Quality Assurance: Key aspects of safety in particle therapy to consider from beam to team

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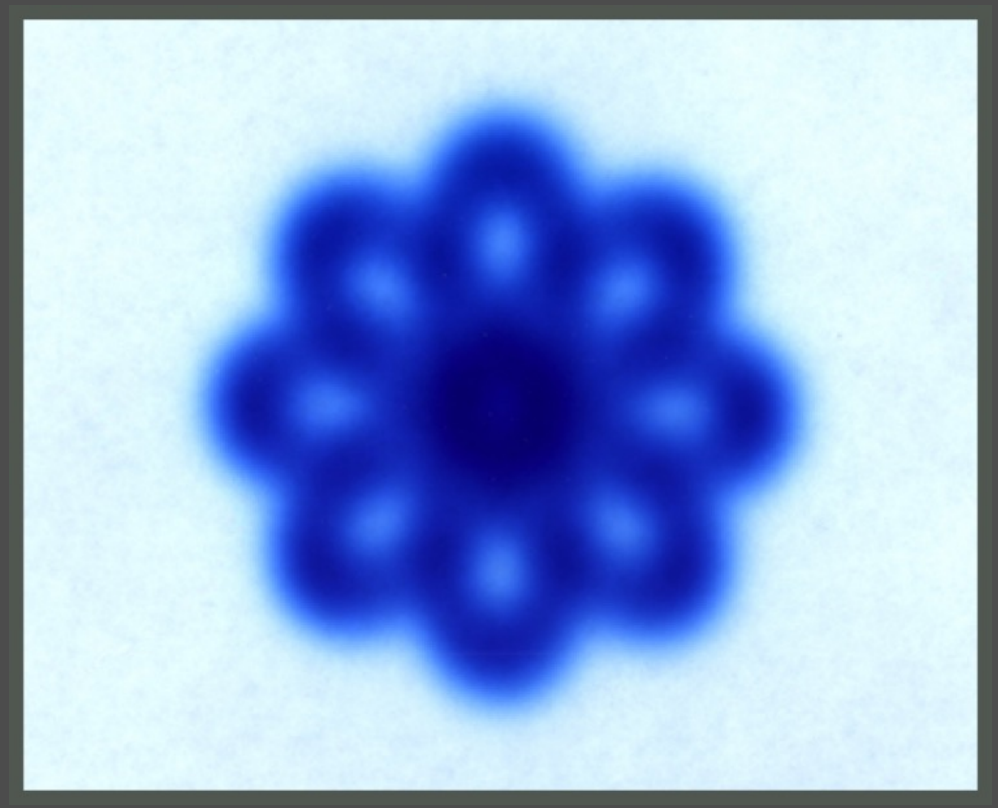
NIH NATIONAL CANCER INSTITUTE

Disclosures

- Employer: National Cancer Institute (NCI) of the United States.
- Conflicts: “I have no conflicts of interest to disclose.”
  - Any vested interest or intention to discuss off-label and/or investigational use of pharmaceuticals or devices.
    None
  - The existence of any financial or other relationship you have with the manufacturer(s) or any commercial product(s) or provider(s) of any commercial services discussed in an educational presentation IF your disclosure that is displayed on the disclosure slide is not current.
    None
- The opinions stated in this talk represent those of the speaker and do not necessarily reflect those of the NCI.

Learning Objectives

- To make it clear how important Q/A is to everything we do at every level.
- To comment on process. And the team. (Not a lot on devices/tools. Not a lot on software/code quality.)
- To comment on what is in the literature and what people do at a high level (consortium).

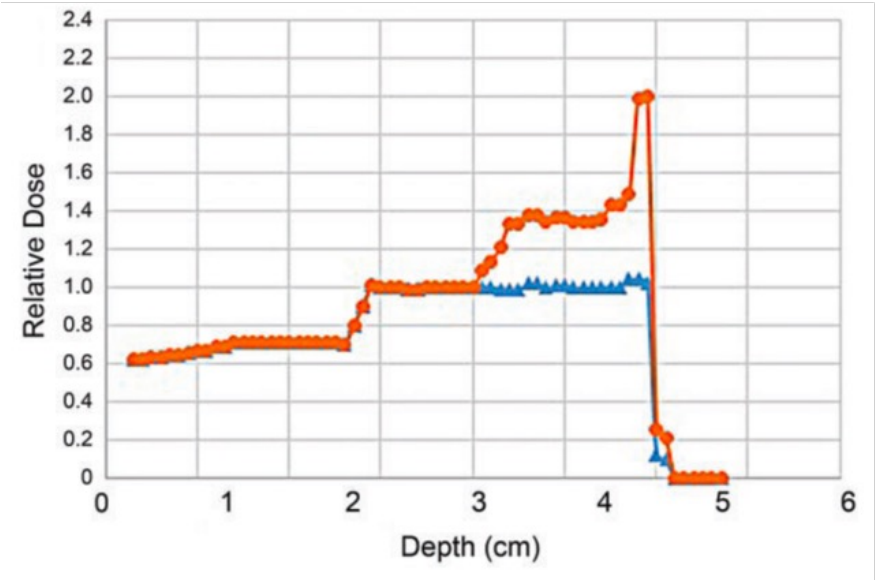


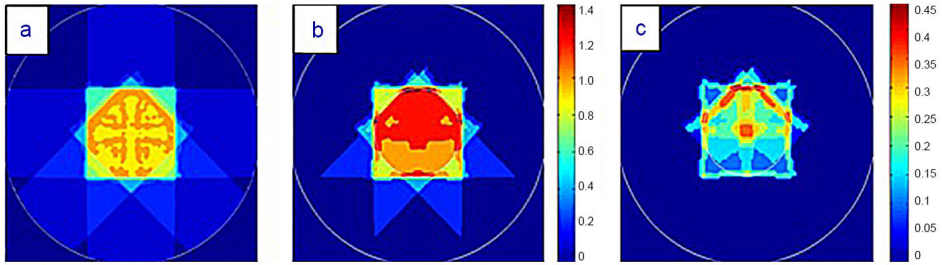
The most beautiful science is that which is reproducible.

The only science is that which is reproducible.

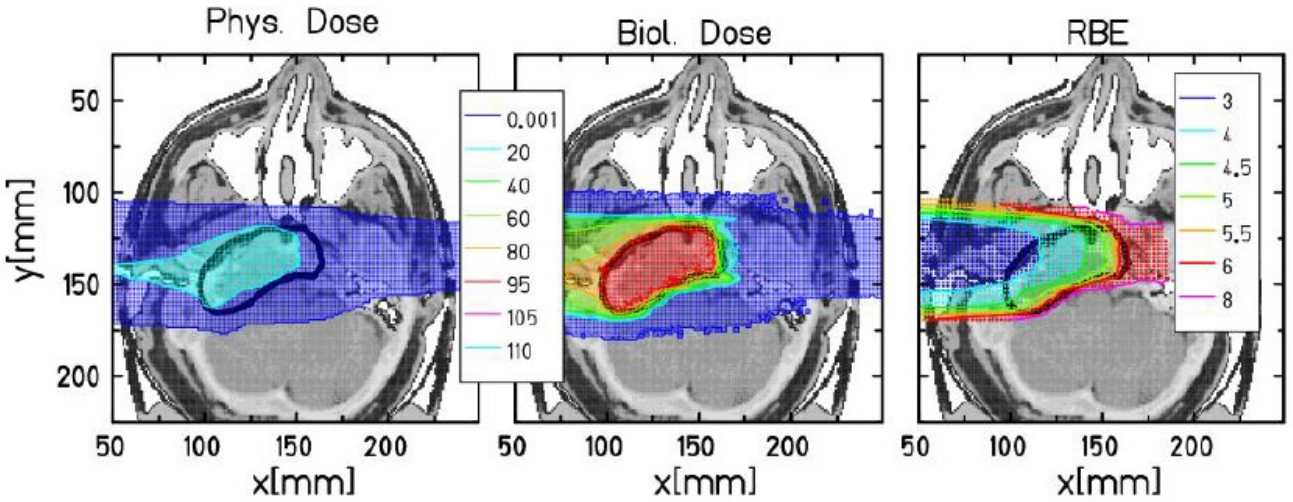
Where is Q/A

We are learning lessons from Protons and Carbon





https://link.springer.com/article/10.1186/1748-717X-9-2



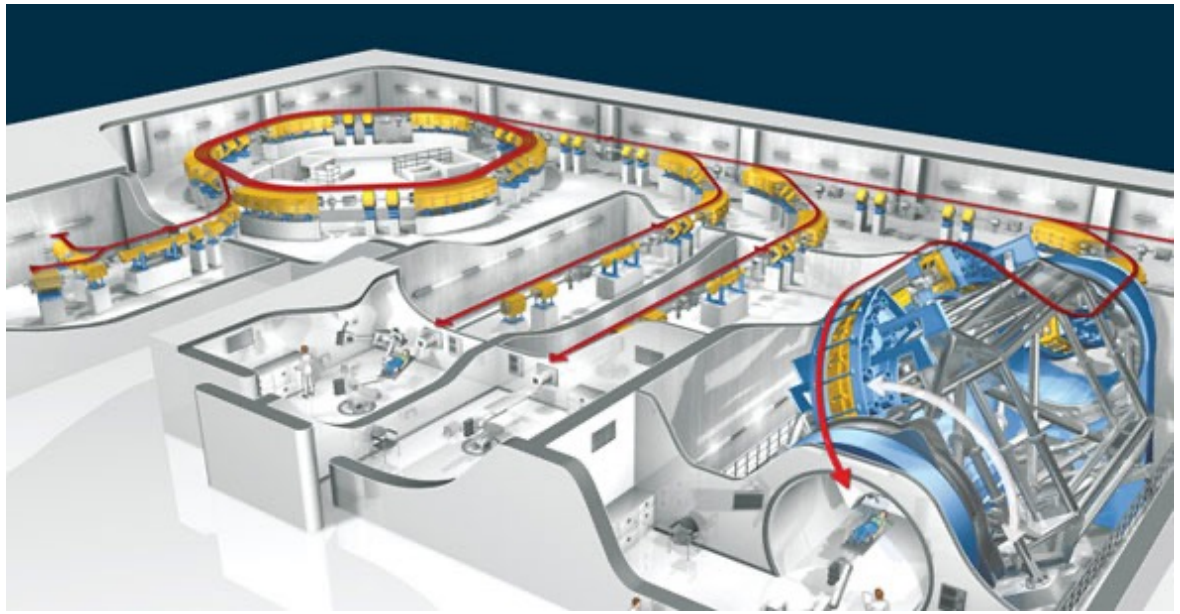
The biological effective dose (center) is the product of the physical absorbed dose (left) with the relative biological effectiveness (Michael Kraemer, GSI)

History of the heavy ion therapy at GSI. Kraft G. https://three.jsc.nasa.gov/articles/Krafts_GSI.pdf. 04-26-2013.

But we cannot learn lessons unless we can trust our data.

Beautiful, elegant machines were conceived and constructed to treat patients – and do.

Each point on the beamline needs to have a process of q/a and feedback associated with it, ideally in real-time. We heard a bit about control systems earlier on this (hardware/software).



https://www.researchgate.net/publication/276467287_History_of_hadrontherapy/figures?lo=1

Injector function/contamination.
Acceleration calibration.
Beam optics/vacuum/current.
Gantry isocentricity.
Imaging to beam alignment.
Robotic table positioning.
Patient immobilization.
Contouring checks.
Plan review process.
Therapy delivery process.
Physician consent process.
Emergency procedures.
Radiation safety and shielding.

IROC in the NCTN

https://www.irocqa.org/

Background: IROC

Imaging and Radiation Oncology Core (IROC) QA Centers provide **quality assurance** for **clinical trials** in the US

1. **Site Qualification**
   FQs, ongoing QA, **proton approval**
2. Trial Design Support/Assistance
   protocol review, help desk
3. **Credentialing**
   phantoms, IGRT, knowledge assessments, benchmarks
4. Data Management
   pre-review, use of TRIAD, post-review for analysis
5. Case Review
   pre-, on-, post-treatment clinical reviews

Importance of Credentialing

Goal of credentialing: ensure comparability and consistency across centers participating in trials

Peters, *et al.* found that noncompliant RT resulted in a **40% decrease in Overall Survival**

Journal of Clinical Oncology > List of Issues > Volume 28, Issue 18 >

ORIGINAL REPORTS | Head and Neck Cancer

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

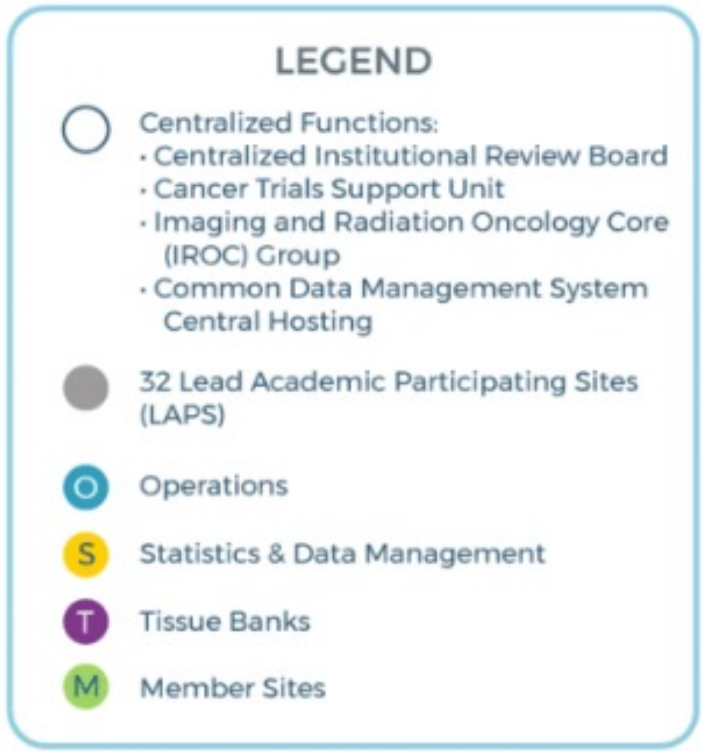
Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernierjean Bourhis, Kally Yuen, Richard Fisher, Danny Rischin

From the Departments of Radiation Oncology and Medical Oncology, and Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre; University of Melbourne, Melbourne, Australia; Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada; Department of Radiation Oncology, Hospital General Vall d'Hebron, Barcelona, Spain; Department of Radiation Oncology, University of Massachusetts Medical Center, North Worcester, MA; Department of Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; Department of Radiation Oncology, Genoller Swiss Medical Network, Geneva, Switzerland; Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; Quality Assurance Review Center, Providence, RI.

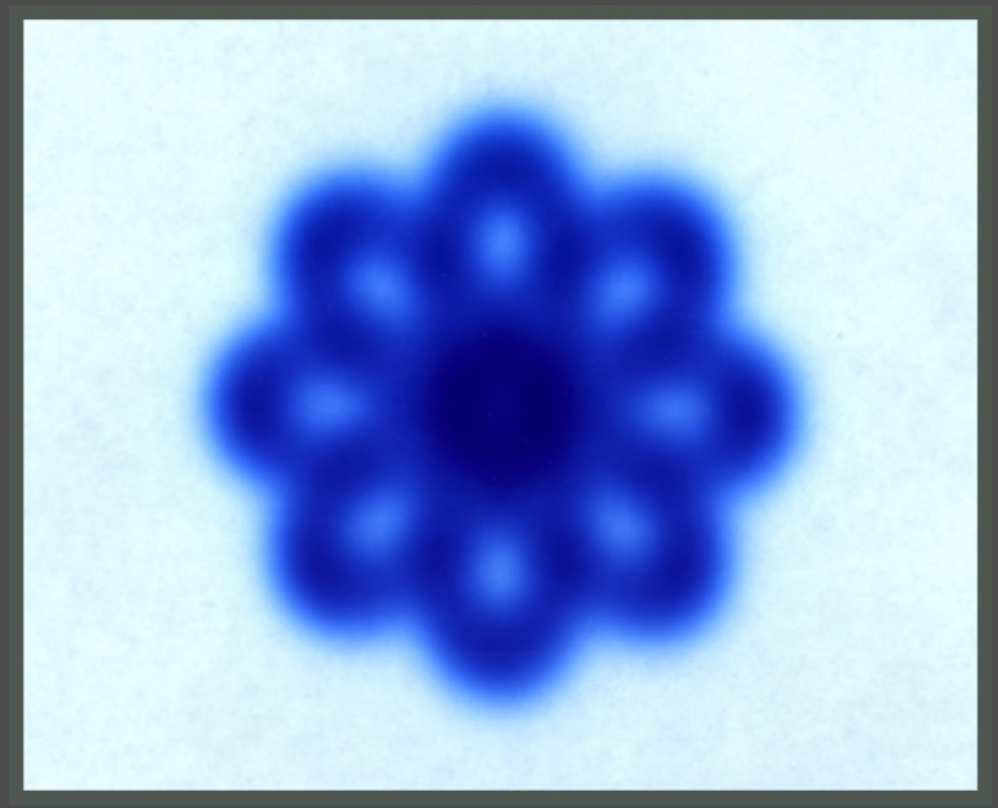
- (NCTN) 25 protocols open that allow protons or randomize proton vs. photon
- Receiving more requests for proton services for fee
  - 20 institutions have requested OP check or phantoms outside of NCTN
  - Some we expect to eventually participate in trials; others just checking their systems

NCI National Clinical Trials Network Structure

NCI's National Clinical Trials Network (NCTN) is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than **2,200 sites** across the United States, Canada, and internationally. NCTN provides the infrastructure for NCI-funded treatment and primary advanced imaging trials to improve the lives of people with cancer.



cancer.gov

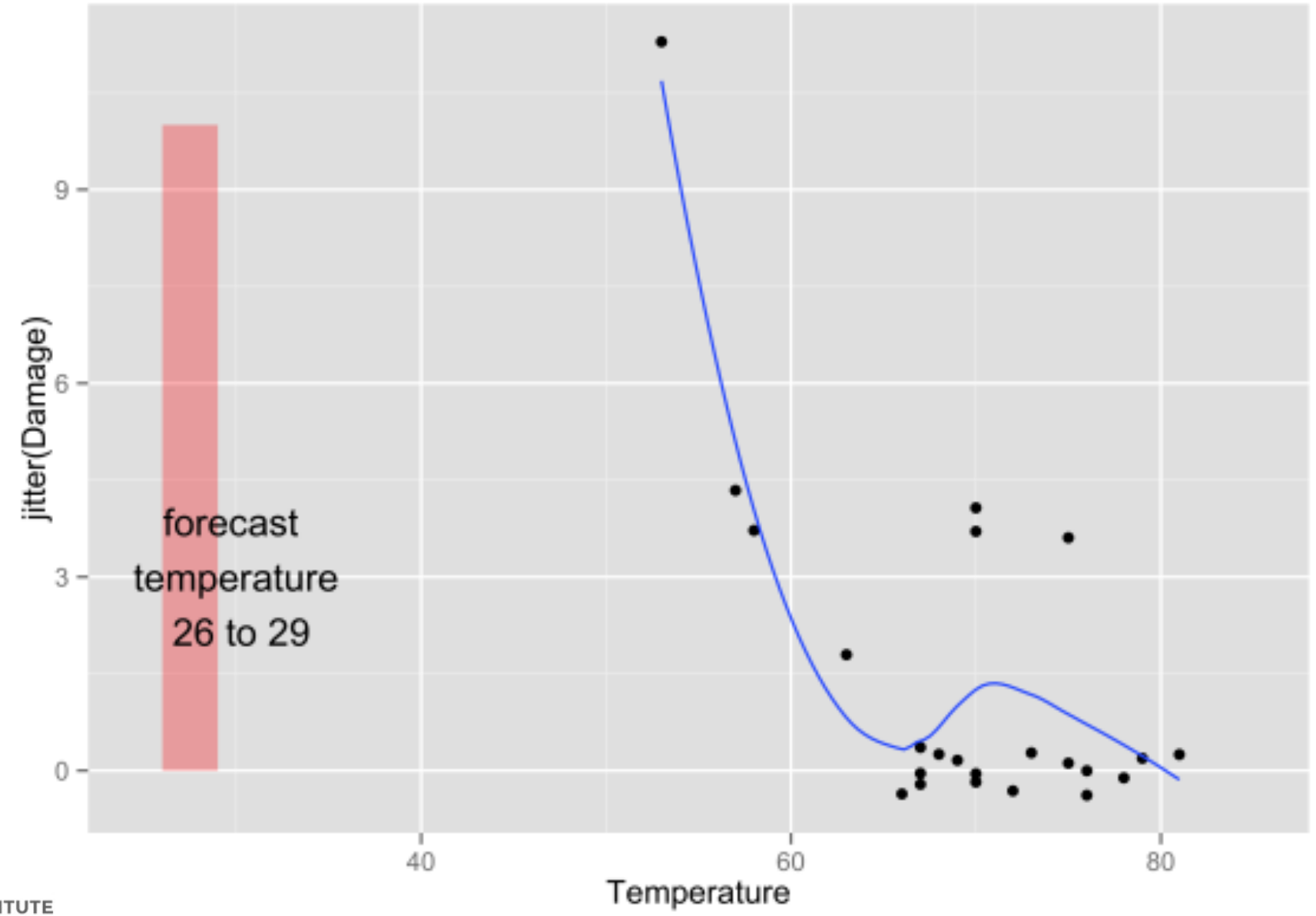


1. Q/A is important

1. Q/A is a fundamental part of all of the science and care we do. All of it. Every day.

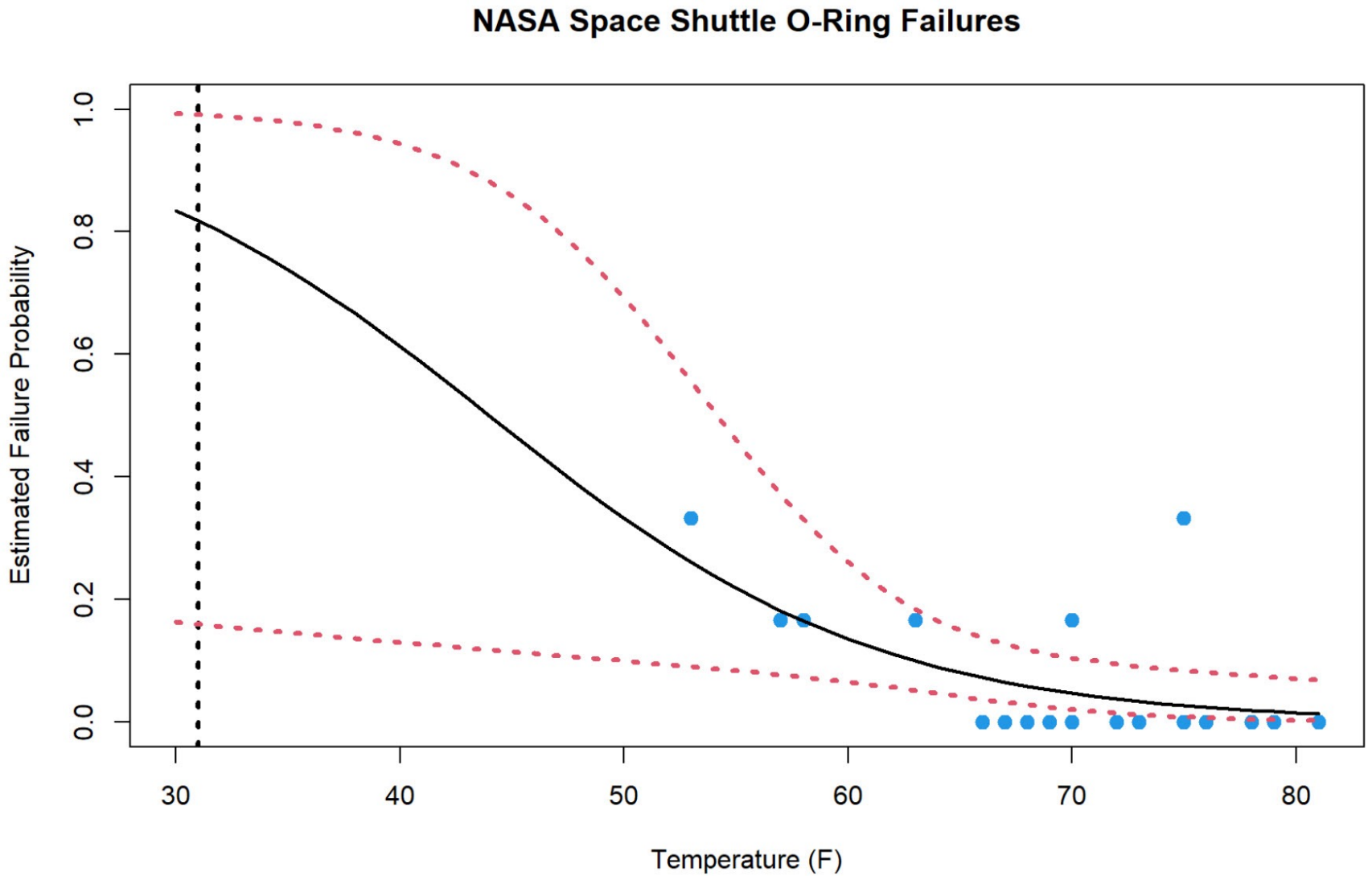
- Can we trust the results of a prospective, randomized trial that is high impact with high LET on a common cancer – a gamechanger trial? Will it translate? Can I reproduce it?
- Do we understand the biology of regular radiation well? How is Q/A done for “normal” radiation research?
- Do we capture data well? Do we share/communicate it well? Do we store it well? Do we know all of the parameters that went into the data making it fully reproducible?
- Do our trials reflect the broad scope of human variation well?
  - Equity
  - Enrichment
  - Economics (the major league team analogy...)
- Do we validate our pre-clinical work well? *Do we fund such?* Do we reward such? *Do we demand rigorous validation and its publication?*
- Do we have realistic models? Why not?
- Do we study our failures and negative trials well?

Example: Communication and Decision Making

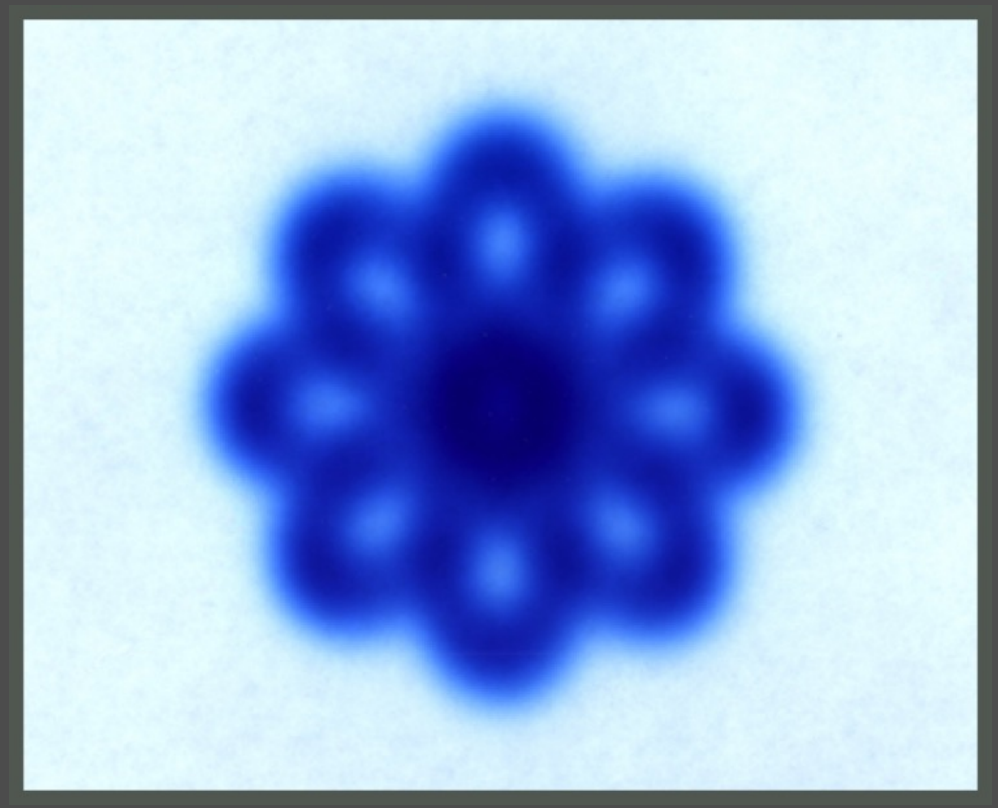


https://p4a.seas.gwu.edu/2019-Fall/challengerExplosion.html

Example: Communication and Decision Making



https://www.cfholbert.com/blog/challenger-disaster/



2. Process and Team

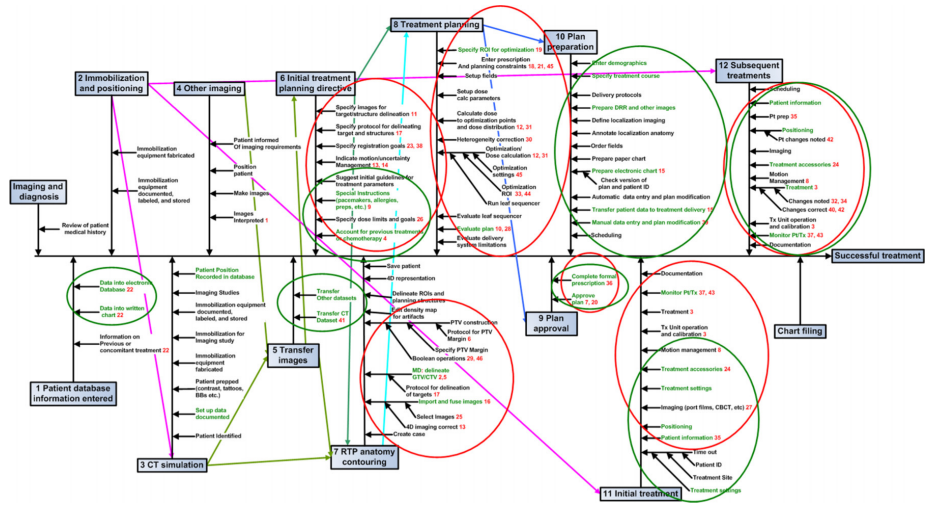
2. Process

Radiation Oncology is Expert at Matching Complex Engineering to Patient Safety

Examples of how the field takes complexity and safety very seriously.

IMRT Process Map

AAPM TG100. Application of risk analysis methods to radiation therapy quality management



https://doi.org/10.1118/1.4947547

Proton Therapy Robustness Reporting Data Elements

Table 1 Elements required for unambiguous reporting of uncertainty scenarios and their dosimetric effects

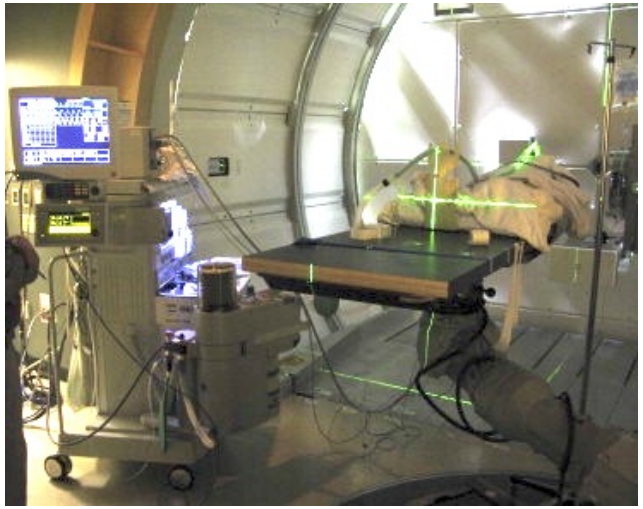
Element to report	Example(s)
For reporting uncertainty scenarios	
Type of uncertainty	• Lateral translations • Rotations (pitch around lateral axis) • Hounsfield unit uncertainty
Magnitude of uncertainty value	±1 cm
Relative likelihood of uncertainty value	Represented as a probability distribution
Correlation between uncertainties	Covariance matrix for a multivariate normal distribution
Number of sample scenarios	1000 random samples
Determination of dose for each scenario	• Dose recalculated • Dose resampled from the nominal dose distribution
For reporting dosimetric effects of uncertainty scenarios	
Form of the dosimetric representation	• Three-dimensional dose distribution • DVH • Equivalent uniform dose
Dosimetric representation descriptor	• Mean • Standard deviation • Minimum • Maximum • n^{th} percentile
Determination of the dosimetric descriptor	• Minimum DVH as DVH derived from minimum dose per voxel of 3-dimensional dose distributions under uncertainty scenarios • Minimum DVH as dose-bin-wise minimum value of many DVHs under uncertainty scenarios

Abbreviation: DVH = dose-volume histogram.

https://doi.org/10.1016/j.prro.2018.12.002

What do you **do** about Q/A.

- Learn what is done at your center (variations are many) and why. The why matters.
- Master it. Study it. Improve it. Teach it. Publish it.
- Learn what is done elsewhere. And why. Above. And collaborate.
- Build in random deep checks. Get certifications and keep them up to date.
- Preclinical Q/A work is very important.
  - Example: The PCRTC U01's at NCI.
- Q/A is a team sport.
  - Example: Star shot.
  - Example: Safety and running codes. https://doi.org/10.1016/j.ijrobp.2012.10.006



3/4045	0.0074%	Complications described in text: aspiration = 2; fall = 1	Sum of events included simulations

Devices.
(a Google search finds a lot of these now for sale)

Training.

Recording.

Analysis.

Discussion/Review.

Improvement.

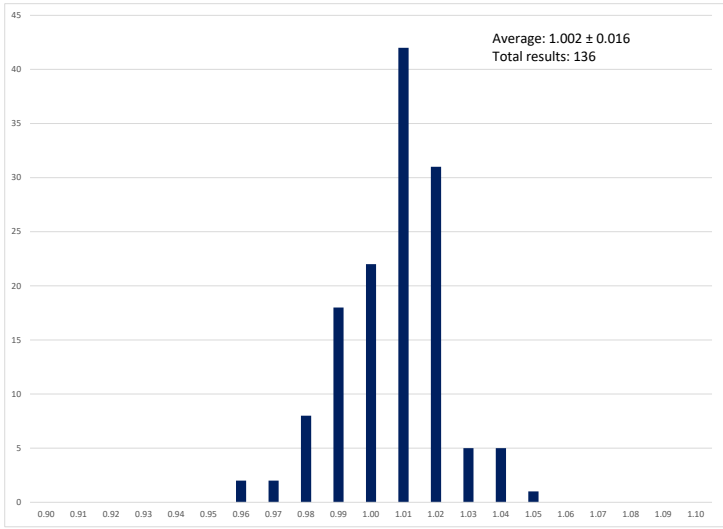
IROC process

Proton Activities Overview

Baseline Approval
- Proton FQ
- Machine OP Check
- Baseline phantoms
- On-site visit

Credentialing
- Additional phantoms
- IGRT credentialing
- Knowledge assessments

Output Checks: Proton Therapy



Credentialling: H&N as an example

Proton H&N Phantom

Planning constraints:

- 6.6 Gy(RBE) covers ≥95% of the PTV

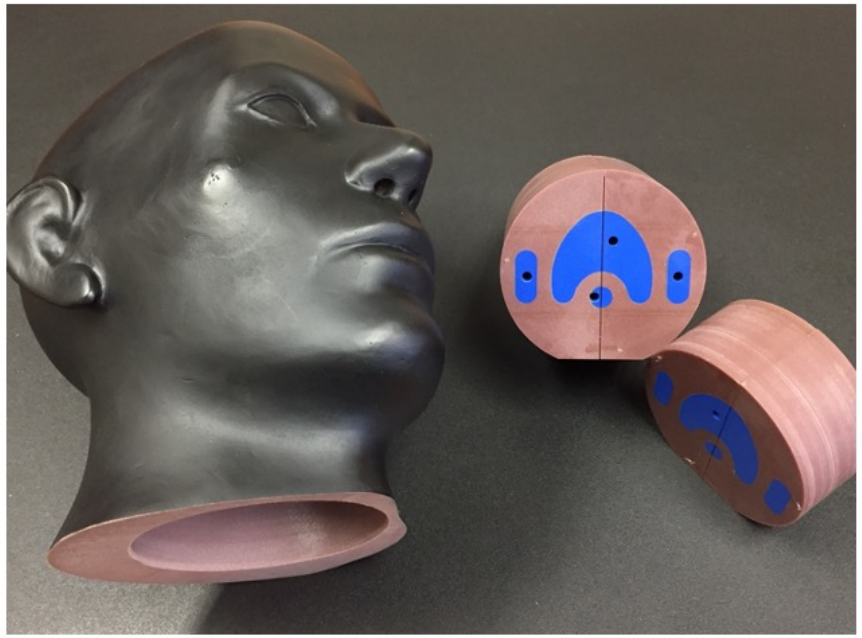
  (*variation acceptable* ≥90%)

- Max dose to 0.03 cc ≤4.5 Gy(RBE)

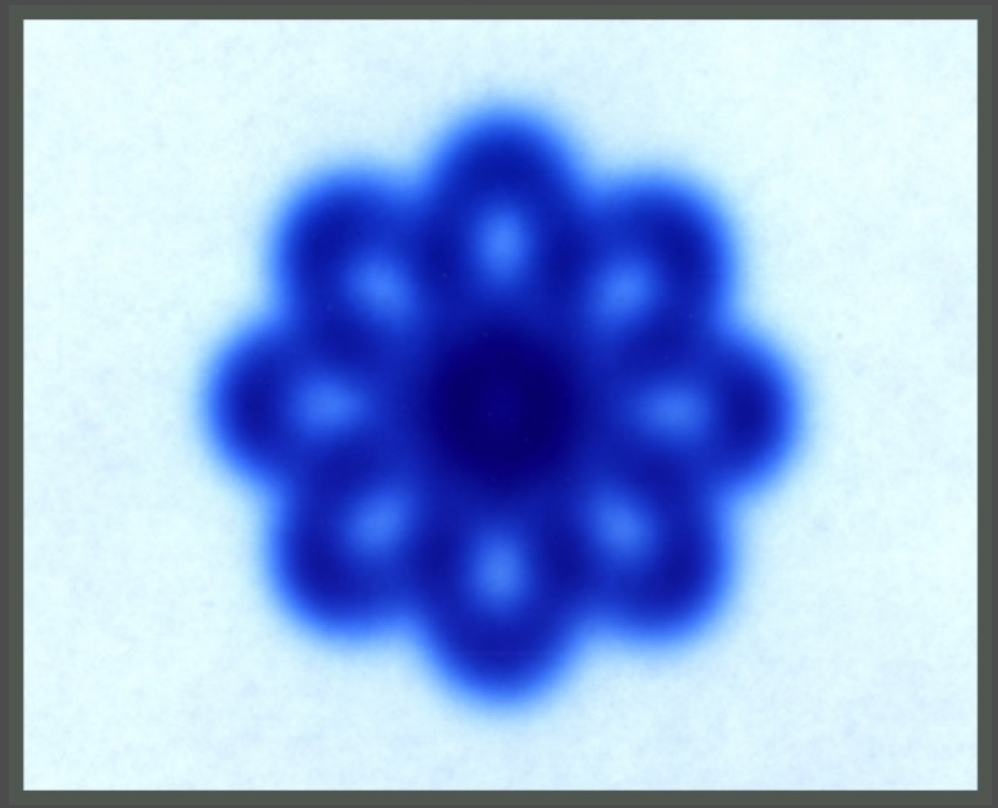
  (*variation acceptable* ≤5.0 Gy(RBE))

- Mean dose to both parotids ≤2.6 Gy(RBE)

  (*variation acceptable* ≤3.3 Gy(RBE))

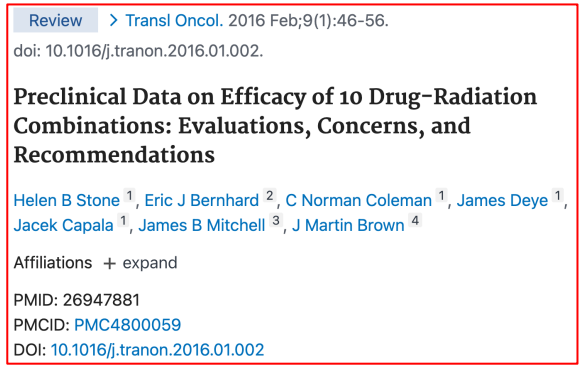


The anthropomorphic proton H&N phantom shown with insert (right). The target, cord, and parotid structures can be seen in blue.



3. Q/A Literature - Comments and Thoughts

Preclinical Q/A



Furthermore, highly cited journals are more likely to document fewer parameters.

Pre - Clinical Q/A – Radiobiology 2021

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Novel Drug/Radiation Therapy Combinations

Accurate Dosimetry for Radiobiology

Larry A. DeWerd, PhD, FAAPM, and Keith Kunugi, MBA, MS

Department of Medical Physics, Medical Radiation Research Center, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin

Received Jul 12, 2021; Accepted for publication Sep 1, 2021

Purpose: Accurate radiation dose is required to ensure reproducibility in establishing the radiobiological effect in biological systems among institutions. The dose should be the most precise and accurate parameter of the entire process. The goal is a system to provide uniform radiation dose verification among institutions that is traceable to the National Institute of Standards and Technology (NIST) through an Accredited Dosimetry Calibration Laboratory.

Methods and Materials: Radiobiological beams are not NIST traceable but can be approximated based on the radiograph's half value layer. Phantoms have been developed containing detectors to measure the dose from total body irradiation of mice and others. Ionization chambers calibrated to NIST-traceable beams are the best detectors for precise and accurate dose determinations. However, thermoluminescent dosimeters have been mostly used for this application for comparison between institutions.

Results: A comparison of thermoluminescent dosimeters results among surveyed institutions showed a large variation in delivered dose. The range of radiograph doses that were measured deviated from the standard dose by 12% to 42%. The results have an uncertainty of 2.5% at 1 standard deviation. The surveyed radionuclide irradiators demonstrated a dose range variation of 1.6% to 13.5% from target dose. There is less variation among high energy (linacs) because a calibrated ionization chamber is generally used by personnel (eg, medical physicist) and the output is determined for radiation therapy applications as well.

Conclusions: Radiobiological dosimetry is lacking with respect to its precision and accuracy. The accuracy of radiograph calibrations for radiobiology can be estimated to be approximately 5%, because there are no NIST-traceable beams. However, among institutions, the variations can be up to 42%. Intercomparisons between institutions is important to have a clear understanding of the transference of dose between given studies.

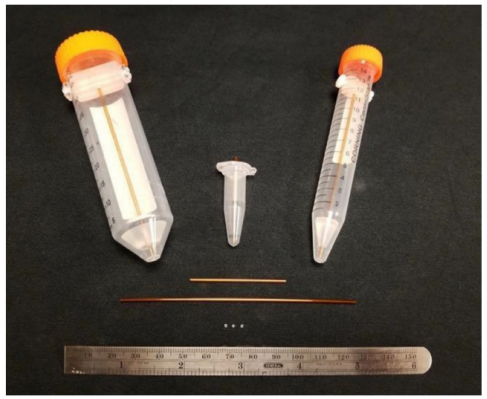


Fig. 1. Cell culture phantoms shown with the 1 mm × 1 mm × 1 mm cube thermoluminescent dosimeters shown. The Kapton inserts are shown above the thermoluminescent dosimeters.

Fig. 3. Examples of mouse phantoms: the torso, with thermoluminescent dosimeters insert, is shown on the left with the head in the center and the flank on the right. Note the 1 mm cube thermoluminescent dosimeters that are put in the inserts shown under the phantom.

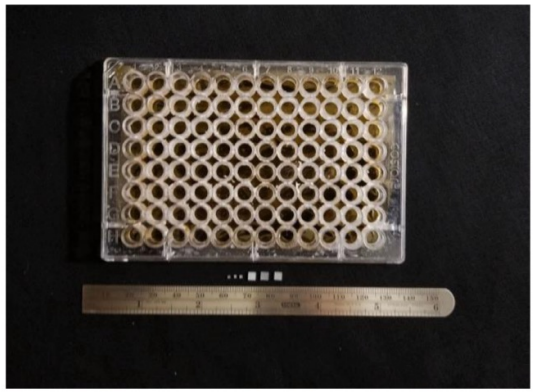


Fig. 2. A well dish phantom for cells. Thermoluminescent dosimeters (TLDs) are placed at the bottom of the wells. 1 mm × 1 mm × 1 mm cube TLDs are shown as well as 3 mm × 3 mm × 1 mm TLDs.

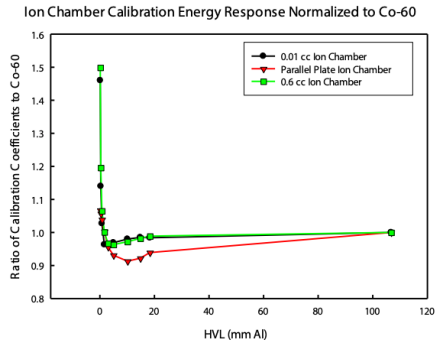


Fig. 5. Typical ionization chamber response to National Institute of Standards and Technology traceable x-ray beams (M series), normalized at ^{60}Co.

Clinical Q/A – Example: Particle Credentialling

Int J Radiat Oncol Biol Phys. 2016 May 1; 95(1): 242–248. doi:10.1016/j.ijrobp.2016.01.061.

RESULTS FROM IROC HOUSTON'S ANTHROPOMORPHIC PROTON PHANTOMS USED FOR CLINICAL TRIAL CREDENTIALING

PAIGE A. TAYLOR, M.S.*, STEPHEN F. KRY, PH.D.*, PAOLA ALVAREZ, M.S.*, TYLER KEITH, B.S., CARRIE LUJANO, B.S.*, NADIA HERNANDEZ, B.S.*, and DAVID S. FOLLOWILL, PH.D.*

*Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030-4009, USA

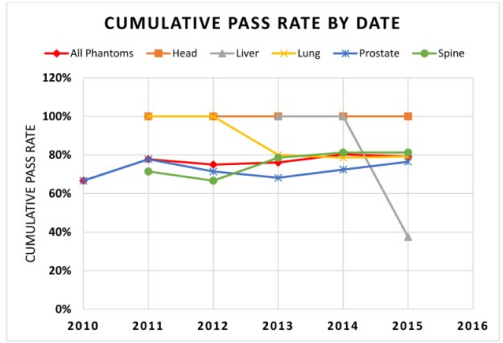


Figure 4.
Cumulative pass rate over time for each proton phantom.

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

AAPM Scientific Report | Free Access

AAPM task group 224: Comprehensive proton therapy machine quality assurance

Bijan Arjomandy, Paige Taylor, Christopher Ainsley, Sairos Safai, Narayan Sahoo, Mark Pankuch, Jonathan B. Farr, Sung Yong Park, Eric Klein, Jacob Flanz, Ellen D. Yorke, David Followill, Yuki Kase

First published: 24 May 2019 | https://doi.org/10.1002/mp.13622 | Citations: 45

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 112, Issue 4, 15 March 2022, Pages 1004-1011

Physics Contribution

The Value of On-Site Proton Audits

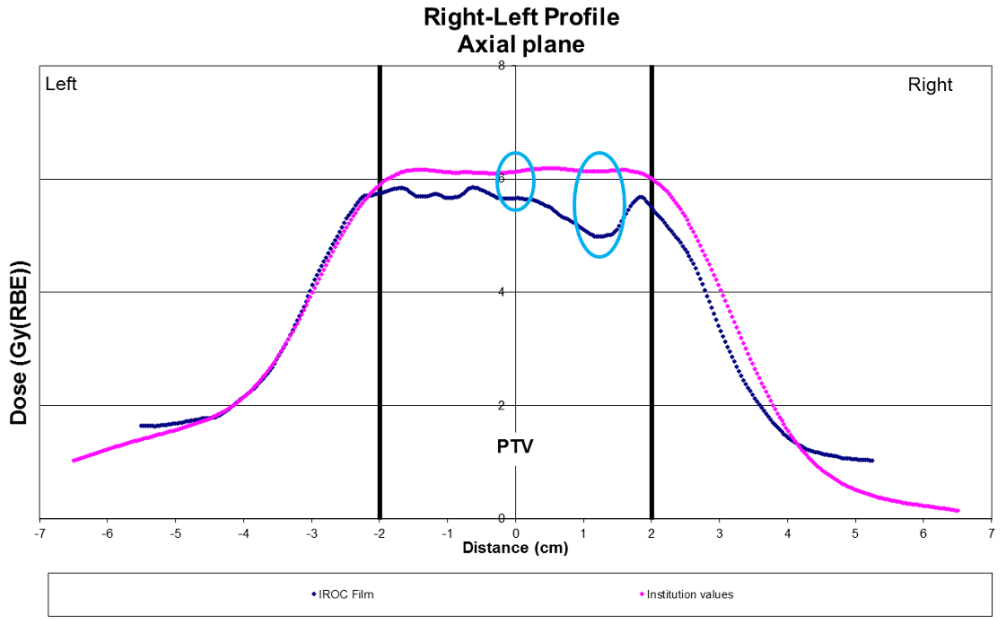
Paige A. Taylor MS, Jessica Lowenstein MS, David Followill PhD, Stephen F. Kry PhD

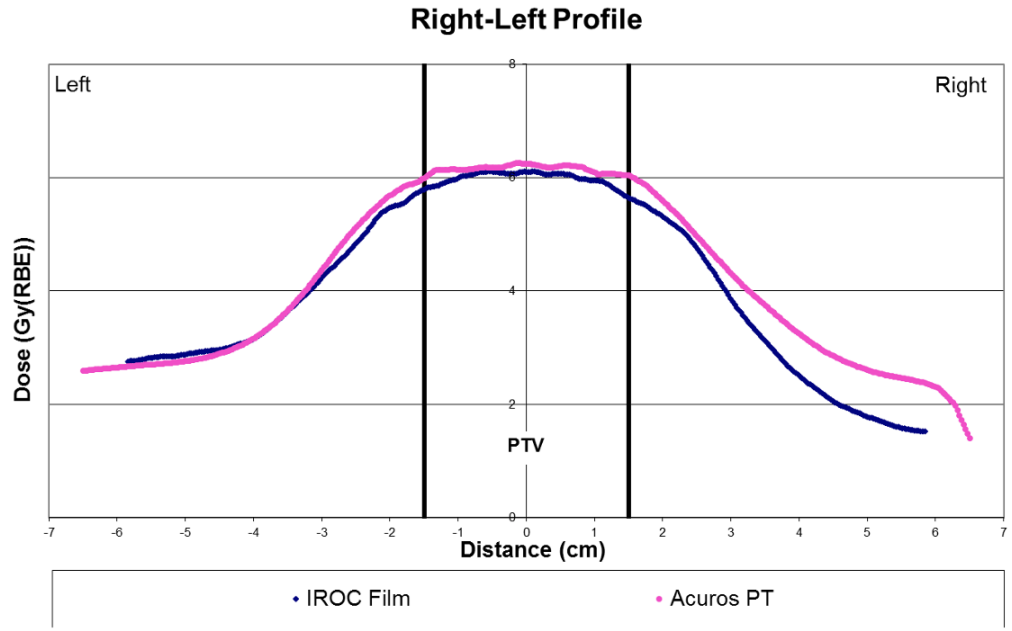
Updated – NCTN as of May 2022

	Brain	H&N	Liver	Lung	Prostate	Spine	TOTAL
Total Irradiations	34	31	66	72	45	30	278
# Passed	33	28	34	50	37	23	205
Pass Rate [%]	97%	90%	52%	69%	82%	77%	74%

Rainy day reading: Institutions received an average of 3 (range, 1-8) recommendations for practice improvements. The number of deficiencies did not decrease over time, highlighting the continued need for this type of peer review. The most common deficiencies were for Task Group-recommended QA compliance (97% of centers), computed tomography number (CTN) to relative linear stopping power conversion (59%), and QA procedures (53%). In addition, **32% of institutions assessed failed at least 1 lateral beam profile measurement** (<90% of pixels passing 3% [global]/3 mm; 10% threshold), despite passing internal QA measurements. These failures occurred for several different plan configurations (large, small, shallow, and deep targets) and at different depths in the beam path (proximal to target, central, and distal). CTN to relative linear stopping power conversion curves showed deviations at low, mid, and high CTNs and highlighted areas of inconsistency between proton centers, with many centers falling outside of 2 sigma of the mean curve of their peers. All deficiencies from the peer review were discussed with the institutions, and many implemented dosimetric treatment planning and practice changes to improve the accuracy of their system and consistency with other institutions.

Proton Lung Phantom Results





Paige Taylor, MS, DABR

PB vs. MC in Other Disease Sites?

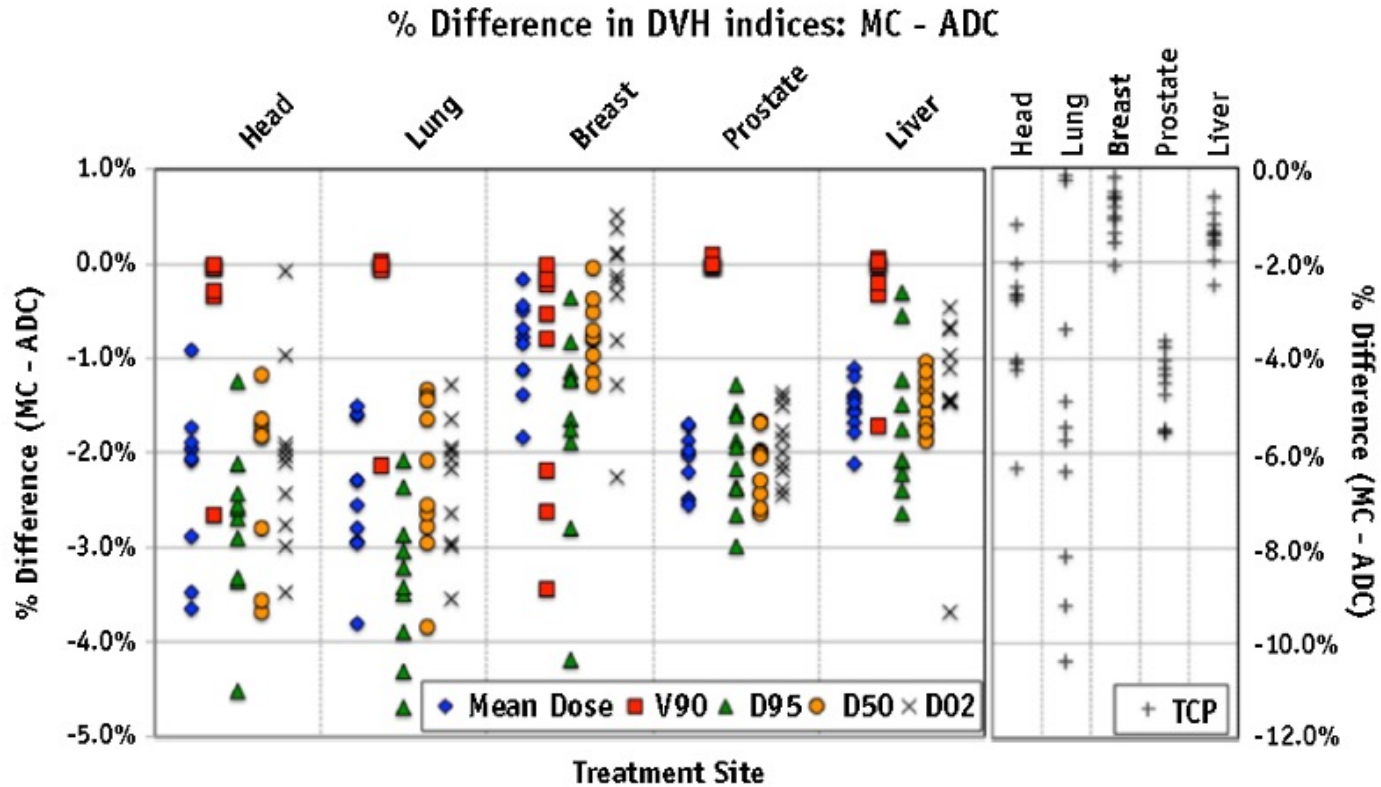
International Journal of Radiation Oncology biology • physics

www.redjournal.org

Physics Contribution

Assessing the Clinical Impact of Approximations in Analytical Dose Calculations for Proton Therapy

Jan Schuemann, PhD, Drosoula Giantsoudi, PhD, Clemens Grassberger, PhD, Maryam Moteabbed, PhD, Chul Hee Min, PhD, and Harald Paganetti, PhD



Clinical Q/A – Example: FLASH

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

SPECIAL ISSUE PAPER | Open Access

A roadmap to clinical trials for FLASH

Paige A. Taylor, Jean M. Moran, David A. Jaffray, Jeffrey C. Buchsbaum

First published: 02 April 2022 | https://doi.org/10.1002/mp.15623

SECTIONS PDF TOOLS SHARE

Abstract

While FLASH radiation therapy is inspiring enthusiasm to transform the field, it is neither new nor well understood with respect to the radiobiological mechanisms. As FLASH clinical trials are designed, it will be important to ensure we can deliver dose consistently and safely to every patient. Much like hyperthermia and proton therapy, FLASH is a promising new technology that will be complex to implement in the clinic and similarly will require customized credentialing for multi-institutional clinical trials. There is no doubt that FLASH seems promising, but many technologies that we take for granted in conventional radiation oncology, such as rigorous dosimetry, 3D treatment planning, volumetric image guidance, or motion management, may play a major role in defining how to use, or whether to use, FLASH radiotherapy. Given the extended time frame for patients to experience late effects, we recommend moving deliberately but cautiously forward toward clinical trials. In this paper, we review the state of quality assurance and safety systems in FLASH, identify critical pre-clinical data points that need to be defined, and suggest how lessons learned from previous technological advancements will help us close the gaps and build a successful path to evidence-driven FLASH implementation.

Volume 49, Issue 6
June 2022
Pages 4099-4108
This article also appears in:
FLASH: Current status and the transition to clinical use

Figures References Related Information

Recommended

Ultra-high dose rate dosimetry: Challenges and opportunities for FLASH radiation therapy

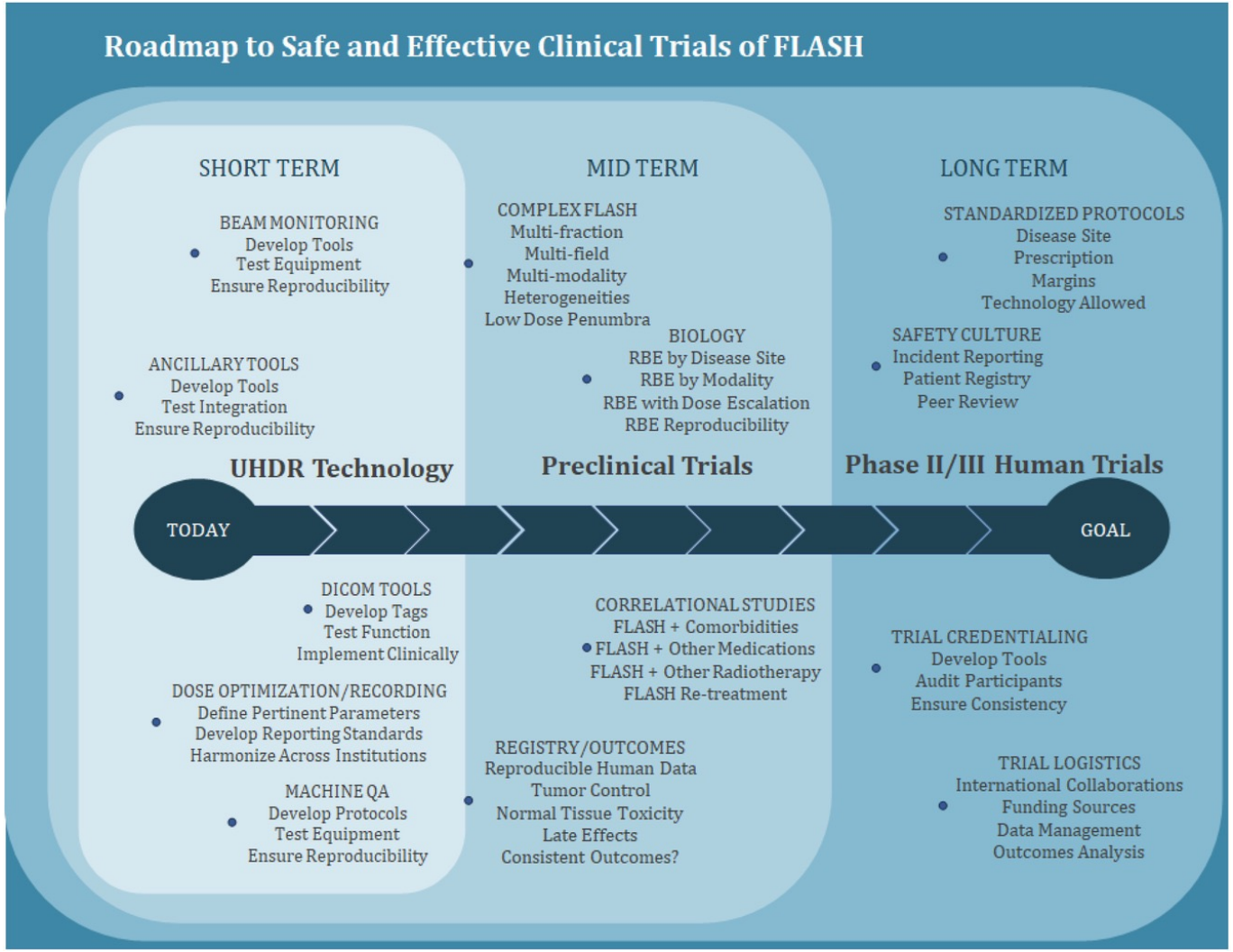
Francesco Romano, Claude Bailat, Patrik Gonçalves Jorge, Michael Lloyd Franz Lerch, Arash Darafsheh

Medical Physics

Image guidance for FLASH radiotherapy

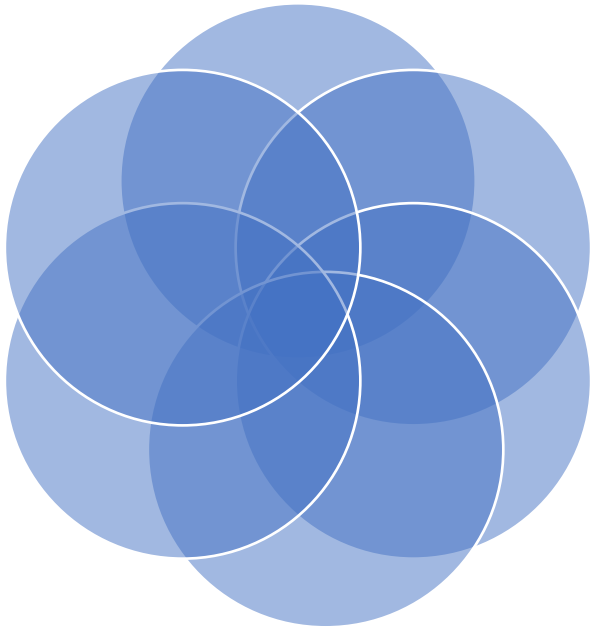
Issam El Naqa, Brian W. Pogue, Rongxiao Zhang, Ibrahim Oraiqat, Katia Parodi

Medical Physics



Need to Integrate Pre-Clinical and Clinical Q/A

The technology and data we heard about this week.



New agreement on standards and validation methods

- More sharing of valid date
- Assurance of data validity

New computational methods and tools

- AI/ML
- Quantum computing
- Q/A for DEI/equity

New physics

- e.g. High T affordable magnets (high temp SC)
- Machine design and function Q/A. FLASH as an example.

Research support (example of NCI)

- generic R01, R21, P01, etc.
- The High LET RFA
- ROBIN
- We plan to continue our efforts to support RT
- And Q/A
- Could be any funding agency...all of them really.

Pharma

- RPT, Biologics, sensitizers, senolytics, etc.
- Reproducibility.
- Supply Q/A.

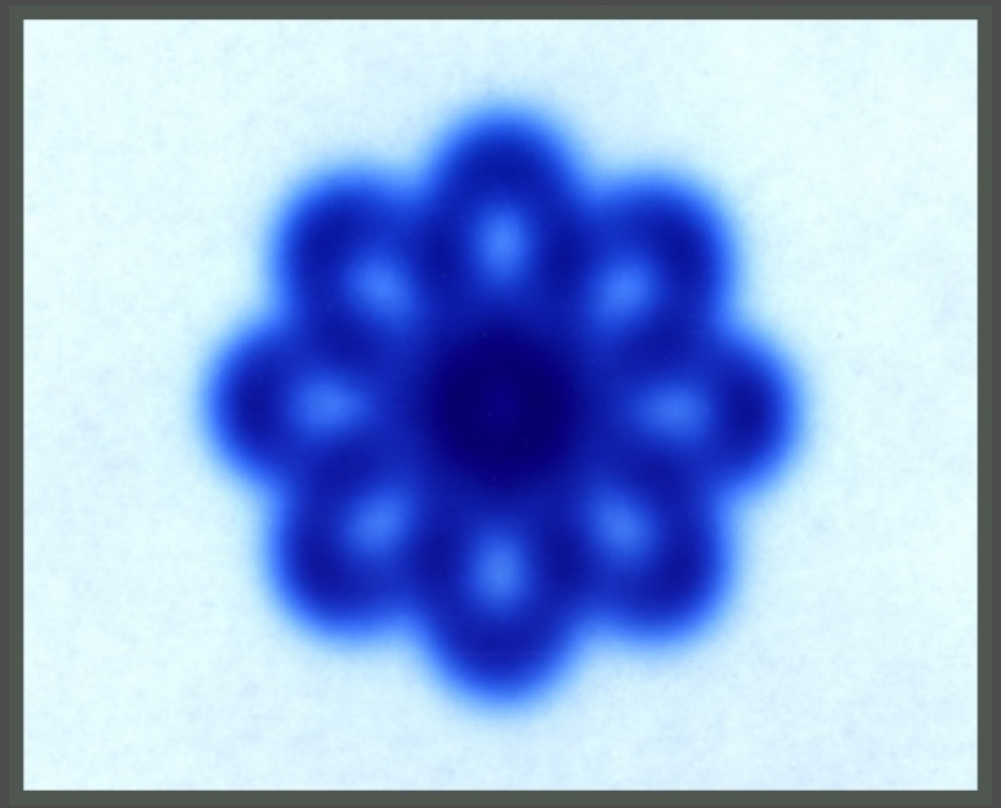
Knowing limits of each impacts what can be studied and how to design experiments.

We need to enrich our patient selections via biology that is valid.

We need to use modern data science (AI, etc.) to achieve real breakthroughs (data quality)

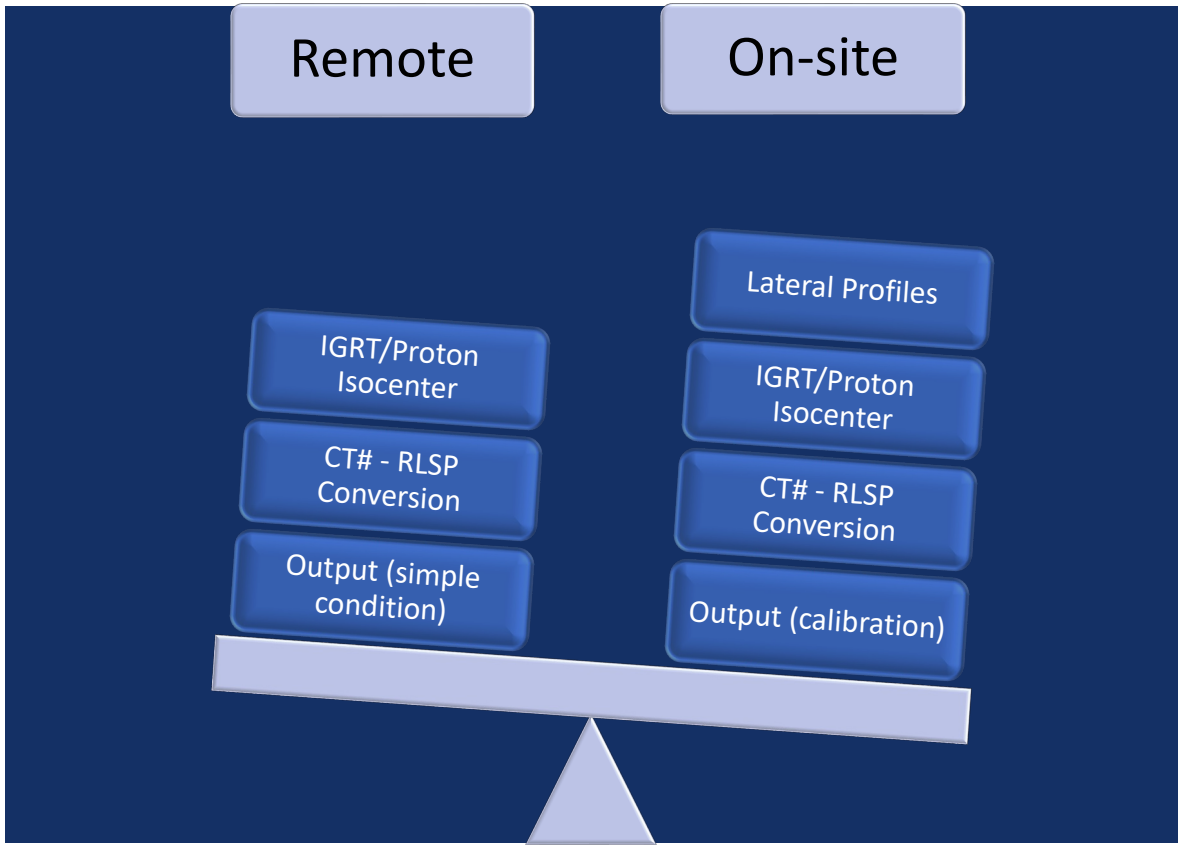
We need to focus on broad data availability in the long term across the globe.

We need to focus on mentorship and expertise diversification and collaboration. Q/A valued and taught.



Carbon Beam QA

Where to do Q/A



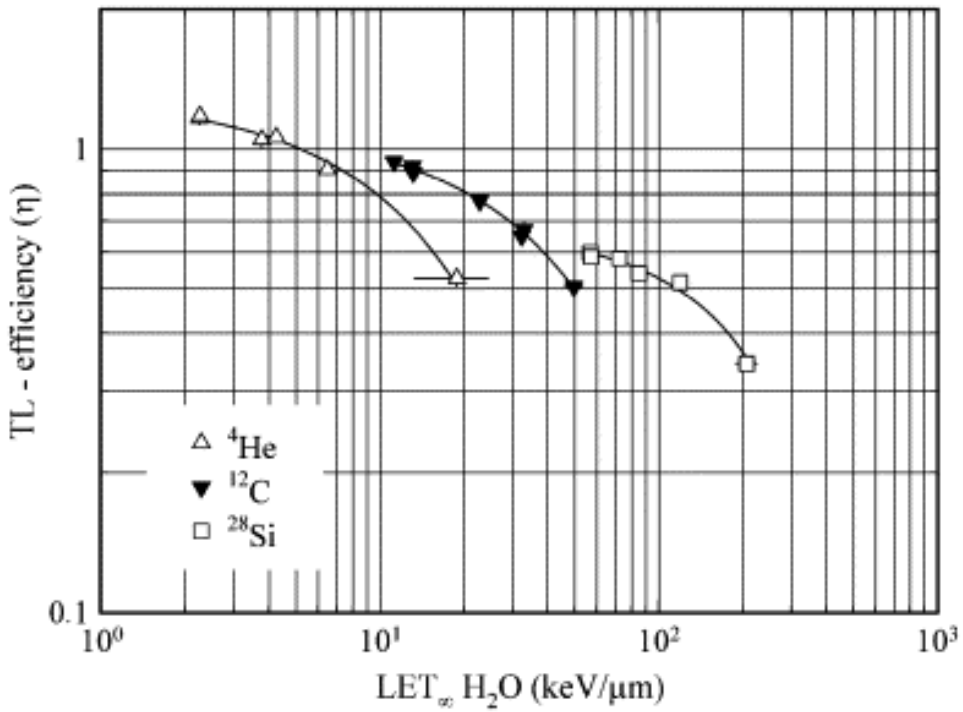
- In a review of recent remote audits vs. on-site audits:
  - 80% of deficiencies could have been identified through remote proton audits
  - 20% of deficiencies would have been missed with a remote program

Per (unpublished) Paige Taylor

Carbon Q/A (from the IROC/NCTN perspective)

- **Parallel** existing approval and credentialing for proton therapy
  - Annual output checks
  - Phantom irradiations
  - On-site audit
  - Measurement based assessment of RBE
- **Collaborating** with CNAO (Pavia, Italy) for Carbon experiments
  - Will work on TLD, OSLD, film, and microdosimeter characterization, examining LET and ion species dependence

- Our current dosimeters (film, TLD, OSLD) **poorly characterized in carbon beams**
  - Response dependent not only on LET, but also ion species
- Current carbon centers use **variety of RBE/dose models** (MKM, LEM I-IV)
  - How do we verify the accuracy and comparability of these models?



T. Berger, M. Hajek. TL-efficiency—Overview and experimental results over the years. Radiation Measurements, 43:2–6, 2008, Pages 146-156. https://doi.org/10.1016/j.radmeas.2007.10.029.

Models in Carbon Therapy: Variability

RBE Model	Cell Line	α_x (Gy^{-1})	β_x (Gy^{-2})	α_c (Gy^{-1})	β_c (Gy^{-2})
MKM	HSG Tumor*	0.19	0.05	Microdosimetry	0.05
SMKM				Microdosimetry	Microdosimetry
RMF	NSCLC H460*	0.29	0.083	Microdosimetry & Monte Carlo	Monte Carlo
LEM	Chordoma*	0.1	0.05	Monte Carlo	Monte Carlo

- Possibly can be measured with a Tissue Equivalent Proportional Counter
- Direct input into one of the clinical RBE models
- Not going into the above in detail due to time constraints - just something you need to know about and appreciate in this field

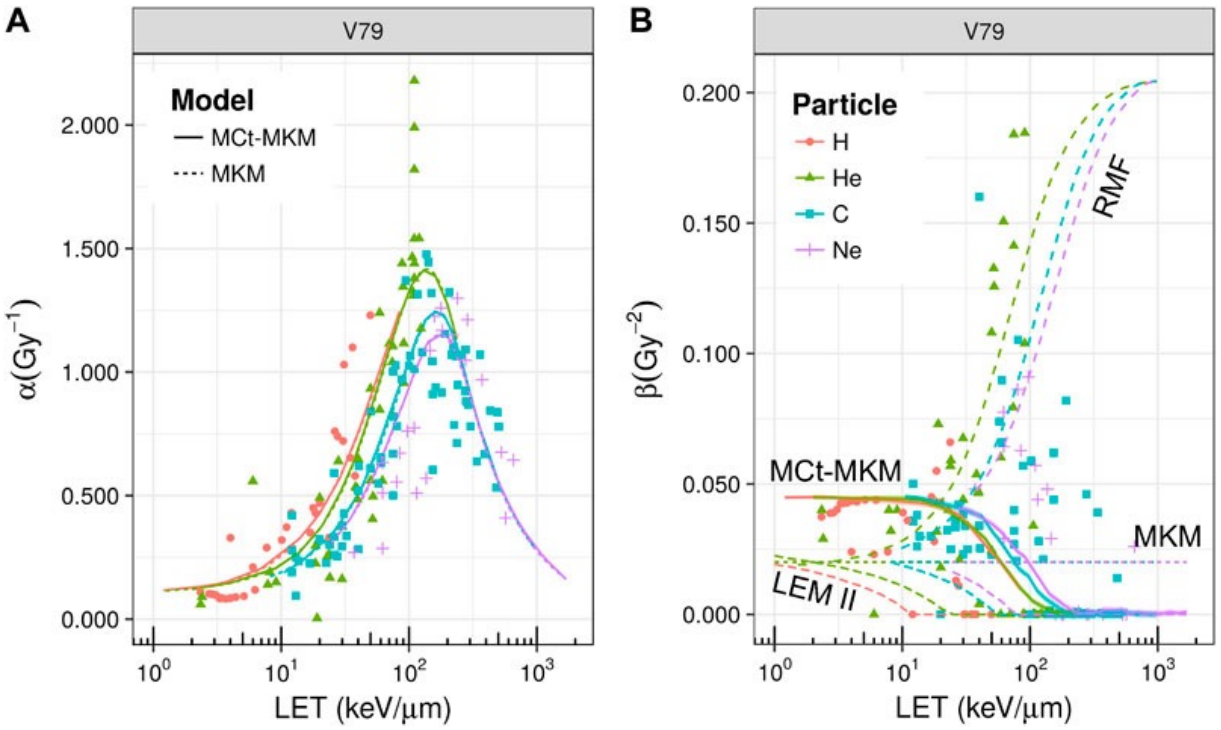
Table from Shannon Hartzell, MS and Paige Taylor

Q/A challenge: model parameter variability and validation status

Linear quadratic α(PANEL A) and β(PANEL B) parameters as a function of LET for the irradiation of V79 cells with different ions.

Data needed: OTHER CELLS, OTHER ENERGIES, MORE COMPLEX MODELS, ANIMALS, HUMANS, DAY TO DAY VARIATION....IT GETS COMPLEX VERY RAPIDLY)

Rainy day reading: Points represent experimental data taken from PIDE [82], different colors/gray levels and shapes refer to H, He, C, and Ne ions, respectively (the color/gray level and shape legend refers both to PANELS A AND B). In panel A, solid and dashed lines represent, respectively, the extrapolation with the MCt-MKM and the original MKM, while in panel B, a comparison between different models is reported (namely, MKM, MCt-MKM, LEM-II, and RMF). In the case of the MCt-MKM, overlapped to the α and β curves, the MC statistical confidence bands (68%) are reported. These bands are small due to the high statistics and they blend with the curves' thickness. A saturation effect is observed for both α and β parameters. Plot taken from [23].

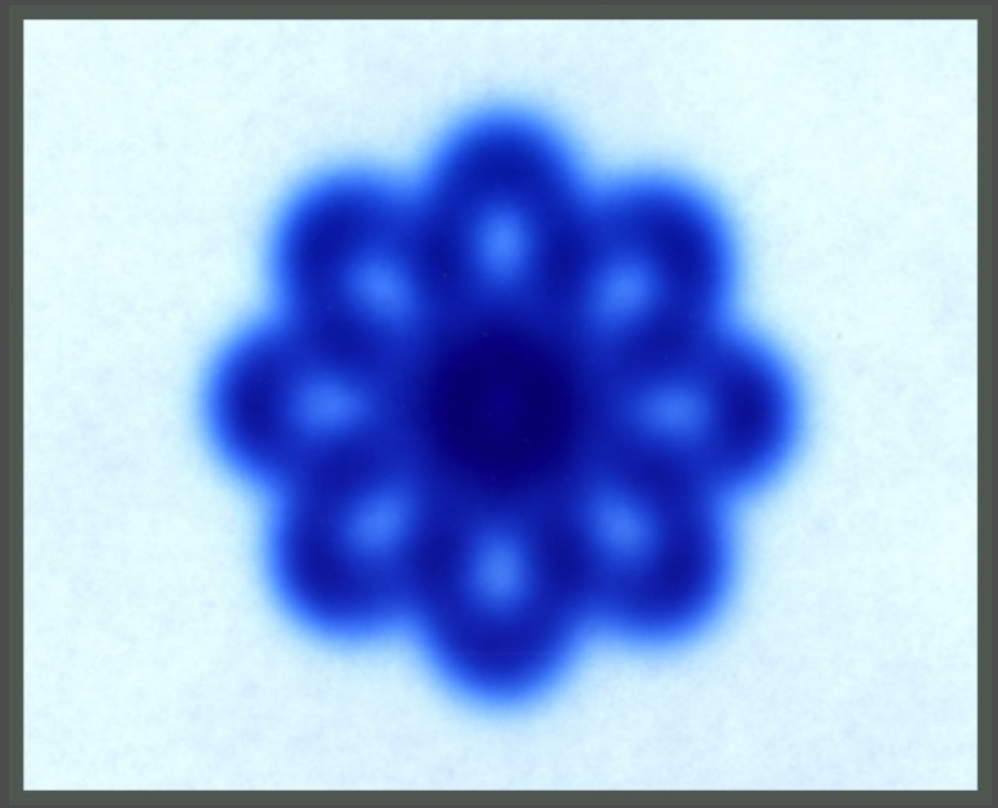


Front. Phys., 10 February 2021
Sec.Medical Physics and Imaging
https://doi.org/10.3389/fphy.2020.578492

82. Friedrich T, Scholz U, Elsässer T, Durante M, Scholz M. Systematic analysis of RBE and related quantities using a database of cell survival experiments with ion beam irradiation. *J Radiat Res* (2013) 54:494–514. doi:10.1093/jrr/rrs114

23. Manganaro L, Russo G, Cirio R, Dalmasso F, Giordanengo S, Monaco V, et al. A Monte Carlo approach to the microdosimetric kinetic model to account for dose rate time structure effects in ion beam therapy with application in treatment planning simulations. *Med Phys* (2017) 44:1577–89. doi:10.1002/mp.12133

In clinical treatment planning, the RBE has to be calculated by radiobiological mathematical models, which, in spite of all validation efforts, still involve significant sources of uncertainty.



Final Thoughts

Concluding Thoughts

We need to focus more on the interface of **biology** and **physics**. Q/A in this context is complex, difficult, and a research topic.

We need to embrace collaboration. And Q/A is a critical part of that.

We need to bring all of our tools forward and share best practices.

We need to mentor and to help each other.

We need to make sure we do Q/A at every level.

Thank you