

# Supplementary Material

## **MR-guided adaptive radiotherapy for head-and-neck cancer: prospective evaluation of migration of the salivary glands and anatomical changes**

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**Table S1.** Literature overview of all identified studies that investigated the change in dose, volume or migration of salivary glands during the course of radiotherapy, sorted according to publication year and alphabetic using the first author's surname. HNC = Head-and-neck cancer, CT = Computer tomography.

First author	Year	Patients	Imaging	Glands	Volume	Migration	Dose – compared to planning	Dose – compared to no re-planning
Barker[1]	2004	14 HNC	CT scans three times weekly	Parotids	Mean: -28.1% (0.6%/day)	Median medial shift: 3.1 mm		
Nishimura[2]	2005	33 Pharyngeal	mid-treatment CT	Parotids	Mean: -26%			
Hansen[3]	2006	13 HNC	mid-treatment CT	Parotids	Mean: -15.6-21.5%			Dmean -0.2 - -2.9 Gy
Robar[4]	2007	15 HNC	weekly CT	Parotids	Mean: -4.7% - 5.0%/week	Mean medial shift: 0.85 mm/week	Dmean: +0.2% - +2.6%	
O'Daniel[5]	2007	11 HNC	biweekly CT	Parotids			Dmean: +1.0 Gy	
Lee[6]	2008	10 HNC	daily MV CT	Parotids		Medial shift	Dmean: +15%	
Vasquez Osorio[7]	2008	10 Oropharyngeal	FU CT two weeks after end RT	Salivary glands	Mean: -5%-20%	Parotids medial shift: 1 mm Submandibular glands superior		
Han[8]	2008	5 Nasopharyngeal	daily MV CT	Parotids	Mean: -40.2% (1.1%/day)		Dmedian: +2.2% per day	
Wang[9]	2009	82 HNC	mid-treatment CT scans	Salivary glands	Mean: -16.8%-26.9%			
Wu[10]	2009	11 HNC	weekly CT	Parotids	Mean: -15%		Dmean: +10%	Dmean: -8%
Bhide[11]	2010	20 HNC	weekly CT	Parotids	Mean: -35%		Dmean: +2.8 Gy	
Broggi[12]	2010	87 HNC	MV CT or kV CT at the end of treatment	Parotids	Median: -26%			
Castadot[13]	2010	10 HNC	weekly CT	Salivary glands	Mean: -0.9% --1.3%/day	Parotids mean medial shift: 3.4 mm Submandibular superior shift: 1.7 mm		
Height[14]	2010	10 HNC	repeat CT after fifth week of treatment	Parotids	Median: -20.5% - -23.6%	Medial shift: 0.3 - 1.9 mm	No detectable change	
Teshima[15]	2010	20 Oral squamous cell carcinoma	CT or MR at the end of treatment	Parotids	Mean: -29%			
Wang[16]	2010	15 Nasopharyngeal	repeat CT after 18 fractions	Parotids	Median: -19.8%-20.6%	Median medial shift: 4.3-4.8 mm	Dmean: +2.57-2.97 Gy	
Houweling[17]	2011	18 Oropharyngeal cancer	FU MRI 6 weeks after end of treatment	Salivary glands	Mean: -25%			
Loo[18]	2011	5 HNC	daily MV CT	Parotids	Mean: -17.5% - -30.2%	Medial shift	Dmean: +8.9% - +19.3%	
Ricchetti[19]	2011	26 HNC	weekly CT	Salivary glands	Mean: -26.4% - -31.9%			
Beltran[20]	2012	16 HNC	repeat CT after 15 and 25 fractions	Parotids	Mean: -30% (1.5%/day)		Dmean: +4.7% - +6.1%	

Capelle[21]	2010	20 HNC	repeat CT after 15 fractions	Parotids	Mean: -17.5%			Dmean: -0.6 Gy
Fiorentino[22]	2012	10 HNC	daily CBCT	Parotids	Mean: -43.5% - -44.0% (1.8%-1.6%/day)			
Fung[23]	2012	10 Naropharyngeal	repeat kV CT after ~25 and ~35 fractions	Parotids	Mean: -32.4% - -33.3%			Dmean: -0.84 - -1.25 Gy
Lu[24]	2012	43 Naropharyngeal	repeat CT after 20 fractions	Parotids	Mean: -35.5% - -36.8%			
Hunter[25]	2013	18 Oropharyngeal	daily CBCT	Parotids	Mean: -13.3%			Dmean: -0.92 Gy
Jin[26]	2013	9 Nasopharyngeal		Parotids	Mean: -38.4% - -40.7%			Dmean: -0.31 - -0.62 Gy
Nishi[27]	2013	20 HNC	repeat CT 3-4 weeks after start RT	Parotids	Mean: -18.1%	Mean medial shift: 4.2 mm		Dmean: +5.0 Gy
Schwartz[28]	2013	22 Oropharyngeal	daily CT	Parotids	Mean: -26%			Dmean: -0.8 - -4.1 Gy
Sanguineti[29]	2013	85 Oropharyngeal	weekly CBCT	Parotids	Mean: -30.7% - -34%			
Belli[30]	2014	46 HNC	kV CT mid-treatment and during last week of RT	Parotids	Mean: -146 mm3/day			
Fung[31]	2014	30 Naropharyngeal	two repeat CT mid-treatment	Parotids	Mean: 47.5% (1.35%/day)	Mean medial&superior shift: 1 mm/day		
Castelli[32]	2015	15 HNC	weekly CT	Parotids	Mean: -28.3%	Parotid-CTV distance -4.3 mm for 74%		Dmean: -3.6 Gy
Chitapanarux [33]	2015	17 Nasopharyngeal	repeat CT after 17 fractions	Parotids	Mean: -24.3% - -30.5%			Dmean: -1.1 Gy
Huang[34]	2015	19 Nasopharyngeal	repeat CT after each 5 fractions and at the end of treatment	Parotids	Mean: -38.0% - -39.2% (7.8%-7.9%/week)	Mean medial shift: 2.7 mm – 3.1 mm		Dmean: -3.1 - -5.6 Gy
Marzi[35]	2015	34 HNC	MRI at start, mid-treatment, and end of RT	Parotids	Mean: -31%			
Yao[36]	2015	50 Nasopharyngeal	weekly MV CT	Parotids	Median: -35% (1.07%/day)			
Dewan[37]	2016	30 HNC	repeat CT after 4 weeks of treatment	Parotids	Mean: -31.1% - -33.7%	Mean medial shift: 2.7 mm – 3.3 mm		Dmean: -5.6 Gy
Raghavan[38]	2016	6 HNC	daily MRI	Parotids	Median: -21.8% - -31.3%	Median medial shift: 0.9 mm – 1.4 mm		Dmean: +0.008 Gy – 0.01 Gy
Zhou[39]	2016	18 Nasopharyngeal		Parotids	Mean: -26.5%			
Zhang[40]	2016	13 Oropharyngeal	weekly CT	Parotids	Mean: -28.0% - -34.5%			Dmean: -3.3 Gy
Mahmoud[41]	2017	22 HNC	repeat CT after 3 weeks and after 6 weeks of treatment	Parotids	Mean: -23.1% - -30.9%			Dmean: -9.1% - -16.4%
Zhang[42]	2017	39 Nasopharyngeal	kV CT at 10th, 20th and 30th fractions of RT	Parotids	Mean: -37.5%	Mean medial shift: 3.0 mm Mean superior shift: 1.5 mm		
Hu[43]	2018	40 Nasopharyngeal	repeat CT after ~22 fractions	Parotids	Mean: -17.2% - -20%			Dmean: -0.1 Gy - -0.7 Gy

Marzi[44]	2018	40 Oropharyngeal	repeat MRI after 10 fractions and FU MRI 8 weeks after RT	Parotids	Mean: -18.2%	Medial and superior shift	
Ilangovan[45]	2020	45 HNC	repeat CT after 15 and 25 fractions	Parotids	Mean: -33.6% - -36.0%		Dmean: +4.8 Gy - +6.3 Gy
Lee[46]	2020	64 HNC	weekly CBCT	Parotids	Mean: -25%		
Wellington dos Santos[47]	2020	49 HNC	CT at end of RT	Parotids	Mean: -20% - -21%		
Verma[48]	2020	10 HNC	repeat CT at week 3 and 5	Parotids	Mean: -33.6 - -35.6%	Mean medial shift: 2.8 mm – 3.6 mm	Dmean: +33% - +48.9%
McDonald[49]	2021	10 HNC	daily MRI	Parotids	Range: +0.2% - -11%		Dmean: -0.50 Gy

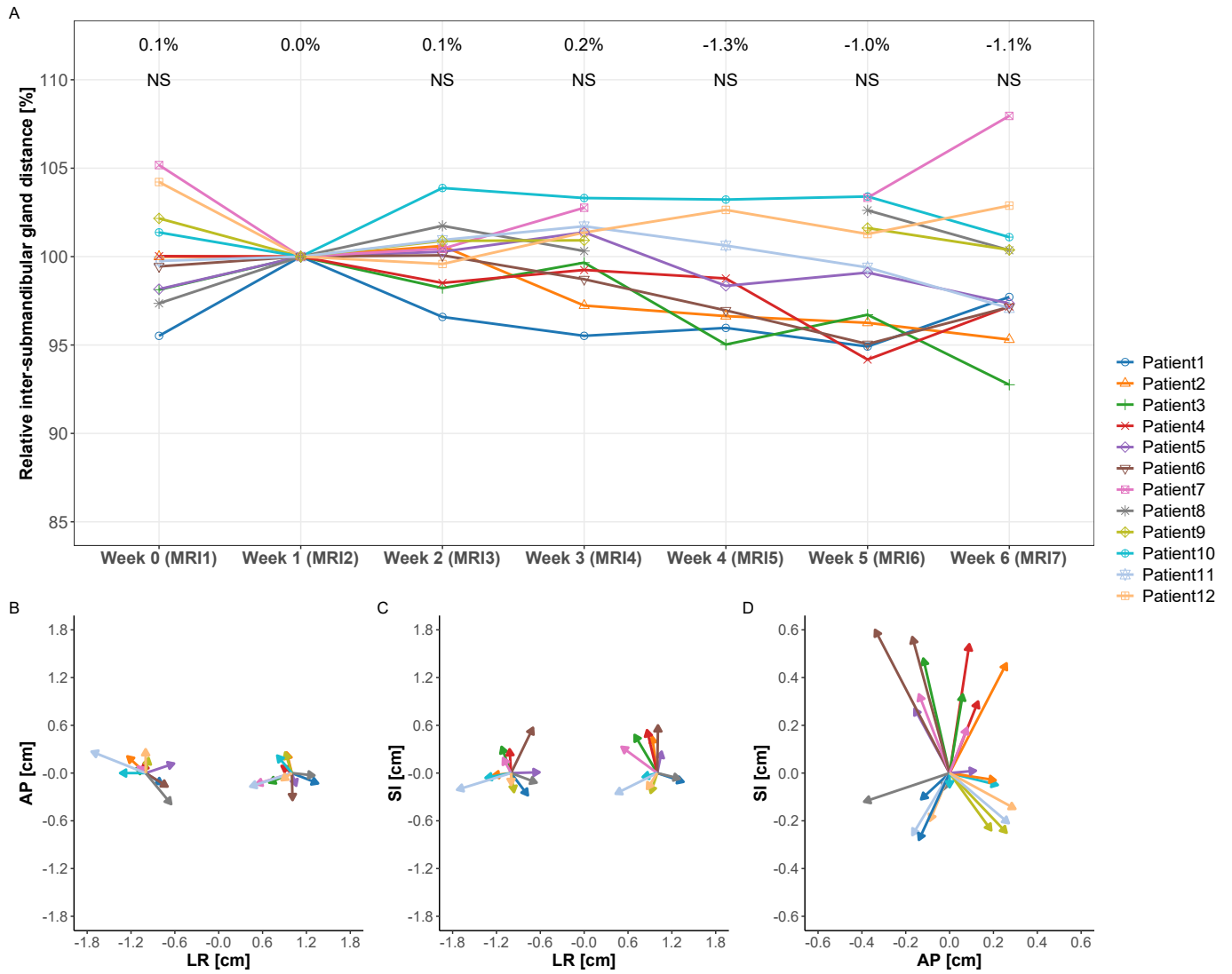


Figure S1: Migration of submandibular glands during radiotherapy. A) Change of inter-submandibular gland distance. B-D) Submandibular gland migration in AP/LR, SI/LR and SI/AP. For this representation the submandibular gland locations was corrected with the brainstem location, and then the baseline submandibular gland location was set to (-1,0) for the right submandibular gland and (1,0) for the left submandibular gland. AP = Anterior-posterior, LR = left-right, SI = superior-inferior. NS: Not significant.

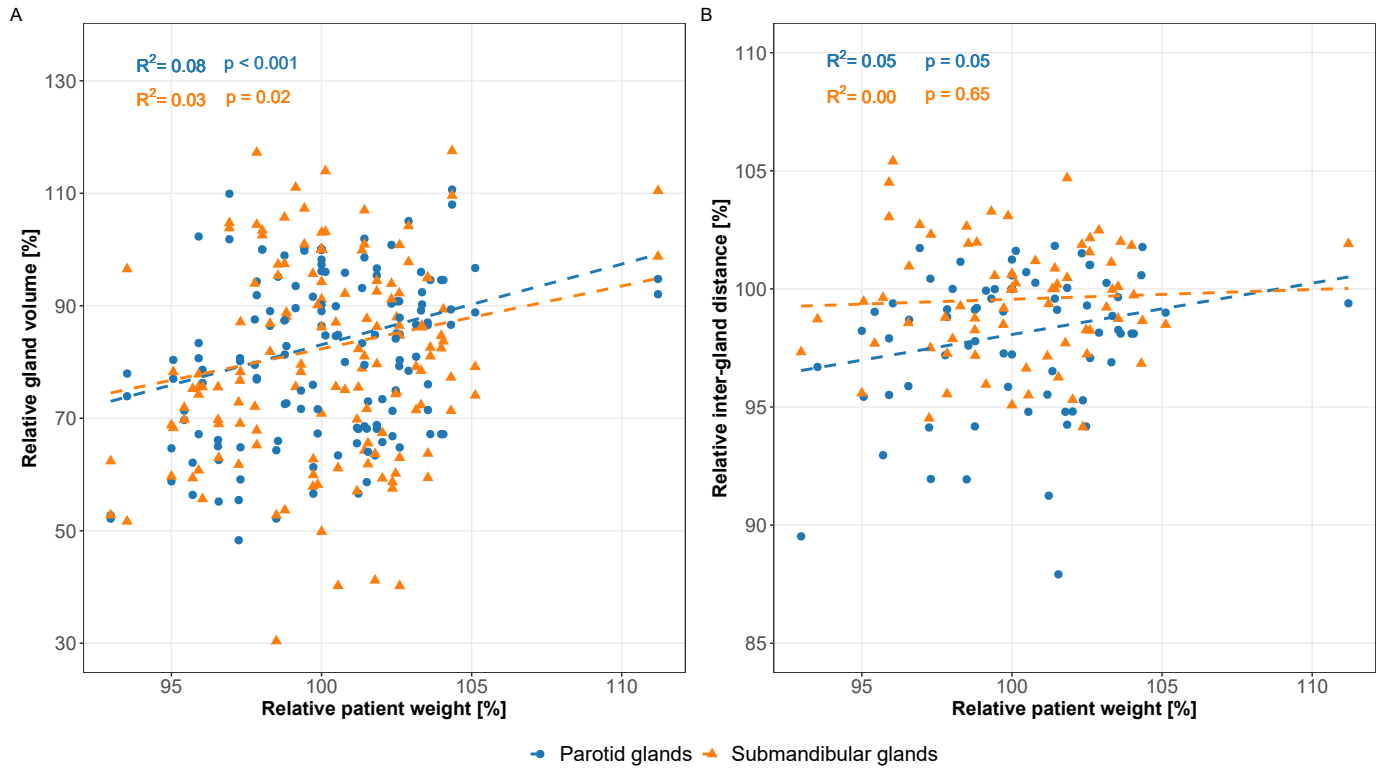
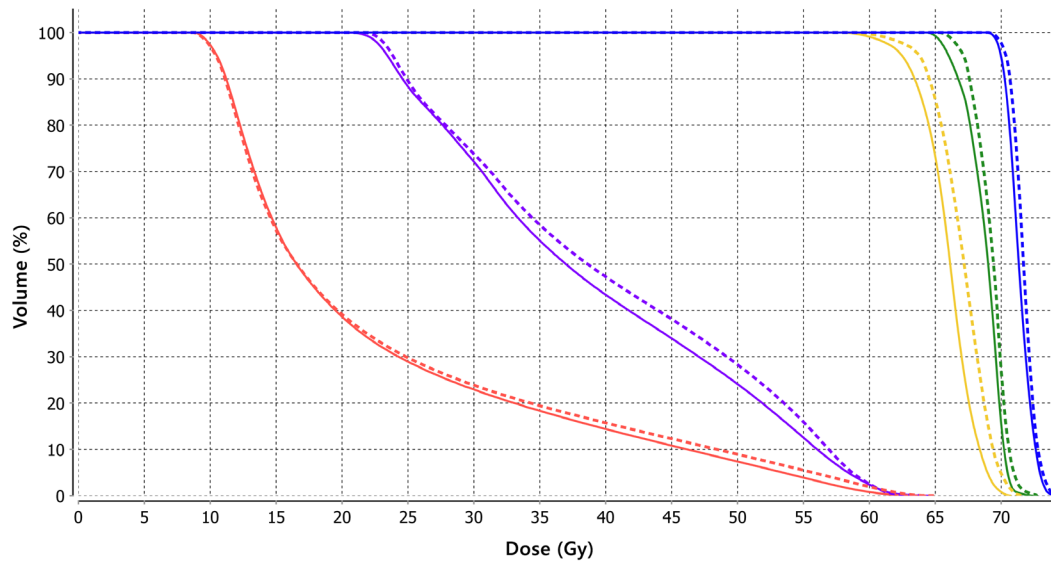
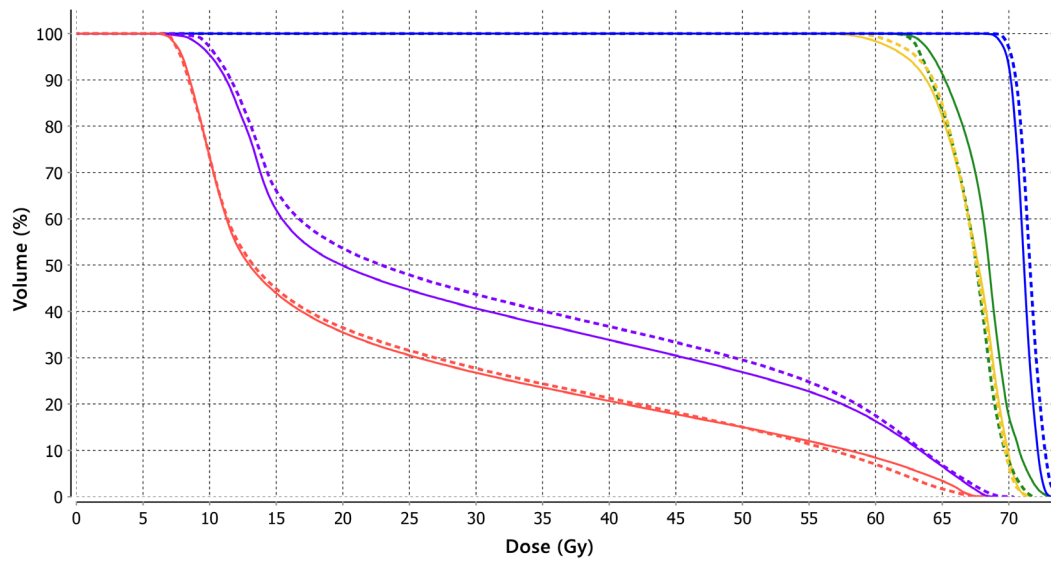
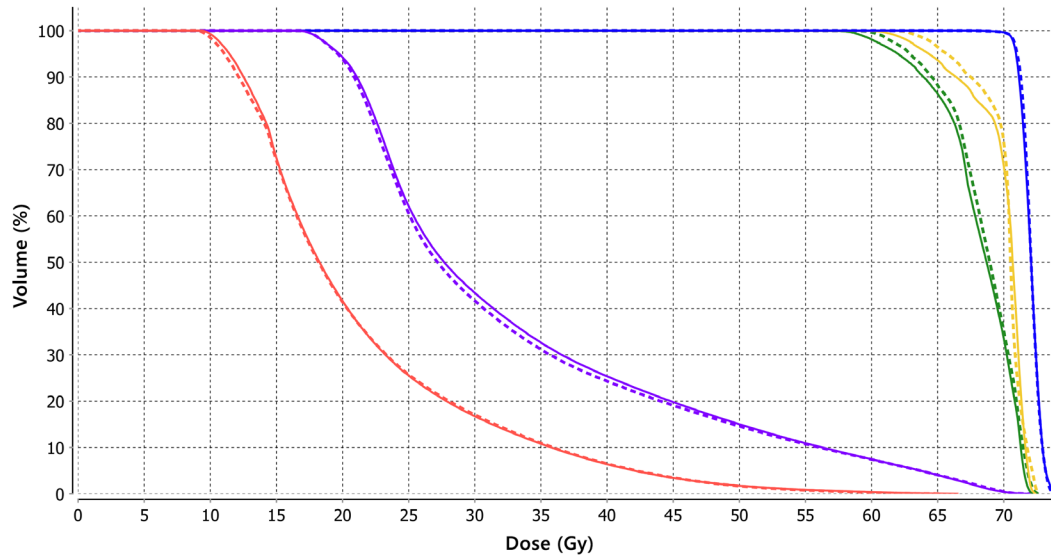


Figure S2: Scatterplot between patient weight and relative gland volume (A) or inter-gland distance (B).



— Left parotid      — Right parotid      — Left submandibular gland  
 — Right submandibular gland      — GTV  
 — Planned dose      - - - - - Predicted dose

Figure S3: Cumulative-planned dose (solid lines) and cumulative-predicted dose (dashed lines) for weekly adaptations. Red is the left parotid, purple the right parotid, yellow the left submandibular gland, green the right submandibular gland, and blue the gross tumor volume (GTV).

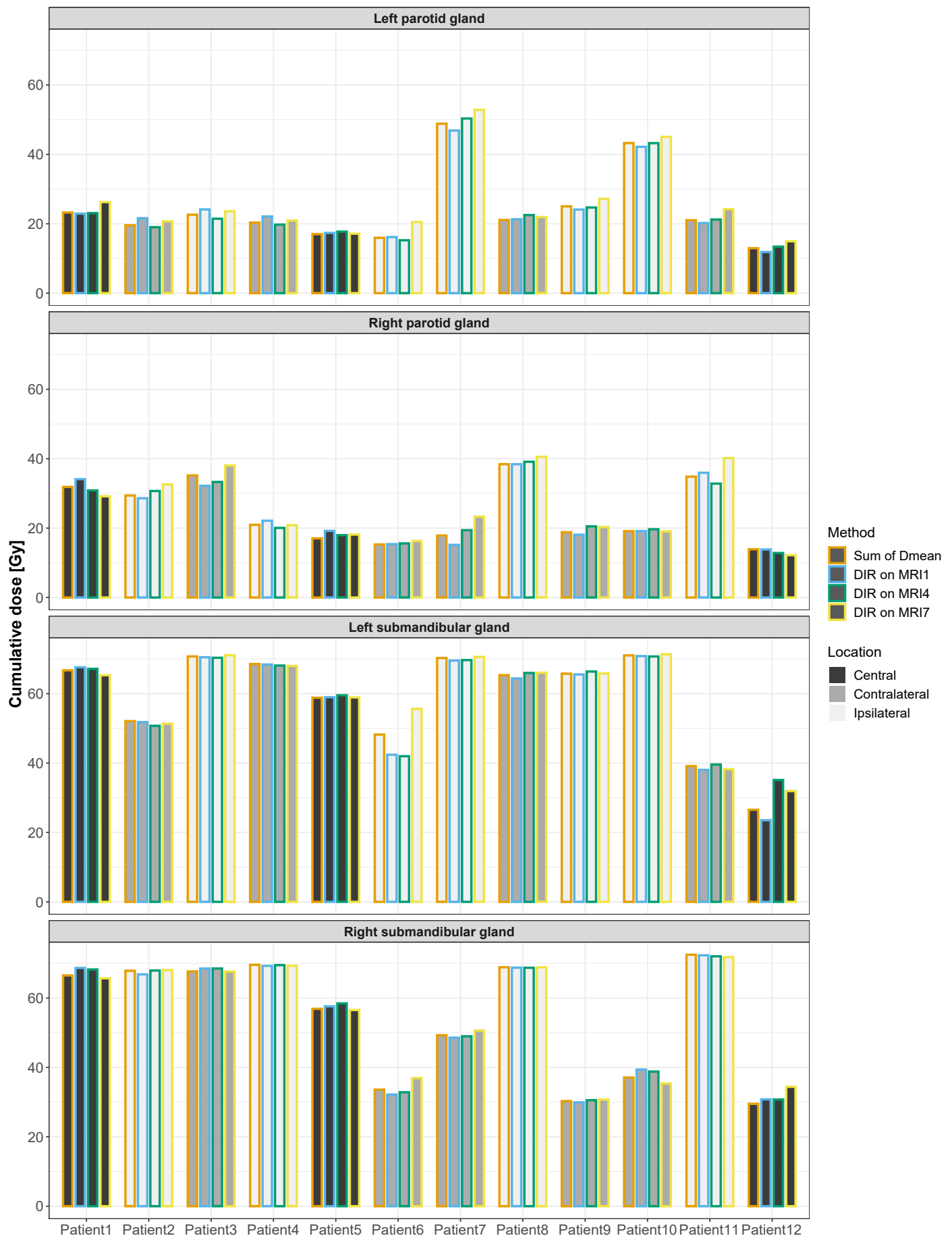
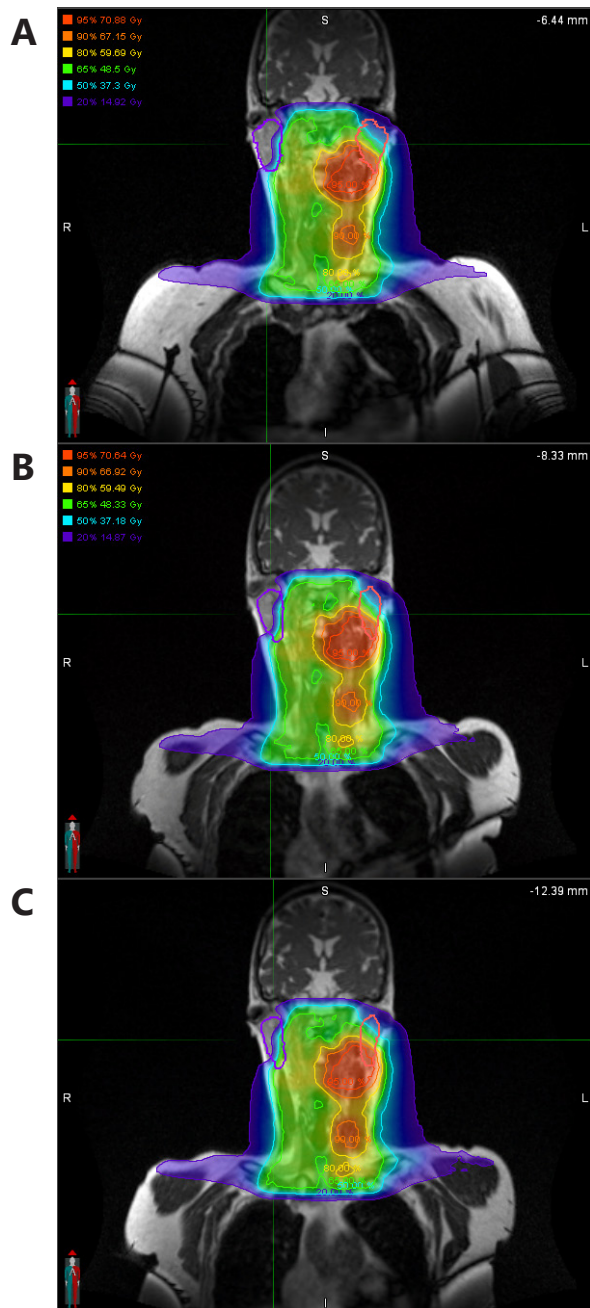


Figure S4: Differences between dose accumulations. Left) linear summation of the glands' Dmean at each time point, Second) DIR-based cumulative dose mapped onto MR1, Third) DIR-based cumulative dose mapped onto MR4 (see Figure 4) and Right) DIR-based cumulative dose mapped onto MR7. Patient 7 is shown as an example in Figure S5.





Dose warped onto MRI1  
Right parotid Dmean = 15.2 Gy

Dose warped onto MRI4  
Right parotid Dmean = 19.4 Gy

Dose warped onto MRI7  
Right parotid Dmean = 23.3 Gy

Figure S5: Example patient with the DIR-based cumulative-dose mapped onto MR1 (A), MR4 (B) or MR7 (C)

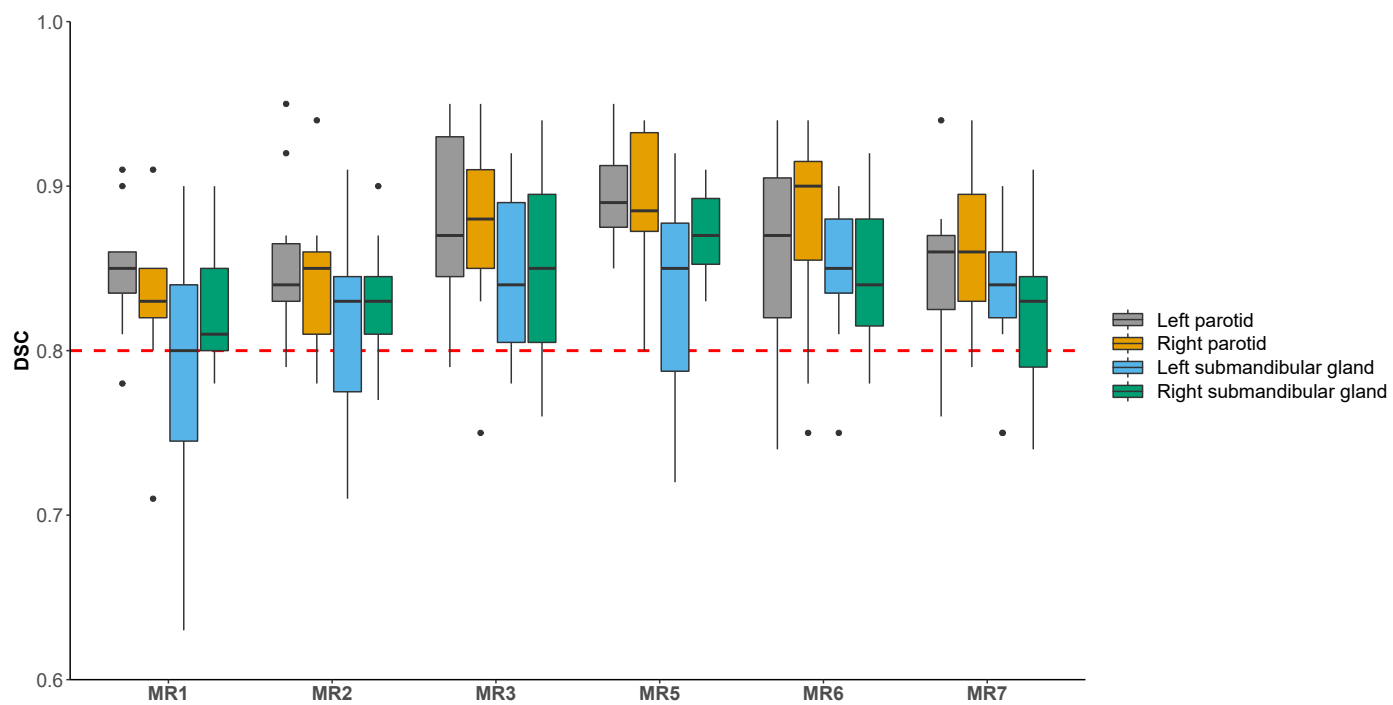


Figure S6: Dice similarity coefficient (DSC) values between the salivary glands contoured on MR4 and after deformable image registration with the remaining MRIs.

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