ACCURAY

IMPROVING OUTCOMES THROUGH THE USE OF LIVE TUMOR TRACKING WITH SYNCHRONY®

JIMM GRIMM, PHD, DABR, FAAPM

LEAD CYBERKNIFE® PHYSICIST

GEISINGER MEDICAL CENTER, DANVILLE, PENNSYLVANIA

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100

"Make it the Best"

Abigail Geisinger
1827-1921

Improving Outcomes through the use of Live Tumor Tracking with Synchrony®

ASTRO 2022
Jimm Grimm, PhD, DABR, FAAPM

Accuray Disclaimers and Disclosure

Disclosure

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An honorarium is provided by Accuray for this presentation.

Medical Advice Disclaimer

Accuray Incorporated as a medical device manufacturer cannot and does not recommend specific treatment approaches. Individual results may vary.

Safety Statement

Most side effects of radiotherapy, including radiotherapy delivered with Accuray systems, are mild and temporary, often involving fatigue, nausea, and skin irritation. Side effects can be severe, however, leading to pain, alterations in normal body functions (for example, urinary or salivary function), deterioration of quality of life, permanent injury and even death. Side effects can occur during or shortly after radiation treatment or in the months and years following radiation. The nature and severity of side effects depend on many factors, including the size and location of the treated tumor, the treatment technique (for example, the radiation dose), the patient's general medical condition, to name a few. For more details about the side effects of your radiation therapy, and if treatment with an Accuray product is right for you, ask your doctor.

Conflicts of Interest

Caring

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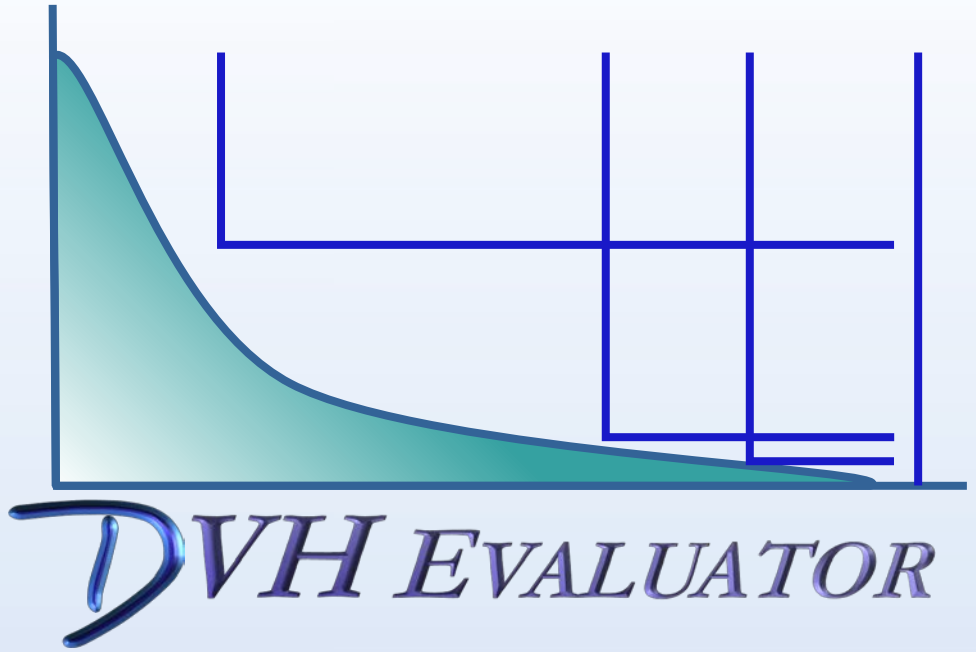
Dr. Grimm designed and holds intellectual property rights to the

DVH Evaluator software tool

(www.DiversiLabs.com) which is an FDA-cleared product in commercial use, and which has been used for this analysis

Funding from Accuray, NovoCure



FDA 510k Number K092928 Rx Only US Patents 9,019,307 & 9,192,782

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Soli Deo Gloria

Radiation has a Dose Response

- Edith Quimby
- 1928, RSNA
- Erythema dose

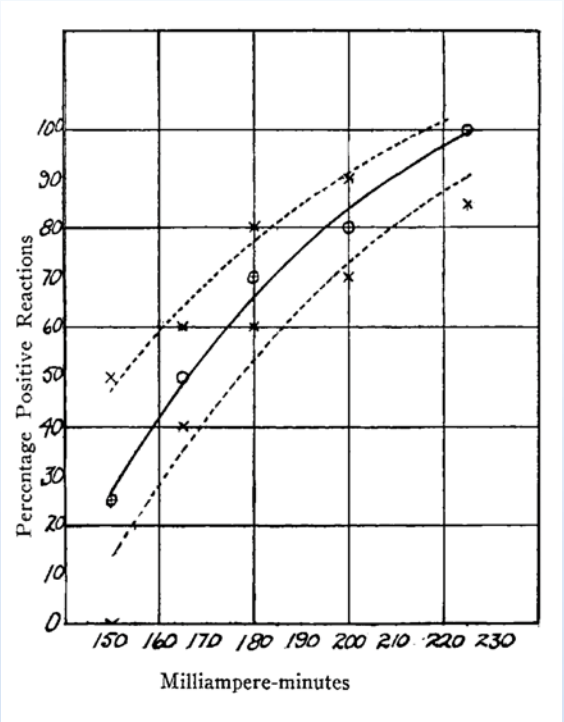
- The first electronic computer wasn't invented until a decade or so later!

- Graph paper!

- Confidence intervals via "add one" and "omit one"

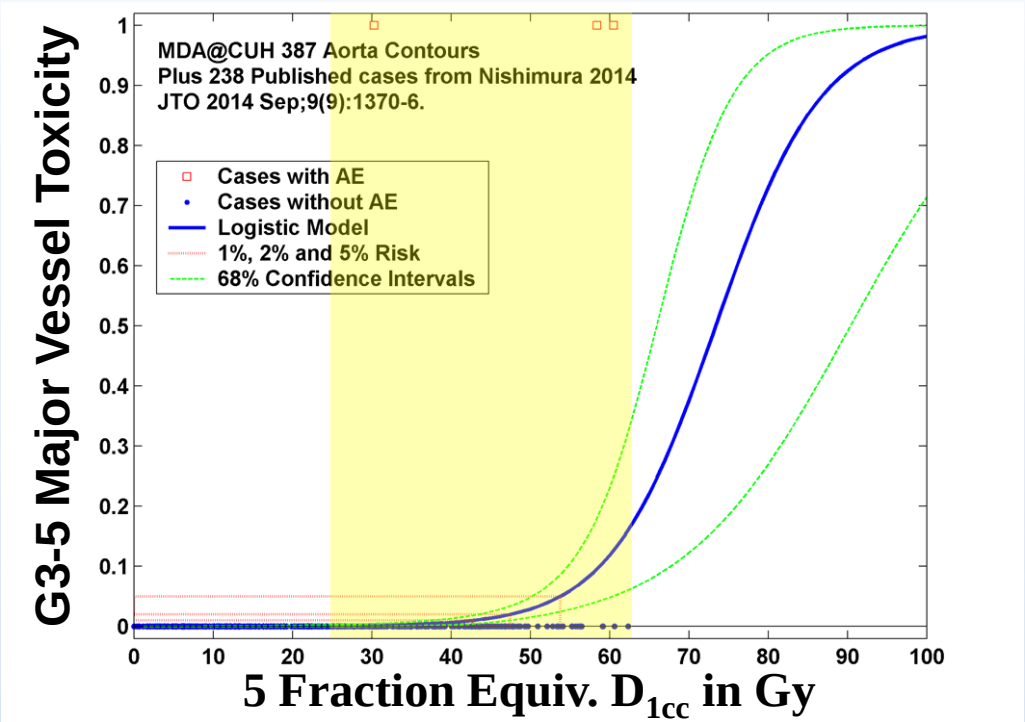
How it Started:

Quimby 1928, graph paper



How it's Going:

Aorta and Major Vessel data from 625 Cases, Xue 2016



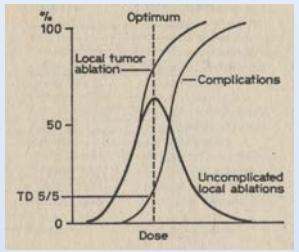
For 80% risk level, only need about a dozen cases…

For 1% risk level, need about 1000!

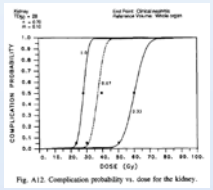
Rubin → Emami → QUANTEC → HyTEC → ____?____

TCP: Tumor control probability
NTCP: Normal tissue complication probability

Our Next Project



Rubin



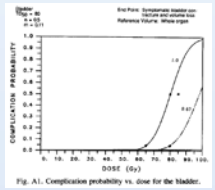
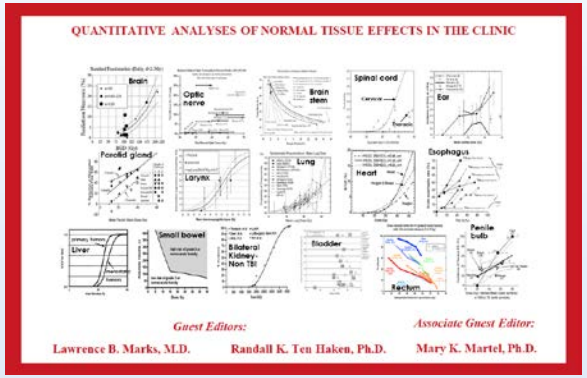


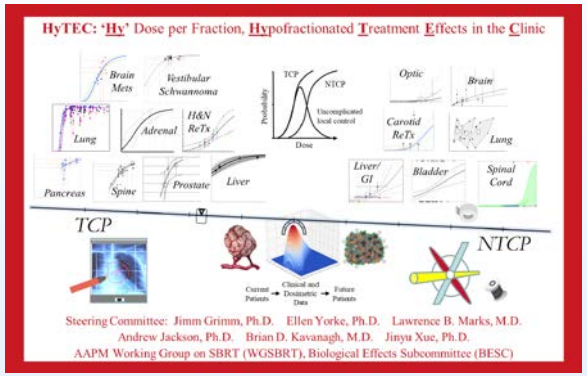
Table 1. Normal tissue tolerance to therapeutic irradiation

Organ	TD 5/5 Volume			TD 50/5 Volume			Selected endpoint
	1/1	2/3	3/3	1/1	2/3	3/3	
Kidney I	5000	3000*	2300	—	4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic

Emami

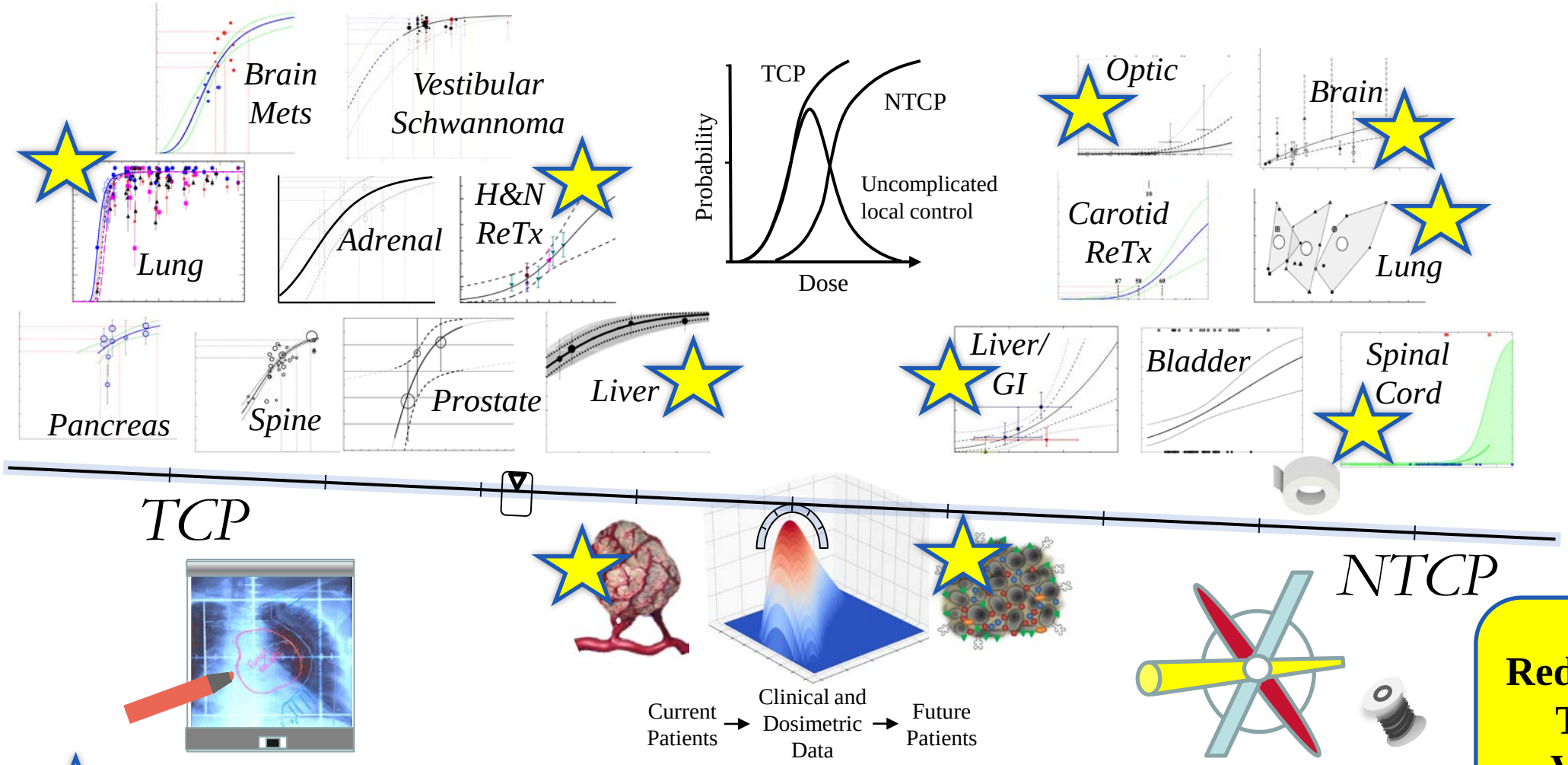


QUANTEC



HyTEC

HyTEC: 'Hy' Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



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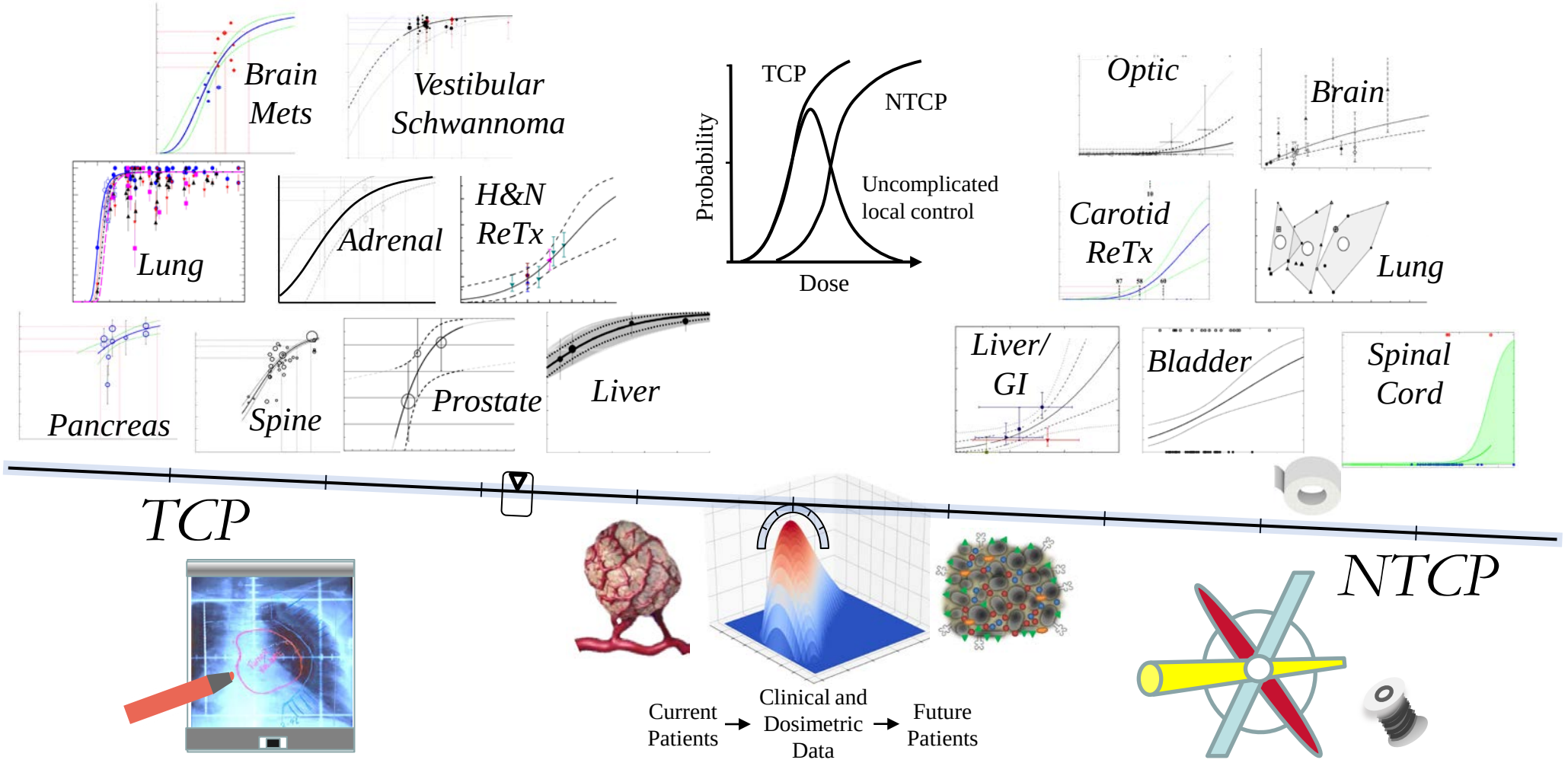
Andrew Jackson, Ph.D. Brian D. Kavanagh, M.D. Jinyu Xue, Ph.D.
AAPM Working Group on SBRT (WGSBRT), Biological Effects Subcommittee (BESC)

Red Journal Top 20 Viewed Papers Yom 2022

HyTEC: 'Hy' Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



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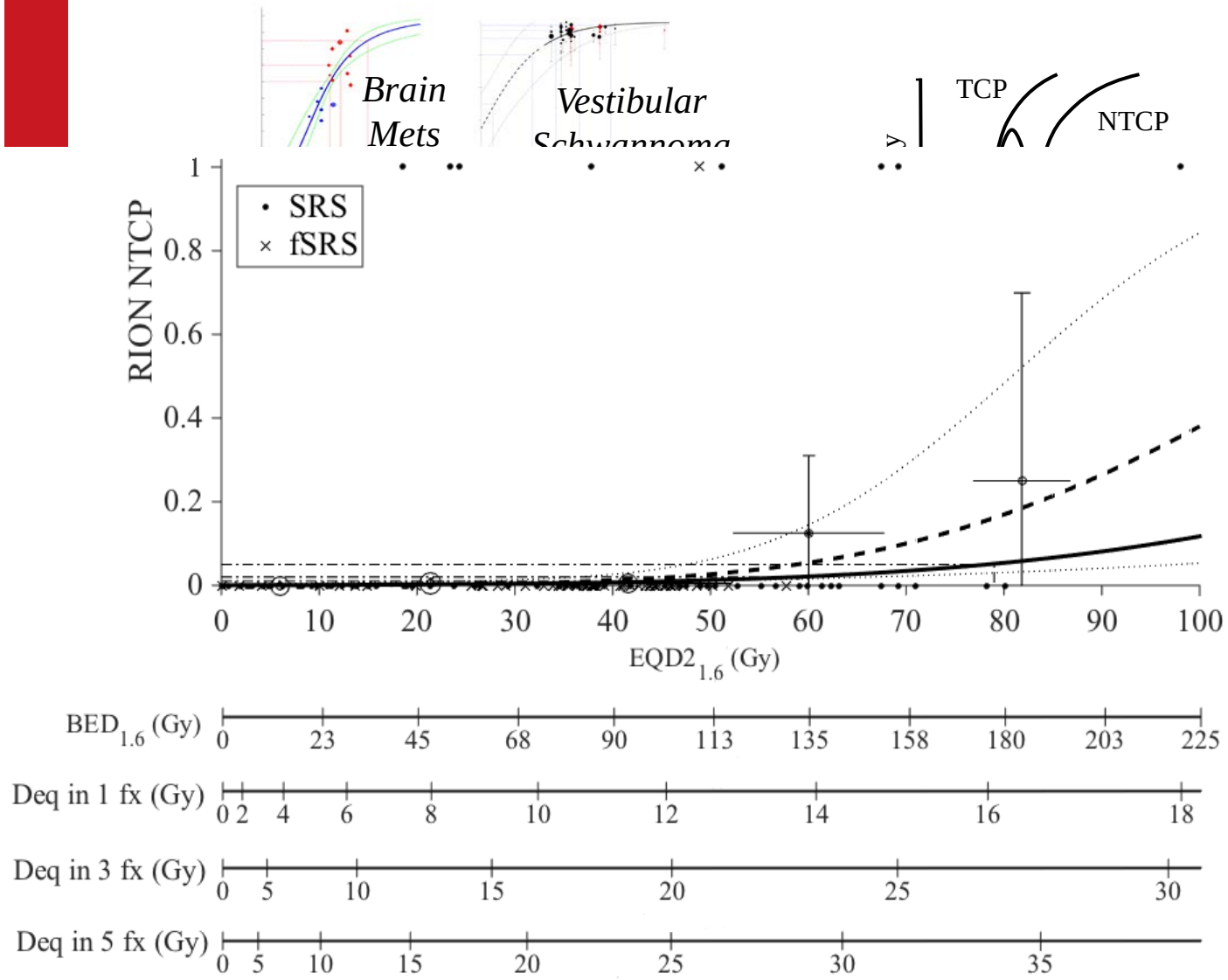
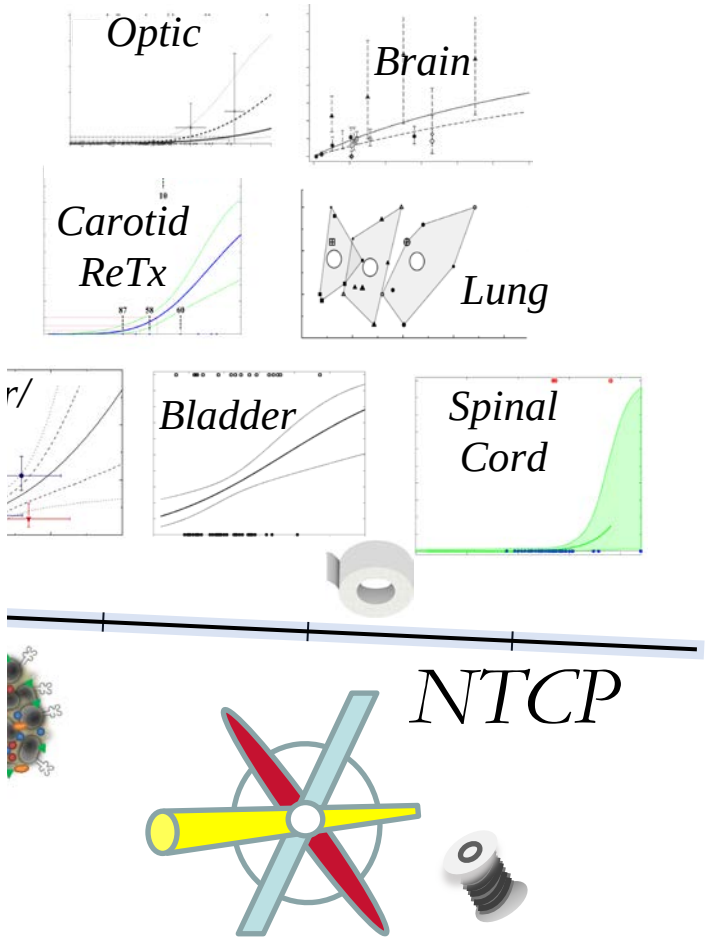
HyTEC: '<u>Hy</u>' Dose per Fraction, <u>Hy</u>pofractionated <u>T</u>reatment <u>E</u>ffects in the <u>C</u>linic





). Lawrence B. Marks, M.D.

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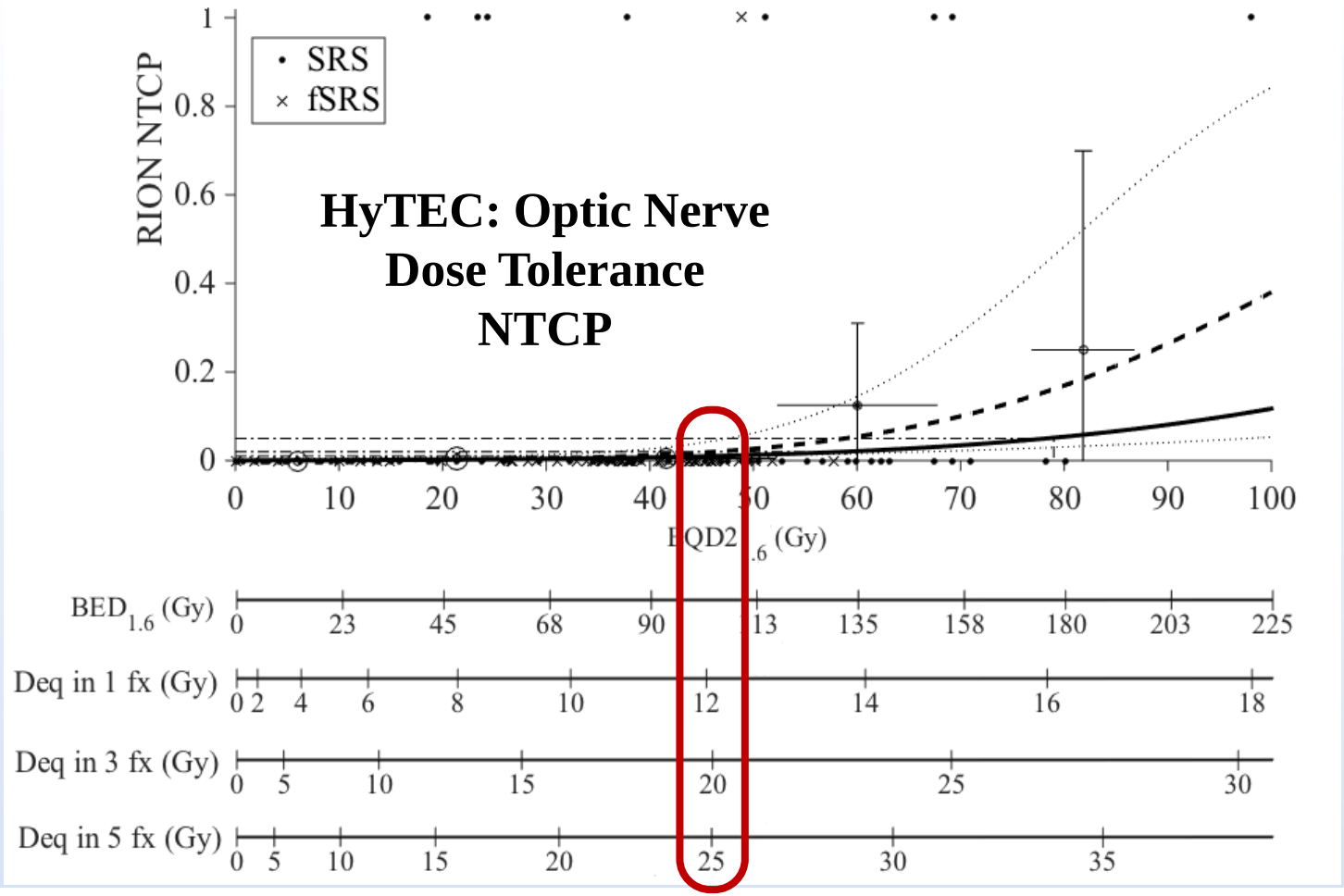
AAPM Working Group on SBRT (WGSBRT), Biological Effects Subcommittee (BESC)

Optic NTCP: Single- and Multi-Fraction Stereotactic Radiosurgery Dose Tolerances of the Optic Pathways

Milano MT, Grimm J, Soltys SG, Yorke E, Moiseenko V, Tomé WA, Sahgal A, Xue J, Ma L, Solberg TD, Kirkpatrick JP, Constine LS, Flickinger JC, Marks LB, El Naqa I.



- Pooled data from 34 studies
- 1578 patients
- Linear Quadratic (LQ) with $\alpha/\beta=1.6$ Gy
- Dose tolerance for Grade 3 or higher radiation induced optic neuropathy:

Separate Model SRS Only

Number of fractions	Dose (Gy) or dose-volume parameters	Rate (%)*
1	D_{max} < 10-12 Gy	< 1%
3	D_{max} < 20 Gy	< 1%
5	D_{max} < 25 Gy	< 1%

*** Read the fine print in the HyTEC papers:** Although the source data may have included some patients who had undergone reirradiation (refer to the individual reports for specifics), unless stated otherwise, the NTCP risks from the compiled data are meant to apply for patients who received no prior radiotherapy. Acceptable risk in any given patient should reflect the clinical decision making of the physician and consent of the patient. Providers are strongly advised to use the individual HyTEC articles to assess the full context and applicability of these values for each scenario. Because the overall survival duration is limited in many patients who receive SRS/SBRT, the long-term NTCP may not be accurately represented by the reported data. There are several other reference documents that address these and other sites (e.g., Seminars in Radiation Oncology 37,38).

Table 2 Summary of NTCP[6] estimates after SRS/SBRT from the HyTEC reports*

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)*	Notes
Brain; for metastasis	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 5$ cm^3	10%	From Table 3 and Figs. 4 and 5 in paper.
		1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	15%	Consistent with QUANTEC.
		1	Symptomatic necrosis	$V_{12Gy} \leq 15$ cm^3	20%	Prior whole brain RT appears to not markedly increase risks in most reports (with the exception of brain stem).† However, repeat SRS/fSRS to the same area has been associated with markedly increased risks.
		3	Edema or necrosis	$V_{20Gy} \leq 20$ cm^3	$\leq 10\%$	
		3	Edema or necrosis	$V_{20Gy} \leq 30$ cm^3	$\leq 20\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 20$ cm^3	$\leq 10\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 30$ cm^3	$\leq 20\%$	
Brain; SRS for arteriovenous malformation	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	$\leq 10\%$	From Figure 2 in paper
Optic pathway	Optic nerves and chiasm	1	Neuropathy	$D_{max} < 10$-12 Gy	$< 1\%$	From Table 3 in paper.
		3	Neuropathy	$D_{max} < 20$ Gy	$< 1\%$	Consistent with QUANTEC.
		5	Neuropathy	$D_{max} < 25$ Gy	$< 1\%$	Prior RT exposure of the

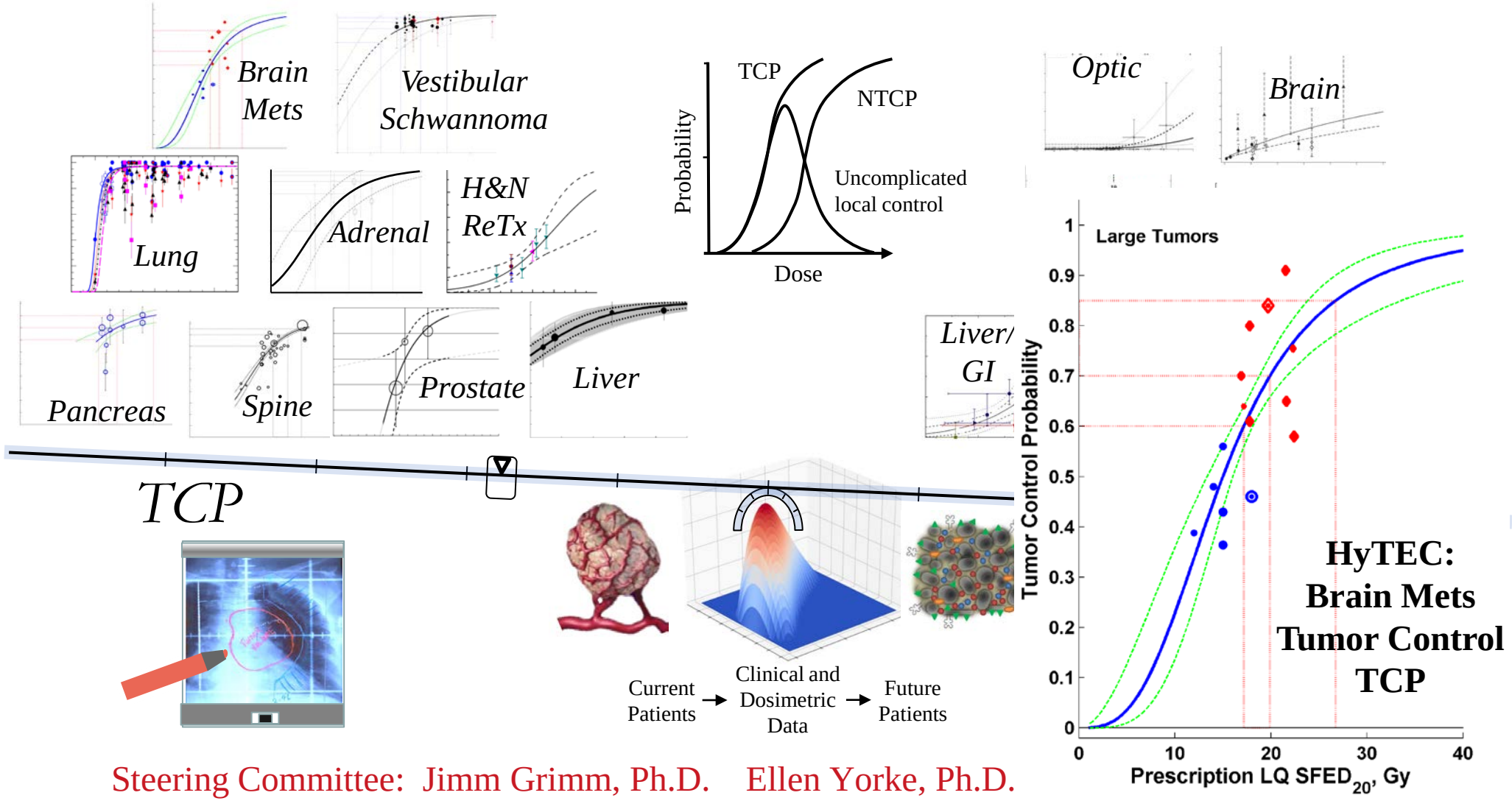
HyTEC Summary Table: NTCP

Table 3 Summary of TCP estimates from the HyTEC reports*

Tumor site/type	Volume segmented, margin	Number of fractions	Endpoint†	Dose (Gy), or dose-volume parameters‡	Rate (%)†	Notes
Brain metastases	GTV + 0-2 mm margin§	1	2-year local control, by lesion size	≤2 cm, 18-24 Gy	80%-95%	1-year local control ≈ ≥85%-90%
		1		2-3 cm, 18 Gy	66%	1-year local control ≈ 75%
		1		>3 cm, 15 Gy	47%	1-year local control ≈ 70%
		3		2-3 cm, 24-30 Gy	65%-84%	1-year local control ≈ 80%
		3		>3 cm, 21-27 Gy	53%-69%	1-year local control ≈ 75%
		5		2-3 cm, 30-35 Gy	75%-85%	1-year local control ≈ 80%
		5		>3 cm, 25-30 Gy	59%-69%	1-year local control ≈ 75%
Vestibular Schwannoma	GTV+ 0-2 mm margin‖	1	3-5 year local control	≥12 Gy	≥91%	Variable PTV margins used. Most available data are with a single fraction.
		3		18 Gy	≥91%	
		5		25 Gy	≥91%	
Head & neck; retreatment	GTV + 0-6 mm margin	5	2-year local control	45 Gy	50%	Majority of newer studies used 2-6 mm margin
Lung; T1-2 lesions¶	ITV or IGTV + 3-8 mm	3	1-5 year local control	33 Gy	<50%	Based on minimal data
		3	1-5 year local control	45-54 Gy	≥75%	In most studies
		3	1-5 year local control	≥60 Gy	≥80%-85%	In most studies
		4	1-5 year local control	42-48 Gy	≥70%	In most studies
		4	1-5 year local	>52 Gy	≥80%-85%	In most studies

HyTEC Summary Table: TCP

HyTEC: 'Hy' Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



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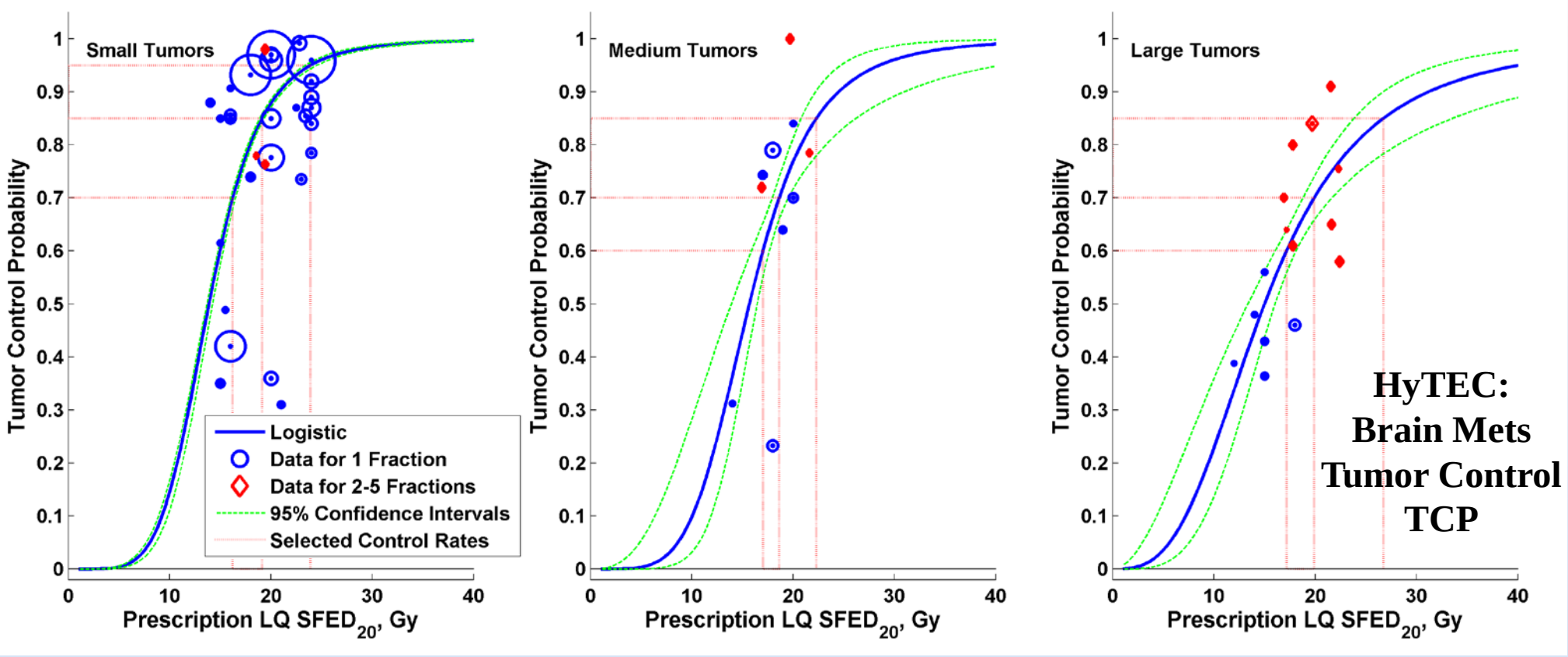
Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Redmond KJ, Gui C, Benedict S, Milano MT, Grimm J, Vargo JA, Soltys SG, Yorke E, Jackson A, El Naqa I, Marks LB, Xue J, Heron DE, Kleinberg LR.



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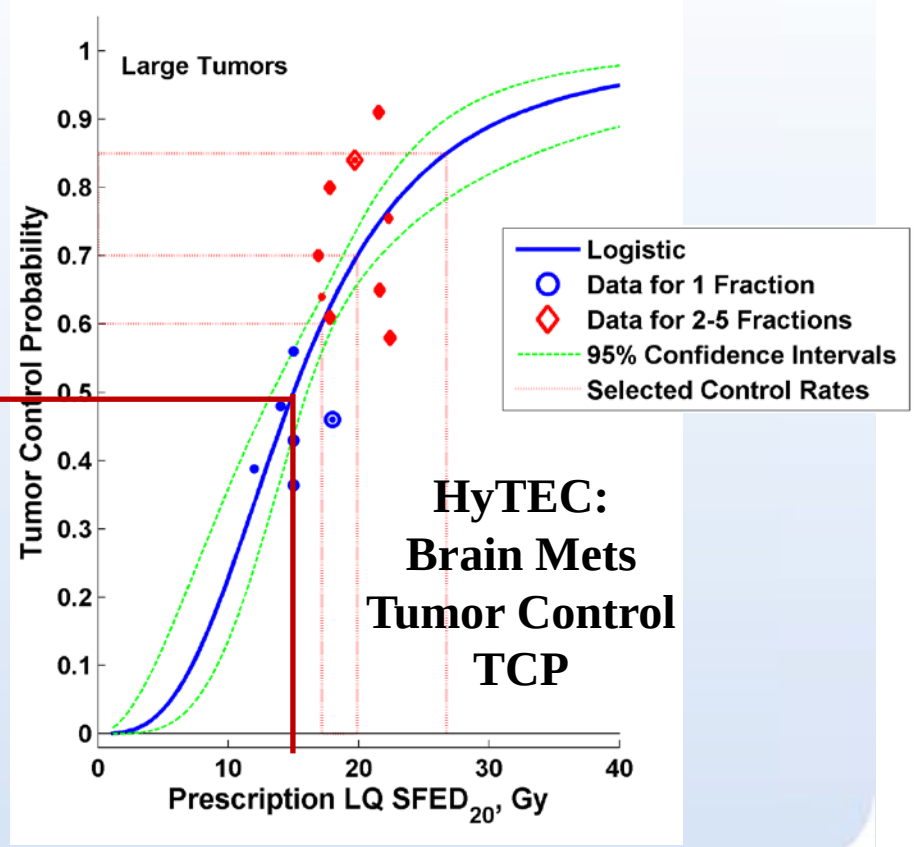
- Pooled data from the 56 of 2951 studies with data
- Linear Quadratic (LQ) with α/β=20 Gy
- 2-year local control by lesion size:

Number of fractions	Dose (Gy), or dose-volume parameters‡	Rate (%)†
1	≤2 cm, 18-24 Gy	80%-95%
1	2-3 cm, 18 Gy	66%
1	>3 cm, 15 Gy	47%
3	2-3 cm, 24-30 Gy	65%-84%
3	>3 cm, 21-27 Gy	53%-69%
5	2-3 cm, 30-35 Gy	75%-85%
5	>3 cm, 25-30 Gy	59%-69%

15Gy/1fx



†‡ **Read the fine print in the HyTEC papers:** † Some reports estimate local control via an actuarial method. Care is needed when interpreting actuarial data in the setting of metastatic cancer. Often, the local control is estimated by censoring patients at the time of death, and the accuracy of actuarial techniques requires that censoring events should be independent of the endpoint under consideration. Because the pace of disease beyond the treated site (that can cause the censoring event of death) and the pace of regrowth of treated site (that obviously impacts local recurrence) are likely related, actuarial estimates may not be accurate and may overstate the local control. (Gelman 1990). Similarly, for many tumor sites, local recurrence is difficult to establish with certainty by noninvasive imaging methods, and there are other statistical issues (e.g., a failure to consistently assess for local failure in patients with systemic disease, and favorable patient selection for both retrospective analyses and prospective studies) that collectively may tend to overestimate the true local control rates across an entire population.

‡ BED, biological effective dose, calculated per linear quadratic model = total dose * (1+(dose per fraction) / (α/β))

Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

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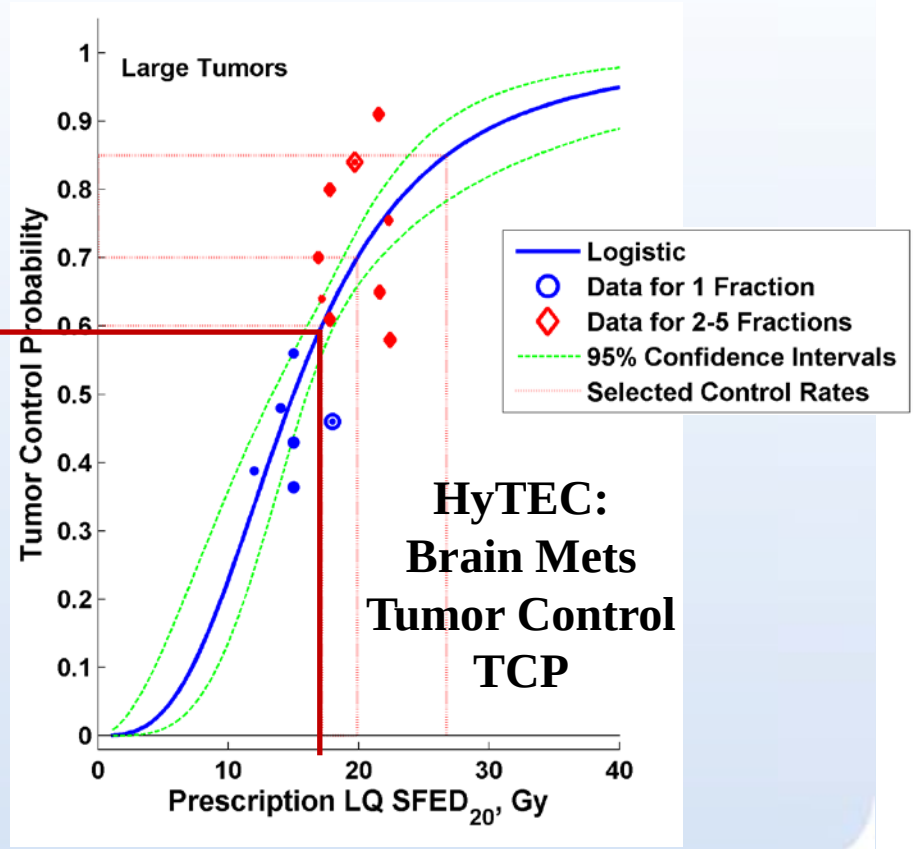
5	2-3 cm, 30-35 Gy	75%-85%
5	>3 cm, 25-30 Gy	59%-69%

25Gy/5fx ~ 17Gy/1fx



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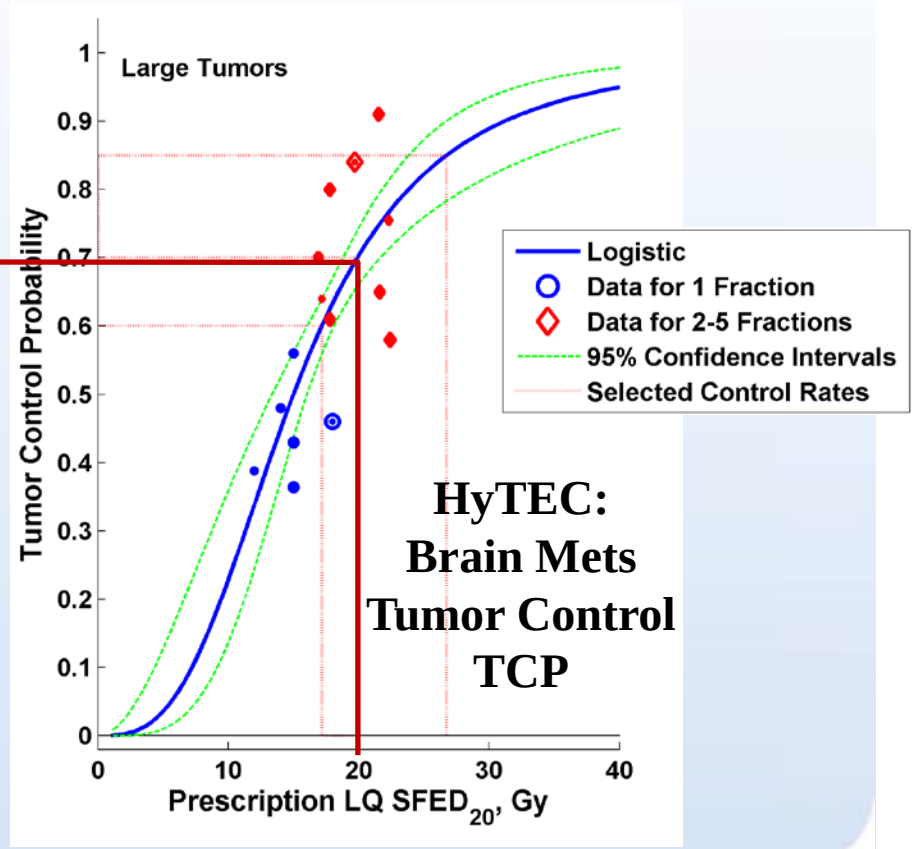
5	2-3 cm, 30-35 Gy	75%-85%
5	>3 cm, 25-30 Gy	59%-69%

27Gy/3fx ~ 20Gy/1fx
30Gy/5fx ~ 20Gy/1fx



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Does targeting accuracy make a difference?

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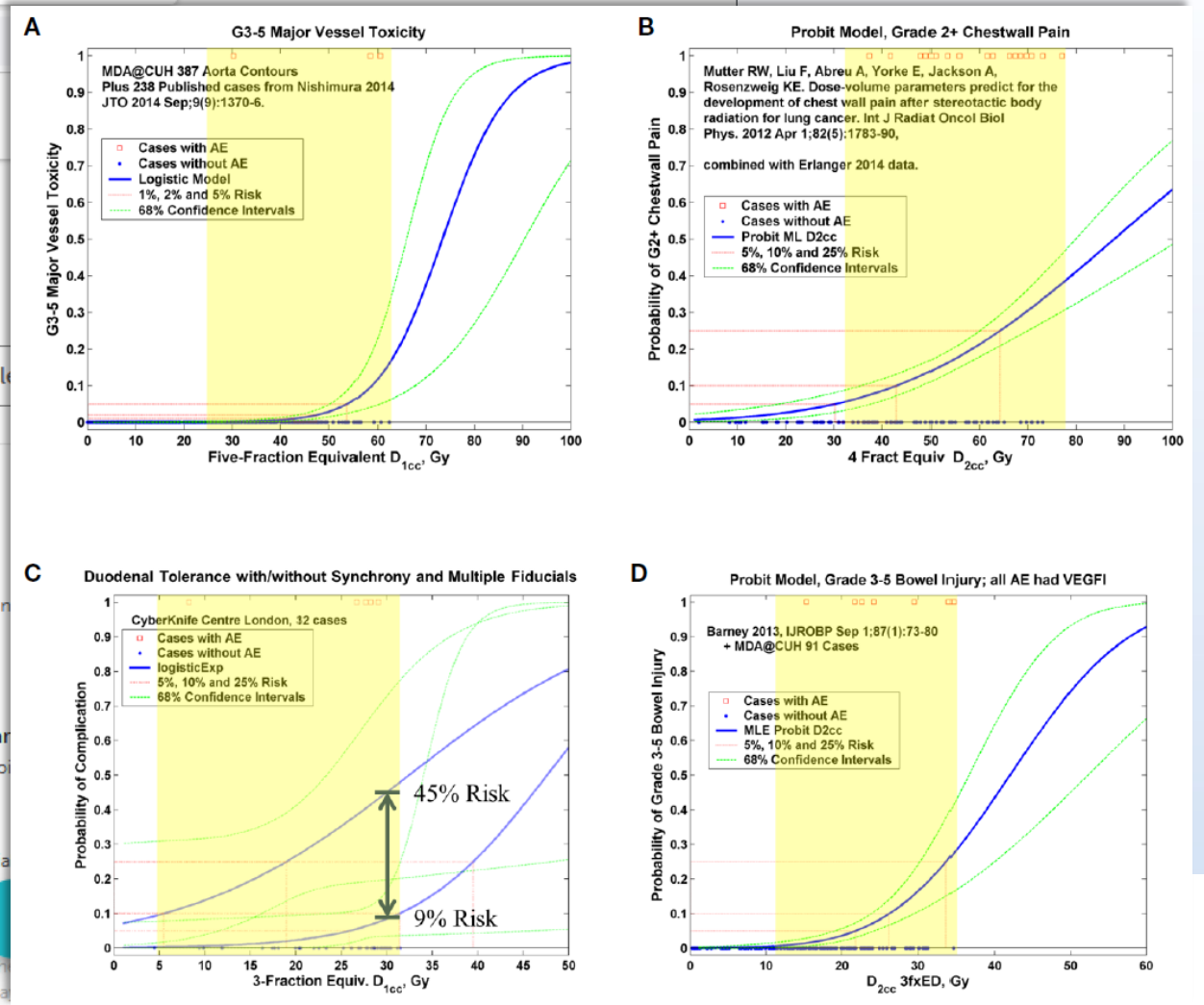

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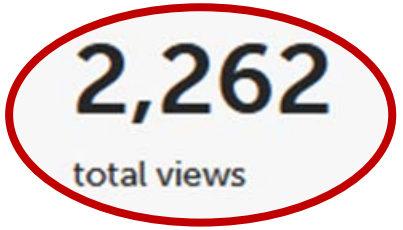


10 Times Lower Risk

	Total number of patients in dose range		Grade 3 or higher complications		
	CyberKnife® with Synchrony®	Linac or no Synchrony	CyberKnife with Synchrony	Linac or no Synchrony	p-value
Aorta/Major Vessels D1cc	111	133	0	3	0.253
Chestwall D2cc	25	114	0	19	0.024
Duodenum D1cc	32	11	2	3	0.097
Small Bowel D2cc	47	65	0	7	0.021
Total	215	323	2	32	

1% **10%** **$p < 0.0002$**

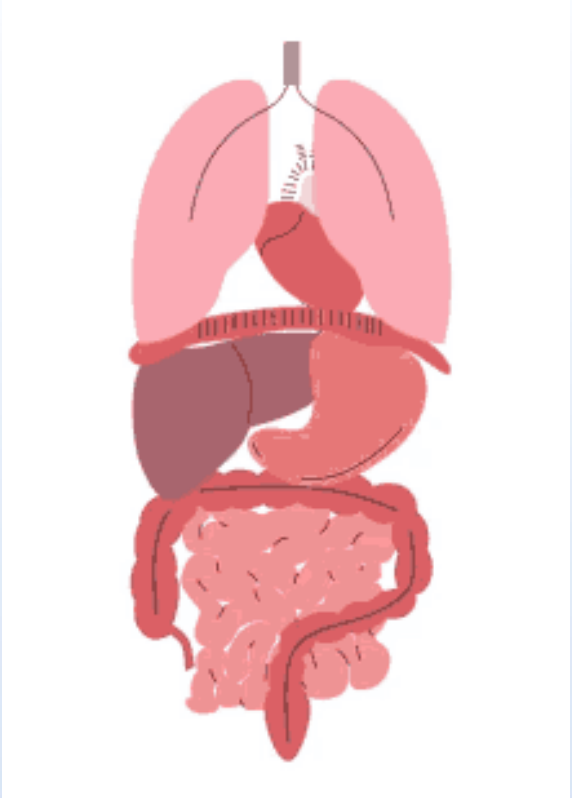
because Submillimeter End-to-End Tracking

From HyTEC to Personalized, Jimm Grimm, PhD

Frontiers in Oncology, Feb 2021, PMID: 33634020

Geisinger

Clinical Challenge
Targets move - Life is always in motion



Methods of correcting for breathing, circulation, and digestion

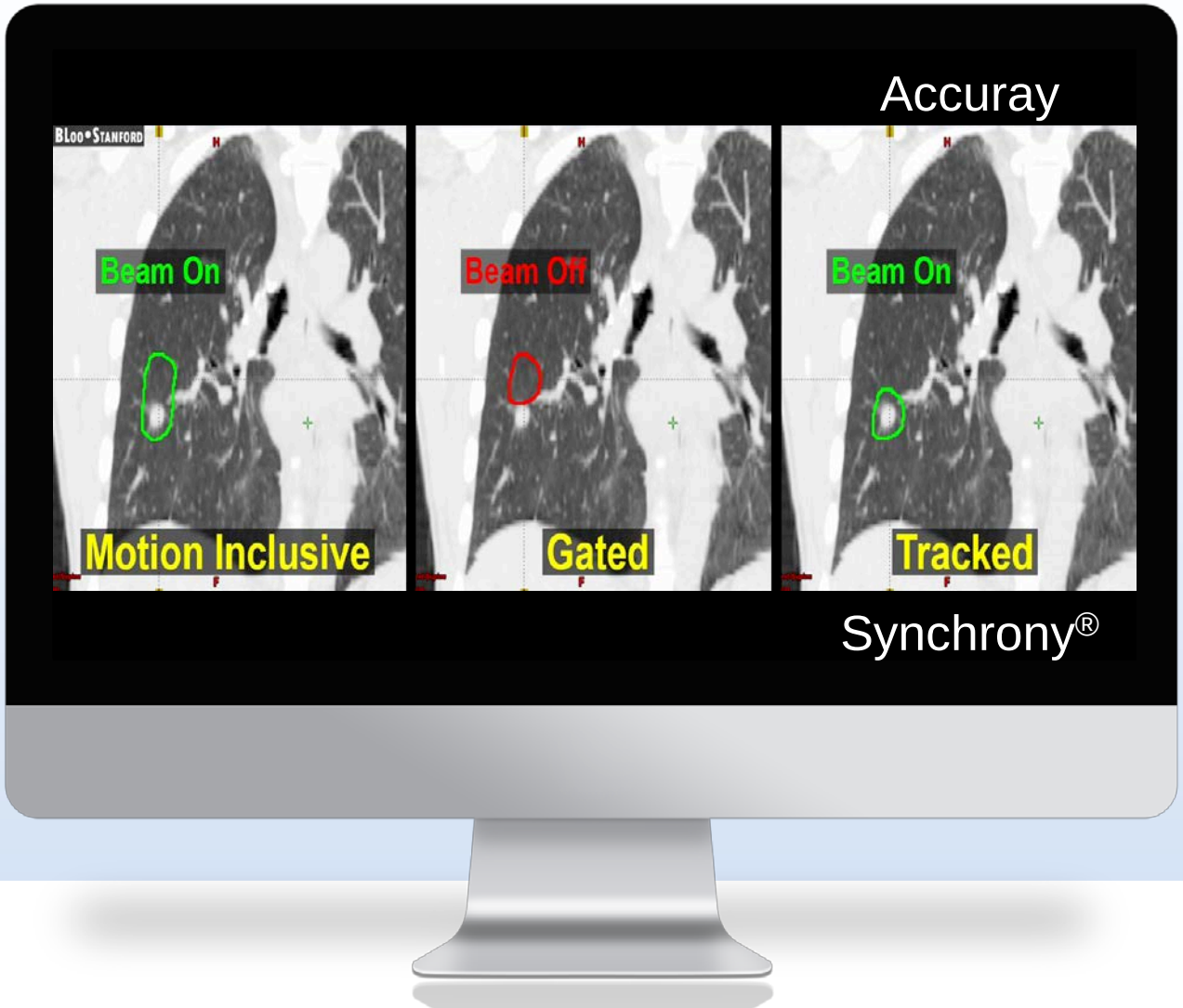
Expand treatment margins and treat the entire motion envelope – ITV

Manage breathing, and turn the beam ON/OFF depending on tumor position – gating

Efficiently follow the dynamically moving target with the beam – Accuray Synchrony® motion tracking

Geisinger

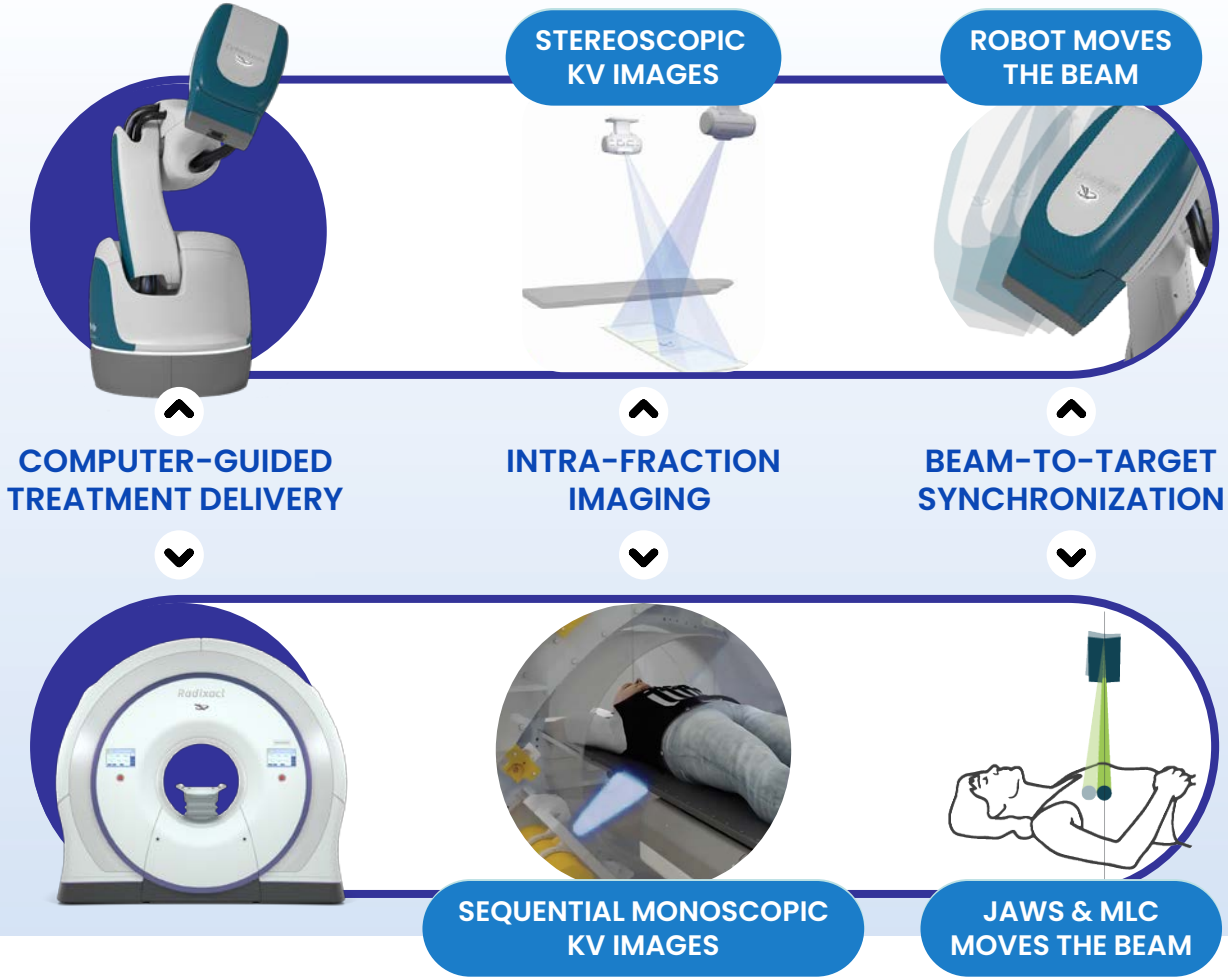
Key Challenge: Hitting Moving Targets



Current “motion management” for precise RT

Geisinger

Synchrony® is Accuray Exclusive



- Artificial intelligence (AI) driven
- Real-time adaptive treatment delivery
- Continuously personalized to each patient
- Indication specific
- Random or cyclic motion
- Sub-millimeter delivery precision and accuracy

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Factors Affecting Outcomes
(*Like Section 5 of all QUANTEC and HyTEC papers*)

Equal by default, or if some fiducials were only tracked some of the time you can set items 5 and 6 to be different

=C8

A	B	C
	Per Patient:	
	Factors Potentially Affecting Reported Outcomes in CyberKnife and Radixact Synchrony Tracking	
Item		
1	Tracking Method	Synchrony with Fiducials
2	Fiducial Geometry Quality	2 Good
3	Tumor Visualization During Treatment (LOT or Fiducials)	2 Good
4	Type of Fiducials	Visicoil Twinline Tandem Markers
5	Max Number of Fiducials Tracked for at least 50% of a Fraction	4
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	Per Institution. Only update these items per patient when altering from default practice:	
	Institutional Default Practice - Only need to change these if an individual patient is different than normal practice	
7	Planning CT Datasets	Normal Exhale and Normal Inhale
8	For Breath-Hold CT Scans, Method used to Visualize Breathing	Varian RPM
9	Dose Calculation Algorithm	Monte Carlo <= 1% Uncertainty
10	Dose Calculation Resolution	High
11	Planning CT Slice Thickness	<= 1mm

Number of Fiducials Tracked
How many fiducials were tracked during treatment for this patient

Factors Affecting Outcomes

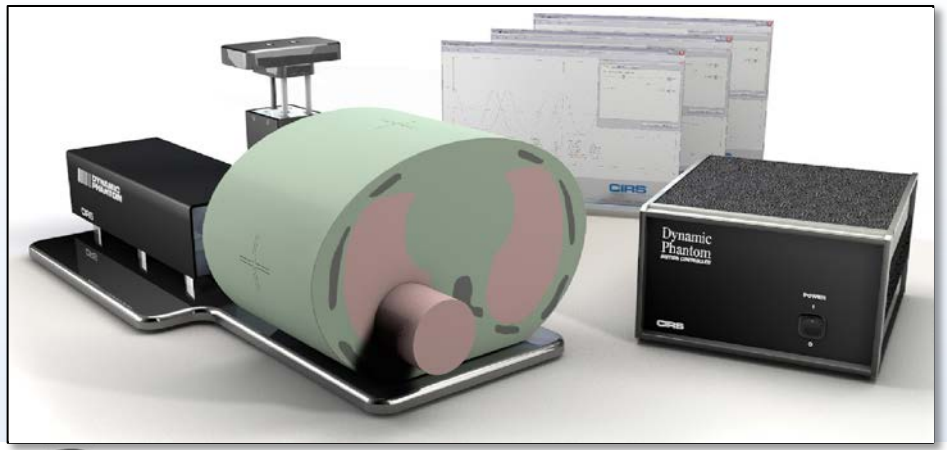
CT Acquisition Guidelines

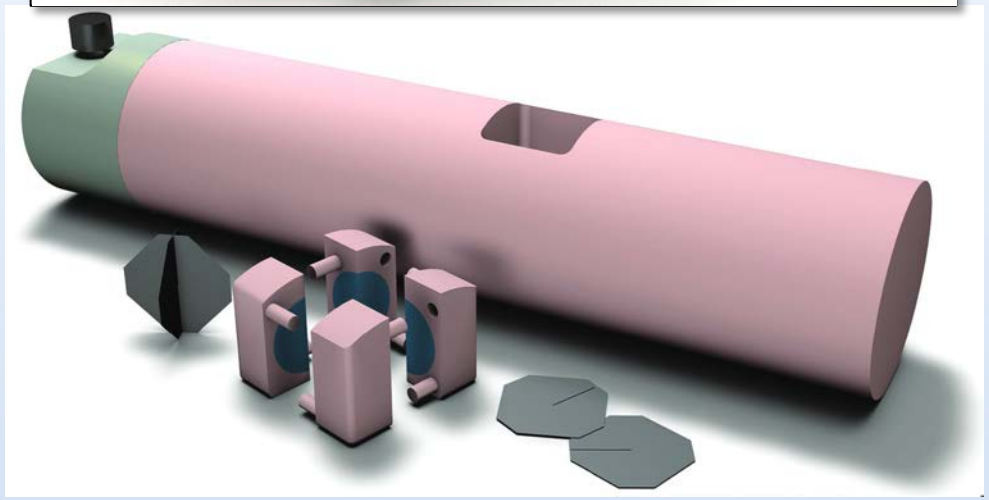
(In addition to standard non-motion guidelines for the Radixact System)

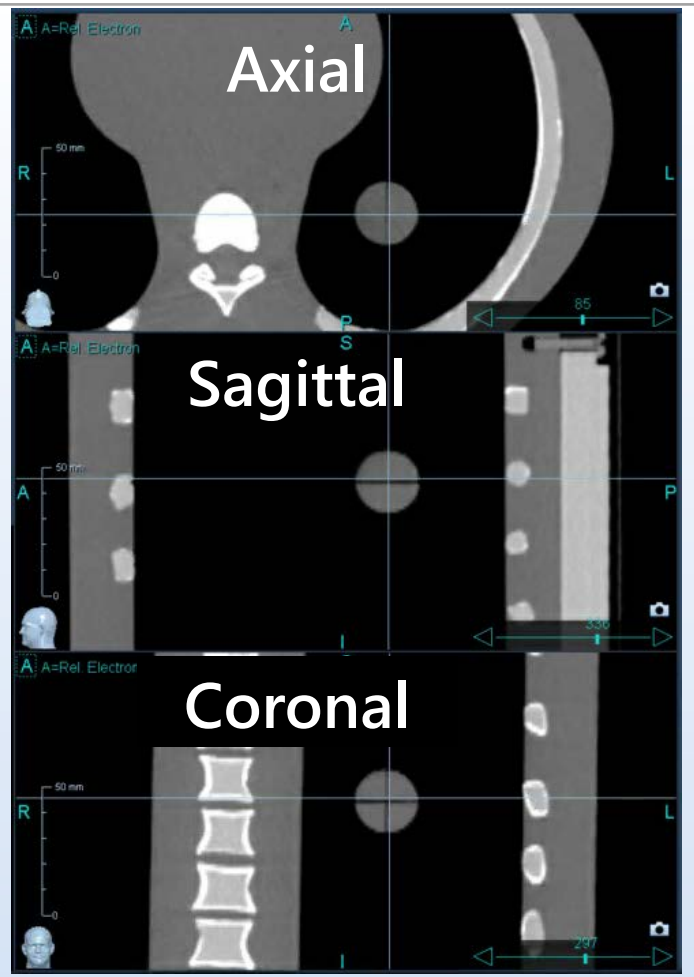
- ✓ Planning image must be kVCT (not MVCT)
- ✓ Acquire scan at patient's natural end-exhale for best visualization
  - To avoid blurred images, it is not recommended to use 4DCT
  - If 4DCT is the only option, contour the target near the middle of the breathing phase
- ✓ Use high resolution to facilitate comparison between DRRs and radiographs:
  - 1 mm slice thickness
  - 50-cm field of view (use a larger field of view if necessary to contain anatomy)
  - 512 x 512 pixels
- ✓ Set up target as close to isocenter as possible, so target/fiducials are visible on kV detector panel:
  - If possible, position target within a 10-cm radius of isocenter in the transverse plane
  - If the target cannot be positioned within 10 cm of isocenter, you will need to choose imaging angles that ensure target visibility during planning
- ✓ Use same patient setup for the planning CT scan as for daily treatments

ACCURAY CENTER FOR EDUCATION

Deformation: 4DCT of A Perfect Sphere







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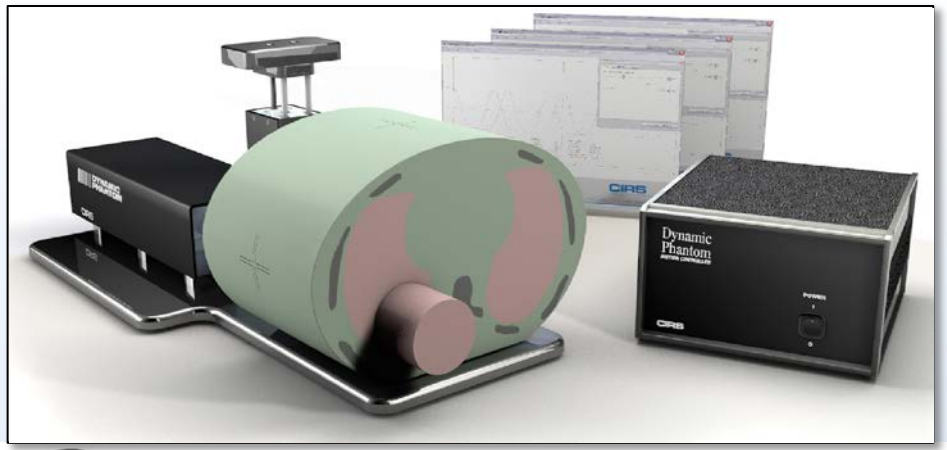
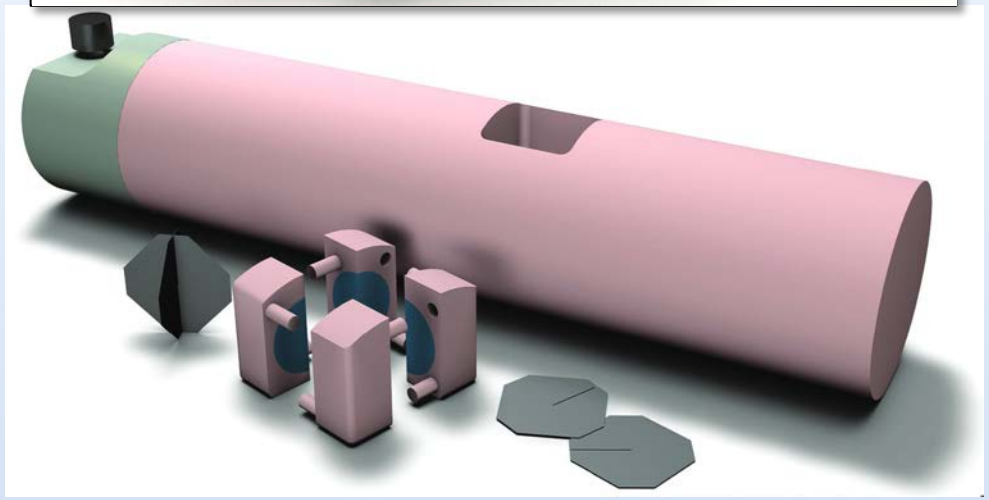
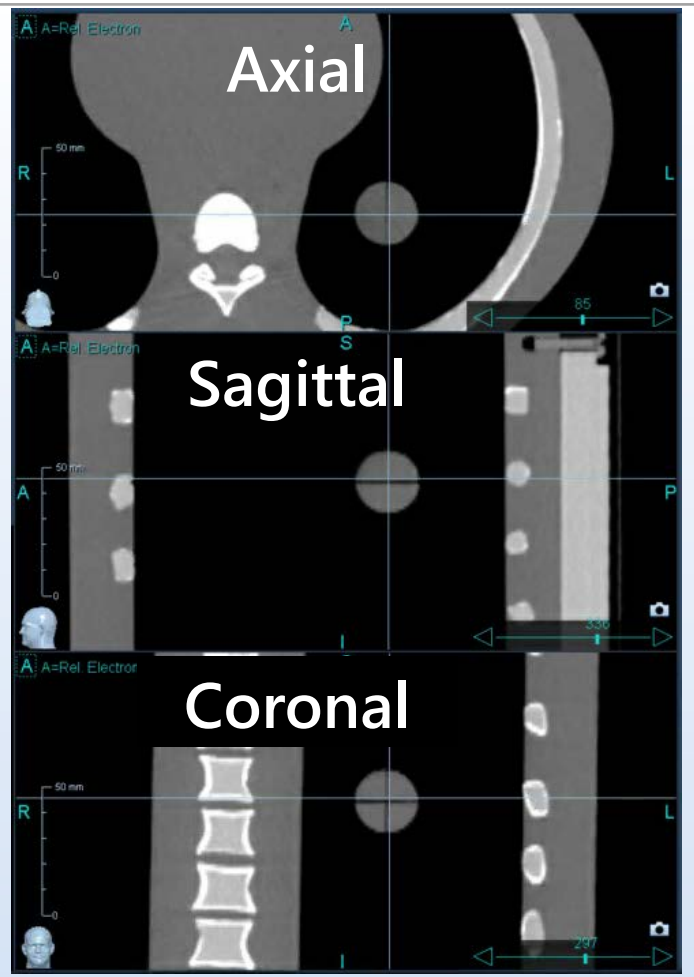






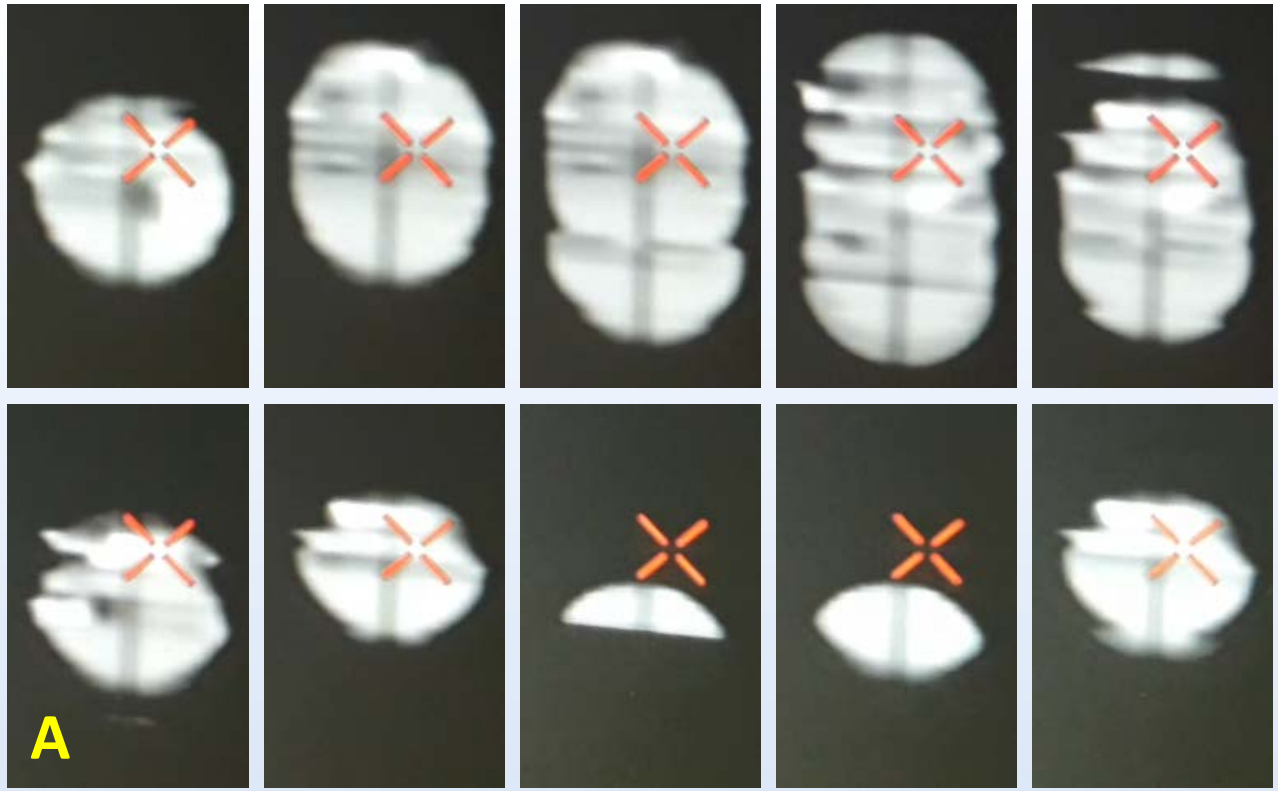
4DCT

4DCT artifact can look like deformation

Which two phases would you use for normal exhale and normal inhale?

My answer: None of these will give submillimeter end-to-end, to put it nicely…

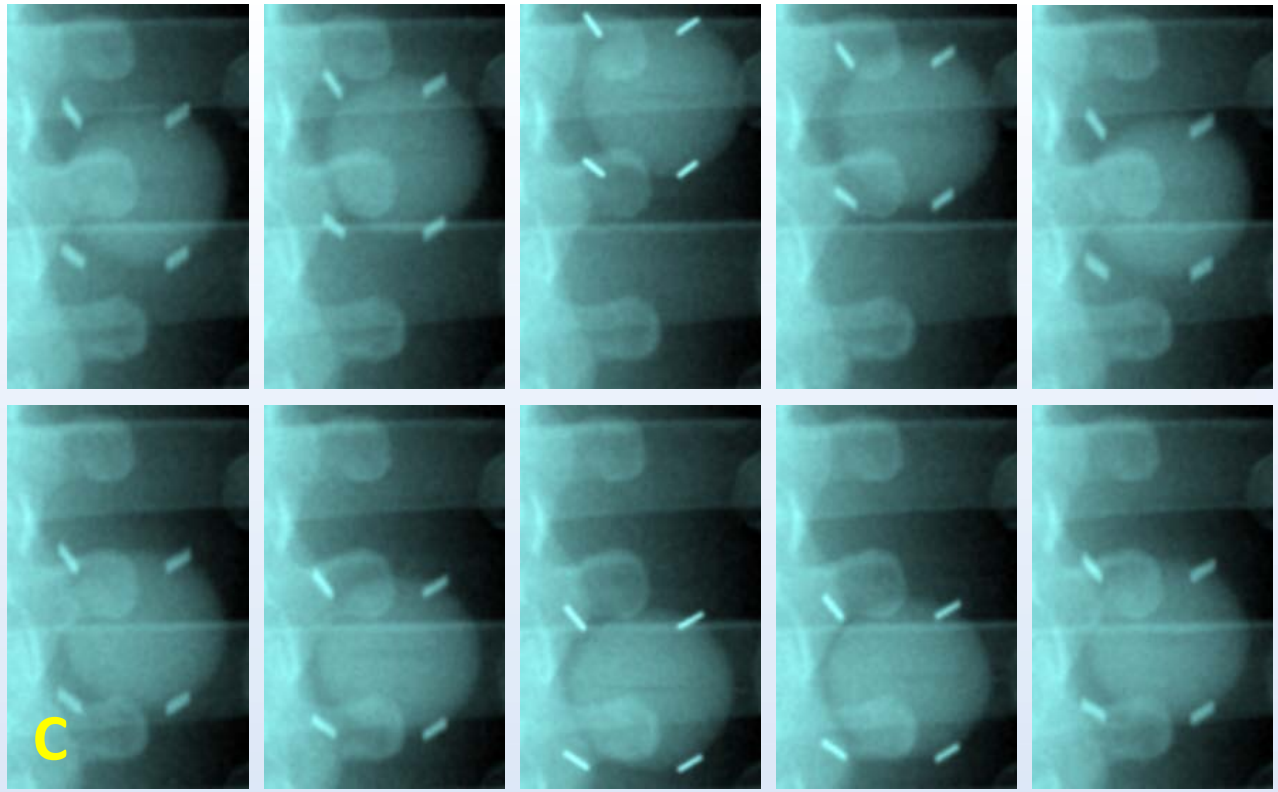
- If you have a 4D CT scanner that you are absolutely certain is submillimeter end-to-end in all phases, I would be interested.
- **Until then, this is not meeting CyberKnife® accuracy requirements**
- 4D CT can verify the extents of normal breathing if fused as a secondary scan, but not for the planning CT
- Spirometer, Varian RPM, etc. can ensure good breath-hold scans
- If people use the CyberKnife in a non-ideal way, they may get suboptimal results



We know the phantom is a perfect sphere.
This is entirely artifact, not deformation.

Compare to Synchrony® live Tracking during treatment

- Clear as day!



Submillimeter end-to-end Specification

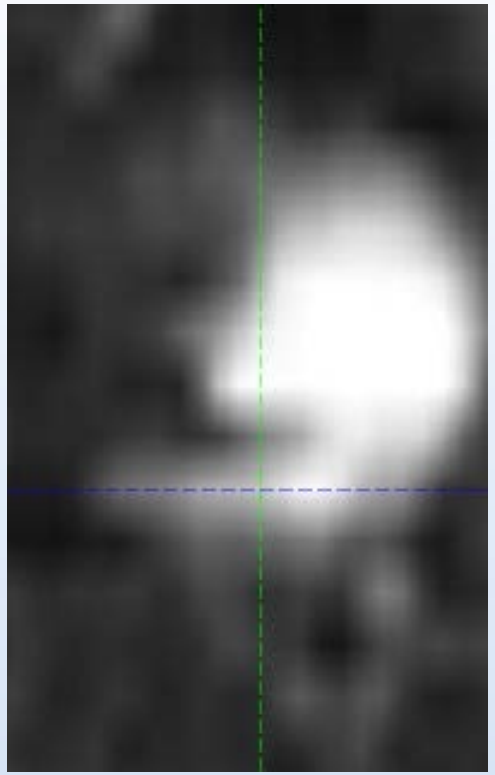
Deformation or Artifact?

Synchrony interpolates 15 phases and optically updates tracking 100 times per second

Synchrony®

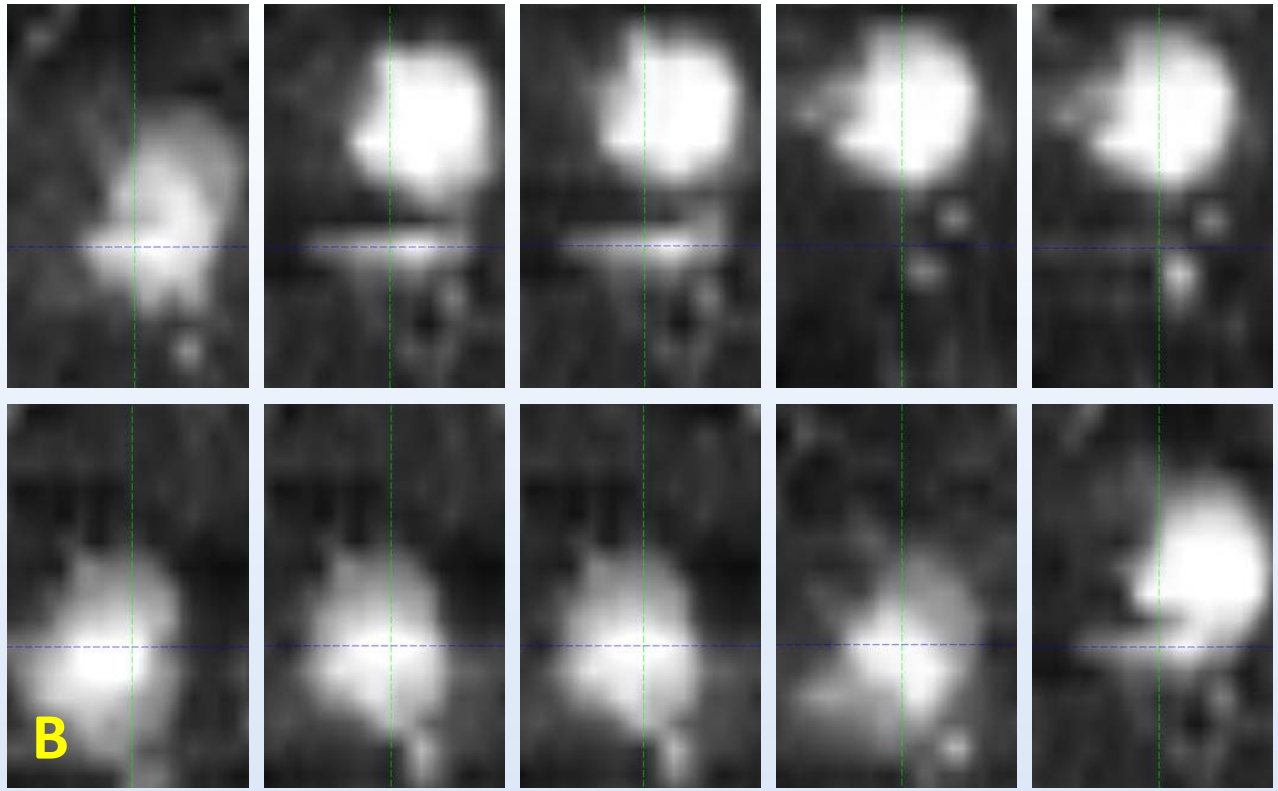
4DCT

4DCT



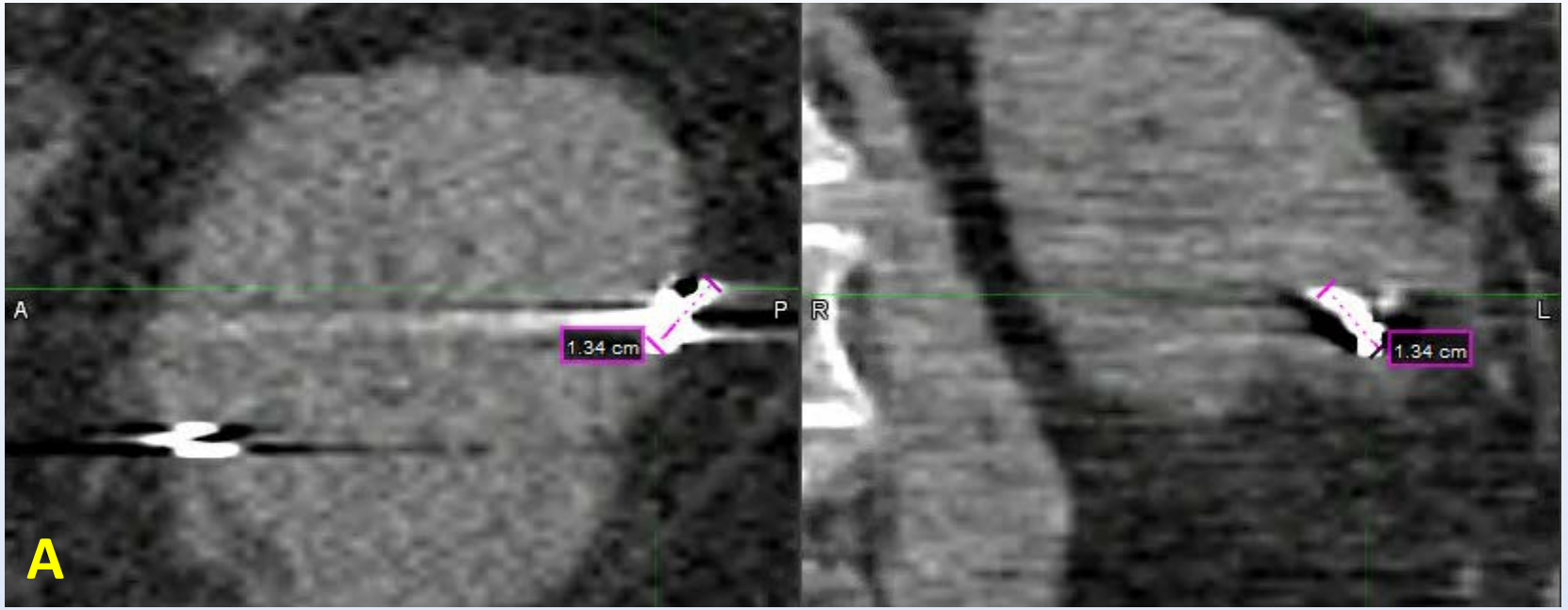
Could this artifact ever happen on a real patient?

- How likely is it that this tumor actually separates into two pieces and rejoins itself?



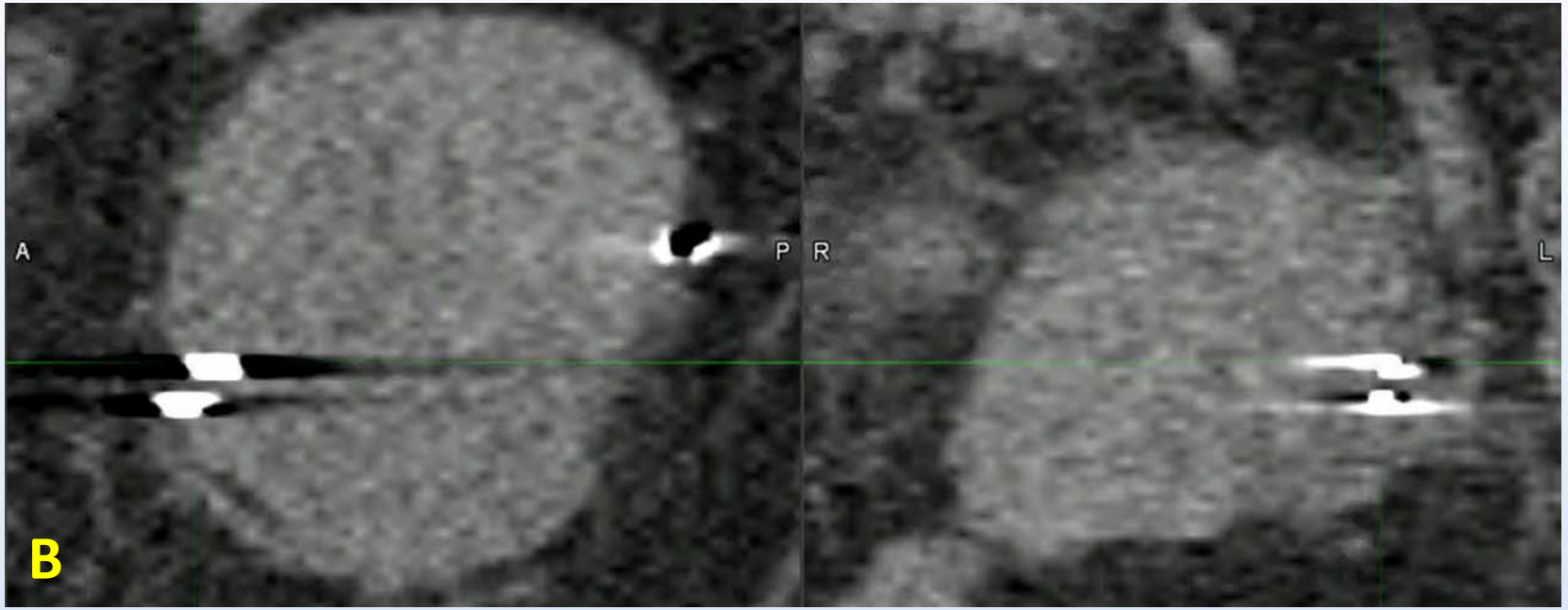
Renal Case Study: 80% phase. A fiducial is >2x known length

Sagittal **Coronal**



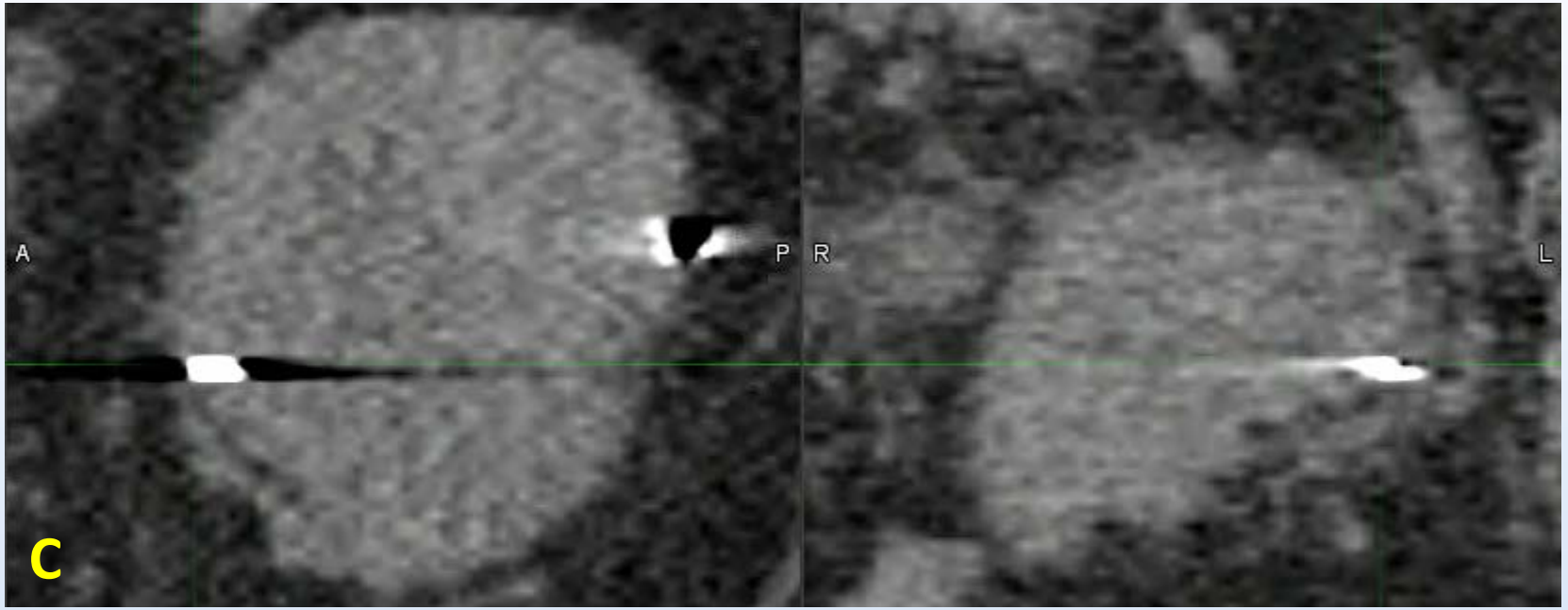
Renal Case Study: 90% phase. Is one fiducial a double?

Sagittal **Coronal**

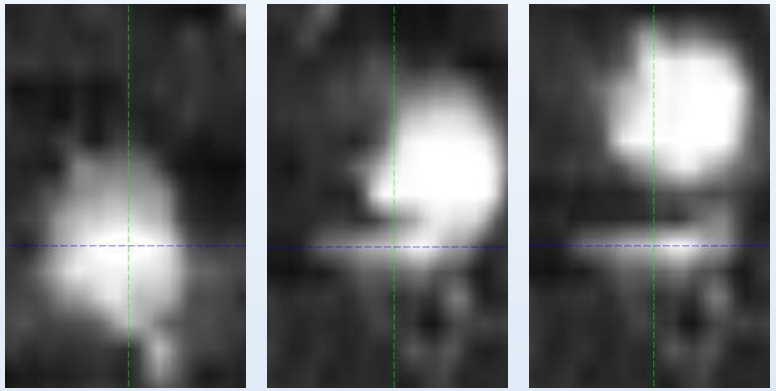


Renal Case Study: 0% phase. No, it was just 4DCT artifact!

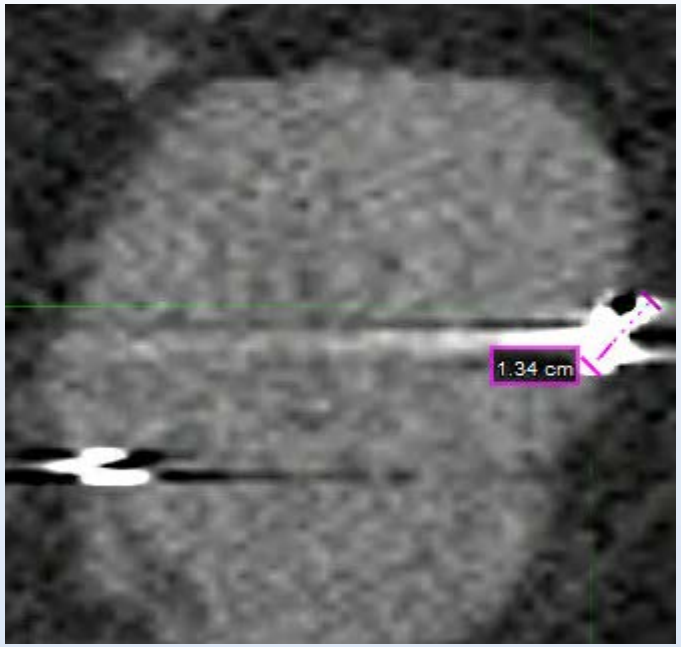
Sagittal **Coronal**



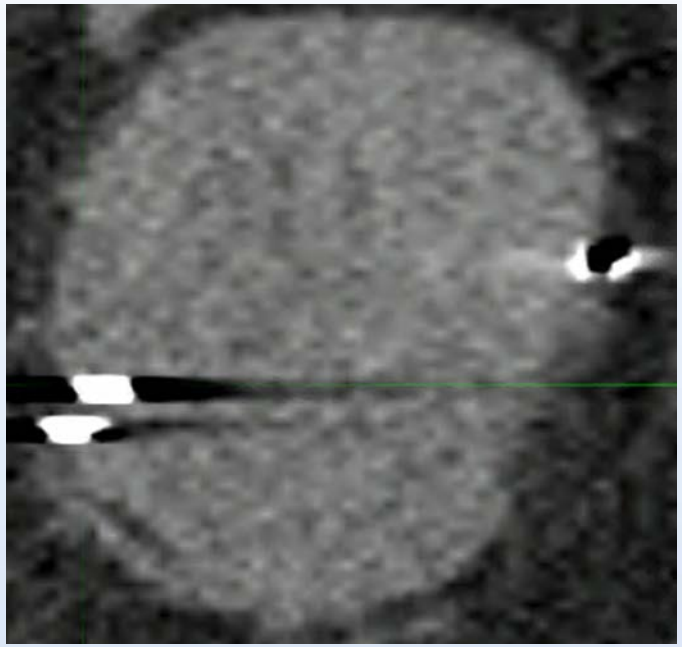
This 4DCT is not Submillimeter End to End!



Sagittal, 80% phase



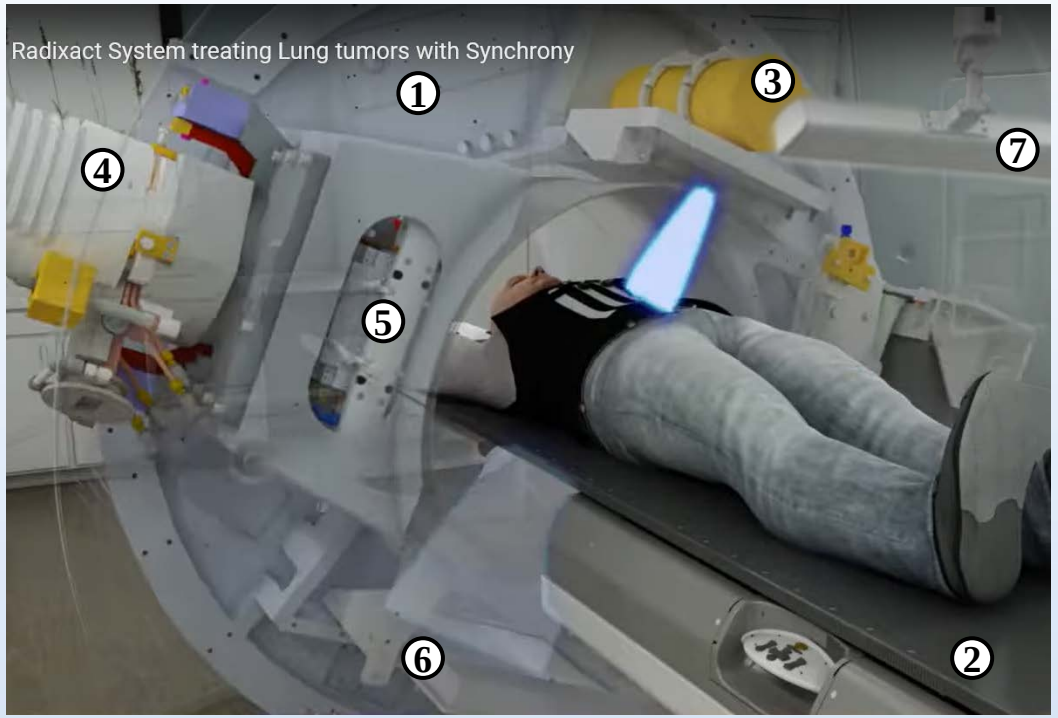
Sagittal, 90% phase



Synchrony® is designed to solve these problems

CyberKnife® Synchrony Tracking, since 2004

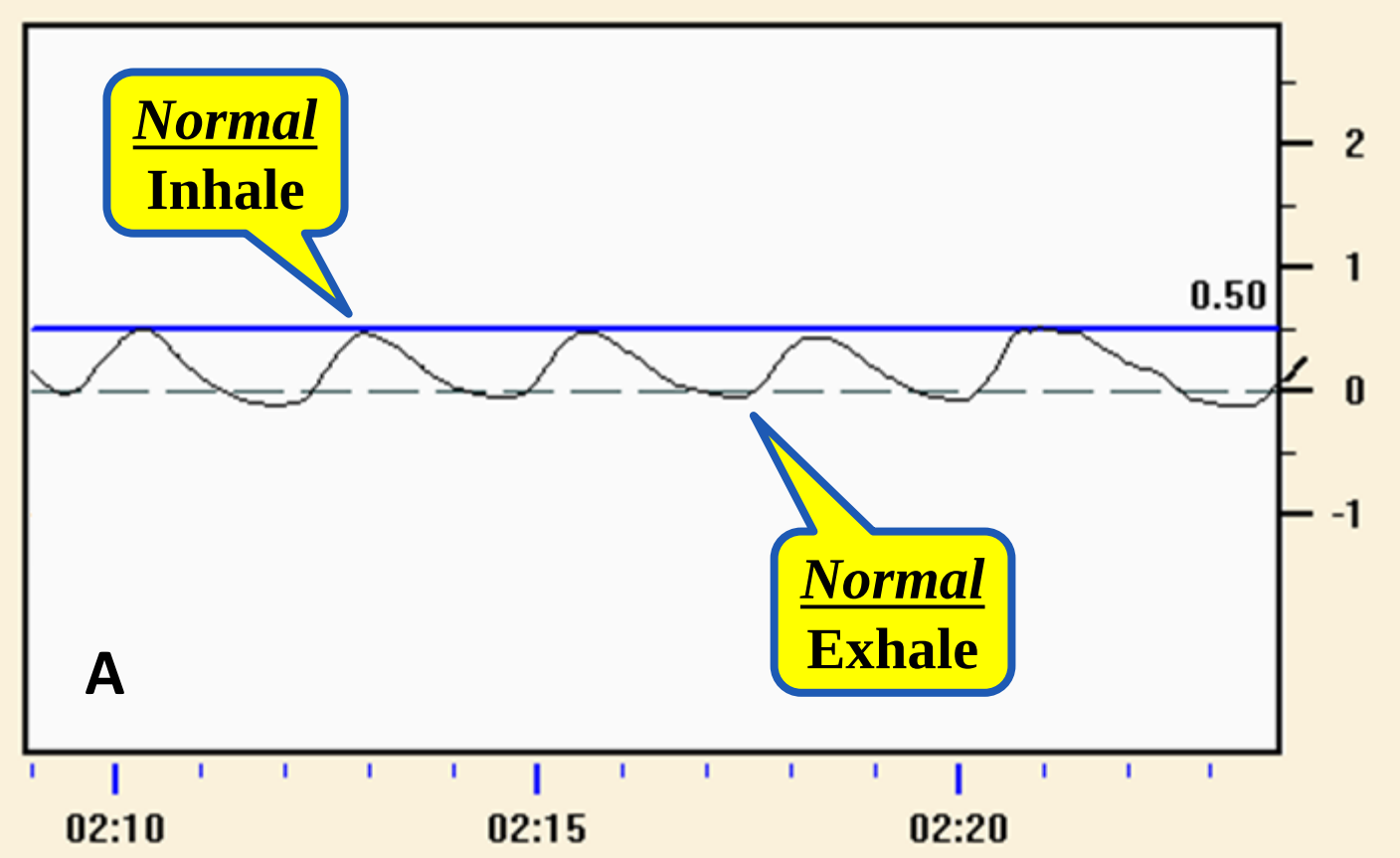
Synchrony is now available on Radixact® as well



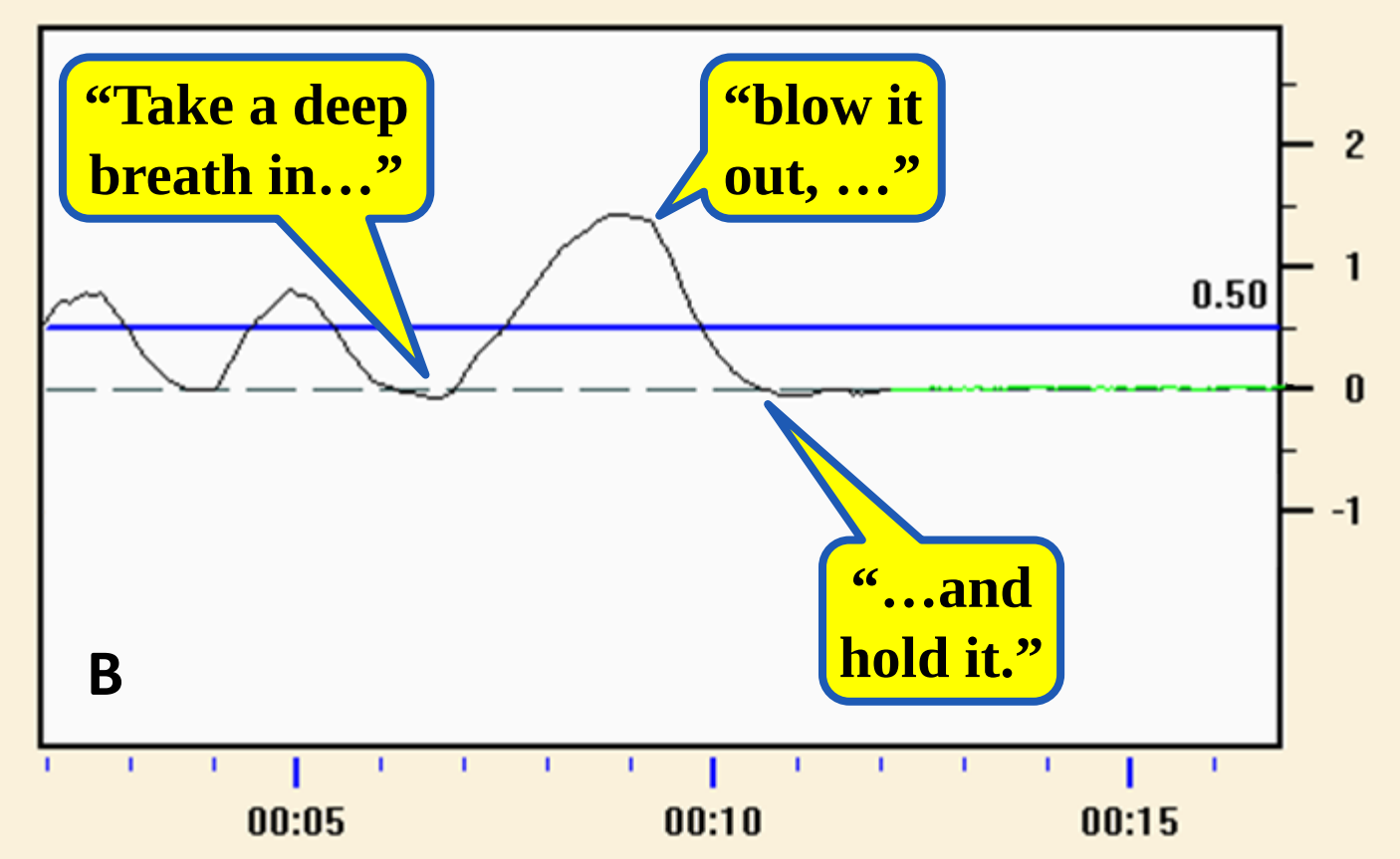
1. Ring gantry
2. Patient positioning system
3. kV X-ray source
4. Linear accelerator (LINAC)
5. Jaws and binary Multileaf Collimator
6. X-ray detector
7. Synchrony® Respiratory Camera Array (option)

- Normal BreathHold scans
  - combined with Synchrony® tracking
    - can solve this problem:

First watch the patient's breathing to determine *Normal* Inhale and *Normal* Exhale positions



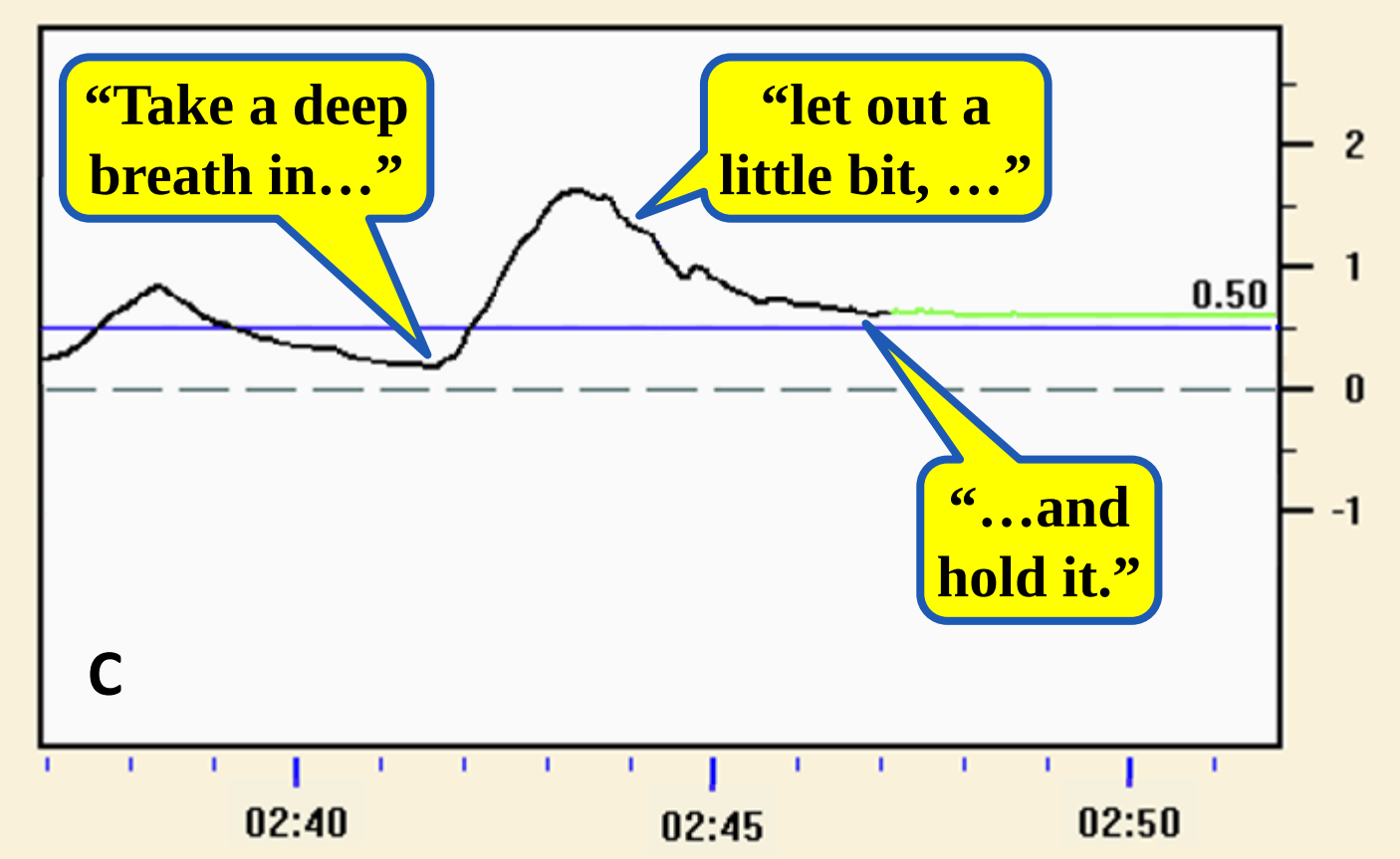
Normal Exhale:
Practice with the patient several times before the scan



This by itself is not submillimeter anything – it is just breathhold in a reasonably representative position

Synchrony fiducial tracking during treatment can make it submillimeter end-to-end

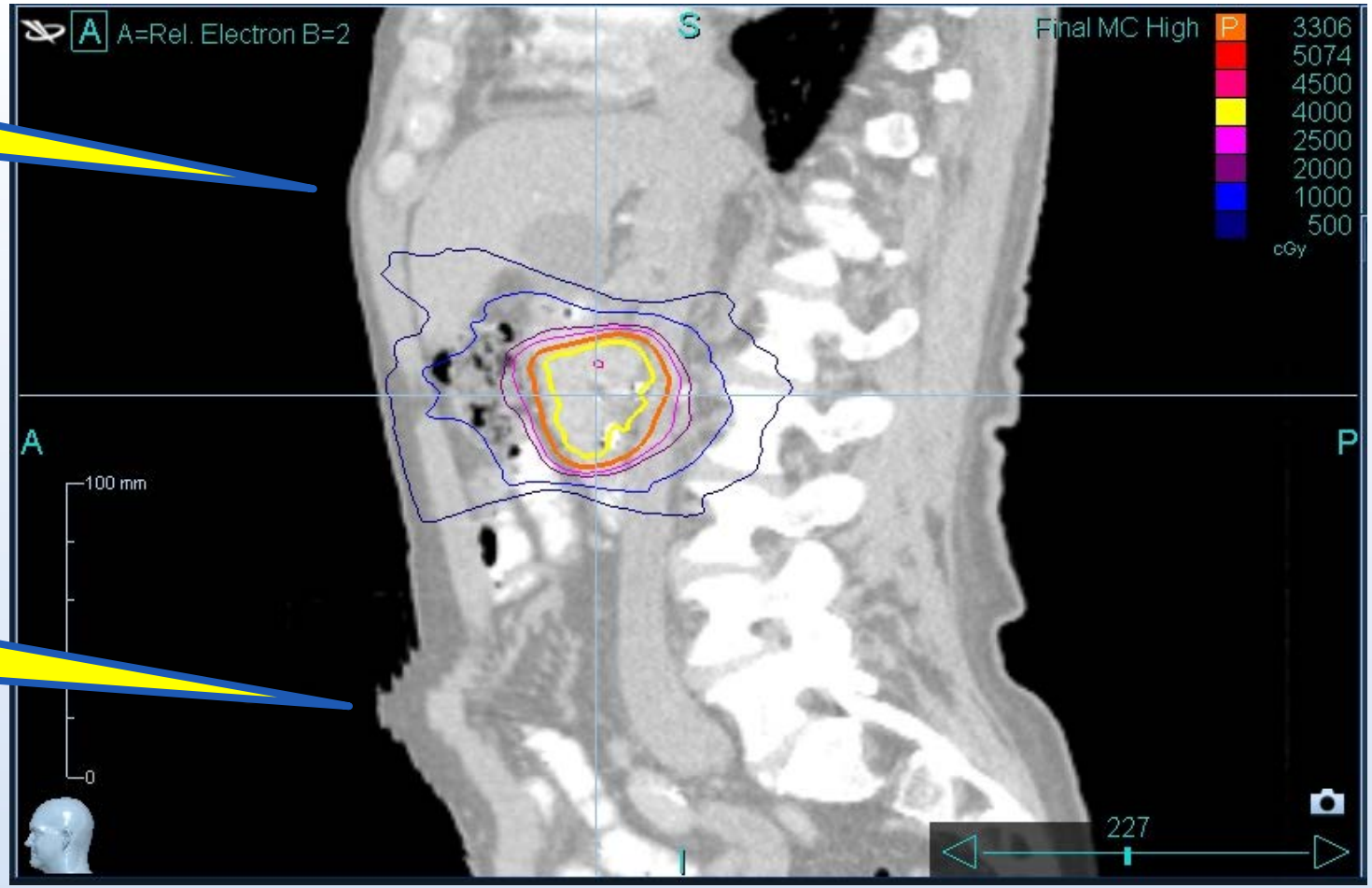
Normal Inhale:
Practice with the patient several times before the scan



There is no need to hit the exact mark – just try to ensure no motion during the CT scan, in a representative position

Synchrony fiducial tracking during treatment can make it submillimeter end-to-end

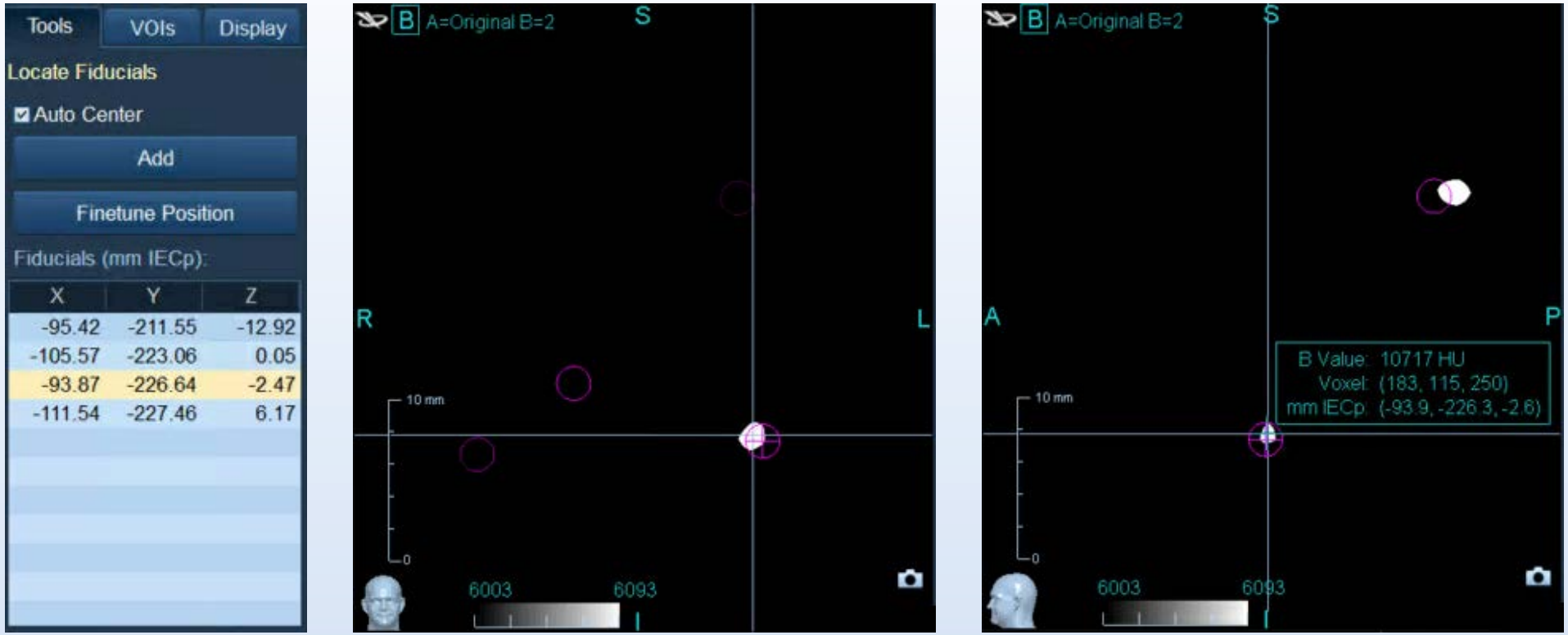
For slow CT scanners, the breath hold only needs to be near the tumor



"…and hold it."

"OK you can breathe!"

Compare fiducial locations in each breath hold scan



Normal Exhale and Normal Inhale matched within 1mm

FID	Best Exhale, Reference, mm			Rejected Exhale, mm				Inhale, mm				Re-Scanned Exhale, mm			
	X	Y	Z	X	Y	Z	3D Err	X	Y	Z	3D Err	X	Y	Z	3D Err
1	-95.4	-211.6	-12.9	-95.9	-213.7	-10.7	3.1	-94.8	-211.3	-13.4	0.8	-95.6	-211.8	-12.7	0.4
2	-105.6	-223.1	0.1	-105.0	-222.9	-0.5	0.8	-105.4	-222.9	-0.4	0.5	-105.4	-223.4	0.0	0.4
3	-93.9	-226.6	-2.5	-93.5	-226.4	-2.7	0.5	-94.5	-226.3	-2.6	0.7	-94.0	-226.3	-2.7	0.4
4	-111.5	-227.5	6.2	-111.2	-226.6	6.1	0.9	-111.1	-227.2	6.4	0.6	-111.5	-227.6	6.2	0.1

Mismatch detected, so rescanned

Submillimeter

Submillimeter

It is very important to follow Accuray recommendations!

CT Acquisition Guidelines

(In addition to standard non-motion guidelines for the Radixact System)

- ✓ Planning image must be kVCT (not MVCT)
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  - To avoid blurred images, it is not recommended to use 4DCT
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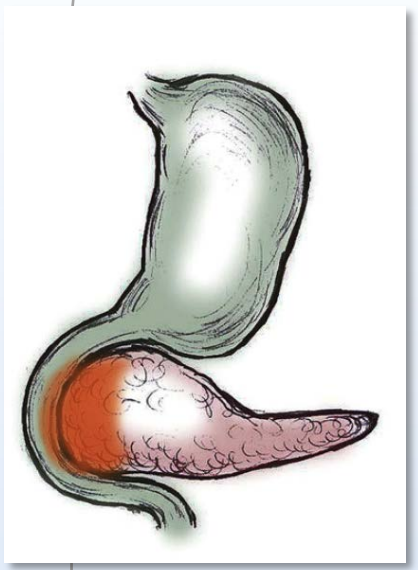
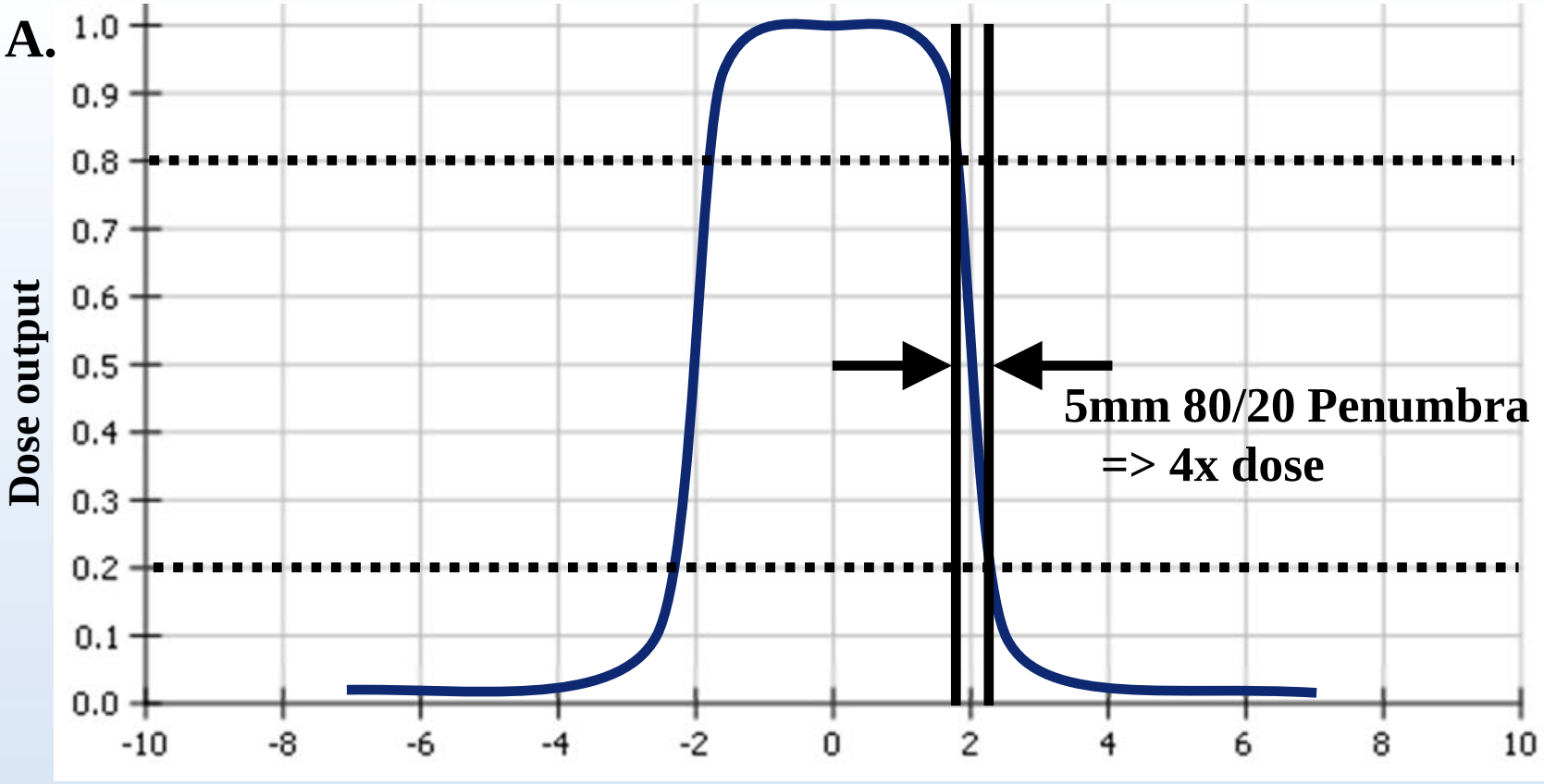
- ✓ Use same patient setup for the planning CT scan as for daily treatments

ACE ACCURAY CENTER FOR EDUCATION

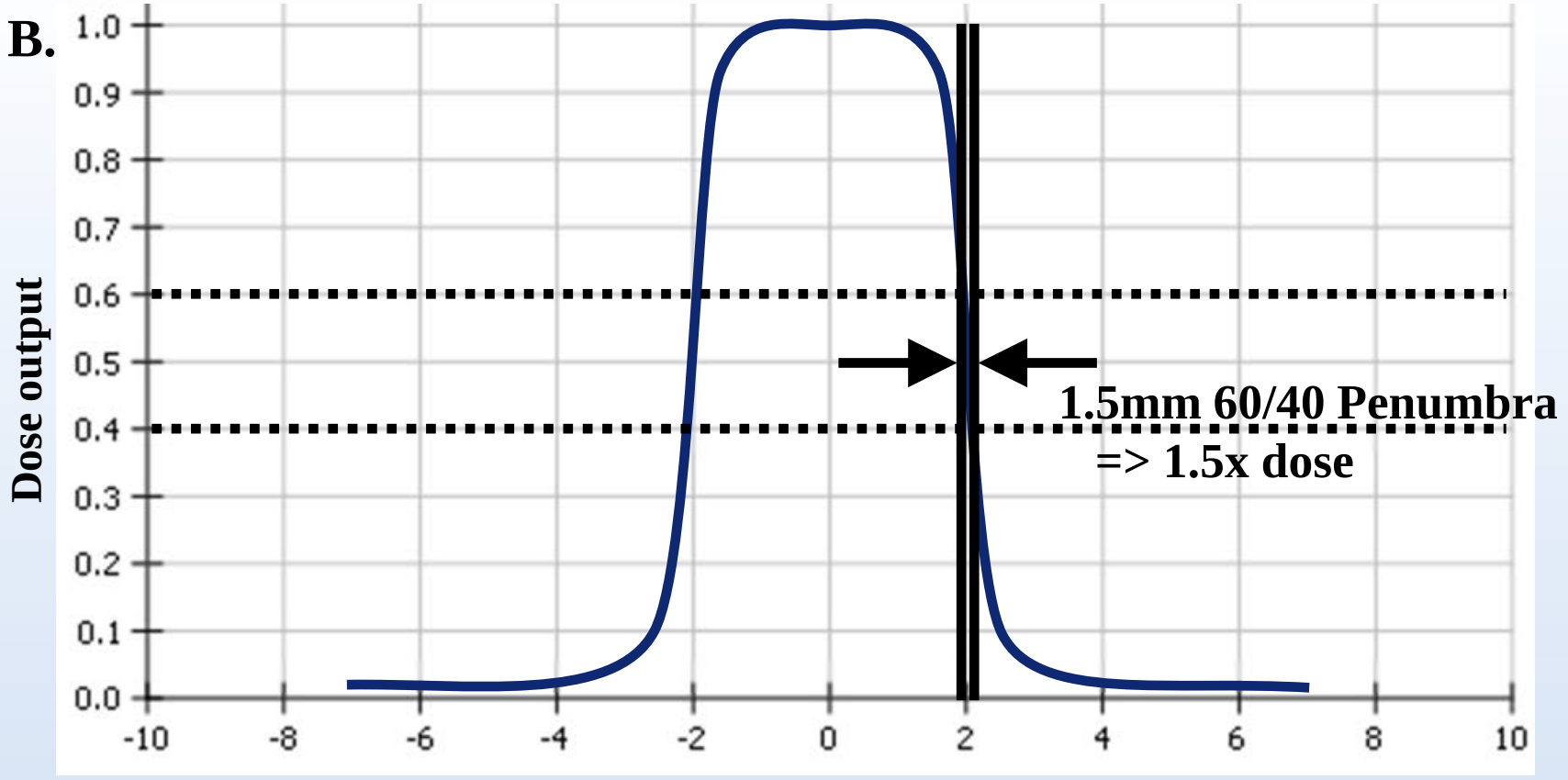
A typical Linac beam profile explains a lot:
Linac 80/20 Penumbra: 5mm => 4x dose



Mahadevan et al. 2021, IJROBP May 1;110(1):206-216.



A typical Linac beam profile explains a lot:
Linac 60/40 Penumbra: 1.5mm => 1.5x dose



A reviewer said: but that's just from a single beam!

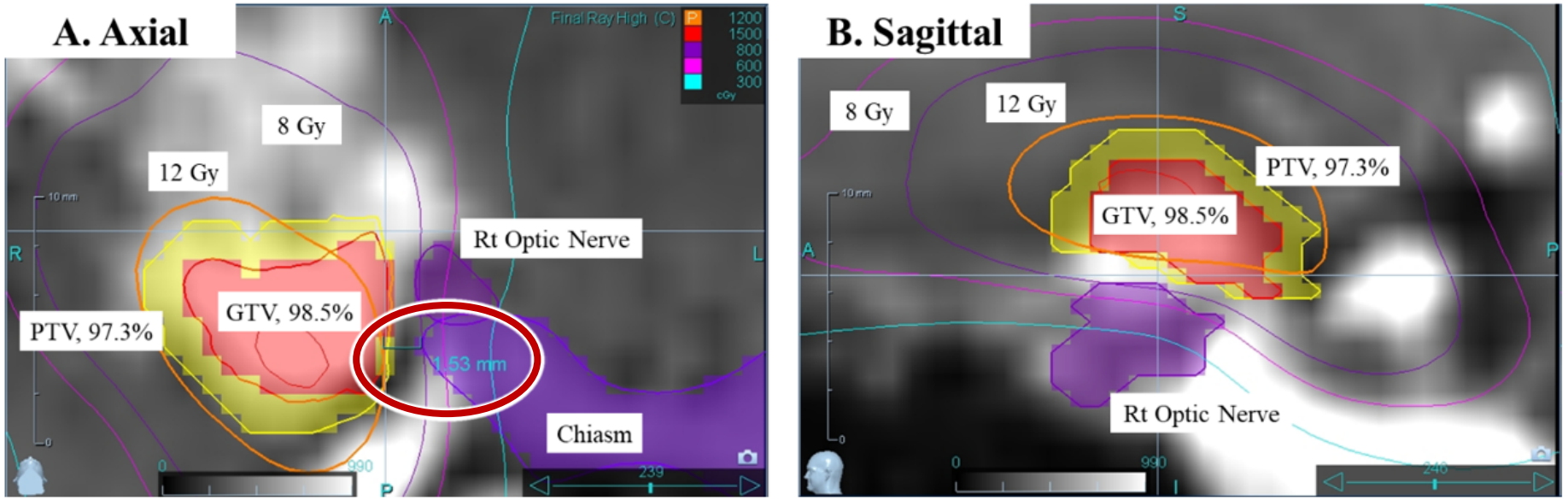


Fig. A5. Sphenoid meningioma adjacent to chiasm and optic nerve. Axial (A) and Sagittal (B) planes are shown for a single-fraction plan with 7.5mm and 12.5mm fixed cones, 40 non-isocentric beams, with an estimated 21-minute delivery time. The 12 Gy prescription line is 50% higher than the 8 Gy chiasm limit from Tishler 1993 (48) which is 1.53mm away, comparable to the conceptual example of 50% dose gradient in 1.5mm as in Fig. 4B. This single-fraction plan would have had PTV coverage of 97.3% and GTV coverage 98.5%, but ultimately the physicians decided to use 5 fractions instead so that better tumor coverage would be achievable.

8Gy limit, 12 Gy script

50% gradient, 1.53mm

Acknowledgement

The authors would like to thank Dr. Michel Lacroix and dosimetrists Maria Zulkowski and Richard Lanzendorfer, for allowing us to use this morning's sphenoid meningioma case as an example in Fig. A5.

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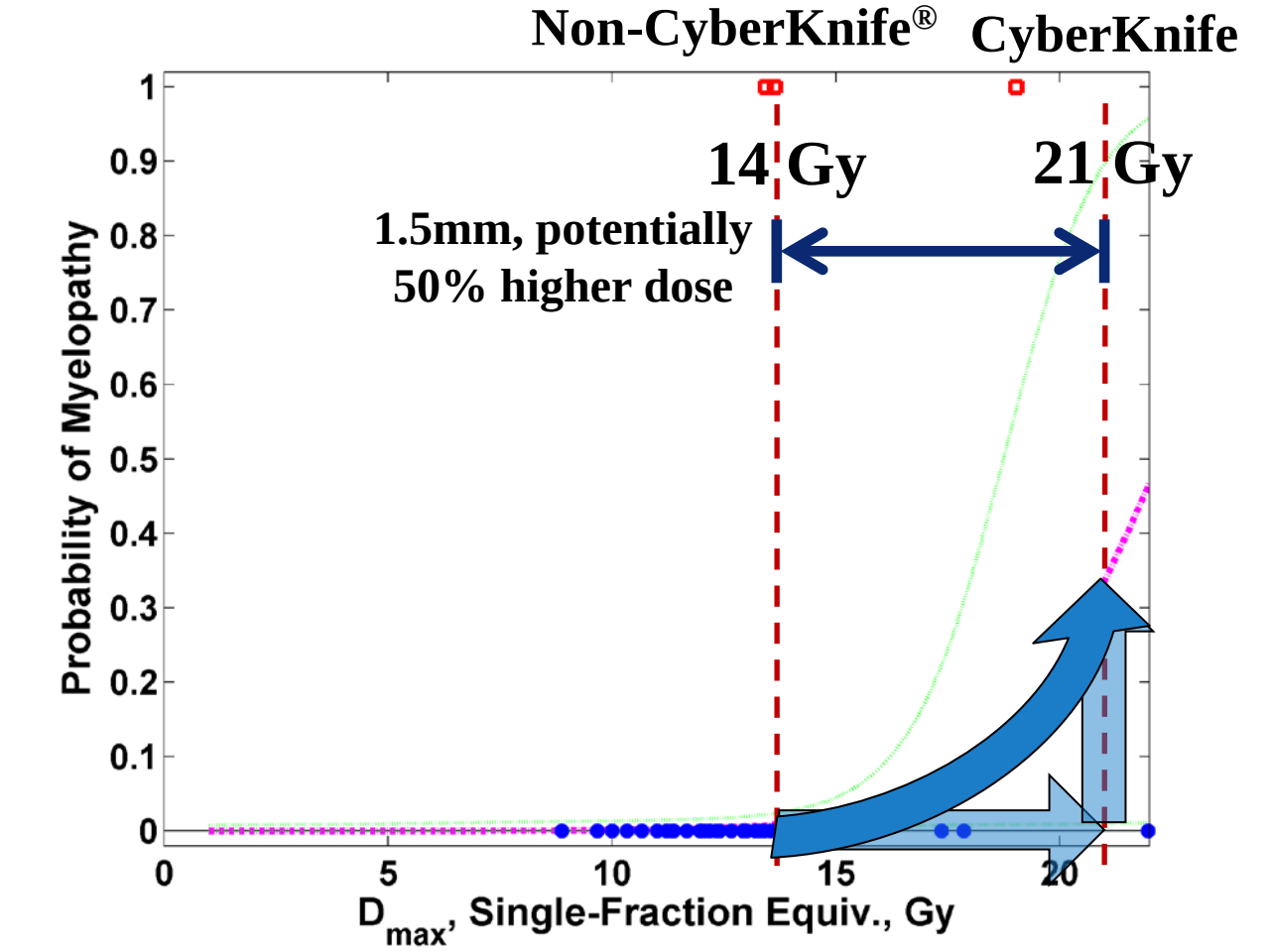
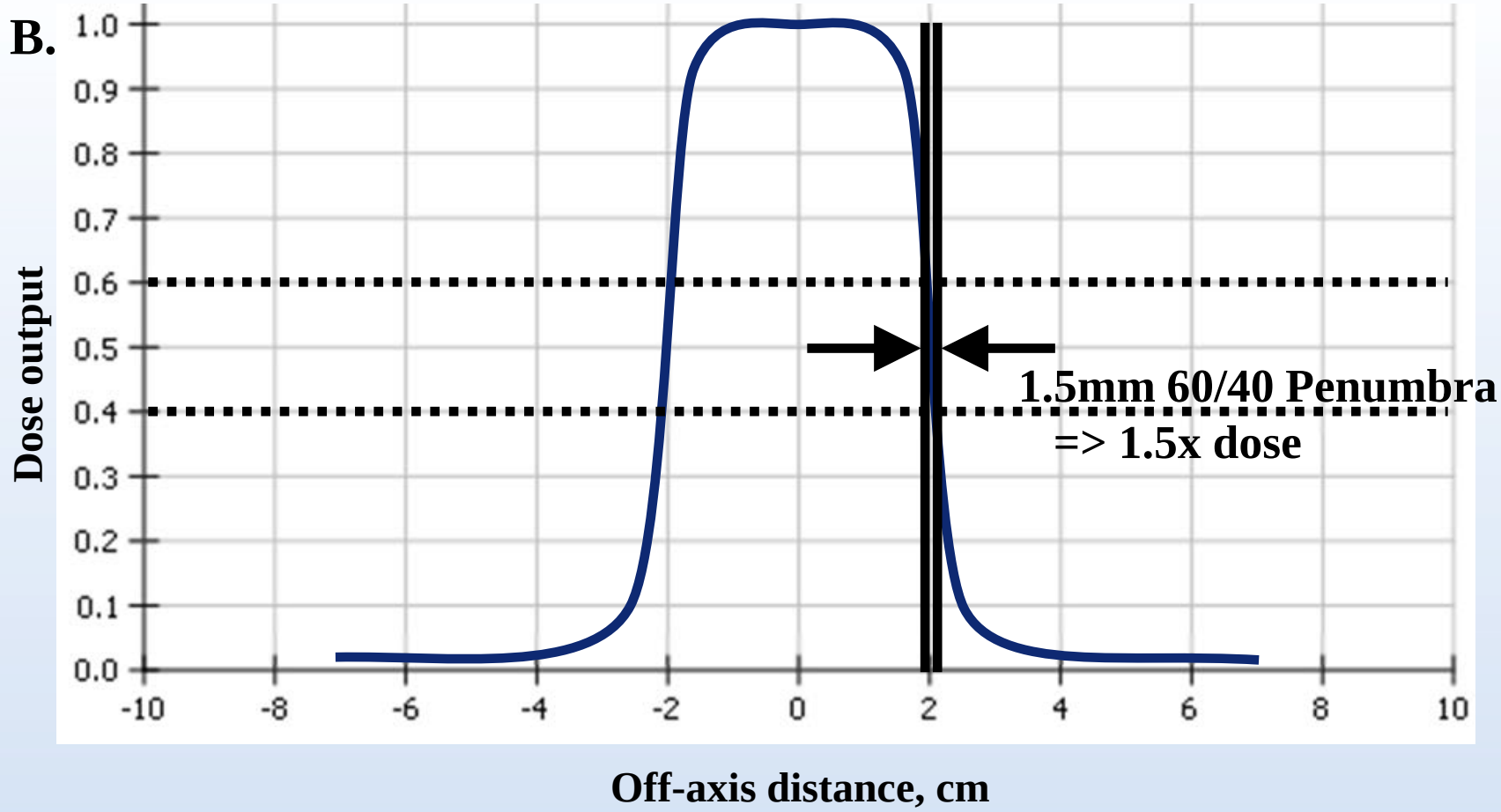
Spinal cord example, 1.5mm could correspond to 50% higher dose



- If the 14Gy/1fx had a 1.5 mm targeting uncertainty…
- 14*60/40 = 21 Gy
- Recall the shape of a single beam
- **Need models accounting for targeting errors and volume effects, including random direction of errors**

What if tracking was not submillimeter end-to-end?



4DCT

Many more factors affecting outcomes

- Monte Carlo dose calculation
- Fiducial placement guidelines, 4-6 fiducials
- Migration-resistant fiducials
- LOT: make sure you can see the tumor
- Multiphasic contrast for liver and pancreas
- MRI with 3D distortion correction
- Fiducial placement skill. SuperDimension / endoscopic / CT guided, etc.
- Increased margin for the smallest tumors, to ensure not missed entirely
- Synchrony®: breathing coaching for irregular breathers
- Synchrony: delete old peaks instead of new ones, if new peaks mismatch
- Synchrony: center rotations across peak and valley to remain within ±1.5°
- Synchrony: Spirometer or RPM to ensure normal exhale and inhale CT
- Immunotherapy
- Prostate: bladder and bowel prep
- Bath and shower – ensure low dose to large volumes
- Vascular damage may help TCP if you can get above 10Gy/fraction
- Pass IROC phantoms to ensure accurate dose calculation and targeting
- Treating far off-axis only works well when the patient doesn't deform
- Gas can affect spine tracking – use a mild bowel prep even for spines
- Is it OK to import contours from every other system? Are you sure they are accurate?
- Tumors grow exponentially until treated – therefore minimizing the time from diagnosis to treatment can improve outcomes.

Etc.

Need to handle these efficiently and cost-effectively within the clinical workflow

Factors Affecting Outcomes
Best Subset: The most benefit within feasible efficiency

Equal by default, or if some fiducials were only tracked some of the time you can set items 5 and 6 to be different

=C8

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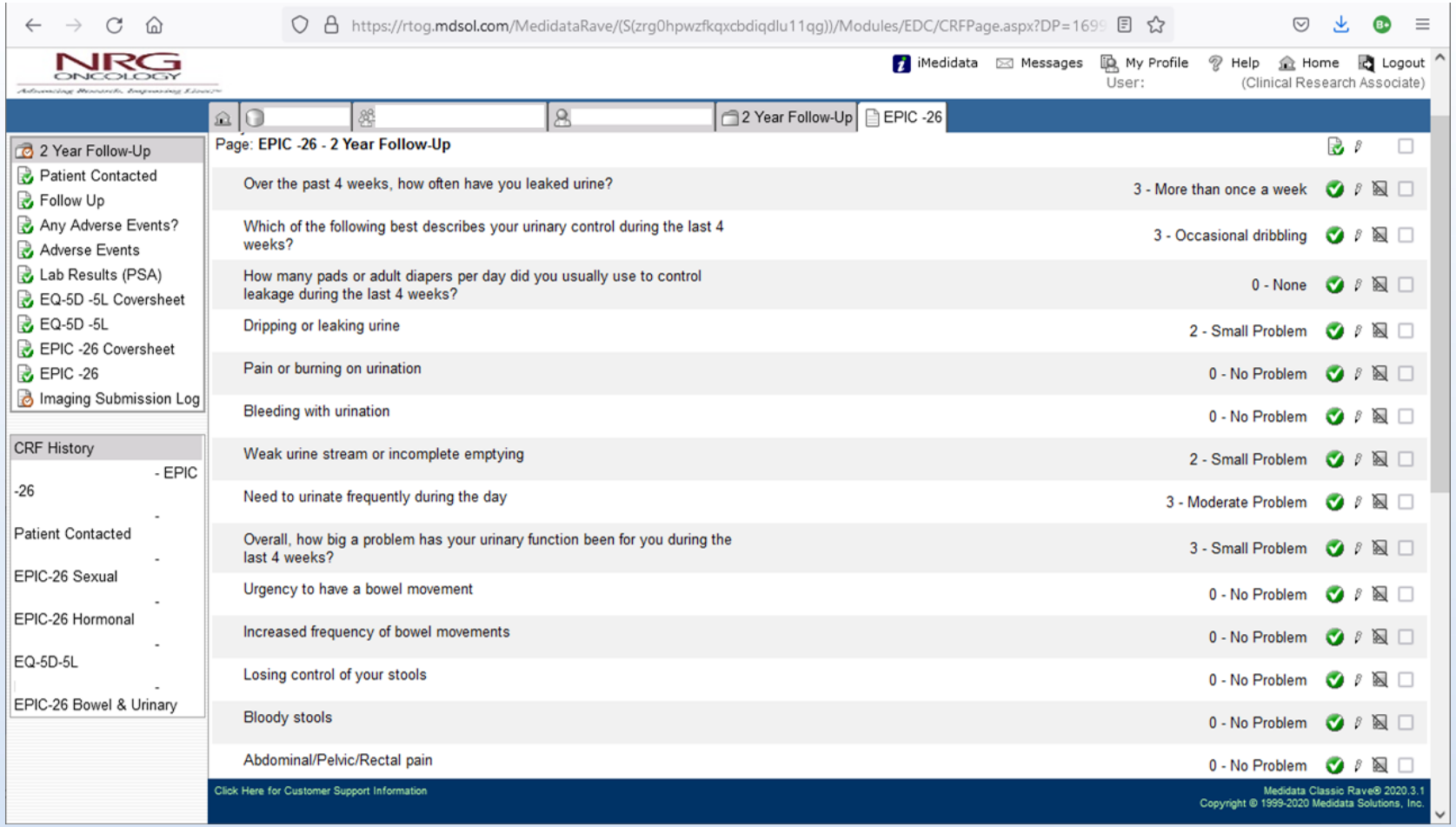
Number of Fiducials Tracked
How many fiducials were tracked during treatment for this patient

We can save data from our own patients on NCI sponsored studies



Conclusions

- **Synchrony® has potentially 10x lower risk:**
  - **“Pooled logistic and probit models for grade 3 or higher toxicity for aorta, chest wall, duodenum, and small bowel suggest a significant difference when live motion tracking was used for targeting tumors with move with respiration which was on the average 10 times lower, in the high dose range.”**
  - **Frontiers in Oncology, Feb 2021, PMID: 33634020**

- **Need to define the best treatment techniques with Synchrony to ensure best outcomes**
- **Need to accumulate prospective long-term data to fine-tune**

Caring

From Coal Miner to Data Miner in 3 Generations

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This is not the end – just the beginning!

If you treat patients you have data – let's analyze and publish it together!

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