

Supplement 1

Radiation Dosimetry and Technique

Dose Specification and Fractionation (Cohort 1)

The target dose was specified as 40Gy in 5 fractions. Treatment was only permitted if the normal tissue criteria were met as specified in Table S1. If the normal tissue criteria were not met, or per discretion of radiation oncologist, treatment down to a dose level of 6 Gy x5 was permitted. The dose per fraction was 8 Gy specified to the isodose line at the edge of the planning treatment volume (PTV) as specified in Dosimetry section below. The first dose was delivered on Monday and the subsequent fractions were delivered on sequential days such that the final dose was delivered on a Friday, though schedule shift was allowed as necessary to accommodate holidays, inclement weather or equipment servicing.

Dose Specification and Fractionation (Cohorts 2-4)

The target dose as specified as 24Gy in 3 fractions. Treatment is only permitted if the normal tissue criteria were met as specified in Table S1. If the normal tissue criteria were not met, or per discretion of radiation oncologist, treatment down to a dose level of 6 Gy x3 was permitted. The dose per fraction was 8 Gy specified to the isodose line at the edge of the planning treatment volume (PTV) as specified in Dosimetry section below. The first dose was delivered on Monday and the subsequent fractions were delivered every other day such that the final dose was delivered on a Friday, though schedule shift was allowed as necessary to accommodate holidays, inclement weather or equipment servicing.

Physical Factors

Only 6 MV photons were allowed on study. Linear accelerators with daily image guidance were required. Static IMRT or VMAT technique were required.

Localization, Simulation and Immobilization.

Patient positioning was used base on clinical judgment to best achieve the ideal dose distribution typically in the supine position with the head in a custom head rest. Patients were positioned in a stable position that allows accurate reproduction on the target position between planning and each treatment. A thermoplastic mask with S frame was used as an immobilization system. CT based simulation with IV contrast was required unless patient has a contrast allergy refractory to premedication or if the treating physician determined that the risk of IV contrast would not permit its safe use. In that event, an MRI or PET scan fused to the CT simulation for adequate target delineation was utilized. Axial scans were required with spacing ≤ 3 mm between slices.

Localization-Cone-beam CT was obtained at each treatment on the treatment unit immediately prior to each treatment to ensure proper alignment. If CBCT imaging was offline, isocenter port localization films were used instead at the discretion of the treating physician.

Treatment Planning/Target Volumes

The target lesions was outlined by either MC or KY and designated as gross tumor volume (GTV). This primary target was not enlarged for prophylactic treatment and only abnormal CT signal consistent with gross tumor was included (clinical exam, MRI or PET imaging can be used in the determination of areas of disease). The GTV was expanded by an additional 2-3 mm uniformly to create a planning target volume (PTV). Critical OAR was expanded by 3 mm. If there was overlap with the PTV, the PTV was edited out of the expanded OAR structures to form the modified PTV (mPTV). The mPTV included the physician delineated GTV irrespective of OAR expansion. Smoothing of the final modified PTV was allowed if sharp edges were created from

the expansion.

Treatment technique

Static IMRT or VMAT was used with 9-12 non-coplanar static IMRT fields or 1-3 arc fields incorporated in the radiation treatment plan. For this protocol, the isocenter was defined as the common point of gantry and couch rotation.

Dosimetry

Dose was prescribed to a peripheral isodose covering the PTV. The treatment plan was created such that there was 100% correspondence to the maximum dose delivered to the patient within the PTV. The prescription isodose lines covering the PTV were typically the 60-90% line and the hotspots were manipulated to occur within the target and not in the adjacent normal tissue. The prescription isodose was chosen such that 95% of the PTV was covered by the prescription isodose surface and 99% of the PTV received a minimum of 90% of the prescription dose. The maximum dose for the purposes of this protocol was defined at 0.035cc of volume. The maximum PTV dose was at least 110% but not more than 160%.

The cumulative volume of all tissue outside the PTV receiving greater than 105% of the prescription dose was no more than 15% of the PTV volume. Conformality was judged such that the ratio of the volume of the prescription isodose meeting the above criteria to the volume of the PTV as <1.2. For tumors <2.5 cm axial and <1.5cm craniocaudal conformality ratio was not able to be tested.

For the purpose of this study, organs at risk included spinal cord, cochlea, brainstem, esophagus/cricopharyngeus, brachial plexus, mandible, larynx, optic pathway, carotid artery, parotid glands(non-critical), skin. The absolute limits for maximum dose to a point were defined at 0.035 cc.

Table S1
Organs at Risk Dose Constraints

Critical Structure	Volume	Volume Max (Gy)		Max Point Dose (Gy)		Endpoint (≥Grade 3)
		Cohort 1	Cohort 2-4	Cohort 1	Cohort 2-4	
Optic Pathway	<0.2 cc	23 Gy	15.3 Gy	25 Gy	17.4 Gy	Neuritis
Cochlea				25 Gy	17.1 Gy	Hearing loss
Brainstem	<0.5 cc	23 Gy	18 Gy	31 Gy	23.1 Gy	Cranial neuropathy
Spinal Cord	<0.35 cc <1.2 cc	22 Gy 14.5 Gy	18 Gy 12.3 Gy	28 Gy	21.9 Gy	Myelitis
Spinal Cord (5-6mm above & below)	<10% of subvolume	23 Gy	18 Gy	28 Gy	21.9 Gy	Myelitis
Esophagus & cricopharyngeus	<5 cc	19.5 Gy	17.7 Gy	35 Gy	25.2 Gy	Stenosis or fistula
Brachial Plexus	<3 cc	27 Gy	20.4 Gy	32 Gy	24 Gy	Neuropathy
Carotid Artery	<10 cc	27 Gy	20 Gy	34 Gy	27 Gy	Carotid blowout
Skin	<10 cc	36.5 Gy	30 Gy	38.5 Gy	33 Gy	Ulceration
Larynx	<3 cc	32 Gy	24 Gy	40 Gy	30 Gy	Necrosis

Mandible	<5 cc	30 Gy	21.9 Gy	43 Gy	30 Gy	Necrosis
Parotid Glands (each separate)	<7 cc Mean dose	20 Gy <24 Gy	20 Gy <24 Gy	40 Gy	40 Gy	Xerostomia

Contouring Normal Tissue Structures

- Spinal Cord: The spinal cord was contoured based on the bony limits of the spinal canal. It was contoured at least 10 cm above and below the superior and inferior extent of the PTV respectively.
- Optic pathway: Optic nerves and chiasm were contoured if within 10 cm of the PTV.
- Cochlea: The cochlea were contoured if it falls with 10 cm of the PTV.
- Brain Stem: Contoured at least 10 cm above and below the superior and inferior extent of the PTV.
- Esophagus/cricopharyngeus: The esophagus and the cricopharyngeus were contoured starting at least 10 cm above and below the superior and inferior extent of the PTV.
- Brachial Plexus: The ipsilateral brachial plexus was for the purpose of this study a normal tissue constraint that included the neural foramina of C5-T1 from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles. For CT slices where no neural foramen is present, the space was contoured between the anterior and middle scalene muscles. The brachial plexus was contoured as the posterior aspect of the subclavian neurovascular bundle inferior and laterally to one to two slices below the clavicular head. The first and second ribs served as the medial limit of the OAR.
- Carotid Artery: The ipsilateral carotid artery was contoured.
- Skin: The skin was defined as the outer 0.3cm of the body surface.
- Larynx: Contoured in its entirety from cricoid cartilage to the top of the arytenoids.
- Mandible: The mandible was contoured in its entirety.
- Parotid glands: Both right & left contoured in their entirety and defined as 2 structures.

Dosimetry Compliance

The Dosimetry section above describes appropriate conduct for treatment planning dosimetry. See the Organs at Risk section for dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constituted a minor protocol violation. Exceeding these limits by more than 5% constituted a major protocol violation.