

SUPPLEMENTARY MATERIAL

Derived metrics

Various definitions are available for ID, CI and HI. The following were employed in this study:

$$ID = V_S * D_{\text{mean}}$$

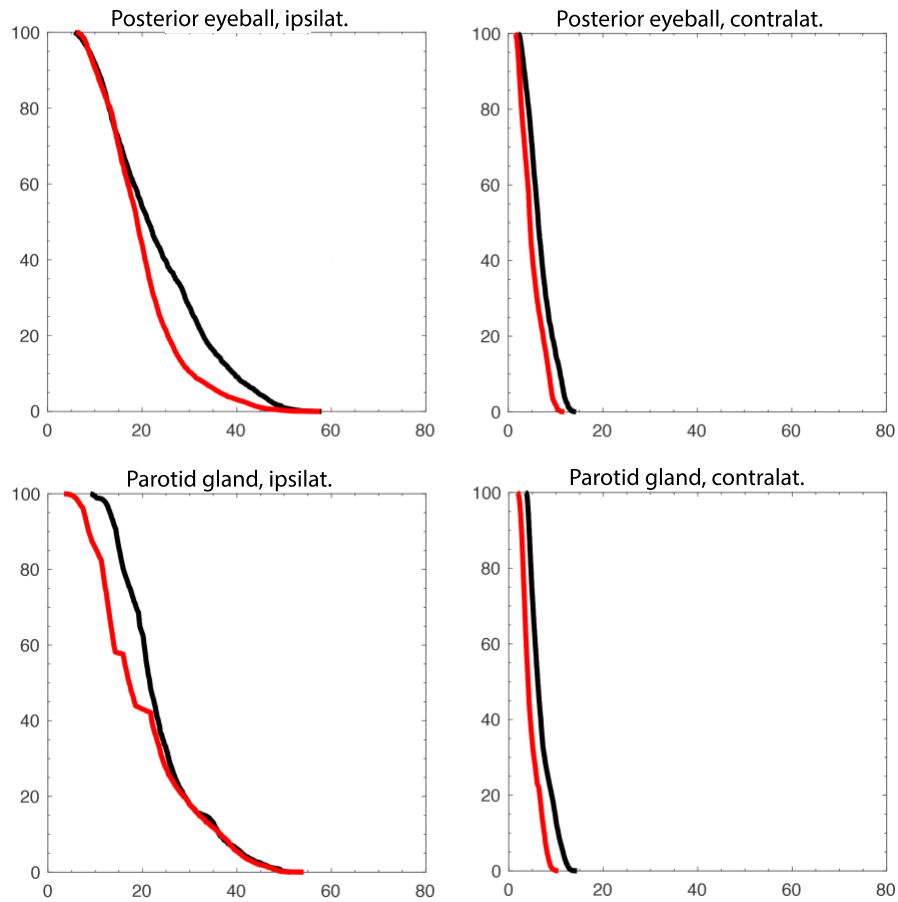
where V_S is the subject volume exclusive of target volumes and D_{mean} is the mean dose applied to V_S , and

$$CI = \frac{V_{T,pi}}{V_{pi}} \quad \text{and} \quad HI = \frac{D_{95\%}}{D_{5\%}}$$

where $V_{T,pi}$ is the subset of the target volume (T) receiving the prescription isodose (pi) or greater, and where V_{pi} is the volume enclosed by the prescription isodose (a CI variant proposed by Lomax et al. [1]), and where $D_{5\%}$ and $D_{95\%}$ specify the minimum doses delivered to the hottest 5% and 95% of the target volume.

Reference

[1] Lomax NJ, Scheib SG. Quantifying the degree of conformity in radiosurgery treatment planning. Int J Radiat Oncol Biol Phys. 2003;55:1409-19.



Supplementary Figure S1. Cumulative dose-volume histograms for additional OARs. *The abscissa displays the volume in %. The ordinate displays the dose in GyE. Black marks the clinical separated planning strategy. Red marks the experimental integrated planning strategy.*

Supplementary Table S1. The patient cohort for this study. All cases were of primary tumors and presented for adjuvant or definitive RT. *Elective target volumes are inclusive of the boost volumes.* PNS: paranasal sinuses.

#	Age Sex	Entity	Site	Elective vol (cm ³)	Boost vol (cm ³)	Setting
01	50 M	Adenocarcinoma (adenoid cystic)	PNS and orbit (left)	393	155	Adjuvant
02	41 M	Malignant ductal tumor (uncertain differentiation)	Orbit (right)	106	60	Adjuvant
03	49 W	Adenocarcinoma (adenoid cystic)	Soft palate	350	155	Adjuvant
04	35 W	Adenocarcinoma (adenoid cystic)	Parotid gland (left)	240	108	Adjuvant
05	63 M	Adenocarcinoma (basal cell)	Maxilla and sphenoid (left)	348	184	Adjuvant
06	74 W	Adenocarcinoma (unknown differentiation)	Nasal cavity and PNS (right)	385	165	Adjuvant
07	40 M	Adenocarcinoma (adenoid cystic)	Parotid gland (right)	459	245	Definitive
08	68 M	Adenocarcinoma (intestinal-type)	Nasal cavity and PNS (left and right)	268	136	Adjuvant
09	29 M	Adenocarcinoma (adenoid cystic)	Parotid gland (left)	188	117	Adjuvant
10	56 M	Malignant mucosal melanoma	PNS (left)	298	205	Adjuvant

Supplementary Table S2. Overview of the dosimetric parameters that were derived from the cumulative dose distributions. Different subsets of the parameters listed above were evaluated for OARs, depending on their serial or parallel architecture as well as common clinical practice.

Parameter	Definition
<i>Targets</i>	
D _{99%} , D _{98%}	Near-minimum doses, i.e. the minimum doses to 99% (98%) of the target volume (GyE)
D _{50%}	Median dose to the target volume (GyE)
D _{2%} , D _{1%}	Near-maximum doses, i.e. the maximum doses to 1% (2%) of the target volume (GyE)
Cov _{100%} , Cov _{95%}	Coverages, i.e. the percentage of the target volume receiving at least 100% (95%) of the prescription isodose, therefore 74 GyE (70.3 GyE) and 50 GyE (47.5 GyE)
CI _{boost} , CI _{elective}	Conformity indices, calculated as CI _{74GyE} and CI _{50GyE}
HI _{boost} , HI _{elective}	Homogeneity indices, calculated as HI _{95%}
<i>OARs</i>	
D _{1%}	Near-maximum dose to the organ volume, analogous to the definition above
D _{50%}	Median dose to the organ volume (GyE)
D _{mean}	Mean dose to the organ volume (GyE)
<i>Subject volume</i>	
ID	Integral dose (GyEL)

Supplementary Table S3. Overview of the clinical endpoints and dosimetric parameters that served as the basis for assessment of toxicity risks for OARs.

Volume	Endpoint	Parameter
Temporal lobe	Incidence of symptomatic necrosis <3%	$D_{max} < 60.0$ GyE
Brainstem	Incidence of permanent cranial neuropathy or necrosis <5%	$D_{max} < 54.0$ GyE
Spinal cord	Incidence of grade ≥ 2 myelopathy <1%	$D_{max} \leq 50.0$ GyE
Retina	Incidence of blindness <1%	$D_{max} < 50.0$ GyE
Optic nerve and chiasm	Incidence of optic neuropathy <3%	$D_{max} < 55.0$ GyE
Parotid gland	Incidence of grade 4 xerostomia <20%	$D_{mean} < 20.0$ GyE unilateral $D_{mean} < 25.0$ GyE bilateral

Supplementary Table S4. Absolute minimum and/or maximum doses for CTVs and OARs. Keeping in mind that these metrics are very sensitive and therefore prone to misrepresentation, they are only provided as supplementary material. *Bold denotes statistical significance at level $p < 0.05$.*

Volume (n)	Parameter	Separated Strategy Median (IQR)	Integrated Strategy Median (IQR)	Δ Median (%)	p
CTVboost (10)	$D_{100\%}$	43.8 (16.0)	39.1 (10.2)	-4.7 (-11%)	0.3
	$D_{0\%}$	78.8 (1.8)	78.6 (1.8)	-0.2 ($\pm 0\%$)	0.5
CTVelective (10)	$D_{100\%}$	34.4 (5.8)	32.2 (14.6)	-2.2 (-6%)	0.6
	$D_{0\%}$	77.9 (1.0)	77.0 (0.7)	-1.0 (-1%)	0.2
Temporal lobe ipsilat. (14)	$D_{0\%}$	74.2 (2.7)	71.9 (5.6)	-2.3 (-3%)	<0.001
Temporal lobe contralat. (6)	$D_{0\%}$	24.7 (27.3)	18.5 (22.9)	-6.2 (-25%)	0.03
Brainstem (10)	$D_{0\%}$	46.5 (23.0)	41.7 (29.3)	-4.8 (-10%)	0.002
Spinal cord (10)	$D_{0\%}$	25.2 (7.6)	21.7 (15.8)	-3.5 (-14%)	0.01
Posterior eyeball ipsilat. (14)	$D_{0\%}$	57.7 (34.8)	54.5 (37.1)	-3.2 (-6%)	0.009
Posterior eyeball contralat. (6)	$D_{0\%}$	14.1 (19.3)	11.7 (16.8)	-2.4 (-17%)	0.03
Optic nerve ipsilat. (14)	$D_{0\%}$	50.5 (25.5)	50.3 (43.2)	-0.3 ($\pm 0\%$)	0.17
Optic nerve contralat. (6)	$D_{0\%}$	15.4 (33.3)	11.9 (28.6)	-3.5 (-23%)	0.09
Optic chiasm (9)	$D_{0\%}$	46.6 (31.5)	46.7 (37.1)	+0.2 ($\pm 0\%$)	0.25