
T0/T1/T2	102 (59)	7 (47)	0.355	108 (59)	1 (25)	0.311
T3/T4	71 (41)	8 (53)		76 (41)	3 (75)	
N stage (n, (%))						
N0	60 (35)	6 (40)	0.679	63 (34)	3 (75)	0.125
N1-3	113 (65)	9 (60)		121 (66)	1 (25)	
N side (n, (%))						
Unilateral	60 (53)	6 (67)	0.505	66 (54)	0 (0)	0.459
Bilateral	53 (47)	3 (33)		55 (46)	1 (100)	
N largest size (cm, (SD))	2.3 (1.6)	2.4 (1.5)	0.933	2.4 (1.6)	1.1 (0)	0.439
N largest size (n, (%))						
<3 cm	77 (68)	5 (56)	0.473	81 (67)	1 (100)	1.000
>3 cm	36 (32)	4 (44)		40 (33)	0 (0)	
Dahanca (n, (%))						
No	88 (51)	6 (40)	0.419	93 (50)	1 (25)	0.621
Yes	85 (49)	9 (60)		91 (50)	3 (75)	
Chemotherapy (n, (%))						
No	86 (50)	10 (67)	0.208	94 (51)	2 (50)	1.000
Yes	87 (50)	5 (33)		90 (49)	2 (50)	
PTV margin (n, (%))						
5 mm	90 (52)	0 (0)	<0.0001	90 (49)	0 (0)	0.122
3 mm	83 (48)	15 (100)		94 (51)	4 (100)	

Supplementary Table S3b: Association of characteristics with deterioration over 1 and 2 Gy of the accumulated D₉₉_ETV2 dose versus the planned D₉₉_PTV2 dose.

Target Volume 2	D99 (Threshold 1 Gy Deterioration)			D99 (Threshold 2 Gy Deterioration)		
N	<1 Gy: 154	>1 Gy: 23	<i>p</i>	<2 Gy:170	>2 Gy:7	<i>p</i>
Age (years, (SD))	60.6 (10.7)	62.5 (12.9)	0.427	61.0 (11.1)	58.4 (8.5)	0.558
Gender (<i>n</i> , (%))						
Male	107 (70)	19 (83)		123 (72)	3 (43)	
Female	47 (30)	4 (17)	0.227	47 (28)	4 (57)	0.107
Weight (kg, (SD))	74.8 (17.3)	86.5 (20.0)	0.003	75.7 (17.9)	89.7 (27.3)	0.227
BMI (kg/m ² , (SD))	24.4 (5.2)	27.7 (7.0)	0.007	24.6 (5.1)	31.0 (10.5)	0.160
Location (<i>n</i> , (%))						
Nasopharynx	27 (17)	2 (9)		28 (17)	1 (14)	
Oroph/oral cavity	70 (46)	12 (52)		78 (46)	4 (57)	
Larynx/Hypoph	36 (23)	6 (26)		40 (23)	2 (29)	
Other	21 (14)	3 (13)	0.749	24 (14)	0 (0)	0.738
Pathology (<i>n</i> , (%))						
Squamous cell	144 (94)	22 (96)		159 (94)	7 (100)	
Other	10 (6)	1 (4)	0.691	11 (6)	0 (0)	1.000
T stage (<i>n</i> , (%))						
T0/T1/T2	90 (58)	12 (52)		99 (58)	3 (43)	
T3/T4	64 (42)	11 (48)	0.570	71 (42)	4 (57)	0.459
N stage (<i>n</i> , (%))						
N0	51 (33)	7 (30)		55 (32)	3 (43)	
N1-3	103 (67)	16 (70)	0.798	115 (68)	4 (57)	0.685
N side (<i>n</i> , (%))						
Unilateral	54 (52)	9 (56)		62 (54)	1 (25)	
Bilateral	49 (48)	7 (44)	0.776	53 (46)	3 (75)	0.341
N largest size (cm, (SD))	2.3 (1.6)	2.4 (1.5)	0.921	2.3 (1.6)	2.4 (1.8)	0.988
N largest size (<i>n</i> , (%))						
<3 cm	69 (67)	10 (63)		77 (67)	2 (50)	
>3 cm	34 (33)	6 (38)	0.724	38 (33)	2 (50)	0.602
Dahanca (<i>n</i> , (%))						
No	75 (49)	10 (44)		80 (47)	5 (71)	
Yes	79 (51)	13 (57)	0.640	90 (53)	2 (29)	0.263
Chemotherapy (<i>n</i> , (%))						
No	73 (47)	13 (57)		83 (49)	3 (43)	
Yes	81 (53)	10 (43)	0.414	87 (51)	4 (57)	1.000
PTV margin (<i>n</i> , (%))						
5 mm	81 (53)	3 (13)		84 (49)	0 (0)	
3 mm	73 (47)	20 (87)	0.001	86 (51)	7 (100)	0.015

Supplementary Table S3c: Association of characteristics with deterioration over 1 and 2 Gy of the accumulated D₁_ETV1 dose versus the planned D₁_PTV1 dose.

Target Volume 1	D1 (Threshold 1 Gy Deterioration)			D1 (Threshold 2 Gy Deterioration)		
N	<1 Gy: 181	>1 Gy: 7	<i>p</i>	<2 Gy:184	>2 Gy:4	<i>p</i>
Age (years, (SD))	60.9 (10.9)	66.9 (4.5)	0.011	61.0 (10.9)	66.3 (5.7)	0.337
Gender (<i>n</i> , (%))						
Male	127 (70)	6 (86)		129 (70)	4 (100)	
Female	54 (30)	1 (14)	0.676	55 (309)	0 (0)	0.323
Weight (kg, (SD))	75.6 (17.7)	90.6 (16.9)	0.030	76.0 (17.9)	86.4 (15.9)	0.254
BMI (kg/m ² , (SD))	24.7 (5.0)	28.9 (8.3)	0.048	24.8 (5.5)	25.4 (5.1)	0.846
Location (<i>n</i> , (%))						
Nasopharynx	29 (16)	2 (29)		31 (17)	0 (0)	
Oroph/oral cavity	85 (47)	1 (14)		85 (46)	1 (25)	
Larynx/Hypoph	39 (22)	4 (57)		40 (22)	3 (75)	
Other	28 (15)	0 (0)	0.071	28 (15)	0 (0)	0.089
Pathology (<i>n</i> , (%))						
Squamous cell	167 (92)	7 (100)		170 (92)	4 (100)	
Other	14 (8)	0 (0)	1.000	14 (8)	0 (0)	1.000
T stage (<i>n</i> , (%))						
T0/T1/T2	108 (60)	1 (14)		108 (59)	1 (25)	
T3/T4	73 (40)	6 (86)	0.043	76 (41)	3 (75)	0.311
N stage (<i>n</i> , (%))						
N0	63 (35)	3 (43)		65 (35)	1 (25)	
N1-3	118 (65)	4 (57)	0.698	119 (65)	3 (75)	1.000
N side (<i>n</i> , (%))						
Unilateral	64 (54)	2 (50)		64 (54)	2 (67)	
Bilateral	54 (46)	2 (50)	1.000	55 (46)	1 (33)	1.000
N largest size (cm, (SD))	2.3 (1.6)	1.5 (1.0)	0.289	2.4 (1.6)	1.0 (2.0)	0.143
N largest size (<i>n</i> , (%))						
<3 cm	79 (67)	3 (75)		79 (66)	3 (100)	
>3 cm	39 (33)	1 (25)	0.473	40 (34)	0 (0)	0.550
Dahanca (<i>n</i> , (%))						
No	90 (50)	4 (57)		91 (50)	3 (75)	
Yes	91 (50)	3 (43)	1.000	93 (50)	1 (25)	0.621
Chemotherapy (<i>n</i> , (%))						
No	93 (51)	3 (43)		93 (51)	3 (75)	
Yes	88 (49)	4 (57)	0.716	91 (49)	1 (25)	0.621
PTV margin (<i>n</i> , (%))						
5 mm	86 (48)	3 (43)		89 (48)	1 (25)	
3 mm	95 (53)	4 (57)	0.711	95 (52)	3 (75)	0.622

Supplementary Table S3d: Association of characteristics with deterioration over 1 and 2 Gy of the accumulated D₁_ETV2 dose versus the planned D₁_PTV2 dose.

Target Volume 2	D1 (Threshold 1 Gy Deterioration)			D1 (Threshold 2 Gy Deterioration)		
N	<1 Gy: 170	>1 Gy: 7	<i>p</i>	<2 Gy: 175	>2 Gy: 2	<i>p</i>
Age (years, (SD))	60.6 (11.1)	66.8 (4.5)	0.009	60.8 (11.0)	62.5 (5.0)	0.828
Gender (<i>n</i> , (%))						
Male	120 (71)	6 (86)		124 (71)	2 (100)	
Female	50 (29)	1 (14)	0.675	51 (29)	0 (0)	1.000
Weight (kg, (SD))	75.7 (17.9)	90.6 (16.9)	0.032	76.1 (18.0)	94.0 (19.8)	0.164
BMI (kg/m ² , (SD))	24.7 (5.4)	28.9 (8.3)	0.048	24.8 (5.6)	27.6 (3.3)	0.480
Location (<i>n</i> , (%))						
Nasopharynx	27 (16)	2 (29)		29 (17)	0 (0)	
Oroph/oral cavity	81 (48)	1 (14)		82 (47)	0 (0)	
Larynx/Hypoph	38 (22)	4 (57)		40 (23)	2 (100)	
Other	24 (14)	0 (0)	0.082	24 (14)	0 (0)	0.090
Pathology (<i>n</i> , (%))						
Squamous cell	159 (94)	7 (100)		164 (94)	2 (100)	
Other	11 (6)	0 (0)	0.487	11 (6)	0 (0)	1.000
T stage (<i>n</i> , (%))						
T0/T1/T2	101 (59)	1 (14)		102 (58)	0 (0)	
T3/T4	69 (41)	6 (86)	0.043	73 (42)	2 (100)	0.178
N stage (<i>n</i> , (%))						
N0	51 (33)	7 (30)		58 (33)	0 (0)	
N1-3	103 (67)	16 (70)	0.798	117 (67)	2 (100)	1.000
N side (<i>n</i> , (%))						
Unilateral	54 (52)	9 (56)		62 (54)	1 (25)	
Bilateral	49 (48)	7 (44)	0.776	53 (46)	3 (75)	1.000
N largest size (cm, (SD))	2.4 (1.6)	1.5 (1.0)	0.291	2.6 (1.6)	1.1 (1.4)	0.274
N largest size (<i>n</i> , (%))						
<3 cm	76 (66)	3 (75)		77 (66)	2 (100)	
>3 cm	39 (34)	1 (25)	1.000	40 (34)	0 (0)	0.550
Dahanca (<i>n</i> , (%))						
No	81 (48)	4 (57)		84 (48)	1 (50)	
Yes	89 (52)	3 (43)	0.712	91 (52)	1 (50)	1.000
Chemotherapy (<i>n</i> , (%))						
No	83 (49)	3 (43)		85 (49)	1 (50)	
Yes	87 (51)	4 (57)	1.000	90 (51)	1 (50)	1.000
PTV margin (<i>n</i> , (%))						
5 mm	90 (53)	3 (43)		92 (53)	1 (50)	
3 mm	80 (47)	4 (57)	0.709	83 (47)	1 (50)	1.000

Supplementary Table S4: P values of the independent sample t-test evaluating differences between patients with and without dosimetric deterioration (delivered ETV doses versus planned PTV doses in TV1 and TV2 with thresholds of 1 and 2Gy dose deterioration), testing weight change and tube feeding during treatment.

	D99		D99		D1		D1	
	TV1(1 Gy)	TV1(2 Gy)	TV2(1 Gy)	TV2(2 Gy)	TV1(1 Gy)	TV1(2 Gy)	TV2(1 Gy)	TV2(2 Gy)
ΔG_w1	0.151	0.007	0.685	0.947	0.764	0.630	0.702	0.286
ΔG_w2	0.000	0.023	0.367	0.904	0.733	0.294	0.742	0.746
ΔG_w3	0.006	0.242	0.732	0.986	0.697	0.262	0.707	0.844
ΔG_w4	0.042	0.617	0.046	0.044	0.192	0.095	0.210	0.004
ΔG_w5	0.082	0.550	0.099	0.071	0.262	0.071	0.289	0.004
ΔG_w6	0.097	0.551	0.816	0.863	0.304	0.181	0.328	0.010
Tube feeding	0.952	0.115	0.614	0.694	0.691	1.000	0.694	1.000

Supplementary Table S5: Association of clinical ART with dosimetric deterioration over 1 and 2Gy of accumulated ETV doses versus planned PTV doses, results of the Chi-Square-tests (or Fisher's exact-test in case of less than 5 events in at least one category) evaluating differences between patients with and without dosimetric deterioration.

Clinical ART	1 Gy Threshold			2 Gy Threshold		
	TV1 D ₉₉ (n, (%))			TV1 D ₉₉ (n, (%))		
	<1 Gy: n = 173	>1 Gy: n = 15	p	<2 Gy: n = 184	>2 Gy: n = 4	p
No	154 (89)	10 (67)		162 (88)	2 (50)	
Yes	19 (11)	5 (33)	0.013	22 (12)	2 (50)	0.080
	TV2 D ₉₉ (n, (%))			TV2 D ₉₉ (n, (%))		
	<1 Gy: n = 154	>1 Gy: n = 23	p	<2 Gy: n = 170	>2 Gy: n = 7	p
No	134 (87)	19 (83)		147 (87)	6 (86)	
Yes	20 (13)	4 (17)	0.523	23 (13)	1 (14)	1.000
	TV1 D ₁ (n, (%))			TV1 D ₁ (n, (%))		
	<1 Gy: n = 181	>1 Gy: n = 7	p	<2 Gy: n = 184	>2 Gy: n = 4	p
No	158 (87)	6 (86)		161 (88)	3 (75)	
Yes	23 (13)	1 (14)	0.902	23 (12)	1 (25)	0.424
	TV2 D ₁ (n, (%))			TV2 D ₁ (n, (%))		
	<1Gy: n=170	>1Gy: n=7	p	<2Gy: n=175	>2Gy: n=2	p
No	147 (87)	6 (86)		152 (87)	1 (50)	
Yes	23 (13)	1 (14)	1.000	23 (13)	1 (50)	0.253