Initial Proposed Dosimetry Metrics Including “Best” Supporting Literature References:

1. **CNS brain constraint >100cc diff in 10Gy**
2. **Hippocampus Highest Mean <10 Gy**
3. **Posterior fossa <10Gy mean**
4. **Pituitary <30 Gy**
5. **Cochlea Highest Mean dose <25 Gy**
6. **Oral cavity Mean dose reduction 50%**
7. **Parotid Highest mean <20 Gy**
8. **Esophagus Mean dose 20% reduction**
9. **Lung v5<55% (requiring a v20<20%)**
10. **Mean Heart Dose<10Gy**
11. **LAD v15 <10%**
12. **Liver 30% reduction mean dose**
13. **Bowel(within 5 cm of GTV) 30% reduction mean dose**
14. **Bone Marrow v20 50% reduction**
15. **Immune System 1 nomogram risk group reduction**

Notations:
* Means bilateral structure. The intent is that each side of the bilateral structure must meet the constraint.
Supporting Data Strength. 1 is the weakest level of data in the literature and 5 represents the strongest level of data. The CNS brain constraint is the reference for weakest and Mean Heart Dose is the reference for strongest supporting data.

Implementation Rules: In order to meet trial criteria for randomization, the proton plan must “outperform” the IMRT plan by achieving at least one metric from above that the IMRT plan cannot meet. Likewise, the IMRT plan achieving a single metric that the proton plan cannot achieve will disqualify that patient from proceeding to randomization.

CNS brain constraint >100cc difference in volume treated to 10Gy; (brain minus PTV)
Example: IMRT plan delivers 10 Gy to 250cc of normal brain and Proton plan delivers 10Gy to 149cc.
Supporting Data Strength (1 weakest: 5 strongest): 1

Comment: Very little data supporting normal brain as a constraint. The two strongest references are the hippocampal sparing data vs WBRT and the pediatric medulloblastoma data both of which really lack a CNS metric. One would think there are important metrics in the brain, but they are poorly defined currently. The one chosen is best described as an informed guesstimate.

References:

- Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma DOI: 10.1200/JCO.19.01706
- Dosimetric Comparison of Intensity-Modulated Radiotherapy versus Three-Dimensional Conformal Radiotherapy for Patients with Brain Tumors DOI: 10.4236/ojrad.2014.41011
- Efficacy of Stereotactic Conformal Radiotherapy vs Conventional Radiotherapy on Benign and Low-Grade Brain Tumors A Randomized Clinical Trial doi:10.1001/jamaoncol.2017.0997
- A comparative study of dose distribution of PBT, 3D-CRT and IMRT for pediatric brain tumors https://doi.org/10.1186/s13014-017-0775-2
- A dosimetric comparison between three-dimensional conformal radiation therapy and intensity-modulated radiation therapy in the treatment of posterior fossa boost in medulloblastoma. doi: 10.4103/0973-1482.220416.

Hippocampus* Mean dose <10 Gy
Example: Contralateral Hippocampus- both plans meet. Ipsilateral IMRT plan delivers a mean dose of 11 Gy and the Proton plan delivers an ipsilateral mean dose of 7 Gy.
Supporting Data Strength (1 weakest: 5 strongest): 4

Comment: There is clearly emerging data that protection of the hippocampus delivers improved outcomes. The NRG CC001 is clear randomized prospective data making it arguably the strongest single avoidance data. It is downgraded here as that approach is markedly different than an IMRT vs. Proton for definitive treatment in a partial brain setting.

References:

- Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. https://doi.org/10.1200/JCO.19.02767
- Whole Brain Radiotherapy With Hippocampal Avoidance and Simultaneously Integrated Brain Metastases Boost: A Planning Study DOI: https://doi.org/10.1016/j.ijrobp.2007.05.038
- Hippocampal-Sparing Whole-Brain Radiotherapy: A “How-To” Technique Using Helical Tomotherapy and Linear Accelerator–Based Intensity-Modulated Radiotherapy DOI: https://doi.org/10.1016/j.ijrobp.2010.01.039

Posterior fossa <10Gy mean
Example: IMRT plan dose of 11 Gy and Proton plan delivers mean dose of 2 Gy.
Supporting Data Strength (1 weakest: 5 strongest): 3

Comment: Literature review often coming from the development phase of IMRT in head and neck cancer points to increased nausea with the move from 3D to IMRT. This is thought to be related to increased dose to the posterior fossa with IMRT plans and is a consistent finding in the early 2000’s literature from major institutions. Proton therapy seems to reduce that nausea and delivers less dose to the brainstem and posterior fossa but exact data for this metric is far from defined.

References:

- Proton Radiation Therapy for Head and Neck Cancer: A Review of the Clinical Experience to Date DOI: https://doi.org/10.1016/j.ijrobp.2014.02.029
- Proton radiation for treatment of cancer of the oropharynx: Early experience at Loma Linda University Medical Center using a concomitant boost technique DOI: https://doi.org/10.1016/j.ijrobp.2004.09.064
- Dosimetric Comparison of IMRT and Proton Therapy for Head and Neck Tumors doi:10.1016/j.ijrobp.2006.07.772

Pituitary mean dose <30 Gy
Example: IMRT plan dose of 32 Gy and Proton plan delivers mean dose of 26 Gy.
Supporting Data Strength (1 weakest: 5 strongest): 3

Comment: Good data supporting loss of function with higher doses. Most stems from younger populations and not the trial target population. Data supports dose ranges from 30 Gy to 50 Gy. We purposefully choose at the lower end of this spectrum at planning has likely improved from these papers. Very questionable that it will relate to measurable Gr2/Gr3 toxicity.

References:

- Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose–effect relationship using dose–volume histogram analysis DOI: https://doi.org/10.1016/S0360-3016(00)01387-0
- Endocrine Outcomes for Children With Embryonal Brain Tumors After Risk-Adapted Craniospinal and Conformal Primary-Site Irradiation and High-Dose Chemotherapy With Stem-Cell Rescue on the SJMB-96 Trial DOI: 10.1200/JCO.2008.13.5293
- Fertility of Female Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study DOI: 10.1200/JCO.2008.20.1541

Cochlea* Highest Mean dose <25 Gy
Example: Contralateral Cochlea - both plans meet. Ipsilateral IMRT plan delivers a mean dose of 11 Gy and the Proton plan delivers an ipsilateral mean dose of 7 Gy.
Supporting Data Strength (1 weakest: 5 strongest): 2

Comment: Stronger dosimetry metrics than many sites, but rather wide dose levels. Combined with the lack of certainty that toxicity will be a measurable effect at 3 years of follow-up, it is a low rated metric despite better than average dosimetry publication data.

References:

- Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice. DOI: https://doi.org/10.1016/j.radonc.2015.01.016
- Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy DOI https://doi.org/10.1186/s13014-015-0501-x
- Cochlea sparing effects of intensity modulated radiation therapy in head and neck

cancers patients: a long-term follow-up study https://doi.org/10.1186/s40463-014-0030-x

Oral cavity: 25% reductions in mean dose.
Example: IMRT plan delivers mean dose of 25 Gy and Proton plan delivers mean dose of 18.75 Gy or less.
Supporting Data Strength (1 weakest: 5 strongest): 2

Comment: Surprising, there is little data on such a well defined target that causes treatment related toxicity. The structure is poorly defined and metrics are poorly defined, likely due to the increase in anterior oral cavity dose as the field moved from 3D (less dose anteriorly) to IMRT (more dose anteriorly).

References:
- Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy DOI https://doi.org/10.1186/s13014-016-0600-3
- Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer DOI 10.14338/IJPT-18-00032.1

Parotid* Highest mean or cumulative mean <15 Gy
Example: Contralateral Parotid - both plans meet. Ipsilateral IMRT plan delivers a mean dose of 18 Gy and the Proton plan delivers an ipsilateral mean dose of 14 Gy. Or IMRT delivers combined parotid mean dose of 21Gy and the proton plan delivers dose of 14Gy.
Supporting Data Strength (1 weakest: 5 strongest): 4

Comment: Rated at strong due to the fact that this single metric was utilized to defend IMRT treatment. Somewhat surprisingly, there is early data and then nearly a decade gap to some of the newer attempts to better define metics for current planning.

References:
- Prospective Randomized Study of Intensity-Modulated Radiotherapy on Salivary Gland Function in Early-Stage Nasopharyngeal Carcinoma Patients DOI: 10.1200/JCO.2007.11.5501
- Target Volume Definition for Head and Neck Intensity Modulated Radiotherapy: Pre-clinical Evaluation of PARSPORT Trial Guidelines DOI: https://doi.org/10.1016/j.clon.2007.07.001
- Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial DOI:https://doi.org/10.1016/S1470-2045(10)70290-4
- Dose/Volume histogram patterns in Salivary Gland subvolumes influence xerostomia injury and recovery DOI https://doi.org/10.1038/s41598-019-40228-y
- A Model-Based Method for Assessment of Salivary Gland and Planning Target Volume Dosimetry in Volumetric-Modulated Arc Therapy Planning on Head-and-Neck Cancer doi: 10.4103/jmp.JMP_19_19

- A Nomogram to predict parotid gland overdose in head and neck IMRT DOI https://doi.org/10.1186/s13014-016-0650-6

Esophagus Mean dose 20% reduction
Example: IMRT plan delivers mean dose of 20 Gy and Proton plan delivers mean dose of 16 Gy or less.
Supporting Data Strength (1 weakest: 5 strongest): 3

Comment: Data for esophagus dose correlating with outcome measures varies widely. Some suggest OS survival while others really show limited impact. Clearly it relates to significant toxicity for some patients but the dosimetry metric is poorly defined.

References:
- Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non–Small Cell Lung Cancer DOI: https://doi.org/10.1016/j.jtho.2016.10.018
- Treatment-related Acute Esophagitis For Patients With Locoregionally Advanced Non–Small Cell Lung Cancer Treated With Involved-field Radiotherapy and Concurrent Chemotherapy DOI: 10.1097/COC.0b013e31827de7a2
- Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non–Small-Cell Lung Cancer DOI: 10.1200/JCO.19.01162

Lung v5<55% (requiring a v20<20%)
Example: IMRT plan delivers lung dosimetry of v20 of 18% and v5 of 75%. Proton plan delivers v20 of 19.5% and v5 of 52%.
Supporting Data Strength (1 weakest: 5 strongest): 3

Comment: In light of the Bayesian Adaptive study, the most interesting paper is the first which combines moderate and low dose metrics into a predictive model. What once was an early strong and consistent dosimetry metric that potentially could be a strong opportunity for proton therapy to reduce toxicity, it appears much less likely that reduction in lung volumes will be a primary driver of use but lung dose likely helps drive more broad reaching toxicity metrics.

References:
- Combined Analysis of V20, VS5, Pulmonary Fibrosis Score on Baseline Computed Tomography, and Patient Age Improves Prediction of Severe Radiation Pneumonitis After Concurrent Chemoradiotherapy for Locally Advanced Non–Small-Cell Lung Cancer DOI: https://doi.org/10.1097/JTO.0000000000000187
- Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer DOI: 10.1200/JCO.2017.74.0720
- Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial DOI: 10.1200/JCO.2016.69.1378

Mean Heart Dose<10Gy
Example: IMRT plan delivers mean heart dose of 12Gy and the proton plan delivers a dose of 7Gy.
Supporting Data Strength (1 weakest: 5 strongest): 5

Comment: Arguably the current gold standard for a dosimetry relating directly to outcome. Subtructure dosimetry data continues to build but even then, mean heart dose often continues to hold up as a outcome predictor. A metric supporting the new field of Cardio-Oncologists.

References:

- Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer https://doi.org/10.1016/j.jacc.2019.03.500
- Long-term results from the IDEAL-CRT phase 1/2 trial of isotoxically dose-escalated radiation therapy and concurrent chemotherapy for stage II/III non-small cell lung cancer. doi: 10.1016/j.ijrobp.2019.11.397
- Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. doi: 10.1016/S1470-2045(14)71207-0
- Risk of heart disease after radiotherapy DOI: https://doi.org/10.1016/S1470-2045(13)70115-3

LAD v15 <10%
Example: IMRT plan delivers LAD v15 of 35% and the proton plan delivers a v15 dose of 8%.
Supporting Data Strength (1 weakest: 5 strongest): 4

Comment: While today, the standard appears to be mean heart dose, it will likely be replaced by substructure dosimetry metrics in the near future. As conformality improves and planning awareness improves, there is less correlation between substructures and mean heart dose as noted in the last reference. The chosen metrics is tighter than the first reference and comes from an ASTRO presentation from 2019.

References:

- Left Coronary Artery Dose Exposure Predicts Major Adverse Cardiac Events in Coronary Heart Disease Negative Lung Cancer Patients DOI: https://doi.org/10.1016/j.ijrobp.2019.06.470
- Comparing Whole Heart Versus Coronary Artery Dosimetry in Predicting the Risk of Cardiac Toxicity Following Breast Radiation Therapy DOI: https://doi.org/10.1016/j.ijrobp.2018.06.091
- The Meaningless Meaning of Mean Heart Dose in Mediastinal Lymphoma in the Modern Radiation Therapy Era DOI: https://doi.org/10.1016/j.prro.2019.09.015
- The Relationship of Mean Heart Dose and Cardiac Substructure Dose over Evolving Radiation Techniques in Mediastinal Lymphoma
- Heart toxicity from breast cancer radiotherapy : Current findings, assessment, and prevention. doi: 10.1007/s00066-018-1378-z

Liver 30% reduction mean dose
Example: Whole liver IMRT plan delivers mean dose of 15Gy and Proton plan delivers mean dose of 10.5Gy or less.
Supporting Data Strength (1 weakest: 5 strongest): 3

Comment: Data supports liver dose relating to toxicity and strength of data increased by one based on likelihood of difference having a measurable clinical impact. Dosimetry metrics are weakly defined and often relate to function imaging to help in defining risk.

References:

- Functional Liver Imaging and Dosimetry to Predict Hepatotoxicity Risk in Cirrhotic Patients With Primary Liver Cancer. doi: 10.1016/j.ijrobp.2018.08.029
- A phase I trial of Proton stereotactic body radiation therapy for liver metastases doi: 10.21037/jgo.2018.08.17
- Dosimetric and Radiobiological Comparison of External Beam Radiotherapy Using Simultaneous Integrated Boost Technique for Esophageal Cancer in Different Location. doi: 10.3389/fonc.2019.00674

Small Bowel V20: 30% reduction (defined as small bowel within a 5cm distance of the PTV)
Example: Small Bowel volume at 20 Gy is 90cc with IMRT and 45 cc with proton therapy.
Supporting Data Strength (1 weakest: 5 strongest):3
Comment: Numerous articles comment and describe small bowel dose as a critical structure and further have shown that in dose ranges less the prescription dose, proton therapy can reduce the dose to the small bowel. The metric is less clearly defined and the relationship to outcome is poorly correlated in the current literature despite a good number of informative publications in part due to data from both upper and lower abdomen sites.

References:

- Current and emerging radiotherapy strategies for pancreatic adenocarcinoma: stereotactic, intensity modulated and particle radiotherapy doi: 10.21037/apc.2018.07.03
- Dose escalation with an IMRT technique in 15 to 28 fractions is better tolerated than standard doses of 3DCRT for LAPC DOI: https://doi.org/10.1016/j.adro.2017.02.004
- A Phase 1/2 and Biomarker Study of Preoperative Short Course Chemoradiation With Proton Beam Therapy and Capecitabine Followed By Early Surgery for Resectable Pancreatic Ductal Adenocarcinoma DOI: https://doi.org/10.1016/j.ijrobp.2014.03.034
- Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer doi: 10.3978/j.issn.2078-6891.2013.041
- Dosimetric Comparison of IntensityModulated Proton Therapy and Volumetric-Modulated Arc Therapy in Anal Cancer Patients and the Ability to Spare Bone Marrow DOI 10.14338/IJPT-17-00017

Bone Marrow v20: 40% cc reduction

Example: Bone marrow volume at 20 Gy is 800cc with IMRT and 300 cc with proton therapy.
Supporting Data Strength (1 weakest: 5 strongest): 4
Comment: The two included articles have great dosimetric comparisons between IMRT and proton therapy for patients with pelvic disease. The strength is 4 based on a lack of outcome data more clearly proving this results in less toxicity.

References:

- Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer doi: 10.3978/j.issn.2078-6891.2013.041
- Dosimetric Comparison of IntensityModulated Proton Therapy and Volumetric-Modulated Arc Therapy in Anal Cancer Patients and the Ability to Spare Bone Marrow DOI 10.14338/IJPT-17-00017

Immune System: 1 nomogram risk group reduction
Example: Immune system: Nomogram predicts High risk with IMRT and High-intermediate with proton therapy.
Supporting Data Strength (1 weakest: 5 strongest): 4
Comment: This metric is based upon the EDIC and ERDIC work evaluating radiation's role in lymphopenia. Data supports lymphopenia risk and radiation dose to the immune system with progression free and overall survival and has been validated. In the chest / thorax, this would be a strength of 5 but due to lack of clear data beyond the chest, it is rated as a 4.

References:

- Prediction of Severe Lymphopenia During Chemoradiation Therapy for Esophageal Cancer: Development and Validation of a Pretreatment Nomogram. DOI: https://doi.org/10.1016/j.prro.2019.07.010
- Impact of Radiation Dose to the Host Immune System on Tumor Control and Survival for Stage III Non-Small Cell Lung Cancer Treated with Definitive Radiation Therapy. https://doi.org/10.1016/j.ijrobp.2019.05.064
- Higher Radiation Dose to Immune System is Correlated With Poorer Survival in Patients With Stage III Non–small Cell Lung Cancer: A Secondary Study of a Phase 3 Cooperative Group Trial (NRG Oncology RTOG 0617) DOI: https://doi.org/10.1016/j.ijrobp.2017.06.351
- The Etiology of Treatment-related Lymphopenia in Patients with Malignant Gliomas: Modeling Radiation Dose to Circulating Lymphocytes Explains Clinical Observations and Suggests Methods of Modifying the Impact of Radiation on Immune Cells. doi: 10.3109/07357907.2012.762780

APPENDIX: Lymphopenia Nomogram