Treatment of Lung Cancer

Dr Tejinder Kataria MD
Chairperson Radiation Oncology
Medanta-The Medicity

Incidence of lung cancer

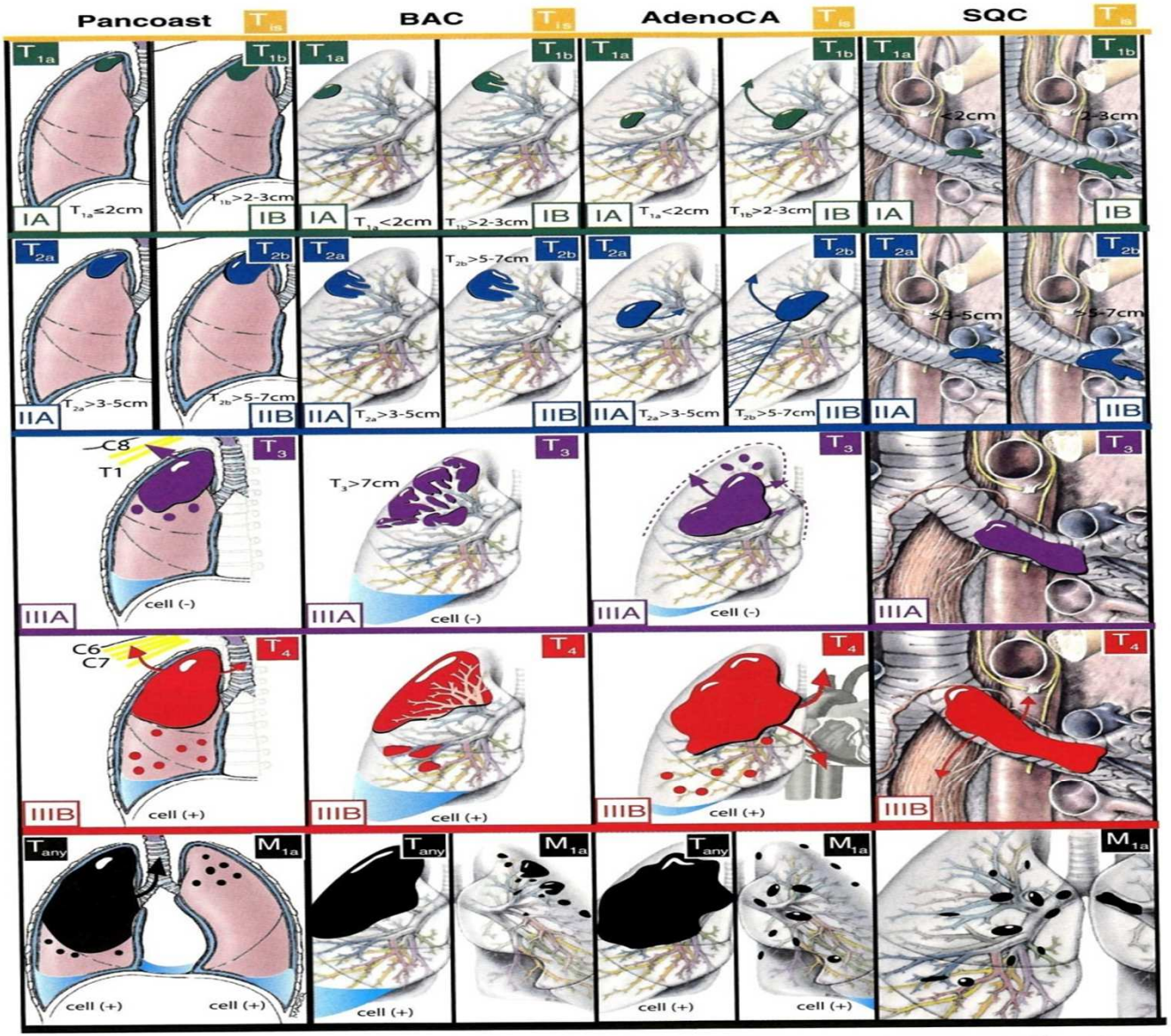
- 13% of all cancers worldwide(1.6million cases)
- 18% of all cancer related deaths(1.4 million)
- Treatment Nihilism due to large number of patients succumbing to primary disease except in EGFR/MET-ALK/EML4 tumours

Orientation of Histogenesis of Primary Cancer Sites

Primary Site Normal Anatomic Structures	Derivative Normal Cell	Cancer Histopathologic Type Primary Site	Thorax Axial Level Assigned*
Terminal bronchiole	Simple cuboidal	Pancoast cancer (adenocarcinoma)	T1-2
Respiratory bronchiole, acini, alveoli	Type II pneumocyte	Bronchioloalveolar cancer	T2-3
Segmental bronchi	Goblet cell ciliated columnar	Adenocarcinoma with mixed subtypes	T3-4
Bronchial neuroendocrine cells	Transdifferentiated neuroendocrine	Large cell anaplastic cancer	T4-5
Main bronchi	Metaplasia of pseudostratified columnar cells	SQCC	T5-6
Lobar bronchi	Dedifferentiated stem cell ~Lung bud	Small cell cancer	T6-7
Visceral parietal pleura and space	Mesothelial cell	Mesothelioma	T7-8
Breast (chest wall)	Breast duct and lobule cells	Adenocarcinoma	T8-9
Esophagus (mediastinum and diaphragm)	Stratified squamous cell	SQCC	T9-10

SQCC, squamous cell cancer.

*Assigned thoracic axial level is designed to encompass and illustrate the different thoracic anatomic sectors and planes.



The T criteria are varied for each histopathologic type of lung cancer in their manifestation due to their anatomic location and origin, the bronchial tree. Pancoast cancer arises in superior sulcus and advances by local invasion into juxta-opposed structures. Bronchioloalveolar cancer (BAC) arises in the acini peripherally and advances by lepidic spread via alveolar pores of Kohn. Adenocarcinomas (AdenoCA) arise in lobar bronchi and advance by producing lobar atelectasis and pneumonitis. Squamous cell cancers (SQC) tend to arise in main bronchi and advance to the carina. All lung cancer types can become multifocal in the lobe, they arise in T3, or spread into lung of origin T4, or spread to contralateral lung M1.

Orientation of Sentinel Lymph Nodes (see Fig. 12.5)

Primary Site Structure	Sentinel Node(s) (Fig. 12.5)	AJCC Thorax Number Assigned (Fig. 12.5B)
Pancoast	Scalene	IR/IL
Bronchioloalveolar	Intrapulmonary, hilar	12, 10
Adenocarcinoma	Interlobar, hilar	11, 10
Large cell anaplastic	Hilar	10
SQC	Carinal	4R/4L/7
Small cell cancer	Mediastinal	3, 4, 5, 6
Mesothelioma	Intercostal (posterior, mediastinal, hilar)	3p, 8, 9
Breast	Axillary, internal mammary	1, 2, 5
Mediastinum	Paratracheal, pericardial	2, 3, 4, 5, 6
Esophagus	Paraesophageal	2, 3, 4, 5, 6

AJCC, American Joint Committee on Cancer; SQC, squamous cell cancer.

Anatomic Distribution of Distant Metastases of Lung

Site of Metastasis	Squamous (%)	Small Cell Anaplastic (%)	Large Cell Anaplastic (%)	Adenocarcinoma (%)
Lymph nodes	137 (54)	163 (85)	135 (76)	42 (75)
Liver	58 (23)	122 (54)	67 (38)	26 (47)
Adrenals	54 (21)	84 (44)	69 (39)	17 (30)
Bones	59 (21)	75 (39)	53 (30)	23 (41)
Brain	26 (17)	45 (42)	30 (24)	13 (39)
Kidney	39 (15)	28 (14.5)	24 (13.5)	11 (20)
Pancreas	9 (3.5)	46 (24)	25 (14)	3 (5)
Lung	31 (12)	13 (7)	15 (8)	8 (14)
Pleura	18 (7)	21 (11)	9 (5)	3 (5)
Total	255	191	179	56

From Line DH, Deeley TJ. The necropsy findings in carcinoma of the bronchus. *Br J Dis Chest* 1971;65:238–242, with permission.

Imaging Modalities for Diagnosis and Staging

Method	Capability	Recommended
Primary tumor and regional nodes workup		
Chest films	**Baseline image**	**Yes**
CT/spiral CT	Most useful of all modalities for determining characteristics of T and N in the thorax and M in the brain and liver	Yes
MRI	**Not as good as CT**	**No**
Percutaneous needle biopsy	Guided by fluoroscopy or CT, accurate in establishing cytologic diagnosis from T (particularly peripheral lung lesions); M (especially liver or bone); less experience with N	Yes
Mediastinoscopy/ thoracoscopy	**Confirmation of nodal involvement**	**Yes**
Metastatic work-up for clinically suspected metastases		
CT/echography	**For liver, adrenals**	**Yes**
CT/MRI	For brain	Yes
Bone scan	**For the bone**	**Yes**
PET scan	Diagnosis of peripheral lesions can differentiate between cancer and benign lesions. Staging of true extent of primary and lymph node involvement.	Yes, if clinically indicated

CT, computed tomography; M, metastasis; MRI, magnetic resonance imaging; N, node; PET, positron emission tomography; T, tumor.

Summary of changes in Seventh edition

- NSCLC,SCLC and Carcinoids are staged through TNM
- T-Classification revision-
- T1 subclassified into-T1a(<2cm)and T1b(>2-3 cm)
- T2 subclassified into T2a(>3-5cm)and T2b(5-7cm)
- T2(7cm)has been reclassified as T3
- Multiple tumour nodulesin same lobe are now T3 and not T4
- Multiple tumor nodules in same lung but different lobe are now T4 and not M1
- No change in N stage
- M-M1a-malignant pleural and pericardial effusion are now M1a and not T4
- M1b-distant metastases

Stage summary Matrix

	N0	N1	N2	N3	M1
T1	IA	IIA	IIIA	IIIB	IV
T2	IB	IIB	IIIA	IIIB	IV
T3	IIB	IIIA	IIIA	IIIB	IV
T4	IIIB	IIIB	IIIB	IIIB	IV

Thorax : Lung Cancers

- **N stage determines stage group**
  - **N0, N1, N2, N3a, N3b are stage group I, II, IIIA, IIIB**
- **N1 can be associated with T1 or T2**
- **T stage modifies substages**
  - **T1, T2, N0= IA, IIB and Tq, T2 N2= IIA, IIB**
- **M stage is a separate stage**
  - **M1=IV**
- **Exceptions are:**
  - **BAC only has T progression by definition**
  - **SCA is either limited or extensive (i.e., M0 or M1 independent of T or N stages)**

Treatment Algorithms

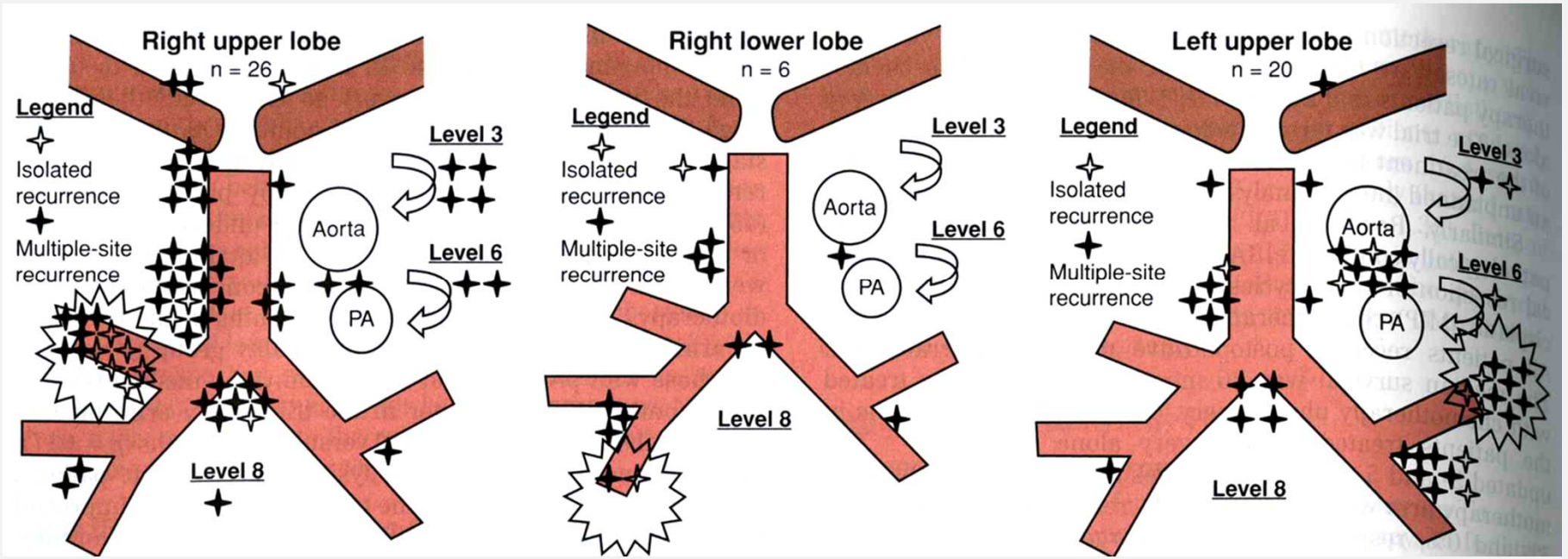
- NSCLC-50%patients present with disseminated disease
- Stage I and II-Surgical resection is the treatment of choice with lobectomy or pneomonectomy +mediastinal lymphadenectomy.
- LCSG showed 17% risk of failure with wedge resction vs 6% with lobectomy in 276 patients of T1N0,T2N0 disease.
- Series from MSKCC showed an 82% survival at 5 years and 74% at 10 years in T1N0 and 68%@5 years /60% @10 years for T2N0tumors
- ACOSOG Z0030-1,111 patients randomized to mediastinal lymph node sampling vs mediastinal lymph node dissection-68% vs 69% 5 years DFS

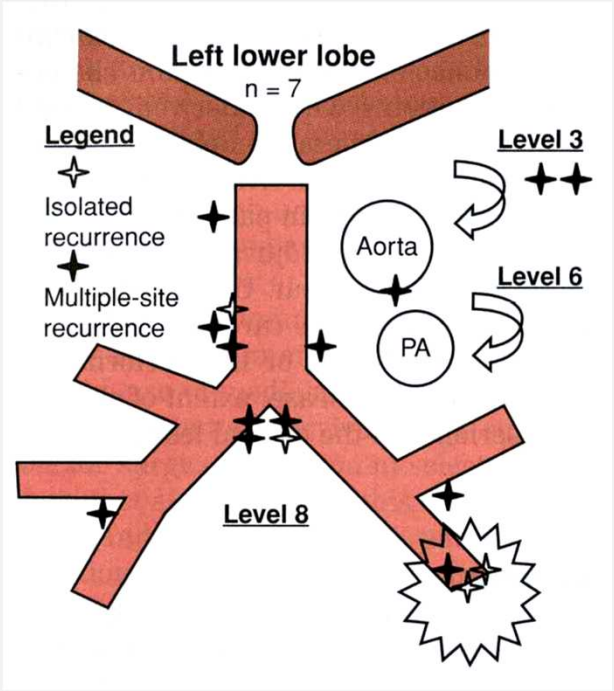
- EGFR /MET-ALK/EML4-Different category of tumours

- Cochrane Reviews1995-2010

Treatment Algorithms-SCLC

- Limited disease-Chemotherapy and concurrent radiation with Cycle 1 or 2(50-64Gy,once or twice daily protocols)
- Prophylactic cranial radiation after 4 weeks of completion of chemotherapy(36-40Gy)
- Extensive disease-Chemotherapy followed by thoracic radiation 45-54GY gives better results
- (RTOG-0937 and CREST-The Dutch study are ongoing and results are awaited)


Right upper lobe
n = 26
Legend
Isolated recurrence
Multiple-site recurrence
Aorta
PA
Level 3
Level 6
Level 8
Right lower lobe
n = 6
Legend
Isolated recurrence
Multiple-site recurrence
Aorta
PA
Level 3
Level 6
Level 8
Left upper lobe
n = 20
Legend
Isolated recurrence
Multiple-site recurrence
Aorta
PA
Level 3
Level 6
Level 8


Left lower lobe
n = 7
Legend
Isolated recurrence
Multiple-site recurrence
Aorta
PA
Level 3
Level 6
Level 8

SURGERY ALONE VERSUS NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY IN STAGE III NON-SMALL LUNG CANCER

Author	Patients	CT	Stages	Resection Rates PCT/Surgery (%)	Or Rates (%)	pCR	Operative Mortality PCT/Surgery (%)	Median Survival PCT/Surgery (Months)
Dautenberg et al	26	C/V/P	I, II, IIIA	-	45	-	0	23 vs 21
Depierre at al	375	M/I/P	IB, II, IIIA	92 vs 86	64	11	7.8 vs 4.5	37 vs 26 (p=0.09)
Pass et al	27	E/P	IIIA N2	85 vs 86	61	7.6	0	28.7 vs 15.6 (p=.09)
Rosell et al	60	M/I/P	IIIA	85 vs 90	53	3.3	6.6 vs 6.6	26 vs 8 (p=.001)
Roth et al	60	C/E/P	IIIA	61 vs 66	35	3.6	3 vs 6	21 vs 14 (p=.056)

Outcome of Radiation therapy/dose and treatment volume for Early stage NSCLC

Author (Reference)	Patients	Dose (Gy)	Local Field (%)	Grade 3-5 Toxicity	Intercurrent Death	Overall survival (%)		Cause-Specify Survival (%)	
						1 year	2 year	3 year	5 year
Dosoretz et al	152	76% , 60-69	Minority	0%	11	-	10	-	-
Graham et al	103	Median, 60	20	1%	28	-	13	-	-
Haffty et al	43	59 Continuous or 54 split	-	0%	-	36	21	-	-
Kaskowitz et al	53	Median, 63	<10	8%	27	19	6	33	13
Krol et al	108	60 or 65	100	0%	34	31	15	42	31
Noordijk et al	50	60 split	100	0%	40	33	17	-	-
Rosenzweig et al	55	≥80	100	7%	2	-	36	-	-
Sandler et al	77	Median, 60	10	Minimal	16	17	14	22	17
Sibley et al	141	Median, 64	27	1.5%	43	24	13	-	-
Talton et al	77	60	0	0%	-	21	17	-	-
Zhang et al	44	50%, 55-61, 50%, 69-70	0	1 myelitis	20	55	32	-	-

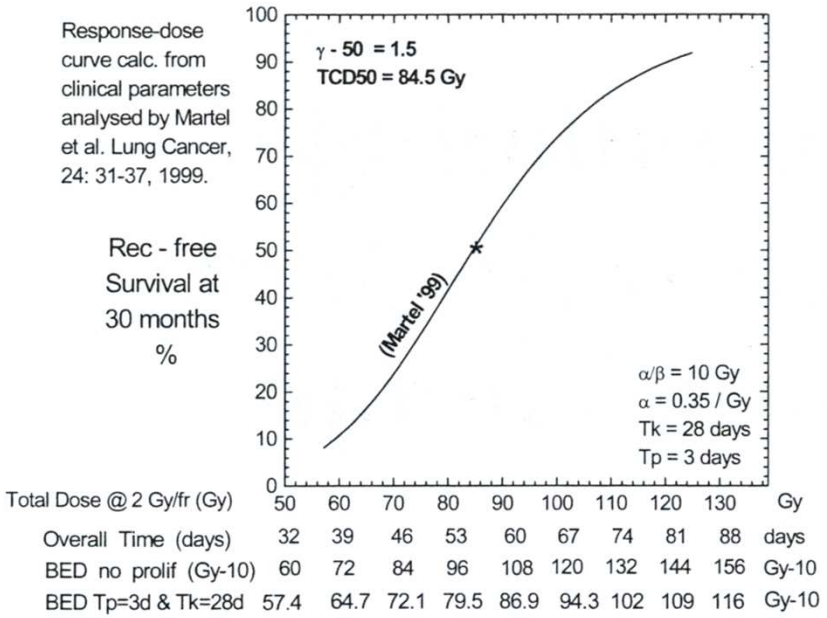
Sequential chemotherapy versus radiation therapy alone for locally advanced non-small cell lung cancer

Author (Reference)	RT (Gy)	CT	Sequence	No. of Patients	Median Survival (Months)	Overall survival (%)			
						1 year	2 year	3 year	5 year
Le Chevalier et al	65 65	- VCPC	- CT→RT→CT	177 176	10 12	41 51	14 21	4 12	- -
Morton et al	60 60	- MACC	- CT→RT	58 56	9.6 10.4	43 47	12 23	- -	7 5
Sause et al	60 60 69.6	- - PV	- CT→RT -	149 151 152	11.4 13.2 12	46 60 51	19 32 24	6 15 13	5 8 6
Diliman et al	60 60	- PV	- CT→RT	77 79	9.7 13.8	40 55	13 26	11 23	7 19
NSCLC Collaborative	32-65	Various	Neoadjuvant CT ;no concurrent CT	3,033	-	41 45	15.7 17.7	6.7 10.1	2.7 4.8

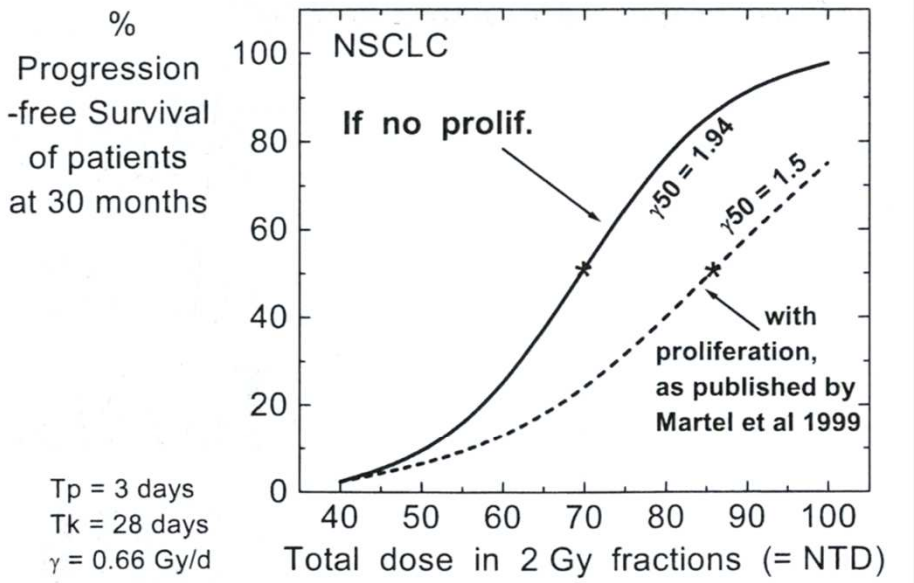
Concurrent chemo/radiotherapy for stage III NSCLC

Trial (reference)	Phase	Number of Patients	Additional Nonconcomitant Agents	Concomitant Chemotherapy	XRT Dose (Gy)	Median PFS (Months)	Median OS (Months)	2- Year OS	4- Year OS	5 – Year OS
RTOG 9801 (230)	III	243	+- Amifostine	Carbo + Pac	69.6bid	9	17.9.	39%	21%	16%
CALGB 9431 (219)	II	62	DDP + Gem	DDP + Gem	66	8.4	18.3	37%	17%	9%
		58	DDP + PAC	DDP + Pac	66	9.1	14.8	29%		
		55	DDP + Vinorelbine	DDP + Vinorelbine	66	11.5	17.7	40%		
Hoosier		203	+- Docetaxel	DDP + VP – 16	59.4	11	21.7	33%	20%	20%
CALGB 39801		182		Carbo + Pac	66	7	12	29%	14%	11%
		184	Carbo + Pac	Carbo + Pac	66	8	14	31%	17%	14%
LAMP (456)		74	Carbo + Pac (Induction)	Carbo + Pac	63	6.7	12.7	25%	NR	NR
		92	Carbo + Pac (adjuvant)	Carbo + Pac	63	8.7	16.3	31%	NR	NR
RTOG 9410 (207)		198	DDP + Vinblastine	_	63	NR	14.6	31%	12%	10
		198	-	DDP + Vinblastine	63	NR	17	37%	21%	16%
		198	-	VP- 16+ DDP	69.6bid	NR	15.2	32%	17%	13
West Japan (205)		156	-	MMC + Vindesine	56	10	15	35%	17%	15%
				+ DDP						
Czech (457)		102	-	DDP + Vinorelbine	60	11.9	16.6	NR	NR	NR
WJTOG0105 (221)		153	DDP + Vindesine +MMC	DDP + Vindesine	60 Split	8.2	20.5	45%	28%	175%
				+ MMC						
		152	Carbo + CPT – 11	Carbo + CPT – 11	60	8	19.8	40%	20%	17.8%
		156	Carbo + Pac	Carbo + Pac	60	9.5	22	45%	22%	19.5%
OLCSG 0007 (218)		99		DDP + Docetaxel	60	13.4	26.8	60.3%	30%	23%
		101		MMC + Vindesine	60	10.5	23.7	48.1%	23%	16%
				+ DDP						

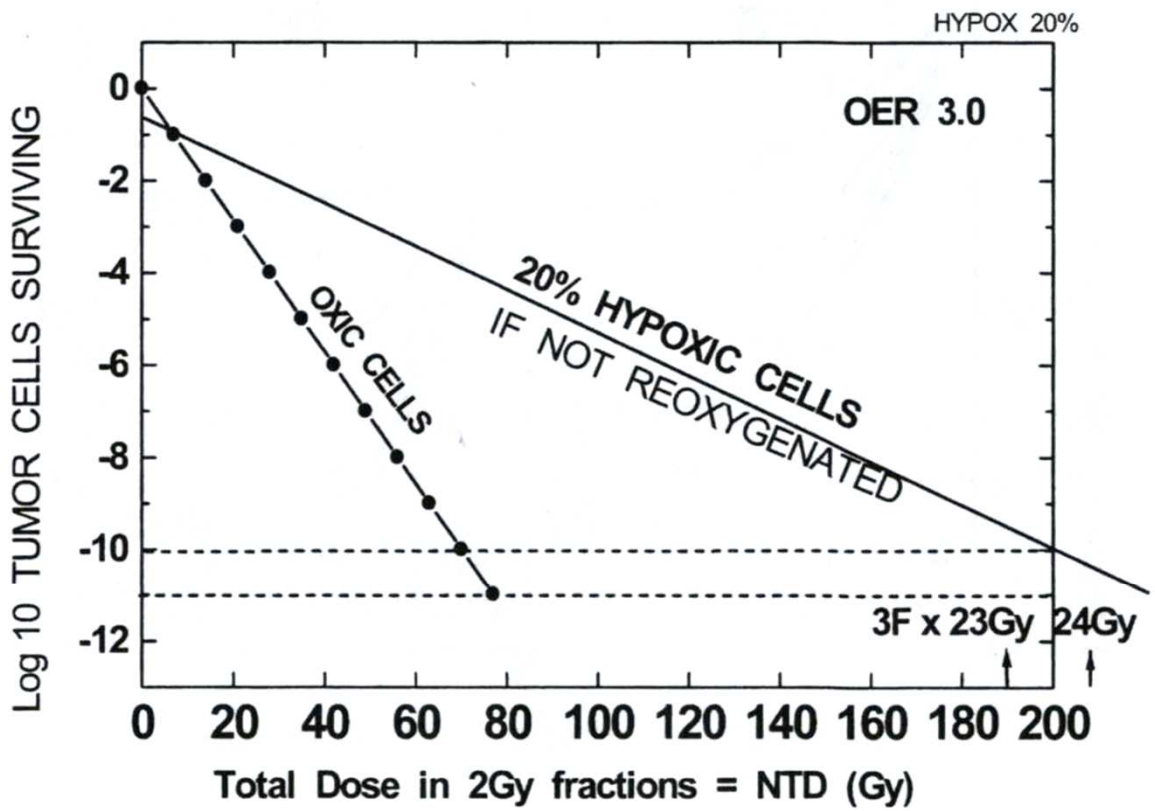
XRT radiotherpay; PFS progession – free survival ; OS, overall survival; carbo, carboplatin; Pac, paclitaxel; bid, twice daily; DDP, ciplatin; Gem, gemcitabine ; VP – 16, etoposide, NR, not reached ; MMC, miomycin C; CPT- II, irinotecan



Recurrence-free survival percentage at 30 months, calculated from Martel's parameters (14). In addition to the doses in 2 Gy per fraction at 5 F per week, the ordinate values also show the overall time in days, the BED (Gy 10) if zero proliferation is assumed, and (*fourth* line) the BED if proliferation at a cell doubling time of 3 days, starting at Time to repopulation (Tk) = 28 days (34), is assumed.



Recurrence-free survival percentage at 30 months. Lower [(*dashed*) *curve:* as in Fig. 1.1 including repopulation with 2 Gy given five fractions per week]. Upper (*full*) curve: the same data after subtracting the effect of proliferation from the x-axis at 0.66 Gy per day from the 28th day after starting irradiation of NSCLC, assuming Tk = 28 days, potential doubling time (Tp) = 3 days, $\alpha = 0.35$ ln/Gy, and $\alpha\beta = 10$ Gy.



Schematic diagram of cell survival curves for well-oxygenated cells (*full line with filled circles*), with a line of less slope representing 20% hypoxic cells remaining hypoxic throughout radiotherapy with 2-Gy fractions. The oxygen enhancement ratio is assumed to be 3. To reduce the proportion of surviving cells to 10^{-11} would require three fractions of more than 24 Gy.

For Typically Used Stereotactic Body Radiotherapy Schedules, the Tumor BEDs and NTDs Were Calculated by LQ with $\alpha\beta$ = 10 Gy. Then Progression-Free Survival of Patients with NSCLC at 30 months was Estimated from Martel (14) *with Proliferation Subtracted at Tp = 3days and Tk = 28 days (Fig. 1.2).* No Repopulation was Assumed to Occur in any SBRT Schedule, but it is Included in the 6- and 7-Week Standard Schedules

Total Dose	*Reference*	*BED Gy10*	*NTD, Gy 2-Gy Fractions)*	*Estimated Progression-free Survival at 30 Mo. (Assuming No Hypoxia)*
Conventional fractionation	—	(Fig. 1.8)	—	—
60 Gy, 30 fractions	—	72	60	15%
70 Gy, 35 fractions	—	84	70	24%
SBRT	—	(Fig. 1.9)	—	—
48 Gy, 4 fractions	(6)	106	63	34%
45 Gy, 3 fractions	(2)	113	94	95%
48 Gy, 3 fractions	(2)	125	104	99%
60 Gy, 5 fractions	(12)	132	110	>99%
60 Gy, 3 fractions	(3)	180	150	>99%
69 Gy, 3 fractions	(33)	228	190	>99%

BED, biologically equivalent dose; NTD, normalized total dose in 2-Gy fractions; SBRT, stereotactic body radiation therapy; NSCLC, non–small cell lung cancer; Tk, time to repopulation; Tp, potential doubling time; LQ, linear–quadratic.

Late-reaction BED and NTD for Some SBRT Schedules, Calculated by LQ with $\alpha\beta = 3$ Gy. For Comparison with the Lung Tolerance Dose Versus Veff Modeling from Ann Arbor, Amsterdam, and Stockholm (Figs. 1.11 and 1.12)

Total dose	*BED Gy3*	*NTD, Gy (2-Gy Fractions)*
Conventional fractionation		
70 Gy, 35 fractions	117	70
SBRT		
45 Gy, 3 fractions	270	162
48 Gy, 3 fractions	303	182
60 Gy, 5 fractions	300	180
60 Gy, 3 fractions	460	276
69 Gy, 3 fractions	598	359

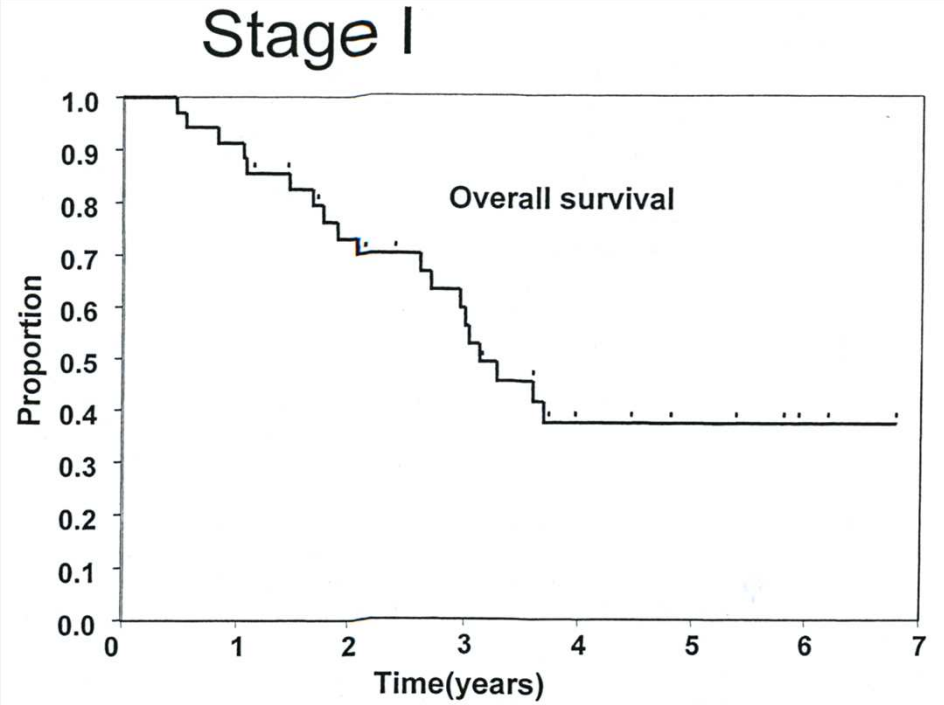
BED, biologically equivalent doses; SBRT, stereotactic body radiation therapy; NTD, normalized total dose in 2-Gy fractions.

Comparison of Biologic Equivalent Doses (Linear Quadratic Method, $\alpha/\beta = 10$) of Representative Dose Regimens Used in Stereotactic Body Radiation Therapy Versus Conventional Radiotherapy for Early-stage Non–Small Cell Lung Cancer.

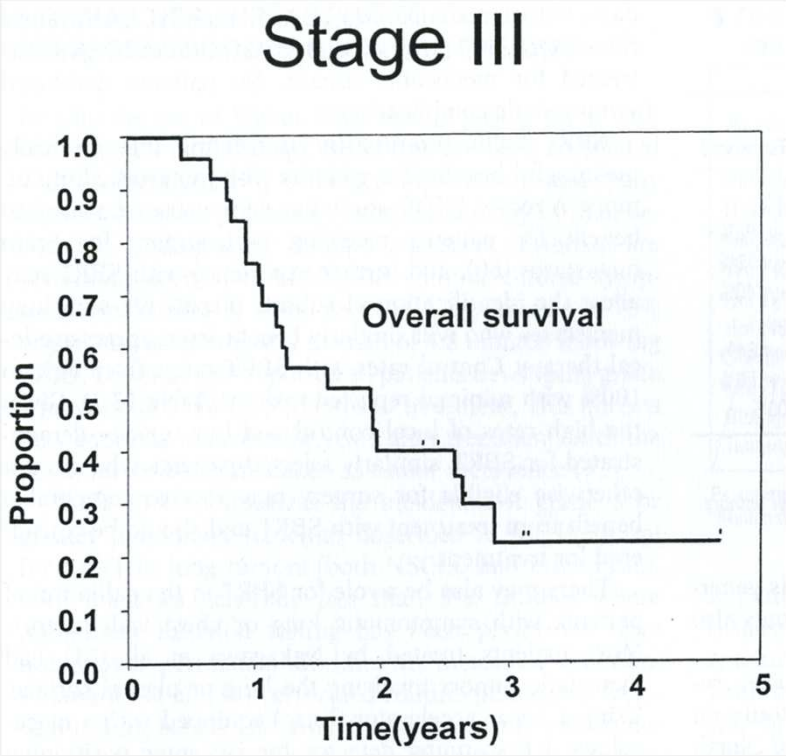
Author	*Dose*	*Biologic Equivalent Dose*
Standard radiotherapy	2 Gy × 30–33 fx	72–79 Gy
Hara (58)	30 Gy × 1 fx	120 Gy
Nagata (50)	12 Gy × 4 fx	105 Gy
Timmerman (51)	20 Gy × 3 fx	180 Gy

Common Terminology Criteria for Adverse Events Version 3.0 for Radiation Pneumonitis.

Grade	*Clinical Description*
0	No pneumonitis
1	Asymptomatic; radiographic findings only
2	Symptomatic; not interfering with activities of daily living (ADLs); steroids indicated
3	Symptomatic; interfering with ADLs; supplemental oxygen indicated
4	Life threatening; ventilatory support indicated
5	Death



Kaplan-Meier overall survival for patients with stage I non–small cell lung cancer treated at the Karolinska Hospital with stereotactic body radiation therapy. The 5-year survival is around 35%.



Kaplan-Meier overall survival for patients with stage III non–small cell lung cancer treated at the Karolinska Hospital with stereotactic body radiation therapy. The 2-year survival is around 40%.

Results of Stereotactic Body Radiation Therapy for Early-stage Non–Small Cell Lung Cancer.

Author	*No. of Patients*	*Median Follow-up*	*Local Control*	*Survival*
Timmerman (57)	37	15 m	83%	54%
Uematsu (47)	43	20 m	100%	3-yr 66%
Nagata[a] (50)	16	16 m	100%	2-yr 79%
Wulf[b] (62)	12	8 m	85%	2-yr 40%
Hara (58)	5	20 m	100%	
Hof (48)	10	15 m	80%	2-yr 64%
Onishi[c] (49)	241	18 m	90%	3-yr 56%
Lee (59)	9	18 m	90%	100%

[a]Only T1 N0 patients shown.
[b]Included some patients with T3 N0 and recurrent disease.
[c]Multiinstitutional study; may contain overlapping patients from other authors.

SBRT for primary lung cancer

Author	No. of patients	Dose	Local control	Overall survival
Nagata (2005)	45	48 Gy/4 fr at IC	95% (T1) 100% (T2)	83% (T1, 3 yr) 72% (T2, 3 yr)
Timmerman et al. (2006)	70	60–66 Gy/3 fr at PTV periphery	95% (2 yr)	54.7% (2 yr)
Hoyer et al. (2006)	45	45 Gy/3 fr at IC	85% (2 yr)	48% (2 yr)
Zimmermann et al. (2006)	68	24–40 Gy/3–5 fr at PTV periphery	88% (3 yr)	51% (3 yr)
Hof et al. (2007a)	42	19–30 Gy/1 fr at IC	67.9% (3 yr)	37.4% (3 yr)
Koto et al. (2007)	31	45 Gy/3 fr, or 60 Gy/8 fr at IC	77.9% (T1, 3 yr) 40.0% (T2, 3 yr)	71.7% (3 yr)

Abbreviations: *IC* isocenter, *fr* = fraction, *yr* = year

Complications of Lung Stereotactic Body Radiation Therapy.

Author	No. of Patients	Dose	Grade 3 Toxicity
Uematsu (47)	66	30–76 Gy, 5–15 fx	0%
Nakagawa (61)	22	15–24 Gy, 1 fx	0%
Nagata (50)	40	40–48 Gy, 4 fx	0%
Wulf (62)	61	26–37.5 Gy, 1–3 fx	3%
Hara (58)	23	20–30 Gy, 1 fx	4%
Hof (48)	10	19–26 Gy, 1 fx	0%
Onishi[a] (49)	241	18–75 Gy, 1–22 fx	2%
Lee (59)	28	30–40 Gy, 3–4 fx	0%
Blomgren (63)	13	15–45 Gy, 1–3 fx	
Timmerman (51)	37	24–60 Gy, 3 fx	5.4%

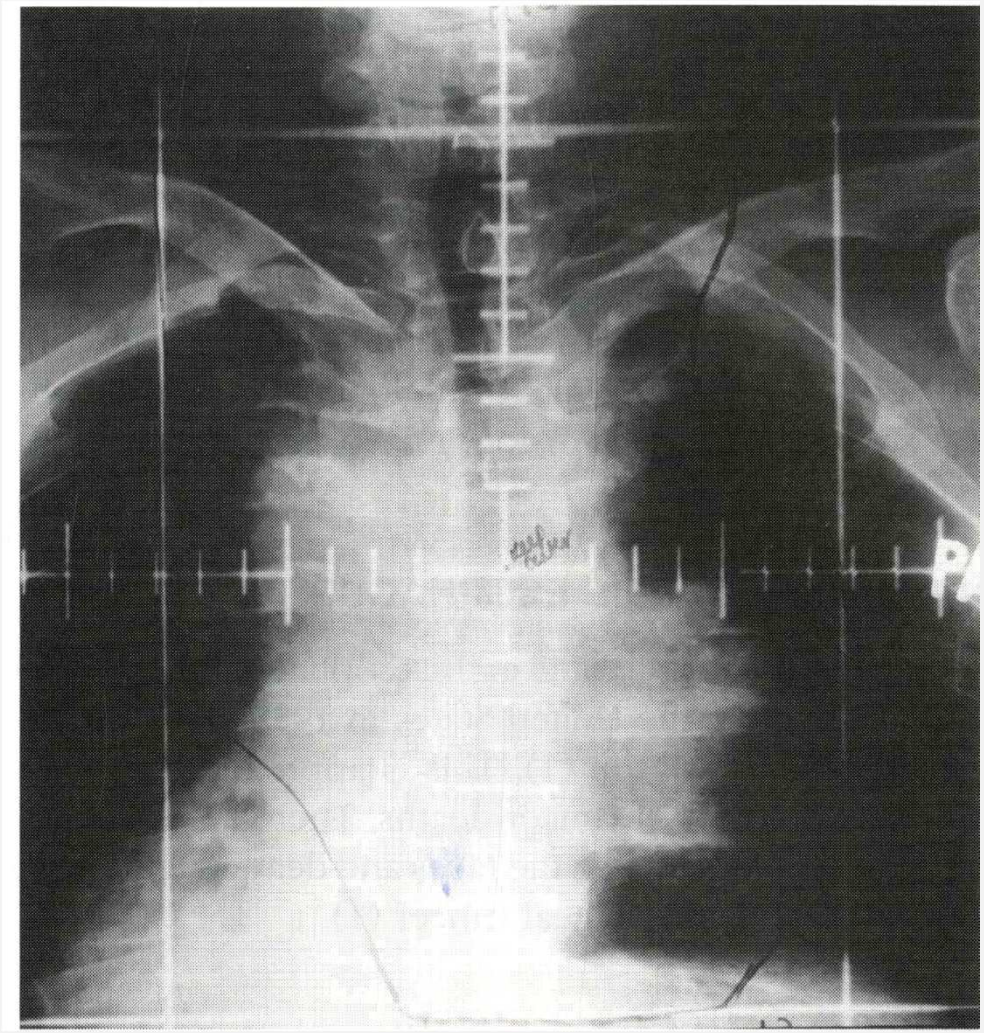
Fx, fraction.
[a]Multiinstitutional study; may contain overlapping patients from other authors.

Radiation Therapy Oncology Group–Proposed Radiation Tolerances of Thoracic Normal Tissue with Tumor Prescription of 60 Gy Total in Three Fractions.

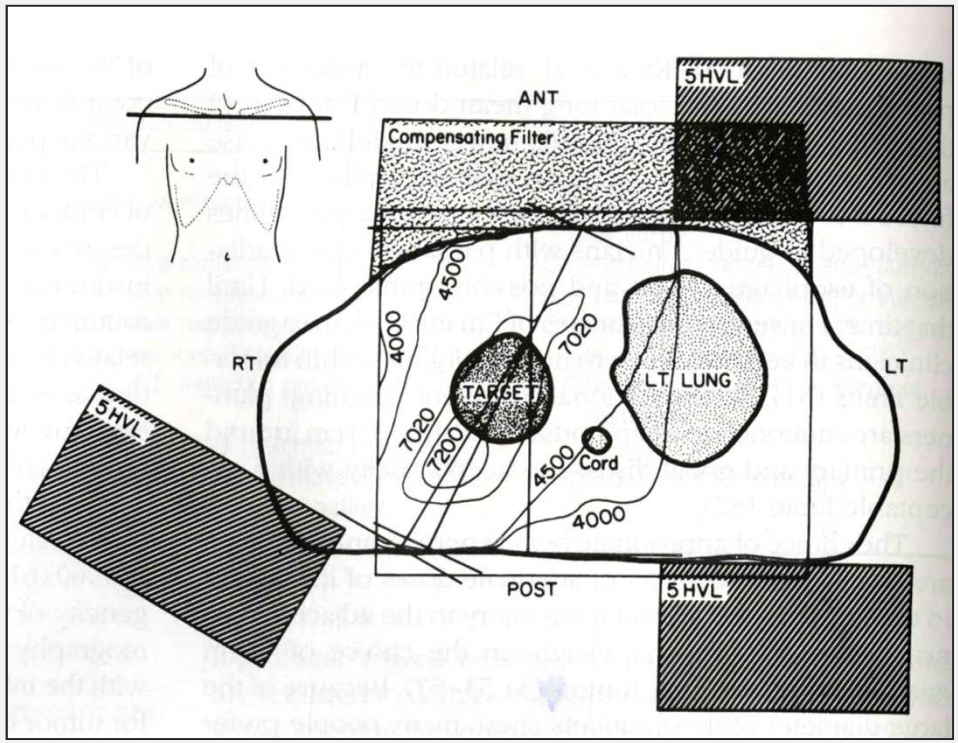
Organ	*Volume*	*Dose (cGy)*
Spinal cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and ipsilateral bronchus	Any point	30 Gy (10 Gy per fraction)

Dose constraints of organs at risk (OARs) for the Japan Clinical Oncology Trial 0403 protocol (as of September 2008)

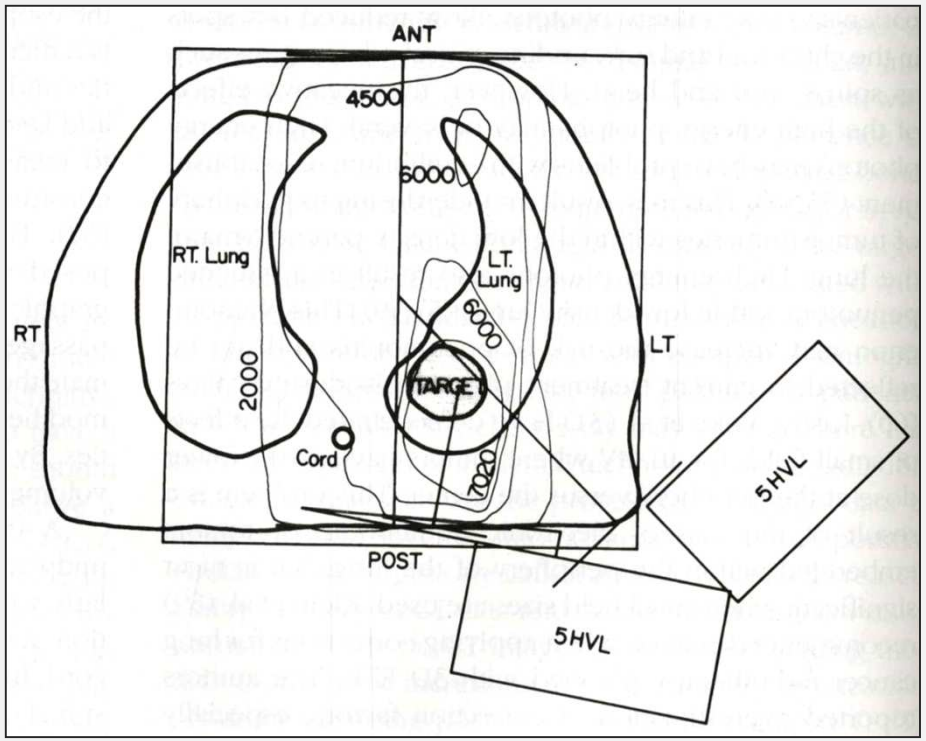
PRV	Constraints
Lung	Mean dose ≤ 18 Gy
	40-Gy irradiated volume ≤ 100 cc
	V15 ≤ 25%
	V20 ≤ 20%
Spinal cord	Maximal dose ≤ 25 Gy
Esophagus and pulmonary artery	40-Gy irradiated volume ≤ 1 cc
	35-Gy irradiated volume ≤ 10 cc
Stomach and intestine	36-Gy irradiated volume ≤ 10 cc
	40-Gy irradiated volume ≤ 100 cc
Trachea and main bronchi	40-Gy irradiated volume ≤ 10 cc
Other organs	48-Gy irradiated volume ≤ 1 cc
	40-Gy irradiated volume ≤ 10 cc



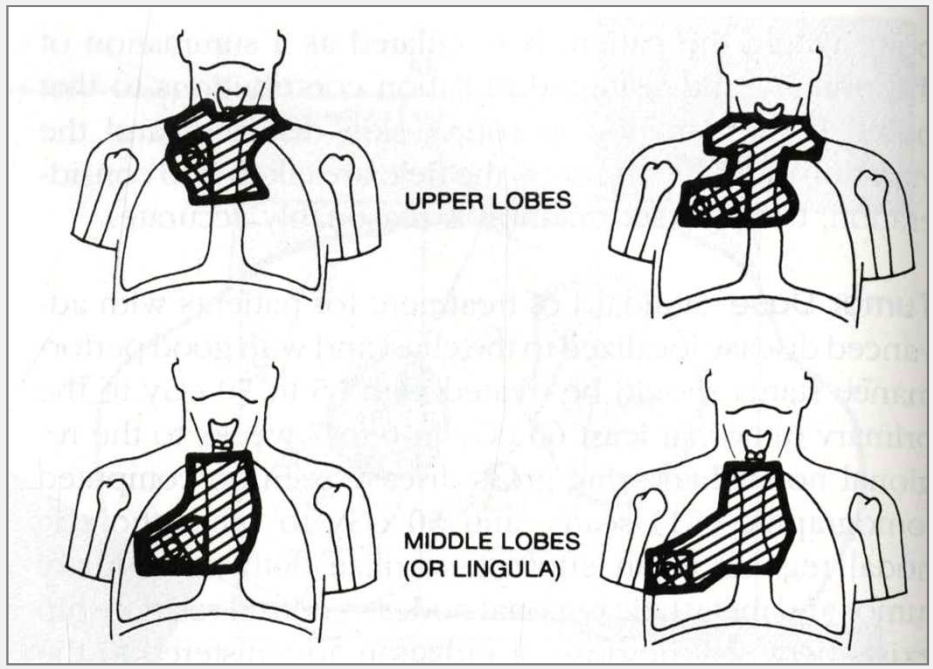
Traditional small cell portal

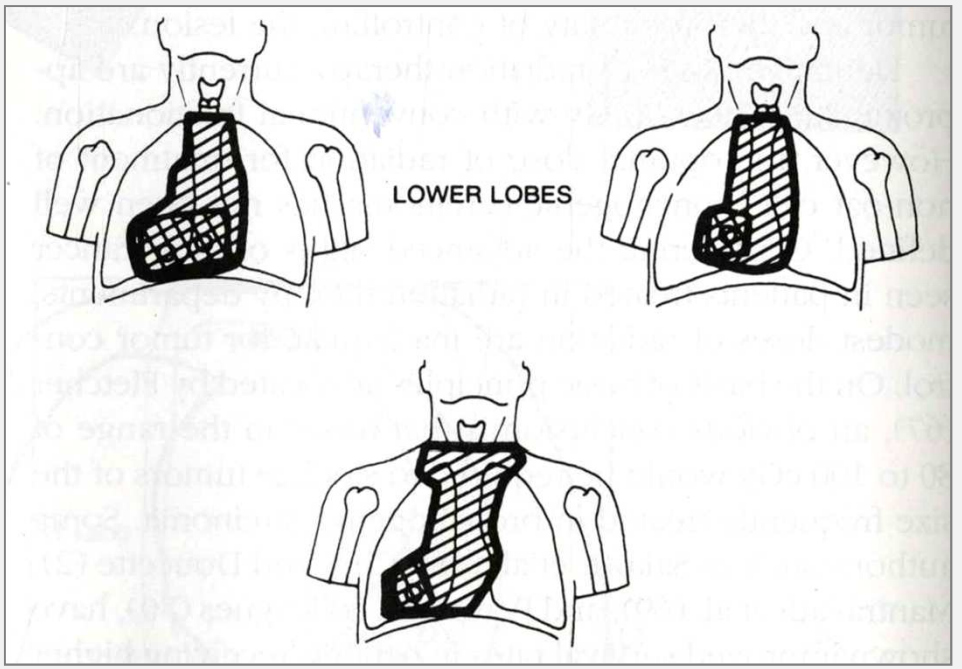


Optimized treatment plan for right lower lobe tumour



Optimized treatment plan for left lower lobe tumour

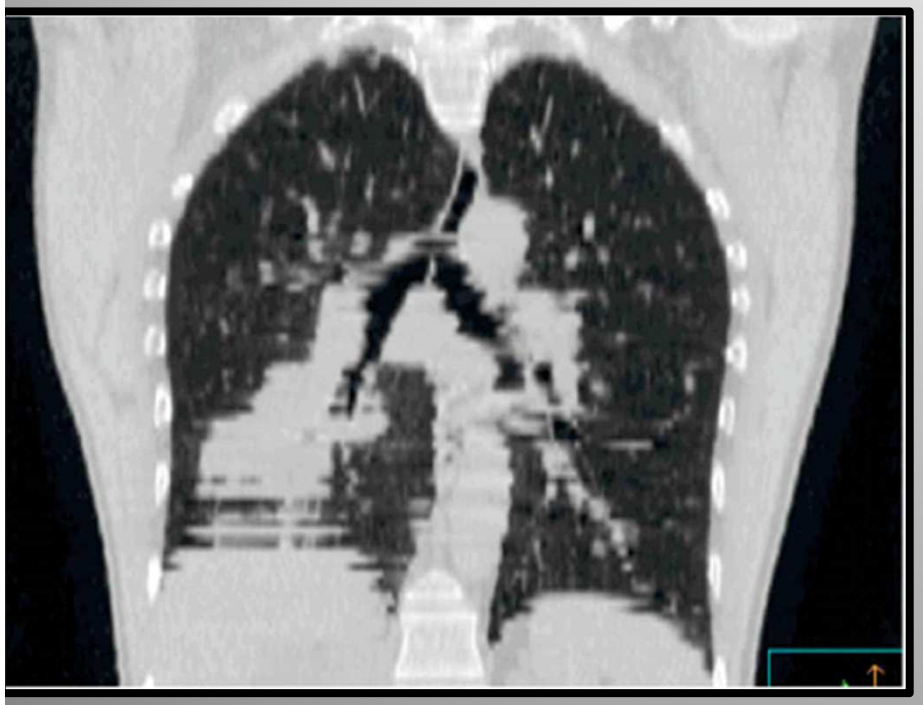




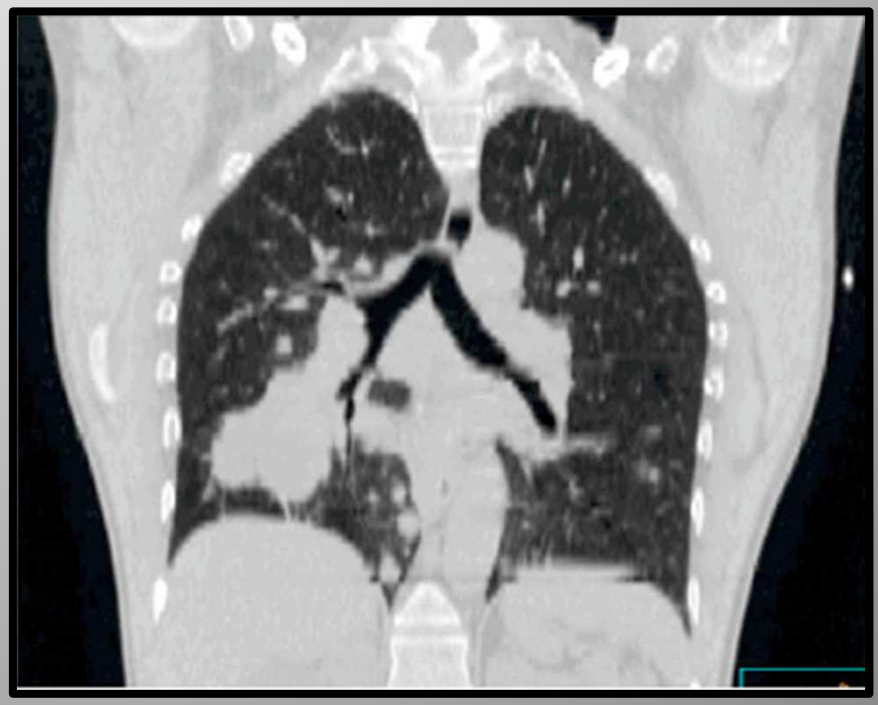
Portals used for irradiation of non-oat cell carcinoma of lung, depending on anatomic location of primary tumor. Tumor and grossly enlarged lymph nodes are treated to higher doses (cross-hatched area).

In CT Simulation

Free Breathing

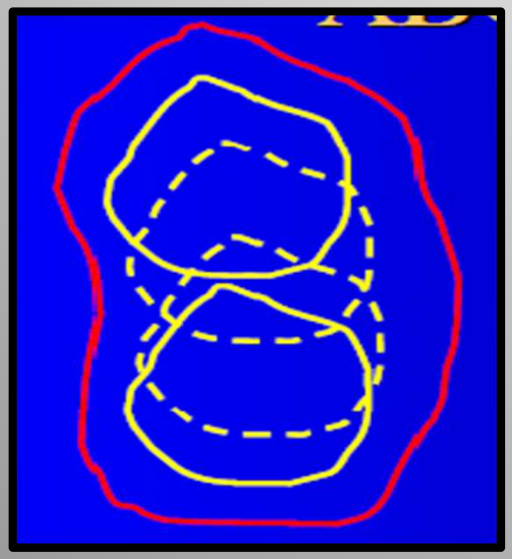


Breath-hold

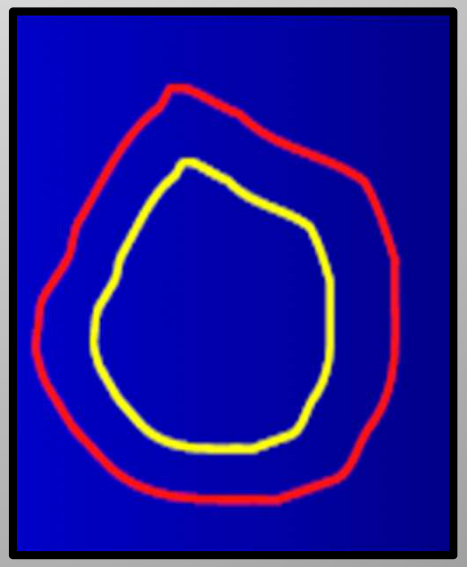


In Treatment Planning

Free Breathing



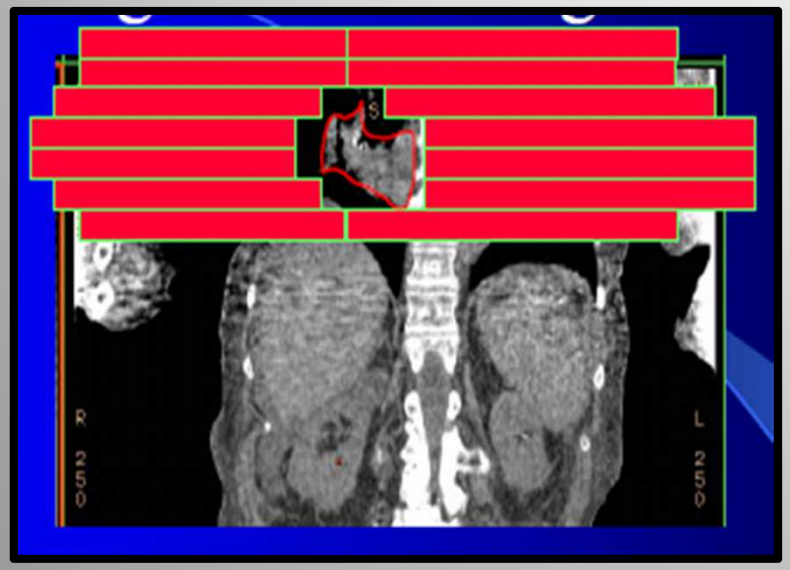
Breath-hold

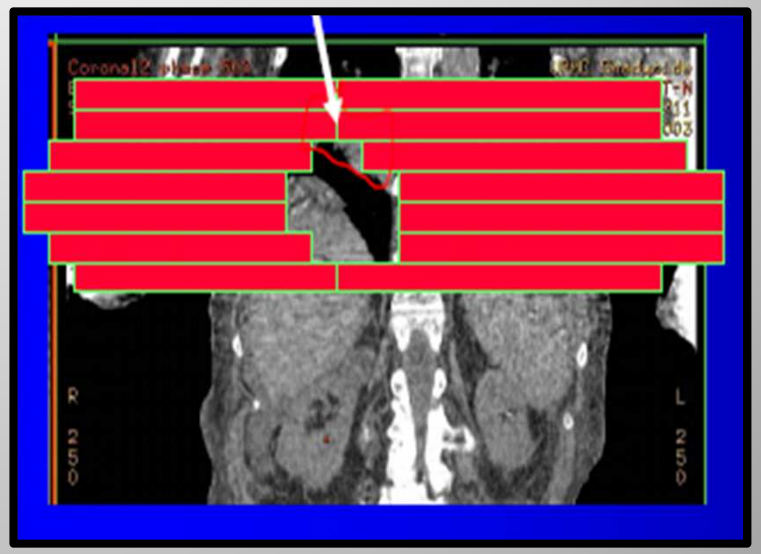


In Treatment Delivery

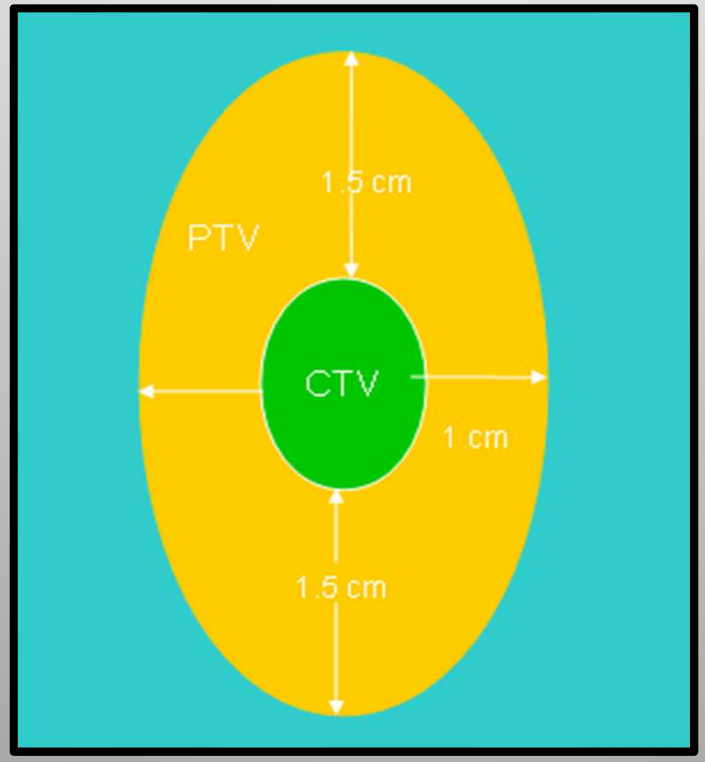
- Intrafractional Errors
- Interfractional Errors
- Target Miss or Organ Hit

Target Miss or Organ Hit





Target Movement- 3D Solution



Target Movement- 3D Solution

Problems-

- Difficult to generate isodose distribution conforming to the moving target.
- Unable to minimize the dose to the surrounding tissues
- Limits total dose and dose per fraction

Management Of Respiratory Motion

1.Tracking Technique

Dynamic Tracking
Real Time Tracking

2.Gating Technique

3.Breath Hold Technique

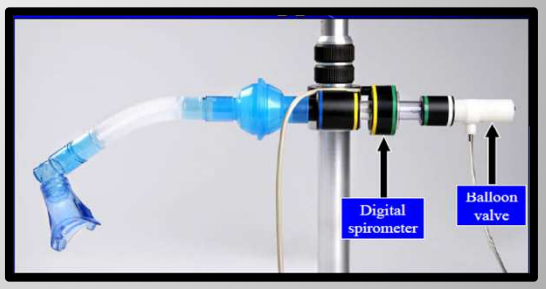
Active Breathing Coordinator

- **It is a device to deliver radiation in breath hold position. It is non-invasive device that pauses the breathing movements of patient to increase the accuracy of treatment planning and treatment delivery.**

Procedure For Treatment Using ABC

- **Patient Selection**
- **Patient Training**
- **Patient Set-Up**
- **CT Simulation**
- **Planning**
- **Patient set-Up For Treatment**
- **Verification**
- **Execution**

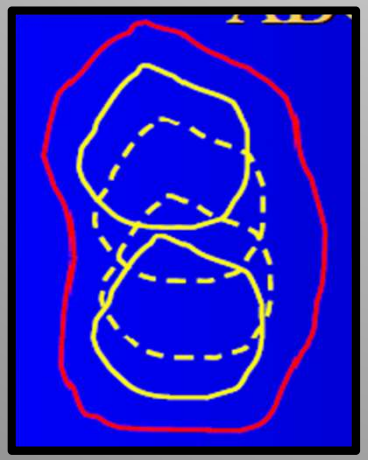
Patient Set-Up



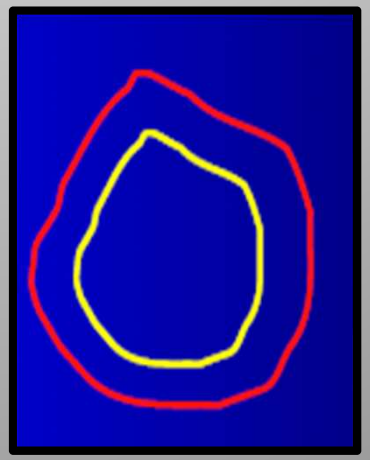
Planning

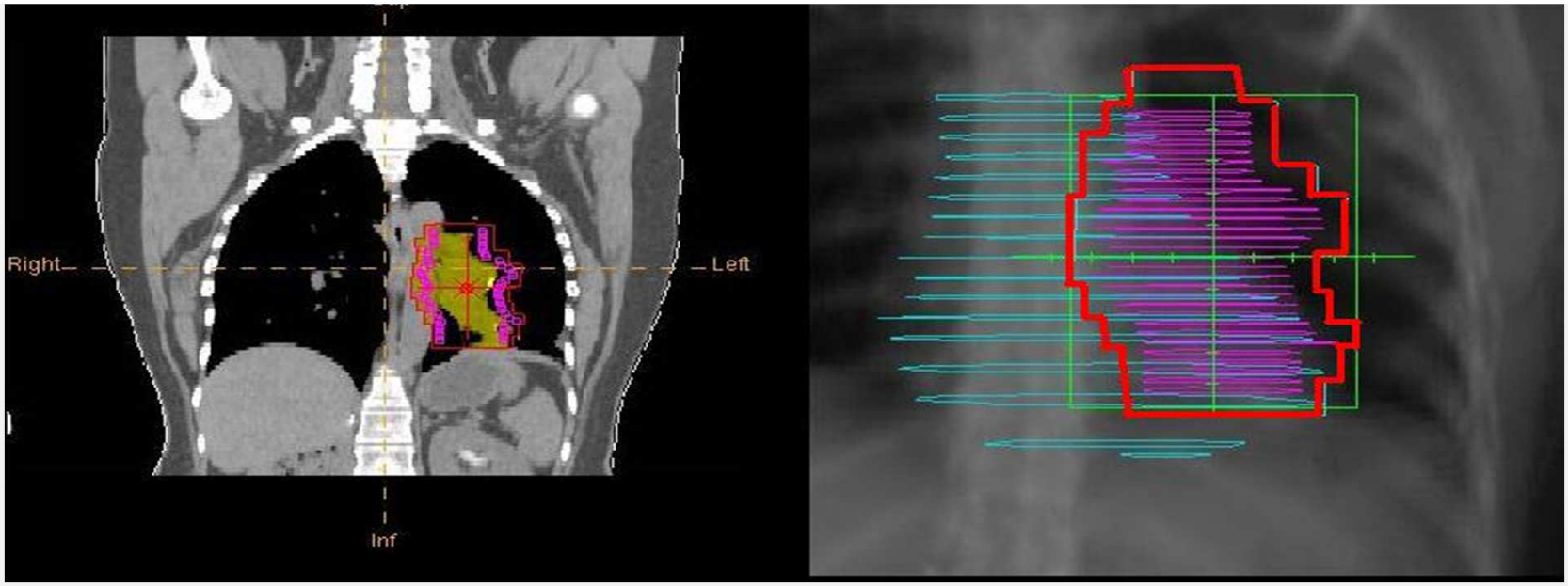
- Contouring and treatment planning on breath-hold CT
- PTV margin can be reduced to 5mm
- Planning margins can be decided on the basis of verification strategy or technique of treatment

Free Breathing

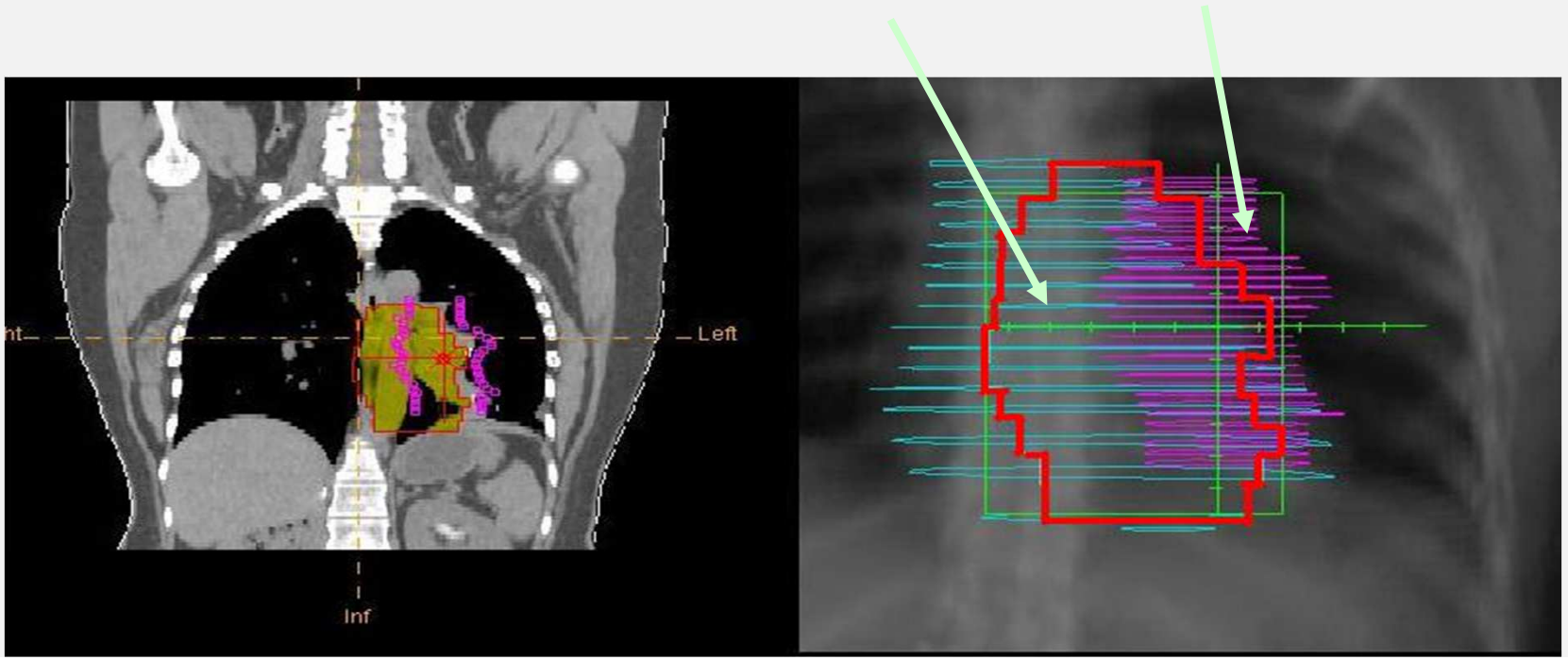


Breath-Hold





Problems with respiratory movement: Organ Hit & Tumor miss

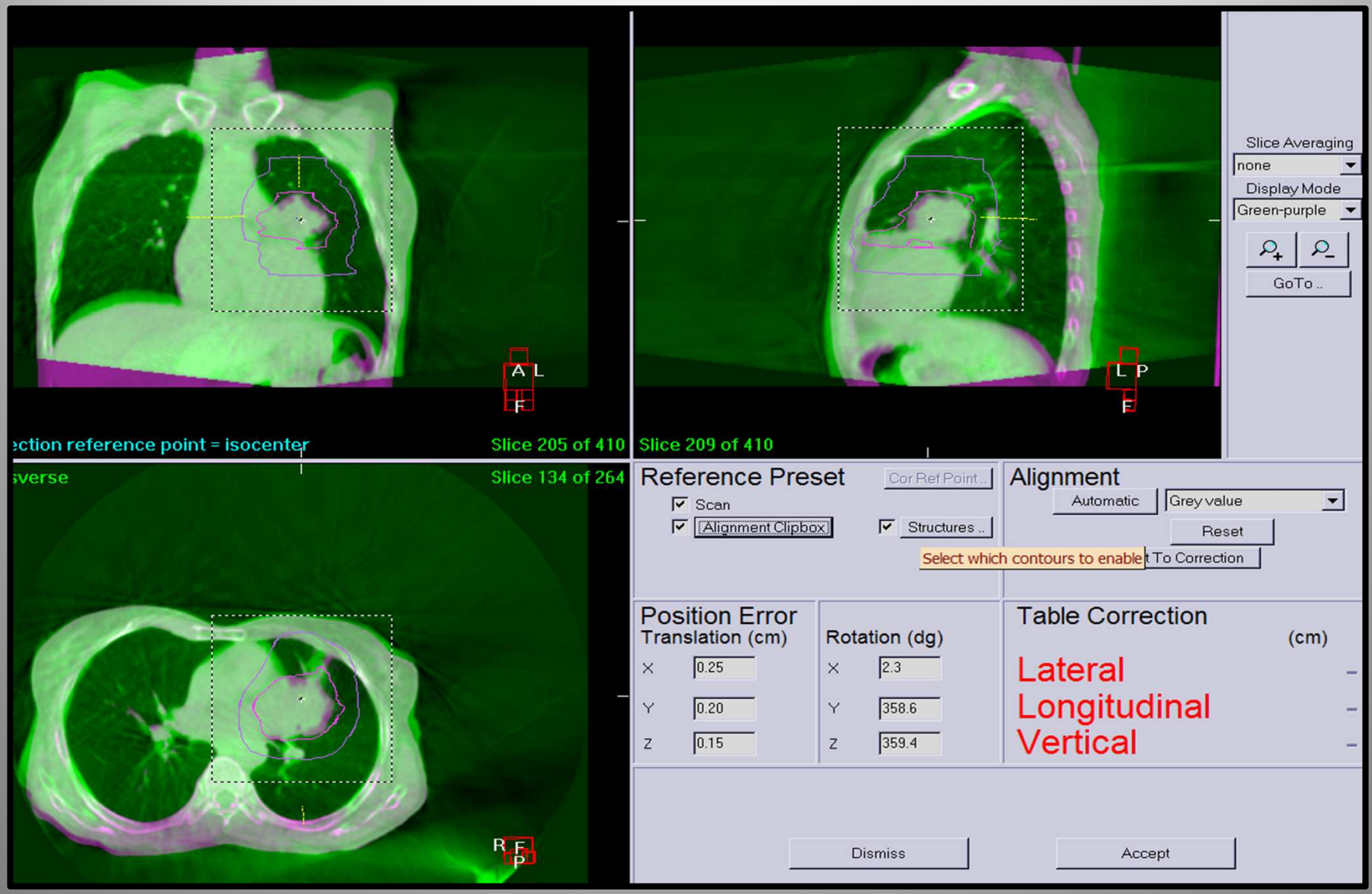


- Patient Set-Up For Treatment With ABC

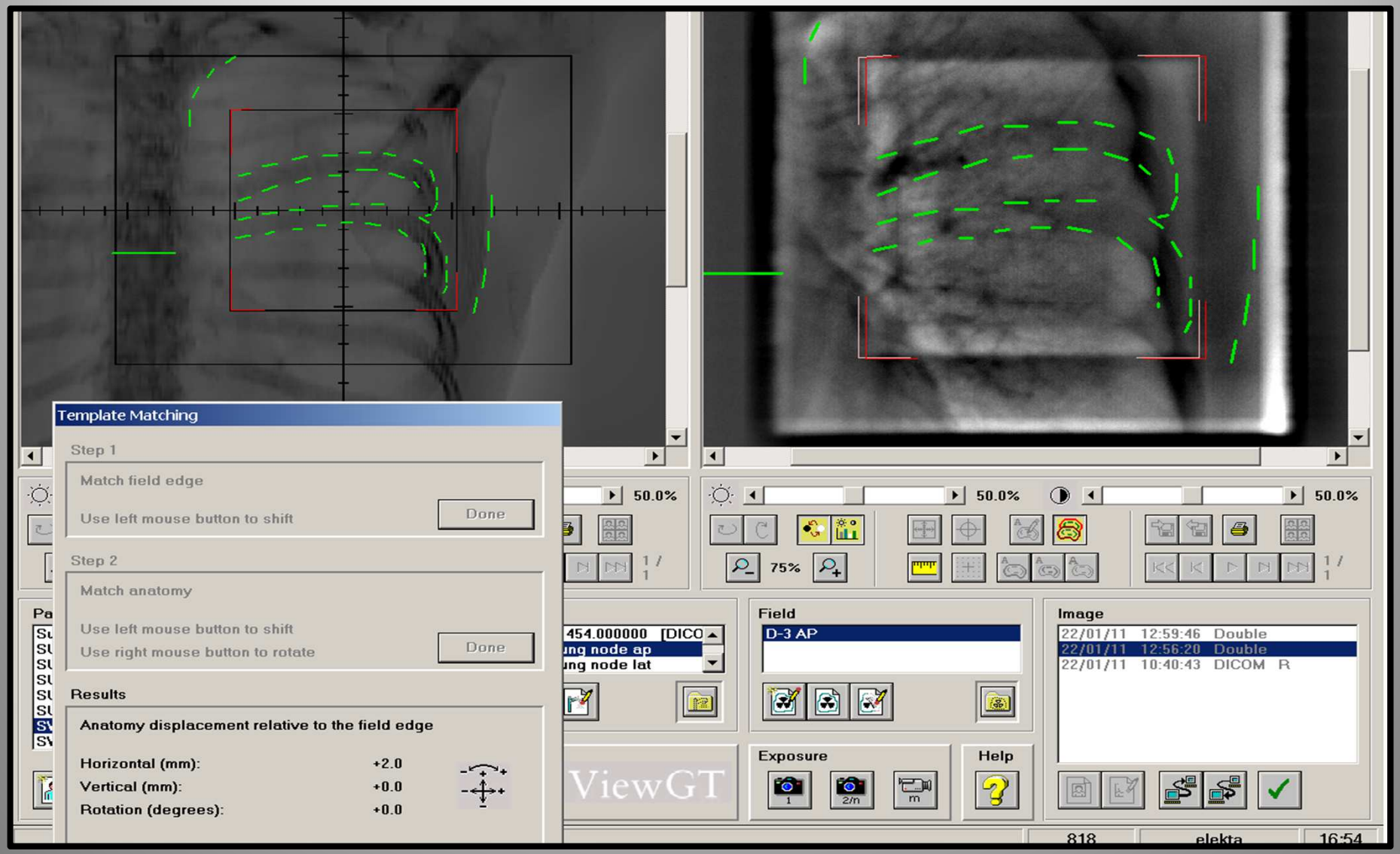
Verification

- Isocenter shift from free breathing CT
- CBCT done and matched with free breathing CT
- IVGT in Breath-hold

Cone Beam CT


A L
F
ection reference point = isocenter
Slice 205 of 410
L P
F
Slice 209 of 410
Slice Averaging
none
Display Mode
Green-purple
GoTo ..
sverse
Slice 134 of 264
R F
P
Reference Preset
Cor Ref Point ..
Scan
Alignment Clipbox
Structures ..
Alignment
Automatic
Grey value
Reset
Select which contours to enable
t To Correction
Position Error
Translation (cm)
X 0.25
Y 0.20
Z 0.15
Rotation (dg)
X 2.3
Y 358.6
Z 359.4
Table Correction
(cm)
Lateral
Longitudinal
Vertical
Dismiss
Accept

IViewGT

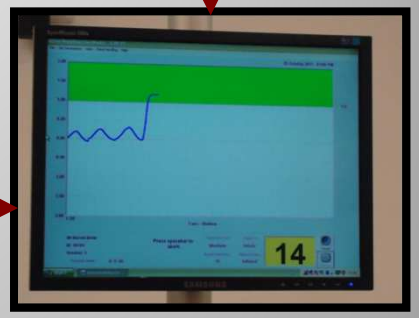

Template Matching
Step 1
Match field edge
Use left mouse button to shift
Done
Step 2
Match anatomy
Use left mouse button to shift
Use right mouse button to rotate
Done
Results
Anatomy displacement relative to the field edge
Horizontal (mm): +2.0
Vertical (mm): +0.0
Rotation (degrees): +0.0
50.0%
50.0%
50.0%
75%
Field
D-3 AP
Image
22/01/11 12:59:46 Double
22/01/11 12:56:20 Double
22/01/11 10:40:43 DICOM R
Exposure
Help
ViewGT
818
elekta
16:54

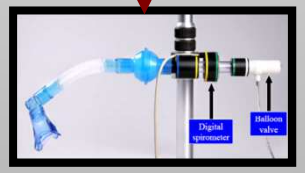
- Execution

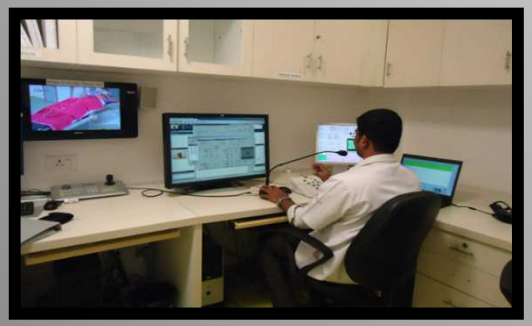

PREPARE PATIENT
INITIATE BREATH_HOLD
BEAM ON
BEAM OFF
REALESE BREATH
ALLOW BREATHING TO STABALIZE

Console Room

Treatment Room





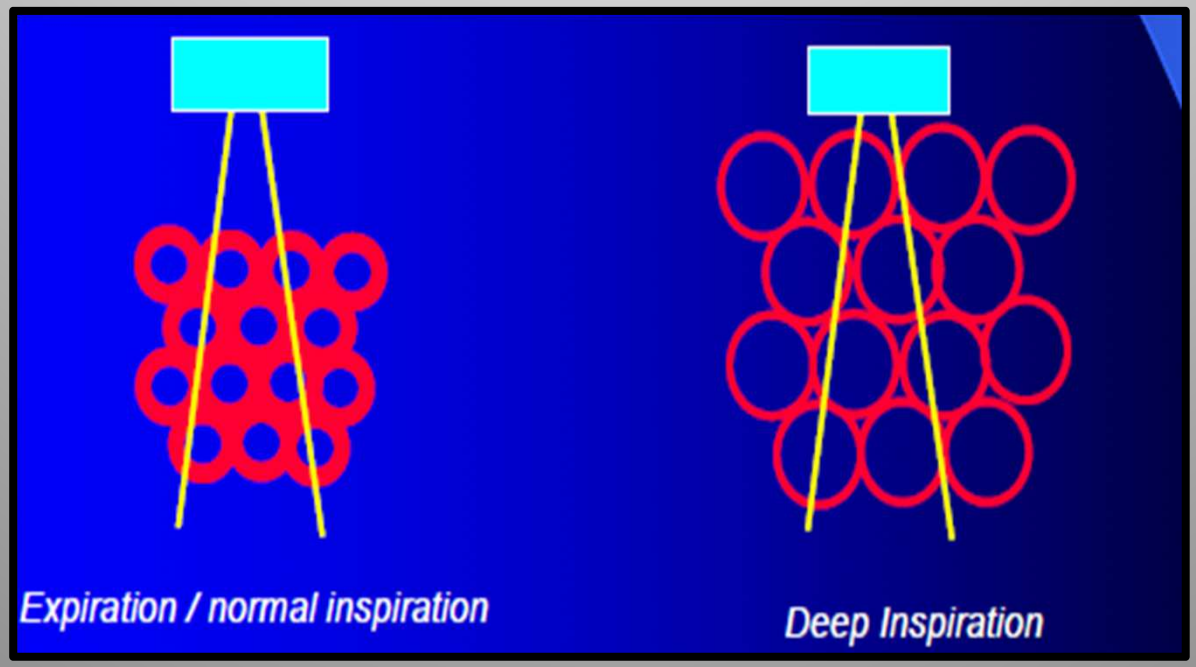


Clinical Advantages of Using ABC

- Increases quality of CT images
- Decreases Intrafractional as well as Interfractional errors
- Ensures accuracy of target treatment
- Spares normal tissue
- Improves Treatment Planning

Additional Advantages of Using ABC in Deep Inspiration

- Increased lung volume and decreased lung density in deep inspiration allows less healthy tissue to be irradiated.



Additional Advantages of Using ABC in Deep Inspiration

- SBRT or hypo fractionation regime, higher dose per fraction and less total no. of fractions are useful with conventional radiotherapy. This results in shorter treatment time for patient, together with improved efficiency.

Limitations

- **Difficult in patients with severely compromised lung/ cardiac functions**
- **Needs extra treatment time**
- **Comes closest to reducing uncertainties but never equal to real time treatment**

Limitations

- **Breath hold may not be reproducible sometimes**
- **Extended patient set up time**
- **Repeatability of breath holding**

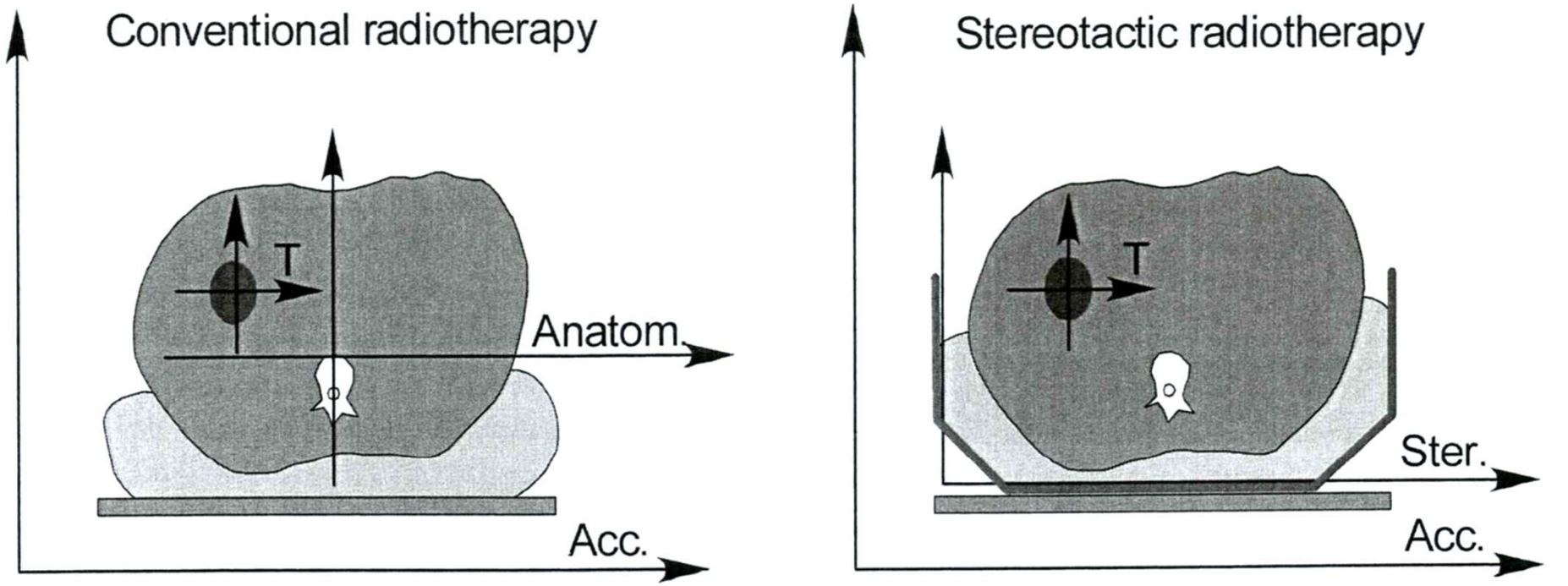
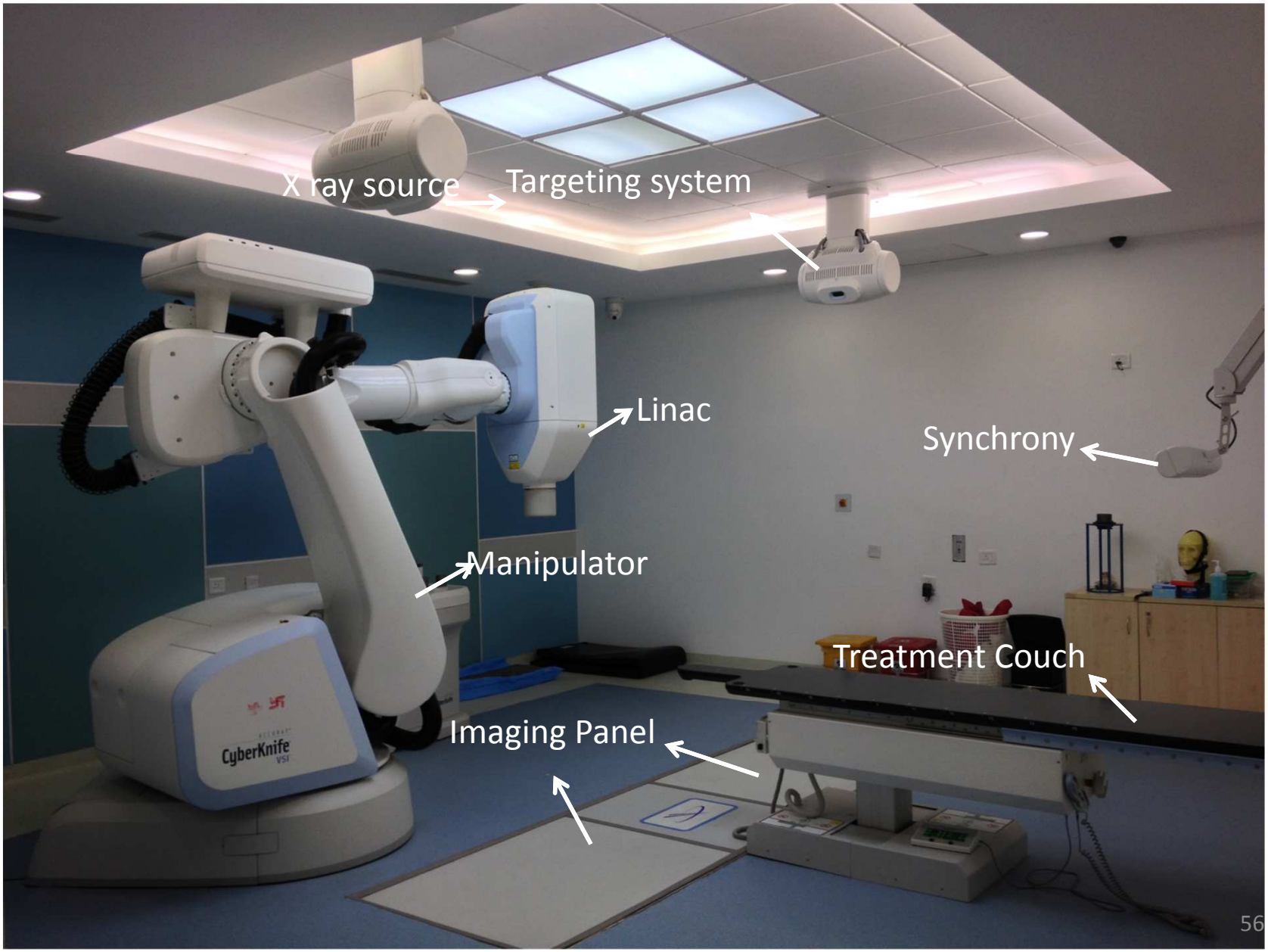
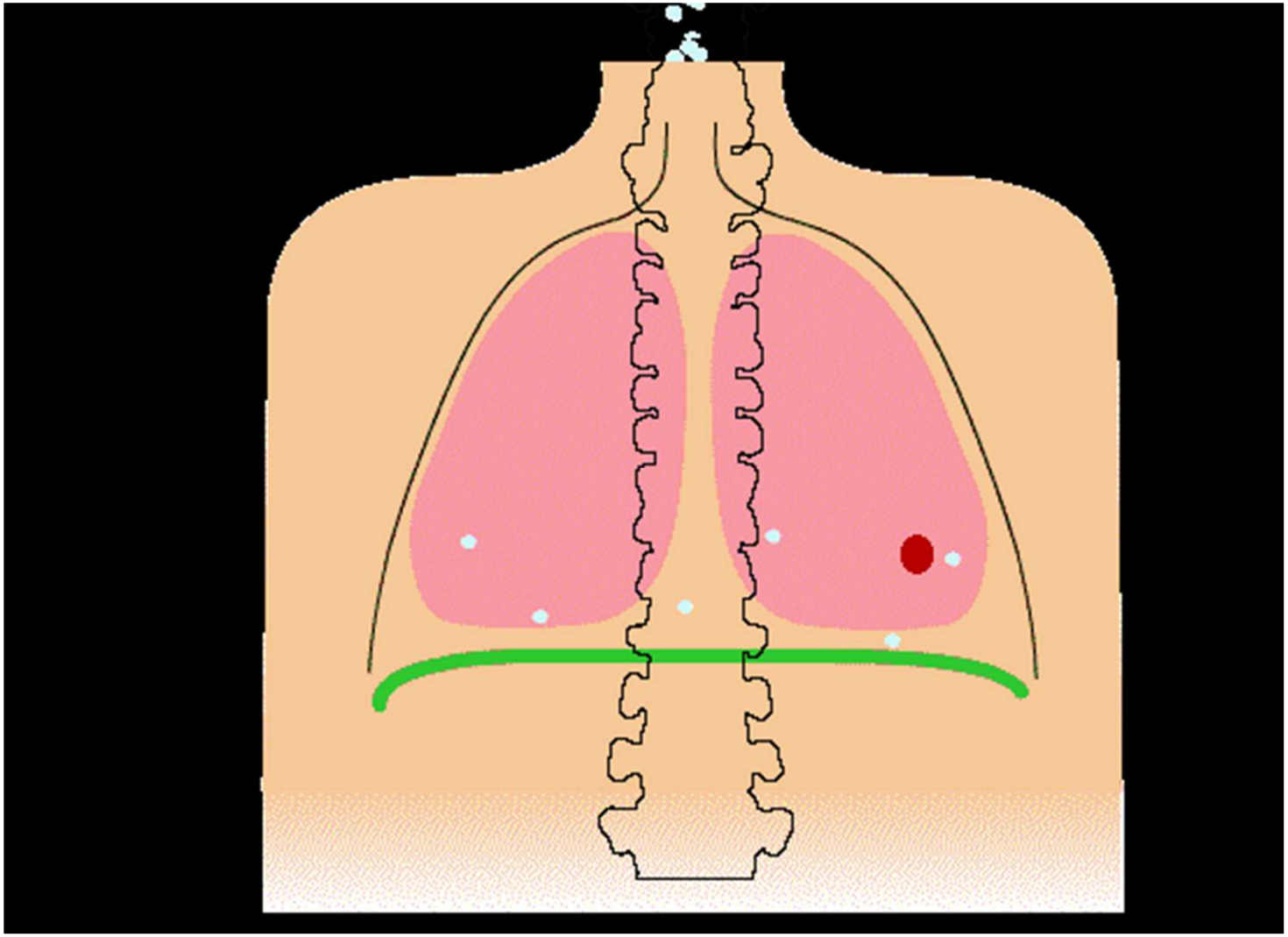


Illustration of coordinate systems used in conventional radiotherapy (**left**) and stereotactic body radiation therapy (**right**).

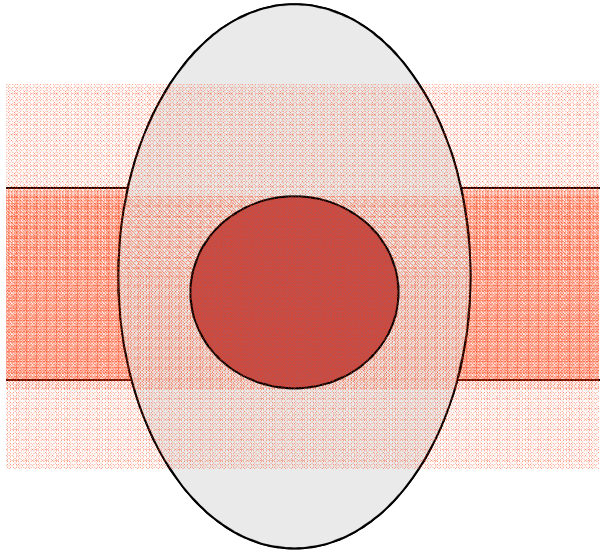

X ray source
Targeting system
Linac
Synchrony
Manipulator
Treatment Couch
Imaging Panel
CyberKnife

Challenge



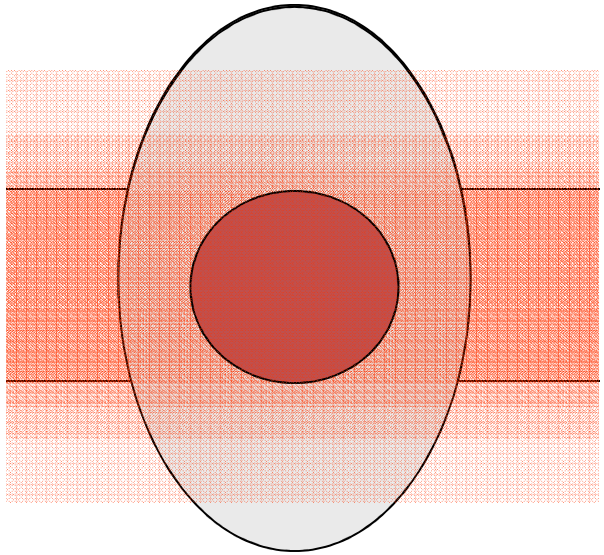
Traditional Radiation Therapy

- Imaging and Tumor Targeting
  - Traditional IGRT daily set-up imaging maybe inadequate for sub-millimeter accuracy
  - Localization
  - Targeting
  - How to account motion



Traditional Radiation Therapy

- Imaging and Tumor Targeting
  - Traditional IGRT daily set-up imaging may be inadequate for sub-millimeter accuracy
  - Localization
  - Targeting
- Breath Hold
- Gating
- Stereotactic



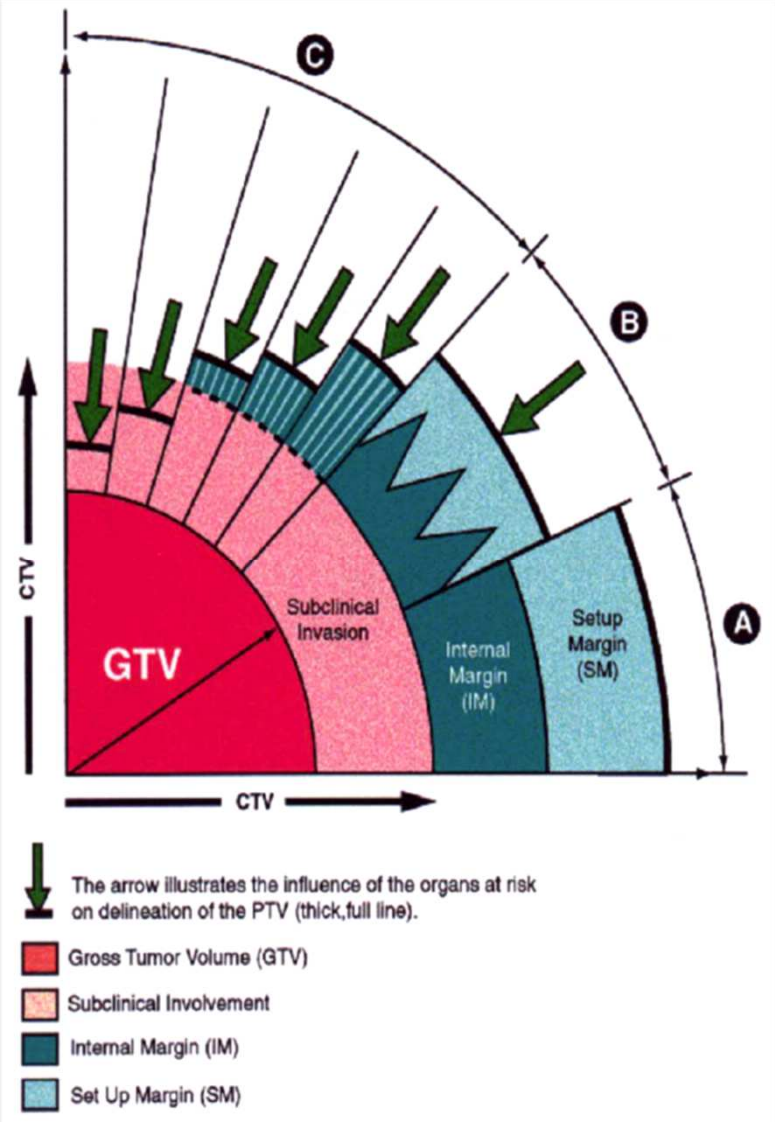
GTV

The GTV consists of the primary tumor, clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or on pre-treatment PET/CT scan (SUV > 3), and any known involved nodal level found on mediastinoscopy or biopsy, regardless of CT or PET/CT findings.

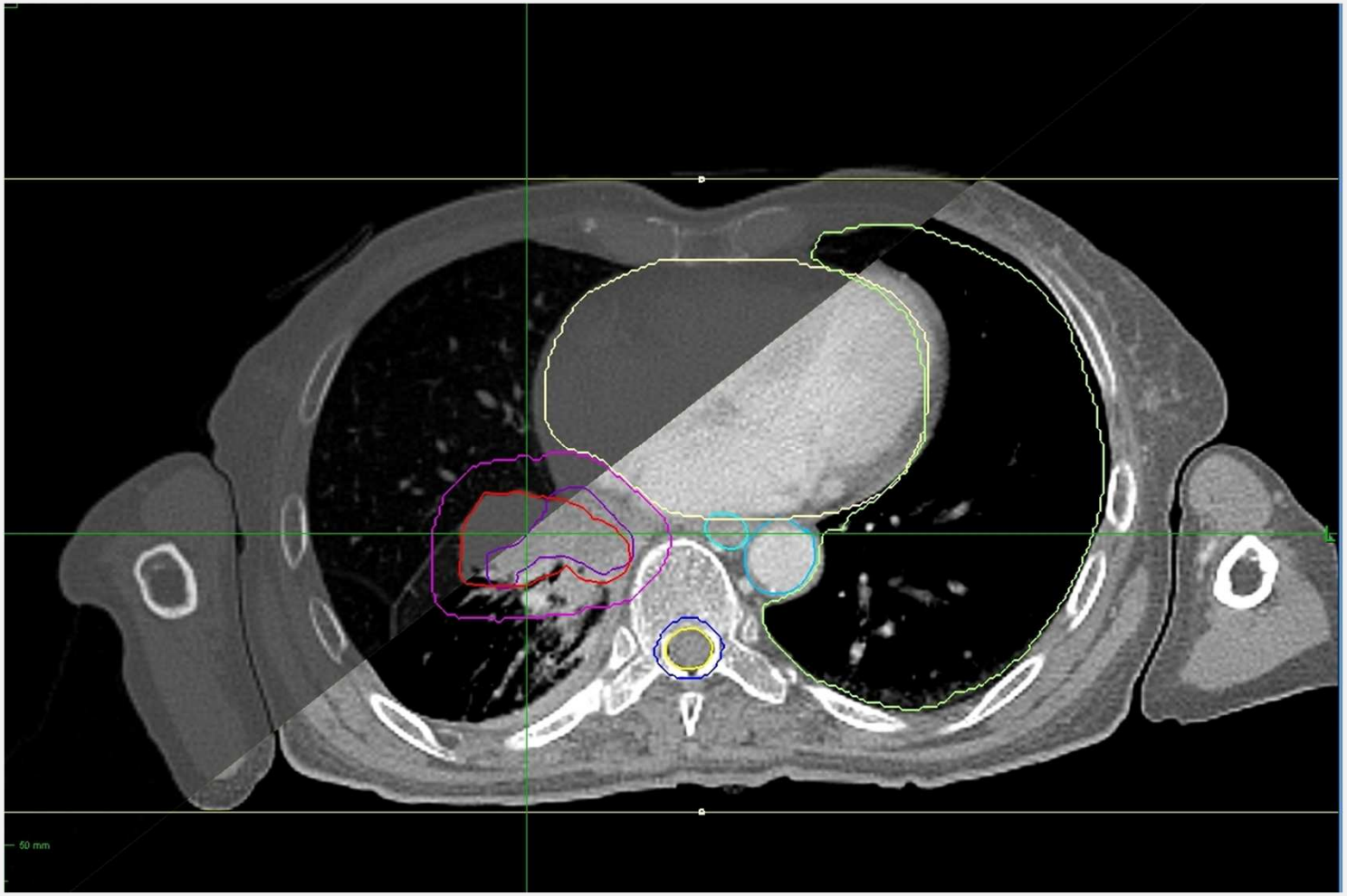
Volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET/CT to distinguish tumor from fluid/atelectasis is encouraged.

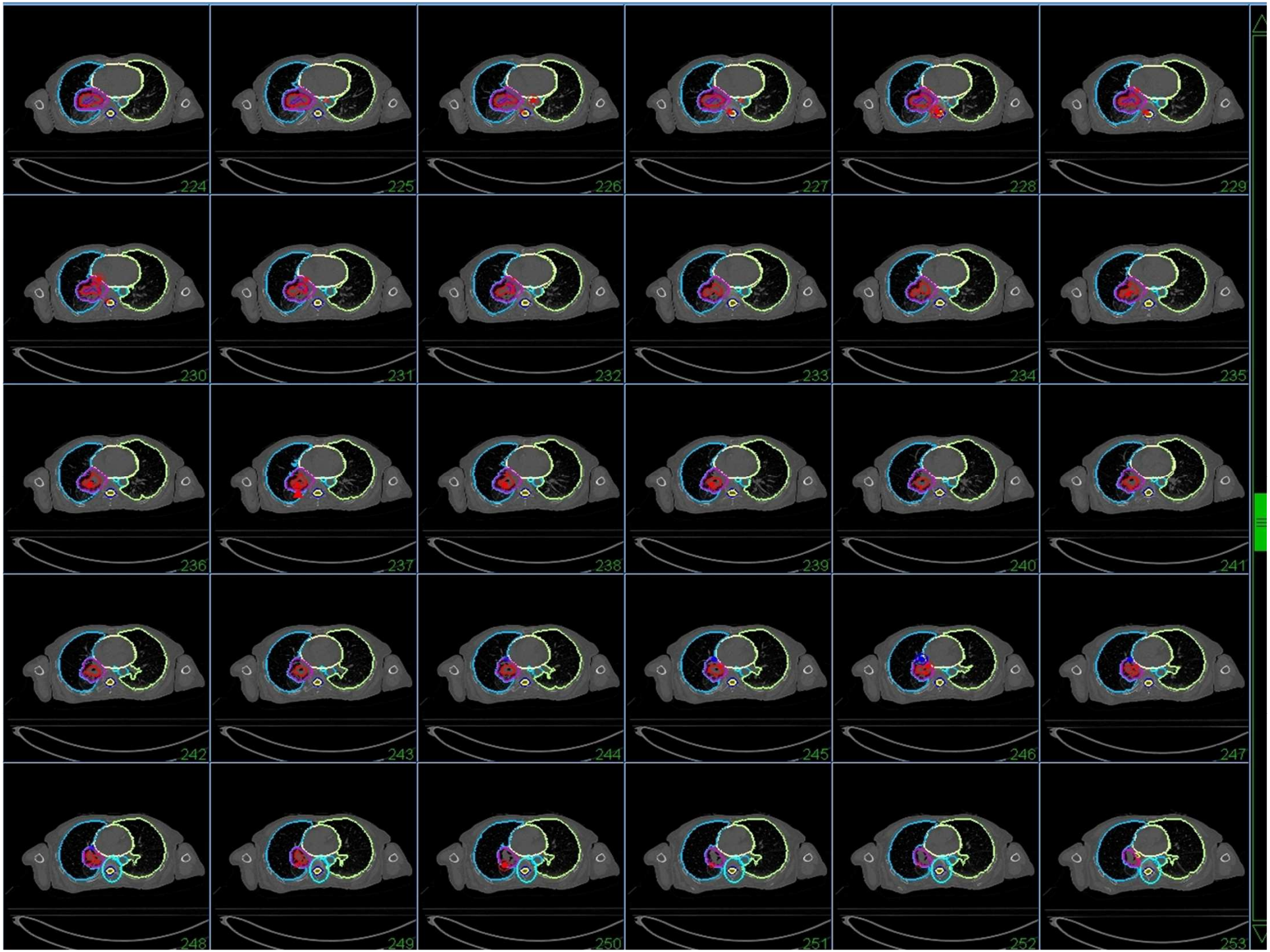
Target Volumes in Radiation Oncology: ICRU 50 and 62:

- Gross Tumor Volume: GTV
- Clinical Target Volume: CTV
- Internal Target Volume: ITV
- Planning Target Volume: PTV
- Organ at Risk: OAR
- Planning Organ at Risk Volume: PRV

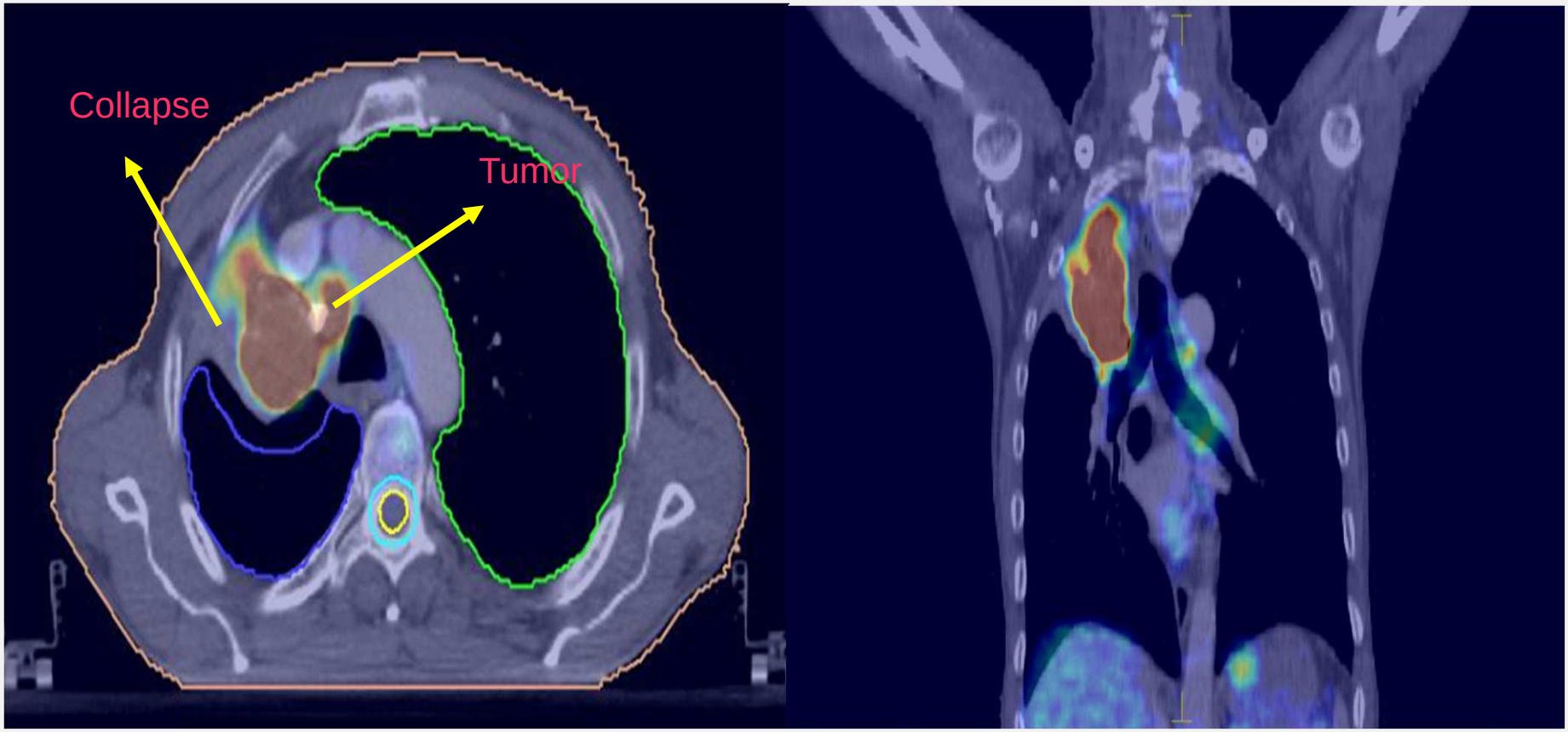


Planning CECT images




224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253

PET-CT – differentiates tumor from collapse

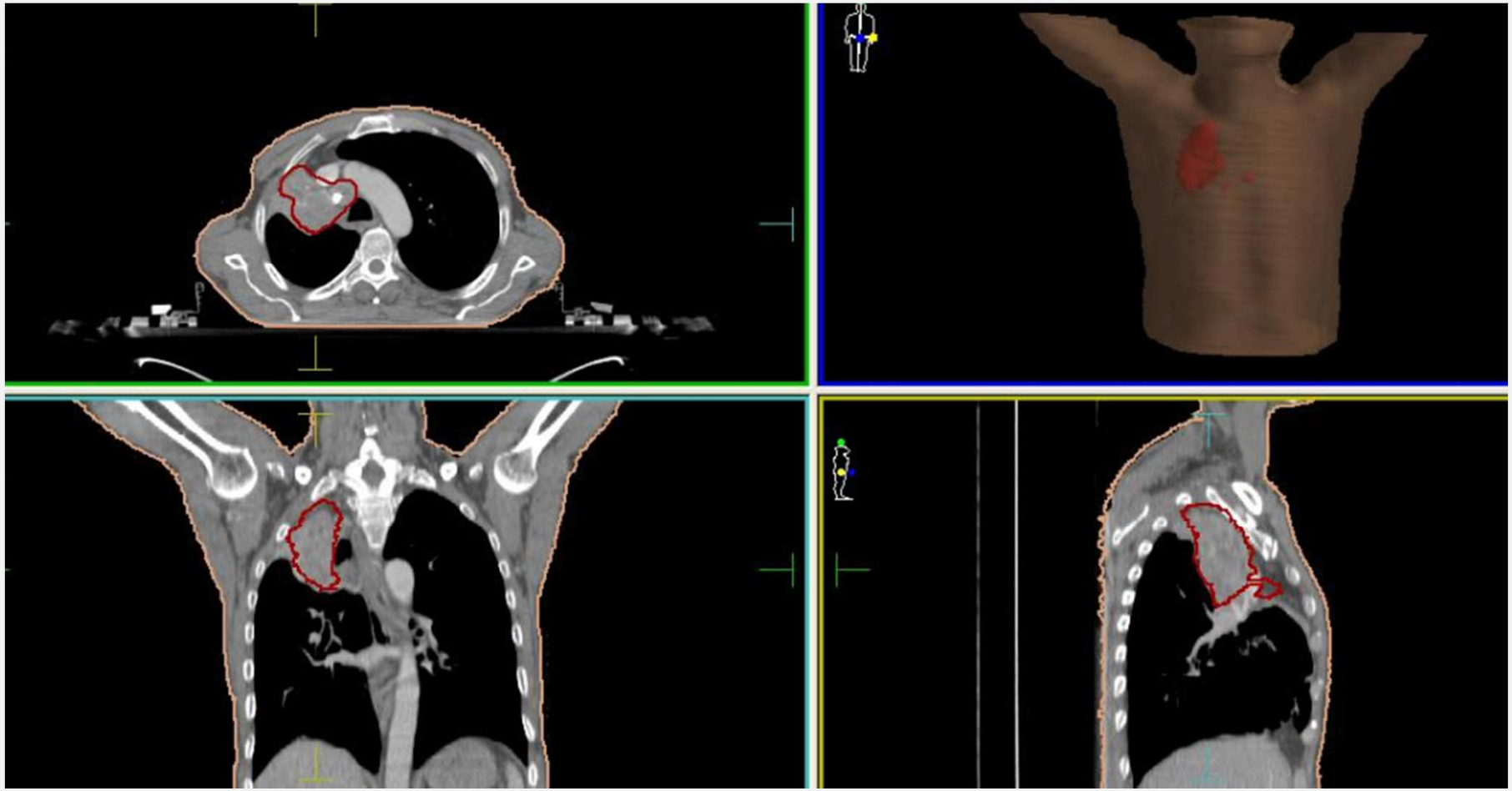


Mediastinal GTV Proposal

Nodal diameter and PET	Action
<1cm PET positive	Include in GTV
<1cm PET Negative	Exclude in GTV
>1cm PET positive	Include in GTV unless cytology negative
>1cm PET Negative	Include in GTV if primary PET negative If primary PET + Exclude from GTV
>1cm or conglomerate of LN on CT	Include in GTV

Senan et al Radiotherapy and oncology. 2000

Contouring: GTV

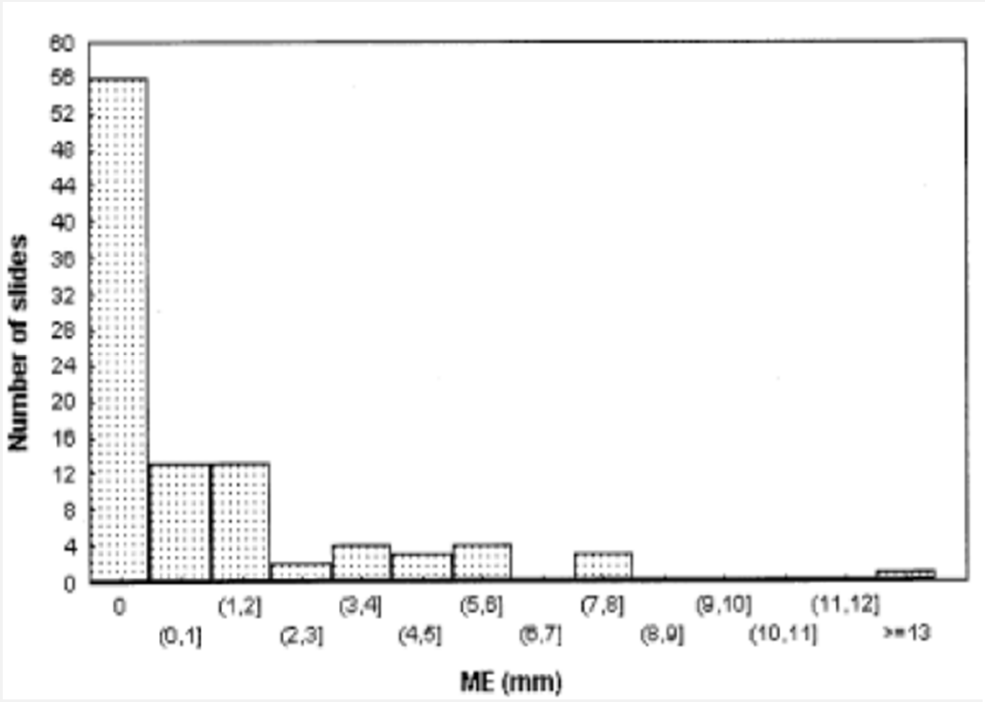


Clinical Target Volume

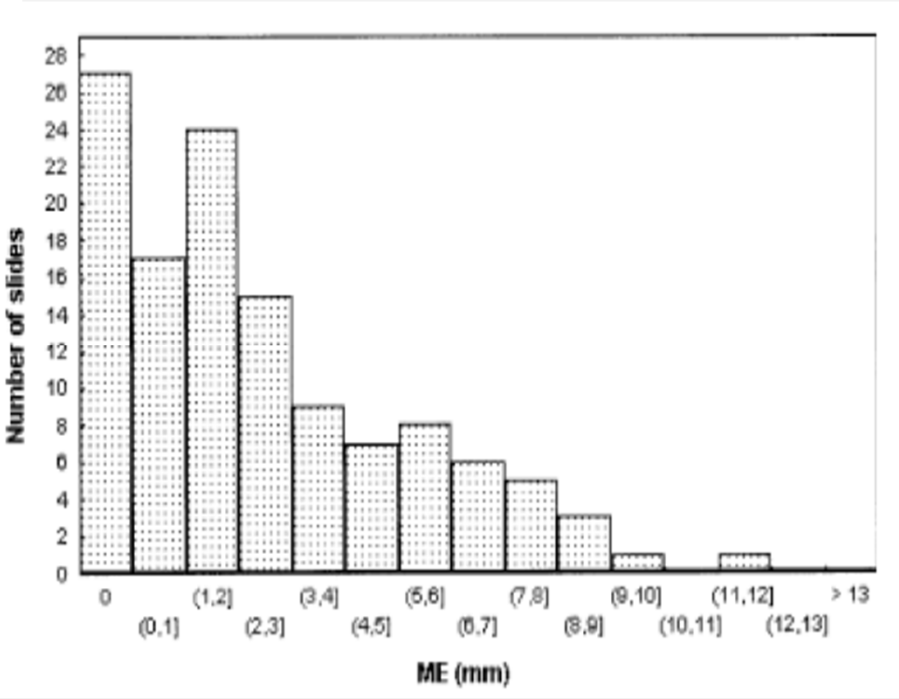
- CTV is defined as the GTV plus a 0.5-1 cm margin to account for microscopic tumor extension.
- CTV for node – average of 5 mm is sufficient

RTOG 0839

Clinical Target Volume



Microscopic extension for SCC 6mm



Microscopic extension for Adenocarcinoma 8mm

Giraud et al. IJROBP 2000:48;1015

Planning Target Volume

- PTV: PTV consists of CTV + Tumor motion margin + Setup margin

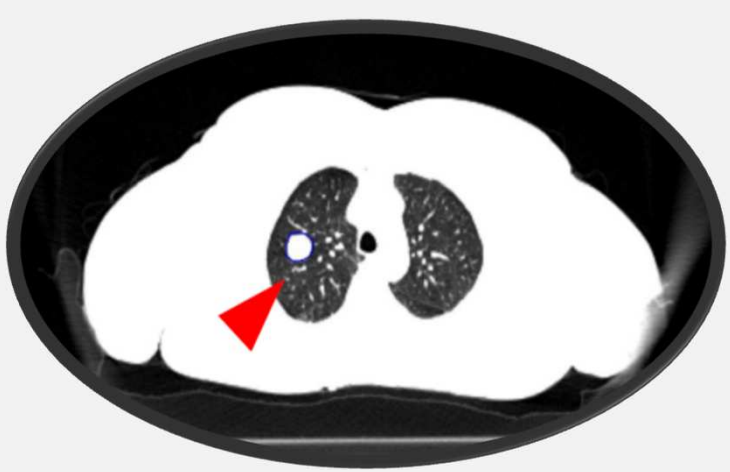
Internal Target Volume

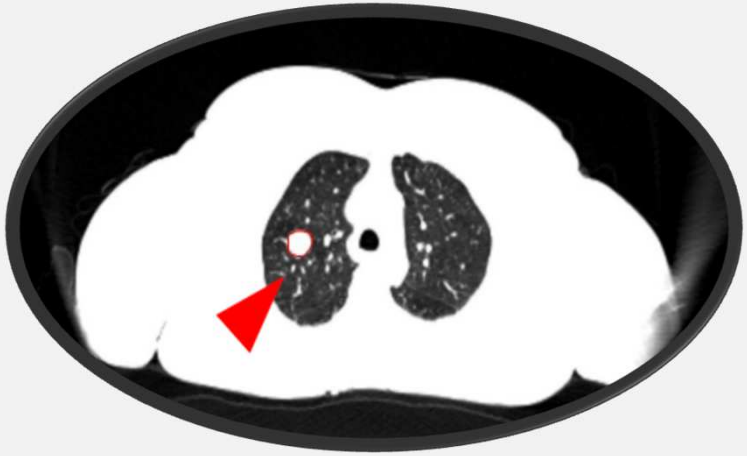
- Free Breathing, Non-ITV Approach CT plus 1 cm in the inferior-superior direction and 0.5 cm in the axial plane.
- Breath-hold or Gating Non-ITV Approach CTV plus 0.5 cm in the superior-inferior direction and 0.3 cm in the axial plane.
- 4D CT Approach No additional margin is required for the ITV (encompasses the tumor motion for a complete respiratory cycle).
- Abdominal Compression CTV contoured on a free-breathing CT with abdominal compression plus 0.8 cm in the superior-inferior direction and 0.5 cm in the axial plane.

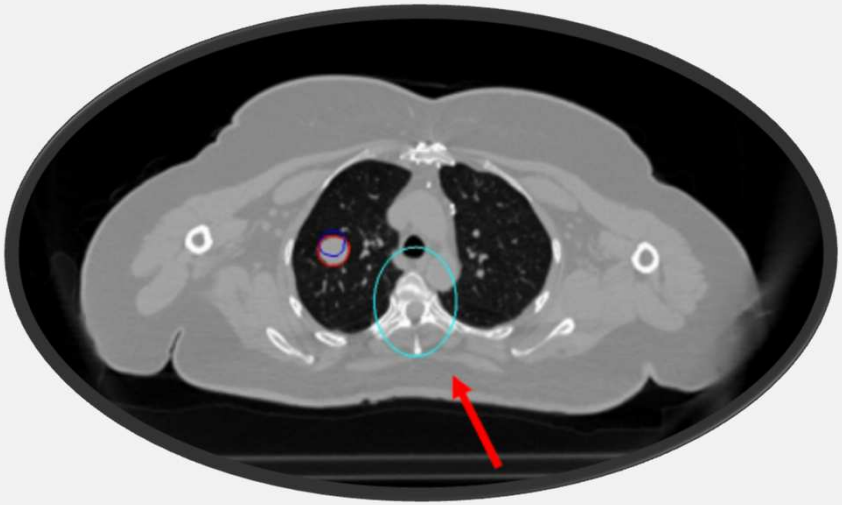
RTOG 0839

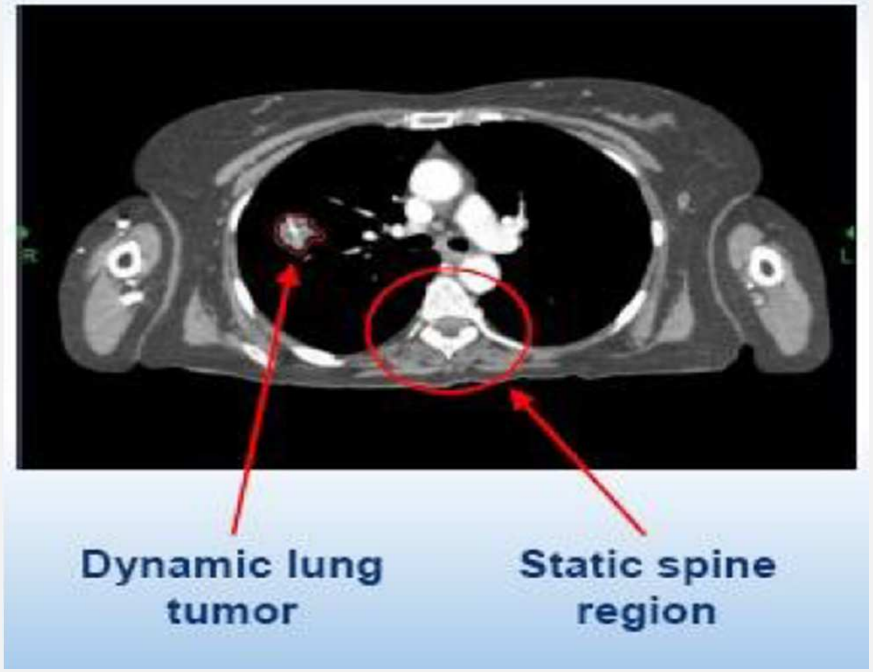
END Expiration

END Inspiration





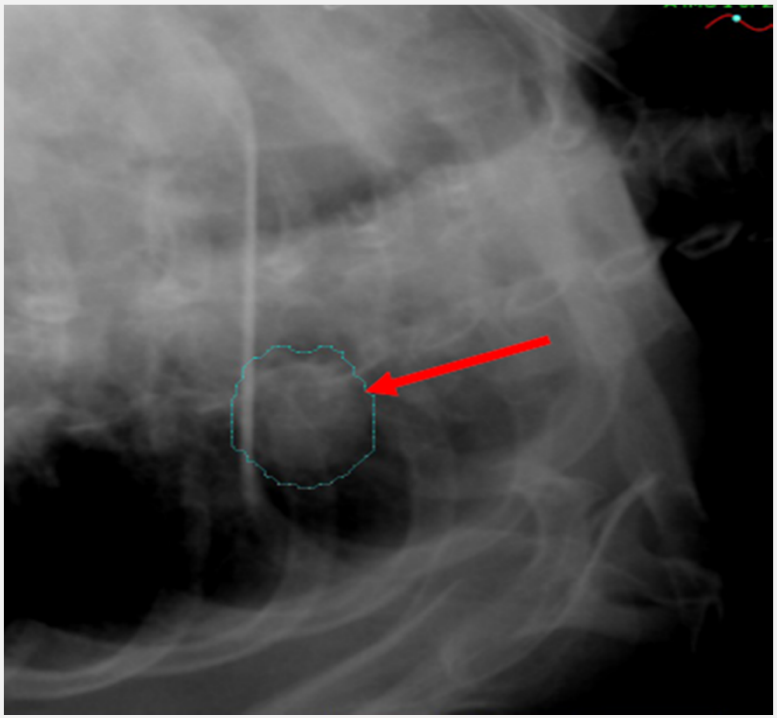




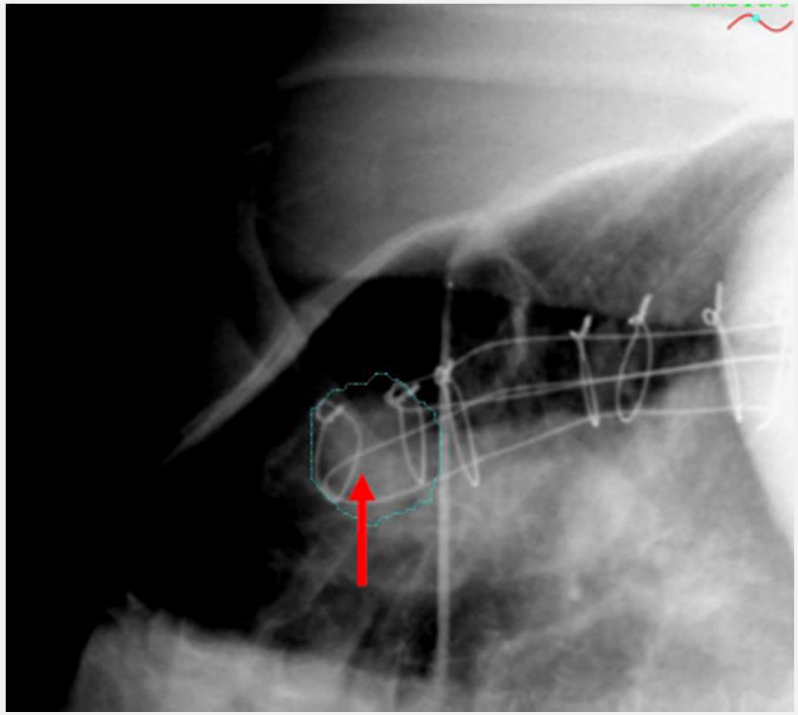
Internal Target Volume

Dynamic Tumour Tracking

Camera A

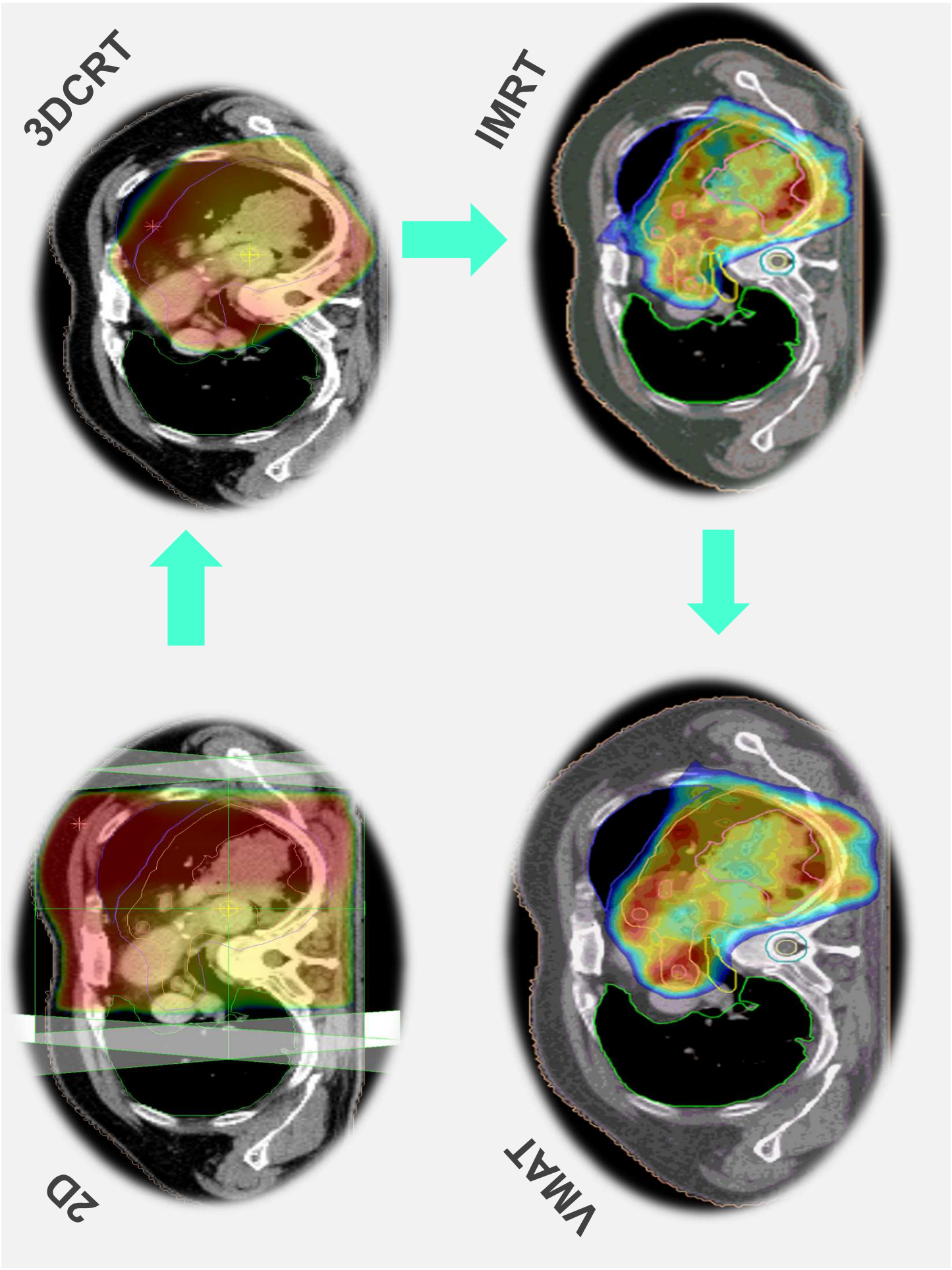


Camera B



	Internal Margin	Set up Margin	PTV Margin
Free-breathing CT + Freebreathing delivery without daily IGRT	1 cm in superior-inferior direction and 0.5 cm in axial directions	0.5 cm uniform expansion	1.5 cm in the superiorinferior direction and 1 cm in the axial directions
Free-breathing CT + Freebreathing delivery + daily IGRT	1 cm in the superiorinferior direction and 0.5 cm in axial directions	0.2-0.3 cm uniform expansion	1.2-1.3 cm in the superiorinferior direction and 0.7-0.8 cm in axial directions
Breath-hold or gating CT + breath-hold or gating delivery + daily IGRT	0.5 cm in the superiorinferior direction and 0.3 cm in axial directions	0.2-0.3 cm uniform expansion	0.7-0.8 cm in the superiorinferior direction and 0.5-0.6 cm in axial directions
4D CT + Free-breathing delivery + daily IGRT	ITV	0.2-0.3 cm uniform expansion	ITV + 0.2-0.3 cm uniform expansion
Abdominal compression CT + abdominal compression freebreathing delivery + IGRT	0.8 cm in the superiorinferior direction and 0.5 cm in axial directions	0.2-0.3 cm uniform expansion	1.0-1.1 cm in the superiorinferior direction and 0.7-0.8 cm in axial directions

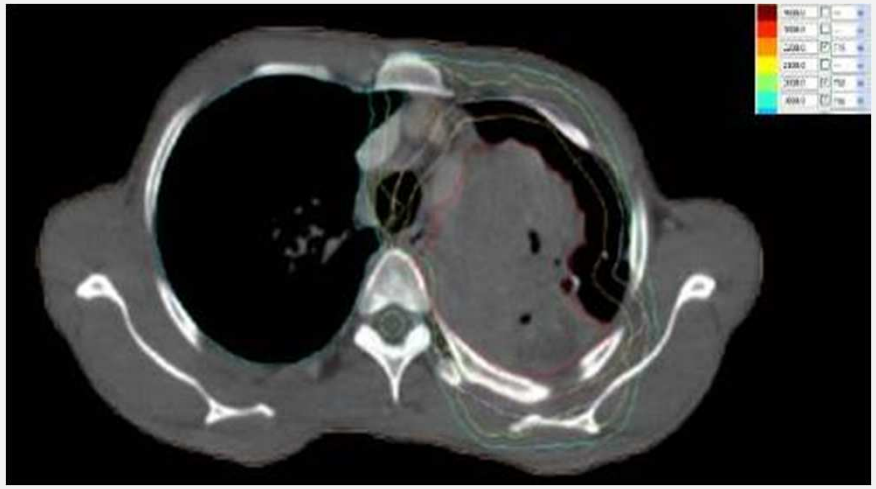
RTOG 0839

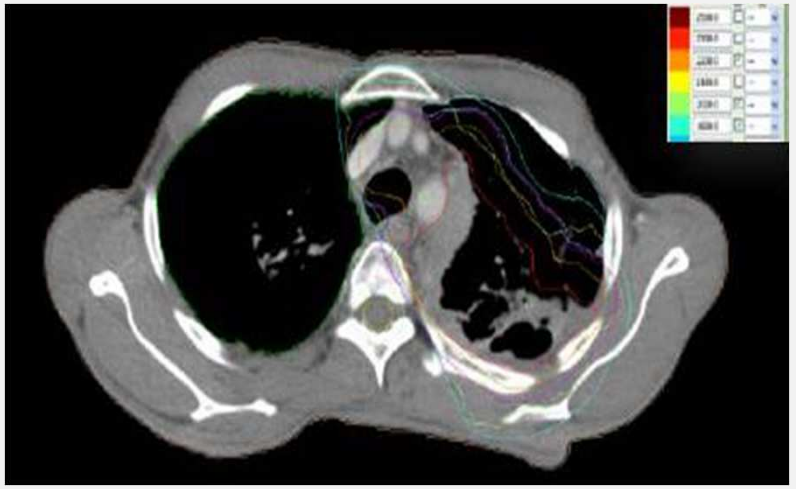

3DCRT
IMRT
2D
VMAT

	2D	3DCRT	IMRT	VMAT
V20_IL-PTV	481cc(45%)	365cc(34%)	258cc(24%)	250cc(23%)
V5_IL	476cc(44%)	466cc(43%)	463cc(43%)	456cc(42%)
Mean_IL	2157cGy	1862cGy	1306cGy	1202cGy
V20_CL	278cc(19%)	469cc(32%)	419cc(29%)	386cc(26%)
V5_CL	316cc(21%)	598cc(41%)	618cc(42%)	619cc(42%)
Mean_CL	405cGy	1235cGy	1289cGy	1228cGy
Heart_V20	116cc(25%)	0cc(0%)	0cc(0%)	0cc(0%)
Mean_Heart	216cGy	205cGy	279cGy	234cGy
Spinal cord_Dmax	6063cGy	5050cGy	4095cGy	3580cGy
Spinal cord_D2	5996cGy	4950cGy	3593cGy	2965cGy
Esophagus_V60	3.4(17%)	4.8cc(24%)	2.4cc(12%)	0.9cc(4.5%)

50Year male
Smoker
SCC
cT4N2M0

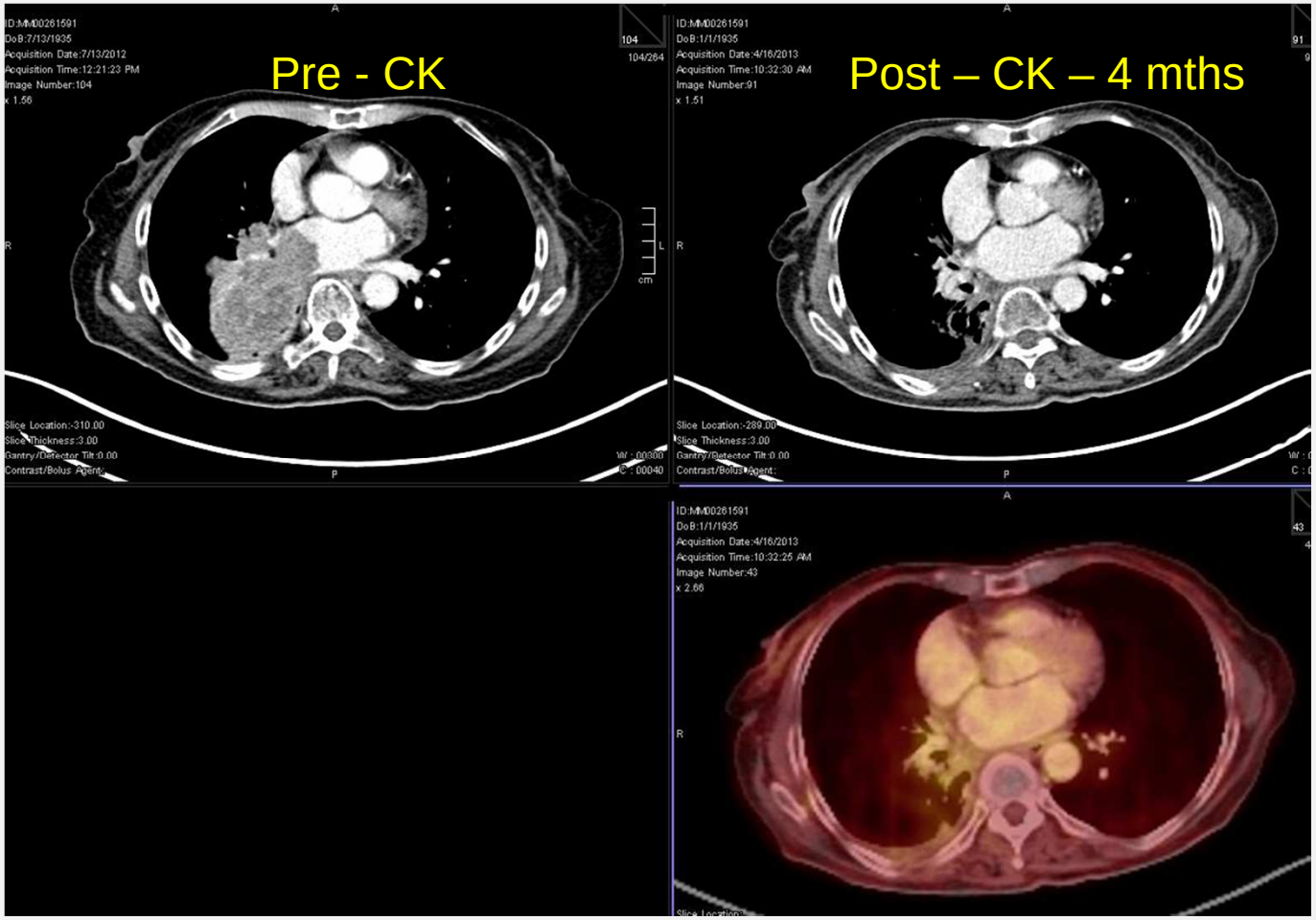
Rescan @ 22fr





	Non- Adaptive plan	Adaptive plan
V20_IL-PTV	484cc(33%)	197.5cc(18%)
V5_IL	795cc(55%)	456cc(42%)
Mean_IL	1360cGy	1280cGy
V20_CL	266cc(18%)	150cc(10%)
V5_CL	516cc(48%)	596cc(39%)
Mean_CL	1289cGy	1040cGy
Heart_V20	0(0%)	0(0%)
Mean_Heart	279cGy	212.8cGy
Spinal cord_Dmax	3940cGy	3760cGy
Spinal cord_D2	3265cGy	3104cGy
Esophagus_V60	5.8cc(29%)	5.6cc(28%)

Post CK response



PET-CT 16/4/13: Significant metabolic regression with near total regression on CT as compared with Dec CECT

- A minimum of 40 hours and a maximum of 8 days should separate each treatment.

- Regimes

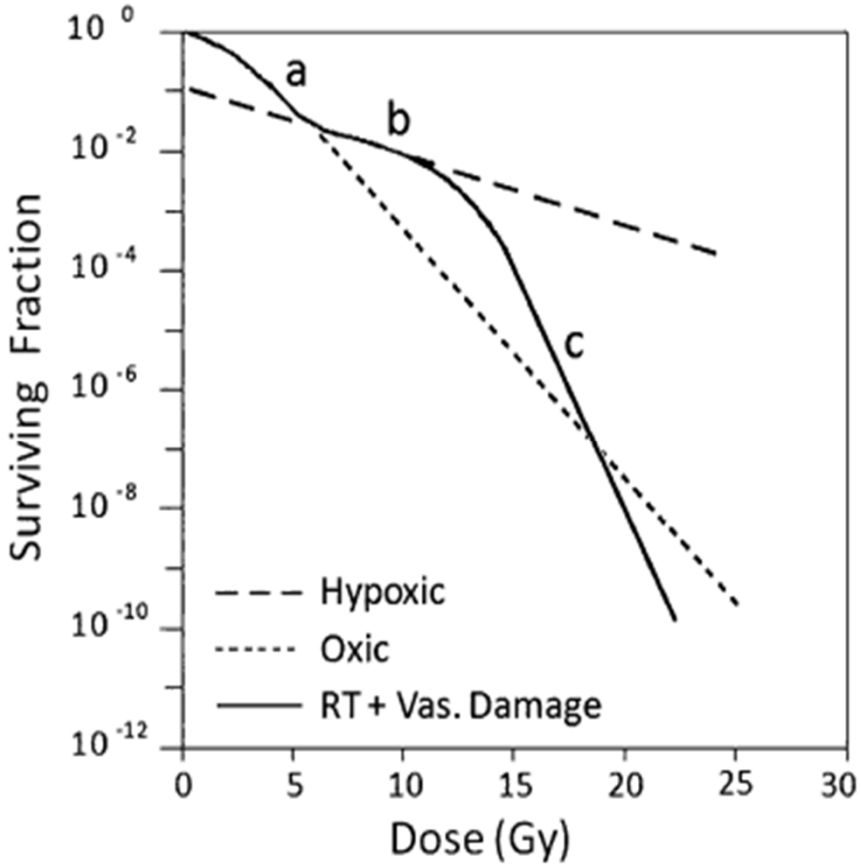
Table. — Selected Reported Results in the Use of Stereotactic Radiotherapy for Treatment of Peripheral Lung Cancers

Authors	Sample Size	Total Dose/# of Fractions (fx)	Local Control	Follow-up (mos)	≥ Grade 3 Toxicity
Uematsu et al[6]	50	50–60 Gy/5–10 fx	94%	60	0.0%
Onishi et al[7]	251	18–75 Gy/1–22 fx	86%	38	5.4%
Nagata et al[8]	45	48 Gy/4 fx	98%	30	0.0%
Timmerman et al[9]	37	60–66 Gy/3 fx	95%	24	5.4%
Baumann et al[10]	138	30–48 Gy/2–4 fx	88%	33	10.1%*
Zimmermann et al[11]	68	37.5 Gy/3 fx	88%	36	3.0%
McGarry et al[12]	47	54–72 Gy/3 fx	87%	15	–
Xia et al[13]	43	50 Gy/10 fx	95%	36	2.3%

*Some of the treated lesions were central in location, not peripheral, athough the report does not clarify whether a central tumor location led to increased risk of treatment toxicity.

Biologic rationale

- Vascular damage:



The total cell death in the tumors receiving SRS or SBRT is the ***product of*** cell death directly caused by radiation ***and*** the cell death indirectly caused by radiation-induced vascular/stromal damage.

Semin Radiat Oncol 18:240–243.

Role of 4 Rs

- Reoxygenation
  - High-dose per fraction, e.g. >10 Gy, significant vascular damage occurs.
  - Consequently, intratumor environment becomes hypoxic and acidic, which not only will prevent reoxygenation of hypoxic cells but also will cause secondary cell death
  - Fowler* also strongly argued that SBRT should be fractionated in order to allow reoxygenation so that the tumors become sensitive to subsequent irradiation.

Repair of sub-lethal Damage

- Considerable repair of sub-lethal radiation damage may take place during the prolonged radiation exposure.

- The estimated loss of radiation effect is greater than 10% when the irradiation of tumors lasts longer than 30 min.

- the vascular injury high-dose fraction SRS and SBRT, may significantly hinder the repair of radiation damage.

- Redistribution
  - Extremely high-doses of irradiation, i.e. >15–20 Gy, in a single fraction, cells are indefinitely arrested in the phases of cell cycle where they were irradiated and undergo interphase death.

- Repopulation:
  - Since SRS or SBRT treatment lasts for a short period, at most 2 weeks, repopulation of tumor cells will not be substantial during the course of SRS or SBRT.

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

Conclusion

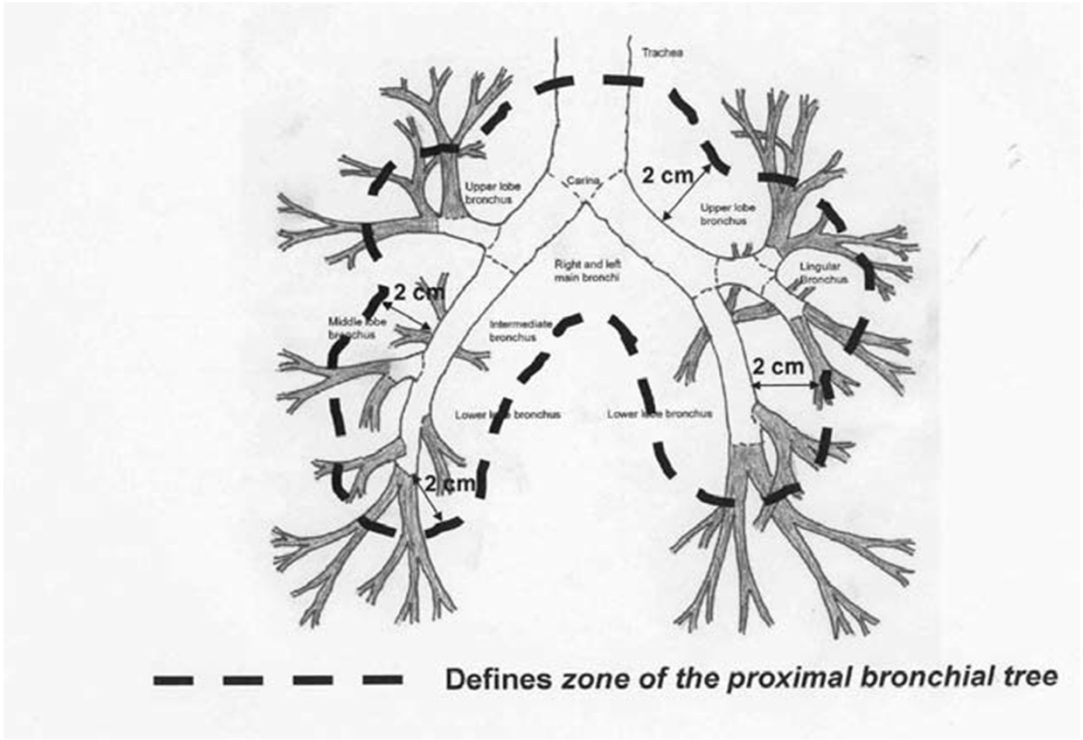
High rates of local control are achieved with this SBRT regimen in medically inoperable patients with stage I NSCLC. Both local recurrence and toxicity occur late after this treatment. This regimen should not be used for patients with tumors near the central airways due to excessive toxicity.

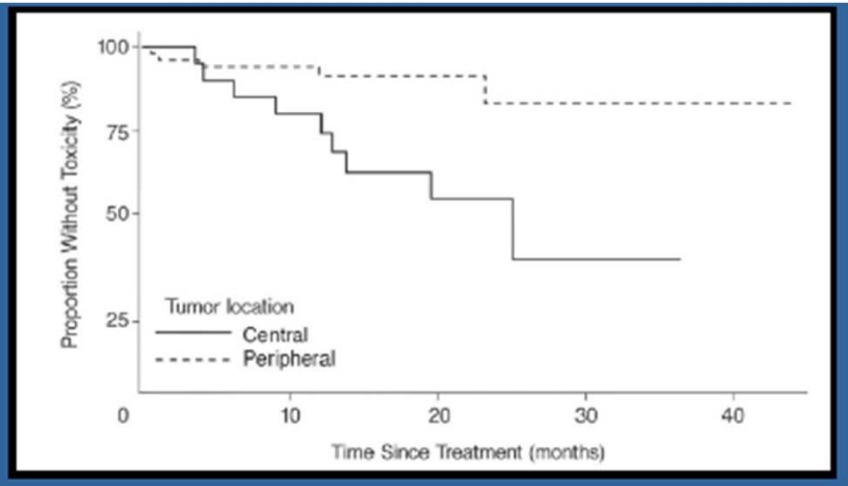
- Median FU: 17.5 months

- *Grade 3 to 5 toxicity occurred in a total of 14 pts*.

- Tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors.

- GTV > 10 cc tumors showing greater toxicity than smaller GTVs.





Freedom from grade 3-5 toxicity


THANKS FOR YOUR ATTENTION!

Patient Selection

- Histologically confirmed of non-small cell cancer
- Inoperability/Operable (RTOG 0618)
- AJCC stage I or II based on only one of the following combinations of TNM staging:
  - T1, N0, M0
  - T2 (≤ 5 cm), N0, M0
  - T3 (≤ 5 cm), N0, M0 chest wall primary tumors only

- Ideally, pleural effusion should not be there, if present, must be deemed too small to tap under CT guidance and must not be evident on chest x-ray.

- Pleural effusion that appears on chest x-ray are permitted only after thoracotomy or other invasive procedures.

Immobilization and CT Simulation

- Patient Positioning
  - accurate reproducibility
  - comfortable for the patient

- Internal Organ Motion Management
  - Abdominal compression,
  - Gating ,
  - Activebreath-holding techniques
  - Synchrony Respiratory tracking System

- Aim: GTV does not deviate beyond the confines of the PTV

- Image Acquisition
  - CT is the primary image platform for targeting and treatment planning.
  - Contrast (+/-)
  - Slice Thickness (1-3mm)
  - PET-CT

Target and OARs delineation

- GTV: Lung windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV.

- PET-Fusion*- 51% Pts.

- The GTV and the, CTV, are identical.

- An additional *0.5cm in the axial plane* and *1.0 cm in the longitudinal plane (cranio-caudal)* is added to the GTV to PTV.

Bradley et al. Int. J. Radiation Oncology Biol. Phys., Vol. -, No. -, pp. 1–8, 2010.

****Sonke J J, et al. Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 2, pp. 567–574, 2009***

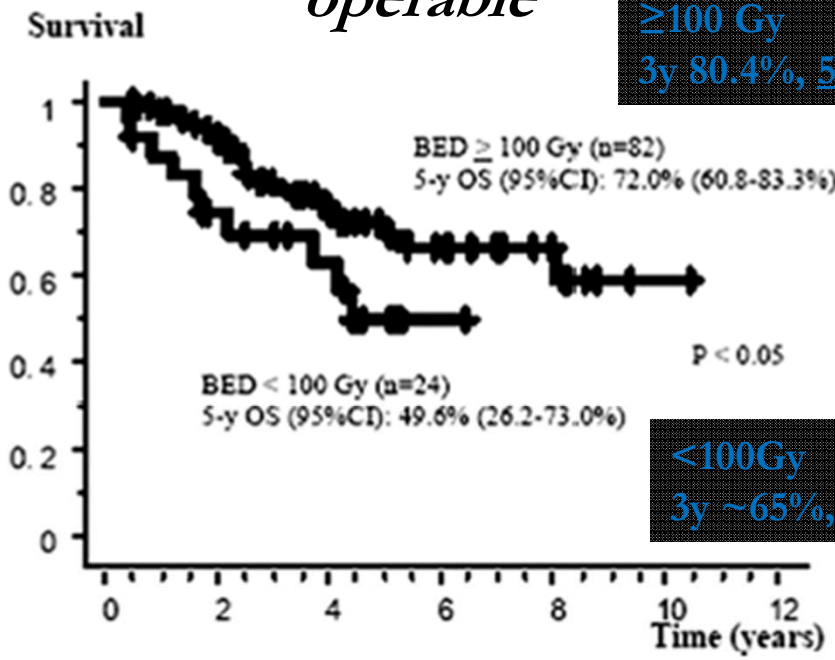
Dose *(Timmerman R, et al. Chest. 124(5): 1946-55, 2003.)*

- The only dose finding study of SBRT (Phase I study of dose escalation).
- Starting with 8 Gy x 3, and escalating to 10, 12, 14, 16, 18, 20 and 22 Gy x 3 fractions, in patients.
- Patients were enrolled into three separate dose escalation groups based on tumor size.
- Protocol-defined maximum tolerated dose (MTD) was only observed in patients with large T2 tumors (5-7 cm in size) at 22 Gy x 3.
- Greater than 90% primary tumor control was observed with 20 Gy x 3.

What dose for peripheral lung cancers?

Medically operable - ***Onishi, J Thorac Oncol 2007.***

5yr OS by BED_{10} in medically operable



≥100 Gy
3y 80.4%, 5y 70.8%

<100Gy
3y ~65%, 5y ~50%

FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

Schemes >100 Gy:

16 Gy x 3

12 Gy x 4

10 Gy x 5

- Planning

  – 1) Normalization:

    - The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV .

  – 2) Prescription Isodose Surface Coverage:

    - The prescription isodose surface is chosen such that 95% of the PTV is conformally covered by the prescription isodose surface, and

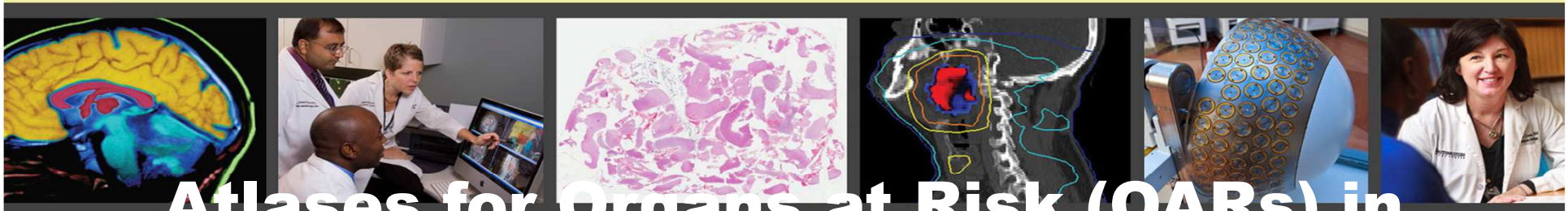
    - 99% of the PTV receives a minimum of 90% of the prescription dose (i.e., 18 Gy per fraction = 54 Gy total)

- High Dose Spillage
  - a) Location: Any dose greater than 105% of the prescription dose (> 21Gy per fraction = 63 Gy total) should occur primarily within the PTV.
  - b) Conformality: PIV/PTV= 1.2

Contouring of Normal Tissue Structures

- Spinal Cord
- Esophagus
- Brachial Plexus
- Heart
- Trachea and
- Proximal Bronchial Tree
- Rt and Lt lung as one structure
    - Including inflated and collapsed lung
    - Excluding GTV/Trachea and ipsilateral bronchus

RTOG®
RADIATION THERAPY ONCOLOGY GROUP



Atlases for Organs at Risk (OARs) in Thoracic Radiation Therapy

Feng-Ming (Spring) Kong MD PhD

Leslie Quint MD

Mitchell Machtay MD

Jeffrey Bradley MD

ACR® AMERICAN COLLEGE OF RADIOLOGY

RTOG 1106 Required OARs

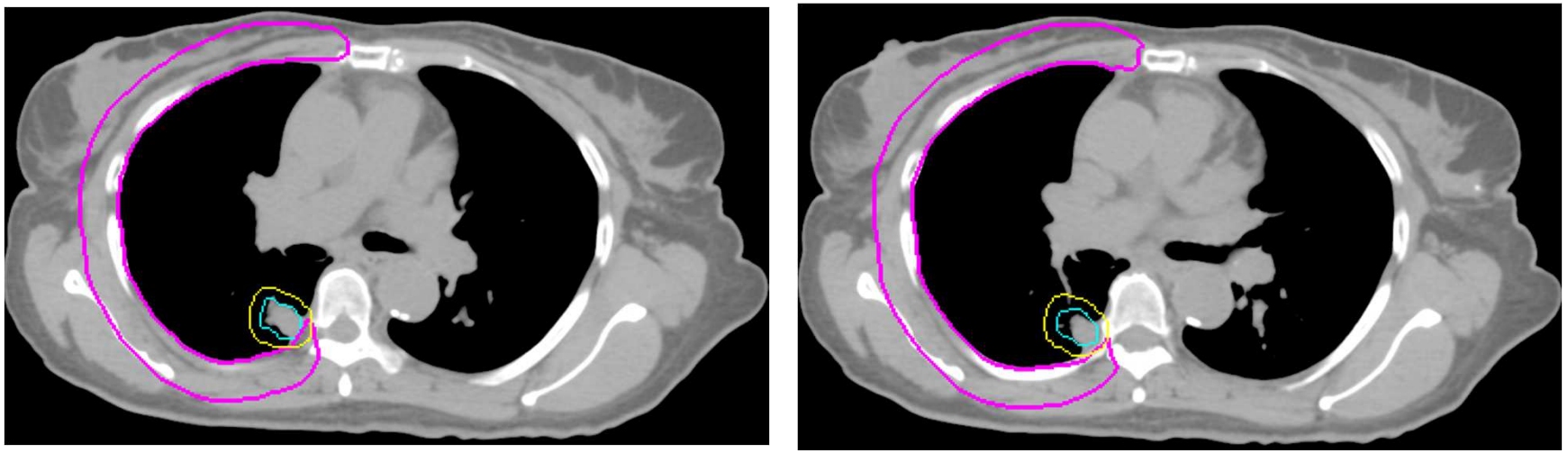
Structure	Description	Structure definition and contouring instructions
Lung	Lungs – PreGTV (composite of CT1GTV and PETMTV)	Both lungs should be contoured using pulmonary windows. The right and left lungs can be contoured separately, but they should be considered as one structure for lung dosimetry. All inflated and collapsed, fibrotic and emphysematic lungs should be contoured, small vessels extending beyond the hilar regions should be included; however, pre GTV, hilars and trachea/main bronchus should not be included in this structure.
Heart	Heart & Pericardium	The heart will be contoured along with the pericardial sac. The superior aspect (or base) will begin at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the apex of the heart.
Esophagus	Esophagus	The esophagus should be contoured from the beginning at the level just below the cricoid to its entrance to the stomach at GE junction. The esophagus will be contoured using mediastinal window/level on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia.
Spinalcord	Spinal Canal	The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at the level just below cricoid (base of skull for apex tumors) and continuing on every CT slice to the bottom of L2. Neuroformanines should not be included.
Brachialplex	Brachial Plexus	This is only required for patients with tumors of upper lobes. Only the ipsilateral brachialplex is required. This will include the spinal nerves exiting the neuroforamine from top of C5 to top of T2. In contrast to prior RTOG lung studies of contouring the major trunks of the brachial plexus with inclusion of subclavian and axillary vessels, this trial requests contouring the nerves according to the CT anatomy on every other CT slice. The structure should extend at least 3 cm above the PTV.

RTOG 1106 Optional OARs

Structure	Description	Structure definition and contouring instructions
Pericard	Pericardium	The structure of pericardium includes pericardial fatty tissue, part of great vessels, normal recesses, pericardial effusion (if applicable) and heart chambers. Pericardium starts at one slice above the top of aortic arch, ends at the last slice of heart apex at diaphragm. Pericardium includes the heart.
Greatves **Aorta** **SVC** **IVC** **PV** **PA**	Great vessels Aorta Superior vena cava Inferior vena cava pulmonary vein pulmonary artery	The great vessels should be contoured separately from the heart, using mediastinal windowing to correspond to the vascular wall and all muscular layers out to the fatty adventitia (5 mm from the contrast enhanced vascular wall). The great vessel should be contoured starting at least 3 cm above the superior extent of the PTV and continuing on every CT slice to at least 3 cm below the inferior extent of the PTV. For right sided tumors, SVC will be contoured, and for left sided tumors, the aorta will be contoured. The ipsilateral PA will be delineated for tumor of either side.
Pbtree	Proximal Bronchial Tree	This structure includes the distal 2 cm of the trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi.
CW2cm	Chest wall 2 cm outside of lung	Chest wall can be autosegmented from the ipsilateral lung with a 2-cm expansion in the lateral, anterior, and posterior directions. Anteriorly and medially, it ends at the edge of the sternum. Posteriorly and medially, it stops at the edge of the vertebral body with inclusion of the spinal nerve root exit site. CW2cm which include intercostal muscles, nerves exclude vertebrate bodies, sternum and skin. This can be accomplished through auto-expansion of the ipsilateral lung (within 3 cm range of PTV).

Chest Wall

CW refers to CW2cm which include intercostal muscles, nerves exclude vertebral bodies, sternum and skin.



Chest wall contours around GTV.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. 796–801, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.027

CLINICAL INVESTIGATION **Lung**

CHEST WALL VOLUME RECEIVING >30 GY PREDICTS RISK OF SEVERE PAIN AND/OR RIB FRACTURE AFTER LUNG STEREOTACTIC BODY RADIOTHERAPY

NEAL E. DUNLAP, M.D.,* JING CAI, PH.D.,* GREGORY B. BIEDERMANN, M.D.,* WENSHA YANG, PH.D.,* STANLEY H. BENEDICT, PH.D.,* KE SHENG, PH.D.,* TRACEY E. SCHEFTER, M.D.,† BRIAN D. KAVANAGH, M.D.,† AND JAMES M. LARNER, M.D.*

The CW volume receiving >20,>30,>40,>50, and >60 Gy was determined and related to the risk of CW toxicity.

A volume threshold of 30 cm3 was observed before severe pain and/or rib fracture was reported.

30% risk of developing severe CW toxicity correlated with a CW volume of 35 cm3 receiving 30 Gy.

Results

- Stanford University
- Erasmus Medical Centre in Rotterdam
- University of Pittsburgh
- Georgetown University
- Cyberknife centre, Miami

Stanford University Clinic(Updated results):

- 32 patients with primary NSCLC (n=20) patients) or single lung metastases (n=12) were treated in a single fraction of 15 Gy/20Gy/25Gy or 30Gy.

- Pulmonary toxicity was encountered at doses 25 Gy or higher, mainly in patients with central tumors or PTV greater than 50 ml

- Analysis of outcomes in this series found the main predictor of local control with single fraction SABR to be tumor volume, with excellent local control of tumors smaller than 12 ml but inadequate control of larger tumors in the dose range tested.

J Thorac Oncol 1, 802-809 (2006).

Radiotherapy and Oncology 91 (2009) 296–300

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

SBRT of lung cancer

Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: Clinical outcome ☆

Noëlle C. van der Voort van Zyp *, Jean-Briac Prévost, Mischa S. Hoogeman, John Praag, Bronno van der Holt, Peter C. Levendag, Robertus J. van Klaveren, Peter Pattynama, Joost J. Nuyttens

Radiation Oncology Department, Daniel den Hoed-Erasmus Medical Center, Rotterdam, The Netherlands

Materials and methods: Seventy inoperable patients with peripherally located early-stage NSCLC were treated with 45 or 60 Gy in three fractions using CyberKnife. Pathology was available in 51% of patients. Thirty-nine patients had a T1-tumor and 31 had a T2-tumor. Markers were placed using the vascular, percutaneous intra-, or extra-pulmonary approach, depending on the risk of pneumothorax.

Results: The actuarial 2-year local control rate for patients treated with 60 Gy was 96%, compared to 78% for patients treated with a total dose of 45 Gy ($p = 0.197$). All local recurrences ($n = 4$) occurred in patients with T2-tumors. Overall survival for the whole group at two years was 62% and the cause specific survival was 85%. The median follow-up was 15 months. Grade 3 toxicity occurred in two patients (3%) after marker placement. Treatment-related late grade 3 toxicity occurred in 7 patients (10%). No grade $\geqslant 4$ toxicity occurred.

Conclusion: Excellent local control of 96% at 1- and 2-years was achieved using 60 Gy in three fractions for NSCLC patients treated with the real-time tumor tracking. Toxicity was low.

University of Pittsburgh group

- N=100,
  - 46 with primary NSCLC,
  - 35 with locally recurrent tumors after prior therapy, and
  - 19 with pulmonary metastasis (14).

- The majority (72 patients) were treated with 20 Gy in a single fraction, while 28 received 60 Gy in 3 fractions.

- With a median follow-up of 20 months, median time to local progression was 22 months and median overall survival was 24 months.

- There was a statistically significantly longer time to local progression with the higher dose.

  - ***Annals of Thoracic Surgery 88, 1594-1600;***

Georgetown University

- N=20 medically inoperable patients with small peripheral stage I NSCLC treated with CyberKnife SABR to an average dose of 53 Gy (range 42-60 Gy) in 3 fractions over a 3-11 day period (37).
- The mean tumor volume in this series was 10 ml (range 4-24 ml).
- With a median follow-up of 43 months, the 2-year actuarial survival was 90% and local control was 95%.
- No regional and 3 distant recurrences were observed.
- Chest wall discomfort occurred in 8 of 12 patients *with tumors near the pleura* and 1 case of subacute *grade 3 pneumonitis was encountered in a patient who had received radiation concurrently with Gefitinib.*

J Hematol Oncol 2, 1 (2009).

Cyberknife centre, Miami

- N=31 with Stage IA or IB NSCLC with tumors ranging in volume from 0.6 ml to 71 ml treated to doses of 60-67.5 Gy in 3-5 fractions (11).

- After a median FU time of 27.5 months, actuarial LC rates of 93.2% and 85.8% were observed at 1 and 4.5 years, respectively, and OS was 93.6% and 83.5% at 1 and 4.5 years, respectively.

- There were no observed grade 3 or higher toxicities.

Author	Treatment	Primary Tumor Control	Single Fraction Equivalent Dose
North America/Europe			
Timmerman, 2006	20-22 Gy X 3	95% (2+ years)	56 – 62 Gy
Bauman, 2006	15 Gy X 3	80% (3 years)	41 Gy
Fritz, 2006	30 Gy X 1	80% (3 years)	30 Gy
Nyman, 2006	15 Gy X 3	80% (crude)	41 Gy
Zimmermann, 2005	12.5 Gy X 3	87% (3 years)	43.5 Gy
Timmerman, 2003	18-24 Gy X 3	90% (2 years)	50 – 68 Gy
Asia			
Xia, 2006	5 Gy X 10	95% (3 years)	32 Gy
Hara, 2006	30-34 Gy X 1	80% (3 years)	30 – 34 Gy
Onimaru, 2003	6 Gy X 8	70% (3 years)	35 Gy
Nagata, 2005	12 Gy X 4	94% (3 years)	43 Gy
Onimaru, 2003	7.5 Gy X 8	100% (3 years)	47 Gy

STARS (Stereotactic Radiotherapy vs. Surgery) trial

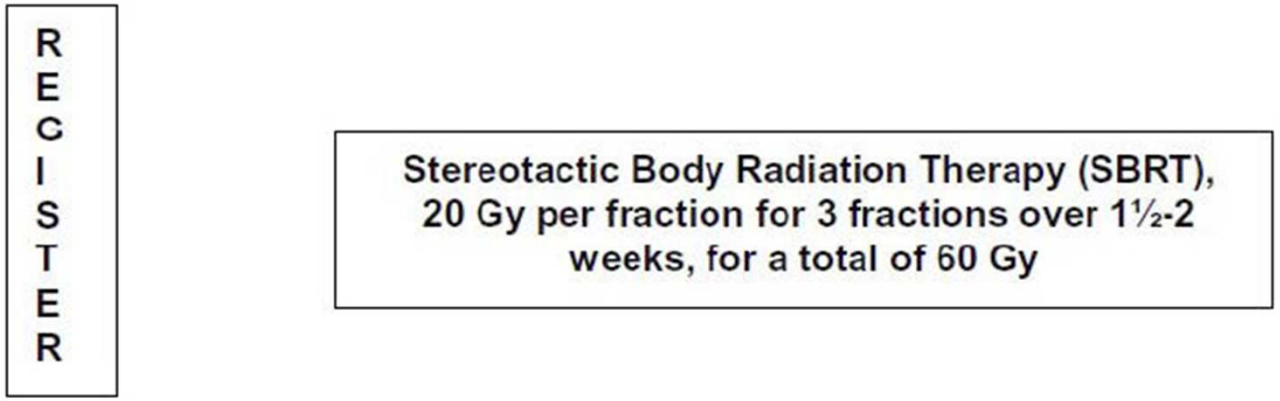
- Randomised study by M.D. Anderson Cancer Center and sponsored by Accuray, Inc.

  - Comparative effectiveness of fractionated SABR (nominally 60 Gy in 3 fractions for peripheral lesions, and 60 Gy in 4 fractions for central lesions) using the CyberKnife system specifically versus surgical lobectomy for stage I NSCLC (41).

RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

SCHEMA

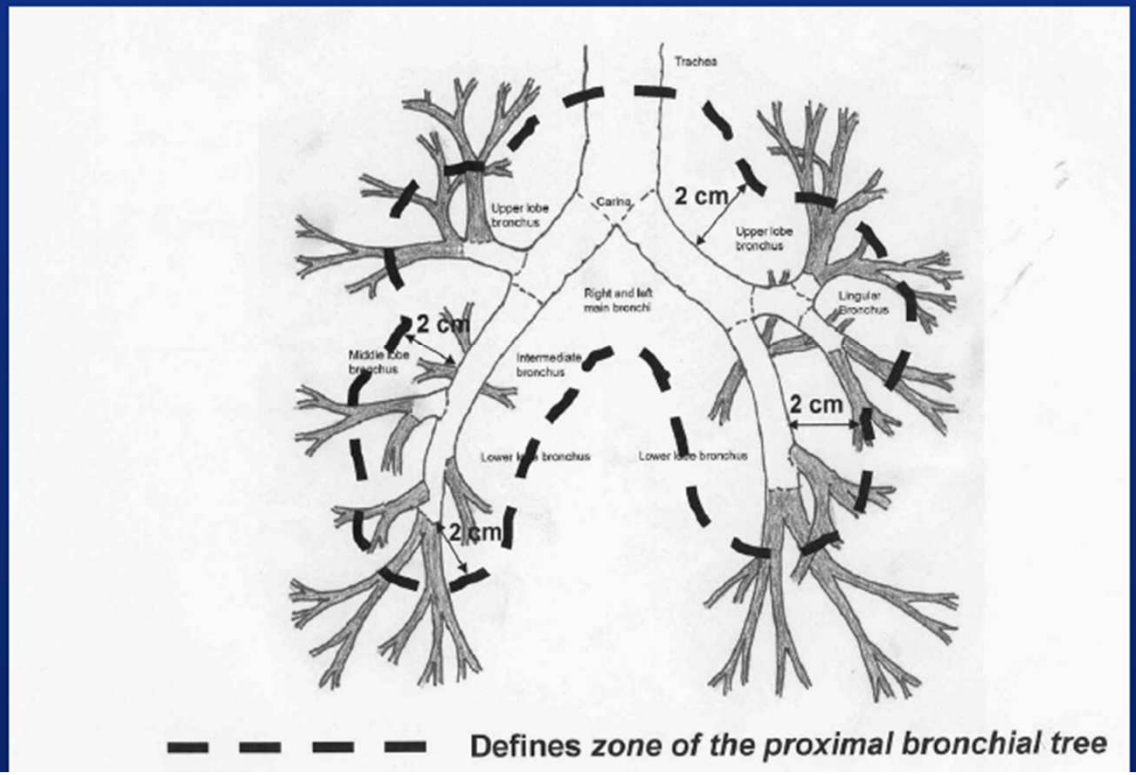


RTOG 0236 Characteristics

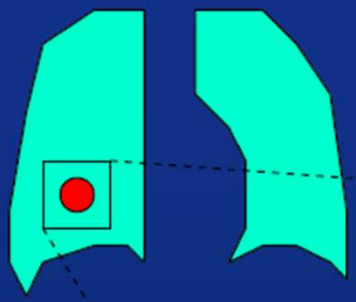
- Opened May 2004 and closed October 2006
- 59 patients enrolled (55 evaluable)
- 62% female, median age 72 years
- Zubrod performance 0 (12 patients), 1 (35), 2 (8)
- 44 patients with T1 tumors, 11 with T2 tumors
- Median follow-up = 34.4 months (range 4.8-49.9 months)

Eligibility

- **Only allowed peripheral tumors outside of "zone of proximal bronchial tree"**

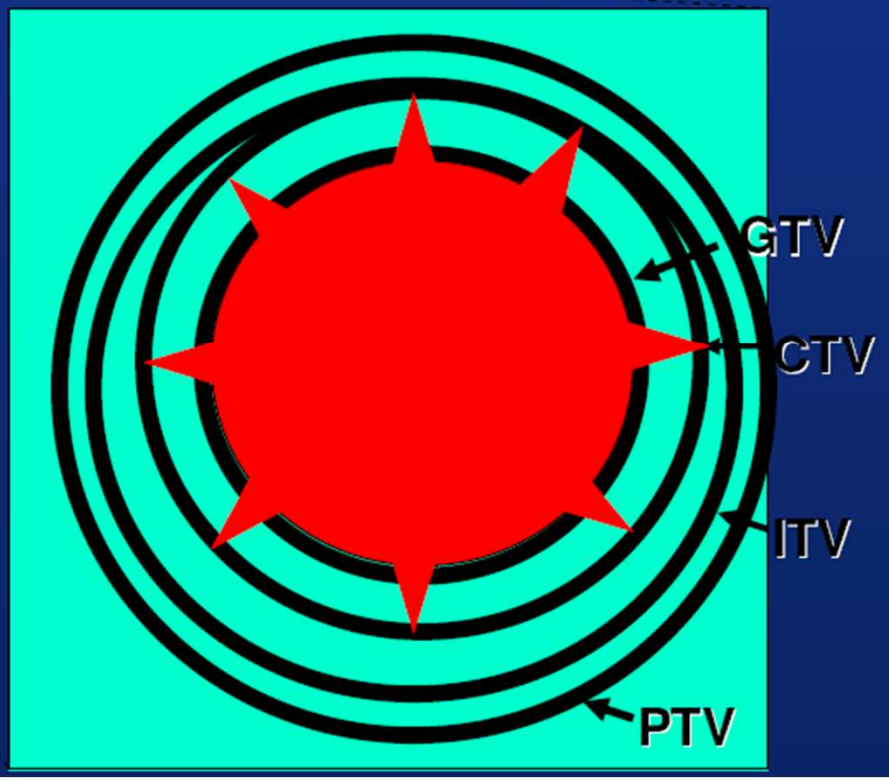


Target Definitions and Dose



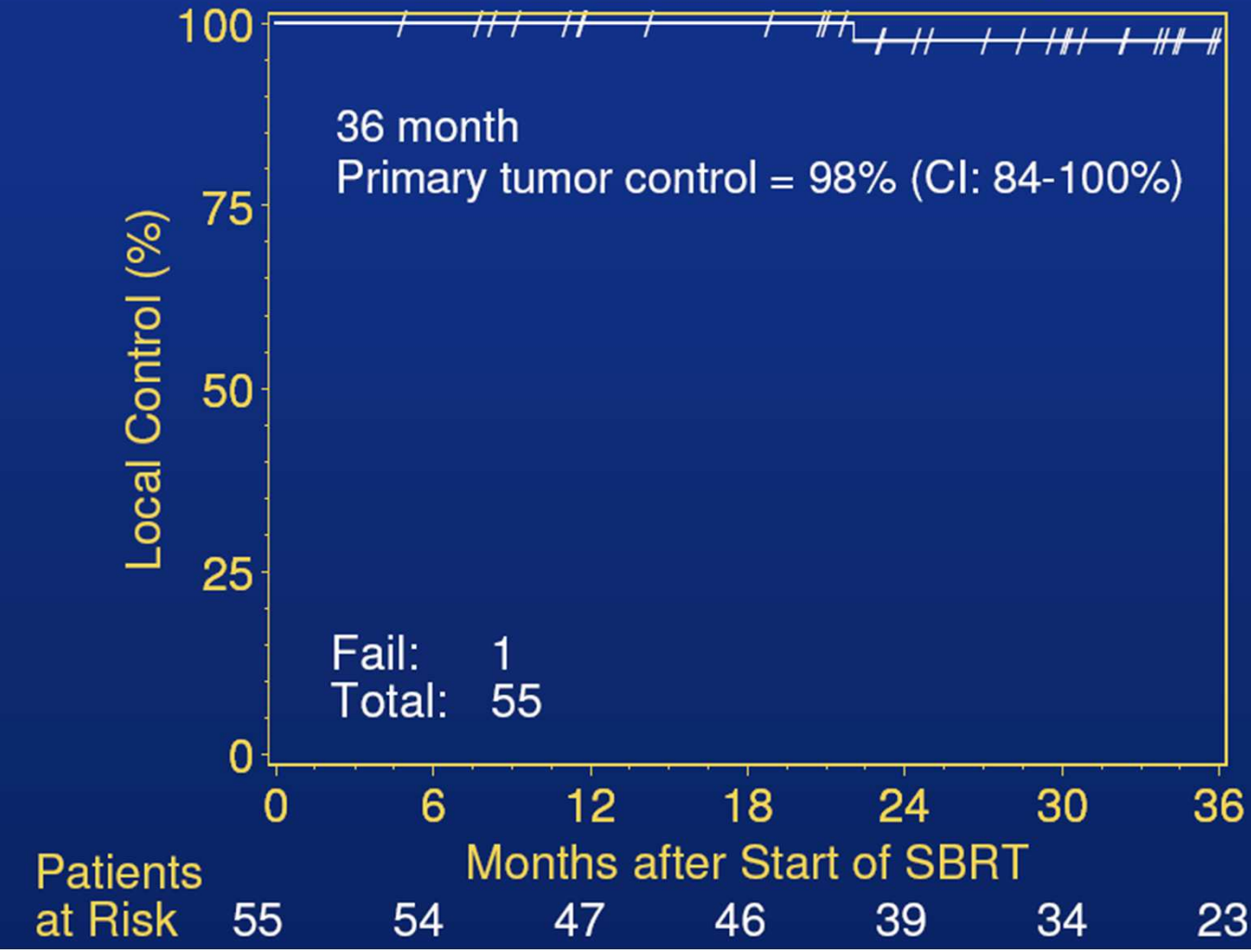
Dose to PTV = 54 Gy given in 3 separate 18 Gy treatments (every other day)*

*accounting for tissue heterogeneity



Primary Tumor Control

1 failure within 2 cm of the primary tumor



Local Control

- Local recurrence is primary tumor failure and/or failure within the involved lobe of the lung

- 1 patient had primary tumor failure

  +

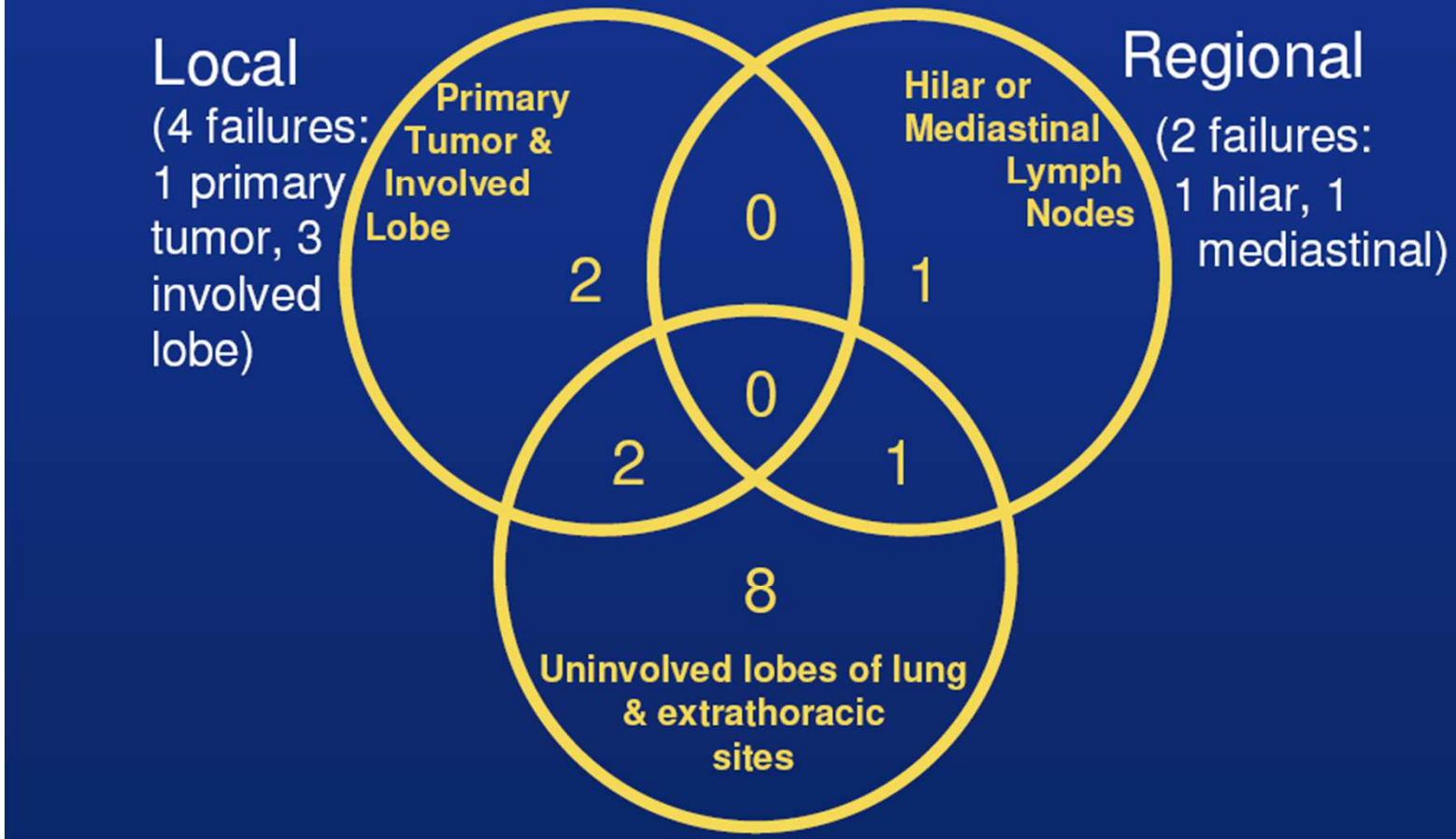
  3 patients had failure within the involved lobe

- 3-year Kaplan Meier local control = 90.7%

Regional Recurrence

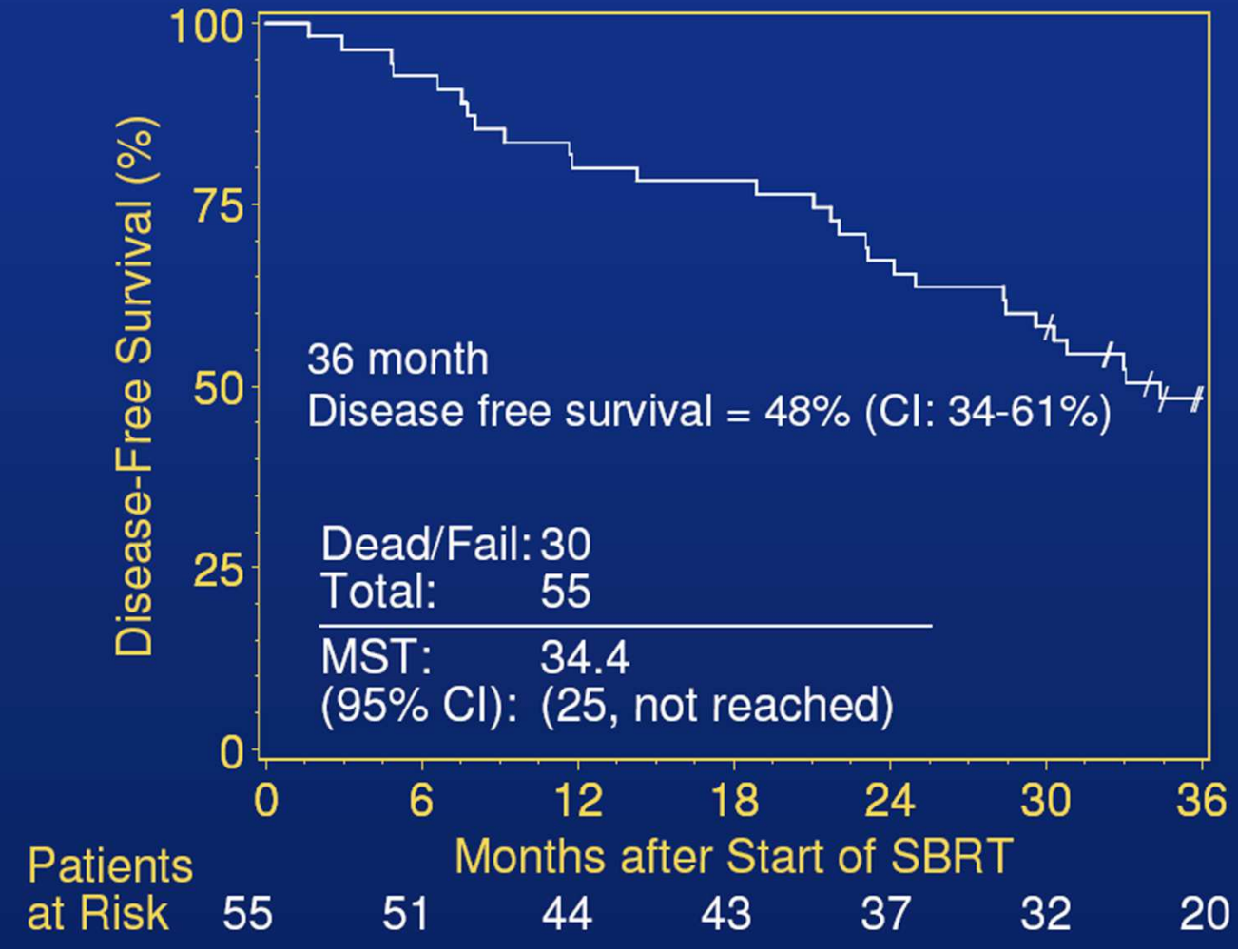
- 2 patients have reported a regional failure, both after 2 years (2.8 and 3.0 years)
- Patients avoiding both local and regional recurrence (loco-regional control) is 87.2%

Patterns of Failure



Disease Free Survival

- 10 patients (18%) death attributed to cancer



Overall Survival

- Median survival is 48.1 months

Encouraging Findings

- Primary tumor control was very high
  - Essential step in affording cancer cure
- Regional control was high
  - No regional therapy included
  - Patient selection/staging was reasonably appropriate
- No toxic deaths
  - Excluded patients with central tumors

Conclusions

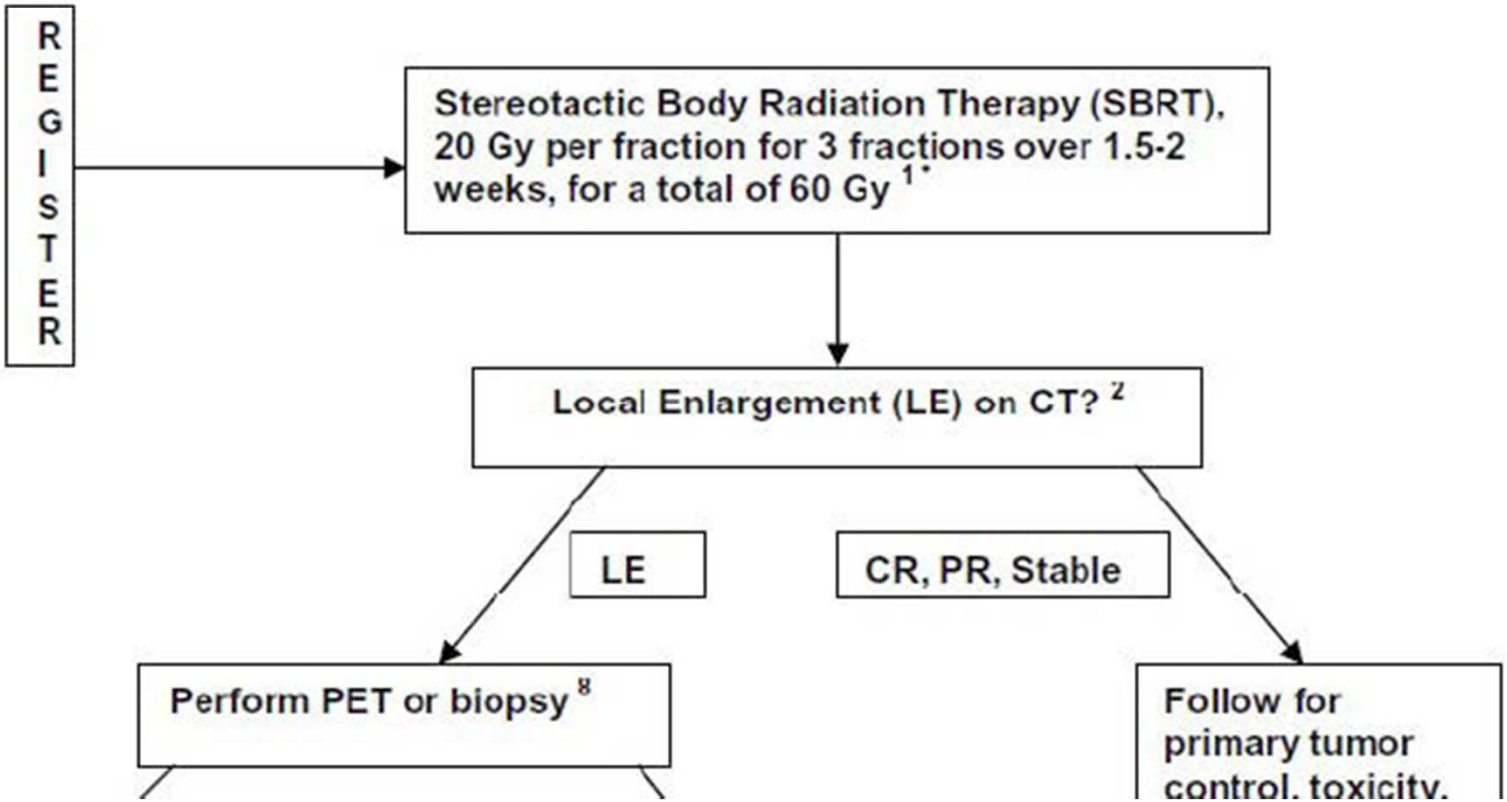
- SBRT controls peripheral early stage lung cancer primary tumors in the large majority of patients resulting in 56% 3-year overall survival
- Despite clinical staging, failure in the lung or lymph nodes within the chest was not common
- Despite comorbidities, SBRT in medically inoperable patients appears well tolerated
- Significant risk of dissemination, often early after therapy, despite loco-regional control
- SBRT with 54 Gy in 3 fractions will be the RTOG standard for peripheral tumors in this population for future trials

Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)
Whole Lung (Right & Left)	(See table in Section 6.4.2)	(See table in Section 6.4.2)

RTOG 0618

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

SCHEMA (2/4/09. 3/25/10)



RTOG 0813

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

SCHEMA

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks									
Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

See Section 5.0 for pre-registration requirements; see Section 6.0 for details of radiation therapy planning and delivery.

to answer that clinical question and to establish the maximum tolerated dose of SBRT for centrally located NSCLC in patients who are not operative candidates.

- The primary endpoint of the study is the maximal tolerated dose (MTD) of a SBRT schedule of *5 fractions*, administered on *alternate days*, over 1½ - 2 weeks, for stage I NSCLC tumors that are touching or within the zone of the proximal bronchial tree or are adjacent to mediastinal or pericardial pleura (as these are also dose-limiting organs for high dose SBRT)
- The MTD for this schedule will be assessed by the adverse events within the *first 12 months* following study entry.

- The starting RT dose for the study will be 10 Gy x 5 fractions every 2 days, over 1½ - 2 weeks (total dose [TD] of 50 Gy). The subsequent dose levels will escalate dose by 0.5 Gy per fraction (i.e., a 2.5 Gy total dose) to a maximum dose of 12 Gy x 5 fractions (TD 60 Gy in 5 fractions).

- Several lower dose levels will be employed if unacceptable dose-limiting toxicity (DLT) is seen with the planned starting dose of 10 Gy.

- Thus, rather than dose limits, we are proposing volume limits and dose guidelines in the protocol, which we expect to be observed for cases in which the tumor is not in the immediate vicinity of a critical organ.
- In such a case, the planning needs to be done so that there is no hot spot within that organ, even if that organ is part of the PTV, i.e., that no part of anyOAR receives more than 105% of the prescribed dose.

Table 2

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.25 cc <0.5 cc	22.5 Gy (4.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

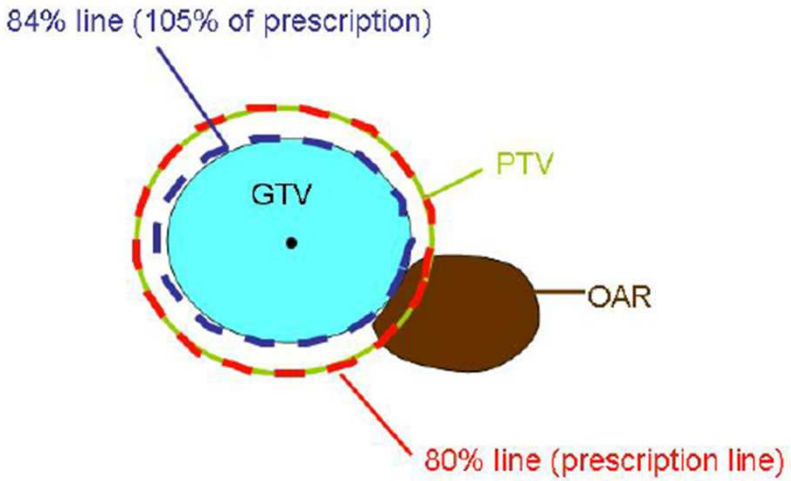


Table 3

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	aneurysm
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	stenosis/fistula

The maximum point dose limits must be respected.

- Parikh et al from Washington University in St. Louis reported initial results from a Phase I/II study of SBRT dose escalation in patients with centrally located Stage I lung cancers.
- Radiation was delivered in five fractions for each of four arms; 9, 10, 11, and 12 Gy per fraction given over two weeks.
- There were five or six patients per group in Phase I with median follow-up approaching two years in the 9-11 Gy/fraction arms.
- No treatment-related Grade 3 or greater toxicity occurred at fractions sized of 9-11 Gy.
- One patient treated at 12 Gy x 5 fractions experienced a grade 3 radiation pneumonitis.
- Based on the Phase I results, this trial has proceeded to the Phase II portion. With 14 patients treated using ≥11 Gy x 5 fractions, there have been no local failures thus far.
- The conclusions of this study are that doses up to 11 Gy x 5 fractions appear to be safe for patients with centrally located Stage lung cancer.

RTOG 0915
(NCCTG N0927)

A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

SCHEMA

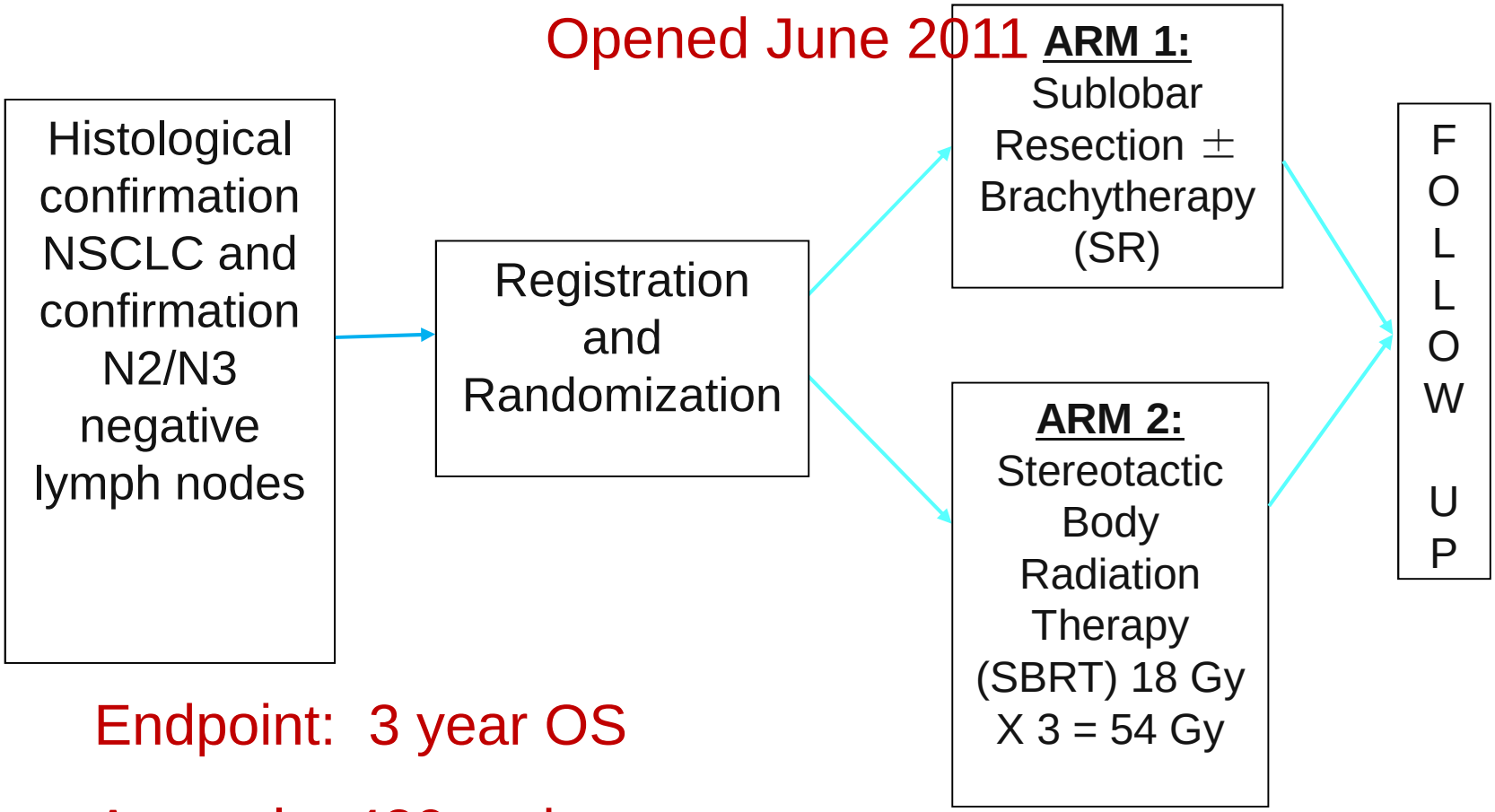
S		**R**	**Stereotactic Body Radiation Therapy (SBRT)**
T	**Zubrod Performance Status**	**A**	
R	1. 0	**N**	**Arm 1**: 34 Gy in 1 fraction
A	2. 1	**D**	
T	3. 2	**O**	
I		**M**	**Arm 2**: 48 Gy in 4 once-daily consecutive fractions
F	**T Stage**	**I**	
Y	1. T1	**Z**	
	2. T2	**E**	

Future studies

Finally, RTOG 0633 (A. Bezjak, J. Bradley, L. Gaspar, co-PIs) will be a phase I dose escalation study for patients with tumors located within the zone of the proximal bronchial tree.

ACOSOG Z4099/RTOG 1021
Phase III Trial

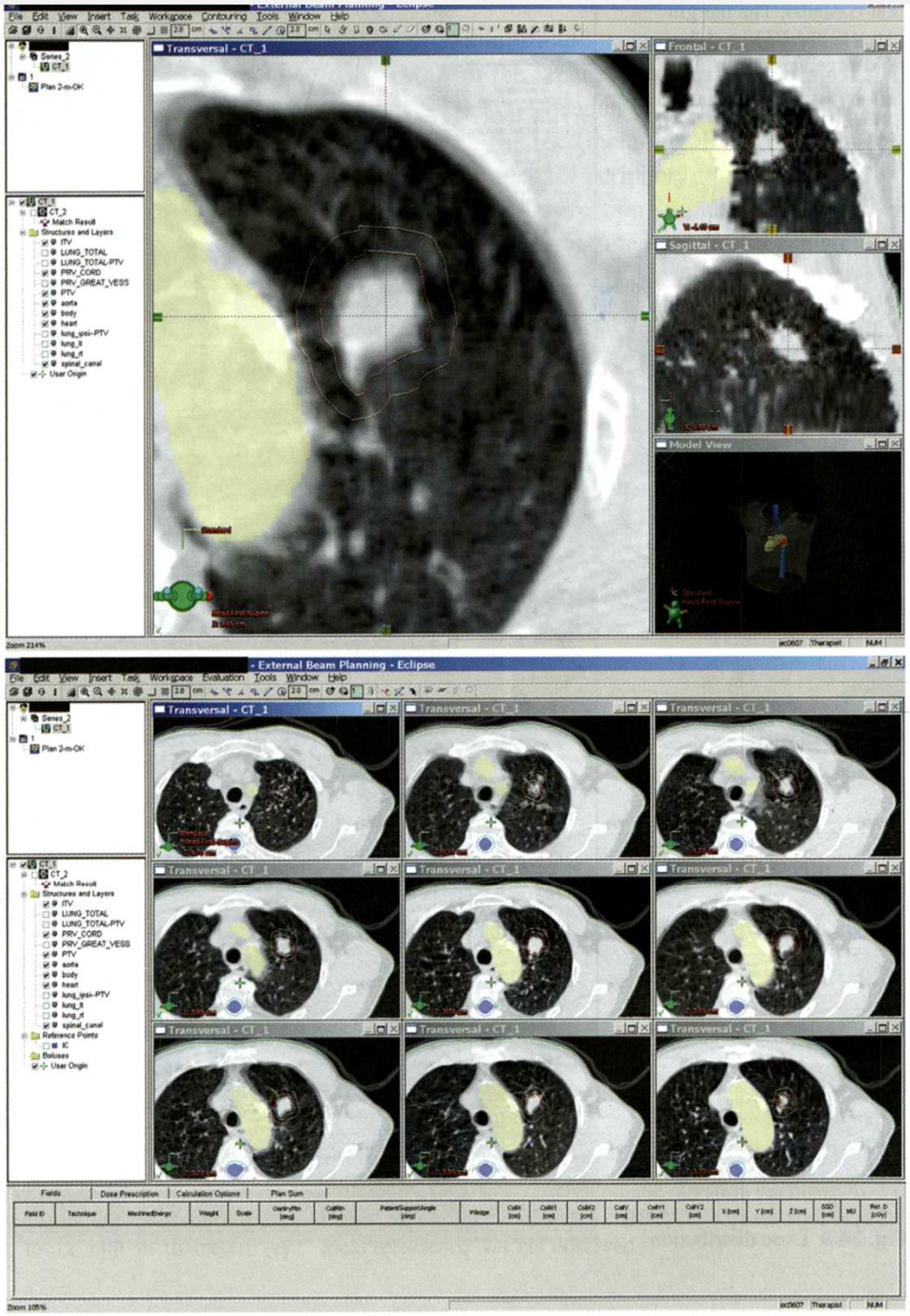
Opened June 2011



Endpoint: 3 year OS

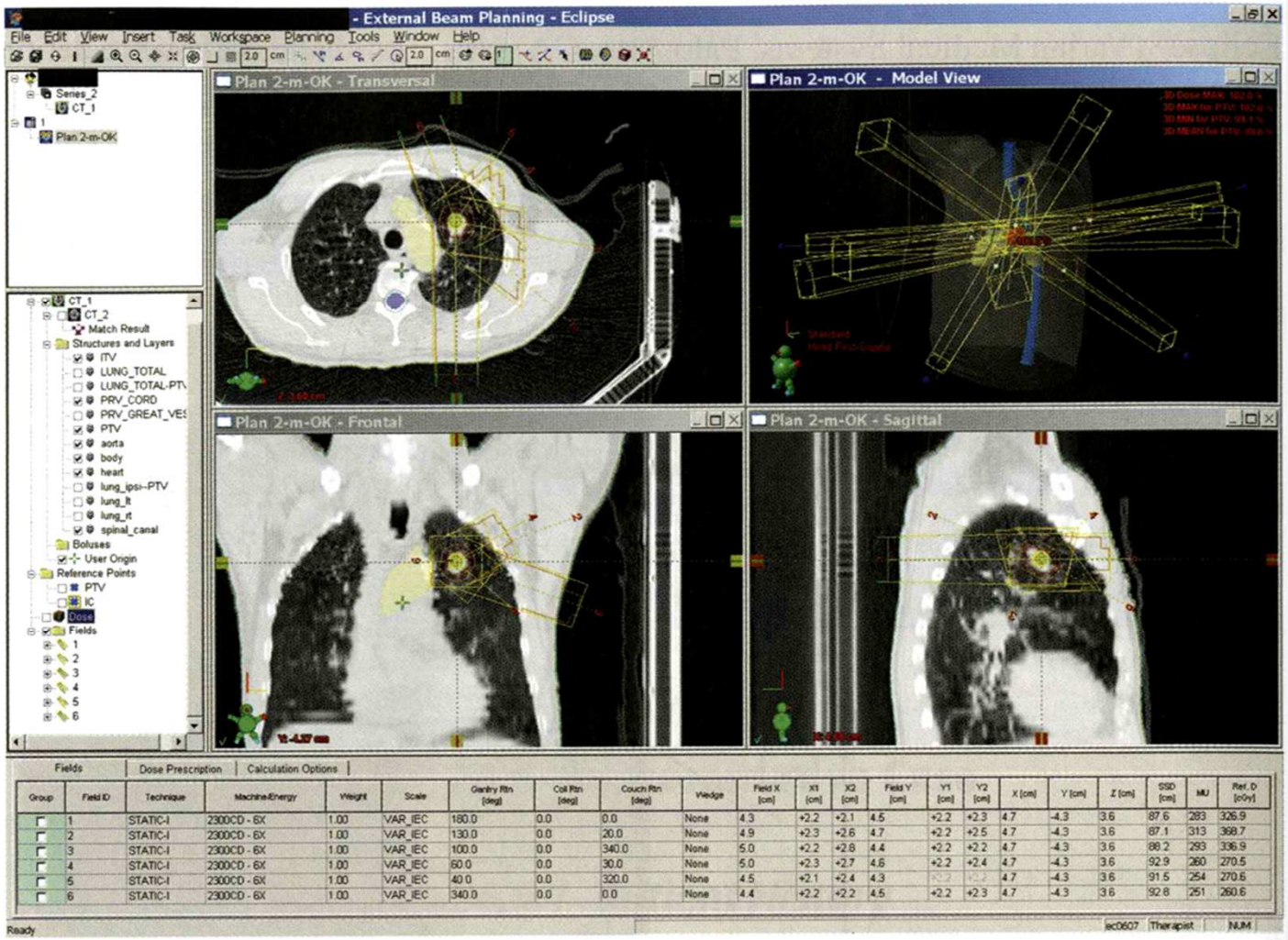
Accrual = 420 patients

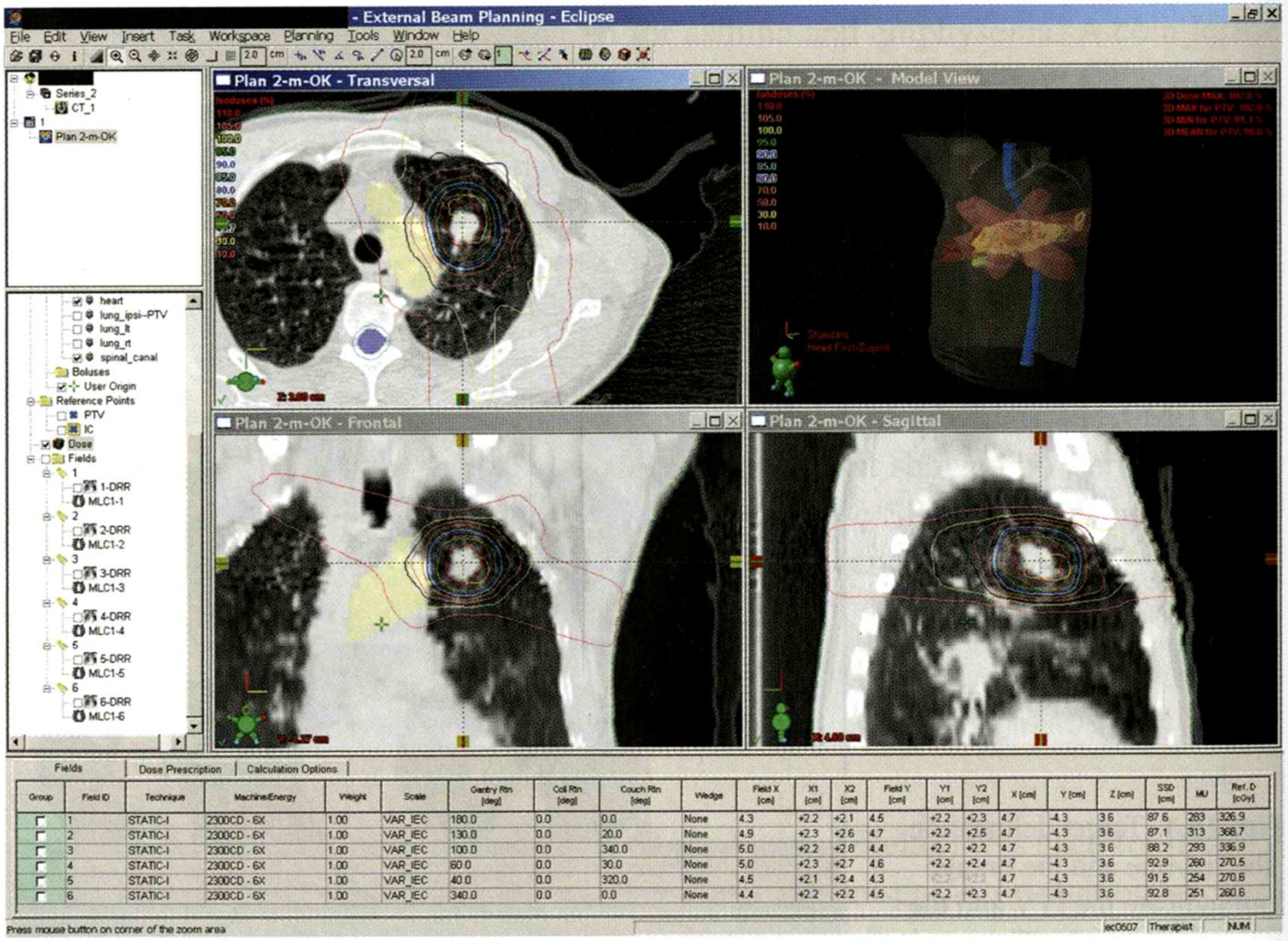
In SBRT, confidence in this accuracy is accomplished by the integration of modern imaging, simulation, treatment planning, and delivery technologies into all phases of the treatment process; from treatment simulation and planning, and continuing throughout beam delivery.



Target delineation. The red line and the orange line indicate the ITV and the PTV, respectively. The margin between the ITV and the PTV was 5 mm

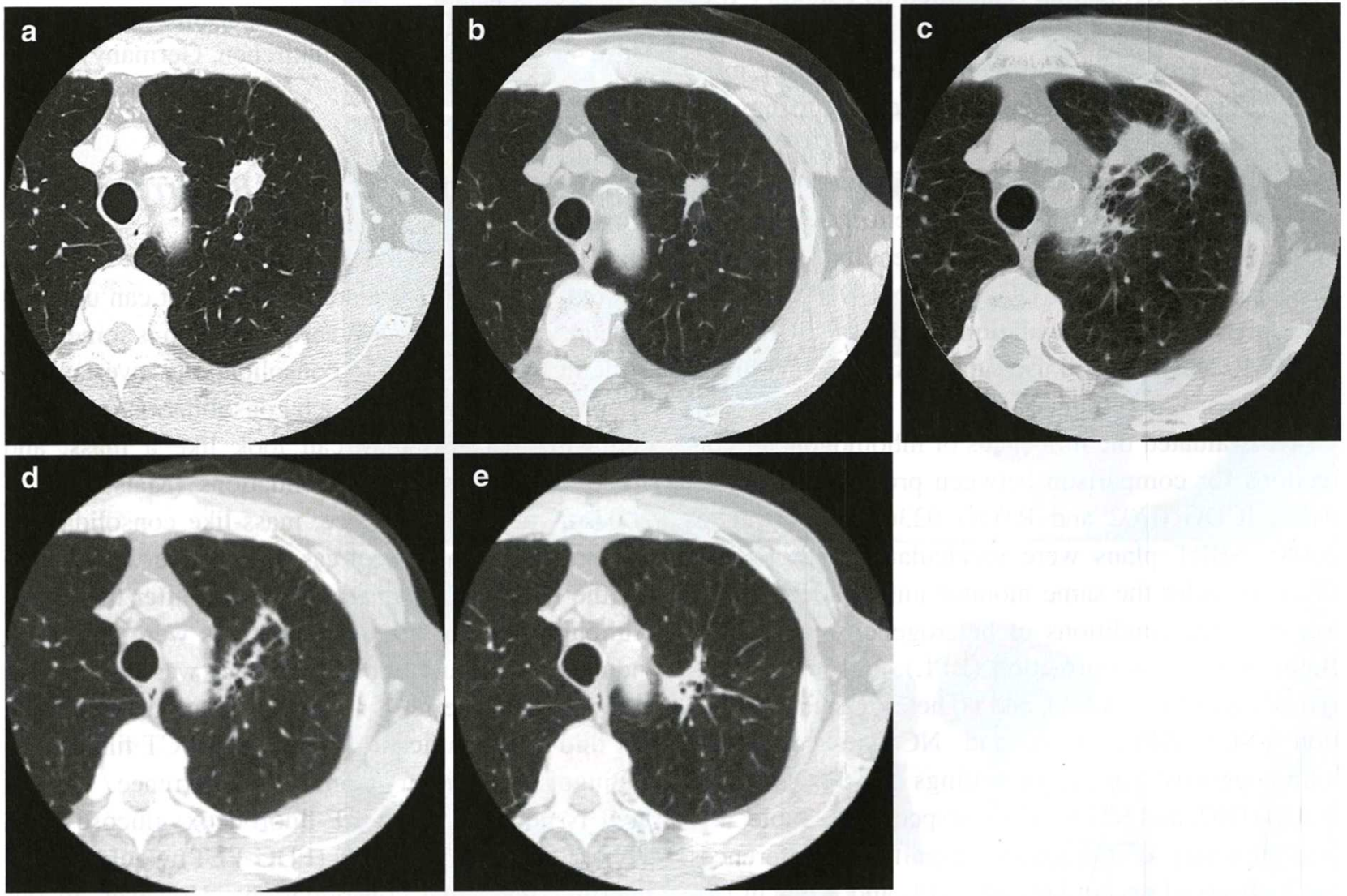
Beam arrangement. Six beams were arranged for the PTV. Two of the six beams were coplanar, and the remaining four beams were non-coplanar. The margin between the PTV and the field edge was 5 mm



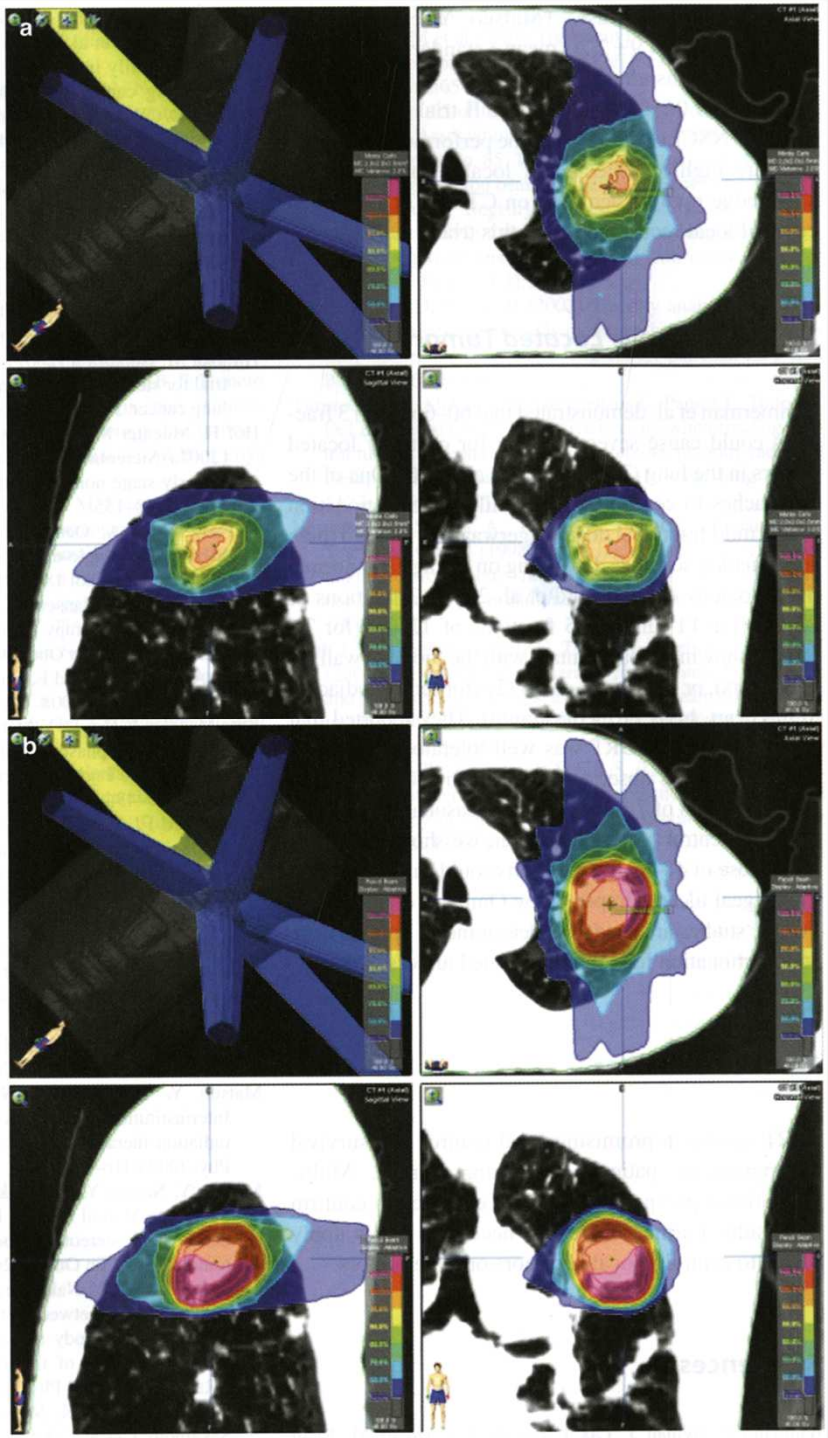


Group	Field ID	Technique	Machine/Energy	Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]	MU	Ref. D [cGy]
	1	STATIC-I	2300CD - 6X	1.00	VAR_IEC	180.0	0.0	0.0	None	4.3	+2.2	+2.1	4.5	+2.2	+2.3	4.7	-4.3	3.6	87.6	283	326.9
	2	STATIC-I	2300CD - 6X	1.00	VAR_IEC	130.0	0.0	20.0	None	4.9	+2.3	+2.6	4.7	+2.2	+2.5	4.7	-4.3	3.6	87.1	313	368.7
	3	STATIC-I	2300CD - 6X	1.00	VAR_IEC	100.0	0.0	340.0	None	5.0	+2.2	+2.8	4.4	+2.2	+2.2	4.7	-4.3	3.6	88.2	293	336.9
	4	STATIC-I	2300CD - 6X	1.00	VAR_IEC	60.0	0.0	30.0	None	5.0	+2.3	+2.7	4.6	+2.2	+2.4	4.7	-4.3	3.6	92.9	260	270.5
	5	STATIC-I	2300CD - 6X	1.00	VAR_IEC	40.0	0.0	320.0	None	4.5	+2.1	+2.4	4.3	+2.2	+2.2	4.7	-4.3	3.6	91.5	254	270.6
	6	STATIC-I	2300CD - 6X	1.00	VAR_IEC	340.0	0.0	0.0	None	4.4	+2.2	+2.2	4.5	+2.2	+2.3	4.7	-4.3	3.6	92.8	251	260.6

Dose distribution



CT changes after SBRT: (**a**) before SBRT – an 18-mm solitary tumor was in the upper lobe of the left lung; (**b**) 6 weeks after SBRT – the tumor shrank to 12 mm in diameter; (**c**) 3 months after SBRT – asymptomatic radiation pneumonitis was observed; (**d**) 10 months after SBRT; (**e**) 3 years after SBRT – local recurrence was not observed



Comparison of dose distributions between algorithms. (**a**) Dose distributions calculated with Monte Carlo algorithm. The isocenter dose was 48.0 Gy. D95 for the PTV was 36.2 Gy. (**b**) Dose distributions calculated with path length correction method under the same monitor units as in Fig. 24.5a. The isocenter dose was 49.3 Gy. D95 for the PTV was 49.4 Gy. Doses for the PTV in path length correction might be overestimated compared with Monte Carlo algorithm