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NRG ONCOLOGY PROTOCOL DEVELOPMENT TEMPLATE FOR RADIATION THERAPY

DISEASE SITE: Head and Neck
SUB-COMPONENT: Photon and proton therapy

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Underlined highlighted texts are either **instructions or suggestions** to be deleted or replaced by PIs with regular texts without highlight.

Regular highlighted texts are **examples** to be selected (remove highlight), deleted or replaced by PIs with regular texts.

5.2 Radiation Therapy

In this section, the modality used to deliver radiation, the method for patient immobilization, and the method to correlate patient geometry and delivery geometry should be clearly described. Requirements for credentialing (including IROC phantom irradiation and the IGRT) should be explicitly specified in the protocol.

[STUDY CHAIRS: Refer to the NRG web site for RTQA Protocol Prescription Guidelines for writing RT prescriptions in NRG protocols *[link to come]*.]

Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) are mandatory for this study. Intensity Modulated Proton Therapy is allowed.

Radiation Therapy Schema

Schema at the beginning of the protocol should be followed.

5.2.1 Treatment Technology

List allowed Treatment Modalities (including energy): photons, protons (Passive Scattering Proton Therapy (PSPT) should be avoided), electron, brachytherapy,

Required Capabilities: IMRT, IGRT, patient immobilization device, etc.

Megavoltage energy photon beam irradiation with energy $\geq 4\text{MV}$ is required (6MV energy is preferred). Proton therapy using pencil beam scanning including intensity modulated proton therapy (IMPT) is allowed. Proton therapy using passive scattered beam with aperture or MLC techniques is / is not allowed.

IMRT techniques including static field IMRT, helical or axial IMRT (Tomotherapy, RefleXion X1), and VMAT are allowed. MRIdian is allowed (only modality that allows Co-60 energy). Treatment machine must be equipped to provide daily MRI, kV, or MV image guidance. The minimum requirements for image guidance are given in Section 5.2.10.

Table 5.2.1A: Treatment Technology

Treatment Technology	Requirements and Recommendations
Beam Modality	Photons or protons are allowed

Beam Energy	$\geq 4\text{MV}$ (6MV preferred), with the exception of the MRIdian (Co-60 delivery).
Treatment Technique	<u>Photons</u>: static field, helical or axial IMRT, VMAT, and MRIdian are allowed. <u>Protons</u>: pencil beam scanning including IMPT is allowed. Passive scattering with aperture is / is not allowed
IGRT	Treatment machine must be equipped to provide daily MRI, kV, or MV image guidance. The minimum requirements for image guidance are given in Section 5.2.10.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

For photon therapy, patients will be treated in a supine position and immobilized with a thermoplastic mask and customized headrest. Intraoral immobilization devices may be utilized for tongue position control or immobilization and should be considered when the targets involve the pharyngeal axis.

For proton therapy, patients will be treated in a supine or seated position and immobilized with a proton-compatible thermoplastic mask and customized headrest. Additional immobilization devices such as a bite block may be used.

The immobilization device should at least include the head and neck. It is strongly encouraged that the participating centers also include the shoulders in the immobilization to further ensure accurate patient set-up on a daily basis. Indexed hand holder position is recommended to help reproducible shoulder position in proton therapy.

5.2.3 Simulation Imaging

This subsection should include information about the extent of CT imaging, the resolution of the scan information including the slice thickness, and details of the allowed use of contrast agents and the handling of tissue densities when contrast is used.

1. Treatment Planning, Imaging, and Localization Requirements

Note: If a treatment planning CT scan is used to determine the extent of disease at the time of radiation simulation (which can occur after registration but prior to treatment), it must be with ≤ 3 mm contiguous slices (specified with contrast or without contrast). Only the non-contrast CT should be used for proton dose calculation.

2. Treatment planning CT and/or MRI scans will be required to define gross target volume(s), and clinical target volume(s). MRI scans and/or PET scans (choose one or both) aid in delineation of the treatment volume and/or critical structures on planning CT scans. The primary treatment planning images (CT or MRI) should be acquired with the patient in the same position and using the same immobilization device as for treatment. If MRI scan is used as primary treatment planning images, techniques used for correcting tissue heterogeneity and geometric distortion should be described. MRI images or synthetic CTs (from other modalities) should not be used as the primary planning images for proton therapy.

3. All tissues to be irradiated must be included in the primary planning images. The slice thickness should be ≤ 3 mm through the region that contains the primary target volumes and critical organs. All tissues receiving irradiation should be included in the planning scan limits. The scanning limits should at least encompass the orbits superiorly and extend at least 1 cm below the suprasternal notch inferiorly. Metal artifact reduction technique in CT scanner can be used for cases with dental filling or other high-density objects. For proton therapy, CT imaging artifact must be carefully addressed (e.g., using density override) for proton therapy. Proper material and density should be used for surgical implants and non-tissue materials involved in the proton beam path. Beams passing through unknown materials (like dental filling) should be avoided with margin. Robust optimization should be used for CTV coverages, with the setup uncertainties at 3mm (the same as the setup margins). Range uncertainties should be used according to their institutions' protocol, preferably at 3% to 3.5%.

4. For patients in whom contrast is contraindicated, FDG-PET/CT and MRI image fusion to the planning CT image set should be used for accurate tumor and normal organ definition. MRI scans assist in definition of target volumes, especially when targets extend near the base of skull. If possible, the patient undergoing an MRI scan should be set up as close as possible to the treatment planning position. Image registration and fusion applications, if available, should be used to help in the delineation of target volumes. Vendor software MRI geometrical distortion correction must be applied if available. All image sets used for structure delineation must be submitted with the RT digital data

5.2.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Entries in the first column of the list below will be entered and edited by the QA Staff. The PIs are required to specify the information in the second, third columns. The detailed specifications have to include crucial items such as boundary definitions and margins.

Table 5.2.4A: Definition of Target Volumes and Margins

Standard Name	Description	Validation (Required/Required when applicable/Optional)
GTV_7000	Primary tumor and involved nodes to receive 7000 cGy	Required
CTV_7000	GTV_7000 + 5 mm margin, excluding anatomic boundaries to tumor spread	Required
PTV_7000	CTV_7000 + 3 mm margin*	Required
PTV_Eval_7000	PTV_7000 minus high risk OARs (subtract 5 mm from skin if needed)	Required when applicable
CTV_6000	- CTV_7000 + 5 mm - nodal levels containing involved nodes 2 cm margin extending from the inferior and superior margin of gross nodal disease covering the nodal fat space - suspicious nodes < 1 cm + 5 mm	Required
PTV_6000	CTV_6000 + 3 mm margin	Required
PTV_Eval_6000	PTV_6000 minus high risk OARs (subtract 5 mm from skin if needed)	Required when applicable
CTV_5400	- Uninvolved, lower risk nodal levels excluding the 2 cm inferior and superior margin defined by CTV_6000 - See Table 5.2.4C for details	Required when applicable

PTV_5400	CTV_5400 + 3 mm margin	Required when applicable
PTV_Eval_5400	PTV_5400 minus high risk OARs (subtract 5 mm from skin if needed)	Required when applicable

Detailed Specifications

Setup margin (SM): Daily IGRT is required for this trial; therefore, the SM will be 3 mm in all directions.

GTV_7000: The primary tumor and clinically positive lymph nodes seen on clinical and endoscopic examinations, planning CT or pre-treatment PET or MRI scan will constitute the GTV. Grossly positive lymph nodes are defined as those with a max SUV greater than 3.0 and/or the short-axis diameter is > 1.5 cm for level II, > 0.8 cm for retropharyngeal and/or > 1 cm for levels IB, III, IV, and V and /or those with central necrosis.

CTV_7000: The CTV is defined to be the GTV plus a 0.5 cm margin as appropriate to account for microscopic tumor extension. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose to a volume (CTV_6000) that is slightly larger than CTV_7000. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues. CTV should be cropped to exclude anatomical barriers to tumor spread such as air cavities, uninvolved bone, and external body contours. Guidelines for CT based delineation of lymph node levels for node negative patients can be found on the NRG Oncology website: <https://www.nrgoncology.org/ciro-head-and-neck>. For patients with positive neck nodes, consult Gregoire et al. (2014) for the delineation of the nodal CTV.

PTV_7000: The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup and internal organ motion. A minimum margin of 3 mm around the CTV is required in all directions to define each respective PTV, except for situations in which:

- the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously at the discretion of the treating physician.
- the CTV results in a PTV that extends beyond the patient's body surface. The PTV should be constrained to at least 3 mm from within the external contour, while still including the CTV. The use of tissue equivalent bolus material is indicated in situations where the disease is at or just under the skin surface. The PTV should align with the skin surface when bolus is used.

PTV_Eval_7000: PTV volume minus impinging high priority OARs created for dosimetric evaluation. In cases where PTV overlaps with critical organs, such as the BrainStem, SpinalCord, OpticChiasm, OpticNrv_R or L, LobeTemporal_R or L, the PTV_Eval_7000 should be created to limit the dose to the OARs (subtract 5 mm from the skin if needed). Other volumes, such as tuning or avoidance or optimization structures, can be employed to drive the IMRT treatment planning process. Such volumes should be considered to be treatment-planning tools that are not reported or sent for review.

CTV_6000: High-risk subclinical sites are defined as areas of:

- potential subclinical tumor infiltration beyond the primary site CTV_7000,
- the first echelon node levels to the primary site irrespective of gross nodal involvement,
- all node levels containing gross nodes.
- In the event of a node excision (≤ 4 per protocol) that occurred at time of diagnosis, the nodal levels that contained grossly involved adenopathy should be included, even if there is no residual post-excision adenopathy.

A CTV_6000 would specifically include the following:

- 5 mm isotropic expansion of CTV_7000.
- 1st echelon node levels based on standard anatomic definitions. In most cases 1st echelon would be ipsilateral level II, but in cases of midline primary site involvement this should include bilateral level II. In cases with soft palate or posterior pharyngeal wall involvement, this should include the lateral retropharyngeal lymph nodes.
- All node levels containing a CTV_7000 that have been assigned to involved nodes (all grossly involved nodal levels).
- At least a 2 cm margin covering the fat of the cervical nodal chain superior and inferior to the node levels that contain/contained gross nodal disease.
- Other high-risk subclinical sites may include nodes < 1 cm not thought to harbor gross disease yet thought to be at risk of containing more than subclinical disease based on their location relative to the primary site. In such cases of clinical concern that do not meet the above criteria, a 5 mm expansion on these nodes can be added to the CTV_6000 at the discretion of the treating clinician.

PTV_6000: The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup and internal organ motion. A minimum margin of 3 mm around the CTV is required in all directions to define each respective PTV, except for situations in which:

- the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously at the discretion of the treating physician.
- the CTV results in a PTV that extends beyond the patient's body surface. The PTV should be constrained to at least 3 mm from within the external contour, while still including the CTV.

PTV_Eval_6000: PTV volume minus impinging high priority OARs created for dosimetric evaluation. In cases where PTV overlaps with critical organs, such as the BrainStem, SpinalCord, OpticChiasm, OpticNrv_R or L, LobeTemporal_R or L, the PTV_Eval_6000 should be created to

limit the dose to the OARs (subtract 5 mm from the skin if needed). Other volumes, such as tuning or avoidance or optimization structures, can be employed to drive the IMRT treatment planning process. Such volumes should be considered to be treatment-planning tools that are not reported or sent for review.

CTV_5400: The CTV will be defined to treat node levels without evidence of gross disease yet at risk of microscopic spread and not contained in CTV_5600. These levels are defined anatomically according to published Intergroup consensus guidelines (Gregoire 2014). The levels to be treated will depend on the site and extent of the primary tumor and any grossly involved lymph nodes and are indicated in Table 5.2.4B.

Table 5.2.4B: Nodal Levels to Receive Prophylactic Microscopic Dose

[CTV_5400]*

Oropharynx primaries

CTV_5400*	Ipsilateral Neck	Contralateral Neck
N0	- Ib (for primary tumor extension into the oral cavity) - II-III - IV at the treating physician's discretion - RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate	- II-III - RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate
N1 with a single node < 3 cm	- Ib (for primary tumor extension into the oral cavity or at the treating physician's discretion) - II-IV - RP (lateral retropharyngeal LN)	- II-III - RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate
N1 with node ≥ 3 cm or multiple nodes	- Ib (for primary tumor extension into the oral cavity or at the treating physician's discretion) - II-IV - RP (lateral retropharyngeal LN)	- II-IV - RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall and/or soft palate - Ib and V at the treating physician's discretion

	• V at the treating physician's discretion	
N2-3	• Ib (for primary tumor extension into the oral cavity or at the treating physician's discretion) • II-IV • RP (lateral retropharyngeal LN) • V at the treating physician's discretion	• II-IV • RP (lateral retropharyngeal LN) • Ib and V at the treating physician's discretion

*Applies to neck levels not included in CTV_6000.

Larynx and hypopharynx primaries

CTV_5400*	Ipsilateral Neck	Contralateral Neck
N0	• II-IV • RP (lateral retropharyngeal LN) for primary tumor extension to posterior pharyngeal wall or hypopharynx primary	• II-IV • RP (lateral retropharyngeal LN) for primary tumor extension to posterior pharyngeal wall or hypopharynx primary
N1 -2b	• II-IV • RP (lateral retropharyngeal LN) • IB and V at the treating physician's discretion	• II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate or hypopharynx primary or at treating physician's discretion
N2c-3	• II-IV • RP (lateral retropharyngeal LN) • IB and V at the treating physician's discretion	• II-IV • RP (lateral retropharyngeal LN) • IB and V at the treating physician's discretion

*Applies to neck levels not included in CTV_6000.

p16-positive unknown primaries

CTV_5400*	<u>Mucosal surface</u>	
	Bilateral oropharyngeal mucosa defined by the bilateral tonsils, soft palate, and base of tongue: Required	
	<u>Involved neck</u>	<u>Uninvolved neck</u>
N2	• II-IV • RP (lateral retropharyngeal LN) • Ib and V (at the treating physician's discretion)	N/A
N3	• II-IV • RP (lateral retropharyngeal LN) • Ib and V (at the treating physician's discretion)	• II-IV • RP (lateral retropharyngeal LN) • Ib and V at the treating physician's discretion

*Applies to neck levels not included in CTV_6000.

Contralateral Neck

The use of unilateral radiation techniques should remain optional, in deference to the established practice and clinical judgment of the enrolling investigator, though 3 groups of patients with respect to neck irradiation are defined below.

Unilateral radiotherapy is recommended (see guidelines below) if it is the institution's established practice, if the primary tumor originates in the tonsillar fossa, and is well-lateralized, with less than 1 cm of involvement of the soft palate or base of tongue, no posterior pharyngeal wall involvement, and with minimal nodal disease burden (single node ≤ 3 cm) as assessed by clinical exam and staging radiology studies. For patients who share these characteristics but have larger nodal disease or multiple nodes confined to ipsilateral level II of the neck, unilateral radiotherapy is optional. Due to the imperative to maintain high PFS for this trial and the lack of prospectively collected data on this controversial subject, for patients with characteristics that fall outside these categorizations, bilateral treatment is required.

Groups of Patients with Regards to Unilateral or Bilateral Neck Irradiation

Group 1: Unilateral treatment is recommended

T1 to T3 tonsillar fossa primaries with < 1 cm clinical or radiographic extension into tongue base and/or soft palate, no posterior pharyngeal wall extension, N0-N1 (single node $\leq$ 3 cm and no extranodal extension).

Group 2: Unilateral treatment is optional

T1 to T3 tonsillar fossa primaries with < 1 cm clinical or radiographic extension into tongue base and/or soft palate, no posterior pharyngeal wall extension, N0-N1 (multiple nodes, all nodes $\leq$ 3 cm and no extranodal extension) with involved adenopathy confined to ipsilateral level II of the neck.

Group 3: Bilateral treatment is mandatory

Tongue base, soft palate, or posterior pharyngeal wall primaries or tonsil primaries with > 1 cm soft palate and/or tongue base extension or any posterior pharyngeal wall extension; patients with any extranodal extension or with involved adenopathy outside of ipsilateral level II of the neck.

PTV_5400: The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup and internal organ motion. A minimum margin of 3 mm around the CTV is required in all directions to define each respective PTV, except for situations in which:

- the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously at the discretion of the treating physician.
- the CTV results in a PTV that extends beyond the patient's body surface. The PTV should be constrained to at least 3 mm from within the external contour, while still including the CTV.

PTV_Eval_5400: PTV volume minus impinging high priority OARs created for dosimetric evaluation. In cases where PTV overlaps with critical organs, such the BrainStem, SpinalCord, OpticChiasm, OpticNrv_R or L, LobeTemporal_R or L, the PTV_Eval_5400 should be created to limit the dose to the OARs (subtract 5 mm from the skin if needed). Other volumes, such as tuning or avoidance or optimization structures, can be employed to drive the IMRT treatment planning process. Such volumes should be considered to be treatment-planning tools that are not reported or sent for review.

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as

indicated.

Entries in the first column of the list below will be entered and edited by the QA Staff. The PIs are required to specify the information in the second, third columns. The detailed specifications such as crucial items such as boundary definitions and margins should be include.

Table 5.2.5: Organ at Risk Nomenclature

For detailed descriptions see below.

OAR Standard Name	Description	Validation (Required/Required when applicable/Optional)
SpinalCord	Spinal Cord	Required
SpinalCord_PRV05	Spinal Cord with 5 mm expansion for Planning Risk Volume (PRV).	Required
BrainStem	Brainstem	Required
BrainStem_PRV03	Brainstem with 3 mm expansion for PRV.	Required
Lips	Lips	Required when applicable
Cavity Oral	Oral Cavity	Required
Parotid_R	Right Parotid Gland	Required
Parotid_L	Left Parotid Gland	Required
GlnD_Submand_R	Right Submandibular Salivary Gland	Required when applicable
GlnD_Submand_L	Left Submandibular Salivary Gland	Required when applicable
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles	Required
Esophagus_S	Upper Cervical Esophagus	Required
Bone_Mandible	Mandible	Required
E-PTV	Unspecified Tissue, External minus all PTVs	Required
External	External border of the patient	Required
BrachialPlexus_R	Right Brachial Plexus	Required when applicable
BrachialPlexus_L	Left Brachial Plexus	Required when applicable
OpticChiasm	Optic Chiasm	Required when applicable
OpticChiasm_PRV03	Optic Chiasm including 3 mm expansion for PRV.	Required when applicable
Thyroid	Thyroid Gland	Optional
Cochlea_R	Right Cochlea	Required when applicable

Cochlea_L	Left Cochlea	Required when applicable
Ear_Middle_L	Right Middle Ear	Optional
Ear_Middle_R	Left Middle Ear	Optional
Eye_R	Right Eye	Required when applicable
Eye_L	Left Eye	Required when applicable
Larynx_SG	Supra Glottic Larynx	Required
Lens_R	Right Lens	Required when applicable
Lens_L	Left Lens	Required when applicable
OpticNrv_R	Right Optic Nerve	Required when applicable
OpticNrv_L	Left Optic Nerve	Required when applicable
OpticNrv_PRV03_R	Right Optic Nerve including 3 mm expansion for PRV	Optional
OpticNrv_PRV03_L	Left Optic Nerve including 3 mm expansion for PRV	Optional
Lobe_Temporal_R	Right Temporal Lobe	Required when applicable
Lobe_Temporal_L	Left Temporal Lobe	Required when applicable
Joint_TM_R	Right Temporomandibular Join	Required when applicable
Joint_TM_L	Left Temporomandibular Join	Required when applicable

The detailed specifications have to include crucial items such as boundary definitions and margins.

All structures should be contoured on the planning CT, using the PET/CT or postoperative MRI for guidance.

Detailed Specifications

SpinalCord: The spinal cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord volume will be defined at approximately T3-4 (i.e., 2-3 cm below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan.

SpinalCord_PRV05: Planning Risk Volume (PRV) spinal cord defined as SpinalCord + 5 mm in all directions.

BrainStem: The most inferior portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purpose of this study, the most superior portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan.

BrainStem_PRV03: Planning Risk Volume (PRV) brainstem defined as Brainstem + 3 mm in all directions.

Parotid_R/L: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. The parotid gland is an irregular shaped gland wedged between the ramus of the mandible and the mastoid process. The superior border is the zygomatic arch, inferiorly, the gland extends to the angle of the mandible. The anterior border is the masseter muscle; in 20% of cases the parotid gland extends anteriorly over the surface of the masseter muscle, and posteriorly, to the anterior border of the sternocleidomastoid. Laterally, it extends to the platysma and medially, to the posterior belly of the digastric muscle, styloid process and parapharyngeal space. The retromandibular vein is included in the parotid gland contour.

Larynx_SG: This will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, the epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, up to but not including the medial border of the thyroid cartilage, and including the cricoid cartilage to the inferior edge of the arytenoid cartilage, but not the hypopharynx. Posteriorly, the contour extends to the anterior edge of the pharyngeal wall.

Pharynx: This will be defined as the pharyngeal mucosa and wall plus adjacent constrictor muscles deemed not to require treatment (external to PTVs). This extends from the superior constrictor region (level of the inferior pterygoid plates) to the cricopharyngeal inlet (inferior level of the posterior cricoid cartilage). The posterior border is the pre-vertebral muscle.

See Figure 5.2.5.1 or <https://www.sciencedirect.com/science/article/pii/S0167814009005659#bib14> for more details.

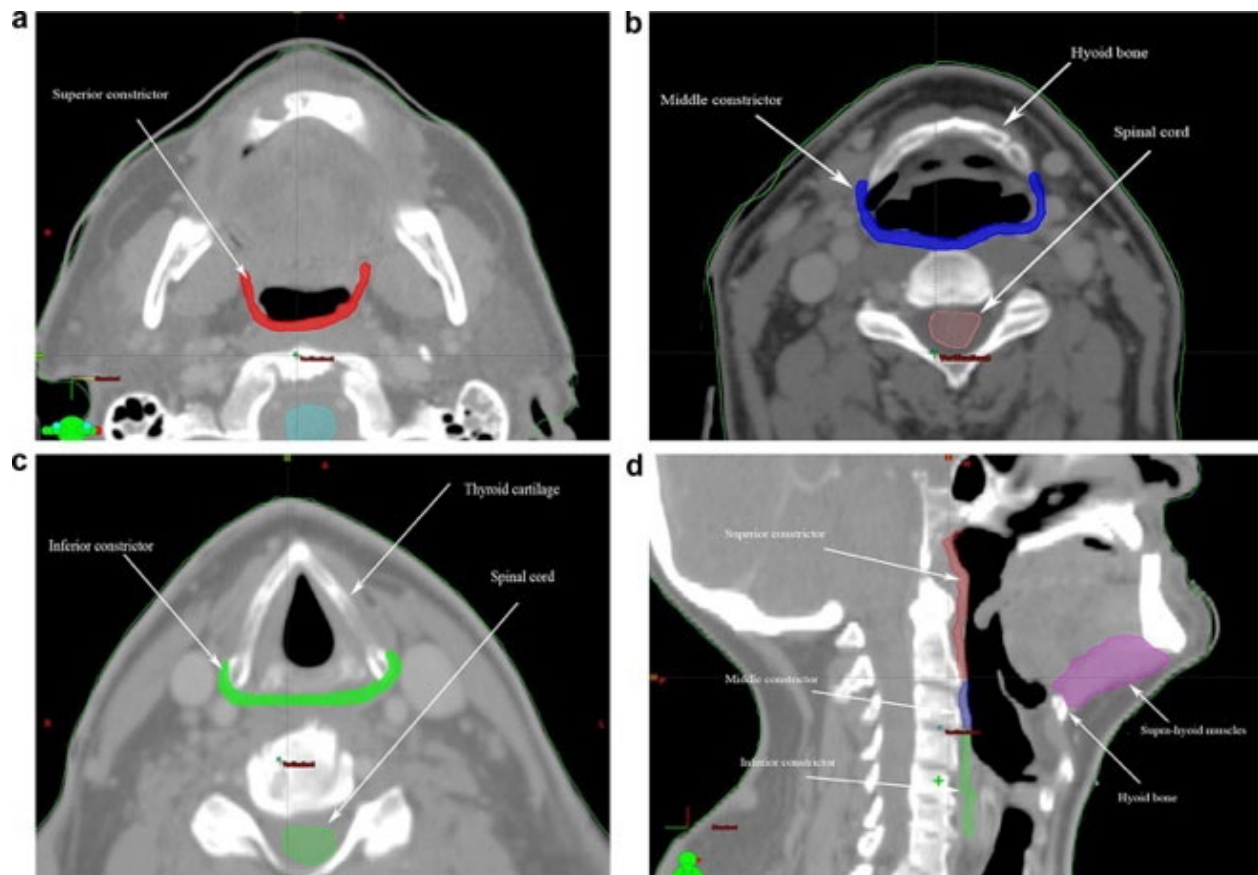


Figure 5.2.5.1. From Bhide et al (2009): Each of the pharyngeal constrictors was outlined as an arch-shaped structure with concavity facing anteriorly, in line with the mucosa (a-c). Posterior border of each of the muscles was the pre-vertebral muscle. Pharyngeal mucosa lining the muscles was included in outlines as it is quite thin and difficult to exclude with great accuracy with currently available CT images. Superior constrictor was outlined from the base of the skull up to the superior end of hyoid. Middle constrictor was outlined from the superior end to the inferior end of the hyoid bone. Inferior constrictor was outlined from the inferior aspect of hyoid to inferior end of cricoid cartilage. A sagittal view of all of the outlined pharynx is shown (d).

Esophagus_S: This will be defined as the cervical or superior (S) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.

Cavity_Oral: The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible (external to PTVs).

Bone_Mandible: This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with PTVs.

Lips: The lip contour extends from the inferior margin of the nose to the superior edge of the mandibular body. The lateral border is at the lateral commissure. The lip contour should include the inner surface of the lips. Lips will be defined in their entirety (upper and lower) based on the treatment planning CT scan.

Gland_Submand_R/L: Submandibular glands will be defined in their entirety based on treatment planning CT scan. The submandibular glands are paired salivary glands composed of a large superficial lobe and a smaller deep process that are continuous with each other around the posterior border of the mylohyoid muscle. The superior border is the mylohyoid muscle and medial pterygoid muscle. Inferiorly, the gland abuts fatty tissue. Anteriorly, the gland is adjacent to the lateral surface of the mylohyoid muscle and posteriorly it abuts the parapharyngeal space and sternocleidomastoid. The lateral border is platysma and the mandibular surface. The medial border is the lateral surface of the mylohyoid muscle and the anterior belly of the digastric. The submandibular gland is often hypodense on CT and can be distinguished from surrounding structures.

BrachialPlexus_R/L: To contour the brachial plexus use a 5-mm diameter paint tool. Start at the neural foramina from C5 to T1; this should extend 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, contour only the space between the anterior and middle scalene muscles. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head. The first and second ribs serve as the medial limit of the OAR contour. See Figure 5.2.5.2 and [https://www.redjournal.org/article/S0360-3016\(08\)00416-1/fulltext](https://www.redjournal.org/article/S0360-3016(08)00416-1/fulltext) for more details.

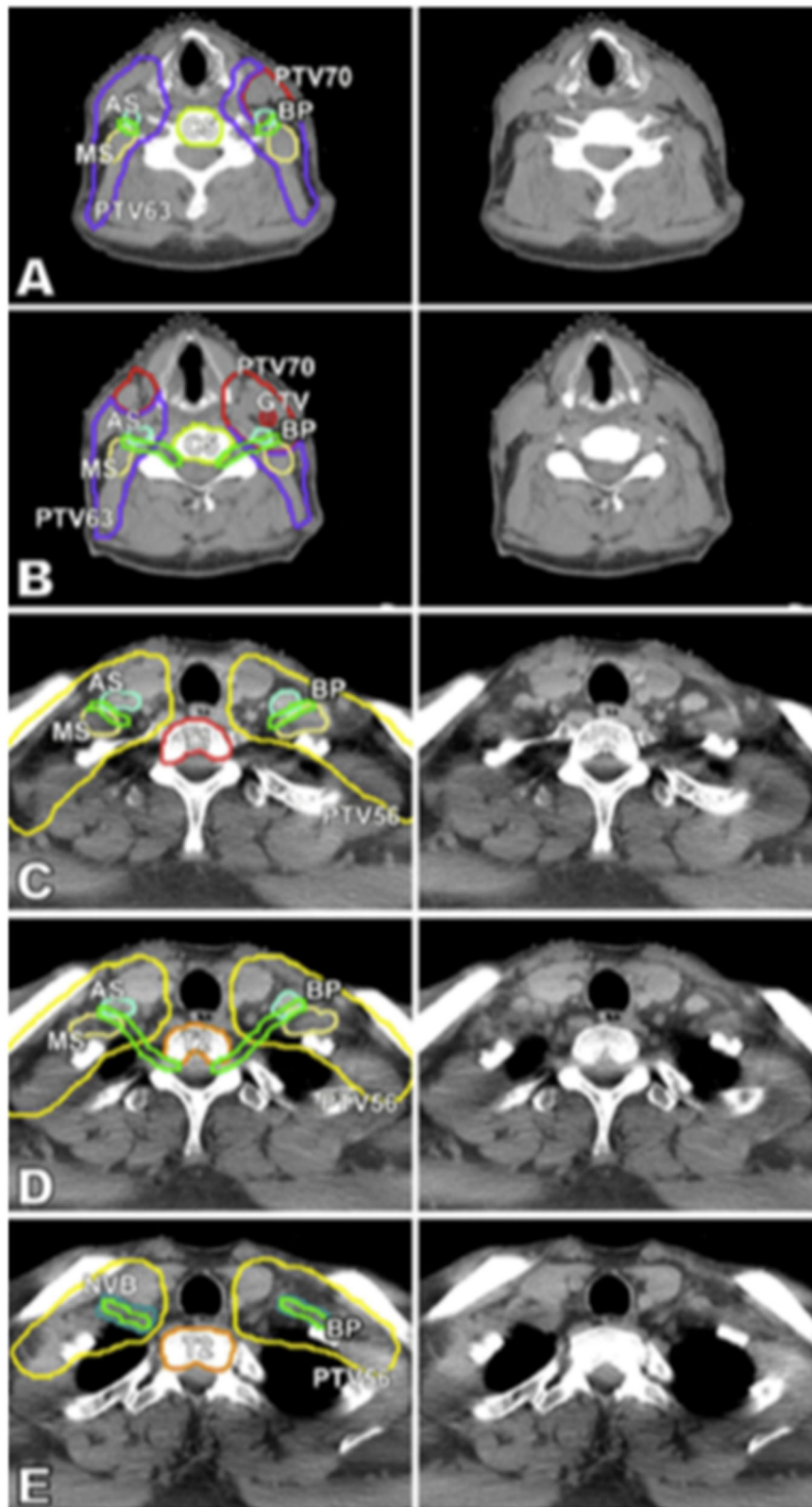


Figure 5.2.5.2 From Hall et al (2008): Major anatomic landmarks (Anterior and Middle Scalene muscles, and the neurovascular bundle) for identifying the brachial plexus on the axial images of a treatment planning computed tomography scan.

Cochlea_R/L: The cochlea should be defined using bone window (window width 3000 to 4500 and window level of 400 to 800). It is well visualized near the most lateral extent of the internal auditory canal. The spiral canals of the cochlea appear as small curved or round lucencies within the temporal bone. The cochlea should be defined in its entirety limited by vestibular apparatus posteriorly and middle ear laterally. See Figure 5.2.5.3 and <https://pdfs.semanticscholar.org/2e9b/73b254b27d7f8724348057291b5a776c7b37.pdf> for more details.

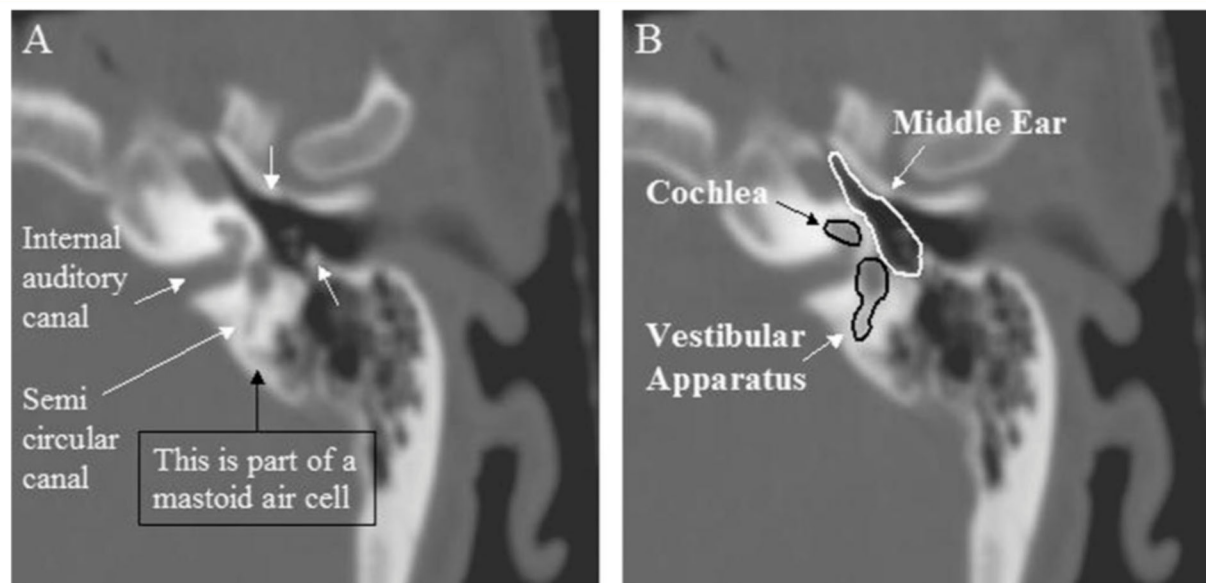


Figure 5.2.5.3 From Pacholke et al (2005): Major anatomic landmarks for identifying the cochlea on the axial images of a treatment planning computed tomography scan. The best way to locate the cochlea is to first identify the internal auditory canal. The image on the left (A) shows the anatomy of the temporal bone at the level of the inner ear without outlines of auditory structures. Important landmarks on this image are the internal auditory canal, the semicircular canals of the vestibular apparatus, and the bony prominences that mark the attachment of the tympanic membrane (un-marked arrows). The spiral canals of the cochlea appear as small curved or round lucencies within the temporal bone (B). Note that portions of a mastoid air cell may look similar to a semicircular canal.

Thyroid: The thyroid gland should be contoured in its entirety based on treatment planning CT scan. The thyroid gland has two connected lobes and is located inferior to the thyroid cartilage. The thyroid gland will have considerable contrast on contrast-enhanced CT compared to the surrounding tissues.

E-PTV: This will be defined as tissue located within external contour of the patient outside of all PTVs.

5.2.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table. For simplicity, proton therapy doses are also specified in cGy but refer to radiobiologically equivalent doses cGy (RBE) with a nominal RBE factor of 1.1.

Photon Therapy Dose Prescription

Doses are prescribed to PTVs. The treatment goal is that 95% of the volume of all PTVs must receive the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 93% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the highest prescription dose.

It is recognized that portions of PTVs close to the skin or critical PRVs (spinal cord and brainstem) may receive significantly less than the prescription doses. This is acceptable in these regions as long as cold spots within these PTVs do not exist within the GTV. In cases of PTVs close to skin, tissue equivalent bolus must be utilized to ensure adequate dose.

It is also recognized that PTVs abutting or enclosing higher dose PTVs will have regions of maximum dose that may exceed their prescribed dose in order to achieve acceptable minimal doses to the higher dose PTVs which are considered a higher priority target.

Proton Therapy Dose Prescription

Robust optimization to the CTVs is recommended for proton therapy, with the setup uncertainties at 3 mm (the same as the setup margins) in all directions. Range uncertainties should be used according to their institutions' protocol, preferably at 3% to 3.5%. Prescription is recommended with V100% $\geq$ 98% to all the CTVs. Robust evaluation criteria are listed in Table 5.2.7C. For proton therapy, several verification CTs may be required during the course of treatment to assess the robustness of the proton plan. Screen capture of DVH and dose statistics for robust evaluation on the planning CT and the verification CTs should be submitted for review.

Cases will be scored using the Compliance Criteria table.

Target Standard Name	Dose [cGy(RBE)]	Fraction Size [cGy(RBE)]	# of fractions	Dose specification technique
PTV_7000 or PTV Eval 7000	7000	200	35	$\geq$ 95% of PTV should receive $\geq$ 7000 cGy
PTV_6000 or PTV Eval 6000	6000	171	35	$\geq$ 95% of PTV should receive $\geq$ 6000 cGy
PTV_5400 or PTV Eval 5400	5400	154	35	$\geq$ 95% of PTV should receive $\geq$ 5400 cGy

5.2.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

VxcGy[cc], VxcGy[%], Vx%[cc], Vx%[%]: Volume [cc or %] receiving Dose [cGy, or %]

Dxcc[cGy], Dxcc[%], Dx%[cGy], Dx%[%]: Dose [cGy or %] to Volume [cc or % of total volume]

Minimum dose is defined to D99%[cGy] or D99%[%]

Maximum dose is defined as D0.03cc[cGy] or D0.03cc[%]

Mean[cGy] or Mean[%]: Mean dose in cGy or %

Normalization of Dose: The plan is normalized such that 95% of the PTV 7000 volume receives prescription dose of 7000 cGy for photon and 98% to the CTV_7000 for the proton.

Dose limitations to normal structures are described in Table 5.2.7A, 5.2.7B and 5.2.7D. For the critical structures listed in Table 5.2.7A and 5.2.7B (SpinalCord, SpinalCord_PRV05, BrainStem_PRV03, OpticNrv_R/L, OpticChiasm, Lobe_Temporal_R/L, Cochlea_R/L), these are mandatory. For other structures recommended limits are provided in Table 5.2.7 D, but the doses delivered should always be as low as reasonably achievable without compromising coverage to PTVs.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria

Planning Target Volume and Critical OAR Constraints and Compliance Criteria

Oropharyngeal cancer example:

Table 5.2.7A: Target Volume and OAR Constraints and Compliance Criteria for photon.

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_7000 or PTV_Eval_7000	D95%[cGy]	7000	> 6860 and <= 7140
	D99%[cGy]	>= 6650	>= 6300

	D0.03cc[cGy]	< = 7700	< = 8050
PTV_6000 or PTV_Eval_6000	D95%[cGy]	> = 6000	> = 5700
PTV_5400 or PTV_Eval_5400	D95%[cGy]	> = 5400	> = 5130
SpinalCord_PRV05	D0.03cc[cGy]	< = 5000	< = 5200
SpinalCord	D0.03cc[cGy]	< = 4500	< = 4800
BrainStem_PRV03	D0.03cc[cGy]	< = 5200	< = 5400
OpticNrv_R/L or OpticChiasm	D0.03cc[cGy]	< = 5400	< = 6000
Lobe_Temporal_R/L	D0.03cc[cGy]	< = 7000	< = 7200

Per Protocol range is excluded from Variation Acceptable range.

*See Table 5.2.7C for target volume and robust evaluation compliance for proton RT.

Proton Therapy Plan Robust Evaluation

For proton plans using robust optimization to the CTVs, robust evaluation should be conducted with the following scenarios: translation setup uncertainty of ± 3 mm in the left-right, anterior-posterior, and superior-inferior directions, and $\pm$ range uncertainties (a total of 8 scenarios, setup and range uncertainties are evaluated separately). Robust evaluation compliance criteria are listed in Table 5.2.7C. For OARs with PRV, the worst case dosimetric parameters for the OARs in the robust evaluation should be used in place of the OARs with PRV in Tables 5.2.7A and 5.2.7B.

Table 5.2.7C: Target Volume and Robust Evaluation Compliance for Proton RT

Name of Structure		Dosimetric parameter	Per Protocol	Variation Acceptable
CTV_7000	Nominal plan	D98%[cGy]	7000	> 6860 and < = 7140
		D99%[cGy]	> = 6650	> = 6300

		D0.03cc[cGy]	< = 7700	< = 8050
	Robust Evaluation plan worst case	D95%[cGy]	> = 7000	> = 6650
CTV_6000	Nominal plan	D98%[cGy]	> = 6000	> = 5700
	Robust Evaluation plan worst case	D95%[cGy]	> = 6000	> = 5700
CTV_5400	Nominal plan	D98%[cGy]	> = 5400	> = 5130
	Robust Evaluation plan worst case	D95%[cGy]	> = 5400	> = 5130

Per Protocol range is excluded from Variation Acceptable range.

Per Protocol range is excluded from Variation Acceptable range. Only the true critical structures, not the PRVs are evaluated. In overlap situations, treatment planning should attempt to balance the tradeoff between minimum dose to the CTV and protection of the critical structure. Dose limitations to normal structures are described below. For the critical structures listed in Table 5.2.7A these are mandatory. For other structures recommended limits are provided, but the doses delivered should always be as low as reasonably achievable without compromising coverage to PTVs.

Table 5.2.7D: Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Structure	Recommended dose acceptance criteria*
BrachialPlexus_R/L	D0.03cc[cGy] < = 6600 if does not overlap with PTV_7000 D0.03cc[Gy] < = 7200 if overlaps with PTV_7000
Parotid_R/L (at least one gland)	Mean[cGy] < = 2600
Larynx_SG (uninvolved)	Mean[cGy] < = 3000
Pharynx (uninvolved)	Mean[cGy] < = 4500
Cavity_Oral (uninvolved)	Mean[cGy] < = 3000
Cochlea_R/L	Mean[cGy] < = 3500

Esophagus_S	Mean [cGy] <= 3000, V5400 [%] <= 15
Lips	Mean[cGy] < = 2000
GlnD_Submand_R/L (contralateral)	Mean[cGy] < = 3900
Eye_R/L	D0.03cc[cGy] < = 5500
Lens_R/L	D0.03cc[cGy] < = 1500
Bone_Mandible, Joint_TM_R/L	D0.03cc[cGy] < = 7350
Thyroid	Mean[cGy] < = 5000
E-PTV	D1cc[cGy] < = 7350

** Please keep OAR doses as low as reasonably achievable without compromising coverage to PTVs.*

Delivery Compliance criteria

Protocol treatment must begin within 14 days after randomization. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should not exceed 3 treatment days at a time and 5 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 4 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Given the importance of timeliness of treatment delivery in this study, it is strongly recommended that patients receive twice-daily treatments with a minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time within the limits defined in Table 5.2.7C.

Table 5.2.7C: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
RT Start date	≤ 14 days after randomization	15-18 days	≥ 19 days

Overall Treatment time	≤ 45 days	46-51 days	≥ 52 days without medically appropriate indication for delay
Interruptions (without medical indication)	≤ 2 days	3-4 days	≥ 5 days

5.2.8 Treatment Planning Priorities and Instructions

- Critical Structure and Target priorities must be listed in order of decreasing importance
Prioritization for IMRT/IMPT planning:

1. SpinalCord and SpinalCord_PRV05
2. BrainStem_PRV03
3. OpticNrv_R/L or OpticChiasm
4. PTV_7000 or PTV_Eval_7000
5. PTV_6000 or PTV_Eval_6000
6. PTV_5400 or PTV_Eval_5400
7. Lobe_Temporal_R/L
8. Eye_R/L
9. BrachialPlexus_R/L
10. Parotid_R/L (contralateral)
11. a. Larynx_SG
b. Pharynx
12. a. Cavity_Oral
b. Lips
13. Esophagus_S
14. Cochlea_R/L
15. GlnD_Submand_R/L (contralateral)
16. Parotid_R/L (ipsilateral)
17. Bone_Mandible, Joint_TM_R/L
18. Thyroid
19. Lens_R/L
20. E-PTV

- Required algorithms

(Convolution/Superposition, Monte Carlo, etc for photon)

Monte Carlo dose engine is required for proton due to its wide availability and better accuracy for superficial targets treated with range shifter.

Acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by IROC

Houston.

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial.

For proton planning, the institution must have passed IROC baseline approval for treating with SOBP and/or PBS, though additional protocol-specific credentialing may be required. Proton dose will be reported in cGy (relative biologic effectiveness, RBE), where $1 \text{ cGy (RBE)} = \text{proton dose cGy} \times \text{RBE}$, $\text{RBE} = 1.1$.

- Primary dataset for dose calculation

In the case in which contrast is present during the treatment planning CT, whether the density of the contrast should be overridden to a representative background electron density should be tested to demonstrate such density overridden is negligible to dose calculation. Only non-contrast CT should be used for proton planning. In addition, image artifacts such as streaks near metal, dental implants, fillings, clips or other high-density objects should be overridden with appropriate HUs. In some instances plastic surgical shuts may appear radio-opaque and require appropriate HU override. Beams passing through unknown materials (like dental filling) should be avoided with margin.

-Dose matrix resolution

Dose grid size should be $\leq 3 \text{ mm}$ in all directions.

Adaptive Planning (Re-planning)

In cases of weight loss $> 10\%$ or substantial shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or re-made in order to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan and not adjusted in cases of disease regression, except to respect clear anatomic barriers such as skin or fascial or muscle planes initially uninvolved by disease. Re-planning DICOM data and final plan sum dose statistics should be submitted at the end of treatment.

For proton therapy, at least weekly CBCT or bi-weekly quality assurance CT is recommended. Replan evaluation based on corrected CBCT images or virtual CT (created based on the CBCT images) is allowed as long as the technique has been fully validated by its institution. Replan criteria for proton plans will be at the discretion of the physics team and treating physician. Replan should be based on the quality assurance CT and all plan criteria should be met the same as the initial plan.

-List treatment planning recommendations and give link to FAQs

5.2.9 Patient specific QA

- Describe technique and give Gamma pass rate recommendation

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For IMRT/VMAT/proton plans, patient specific QA is highly recommended. Any patient-specific QA performed should follow your institutional guidelines. The recommended patient specific QA criteria is for 90% of the comparison points to pass a $\pm 3\%/2\text{mm}$ Gamma Index analysis.

For passive scattered or uniform scanned beam plans that utilize a patch field, patient specific QA must be performed with the compensator.

For IMPT plan QA, measurement in multiple layers is required.

5.2.10 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

The following information should be reviewed for Localization guidance

Will simple isocenter localization technique be used at beginning of treatment and weekly thereafter?

Will more advanced IGRT techniques be used?

Is IGRT tied to margin reduction?

Is daily IGRT required?

Allowed image guidance methods: 2D x-ray, CBCT, electromagnetic localization, optical surface imaging, other

Image registration techniques: fiducial markers, bone as surrogate, soft tissue, other

State the frequency for localization checks

Give recommendations for correcting (e.g. correcting for linear shifts less than 1 mm is not recommended)

Recording of shift information must be provided for the IGRT credentialing process

Other

Here is an example:

Image Guidance for IGRT When Using Reduced Margins:

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (kV) images (e.g. ExacTrac)
- Linear-accelerator mounted kV and MV conebeam CT images
- Linear-accelerator mounted MV helical CT images (e.g. Tomotherapy)
- In room CT or CBCT
- MRI scouts or MRI 2D/3D images
- Other Mechanism, after discussion with the Radiation Oncology Co-chair

The institution's procedure to register treatment day imaging dataset with the reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord;
- If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).
- Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm, the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeated IGRT should be avoided.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding re-imaging to make shifts in patient positioning that are already less than the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

Here is an example:

According to the literature, the estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT were reported to be in range from 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 200 cGy. These are small enough dose contributions that if there is only one imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections of more than 10 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.2.11 Case Review

The Principal Investigators, XXX, MD will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at IROC Philadelphia-RT.

For proton therapy, several verification CTs may be required during the course of treatment to assess the robustness of the proton plan. Screen capture of DVH and dose statistics should be submitted for review.