Supplementary Online Content

Castelli J, Thariat J, Benezery K, et al. Weekly adaptive radiotherapy vs standard intensity-modulated radiotherapy for improving salivary function in patients with head and neck cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online June 1, 2023. doi:10.1001/jamaoncol.2023.1352

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Radiotherapy treatment procedures

All the patients received a total dose of 70 Gy in 35 fractions (2 Gy/fraction/day), with a simultaneous integrated boost technique[1] and concomitant chemotherapy. The following chemotherapy regimens were given: cisplatin 100 mg/m² Q3W;[2] cetuximab at an initial dose of 400 mg/m² D-7 followed by 250 mg/m² weekly;[3] carboplatin (70 mg/m/d², D1–D4 Q3W) and 5FU (600 mg/m²/d, D1–D4 Q3W).[4]

The radiation protocol was as follows in both arms. Three target volumes were generated. The gross tumour volume (GTV) corresponded to the primary tumour along with the involved lymph nodes. The clinical target volume of 70 Gy (CTV70) was equal to the GTV plus a 5 mm 3D margin, which was adjusted to exclude air cavities and bone mass without evidence of tumour invasion. CTV63 corresponded to the area at high risk of microscopic spread, whereas CTV56 corresponded to the prophylactic irradiation area.[5] Adding a 5 mm 3D margin around the CTVs generated planning target volumes (PTVs). Contours and dose-volume constraints were set according to the GORTEC recommendations.[6] In particular, for the PG, the dose constraints were a mean dose (Dmean) < 30 Gy and a median dose < 26 Gy.[7] Treatment parameters were reviewed retrospectively by the Quality Assurance Review Committee (eTable 1 and eTable 2).

For the patients in the ART arm, a weekly CT scan was performed using the same protocol as the initial planning CT (CT0), except for some variations in intravenous contrast agent use, which was not systematically employed, particularly in the context of cisplatin-based chemotherapy. Anatomical structures were manually segmented or automatically propagated using elastic registration on each weekly CT scan. For each patient, the manual correction was performed by a radiation oncologist. In the event of a complete response, the original macroscopically involved areas were still included in CTV70, which was adjusted to exclude any air cavities and bone mass showing no evidence of original tumour invasion. The dose distribution was computed using the same constraints as those used in the initial planning. A maximum of four days was allowed between each weekly CT scan and the start of the treatment using a new dose distribution. As patients were treated five days per week, each weekly CT corresponded to a 10 Gy addition to the PTV (CT1 at 10 Gy, CT2 at 20 Gy, and so on). One replanning, based on the radiation oncologist's decision, was allowed in the standard IMRT

arm.

In both arms, during the treatment course, daily in-room imaging (2D kV imaging, CBCT, or MVCT) corrected set-up errors >5 mm.

eTable 1: Initial planning CT dosimetric parameters for the planned target volume (ITT)

Characteristics	Replanning arm, N = 65[1]	Standard arm, N = 65[1]	p-value[2]
Low risk PTV (56 Gy)			
Median total dose (Gy)	57.66 (2.60)	58.28 (3.09)	0.137
D2%	63.5 (5.3)	63.8 (5.5)	0.387
D98%	52.99 (4.15)	53.73 (2.59)	0.632
Moderate risk PTV (63 Gy)			
Median total dose	65.05 (2.42)	64.92 (2.50)	0.737
D2%	69.36 (2.67)	68.41 (5.10)	0.448
D98%	58.31 (3.12)	58.97 (3.09)	0.440
High risk PTV (70 Gy)			
Median total dose	70.42 (0.61)	70.14 (1.83)	0.187
D2%	72.45 (2.00)	71.99 (2.30)	0.140
D98%	66.13 (3.32)	66.67 (2.90)	0.548

[1]n (%); Mean (SD)
[2]Fisher's exact test; Wilcoxon rank sum test
PTV: planning target volume
Dx%: Dose received by x% of the volume

eTable 2: Initial planning CT dosimetric parameters for the organs at risk (ITT)

Characteristics	Replanning Arm, N = 65[1]	Standard Arm, N = 65[1]	p-value[2]
Ipsilateral parotid glands			
Mean dose (Gy)	33 (11)	31 (8)	0.717
V15Gy (%)	70 (23)	67 (23)	0.485
V30Gy (%)	47 (22)	44 (21)	0.470
V45Gy (%)	33 (22)	29 (17)	0.505
Contralateral parotid glands			
Mean dose (Gy)	24 (7)	26 (7)	0.210
V15Gy (%)	54 (19)	57 (21)	0.363
V30Gy (%)	30 (14)	32 (16)	0.733
V45Gy (%)	16 (11)	18 (13)	0.561
Ipsilateral submaxillary gland			
Mean dose (Gy)	65 (8)	61 (11)	0.047
Contralateral submaxillary gland			
Mean dose (Gy)	58 (9)	55 (12)	0.351
Pharynx			
Mean dose (Gy)	60 (8)	57 (12)	0.257
V55Gy (%)	70 (28)	62 (32)	0.170
V65Gy (%)	41 (26)	35 (25)	0.193
Lip			
Mean dose(Gy)	22 (9)	24 (9)	0.201
Mouth			
Mean dose (Gy)	39 (11)	43 (10)	0.146
V30Gy (%)	68 (24)	73 (22)	0.345
V35Gy (%)	58 (26)	63 (25)	0.299
Larynx			
Mean dose (Gy)	50 (12)	46 (10)	0.078
V50Gy (%)	50 (35)	40 (28)	0.129
Spinal cord			
D2%	37.1 (4.3)	36.4 (6.1)	0.889
Brainstem			
D2%	32 (9)	33 (8)	0.122
Ipsilateral inner ear			
D2%	29 (18)	31 (15)	0.535
Contralateral inner ear			
D2%	20 (13)	25 (15)	0.105
Chiasma			
D2%	3.41 (6.08)	4.12 (5.21)	0.196
Ipsilateral optic nerve			
D2%	3.6 (6.3)	5.8 (8.6)	0.028
Contralateral optic nerve			
D2%	3.21 (4.36)	3.48 (2.38)	0.064
Mandible			
D2%	66.6 (5.7)	66.5 (5.5)	0.867

[1]n (%); Mean (SD)
[2]Fisher's exact test; Wilcoxon rank sum test
Dx%: Dose received by x% of the volume
VxGy: % of volume receiving x Gy

eTable 3: Weekly dosimetric parameters for the target volume in the ART arm (ITT)

Characteristics	CT0, N = 65[1]	CT1, N = 63[1]	CT2, N = 62[1]	CT3, N = 62[1]	CT4, N = 62[1]	CT5, N = 62[1]	CT6, N = 11[1]
Planned target volume low risk (56 Gy)							
Median total dose (Gy)	57.66 (2.60)	56.24 (9.07)	56.17 (9.46)	56.16 (9.38)	56.22 (9.41)	55.86 (9.73)	54.04 (8.77)
D2%	63.5 (5.3)	61.6 (10.7)	61.6 (11.0)	61.7 (11.1)	61.7 (11.0)	61.7 (11.2)	64.3 (5.7)
D98%	52.99 (4.15)	51.81 (8.15)	51.42 (8.67)	51.37 (8.64)	51.63 (8.65)	51.68 (8.68)	52.43 (1.20)
Planned target volume moderate risk (63 Gy)							
Median total dose (Gy)	65.05 (2.42)	63.32 (10.03)	62.22 (13.08)	63.27 (10.33)	63.28 (10.33)	62.82 (10.85)	60.15 (11.66)
D2%	69.36 (2.67)	67.42 (10.64)	67.41 (10.99)	67.50 (11.02)	67.28 (11.11)	67.44 (11.12)	70.03 (2.57)
D98%	58.31 (3.12)	57.28 (9.03)	56.89 (9.39)	56.97 (9.40)	57.03 (9.37)	56.96 (9.37)	57.38 (2.00)
Planned target volume high risk (70 Gy)							
Median total dose (Gy)	70.42 (0.61)	68.49 (10.42)	68.36 (10.86)	68.28 (10.88)	68.43 (10.87)	67.84 (11.56)	64.50 (13.54)
D2%	72.45 (2.00)	70.53 (10.77)	70.39 (11.31)	70.51 (11.26)	70.54 (11.25)	70.48 (11.35)	72.23 (3.96)
D98%	66.13 (3.32)	64.91 (9.95)	64.70 (10.32)	64.46 (10.51)	64.55 (10.40)	64.80 (10.48)	65.92 (1.28)

[1]n (%); Mean (SD)
Dx%: Dose received by x% of the volume

CT0 corresponds to the initial pre-treatment planning CT, CTx corresponds to the planning CT perform at the week number x. CT6 was optional in the replanning arm. No significant difference was found between CT0 and CTx dosimetric parameters (Wilcoxon test).

eTable 4: Weekly dosimetric parameters for the organs at risk in the ART arm (ITT)

Characteristic	CT0, N = 65[1]	CT1, N = 63[1]	CT2, N = 62[1]	CT3, N = 62[1]	CT4, N = 62[1]	CT5, N = 62[1]	CT6, N = 11[1]
Ipsilateral parotid glands							
Mean dose (Gy)	33 (11)	32 (12)	31 (12)	31 (13)	32 (12)	30 (12)	34 (11)
V15Gy (%)	70 (23)	65 (24)	65 (24)	64 (23)	65 (24)	65 (24)	71 (25)
V30Gy (%)	47 (22)	46 (23)	43 (23)	45 (23)	44 (22)	43 (21)	49 (27)
V45Gy (%)	33 (22)	31 (21)	30 (21)	31 (22)	29 (19)	29 (20)	32 (22)
Contralateral parotid glands							
Mean dose (Gy)	23.9 (6.5)	23.0 (7.3)	22.5 (7.4)	22.3 (6.9)	23.0 (6.2)	22.7 (8.9)	27.0 (4.4)
V15Gy (%)	54 (19)	53 (19)	52 (19)	50 (18)	51 (18)	52 (21)	59 (21)
V30Gy (%)	30 (14)	29 (14)	28 (13)	28 (12)	27 (11)	29 (15)	34 (12)
V45Gy (%)	16 (11)	16 (10)	15 (10)	15 (10)	14 (9)	16 (14)	20 (8)
Ipsilateral submaxillary gland							
Mean dose (Gy)	65 (8)	66 (8)	64 (11)	64 (10)	65 (10)	64 (10)	66 (3)
Contralateral submaxillary gland							
Mean dose (Gy)	58 (9)	56 (13)	55 (13)	55 (14)	56 (13)	56 (13)	58 (8)
Pharynx							
Mean dose (Gy)	60 (8)	57 (13)	56 (13)	56 (13)	55 (13)	56 (14)	62 (1)
V55Gy (%)	70 (28)	66 (29)	63 (30)	61 (30)	60 (31)	65 (30)	73 (5)
V65Gy (%)	41 (26)	39 (26)	40 (27)	38 (27)	35 (26)	36 (26)	51 (6)
Lip							
Mean dose (Gy)	22 (9)	21 (9)	20 (8)	21 (8)	20 (8)	20 (8)	23 (6)
Mouth							
Mean dose (Gy)	39 (11)	37 (13)	38 (13)	38 (13)	38 (13)	39 (12)	38 (12)
V30 Gy (%)	68 (24)	65 (25)	66 (24)	65 (25)	66 (24)	67 (22)	62 (27)
V35Gy (%)	58 (26)	56 (26)	57 (27)	56 (26)	56 (26)	57 (25)	52 (31)
Larynx							
Mean dose (Gy)	50 (12)	47 (13)	47 (14)	49 (15)	47 (15)	48 (14)	55 (10)
V50Gy (%)	50 (35)	46 (34)	46 (33)	44 (31)	45 (33)	50 (35)	63 (31)
Spinal cord							
D2% (Gy)	37.1 (4.3)	35.6 (7.2)	35.9 (7.7)	36.1 (7.8)	35.8 (8.5)	35.0 (7.9)	37.3 (4.0)
Brainstem							
D2% (Gy)	32 (9)	31 (10)	31 (10)	31 (10)	31 (10)	31 (10)	36 (3)
Ipsilateral inner ear							
D2% (Gy)	29 (18)	28 (19)	28 (18)	29 (19)	27 (19)	29 (17)	40 (10)
Contralateral inner ear							
D2% (Gy)	20 (13)	21 (16)	21 (15)	20 (16)	19 (14)	20 (13)	32 (8)
Chiasma							
D2% (Gy)	3.41 (6.08)	3.03 (4.48)	4.37 (8.14)	3.10 (5.29)	3.26 (5.74)	3.50 (5.05)	4.05 (0.78)
Ipsilateral optic nerve							
D2% (Gy)	3.64 (6.30)	3.38 (4.29)	3.61 (5.94)	3.33 (5.42)	3.05 (4.48)	3.72 (4.80)	4.75 (0.07)
Contralateral optic nerve							
D2% (Gy)	3.21 (4.36)	3.17 (3.58)	3.07 (3.42)	2.96 (3.46)	2.76 (3.32)	3.46 (4.42)	5.30 (0.71)
Mandible							
D2% (Gy)	67 (6)	65 (12)	65 (12)	65 (12)	63 (15)	65 (12)	66 (7)

[1]n (%); Mean (SD)
Dx%: Dose received by x% of the volume
VxGy: % of volume receiving x Gy

CT0 corresponds to the initial pre-treatment planning CT, CTx corresponds to the planning CT perform at the week number x. CT6 was optional in the replanning arm. No significant difference was found between CT0 and CTx dosimetric parameters (Wilcoxon test).

eTable 5: Excretory function of salivary glands measured by scintigraphy (ITT)

Salivary gland	Time point	Replanning arm[1]	Standard arm[1]	P-value[2]
Parotid gland				
	Inclusion	56 (16)	55 (15)	0.809
	M12	48 (17)	41 (17)	0.015
Submaxillary gland				
	Inclusion	32 (19)	34 (20)	0.519
	M12	4 (9)	6 (11)	0.534

[1] Mean (SD)
[2] Wilcoxon rank sum test

The excretory function of the salivary gland was measured by dynamic image acquisition after injection of 99mTechnetium pertechnetate and oral administration of 10 mL of lemon juice to stimulate salivary secretion. The salivary excretory function was calculated as the difference between the maximum and minimum salivary secretions divided by the maximum salivary secretion (%). Mean and SD are reported. Higher values correspond to better salivary function. M12 = 12 months after radiotherapy

eTable 6: Acute grade ≥ 2 and grade ≥ 3 toxicity occurrence by treatment arm (ITT)

	Replanning arm, N=66 [1]	Standard arm, N=65 [1]	p-value[2]
Xerostomia			
G2+	**19 (28.7%)**	**15 (23.1%)**	**0.46**
G3+	**0**	**0**	**-**
Anemia			
G2+	**6 (9.1%)**	**9 (13.8%)**	**0.39**
G3+	**1 (1.5%)**	**3 (4.6%)**	**0.37**
Leukopenia			
G2+	**8 (12.1%)**	**11 (16.7%)**	**0.44**
G3+	**4 (6.1%)**	**5 (7.7%)**	**0.74**
Dysgeusia			
G2+	**21 (31.8%)**	**24 (36.9%)**	**0.54**
G3+	**1 (1.5%)**	**4 (6.2%)**	**0.21**
Dysphagia			
G2+	**31 (46.9%)**	**29 (44.6%)**	**0.79**
G3+	**9 (13.6%)**	**7 (10.7%)**	**0.62**
Mucositis			
G2+	**29 (43.9%)**	**28 (43.1%)**	**0.92**
G3+	**3 (6.9%)**	**3 (4.6%)**	**>0.99**
Oropharyngeal pain			
G2+	**24 (36.3%)**	**22 (33.8%)**	**0.76**
G3+	**4 (6.1%)**	**5 (7.7%)**	**0.74**

[1] n (%);
[2]: Pearson's Chi-squared test
G2+ = toxicities of grade 2 or more
G3+ = toxicities of grade 3 or more

Only toxicities occurring at a rate superior to 1% are displayed.

eTable 7: Two-year grade ≥ 2 and grade ≥ 3 toxicity rates by treatment arm (ITT)

	Replanning arm[1]	Standard arm[1]	p-value[2]
Xerostomia			
G2+	**52% [38-63]**	**54% [39-64]**	**0.98**
G3+	**5% [0-10]**	**5% [0-10]**	**0.99**
Dysgeusia			
G2+	**30% [18-41]**	**28% [18-41]**	**0.82**
G3+	**3% [0-7]**	**3% [0-7]**	**0.98**
Dysphagia			
G2+	**25% [14-36]**	**16% [6-24]**	**0.17**
G3+	**6% [0-12]**	**3% [0-7]**	**0.4**
Fibrosis			
G2+	**6% [0-12]**	**3% [0-7]**	**0.4**
G3+	**0**	**0**	**NA**
Oropharyngeal pain			
G2+	**15% [5-23]**	**13% [4-20]**	**0.75**
G3+	**0**	**2% [0-5]**	**0.32**

[1]%; [95% C.I.]
[2]: log-rank test
G2+ = toxicities of grade 2 or more
G3+ = toxicities of grade 3 or more

Only toxicities occurring at a rate superior to 1% are displayed.

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eTable 8: Demographic and clinical data of the study population (PP)

Characteristics	Replanning arm, N = 66[1]	Standard arm, N = 65[1]	p-value[2]
Patients			
Gender, male	52 (85·2%)	56 (87·7%)	0·6
Age at inclusion (years)	60 (8) [3]	60 (8) [3]	0·916
OMS performance status			0·391
OMS = 0	26 (42·6%)	25 (39·7%)	
OMS = 1	30 (49·2%)	36 (57·1%)	
OMS = 2	5 (8·2%)	2 (3·1%)	
Tobacco smoking			0·608
Active smoker	22 (36·1%)	19 (30.2%)	
Former smoker	30 (49·2%)	37 (58·7%)	
Non smoker	9 (14·8%)	7 (11.1%)	
Number of pack-year	41 (24) [3]	38 (22) [3]	0·830
Ethylism			0·592
Yes	21 (34·4%)	20 (31·7%)	
Weaned	17 (27·9%)	25 (39·7%)	
No/Occasional	23 (37·7%)	20 (28.6%)	
Diabetes Mellitus			0·593
Insulino-dependent diabetes	2 (3·0%)	3 (4·8%)	
Non-insulin dependent diabetes	7 (10·6%)	4 (6.3%)	
No diabetes	52 (85·2%)	56 (88.9%)	
Clear Fair skin phototype, yes	19 (31·1%)	17 (27·0%)	0·694
Tumors			
Tumor histology			0.833
squamous cell carcinoma poorly differentiated	16 (27·1%)	14 (23.7%)	
squamous cell carcinoma well-differentiated	43 (72·9%)	45 (76.3%)	
p16 gene expression, positive	27 (44·3%)	26 (41.3%)	0.856
Primary tumor localization			0.780
Base of the tongue (anterior wall)	14 (23·0%)	17 (27.0%)	
Pharynx (posterior wall)	1 (1·6%)	1 (1.6%)	
Several regions	35 (57·4%)	30 (47.6%)	
Tonsillar region (lateral wall)	11 (18·0%)	15 (23.8%)	
Tumor laterality			0.959
Bilateral	4 (6·6%)	3 (4.8%)	
Left	26 (42·6%)	27 (42.9%)	
Medial	6 (9·8%)	5 (7.9%)	
Right	25 (41·0%)	28 (44.4%)	
Largest diameter of the primary tumor (mm)	41 (13)	41 (15)	0.973
Lymph Nodes			0.130
Yes, homolateral	32 (52·5%)	35 (55.6%)	
Yes, contralateral	0 (0·0%)	4 (6.3%)	
Yes, bilateral	20 (32·8%)	13 (20.6%)	
No	9 (14·8%)	11 (17.5%)	
Conglomerate of lymph nodes, yes	14 (28·0%)	14 (27.5%)	>0.999
Number of lymph nodes involved (if no conglomerate)	3·06 (1·79)	2.35 (1.03)	0.105
N Stage			0.989
N0	9 (14·8%)	11 (17.5%)	
N1	4 (6·6%)	5 (7.9%)	
N2a	1 (1·6%)	0 (0.0%)	
N2b	27 (44·3%)	28 (44.4%)	
N2c	18 (29·5%)	17 (27.0%)	
N3	2 (3·3%)	2 (3.2%)	
AJCC tumor staging			0.955
Stage III	17 (27·9%)	18 (28.6%)	
Stage IVa	40 (65·6%)	42 (66.7%)	
Stage IVb	4 (6·6%)	3 (4.8%)	

[1]n (%);[2]Fisher's exact test; Wilcoxon rank sum test; [3]Mean (SD)

eTable 9: Treatment characteristics of the patient groups (PP)

Characteristics	Replanning arm, N = 66[1]	Standard arm, N = 65[1]	P-value[2]
Type of chemotherapy			0·430
ARCORO (5Fu carboplatin)	9 (13·6%)	9 (13·8%)	
CDDP	42 (63·6%)	47 (72·3%)	
Cetuximab	15 (22·7%)	9 (13·8%)	
IMRT Modality, by tomotherapy (vs arc therapy)	17 (25·8%)	16 (24·6%)	>0·999
Number of CT scans (including initial planning - CT0)			<0·001
1	2 (3·0%)	58 (89·2%)	
2	2 (3·0%)	7 (10·8%)	
6	51 (77·3%)	0 (0·0%)	
7	11 (16·7%)	0 (0·0%)	
Patients with at least 35 cycles of radiotherapy	63 (95·5%)	65 (100·0%)	0·244
Interruption of treatment			0·295
No	33 (50·0%)	32 (49·2%)	
Yes, definitive	3 (4·5%)	0 (0·0%)	
Yes, temporary	30 (45·5%)	33 (50·8%)	
Overall time of radiotherapy (in days)	50·4 (8·6)	51·6 (4·3)	0·808
Reason of interruptions			0·362
Not related to toxicity	22 (33·3%)	27 (41·5%)	
Toxicity	11 (16·7%)	6 (9·2%)	
No interruption	33 (50·0%)	32 (49·2%)	

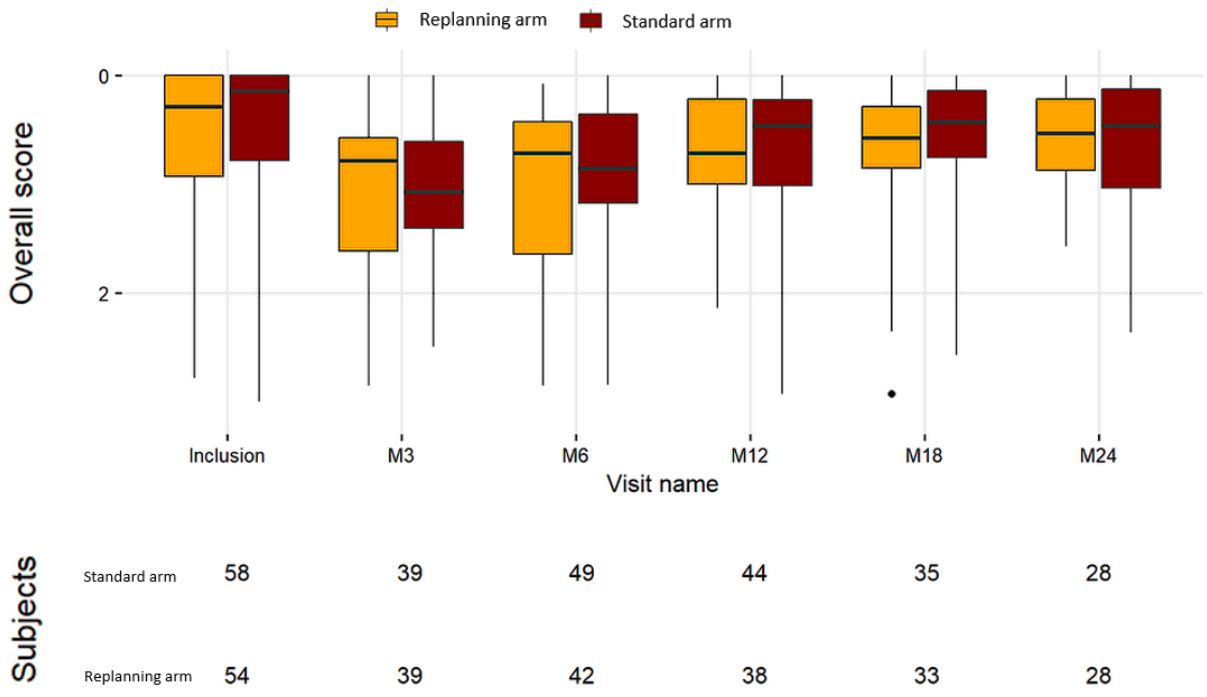
[1]n (%); Mean (SD)
[2]Fisher's exact test; Wilcoxon rank sum test
Interruption is defined as at least one day

eTable 10: Excretory function of salivary glands measured by scintigraphy (PP)

Salivary gland	Time point	Replanning arm[1]	Standard arm[1]	P-value[2]
Parotid gland				
	Inclusion	56 (16)	55 (15)	0·923
	M12	48 (17)	41 (17)	0·026
Submaxillary gland				
	Inclusion	32 (19)	34 (20)	0·479
	M12	4 (9)	6 (11)	0·546

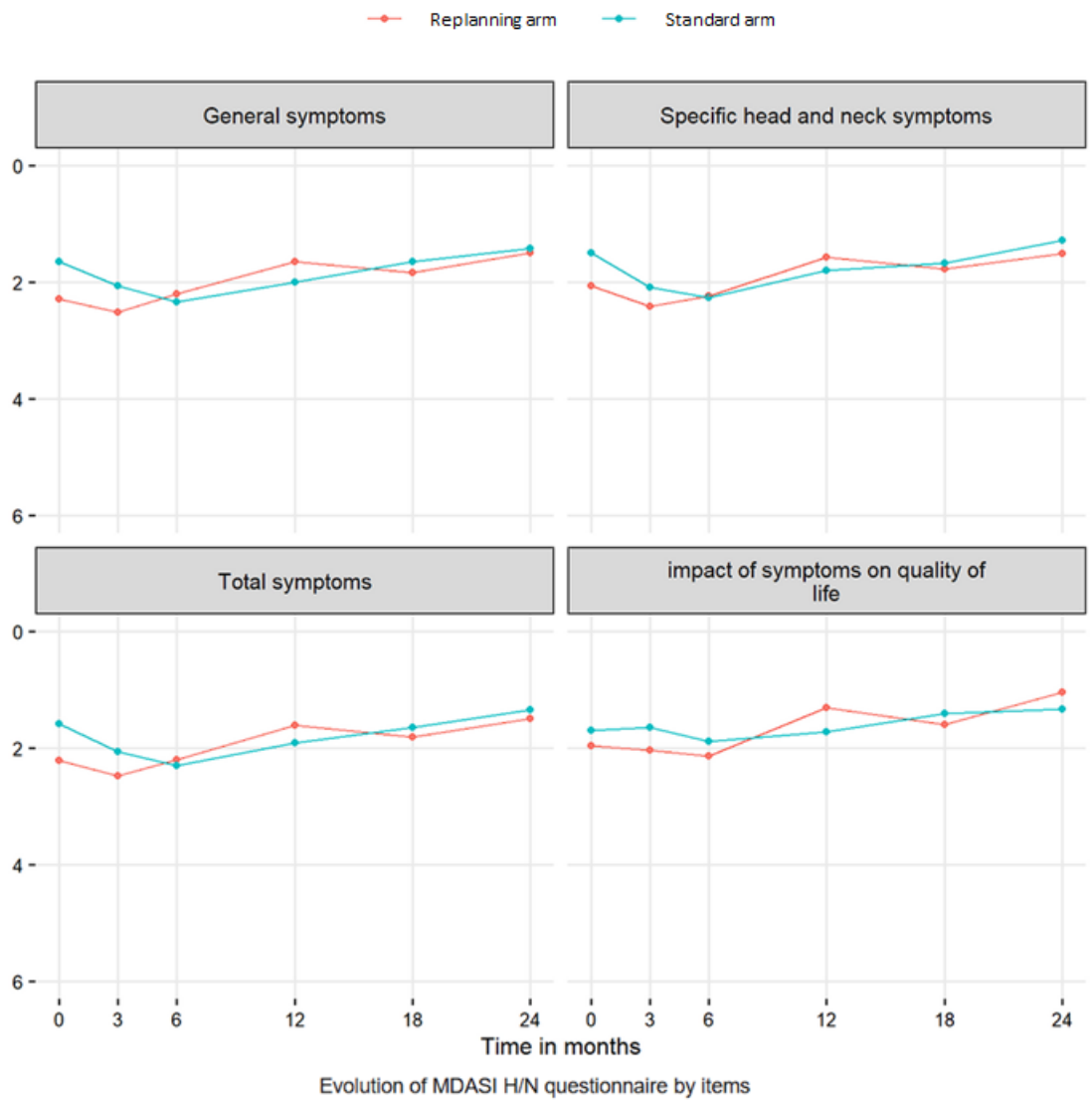
[1] Mean (SD)
[2] Wilcoxon rank sum test

The excretory function of the salivary gland was measured by dynamic image acquisition after injection of 99mTechnetium pertechnetate and oral administration of 10 mL of lemon juice to stimulate salivary secretion. The salivary excretory function was calculated as the difference between the maximum and minimum salivary secretions divided by the maximum salivary secretion (%). Mean and SD are reported. Higher values correspond to better salivary function. M12 = 12 months after radiotherapy



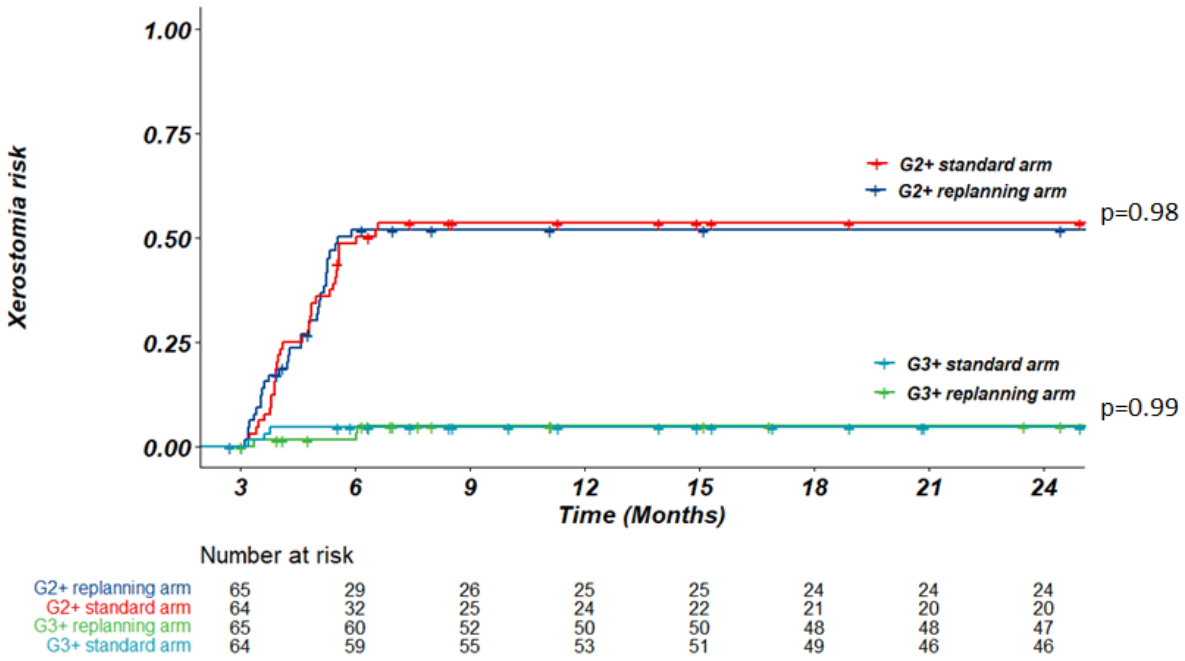
eFigure 1: Trend of the Eisbruch scoring in the treatment arm (ITT)

The questionnaire contained 14 questions and evaluated the extent of xerostomia in patients (5-point scale ranging from “not at all” to “very much”). The scores were transformed into 0–5 scales, with higher scores corresponding to a higher degree of symptoms.[31] Scores were significantly decreased at three and six months compared to baseline for each arm (Wilcoxon signed-rank test). No significant difference was found between baseline and 12, 18, and 24 months. No significant difference was found between the two arms at any given time (Wilcoxon signed-rank test).



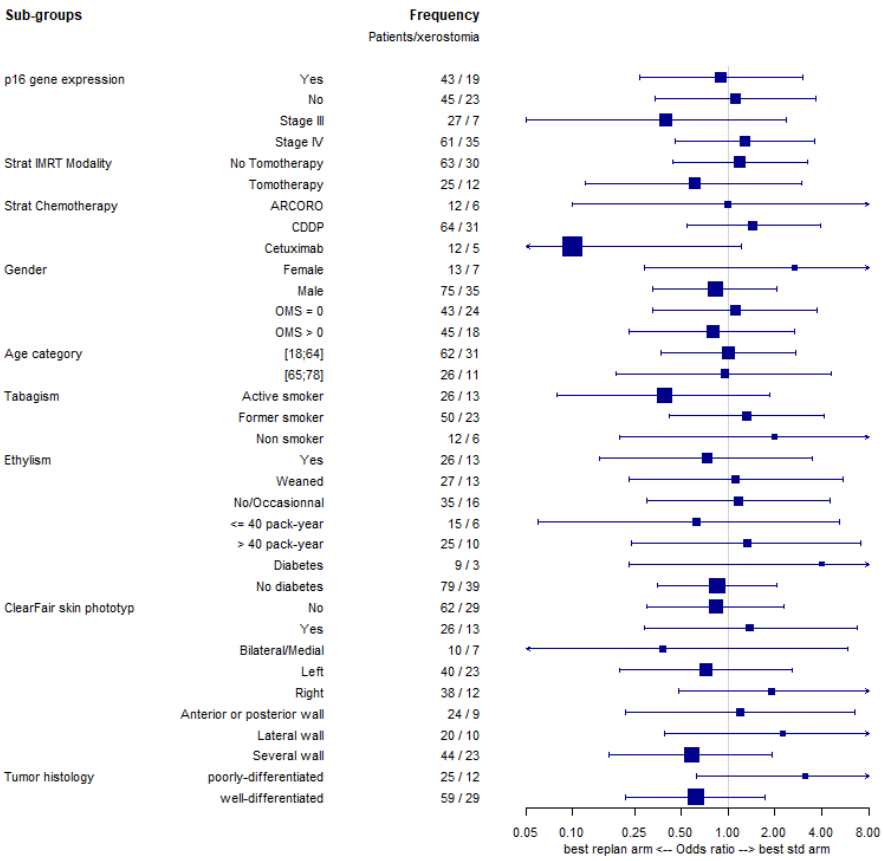
eFigure 2: Trend of the MDASI-HN questionnaire in the treatment arm (ITT)

The MDASI-HN questionnaire consisted of 28 questions on a 10-point scale (a higher score corresponded to a higher degree of symptoms), with three categories of questions: 13 questions on general symptoms, nine questions on the head and neck-specific symptoms, and six questions on the impact of symptoms on quality of life (the same questions may be included in different subgroups). Scores were significantly decreased at three and six months compared to baseline for each arm (Wilcoxon signed-rank test). No significant difference was found between baseline and 12, 18, and 24 months. No significant difference was found between the two arms at any given time (Wilcoxon signed-rank test).



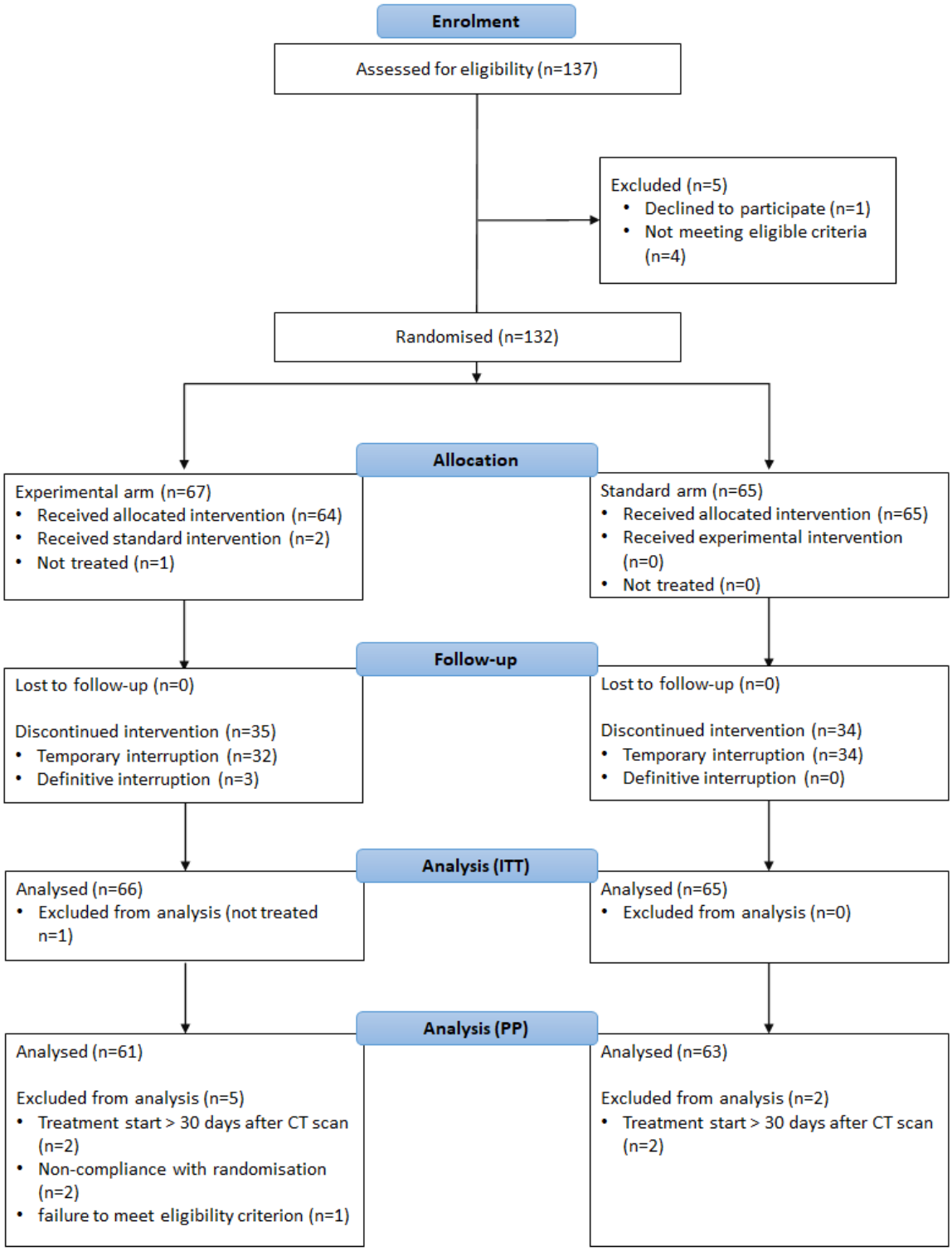
eFigure 3 : Cumulative incidence rate of xerostomia (CTCAE 4.0 grade ≥ 2 and grade ≥ 3) by treatment arm (ITT)

No significant difference was found between the 2 arms regarding the late xerostomia grade ≥2 (G2+) or the late xerostomia grade ≥3 (G3+)

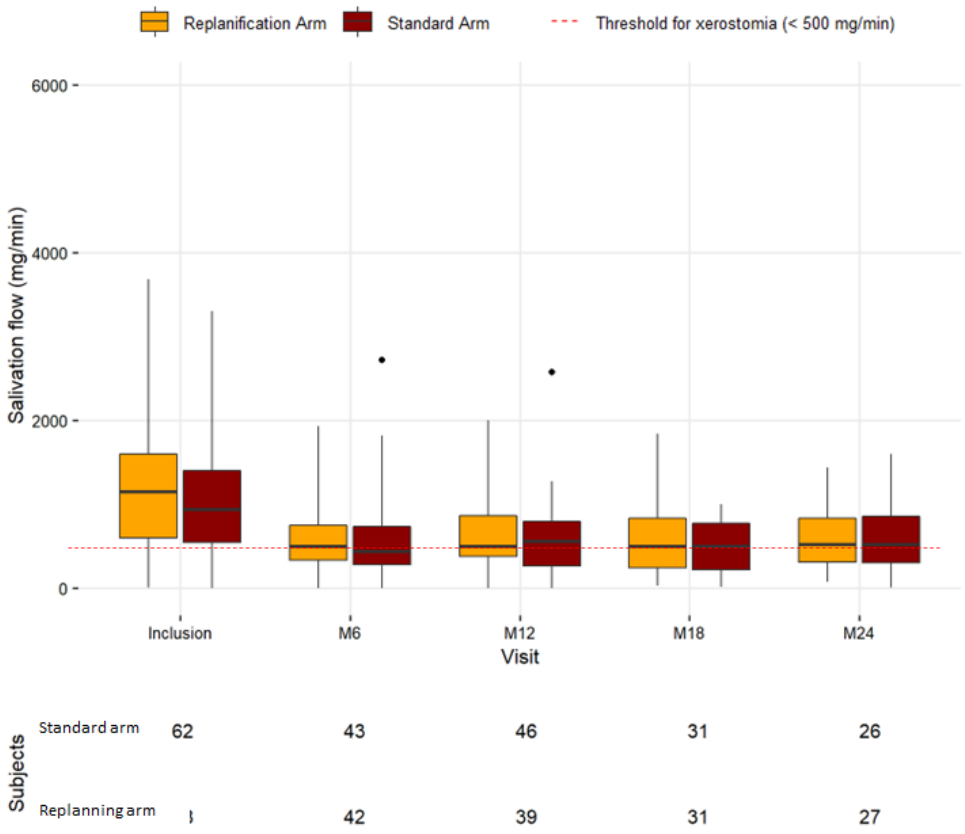


eFigure 4: Sensitivity analysis: impact of the treatment arm on xerostomia (assessed by simulation flow after paraffin stimulation) in subgroup analyses (ITT)

Subgroup analyses measures the effect of the randomization arm on the risk of developing xerostomia separately for each population subgroup defined by sociodemographic, clinical tumor and management characteristics. The effect of the randomization arm is evaluated by odds ratio (OR) from logistic regression where OR lower than 1 signifies that the replanning arm has a lower risk of xerostomia than the standard arm. Xerostomia is defined as a salivary flow < 500 mg/min at 12 months. Regardless the subgroup, no difference was found between the two arms.

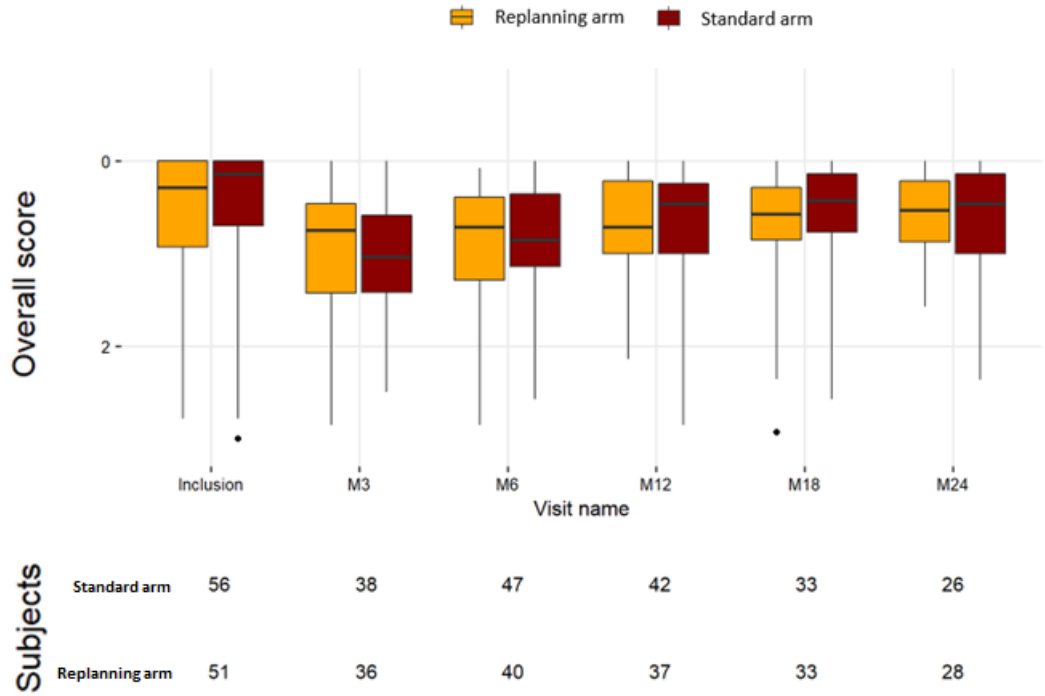


eFigure 5: Figure 1: Flowchart of the patient population (Intent-to-Treat and Per Protocol analyses)



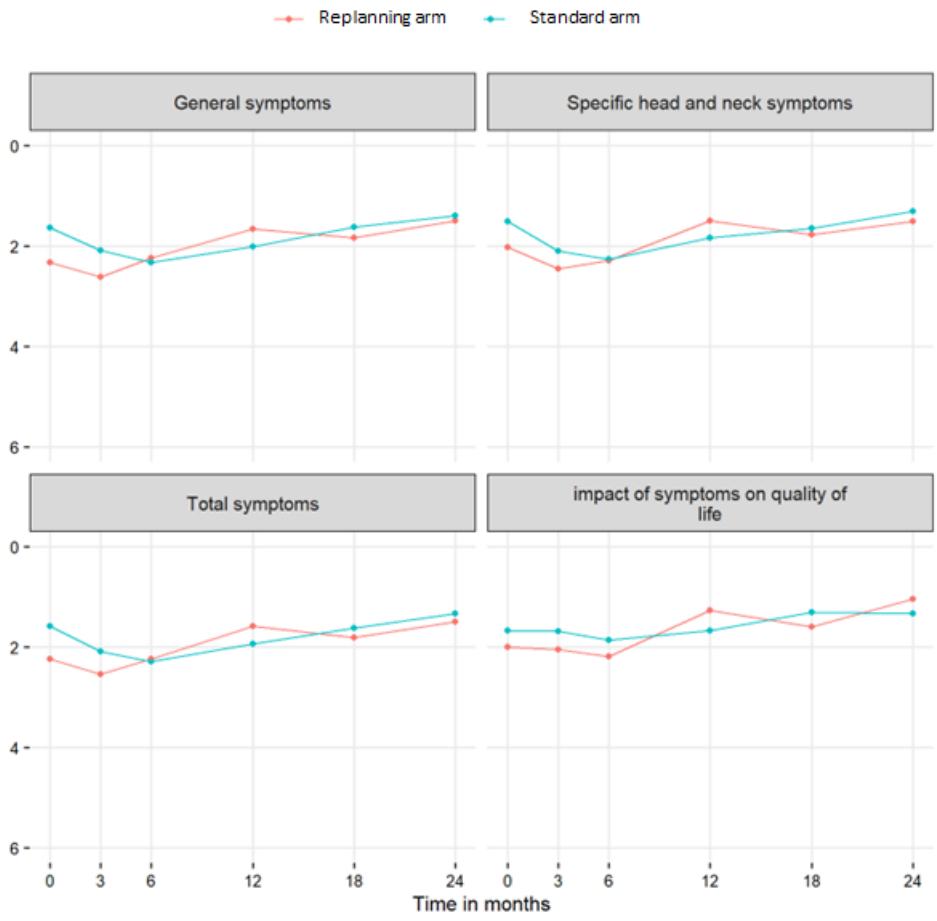
eFigure 6: Evolution of the salivary flow after stimulation by paraffin (PP)

Salivary flow was measured using the formula: weight of the saliva sample/sample collection time in minutes (mg/min). Xerostomia was defined as the salivary flow of < 500 mg/min (red dotted line). The salivary flow was significantly decreased at all time points compared to inclusion in both arms (Wilcoxon signed-rank test). No significant difference in salivary flow was found between the two arms at any given time (Wilcoxon signed-rank test).



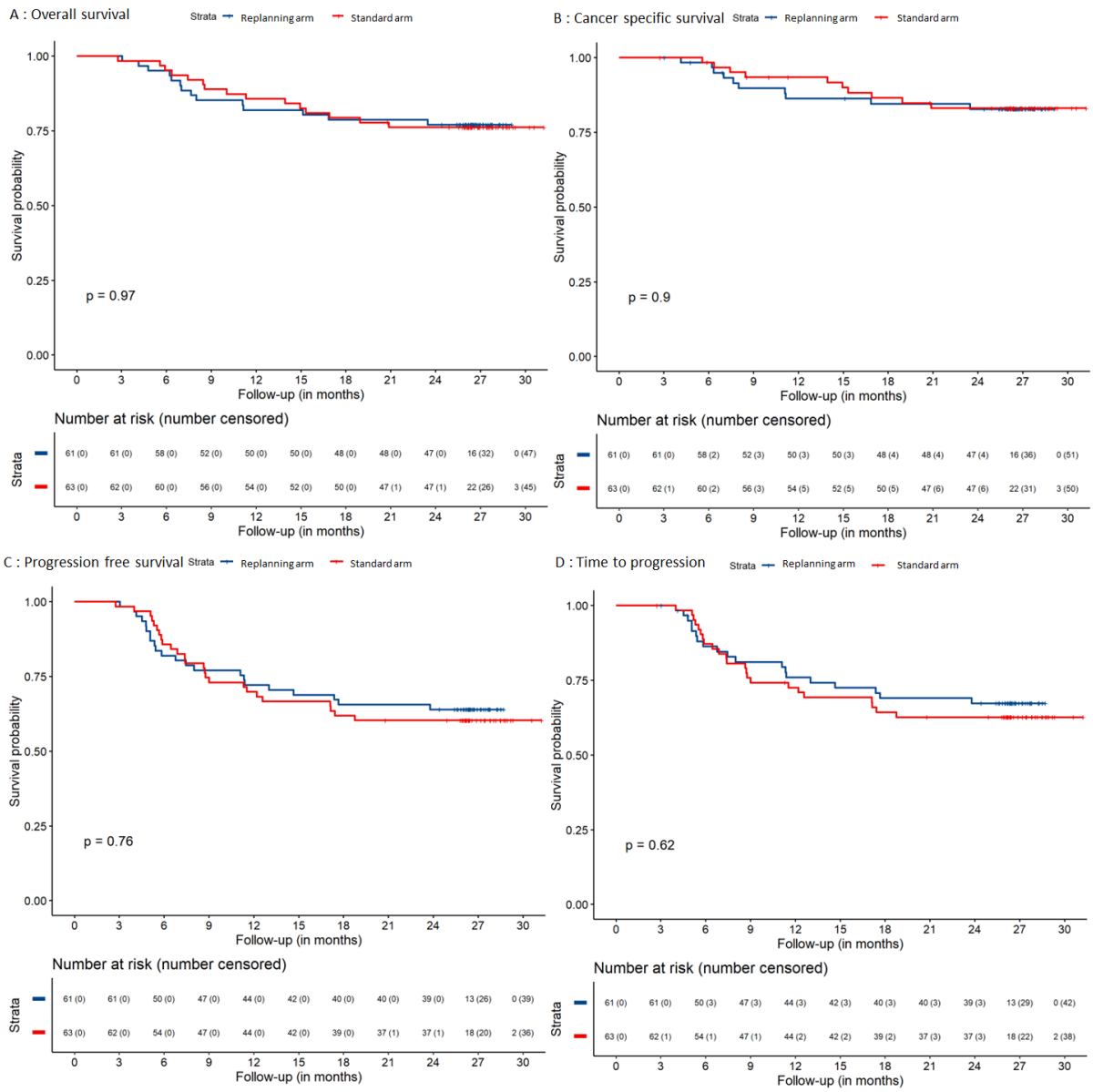
eFigure 7: Trend of the Eisbruch scoring in the treatment arm (PP)

The questionnaire contained 14 questions and evaluated the extent of xerostomia in patients (5-point scale ranging from “not at all” to “very much”). The scores were transformed into 0–5 scales, with higher scores corresponding to a higher degree of symptoms. Scores were significantly decreased at three and six months compared to baseline for each arm (Wilcoxon signed-rank test). No significant difference was found between baseline and 12, 18, and 24 months. No significant difference was found between the two arms at any given time (Wilcoxon signed-rank test).



eFigure 8: Evolution of MDASI HN questionnaire by treatment arm (PP)

The MDASI-HN questionnaire consisted of 28 questions on a 10-point scale (a higher score corresponded to a higher degree of symptoms), with three categories of questions: 13 questions on general symptoms, nine questions on the head and neck-specific symptoms, and six questions on the impact of symptoms on quality of life (the same questions may be included in different subgroups). Scores were significantly decreased at three and six months compared to baseline for each arm (Wilcoxon signed-rank test). No significant difference was found between baseline and 12, 18, and 24 months. No significant difference was found between the two arms at any given time (Wilcoxon signed-rank test).



eFigure 9: Survival curves of the study (PP).

(A) Overall survival, (B) Cancer-specific survival, (C) Progression-free survival, and (D) Time to progression curves. No significant differences were found between the two treatment arms for all endpoints of treatment efficacy.

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