Image Guided Radiation Therapy and Stereotactic Body Radiation Therapy for Lung Cancer

MOUNT SINAI SCHOOL OF MEDICINE

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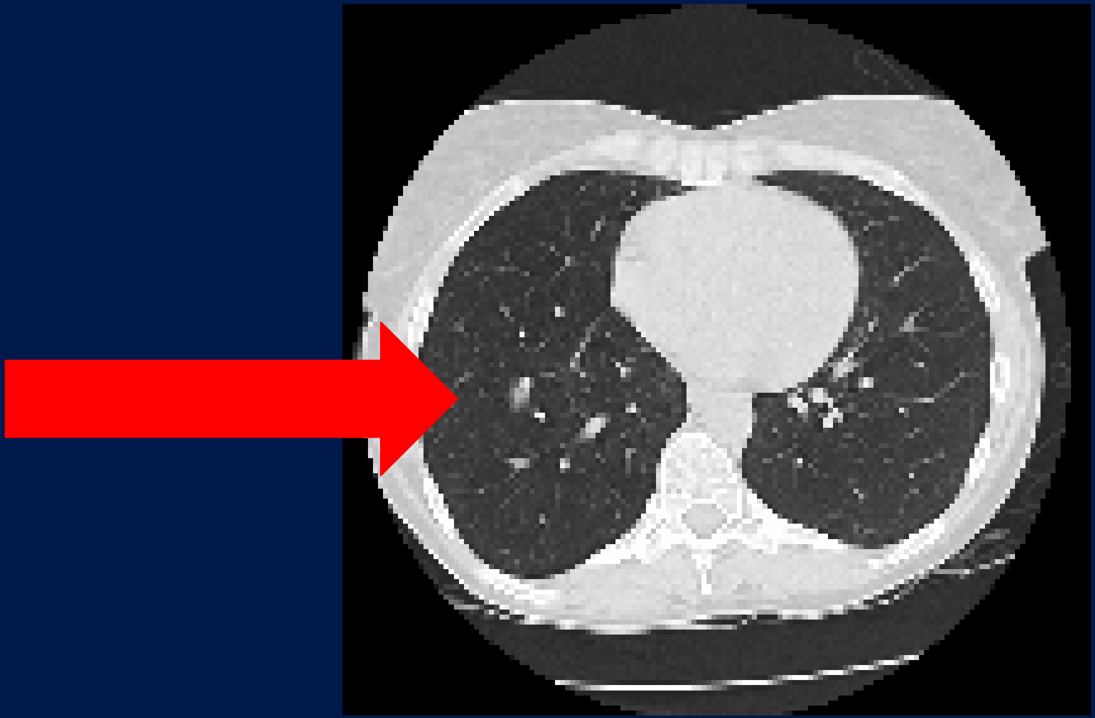
Small Problems

- Early stage tumors



Options for Early Stage NSCLC

- Surgery
  - Wedge, Lobectomy, etc.
- Radiation Therapy
  - Conventional Radiation
  - Stereotactic Body Radiotherapy (SBRT)
- Radiofrequency Ablation

Surgery for Early Stage NSCLC

- Local control ~90%
- 5-year survival 60 – 80%
- Mortality ~2%
- Morbidity ~10-20%

High Dose Conventional RT

	No. patients	Median Survival (months)	5-year local control	5-year overall survival
Stage I/II	55	41	67%	36%

- 5% Grade 3+ acute pulmonary toxicity (2.5% grade 5)
- 7% Grade 3+ late pulmonary toxicity
  - 11% of long-term survivors on chronic oxygen

Lung SBRT Experience

- Onishi, Japan (*Cancer* October, 2004)
- Retrospective multi-institutional study
- 273 patients with Stage I tumors
- Dose was 18 – 75 Gy in 1 – 22 fractions
  - BED ranged from 57 – 180 Gy
- Complication rate 2.4%
- Local failure in 12.5%
  - Improved in good PS patients receiving > 100 Gy BED

	# patients	Median f/u (months)	Dose/fx	Grade 3 toxicity	Local Control	Survival
Kyoto	45	30	4x12 Gy	0	94% 3 yr	T1: 83% T2: 72%
Stanford	20	18	1x15-30 Gy	12.5%	92% 1 yr	85%
Aarhus, Denmark	40	29	3x15 Gy	NA	85% 2 yr	48% 2 yr
Indiana	70	18	3x20-22 Gy	20%	95% 2 yr	55% 2 yr
Hedielberg	42	15	1x19-30 Gy	NA	68% 3 yr	37% 3 yr
Tohuku	31	32	3x15 Gy 8x7,5 Gy	3.2%	T1: 78% T2: 40%	72% 3 yr
Karolinska (Sweden)	57*	23	3x15 Gy	21%	96%	65%
VU (Nether lands)	206*	12	3x20 Gy 8x7.5 Gy	3%	93% 2 yr	64% 2yr

*** not all biopsy proven**

RTOG 0236

PRELIMINARY COMMUNICATION

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

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Context Patients with early stage but medically inoperable lung cancer have a poor rate of primary tumor control (30%-40%) and a high rate of mortality (3-year survival, 20%-35%) with current management.

Objective To evaluate the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer.

Design, Setting, and Patients Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non–small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total) with entire treatment lasting between 1½ and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through August 31, 2009.

Main Outcome Measures The primary end point was 2-year actuarial primary tumor control; secondary end points were disease-free survival (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival.

Results A total of 59 patients accrued, of which 55 were evaluable (44 patients with

RTOG 0236 RT Specifications

- No additional margin for microscopic extension (i.e., no CTV)
- PTV margin was:
  - 5 mm axially
  - 10 mm craniocuadal
- 20 Gy x 3
  - 40 hours apart (max: 8 days)
- No tissue heterogeneity correction allowed
  - Later showed dose was closer to 18 Gy x 3

Organ Tolerance Dose Limits for Radiation Therapy Oncology Group 0236

Table 2. Organ Tolerance Dose Limits for Radiation Therapy Oncology Group 0236[a]

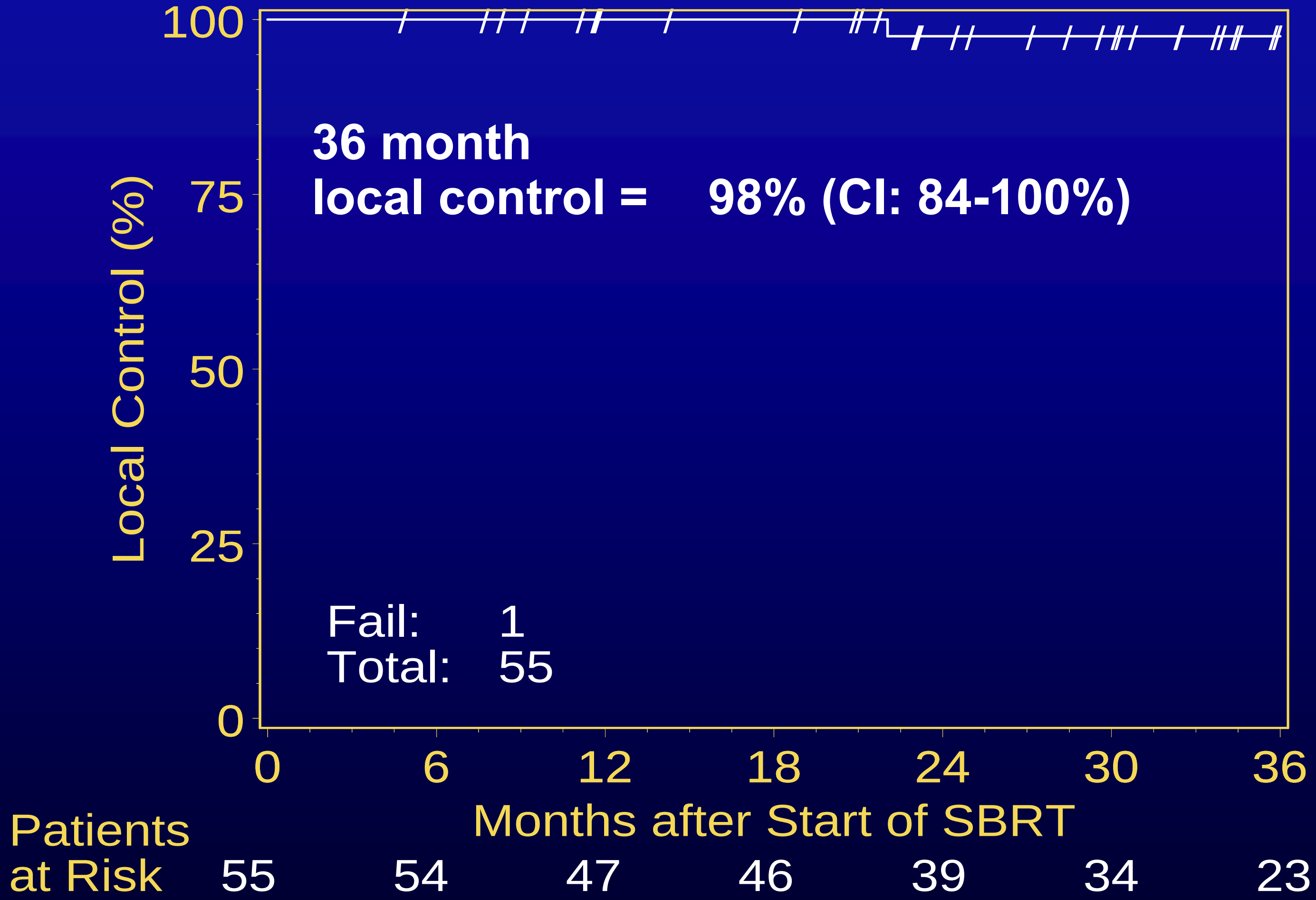
Organ	Volume	Total Dose
Spinal cord	Any point	18 Gy maximum
Esophagus	Any point	27 Gy maximum
Ipsilateral brachial plexus	Any point	24 Gy maximum
Heart	Any point	30 Gy maximum
Trachea and ipsilateral bronchus	Any point	30 Gy maximum
Right and left lung	<10% of volume	20 Gy[b]

[a] Exceeding organ limits by more than 2.5% constituted a minor protocol violation and exceeding these organ limits by more than 5% constituted a major protocol violation.
[b] Also known as V-20 or volume of total lung getting 20 Gy or greater.

Timmerman, R. et al. JAMA 2010;303:1070-1076.

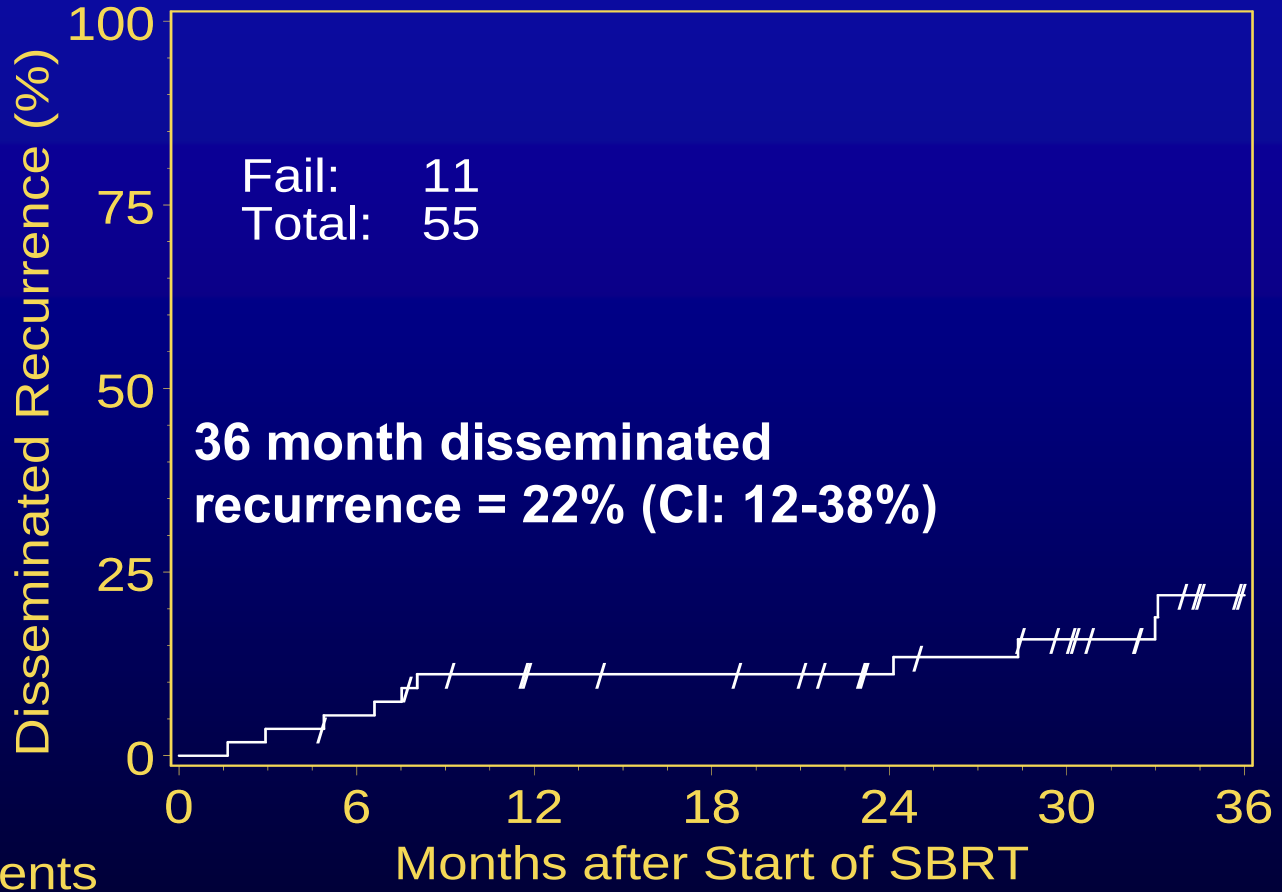
Local Control

- 1 failure within PTV, 0 within 1 cm of PTV



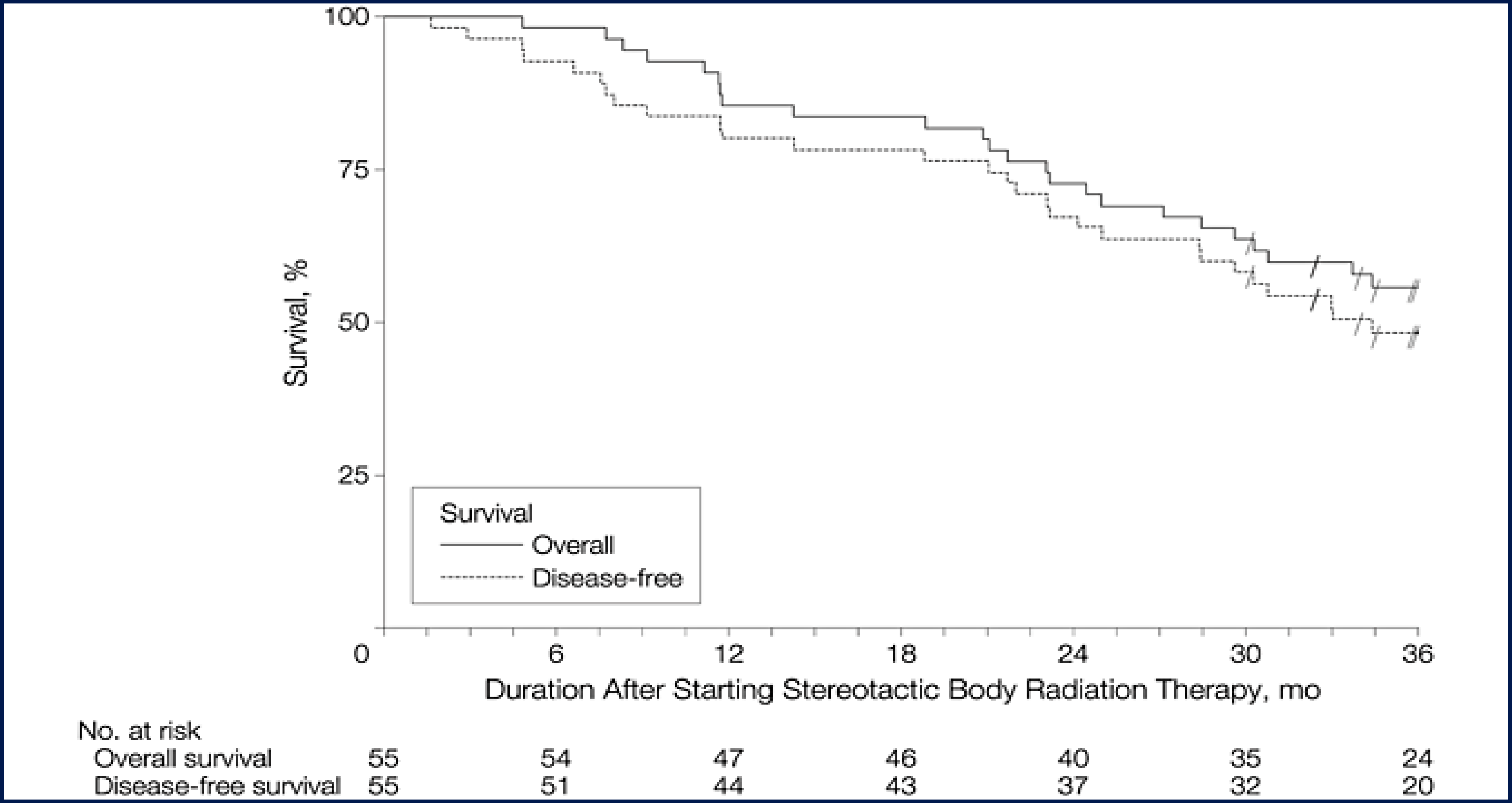
Disseminated Recurrence

- 6 patients (11%) disseminated within 1 year of Rx



Patients at Risk	55	51	44	43	38	33	21

RTOG 0236: Patient Course After Initiation of Stereotactic Body Radiation Therapy



Timmerman, R. et al. JAMA 2010;303:1070-1076.

RTOG 0236: Adverse Events Related to Stereotactic Body Radiation Therapy

Table 4. Adverse Events Related to Stereotactic Body Radiation Therapy[a]

	No. of Patients by Tumor Grade (N = 55)					No. of First Evaluable Patients by Tumor Grade (n = 49)				
	1	2	3	4	5	1	2	3	4	5
Blood or bone marrow	3	1	2	0	0	3	1	2	0	0
Cardiovascular	1	1	0	0	0	1	1	0	0	0
Coagulation	1	0	1	0	0	1	0	1	0	0
Constitutional symptoms	11	8	1	0	0	11	7	1	0	0
Dermatology or skin	3	2	2	0	0	3	1	2	0	0
Gastrointestinal tract	4	1	1	0	0	4	1	1	0	0
Hemorrhage or bleeding	0	2	0	0	0	0	2	0	0	0
Infection	0	1	2	0	0	0	1	2	0	0
Lymphatics	2	0	0	0	0	2	0	0	0	0
Metabolic or laboratory	2	1	1	1	0	2	1	1	1	0
Musculoskeletal or soft tissue	3	5	3	0	0	3	3	3	0	0
Neurology	3	2	1	0	0	3	2	1	0	0
Pain	5	9	0	0	0	5	6	0	0	0
Pulmonary or upper respiratory tract	11	13	8	1	0	11	11	8	1	0
Renal or genitourinary	1	0	0	0	0	1	0	0	0	0
Most severe, No. (%)										
Nonhematologic	13 (24)	17 (31)	13 (24)	2 (4)	0	13 (27)	14 (29)	13 (27)	2 (4)	0
Overall	13 (24)	17 (31)	13 (24)	2 (4)	0	13 (27)	14 (29)	13 (27)	2 (4)	0

[a] Includes adverse events in which relationship to treatment was missing.

Timmerman, R. et al. JAMA 2010;303:1070-1076.

JAMA

Protocol-Specified Adverse Events Related to Stereotactic Body Radiation Therapy

Table 5. Protocol-Specified Adverse Events Related to Stereotactic Body Radiation Therapy[a]

	Patients by Tumor Grade					
	All (N = 55)			First Evaluable (n = 49)		
Adverse Event	3	4	5	3	4	5
FEV_1	2	0	0	2	0	0
Hypocalcemia	0	1	0	0	1	0
Hypoxia	2	0	0	2	0	0
Pneumonitis NOS	2	0	0	2	0	0
Pulmonary function test decreased NOS	3	1	0	3	1	0
Maximum for protocol, No. (%)	7 (13)	2 (4)	0	7 (14)	2 (4)	0

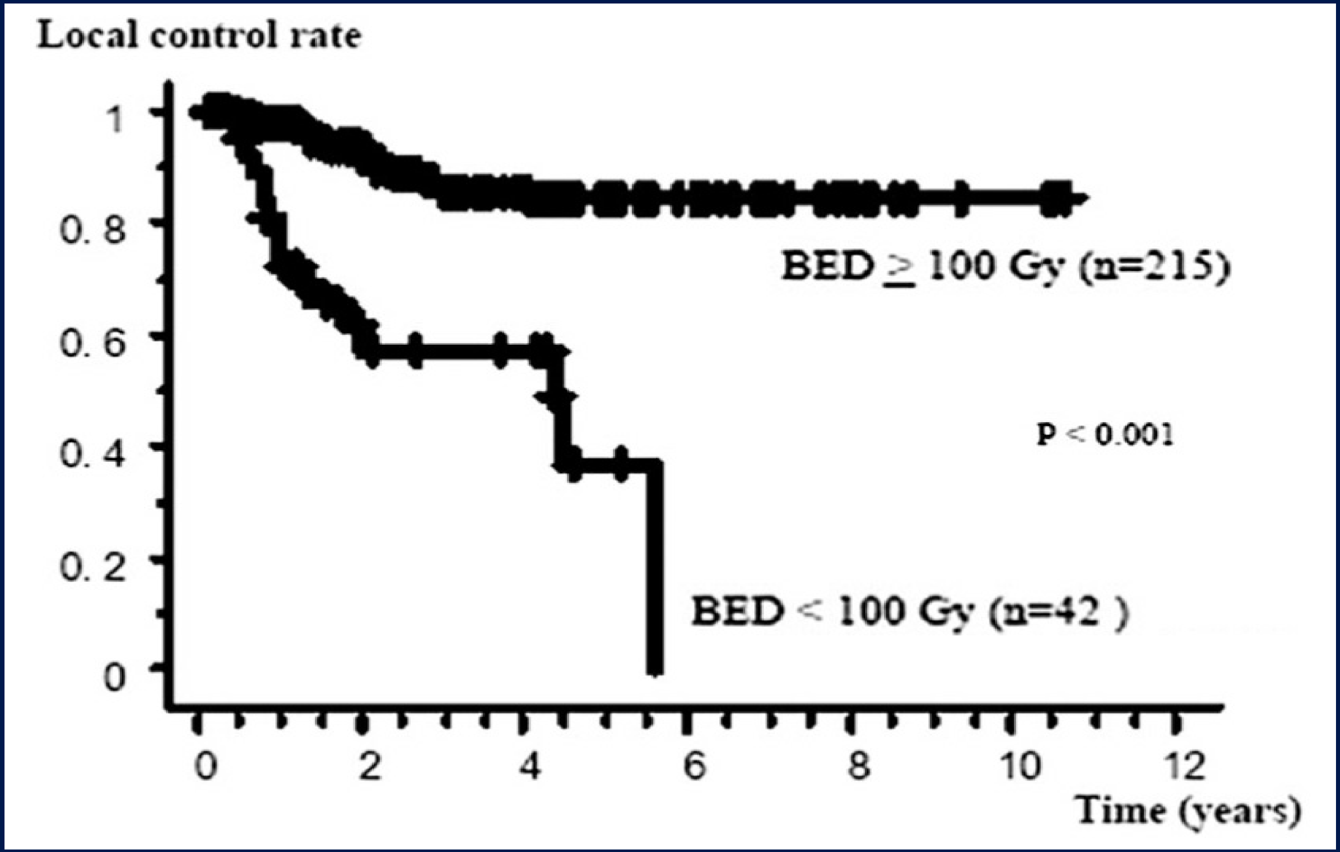
Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; NOS, not otherwise specified.
[a] Includes adverse events in which relationship to treatment was missing.

JAMA

Rationale of High Dose per Fraction RT

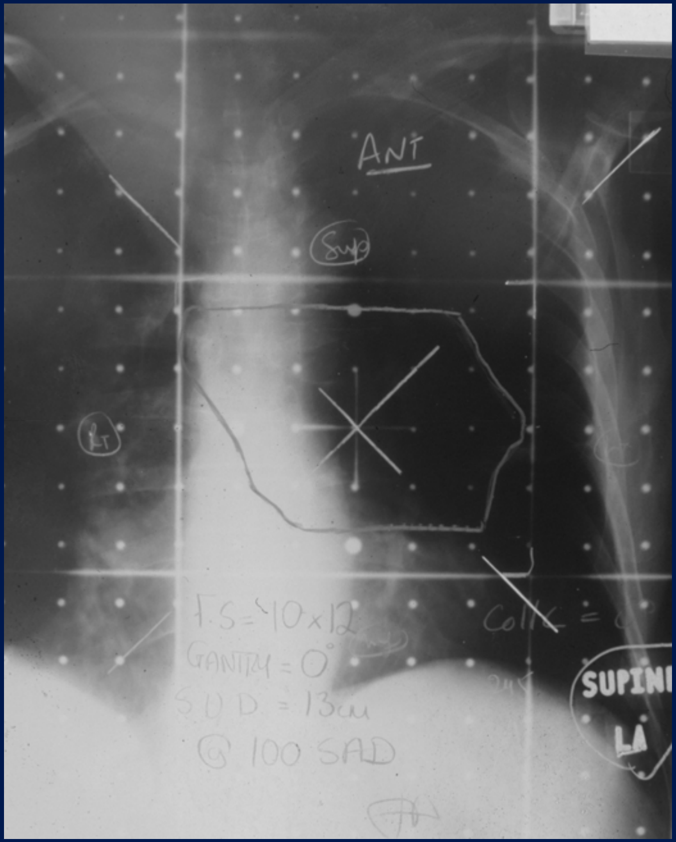
- By radiobiologic principles, the higher dose per fraction, the greater the damage to the tumor (and normal structures)
  - Biologic equivalent dose (BED)
- *BED = nd (1 + d/(α/β))*
- So assuming *α/β* = 10, then 20 Gy x 3 is equivalent to 180 Gy given in conventional fractionation

Results and BED



•Onishi, et al., *J Thor Onc*, 2007

Typical Verification Film



Techniques for IGRT Imaging

- Two dimensional imaging
  - Fluoroscopy-type imaging, Cyber Knife
  - Usually need fiducial marker (gold seed)
- Mega Voltage Cone Beam Imaging
  - Uses the treatment machine as a CT scan
- Kilo Voltage Cone Beam Imaging
  - Adds an extra machine to the treatment machine that functions as a CT scanner

Varian kV Imaging system (OBI)

- kV source, kV detector, and MV detector all mounted on robotic arms

Cyber Knife

Technique for Lung SBRT

- Simulation day
  - Advanced patient immobilization
  - 4D Treatment planning CT
  - Consider PET scan for tumor delineation
- Treatment Planning
  - Five days
- Treatment day(s)
  - Advanced patient immobilization
  - Image guidance
  - Patient adjustment
  - Re-image
  - Treat

Immobilization

Institution	*SBRT*
Beaumont	hybrid α-cradle with BodyFix
MSKCC	α-cradle
UT Southwestern	body frame
Washington U	body frame or BodyFix

4D Planning CT

Institution	*SBRT*
Beaumont	10 phases
MSKCC	10 phases
UT Southwestern	10 phases
Washington U	MIP

PET Fusion

Institution	*SBRT*
Beaumont	100%
MSKCC	0%
UT Southwestern	sometimes
Washington U	rarely

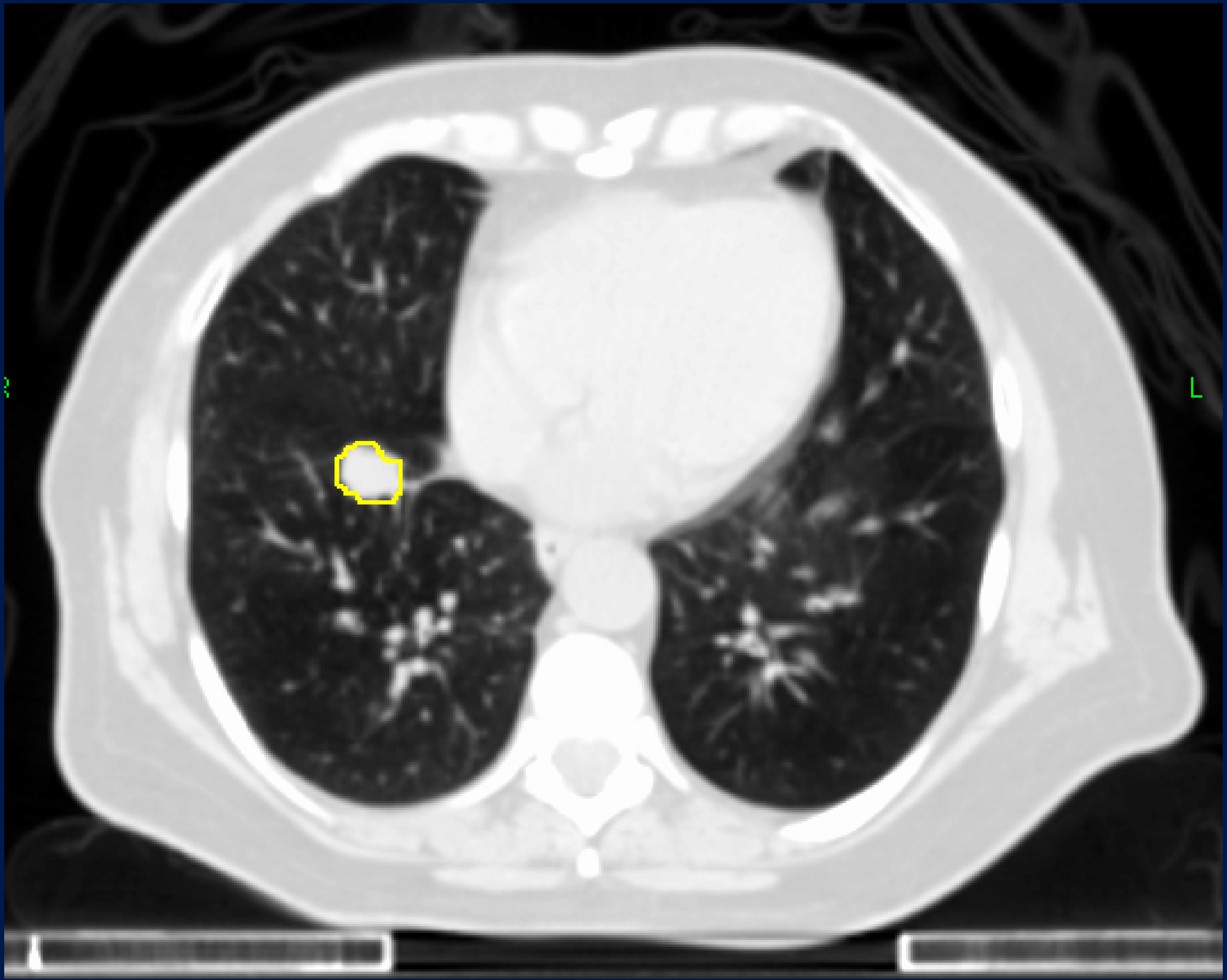
Determining Tumor Volumes

- GTV – gross tumor volume
- ITV – internal target volume
  - Accounts for tumor motion
- CTV – clinical target volume
  - Accounts for microscopic extension
- PTV – planning target volume
  - Accounts for set-up error, etc.

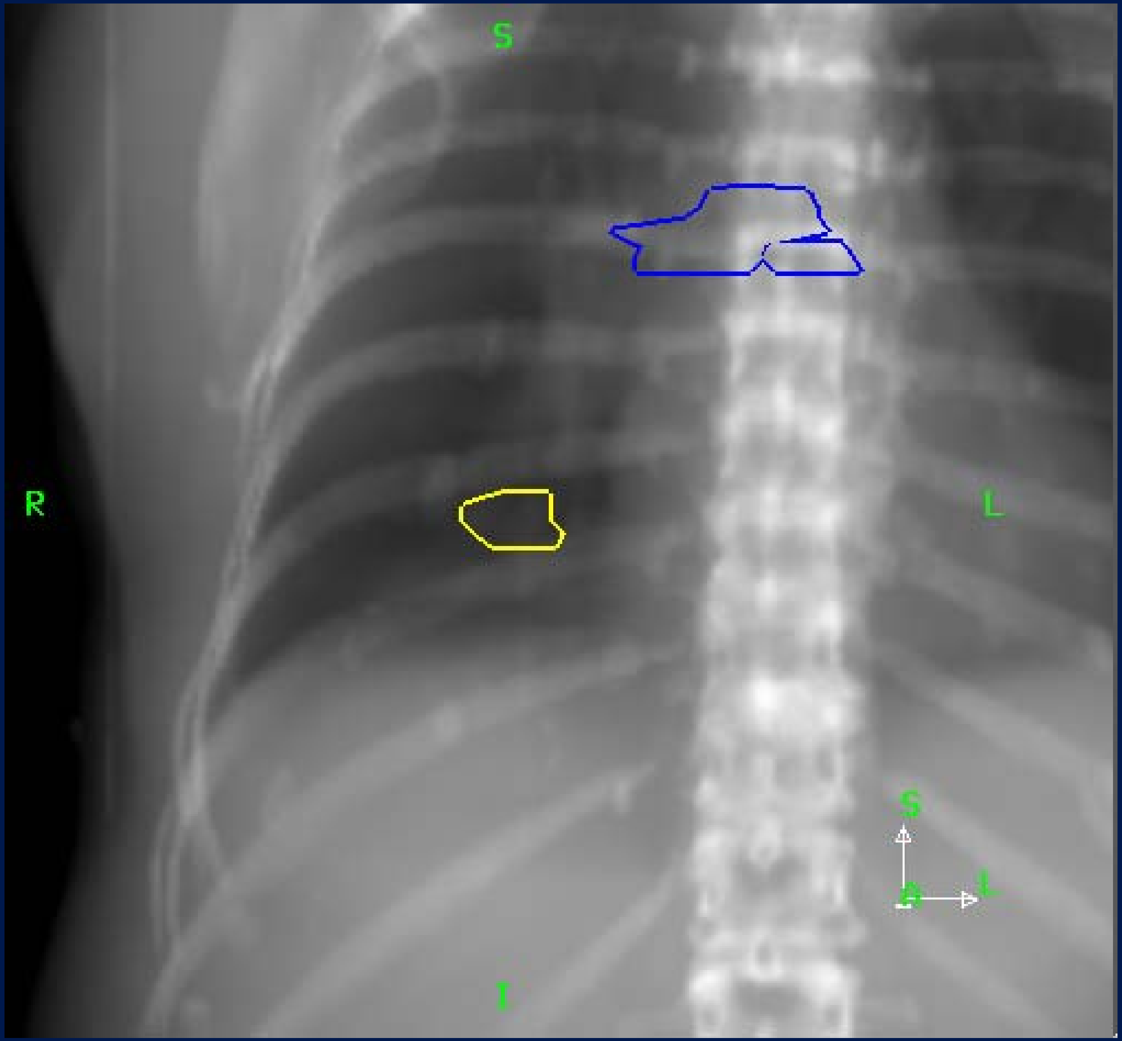
Target Delineation

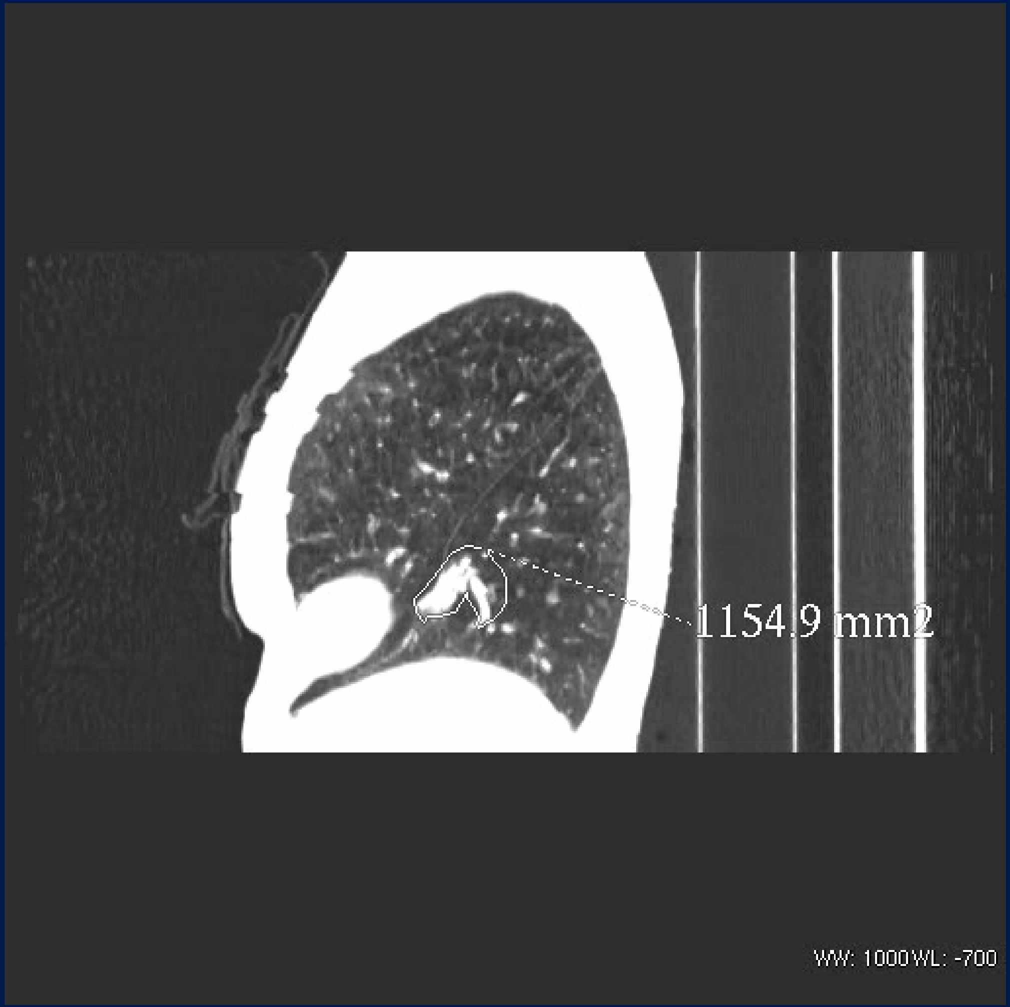
Institution	*ITV*	*CTV*	*PTV*
Beaumont	$GTV_1 \cup GTV_2 \cup \ldots GTV_{10}$	ITV + 5 mm	CTV + 5 mm (IGRT) CTV + 10 mm (no IGRT)
MSKCC	$GTV_1 \cup GTV_2 \cup \ldots GTV_{10}$	ITV + 0-2 mm	CTV + 5 mm (IGRT) CTV + 10 mm (no IGRT)
UT Southwestern	GTV from MIP	ITV + 5-10 mm	CTV + 4 mm (IGRT) CTV + 5-10 mm (no IGRT)
Washington U	GTV from MIP	ITV	CTV + 5 mm (IGRT) CTV + 7 mm (no IGRT)

Determining the GTV

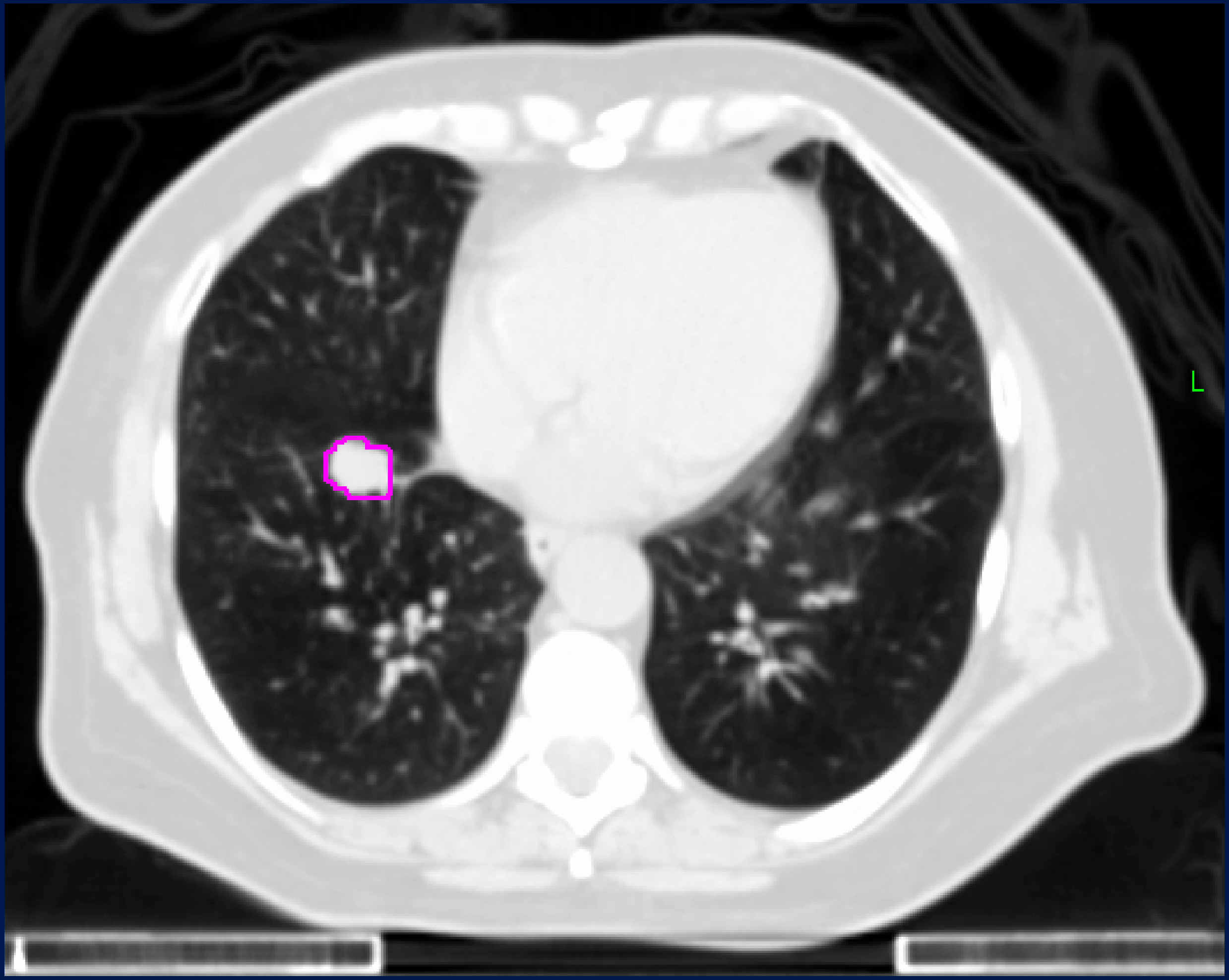


Determining the GTV

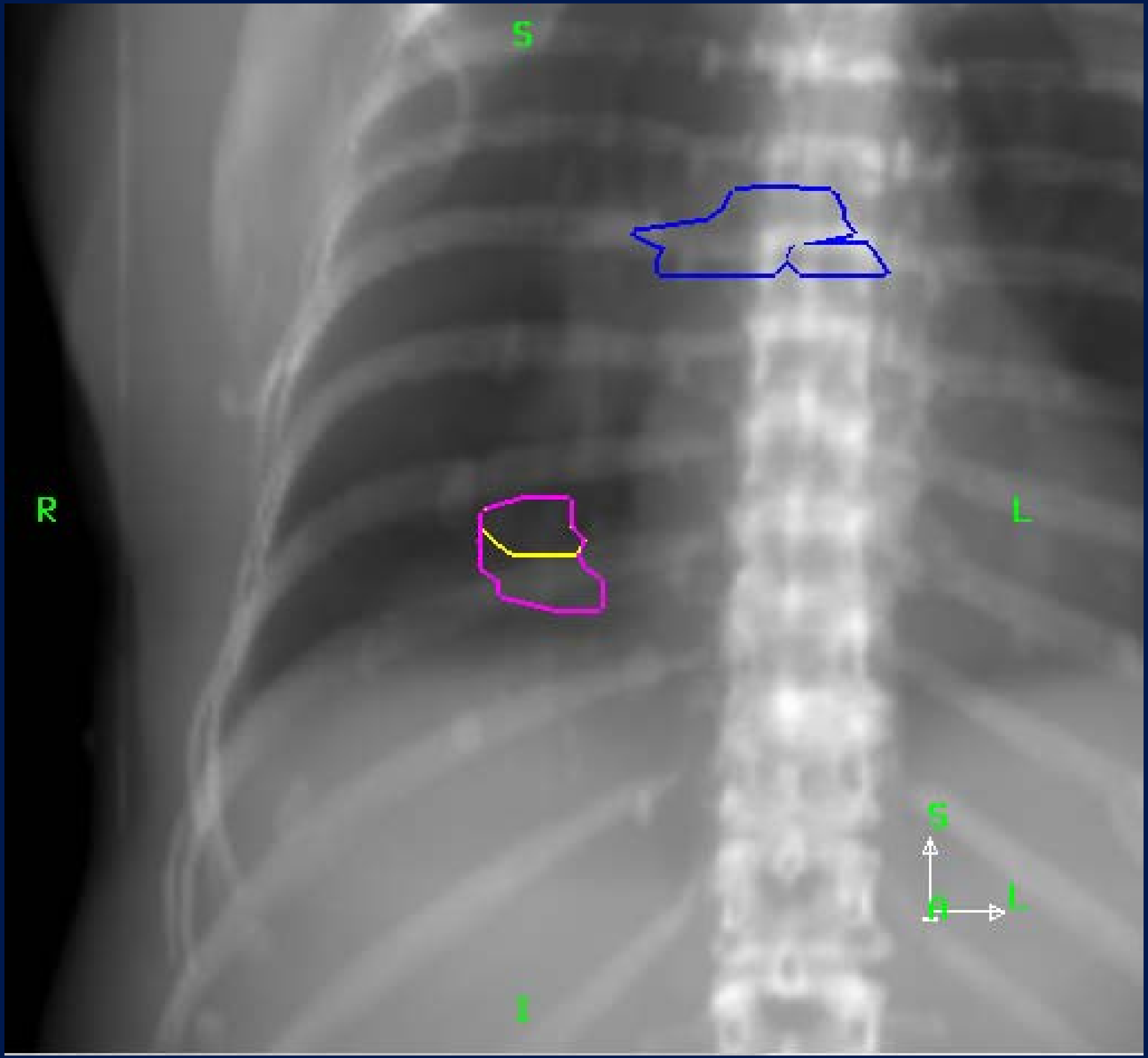



1154.9 mm2
WW: 1000WL: -700

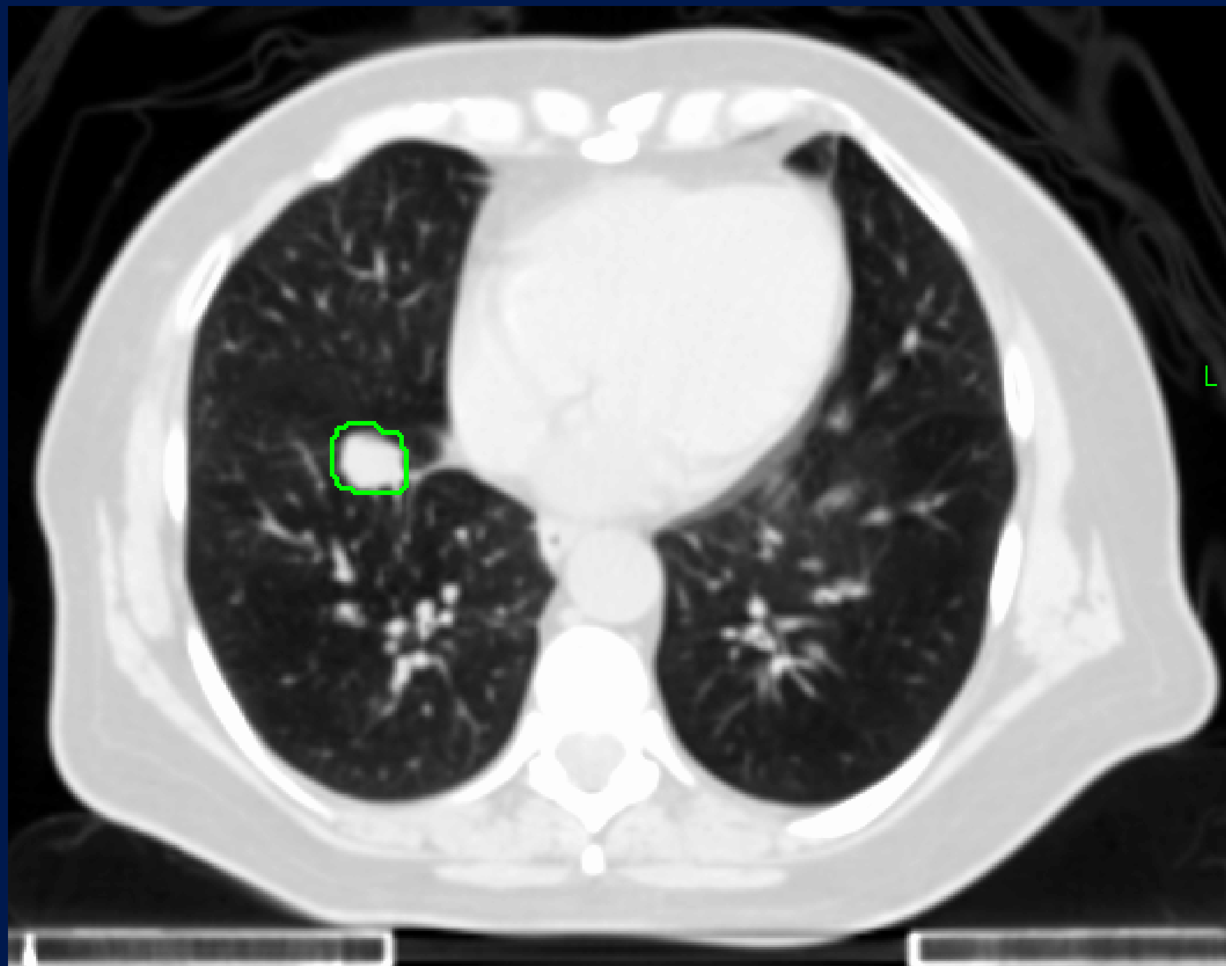
Determining the ITV



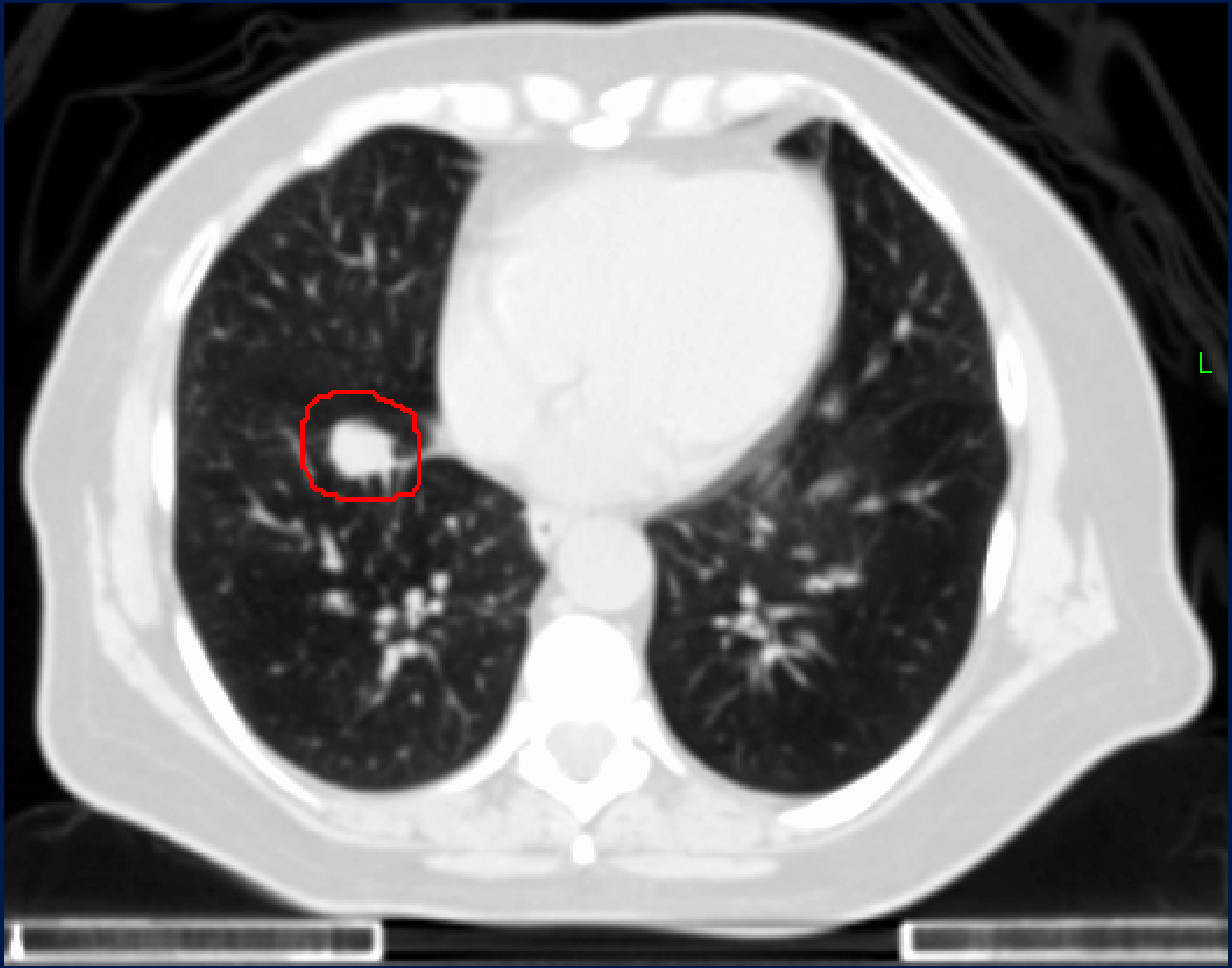
Determining the ITV



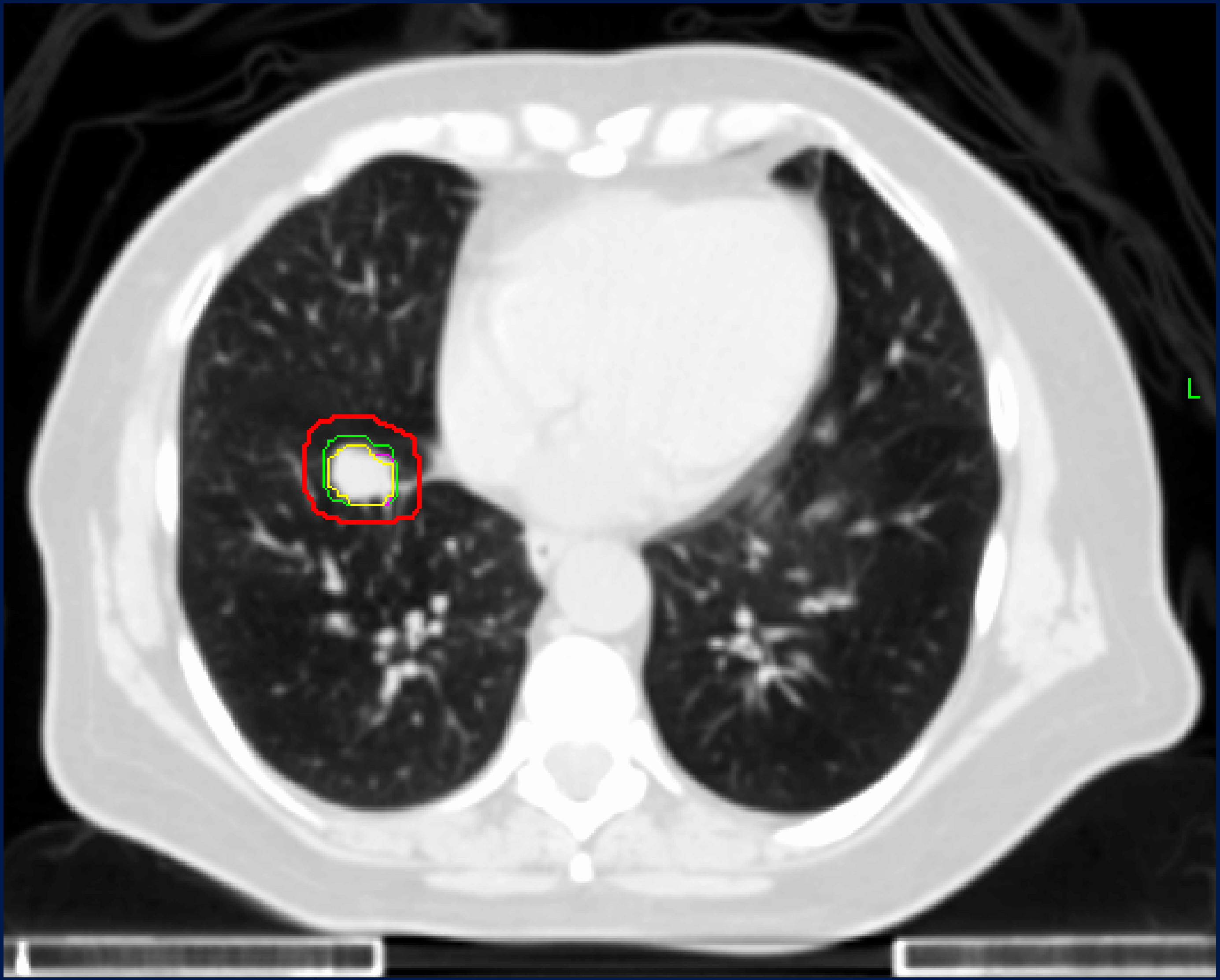
Determining the CTV



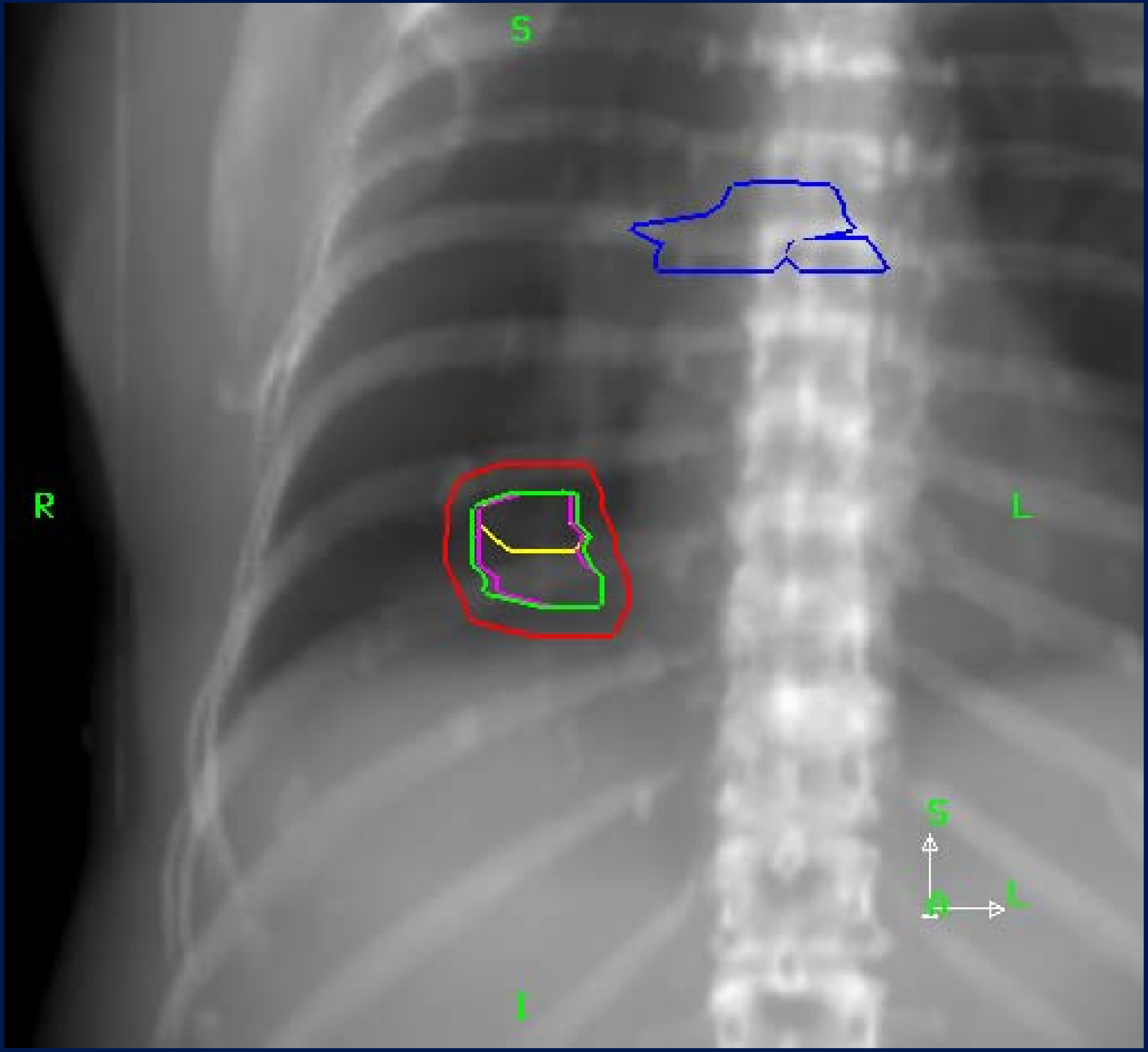
Determing the PTV



All Tumor Volumes



All Tumor Volumes



Normal Structure Constraints – SBRT

Institution	*Lungs*	*Esophagus*	*Spinal Cord*
Beaumont	4 fractions: $V_{20} \leq 10\%$ $V_{12.5} \leq 15\%$	4 fractions: $D_{mean} \leq 30.5$ Gy	4 fractions: cord+3 mm $D_{max} \leq 20.5$ Gy
MSKCC	3 fractions: both lungs $V_{20} < 12\%$ ipsi lung $V_{20} < 25\%$	3 fractions: $D_{max} \leq 30$ Gy	3 fractions: $D_{max} \leq 24$ Gy
UT Southwestern	3 fractions: $D_{1000cc} < 12.4$ Gy $D_{1500cc} < 11.6$ Gy $V_{20} < 15\%$?	3 fractions: $D_{max} < 25.2$ Gy $D_{5cc} < 17.7$ Gy	3 fractions: $D_{max} < 21.9$ Gy $D_{0.35cc} < 18.0$ Gy $D_{1.2cc} < 12.3$ Gy
Washington U	3 fractions: $D_{1000cc} < 12.4$ Gy $D_{1500cc} < 11.6$ Gy $V_{20} < 15\%$?	3 fractions: $D_{max} \leq 27$ Gy	3 fractions: $D_{max} \leq 18$ Gy

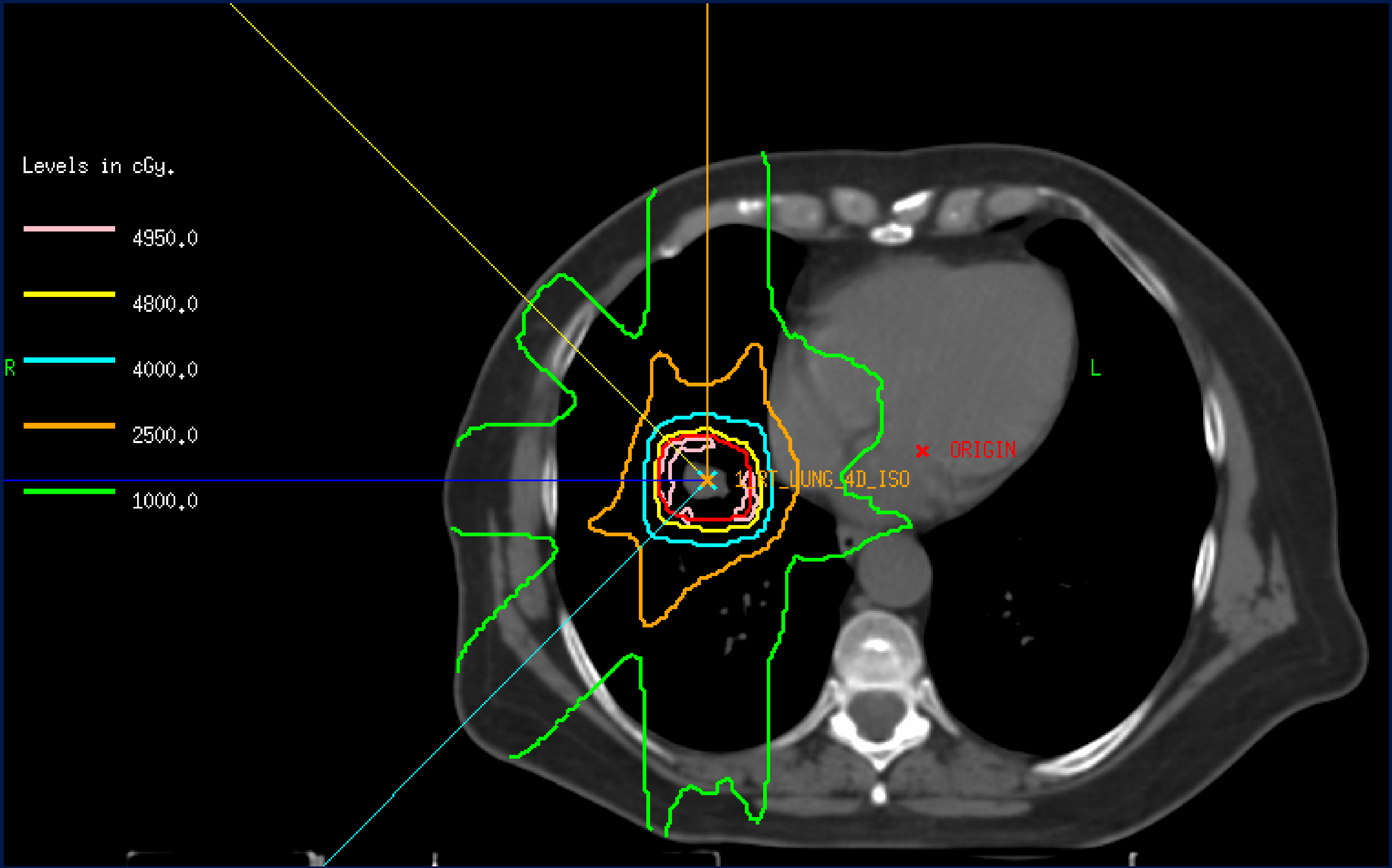
Normal Structure Constraints – SBRT

Institution	*Proximal Bronchial Tree*	*Heart*	*Great Vessels*	*Brachial Plexus*
Beaumont	4 fractions: $D_{max} \leq 34$ Gy	4 fractions: $D_{max} \leq 36$ Gy	4 fractions: $D_{max} \leq 36$ Gy	4 fractions: $D_{max} \leq 27.2$ Gy
MSKCC	3 fractions: $D_{max} \leq 30$ Gy	none	none	3 fractions: $D_{max} \leq 27$ Gy
UT Southwestern	3 fractions: $D_{max} < 30$ Gy $D_{4cc} < 15$ Gy	3 fractions: $D_{max} < 30$ Gy $D_{15cc} < 24$ Gy	3 fractions: $D_{max} < 45$ Gy $D_{10cc} < 39$ Gy	3 fractions: $D_{max} < 24$ Gy $D_{3cc} < 20.4$ Gy
Washington U	3 fractions: $D_{max} \leq 30$ Gy	3 fractions: $D_{max} \leq 30$ Gy	none	3 fractions: $D_{max} \leq 24$ Gy

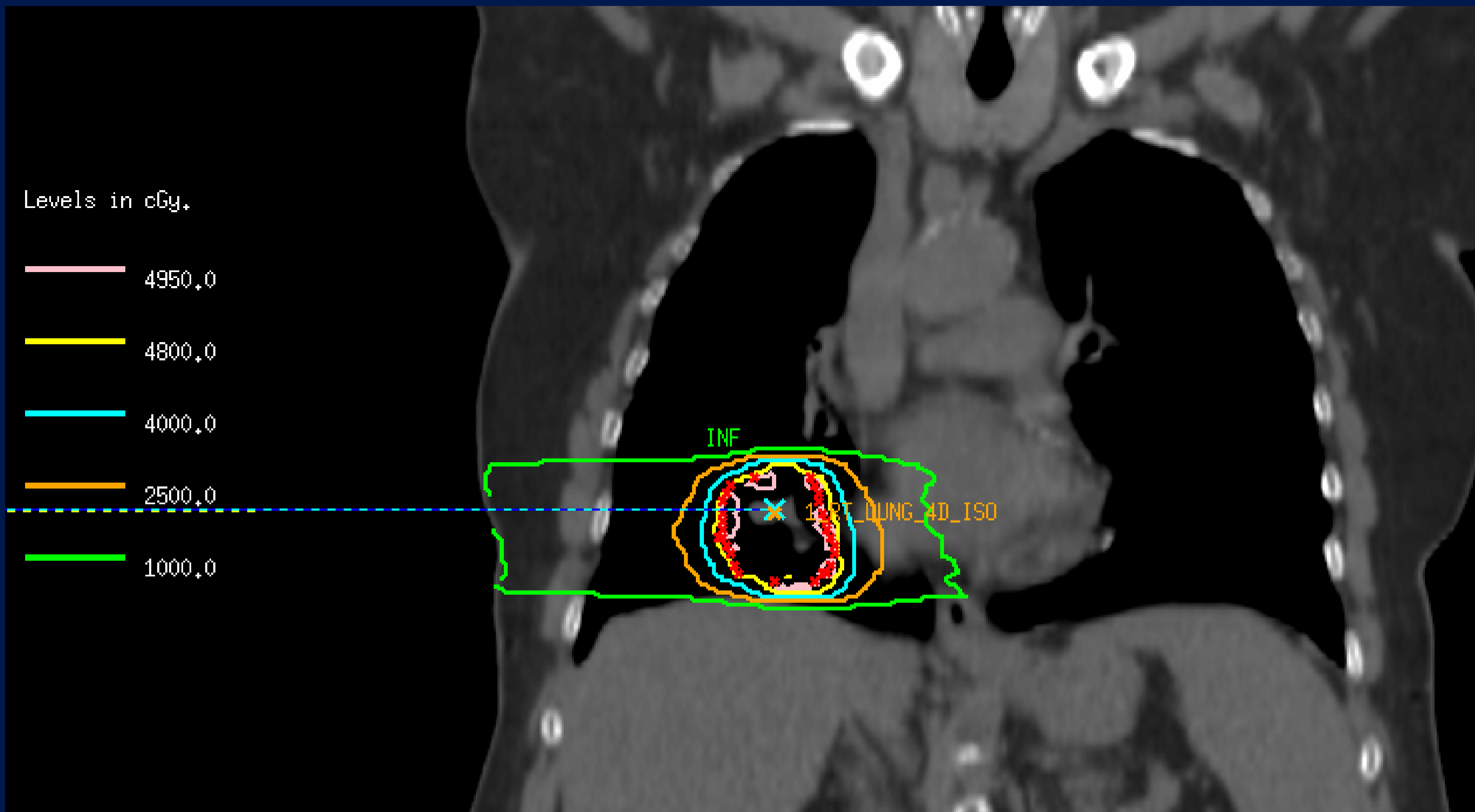
Target Dose for NSCLC SBRT

Institution	*PTV*	*Prescription*
Beaumont	peripheral ≤ 3 cm: 12 Gy × 4 = 48 Gy peripheral > 3 cm: 12 Gy × 5 = 60 Gy central: 10 Gy × 5 = 50 Gy	PTV D_{95} ≥ 100% Rx dose
MSKCC	peripheral: 18-20 Gy × 3 = 54-60 Gy central: 9 Gy × 5 = 45 Gy	PTV D_{95} ≥ 100% Rx dose
UT Southwestern	peripheral: 18 Gy × 3 = 54 Gy chest wall: 12 Gy × 5 = 60 Gy central: 10 Gy × 5 = 50 Gy	PTV D_{95} ≥ 100% Rx dose PTV D_{100} ≥ 90% Rx dose
Washington U	peripheral: 18 Gy × 3 = 54 Gy central: 10 Gy × 5 = 50 Gy	PTV D_{95} ≥ 100% Rx dose

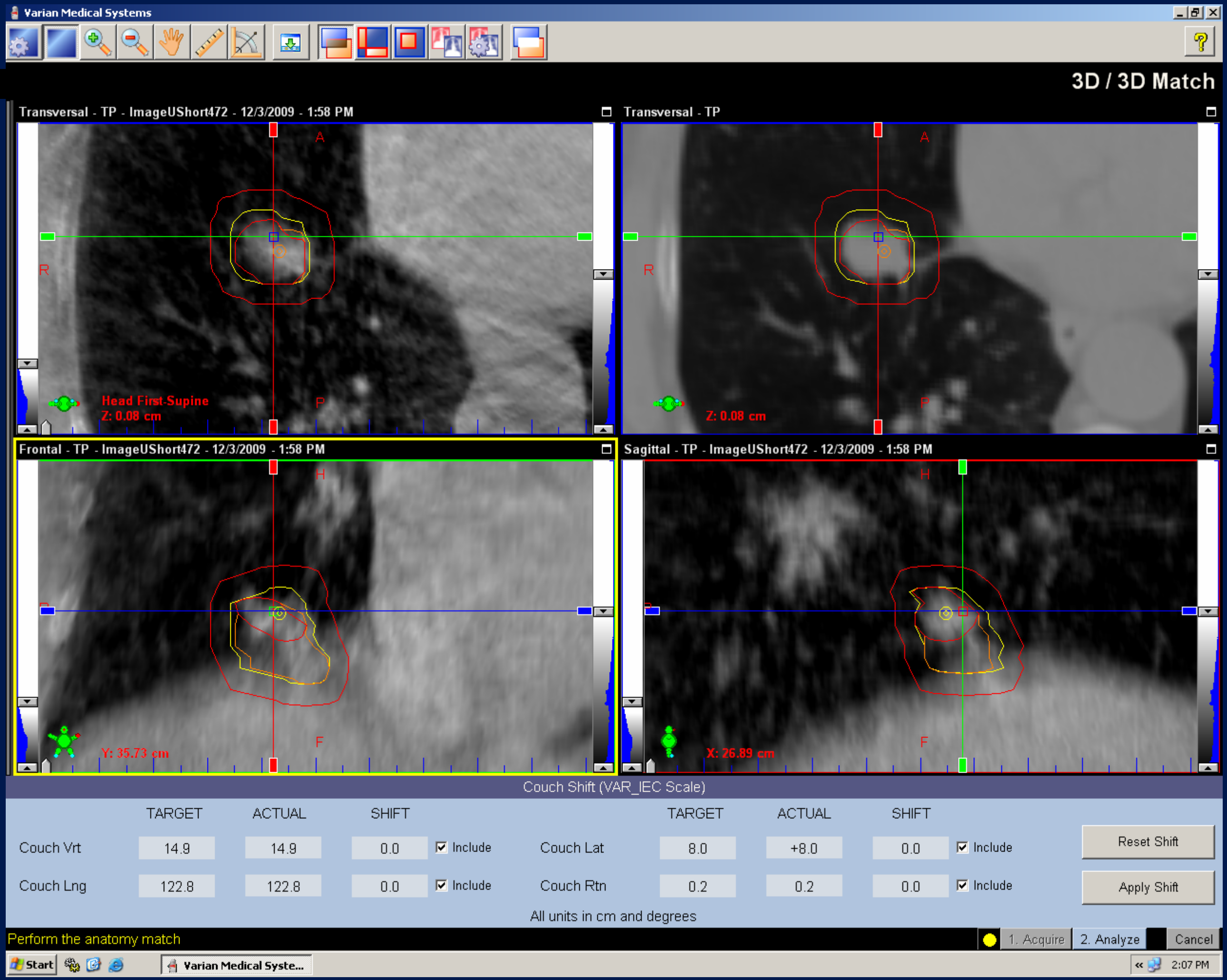
Treatment Plan



Treatment Plan



Verifying Patient Position



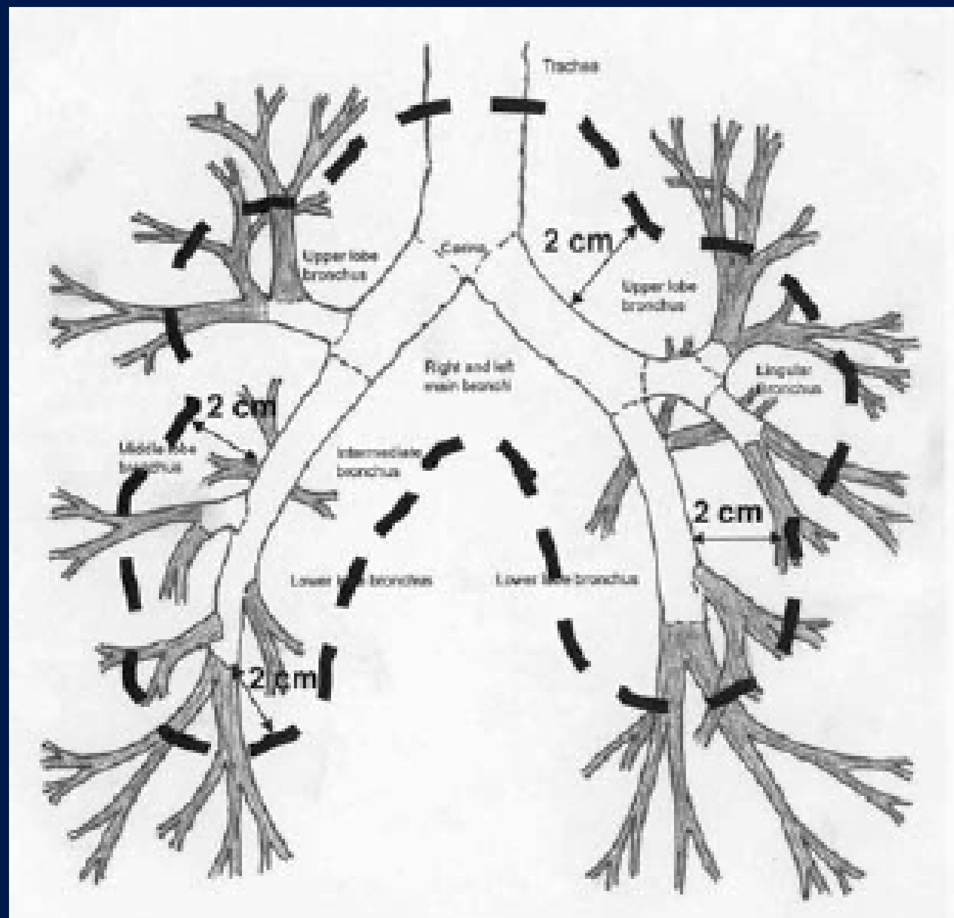
Toxicity of SBRT

- Fatigue
- Skin reaction
- Pneumonitis
- Pain

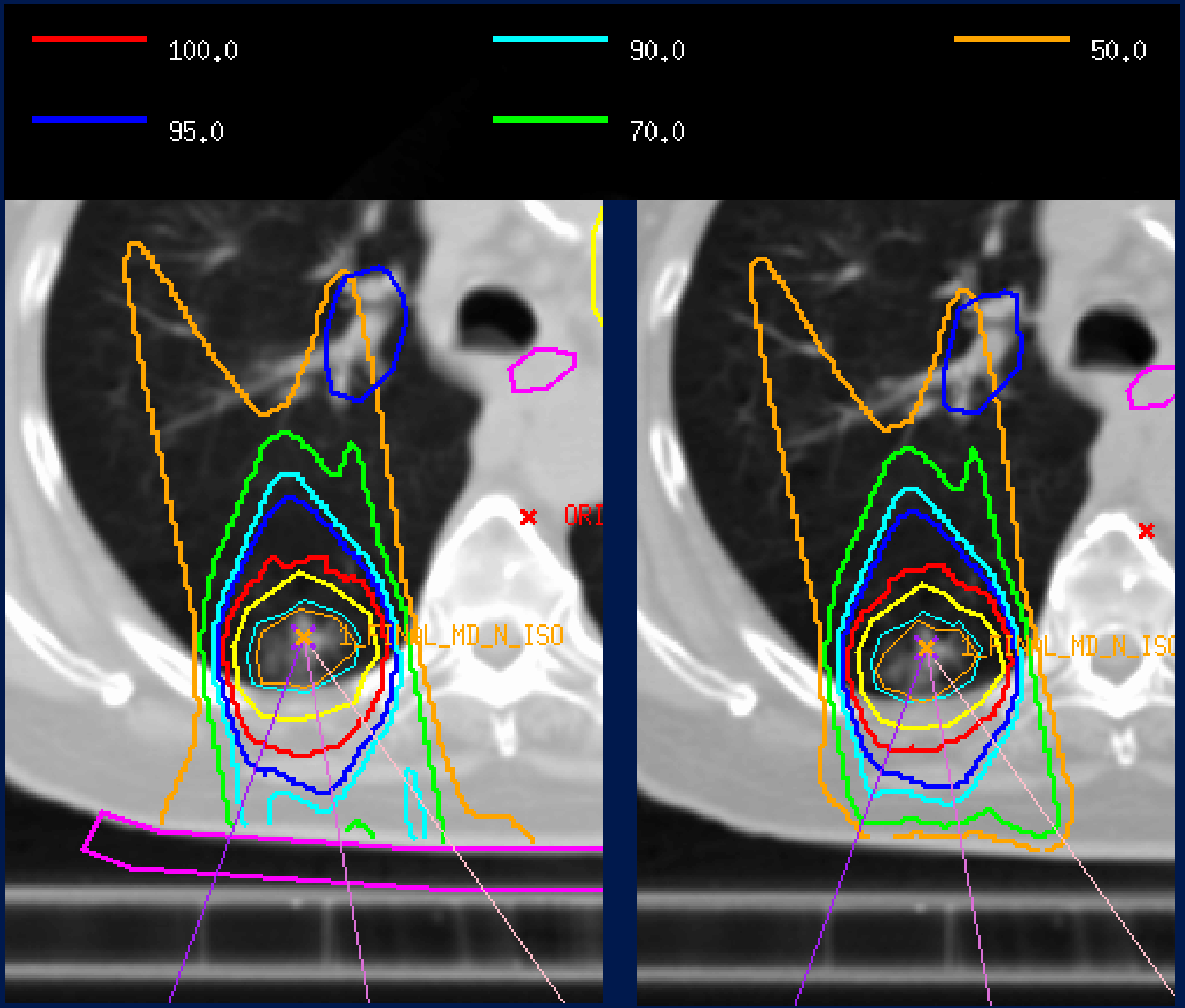
Toxicity of Lung SBRT

- Timmerman, et al. *JCO* 2006
- 70 pts with Stage I NSCLC in a Phase II protocol
- 20 Gy x 3 or 22 Gy x 3
- Median overall survival 33 months, 2 yr OS 55%
- 14 patients had Grade 3 to 5 toxicity
  - 8 Grade 3/4 - ↓PFT's, effusion, pneumonia
  - 6 toxic deaths – pneumonia, pericardial effusion, hemoptysis
  - Central tumors more likely to have toxicity

Limitations of SRS in the Lung
“No Fly Zone”

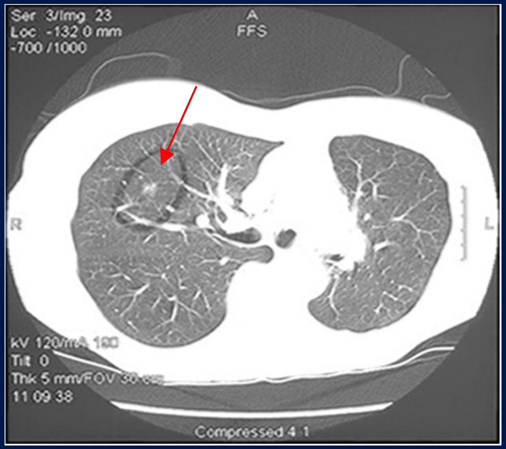



ocean
ocean

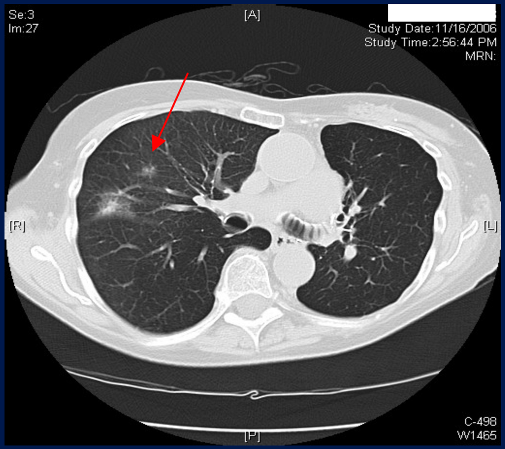


100.0
90.0
50.0
95.0
70.0
ORI
1_FINAL_MD_N_ISO
1_FINAL_MD_N_ISO

Changes in Technique to Limit Skin Toxicity

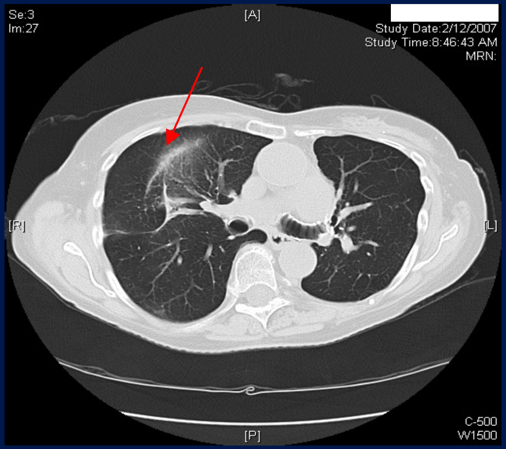
- Use of Alpha cradle to allow lateralized beams
- Use more than 3 beams to prevent overlap
- Evaluate skin as an organ at risk



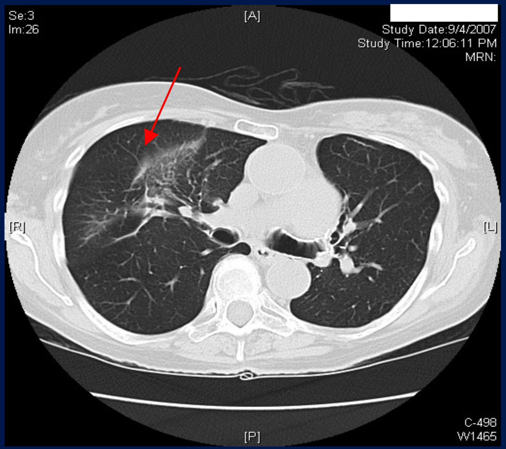
0 months



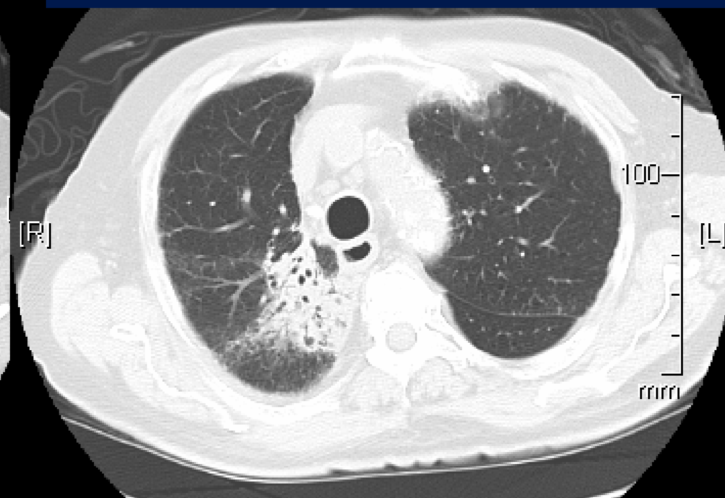
3 months



6 months



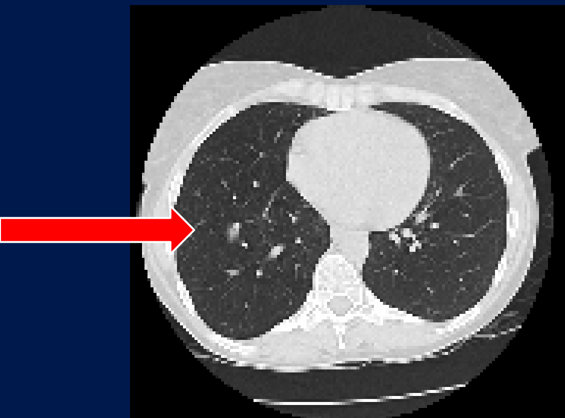
15 months



Pre-treatment

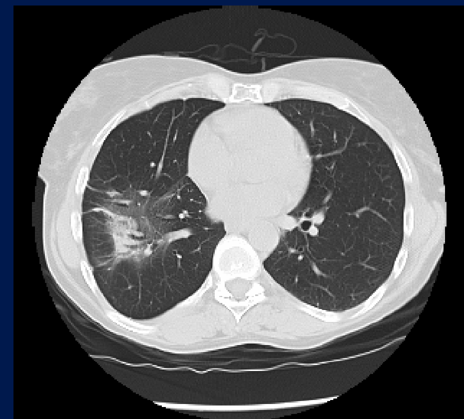
3 month

6 month

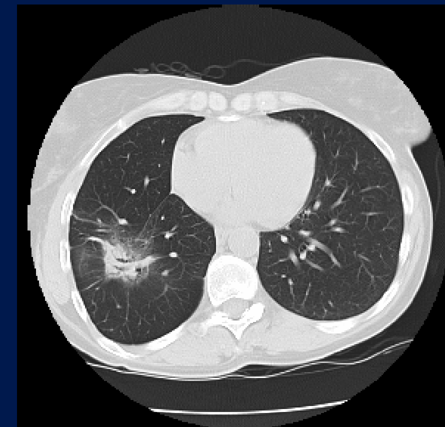


Pre-treatment

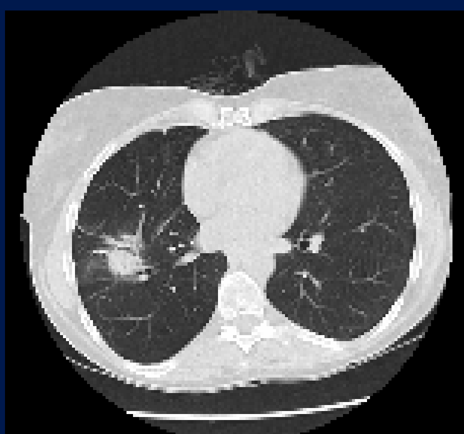
3 month



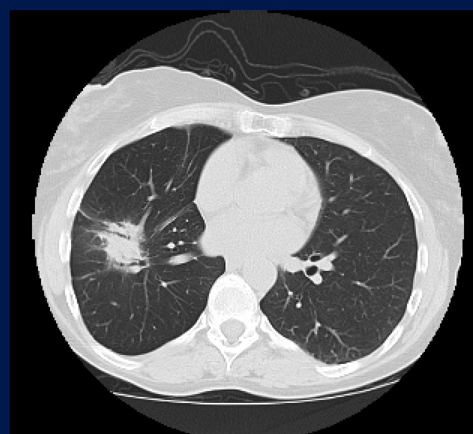
6 month



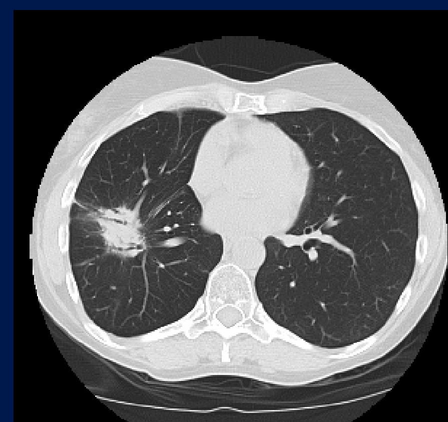
9 month



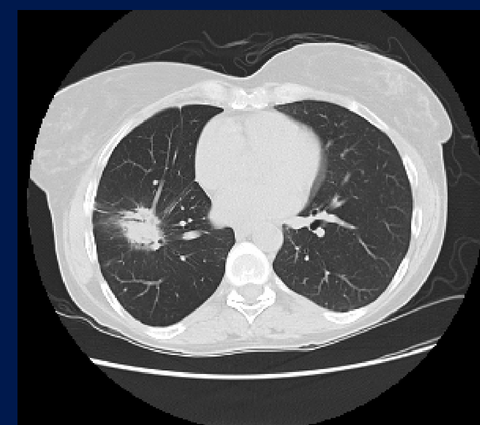
12 month



16 month



20 month



24 month

Differences between centers

- Use of 3D-CRT or IMRT
- Variable use of inhomogeneity corrections
- Use of more beams (8 – 10 in many protocols)
- Image guidance not always used
- Tumor motion not evaluated
- Variability in tumor margins

Why do all techniques work?

- The use of multiple beams and high doses is causing a “haze” of moderate dose radiation (~15 Gy per fraction) that is adequate to kill subclinical disease and account for tumor motion

SBRT – Future Directions

- Standardize CTV, PTV, inhomogeneity corrections, tumor motion control
- Identify best dose
  - Might need to dose **de-escalate**
- Figure out how to treat central tumors
  - Some centers (VU, Wash U.) have been reporting safe early experience with 7. 5 – 10 Gy per fraction
  - RTOG 0813 to address this (currently at 10.5 Gy/fx)
- Test head to head against surgery
  - Japanese are doing this

Future in Early Stage

- Current RTOG protocol in operable patients
  - RTOG 0618 closed May 2010
- Future research needs:
  - Longer term results
  - Better ways to assess response
  - ? Need for a randomized trial vs. standard RT

Future Directions in Toxicity

- For the first time there is a possibility for long-term follow-up in a lung cancer population treated with RT
- Allows for better analysis for the causes of second tumors, specific toxicities (lung fibrosis), etc.