A Medical Physics–Driven Clinical Trial of Temporally Modulated Pulsed Radiotherapy (NRG-CC017)

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ABSTRACT

Purpose: To design and validate reliable treatment planning and delivery verification methods for TMPRT in the phase III NRG CC-017 trial, which compares TMPRT to standard radiotherapy in adults with newly diagnosed MGMT-unmethylated glioblastomas, with these methods being generally applicable to all grade 4 gliomas.

Methods: Treatment planning methodologies were developed utilizing both volumetric modulated arc therapy (VMAT) and three-dimensional conformal radiotherapy (3D-CRT), ensuring adherence to the specifications of the NRG CC-017 protocol. Each plan, including individual fields (pulses), underwent evaluation for homogeneity and conformality, measured by the homogeneity index (HI) and Paddick conformality index (CIPaddick); and compliance with organ-at-risk dose constraints. Deliverability of these treatment plans was assessed through a combination of in-phantom ionization chamber measurements and electronic portal imaging device (EPID) verification, specifically at low dose rates (≤100 MU/min). To support protocol compliance, verification methods for temporal modulation were designed to batch-process treatment delivery records exported from both the Aria and the Mosaiq R&V systems. For each delivered treatment, both immediate effective dose rate and fraction-effective dose rate were calculated to confirm that the fraction-effective dose rate did not exceed 0.067 Gy/min.

Results: Single-arc VMAT plans achieved better dose homogeneity (HI ≤ 0.13) and conformality (CI ≥ 0.84), with sufficient coverage and organ sparing. Multi-arc plans were found to have unacceptably high intra-field heterogeneity. When VMAT was not feasible, 3D-CRT with dynamic or static fields was a suitable fallback. Ionization chamber measurements showed dose accuracy within 1.4%, and EPID gamma analysis (1%/1mm) had pass rates of 91–97%, confirming reliable treatment.

Conclusion: Uniform planning methods are vital to the NRG CC-017 trial's success. Automated post-treatment record analysis supports protocol compliance and improves clinical reproducibility.

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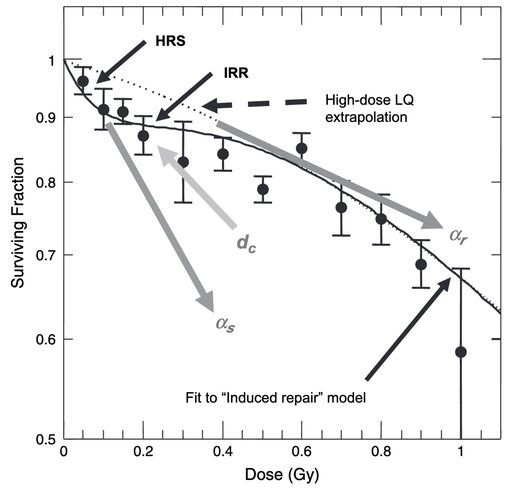
What is SnailRT?

Radiation Hyper-Radiosensitivity (HRS)

- At ≤0.3 Gy/fraction, cells show excess killing vs. LQ-model prediction (HRS); 0.3–1 Gy shows relative radioresistance (IRR) before standard LQ response above 1 Gy
- Mechanism: failure to activate the ATM-dependent early G2 checkpoint at very low doses; above threshold, checkpoint arrest allows NHEJ/HR repair → IRR



Temporally Modulated Pulsed RT (TMPRT)

- Approximates continuous low-dose-rate RT on a standard linac by splitting each fraction into small pulses, without changing instantaneous machine dose rate.
- Delivery: 200 cGy fraction → 10 pulses × 20 cGy, 3-min intervals (start-to-start);
  → effective dose rate = 6.67 cGy/min
- Rationale: exploits inverse dose-rate/HRS biology → greater tumor kill, less normal-tissue injury
- Clinically tested in GBM (*Almahariq 2021*, phase II + TMZ): improved survival signal

NRG-CC017 Trial

- MGMT-unmethylated GBM is less responsive to temozolomide (TMZ)
- No outcome improvements in recent trials
- 80% of patients report cognitive decline

Hypothesis:

- TMPRT may improve survival and reduce neurocognitive decline

Arm 1: Standard RT + TMZ

Concurrent: RT 12-15 min/day, 5 d/wk, for 3 or 6 weeks + TMZ days 1-21 or 1-42
Adjuvant:
TMZ days 1-5 every 28 days x 6 cycles

Arm 2: TMPRT + TMZ

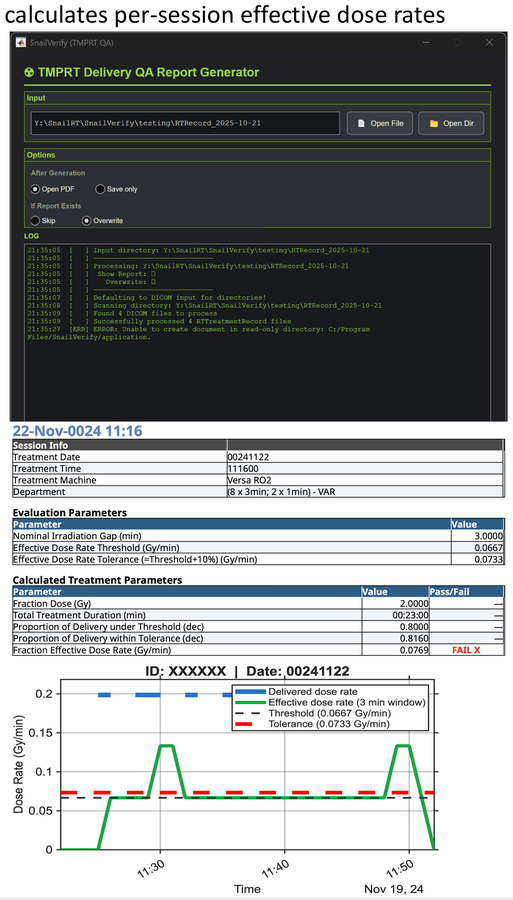
Concurrent: TMPRT 30-40 min/day, 10-13 pulses with 3-min breaks, 5 d/wk, for 3 or 6 weeks + TMZ
Adjuvant:
same TMZ schedule x 6 cycles

Endpoint(s):

- **Neurocognitive failure (primary)**
- TTF, NCF development
- Quality of Life
- Patient-reported cognitive outcomes
- Frailty
- Overall & Progression Free Survival
- Toxicities

Verifying Trial Compliance

- IROC Credentialing using the H&N phantom:
  - IMRT/VMAT Credential
  - TMPRT 3D or TMPRT IMRT/VMAT Credential
- Completion of TMPRT *Delivery Time Sheet* for every fraction + local physicist's review
- Weekly R&V system review
- Departmental standard patient-specific QA (portal dosimetry, phantom measurements)
- Automated QA reporting with *SnailVerify:*
- Ingests treatment history (MOSAIQ CSV / ARIA RTTreatmentRecords) and automatically calculates per-session effective dose rates



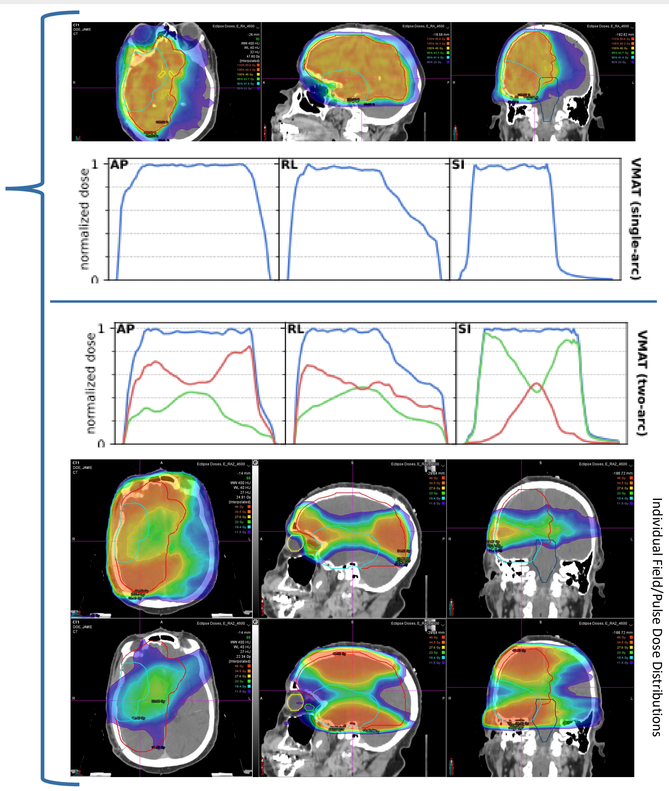
Treatment Planning for SnailRT

- Techniques: VMAT, 3D-DCA, static 3D-CRT
- Delivery of one field/arc corresponds to exactly one dose pulse.

- VMAT is the preferred technique
- Only *single-arc* VMAT plans are acceptable (force identical beam parameters & MLC pattern)

Recipe

- Optimize one full arc at per-pulse dose (20 cGy/fx over many "virtual" fractions), copy/duplicate that single arc 10×
- RayStation workaround allows to use 10× duplicate arcs in optimization with full fraction dose, resulting in identical MLC patterns
- use extended optimization convergence settings (e.g., Eclipse "Extended"/MR3) and fine control-point spacing (≤2°) to compensate for the reduced degrees of freedom of a single arc.
- Collimator angle should be chosen so MLC leaves travel superior-inferior (~90° IEC) for improved modulation in typical GBM geometries with inferior OAR overlap.



CONCLUSIONS

NRG-CC017 and TMPRT more broadly show the important role of Medical Physicists in developing and supporting clinical trials.
Their expertise in radiation physics, radiobiology, mathematical modeling, and development of quality control software and quality assurance programs positions them well to have broad influence.
Increased involvement in the entire clinical trial process will increase physicists' visibility and may help increase quality of clinical trials.

REFERENCES