Investigation of Variability and Standardization in Normal Tissue Dose Limits Across Multi-Institutional Clinical Trials

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INTRODUCTION

Standardization of normal tissue limits in radiotherapy clinical trials is not frequent. The large variation in trial design and dose reporting leads to challenges in result pooling, meta-analysis, and normal tissue constraint recommendations for standard practice.

AIM

To quantify variability in normal tissue dose limits in multi-institutional cooperative group clinical trials across major tumor sites.

METHOD

Normal tissue dose limits were reviewed for 32 trials:

- six breast
- eight brain
- eight prostate
- five lung
- five head and neck.

Protocols reviewed included published, multi-institutional, phase I/II/III protocols from: NRG, Canadian Cancer Trials Group (CCTG), Trans-Tasman Radiation Oncology Group (TROG), Radiation Therapy Oncology Group (RTOG), and ClinicalTrials.gov.

Trials currently accruing (n=18) or closed within last 48 months (n=14) were included.

RESULTS

Breast (For standard fractionation 50Gy in 25)

Normal tissue limits: six unique dose limiting metrics for heart (left) including mean dose of 2 to 5 Gy, limiting heart-in-field to 1.5 cm, and V10%<25Gy. Even Lung V20Gy, ranged from 20-30%.
Target coverage: Three trials use 95% of volume to receive 95% of dose, one only the ICRU point, and one 98% of volume for 95% dose. Hotspot constraints (tied closely to outcome) vary in definition and are not always listed.

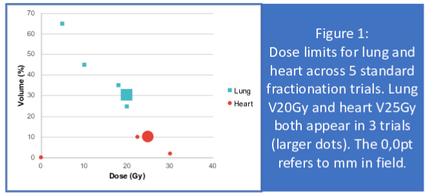
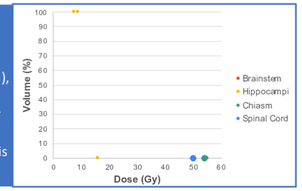


Figure 1: Dose limits for lung and heart across 5 standard fractionation trials. Lung V20Gy and heart V25Gy both appear in 3 trials (larger dots). The 0,0pt refers to mm in field.

Brain

Normal tissue limits: For non-SRS trials, optic nerves, chiasm, and lens are all standardly defined by a small volume (0.03cc) maximum dose. Normal brain, brainstem, hippocampi, cochlea, and retina, are not consistently included, but are similarly dose limited when they are.
Target coverage: A 95% volume to receive 100% of the prescription dose and maximum dose (0.03cc). Trials range in defining volume constraints on 10%, 2%, and 0.1cc on PTV volumes.

Figure 2: Chiasm, cord, brainstem (equivalent chiasm), constraints are consistent (larger dot for multiple use). Hippocampi is not.



Prostate (Standard fractionation and SBRT)

Normal tissue limits: For prostate trials with the same fractionation schema of 70 Gy in 28 fractions, the rectal constraints varied significantly (Figure 3). The two trials also defined the constraints differently: one with volume limits and the other dose limits.
Target coverage: Four protocols addressing prostate SBRT (five fractions) demonstrated significant variation in target dose-volume goals, and only one of the SBRT protocols included both upper and lower bounds on PTV coverage. This could lead to significant variations in actual delivered dose on plans within the same trial.

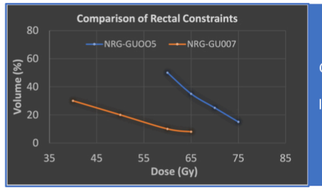
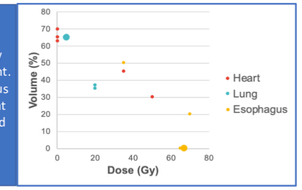


Figure 3: Comparison of rectal dose limits between two prostate trials

Lung

Normal tissue limits: Four of 5 trials have a normal lung constraint of V5Gy less or equal to 65-66%, however, heart, esophagus across trials include either mean dose, point maximum dose, and specific dose-volume limits. Spinal cord and brachial plexus are defined by point max dose.
Target coverage: Four protocols define PTV coverage with D99%, and one D95%; all include a maximum dose but varying whether to a point or to a small volume (0.03cc).

Figure 4: Normal lung dose limits include V5Gy and V20Gy constraint. Heart and esophagus are defined by point doses, non-standard dose volume, and mean dose (not shown).



Head & Neck

Normal tissue limits: The normal tissue dose limits across all trials (figure 5) were consistently defined for optic nerve, chiasm, brachial plexus, and parotids. Large variation was demonstrated in the number of unique structures limiting dose to substructures of surrounding tissues.
Target coverage: PTV coverage was standardly defined by 95% of the volume to receive 100% of prescription dose.

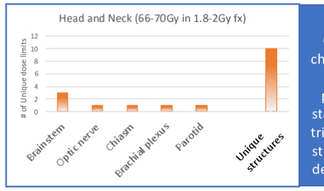


Figure 5: Optic nerve, chiasm, brachial plexus, and parotid were standard across trials. 10 unique structures were defined (1-trial)

CONCLUSIONS

This work is a step towards encouraging standardization of normal tissue limits in radiotherapy clinical trials.

Normal tissue limits in clinical trials both within and between tumor sites vary largely and few commonalities exist, even when the radiotherapy regimen is not the focus of the trial.

The variation in trial design and dose reporting leads to challenges in result pooling, meta-analysis, and normal tissue constraint recommendations for standard practice.

Large-scale normal tissue toxicity reporting, such as QUANTEC, is limited by these inconsistencies in radiation oncology.

CLINICAL TRIALS

NRG: https://www.nrgoncology.org
CCTG: https://www.ctg.queensu.ca
TROG: https://www.trog.com.au
RTOG: https://www.rtog.org (now NRG)
NIH: https://clinicaltrials.gov

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