Clinical Tolerances For Re-Irradiation - Can We Generate Them From Clinical Data?

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with help from

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Disclosures

- None

Acknowledgments

- Thanks to:
- Annemarie Shepherd, Abe Wu, Dillon Li, Kelly Yue, Anna Lee, Nancy Lee - (MSKCC RO)
- **Ellen Yorke,** Aditya Apte, Jie Yang, Joe Deasy - (MSKCC Med Phys)
- Randy Ten Haken, Larry Marks, Drew Hope, Søren Bentzen, Ted Lawrence, **Bo McClatchy**, Chuck Mayo, Dennis Mah

Purpose

- I’m going to discuss re-irradiation in the context of the clinic. In particular I’m going to talk about the problems involved in generating normal tissue constraints for external beam treatment planning.
- Current guidance for treatment planning is not based on quantitative analysis of clinical outcome data.
- Is there any way to remedy that?

Context

- SBRT has made tightly targeted irradiation of metastases feasible in multiple body sites.
- The Comet Trial showed that irradiation of multiple metastases (≤5) improves overall survival, and this is likely to raise the number of re-irradiation treatments going forward.
- Thus, it is more urgent than ever to understand how much additional dose may safely be given after an initial course.

Context

- Constraints for conventional irradiation were generated by QUANTEC* (2010), synthesizing results from published articles.
- QUANTEC noted that, generally speaking, there were three areas that it did not deal with:
  - hypo-fractionation (SBRT)
  - pediatric cases
  - **re-irradiation**

*QUANTEC special issue of the Red Journal , IJROBP: **76S**; 2010

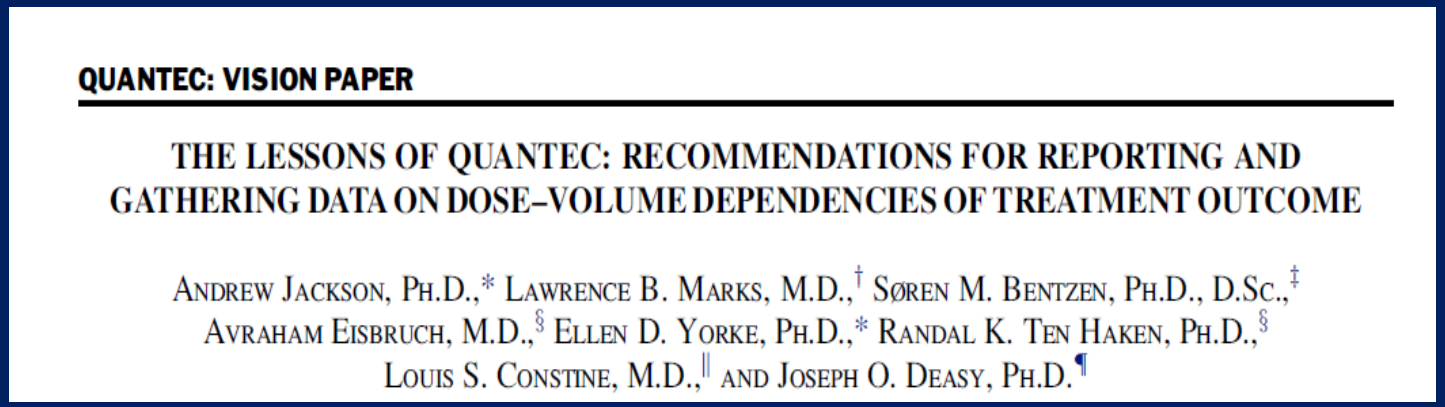
Context

- Since 2010, two efforts have been underway to remedy the first two deficits of QUANTEC. Both synthesizing results of published articles.
- HyTEC: Complications and local control for treatments involving fraction sizes ≥ 5-8 Gy
  - 8 organ and disease specific papers are currently available at the Red Journal & AAPM web sites*; 8 pending.
  - Full HyTEC issue will be finished and published this year.
- PENTEC: Complications of treatments of pediatric cancers.
  - Initial abstracts/talks have been appearing at ASTRO and AAPM over the past two years.
  - First papers will be published on-line at the Red Journal this year. The dedicated PENTEC issue is expected to follow next year.

*https://www.aapm.org/pubs/hytec/

Limitations of Efforts to Synthesize Data from Published Articles

- QUANTEC was chiefly limited by*
  - Poor reporting standards of dose volume data
  - Poor reporting standards of complication endpoints
  - Inconsistent organ definitions



QUANTEC: VISION PAPER

THE LESSONS OF QUANTEC: RECOMMENDATIONS FOR REPORTING AND GATHERING DATA ON DOSE–VOLUME DEPENDENCIES OF TREATMENT OUTCOME

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AVRAHAM EISBRUCH, M.D.,§ ELLEN D. YORKE, PH.D.,* RANDAL K. TEN HAKEN, PH.D.,§
LOUIS S. CONSTINE, M.D.,‖ AND JOSEPH O. DEASY, PH.D.¶

- These limitations apply to all subsequent efforts

*Jackson et al. IJROBP 2010: **76,** S155-160; Deasy et al. IJROBP 2010: **76**, S151-154

Limitations of Efforts to Synthesize Data from Published Articles

- HyTEC had additional limitations:
  - Lack of standardized way to calculate biologically equivalent doses
- PENTEC has yet more limitations:
  - Lack of granular data dealing with patient age/developmental status at treatment time
  - Very long follow up times requiring actuarial modelling methods

Could we generate tolerance doses for re-irradiation by synthesizing published outcome data? (??ReNTEC??)

- To answer this question, we must understand what we are trying to determine when we seek tolerance doses for re-irradiation.
- Crucially: How much residual effect does the initial irradiation have, and how might this fade away as time goes on?
- Clearly we need to know the time between irradiations

Two Kinds of Re-Irradiation

- The classic example of re-irradiation occurs when we directly re-irradiate the site of previous treatment, as may happen after local failure in head and neck patients.
  - Accumulation of dose
  - Creation of a local lesion
- A second kind of re-irradiation occurs when a patient receives a second course to a different part of the same organ, as may happen when irradiating metastases in lung.
  - Accumulation of damaged volumes
  - Inadequate global organ function
- In both cases we need to know the dose to the same pieces of tissue from both courses

What could "ReNTEC" do?

- Reports of outcome of re-irradiation do not contain:
  - the time between irradiations for individual patients.
  - The doses from both courses to the same pieces of tissue.
- Some contain dosimetric analysis of complications based on plan-sums, giving the range of times between irradiations.
  - There are not many such reports.

What could "ReNTEC" do?

Table 2 Reirradiation spine SBRT literature that met the inclusion criteria for this review

Paper	No. of patients	Dose reporting structure	Median prescribed dose (range) / number of fractions (range)	Median prescribed dose of prior RT (range) / number of fractions (range)
Chang 2012[45,*]	54	Thecal sac	Mean $EQD2_2$ 51.1 / NS	NS
Gwak 2005[44,*]	3	Cord	33 (21-35) Gy / 3	50.4 Gy (30-50.4) Gy/ 28 (10-28)
Sahgal 2009[55,*]	25	Thecal sac	24 (8-30) Gy / 3 (1-5)	36 Gy / 14
Sahgal 2012[43,*,‡]	14	Thecal sac	24 (10-30) Gy / 3 (1-5)	$EQD2_2$ = 39.8 (29.0-64.5)
Thibault 2015[35,§]	16	Cord PRV (+1.5 mm)	30 (20-35) Gy / 4 (2-5)	SBRT 24 (20-35)/ 2 (1-5)
Thibault 2015[35,§]	24	Cord PRV (+1.5 mm)	30 (24-35) Gy / 4 (2-5)	cEBRT: 22.5 (20-30); SBRT 24 (20-30)/ 2 (2-5)

Median spinal cord D_{max}, Gy	Median spinal cord D_{max} $EQD2_2$ for SBRT, Gy	Median cumulative spinal cord D_{max} $EQD2_2$ of all RT, Gy	Median follow-up, mo	No. cases of RM
NS	Mean 46.19 ± 35.21	Mean 83.37	Mean 21.8	0
24.1 (19.9-32.9)	60.45†	NS	24	1
12.8 (5.4-27)	18 (10-49)	41.5†	7	0
NS	12.5 (1.9-58.7)	52.4 (39.1-111.2)	12	0
NS	21.9 (12.4-25.0)	51.3	6.8	0
NS	21.9 (17.5-26.7)	73.9	6.8	0

Abbreviations: D_{max} = maximum dose; cEBRT = conventional external beam radiation therapy; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); NS = not specified; PRV = planning organ-at-risk volume; RM = radiation myelopathy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* The results from only the patients who met inclusion criteria are reported in this row (instead of the full cohort of patients from the original study).

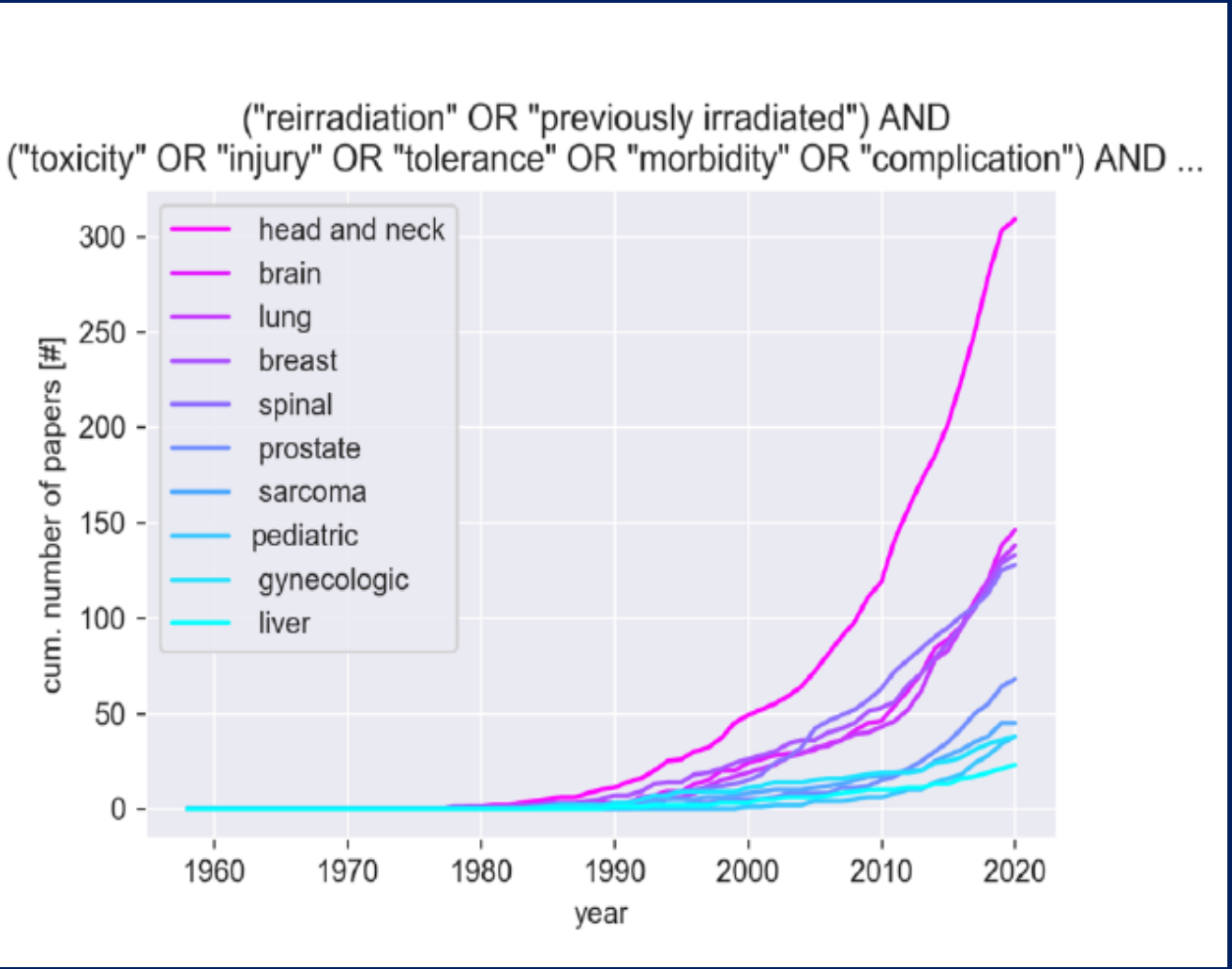
† Cumulative $EQD2_2$ estimated using summary data presented in paper.

‡ The data presented are the controls, not the cases of radiation myelopathy.

§ The same study was broken into 2 cohorts and reported on different rows.

- From Sahgal et al. (HyTEC Spinal NTCP paper)
  - https://www.redjournal.org/article/S0360-3016(19)33862-3/pdf

Literature search – Bo (David) McClatchy*



*Slide from Bo McClatchy, AAPM SCAMP mentee

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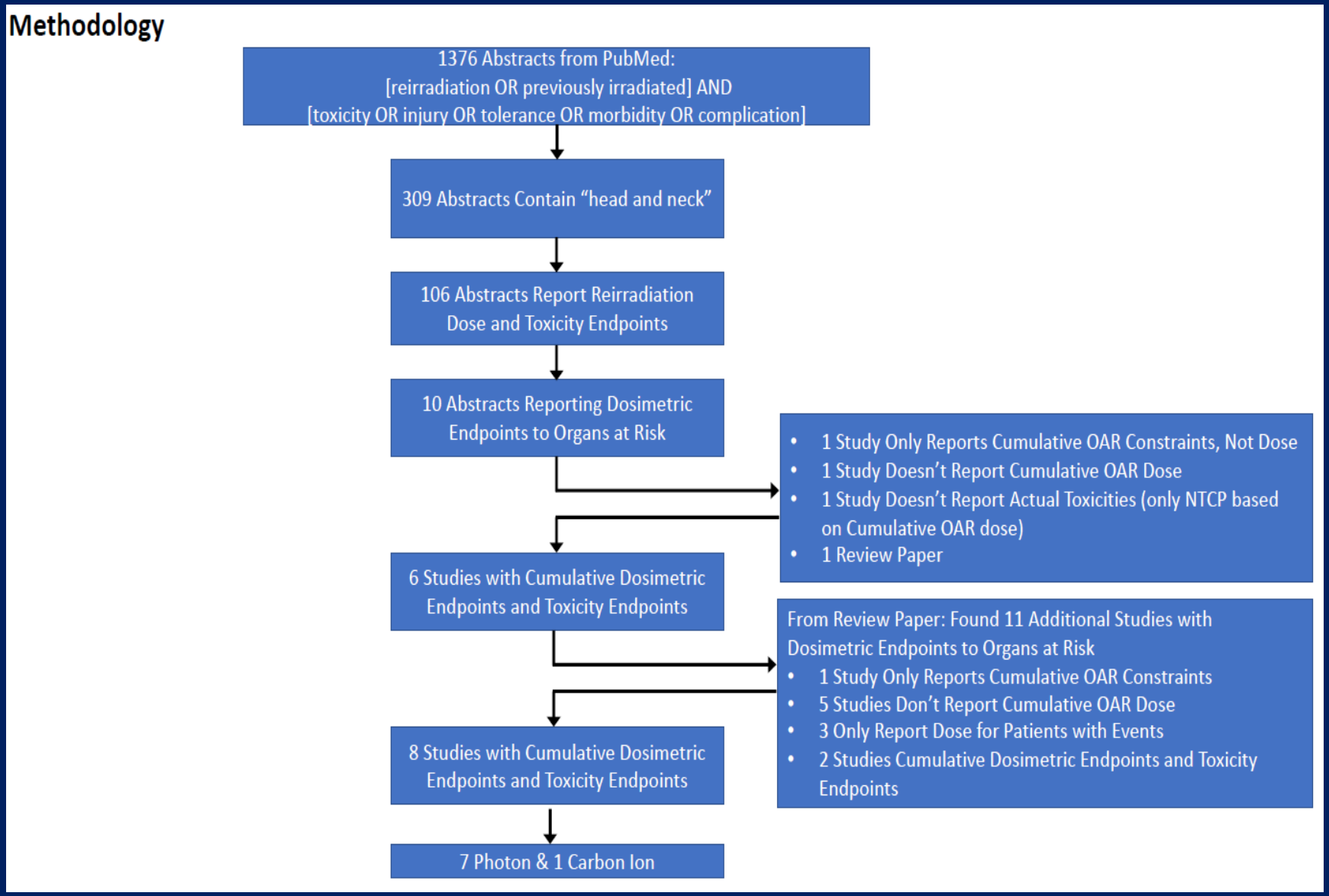

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Literature search – Bo (David) McClatchy*

Number of Patients	Surgey	Systemic Therapy	Median Time Between Radiation	OAR	Endpoint	Cumulative Dosimetric Values to OAR EQD2	NTCP / Rate
115 pts	10 pts	0 pts	3.4 yrs (rng 0.3-13.3 yrs)	Optic Chiasm, Optic Nerve	Late G3+ Optic Nerve Disorder	Median Dmax 51.4Gy, 63.3Gy	5.7%
				Brainstem, Spinal Cord	Late G3+ CNS necrosis	Median Dmax 56.8Gy 28.8 Gy	5.7 %
43 pts	16 pts	16 pts	24 mo (rng 3-144)	Brachial Plexus	1 yr Freedom From Brachial Plexopathy	Dmax<95 Gy	86%
						Dmax>95Gy	67%
						Dmax<95 Gy & ElapsedTime>2yrs	91%
						Dmax>95 Gy & ElapsedTime>2yrs OR Dmax<95 Gy & ElapsedTime<2yrs	81%
						Dmax>95 Gy & ElapsedTime<2yrs	53%
137 pts	108 pts	7 pts	23 mo (rng 6-296 mo)	Bone	G4+ Osteonecrosis	Median Dmax 114 Gy	5.8%
38 pts	0 pts	35 pts	4.2 yrs (rng 1.0–16.3 yrs)	Temporal Lobe	G3+ temporal lobe necrosis (TLN)	Range D1cc 133.4-249.5 Gy	10%
						D1cc<150 Gy	0%
18 pts	0 pts	18 pts	11 mo (rng 3-39)	Oral Mucosa	G2-3 Mucositis	D50 55.6 Gy	25%
						D50 86.5 Gy	30%
						D50 105.5 Gy	33%
						D50 190.8 Gy	50%
50 pts (21 pts with dosimetry information)	24 pts	41 pts	28 mo (rng 6-356 mo)	Carotid Arteries	Carotid Blowout	Median D0.1cc 106 Gy	5%
						D0.1cc < 120Gy	4.6%@6mo, 5.9%@1yr
						D0.1cc > 120Gy	13.3%@6mo, 25% @1yr
				Esophagus	Late G3+ Esophageal Stricture	n.r, but median DVH Reported	14%
				Pharyngeal Constrictors	Late G3+ Dysphagia	Median Dmean 73 Gy	10%
				Spinal Cord	Spinal Myelopathy	Median D0.1cc 50 Gy	0%
38 pts	13 pts	19 pts	43 mo	Spinal Cord, Brainstem	Spinal Myelopathy	Median Dmax 53.4 Gy, 62.7 Gy	0%
				L&R Parotids	G1-3 Xerostomia	Mean Dmean <45 Gy	26%
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Can Major Institutions Go It Alone?

- Can we deal with the heterogeneity of circumstances leading to re-irradiation?
  - Re-irradiation patients have varied clinical histories (surgery, systemic therapy)
  - Sites of re-irradiation vary
  - Complication numbers are usually low and scattered among different endpoint
  - Large range of re-irradiation times
    - This is an advantage given enough patients

Proposal – A Registry

- Accumulate patient data for particular complications from across the major institutions
- Higher numbers let us cover the major sources of heterogeneity in the patient data
  - Variety of times between irradiations
  - Variety of re-irradiation locations
  - Variety of additional treatments between irradiations
    - Surgery, Chemo/immunotherapy

Conditions of entry to the re-irradiation registry

- The following data items are required:
  - Planning scans for initial and final treatments
  - Treatment plans (dose distributions, prescription doses and number of fractions)
  - Time between treatments
  - Relevant clinical variables
  - Commitment to provide ongoing standardized follow up concerning the relevant involved normal tissues

Data Analysis (preliminaries)

- For each patient:
  - Deformably Register the initial to the final scan
  - Determine the dose to the same voxels in the final scan from both the initial and final irradiation:
    - (useful to create a bivariate LQ corrected DVH: $v(d_i,d_f)$)
  - Gather time between irradiations
  - Gather possibly relevant clinical co-variates
  - Gather outcome data
    - Endpoint diagnosis and time, or follow up time since second irradiation

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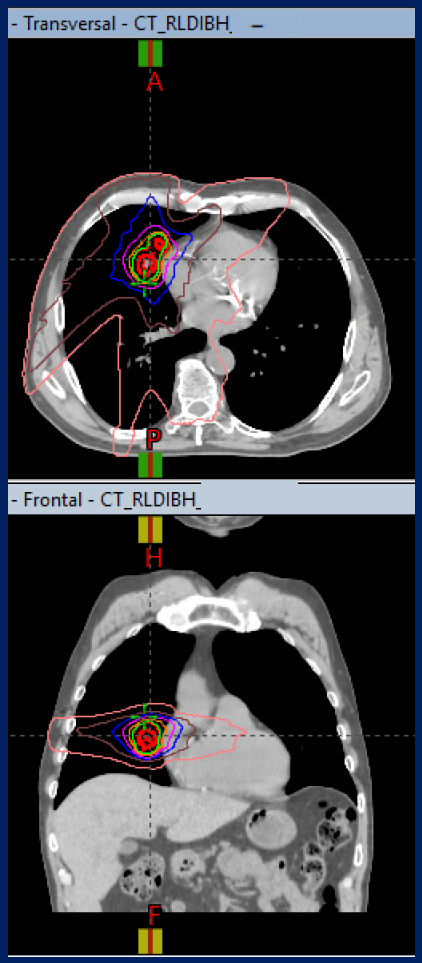
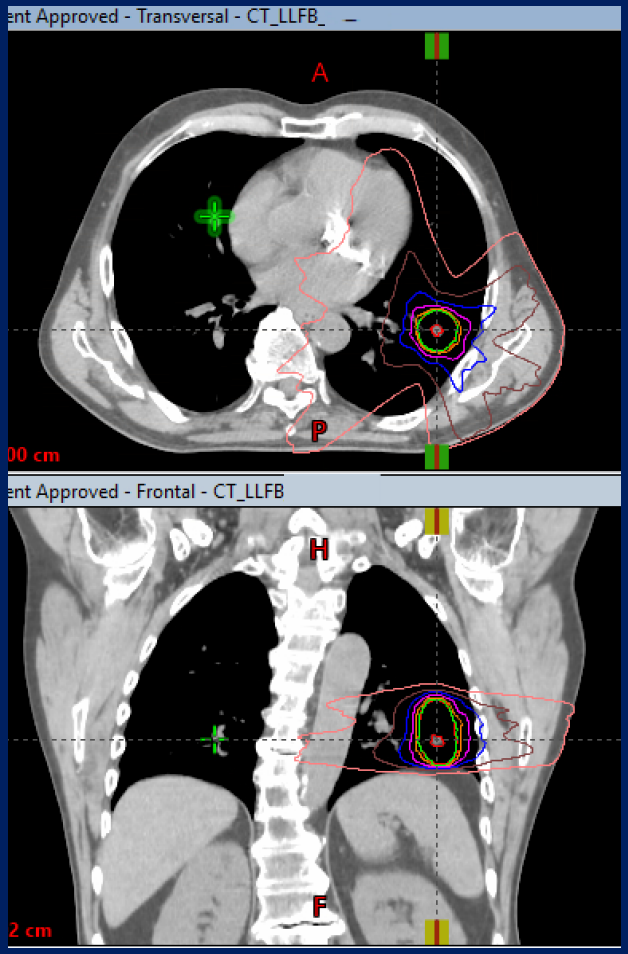
Registration of Initial and Final Scans

- During the time between the scans, the anatomy may have changed
  - tumor shrinkage
  - new tumor grows
  - normal tissue reactions to the initial treatment
- Possible differences in scanning protocols
  - DIBH vs free breathing

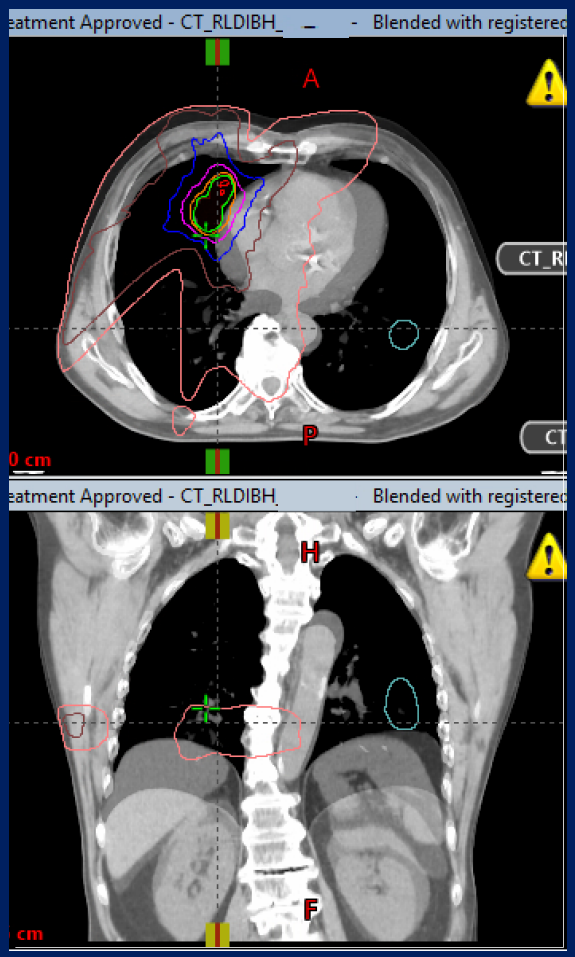
Mixed Scanning Protocols



First scan -FB



Second Scan DIBH



Rigid registration (spine)

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    - useful to create a bivariate LQ corrected DVH: $v(d_i,d_f)$
  - Gather time between irradiations
  - Gather possibly relevant clinical co-variates
  - Gather outcome data
    - Endpoint diagnosis and time, or follow up time since second irradiation

Data Analysis (modeling)

- Create a candidate sigmoidal discount function of the time between irradiations with associated parameters controlling its form
  - $f(t, T_{50}, \gamma_{50}, f_{\infty})$
  - γ_{50}, time scale over which discount occurs
  - T_{50}, time when 50% of eventual discount occurs
  - f_{∞}, possible non-zero plateaux value of discount factor

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- Fit outcome model and discount function to outcome and dosimetric data
  - Create candidate plan-sum DVH for each patient using the candidate discount factor f(t) for each patient
    - Dose for volume $v(d_i, d_f)$ becomes $f(t)*d_i + d_f$
  - Calculate model likelihood
    - Mixture model to account for follow-up time
  - Maximum likelihood method to find best fit model and discount factor

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If we manage to achieve all that, we will have reached our goal:

- Tolerance doses as a function of the time between re-irradiations