Radiotherapy for Non-Small Cell Lung Cancer

I Standard Treatment Options

II Radiotherapy Planning

TNM Staging System

Proposed 7th edition TNM staging system for lung cancer

Primary tumor (T)
T1 - Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T1a - Tumor ≤2 cm in diameter
T1b - Tumor >2 cm in diameter
T2 - Tumor >3 cm but ≤7 cm, with any of the following features:
Involves main bronchus, ≥2 cm distal to carina
Invades visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a - Tumor ≤5 cm
T2b - Tumor >5 cm
T3 - Tumor >7 cm or any of the following:
Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
Atelectasis or obstructive pneumonitis of the entire lung
Separate tumor nodules in the same lobe
T4 - Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional lymph nodes (N)
N0 - No regional lymph node metastases
N1 - Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 - Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 - Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant metastasis (M)
M0 - No distant metastasis
M1 - Distant metastasis
M1a - Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b - Distant metastasis

Disease Staging

- Management is based on disease stage

Stage groupings of TNM subsets			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Adapted from: AJCC Cancer Staging Manual, 6th edition, New York, 2002.

- Stage I-II: early stage
- Stage IIIA: locally advanced (surgery feasible)
- Stage IIIB: locally advanced (surgery not feasible)
- Stage IV: metastatic disease

Types of Staging

-Symptoms and physical findings

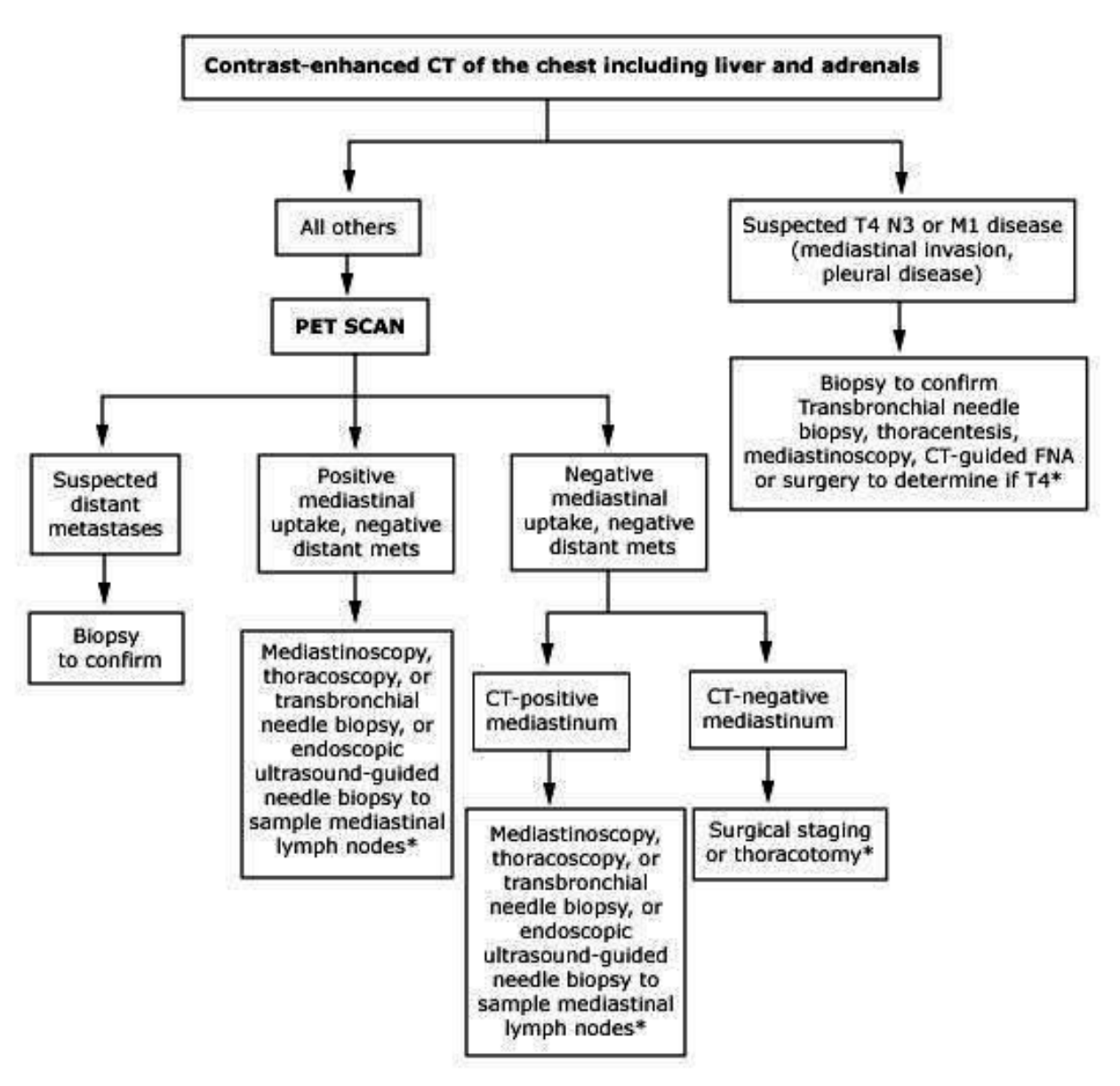
-Laboratory tests

-x-ray, CT, PET

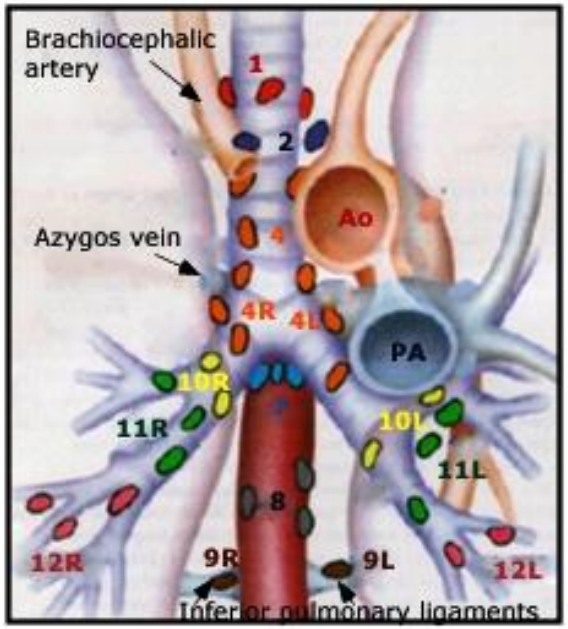
- Mediastinal LN sampling
  - mediastinoscopy
  - thoracoscopy
  - endoscopic ultrasound
  - transbronchial needle aspiration

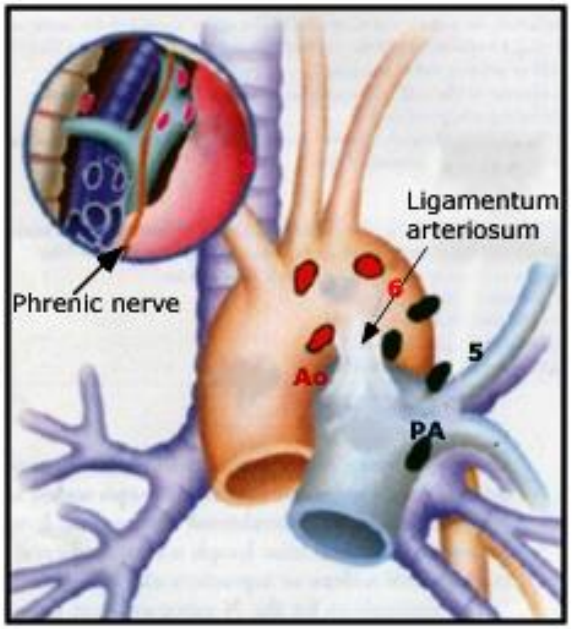
- Cytologic examination of pleural effusions

Staging Algorithm



Lymph Node Map – Nomenclature
(American College of Surgeons)





Superior mediastinal nodes
- 1 Highest mediastinal
- 2 Upper paratracheal
- 3 Prevascular and retrotrcheal
- 4 Lower paratracheal (including azygos nodes)

Aortic nodes
- 5 Subaortic (A-P window)
- 6 Paraaortic (ascending aorta or phrenic)

Inferior mediastinal nodes
- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 nodes
- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

N2 any ipsilateral single digit node
N3 any contralateral or any supraclavicular node

Management of Stage I + II NSCLC

-*Surgery alone is the standard treatment choice !*

-Lobectomy: optimal procedure
-Wedge resection: 3x LR / 30% more mortality (Ginsberg 1995)
but newer series show no worse outcome with limited surgery
(Lee 2003, El Sherif 2006)
-Wedge resection for small tumors (<3cm) and elderly patients
-No randomized trials, but excellent results
(randomized trial 'Surgery – Radiotherapy' underway)

-Adjuvant Cisplatin-based ChT for stage II
for stage IB data is conflicting

-No adjuvant radiotherapy after radical surgery (i.e. R0)

Stage I: Outcome after Surgery

Prognostic significance of anatomic substage in resected stage I NSCLC

Author	Total number of patients	Stage IA (T1NOMO)		Stage IB (T2NOMO)		p Value
		N	Outcome	N	Outcome	
Mountain, CF; 1986	865	429	68 percent 5 yr OS	436	59 percent 5 yr OS	<0.01
Naruke, T; 2001	1545	786	79 percent 5 yr OS	759	58 percent 5 yr OS	<0.01
Gail, MH; 1984	392	NR	77 percent	NR	65 percent	0.004
Pairolero, PC; 1984	328	170	70 percent 5 yr DFS	158	58 percent 5 yr DFS	0.012
Martini, N; 1995	598	291	82 percent 5 yr OS	307	68 percent 5 yr OS	0.009
Inchinose, Y; 1993	151	71	85 percent yr OS	80	67 percent 5 yr OS	0.012
Harpole, DH; 1995	289	173	70 percent 5 yr OS	116	50 percent 5 yr OS	<0.001
Lafitte, JJ; 1996	204	NR	74 percent 5 yr OS	NR	36 percent 5 yr OS	NR
Immerman, S, 1981	77	39	64 percent 5 yr DFS	38	45 percent 5 yr DFS	NR
Van Rens, MT, 2000	1201	404	63 percent 5 yr OS	797	46 percent 5 yr OS	<0.0001

NSCLC: non-small cell lung cancer; OS: overall survival; DFS: disease-free survival; NR: not reported.

Stage I - III: Outcome after Surgery

Survival following resection in NSCLC: data from the National Cancer Database

Stage	Histology	Number of patients	1 Year survival, percent	3 Year survival, percent	5 Year survival, percent
Stage I	Squamous cell carcinoma	6,909	88	70	59
Stage I	Adenocarcinoma	10,468	92	74	63
Stage I	Large cell carcinoma	1,570	85	64	55
Stage II	Squamous cell carcinoma	1,650	72	44	36
Stage II	Adenocarcinoma	1,772	76	45	32
Stage II	Large cell carcinoma	310	68	42	35
Stage IIIA	Squamous cell carcinoma	907	59	34	29
Stage IIIA	Adenocarcinoma	852	59	30	21
Stage IIIA	Large cell carcinoma	330	58	30	24*

* Survival only reported for surgery and radiation therapy in stage IIIA large cell carcinoma.

Data from: Fry, WA, et al. Cancer 1999; 86:1867.

Definitive Radiotherapy for Stage I + II NSCLC

-Alternative for comorbid patients who are not fit for surgery
-For patients who refuse surgery

-60 – 66Gy to primary (+/- 50Gy to part of mediastinum, if feasible)

Review of 26 nonrandomized trials (Powell 2001)

	Cancer-specific Survival	OS (RT)	OS (surgery)
2y	54 – 93%	22 – 72%	67%
3y	22 – 56%	17 – 55%	
5y	13 – 39%	0 – 42%	47%

Non-cancer deaths following RT: 11 – 43%
(reflecting the poor health status of pts. treated in these studies)

-Clinical stage I only in 57% pathologic stage I (Lopez 2005)

Radical RT Stage I – II: Selected Studies

Autor	Jahr / Journal	Stadium	Dosis (Gy)	Resultat
Dosoretz	1992 / IJROBP	T1-3 N0	65	40% (2-JÜ) / 10% (5-JÜ)
Jeremic	1997 / IJROBP	T1-2 N0	69,6 (hyperfrakt.)	30% (5-JÜ)
Jeremic	1999 / Lung Cancer	T1-2 N1	69,6 (hyperfrakt.)	25% (5-JÜ)
Cheung	2002 / IJROBP	T1-2 N0-1	48 (akzell.)	46% (2-JÜ)
Rosenzweig	2005 / Cancer	T1-3 N0-2	<= 81	40% (OS) 52% (2y loc.control rate)

-Results 20-30% worse compared to surgery
-Stage IA: 5y OS 60% (almost comparable to surgery)

Stereotactic Body Radiation Therapy (SBRT)

-Ultra precise treatment planning (fixation, IGRT)
-High doses (e.g. 4x12Gy), but optimal dose /fx not known
-Dose response relationship: BED >100Gy vs. <100Gy

Results (Lagerwaard 2008):

1y- / 2y – OS:	81 / 64%	
1y- / 2y – DFS:	83 / 68%	(88 / 81% for stage IA)
Median OS:	34 months	
Local failure rate:	7%	
Regional failure:	9%	
Distant failure:	11%	
Severe late toxicities:	<3%	

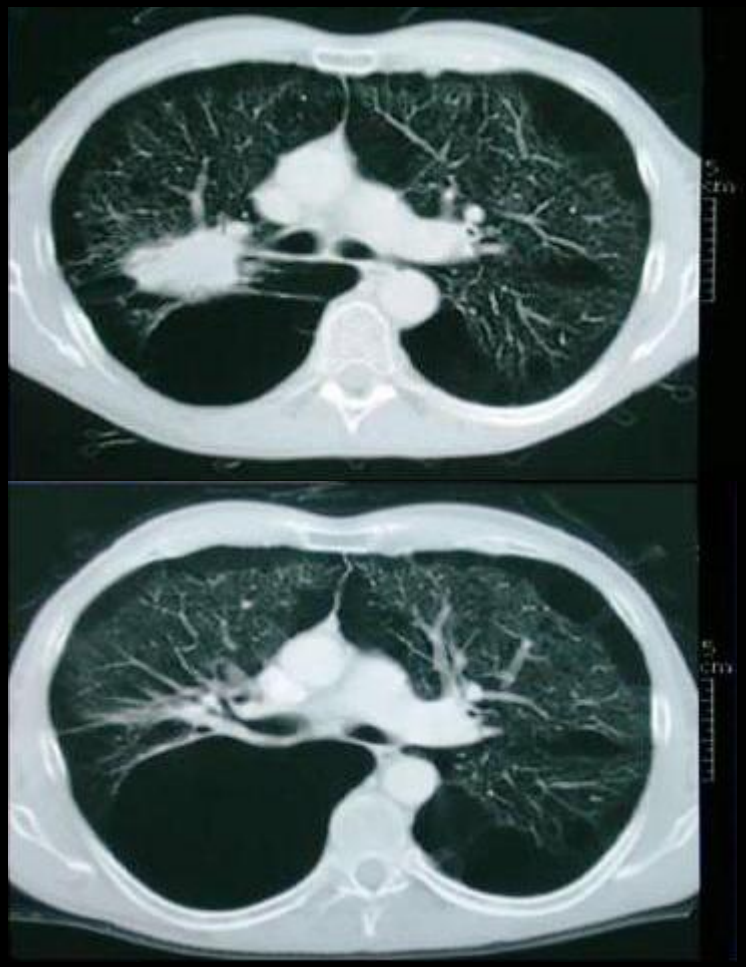
-Results superior to conventional 3D-CRT
-For stage IA results near surgery

SBRT – Example

-T2 N0

-CR after radical radiation

-COPD with emphysema



Other Techniques improving Outcome

Hyperfractionation (Jeremic 1997, 1999)

	Stage I	Stage II
Median survival	33mts.	27mts.
5y-OS	30%	25%

Protons (Bush 2004)

3y local control	74%
Disease-specific survival	72%
Pneumonitis, esophageal or late cardiac toxicity	0%

Adjuvant Radiotherapy for Stage I + II NSCLC

-No postoperative RT after R0-Resection
-54Gy after R1-Resection to the bronchial stump
-60-66Gy after R2-Resection

Randomized trials:

-Local recurrence: reduced
-Survival: unchanged, worse or improved !
(likely relate to different radiation techniques)

PORT-Metaanalysis (1998):

-decreased OS after postoperative RT (55 vs. 48%)

Adjuvant Radiotherapy for Stage I + II NSCLC

PORT-Study has been criticized:

-Bias: 1/3 pts. from French Trial with high fractions + doses (60Gy/2.5Gy)

-Partly used old techniques (e.g. Cobalt)

-*More recent randomized trial: (Trodella 2002)*

Modern 3D-CRT

Safe fractions (1.8Gy) and small doses (50.4Gy)

Target: bronchial stump and homolateral hilum

LR 2% vs. 23%

OS 67% vs. 58%

Long-term toxicity acceptable

Summary: Management of Stage I+II NSCLC

-Pathologic stage I+II represents a minority of cases (staging !)
-In contrast to advanced stages curable with aggressive therapy and have good prognosis

-Surgery is the standard treatment of choice (Lobectomy)
-Adjuvant ChT (Cisplatin) for stage II and selected IB

-Definitive RT as an alternative for medical inoperable patients and for those who refuse surgery
-No adjuvant RT after R0-Resection
-Adjuvant RT after R1-/ R2-Resection

-Further trials are needed to establish the role of RT in a post-operative setting and its optimal dose/fractionation/technique in a radical setting

Management of Stage III NSCLC

-Locoregionally advanced stages

IIIA surgery feasible
IIIB surgery not feasible

-Usually combined therapy approach
-Optimal regime uncertain
-Trend toward trimodality therapy
-Initial nonoperative treatment generally recommended
-No single regime for all patients (clinical heterogeneity)

-Management individually to be discussed (tumor board)

Radiotherapy for Stage III NSCLC

Definitive radiotherapy alone

-for patients who are not fit for combined treatment
-isolated thoracic recurrence after surgery
-palliative for patients with poor performance status or stage IV

Early randomized trial: RT vs. Placebo (Roswit 1968)
modest but significant survival benefit (18 vs. 14% at 1 year)

RT alone:	MS	10mts.
	5y-OS	5%

Factors associated with improved prognosis:
(Basaki 2006, RTOG 93-11 2008)
-small primary tumor
-small total tumor volume

Radiotherapy for Stage III NSCLC

Definitive radiotherapy alone

Should it be given immediately or deferred ?

Randomized trial: immediate RT vs. RT reserved for symptoms (Falk 2002)

-median survival	ns
-rate of symptom control	similar

Palliative symptomatic care is a valuable option for patients with locoregionally advanced NSCLC who are not candidates for combined modality treatment.

Radiotherapy for Stage III NSCLC

Dose and local control

RTOG phase III trial: (Perez 1986)

	40Gy	**50Gy**	**60Gy**	(2Gy/fx)
Local Control	52%	62%	73%	
Survival		similar		

-60Gy / 30 fractions: standard today

-phase II data show better local control with higher doses
-limiting factor: normal tissue tolerance

Improved therapeutic index
-altered fractionation schedules
-Amifostine
-IMRT, IGRT, Tomotherapy, Protons..

Radiotherapy for Stage III NSCLC

Altered Fractionation Schedules

CHART (Saunders 1997,1999):

2y-survival	29%	vs.	20%
Severe dysphagia	19%	vs.	3%

ECOG 2597 (Belani 2005):

No statistical significance reached

Central Cancer Treatment Group (Schild 2002):

No statistical significance in terms of TTP, OS, Toxicities

Management of Stage IIIA NSCLC

-High risk for both local and distal failure after resection
-Role of postoperative RT controversial

-Survival benefit of RT not confirmed in randomized trials

Lung Cancer Study Group, 1986: LR 3% vs. 41%
OS n.s.

PORT Study, 1998: decreased OS 48% vs. 55% (stages I-III)
(subgroup analysis: no clear evidence for stage III)

Studies on toxicities (Lally 2006, 2007):

Limited LN-involvement: decreased OS after RT (31 vs. 41%)
N2-disease: improved OS after postop. RT (27 vs. 20%)
Death from cardiac toxicities:
increased for pts. treated in early studies (1983-1988)
not increased for those treated after 1989

Management of Stage IIIA NSCLC

-Postoperative ChT: modest but significant better OS (4-5%)

-Promising results from preoperative ChT

Induction chemo stage III NSCLC

Phase II trials of induction chemotherapy followed by surgery in stage III NSCLC

Reference, Number of Patients	Induction Regimen	Radiation	Response to Induction	Surgical Resection Therapy (percent)	Median Survival (months)	Long-term Survival, percent (years)
Skarin, 1989	CAP	Sequential	53	88	32	31 (5)
Elias, 1994	CAP	Post-operative	39	54	18	22 (5)
Elias, 1997	PFL	Post-operative	65	62	18	18 (4)
Strauss, 1992	PVF	Concurrent and post-operative	51	61	16	22 (9)
Sugarbaker, 1995	PV	Post-operative	88	62	15	23 (3)
Choi, 1997	PFV	Twice daily, concurrent/post-operative	73	93	25	37 (5)
Martini, 1993	MPVd	Not routinely administered	77	65	19	17 (5)
Burkes, 2005	MPVd	Not routinely administered	68	54	19	22 (10)
Weitberg, 2001	PE	Concurrent	89	51		42 (12)
Reddy, 1992	PF±E	Concurrent	Not reported	72*	18	32 (3)
Weiden, 1991	PF	Concurrent	56	52	13	20 (3)
Albain, 1995	PE	Concurrent	59	76/63•	13/17•	27/24 (3)•
DeCamp, 2003	P/Taxol	Concurrent	62	79	27	32 (5)

CAP: cyclophosphamide, doxorubicin, cisplatin; PFL: cisplatin, 5-fluorouracil (5-FU), leucovorin; PVF: cisplatin, vinblastine, 5-FU; PV: cisplatin,vinblastine; PFV: cisplatin, vinblastine, 5-FU; MPVd: mitomycin, cisplatin, vindesine; PE: cisplatin, etoposide; PF±E: cisplatin, 5-FU ± etoposide; PF: cisplatin, 5-FU. P/Taxol: cisplatin plus pacitaxel.

* 72 percent resectability achieved among 86 patients deemed "eligible for surgery" at outset. Resectability was 47 percent among all 129 patients.

• Resectability rate 76 versus 63 percent for stage IIIA/IIIB disease; median survival 13 versus 17 months for stage IIIA/IIIB disease; long-term survival (3-year) 27 versus 24 percent for stage IIIA/IIIB disease.

Management of Stage IIIA NSCLC

-Better survival after adjuvant ChT
-Promising results of phase II data with induction ChT

→ New Protocols:
-Role of preoperative RT-ChT (SAKK)
-Role of postoperative RT (EORTC)

Summary: Management of Stage IIIA NSCLC

-Pre- or postoperative ChT

-No established role of pre- or postoperative RT
→ RT in Clinical Trials
(e.g. SAKK 16/00: RT/ChT – OP vs. ChT – OP)

-No postoperative RT recommended routinely
Postoperative RT recommended: N2 (multilevel)
R1/R2

-Preoperative RT for Pancoast Tumor (45-50Gy)

-Radical RT (+/- ChT) for medically inoperable patients (60Gy)
(concomitant better than sequential, see stage IIIB)

Management of Stage IIIB NSCLC

-Long Term OS < 5% ! (Hagen 1997)

-Most patients die from metastasis

-Median survival prolonged 8-10 months with RT-ChT for younger patients with good performance status (Sause 1997)

-Other patients: good palliation by RT

-Combined ChT-RT better survival than RT alone (Pignon 1994)

-Concomitant ChT-RT better than sequential, but more toxicities (Furuse 1999, RTOG 9410)

-Role of surgery uncertain (SAKK 16/01: preoperative ChT-RT)

Management of Stage IIIB NSCLC

Definitive Chemoradiotherapy

Objective: treat locoregional and micrometastasic disease

-initially sequential therapy to avoid overlapping toxicities

-initial trials established benefit of combined approach

-subsequent studies compared sequential vs. concurrent chemo-radiotherapy

Management of Stage IIIB NSCLC

Sequential Chemoradiotherapy

Table 8–6. SELECTED RANDOMIZED TRIALS OF SEQUENTIAL PLATINUM-BASED CHEMORADIATION VERSUS RADIOTHERAPY ALONE

Author	No. of Patients	Chemotherapy	Radiotherapy	Median Survival (months)	2-year OS (%)	5-year OS (%)	P Value	Comments
Dillman et al	78 77	Vb/ P x 2 —	60 Gy 60 Gy	13.8 9.7	26 13	17 6	p = 0.012	Vomiting, infections and weight loss more common with combined therapy; no deaths due to treatment in either arm
Sause et al	151 149 152	Vb/ P x 2 — —	60 Gy 60 Gy 69.6 Gy (1.2 Gy BID)	13.8 11.4 12.3	31 20 24	8 5 6	p = 0.04 (CT / RT versus RT alone)	4 deaths on CT/RT arm were felt to be due to treatment Severe esophagitis more likely with BID RT
Le Chevalier et al	176 177	VCyPC x 3 pre- and post-RT —	65 Gy 65 Gy	12 10	21 14	6 3	p = 0.02	Distant metastases rate decreased in combined arm: 67 vs. 45% (p < 0.001) Local control at 1 year: 17% and 15%

Vb = vinblastine; P = cisplatin; V = vindesine; Cy = cyclophosphamide; C = CCNU; CT = chemotherapy; RT = radiotherapy; OS = overall survival.

Management of Stage IIIB NSCLC

Concurrent Chemoradiotherapy

Objective: early treatment of micrometastases
radio-sensitization (better local control)

-randomized trials established this approach as the preferred treatment

-toxicity is increased but manageable

Management of Stage IIIB NSCLC

Concurrent Chemoradiotherapy

Table 8–7. SELECTED TRIALS OF CONCURRENT CISPLATIN-BASED CHEMORADIATION VERSUS RADIOTHERAPY ALONE

Author	No. of Patients	Chemotherapy	Radiotherapy	Median Survival (months)	2-year OS (%)	5-year OS (%)	P Value	Comments
Schaake-Koning et al	108	—	55 Gy, split	NR	13	2	p = 0.009 (RT vs RT with daily P)	Increased nausea and vomiting in those assigned chemotherapy
	98	P weekly on RT	55 Gy, split	NR	19	13		
	102	P daily on RT	55 Gy, split	NR	26	16 (3-yr)		
Blanke et al	111	—	60–65 Gy	10.6	13	2	p = NS	Increased nausea and vomiting, leukopenia, and esophagitis in the combined therapy arm
	104	P x 3 (q 3 weeks)	60–65 Gy	9.9	18	5		
Trovo et al	83	—	45 Gy	10.3	17	NR	p = NS	Increased nausea and vomiting, and severity of esophagitis in the combined therapy arm
	84	P daily on RT	45 Gy	10	20	NR		
Soresi et al	50	—	50 Gy	11	6	2	p = 0.02 (3-year)	Decreased local relapse in the combined arm: 27 vs. 46%; p < 0.04
	45	P weekly on RT	50 Gy	16	24 (3-year)	11	p = 0.07 (5-year)	
Clamon et al	120	Induction P/Vb	60 Gy	13.5	26	10	p = NS	Increased hematologic toxicity in concurrent therapy arm; other toxicities similar
	130	Induction P/Vb; C weekly on RT	60 Gy	13.4	29	13 (4-yr)		

P = cisplatin; Vb = vinblastine; C = carboplatin; OS = overall survival; RT = radiotherapy; NS = not significant; NR = not reported.

Management of Stage IIIB NSCLC

Superiority of Concurrent Chemoradiotherapy over Sequential
Two large multicenter trials

1. Furuse, JCO 1999

Randomized -conc. ChT (CMV) + 56Gy (split course RT)
-same regime sequential

	Concurrent	Sequential
Response Rate	84%	86%
Median Survival	17mts.	13mts.
2y-survival	35%	17%
5y-survival	16%	9%

Management of Stage IIIB NSCLC

Superiority of Concurrent Chemoradiotherapy over Sequential
Two large multicenter trials

2. RTOG 9410

Randomized -conc. ChT (CV) + 60Gy
-same regime sequential

	Concurrent	Sequential
Median Survival	17mts.	14.6mts.
4y-survival	21%	127%
Toxicity	Increased, but nut increased treatment related death	

Management of Stage IIIB NSCLC

Concurrent low dose Chemoradiotherapy

Objective: improved locoregional control
minimize toxicity

-only one randomized trial demonstrate benefit over RT alone (Schaake-Koning, 1992)

-several other studies failed to demonstrate survival benefit

-no trials comparing low dose vs. standard dose ChT

-option for elderly patients

Management of Stage IIIB NSCLC

Recommendations:

-Concomitant ChT-RT
as first choice

-Concomitant daily low-dose Cisplatin + RT 60Gy
elderly patients (Schake-Koning, 1992)

-Sequential ChT-RT: Cisplatin + 60Gy (Dillman, 1990)
for large tumors

-RT only (30 x 2Gy – 13-15 x 3Gy)
poor performance status, palliation

-Surgery only within study protocol or selected patients
(e.g. T4 N0-1 after induction therapy)

Summary: Management of Stage IIIB NSCLC

-Heterogeneous group, therapy to be discussed at tumor board
-Radical multimodality treatment vs. good palliation
-Combined Radio-Chemotherapy is standard treatment
-Concomitant better than sequential (survival benefit) but more toxicities
-Sequential Chemo- Radiotherapy or RT alone for unfit patients
-Induction Chemotherapy for extensive tumor-volume which can not be encompassed in reasonable RT portals

-Role of Surgery uncertain, only selected patients

-Optimal regime not clear, therapy within clinical trials as possible:
Induction-therapy – OP
Accelerated RT schemes
New drugs + concomitant RT
…..

Management of RT Toxicity - Pneumonitis

Pneumonitis: 4-6 wks. after RT (Fibrosis after 12-24 mts.)

Symptoms: fever, cough, illness

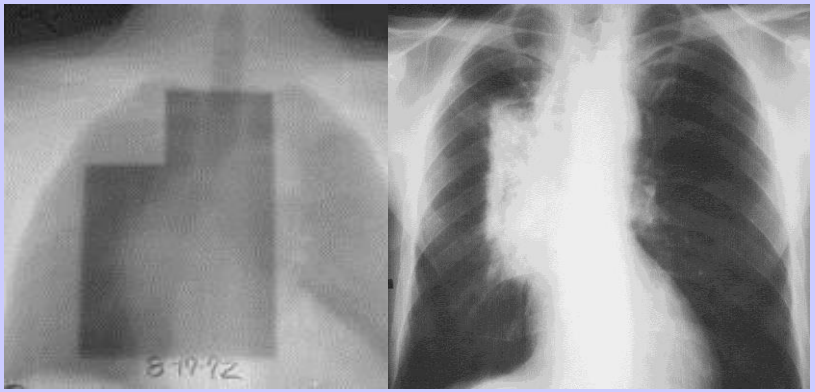
Risk factors:

-Lung function (FEV_1)
-Treated volume: V_{20}=25% (8% pneumonitis)
V_{20}=37% (39% pneumonitis)
V_{10}, V_5, …. $V_{30\text{-}40}$ (fibrosis)
-D_{mean}: <10Gy - very small risk
20Gy - 15% risk
30Gy - 50% risk

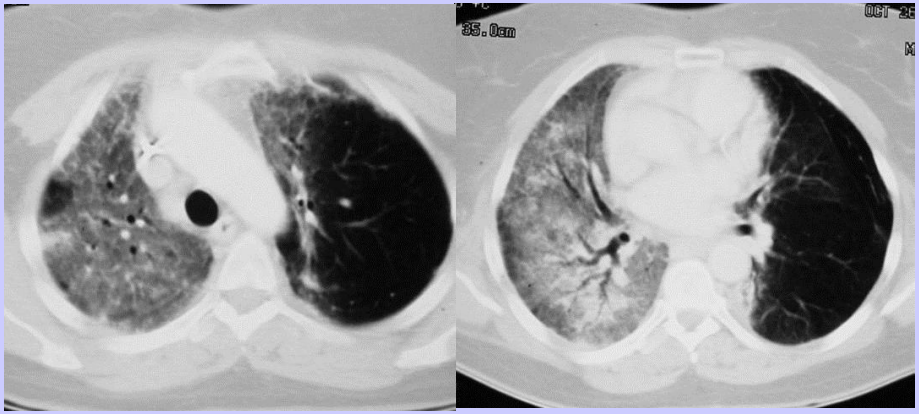
Treatment: Antibiotics (e.g. Roxithromycin) for 10d
Steroids (e.g. Prednisone) beginning with high dose
for 6wks. (reducing doses)

Management of RT Toxicity - Pneumonitis

Radiographic finding: diffuse interstitial infiltrate

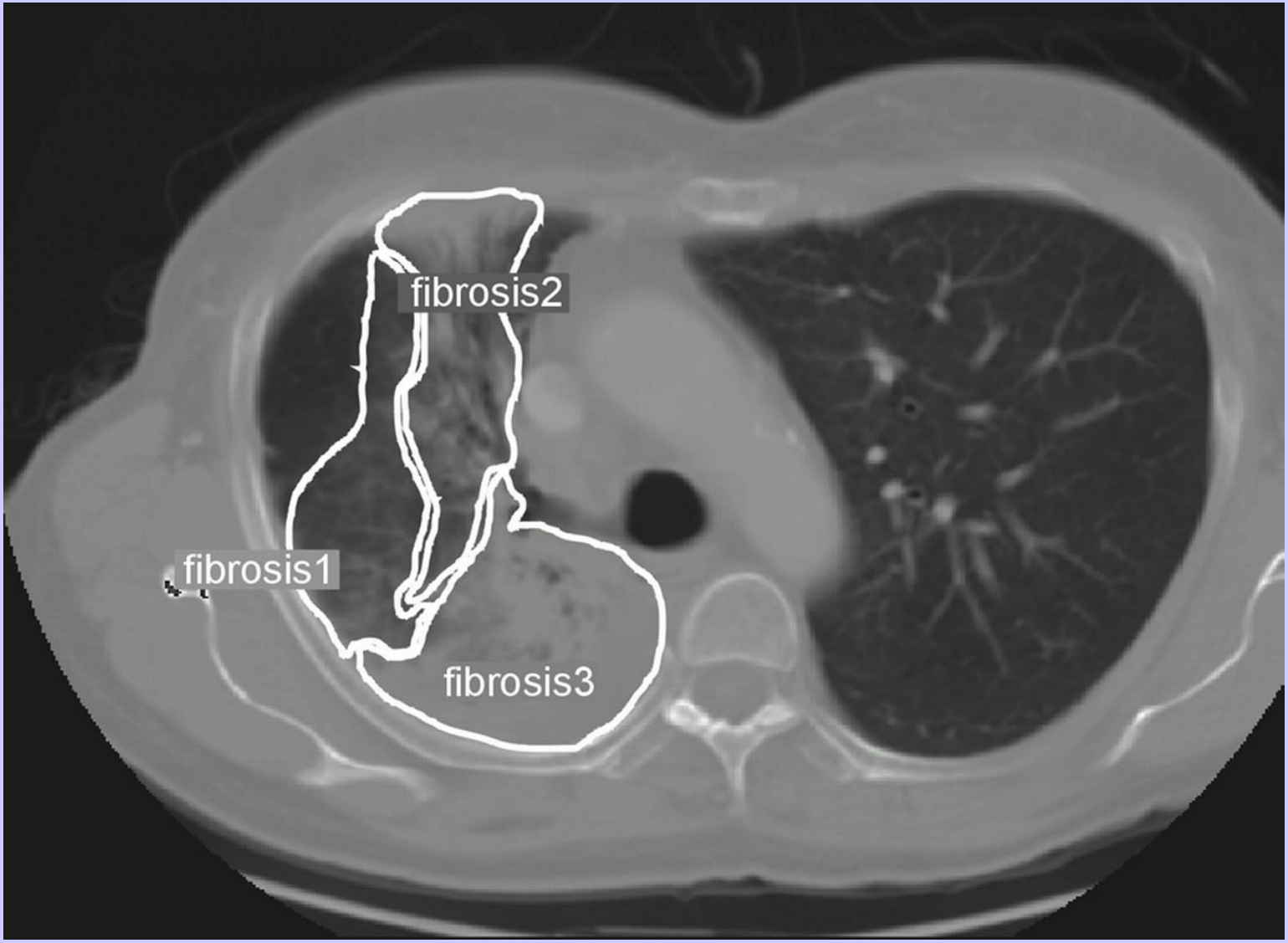


Radiation portal (left) with subsequent radiation pneumonitis



Sequential transverse images through lung showing radiation pneumonitis in right lung

Management of RT Toxicity - Fibrosis



Rosen, I. I. et al. Radiology 2001;221:614-622

RT-Planning – Definition of Target Volumes

ICRU 50 + 62

Gross Tumour Volume

Clinical Target Volume

Planning Target Volume

= critical step

= weakest link in radiotherapy chain

RT-Planning – Defining the GTV

CT: standard imaging modality

Complementary information by MRI and PET scanning

Limiting factors of CT imaging for lung cancer:

-planning-CT without intravenous contrast so as not to disturb the electron density information
interpretation always in conjunction with diagnostic CT

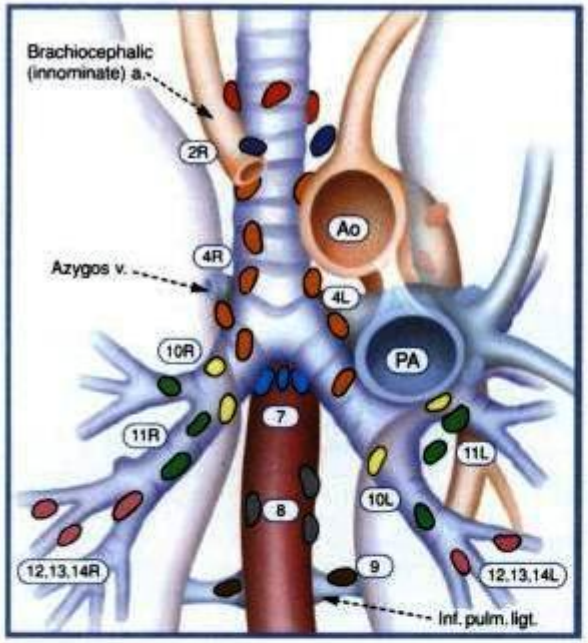
-not routinely possible to distinguish T3 – T4
(MRI some advantages)

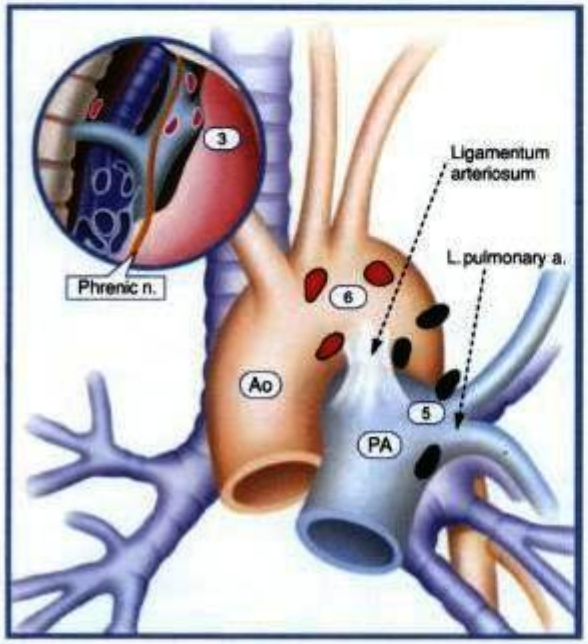
-MRI used for imaging apical primary tumours (Pancoast)

-Sensitivity / specificity only 60 / 77% for LN
knowledge of normal anatomy (LN levels, hilar anatomy) !
knowledge of patterns of lymphatic drainage

RT-Planning – Defining the GTV

Knowledge of anatomy
LN levels
(American College of Surgeons)





Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

CHEST

Official publication of the American College of Chest Physicians

Regional Lymph Node Classification for Lung Cancer Staging

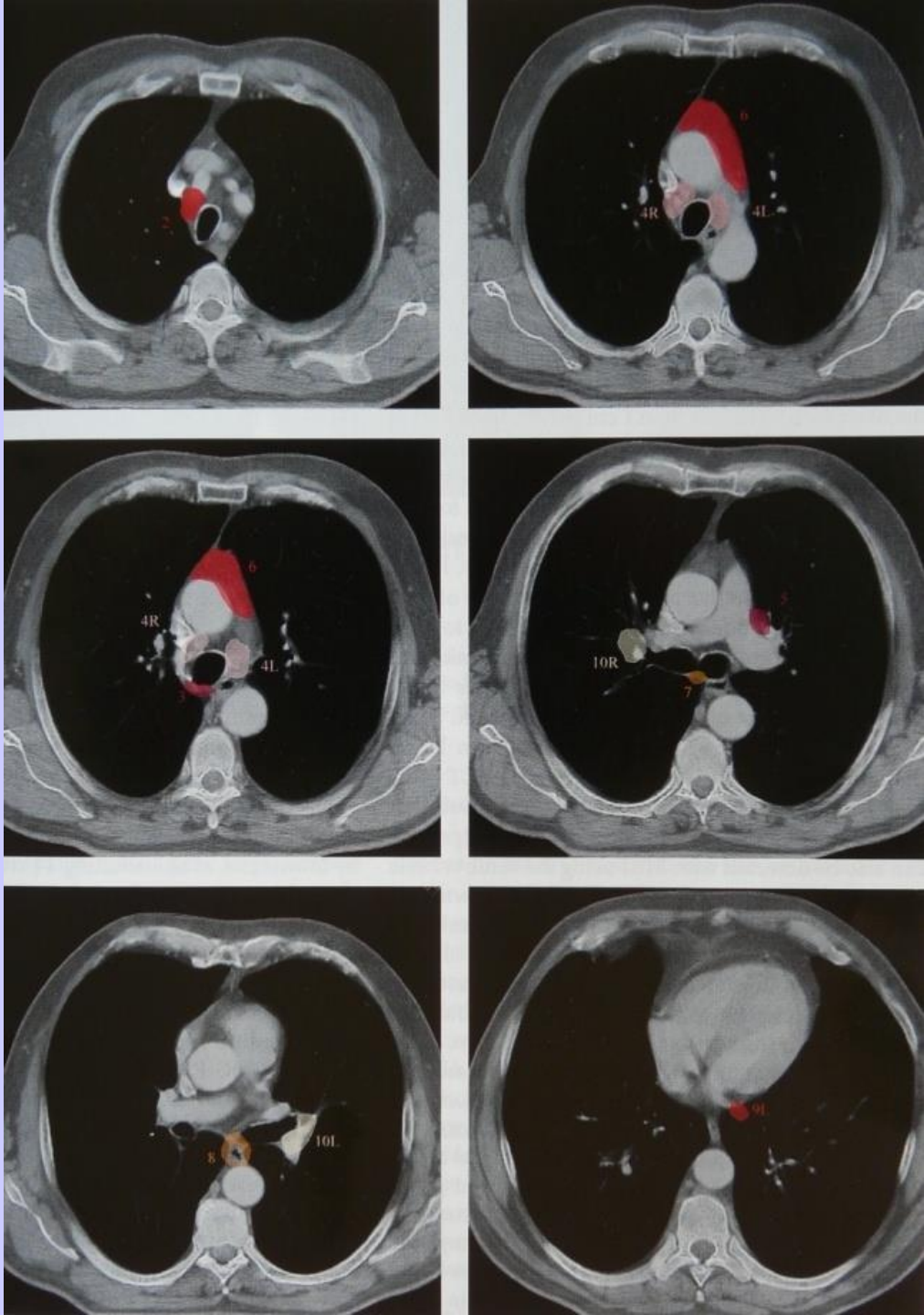
Clifton F. Mountain and Carolyn M. Dresler

Chest 1997;111;1718-1723
DOI 10.1378/chest.111.6.1718

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
http://chestjournal.org/cgi/content/abstract/111/6/1718

RT-Planning
Defining the GTV

Knowledge of anatomy
LN levels -
Cross Sectional Anatomy



Murray JG, Eur J Radiol, 1993,17:61-68.

CT Demonstration of the 1996 AJCC-UICC Regional Lymph Node Classification for Lung Cancer Staging[1]

Michel Cymbalista, MD • Albert Waysberg, MD • Claude Zacharias, MD • Yves Ajavon, MD • Marc Riquet, MD, PhD Genevieve Rebibo, MD • Philippe Grenier, MD

The new international lymph node classification adopted by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) is described and illustrated with computed tomography (CT). Anatomic landmarks for 14 hilar, intrapulmonary, and mediastinal lymph node stations are designated. Main differences between the new international classification and the American Thoracic Society (ATS) one are emphasized. In particular, mediastinal pleural reflection is now used to differentiate N2 from N1 nodes. The ATS 10L (left peribronchial nodes) and 10R (right tracheobronchial nodes) stations are now replaced by the AJCC-UICC station 10 (hilar nodes) and the AJCC-UICC station 4 (lower paratracheal, including azygos, nodes), respectively. This very important difference from the ATS classification helps classify the 4 lower paratracheal nodes as N2 nodes, even though the pleural reflection is not seen with CT. The 5 AJCC-UICC nodes are renamed subaortic nodes instead of aortopulmonary ATS nodes. Paraaortic nodes, which previously were classified as 5 ATS nodes, are now included with the 6 AJCC-UICC nodes (now renamed paraaortic nodes instead of anterior mediastinal ATS nodes). This change helps accurate labeling because the border between 5 and 6 ATS nodes was not always clear on CT scans. Radiologists should be familiar with this new classification to be able to more accurately compare the lung cancer staging done in different institutions around the world.

Abbreviations: AJCC = American Joint Committee on Cancer, ATS = American Thoracic Society, UICC = Union Internationale Contre le Cancer

Index term: Lung neoplasms, staging, 60.32

RadioGraphics 1999; 19:899

[1]From the Departments of Radiology (M.C., A.W., Y.A.) and Respiratory Diseases (C.Z.), Montfermeil Hospital, 10 rue du General Leclerc, 93370 Montfermeil, France; the Department of Thoracic Surgery, Laennec Hospital, Paris, France (M.R.); the Department of Radiology, Foch Hospital, Suresnes, France (G.R.); and the Department of Radiology, Pitié-Salpétrière Hospital, Paris, France (P.G.). Recipient of a Certificate of Merit award for a scientific exhibit at the 1998 RSNA scientific assembly. Received February 17, 1999; revisions requested March 29 and received April 20; accepted April 20. **Address reprint requests to** M.C.

RadioGraphics

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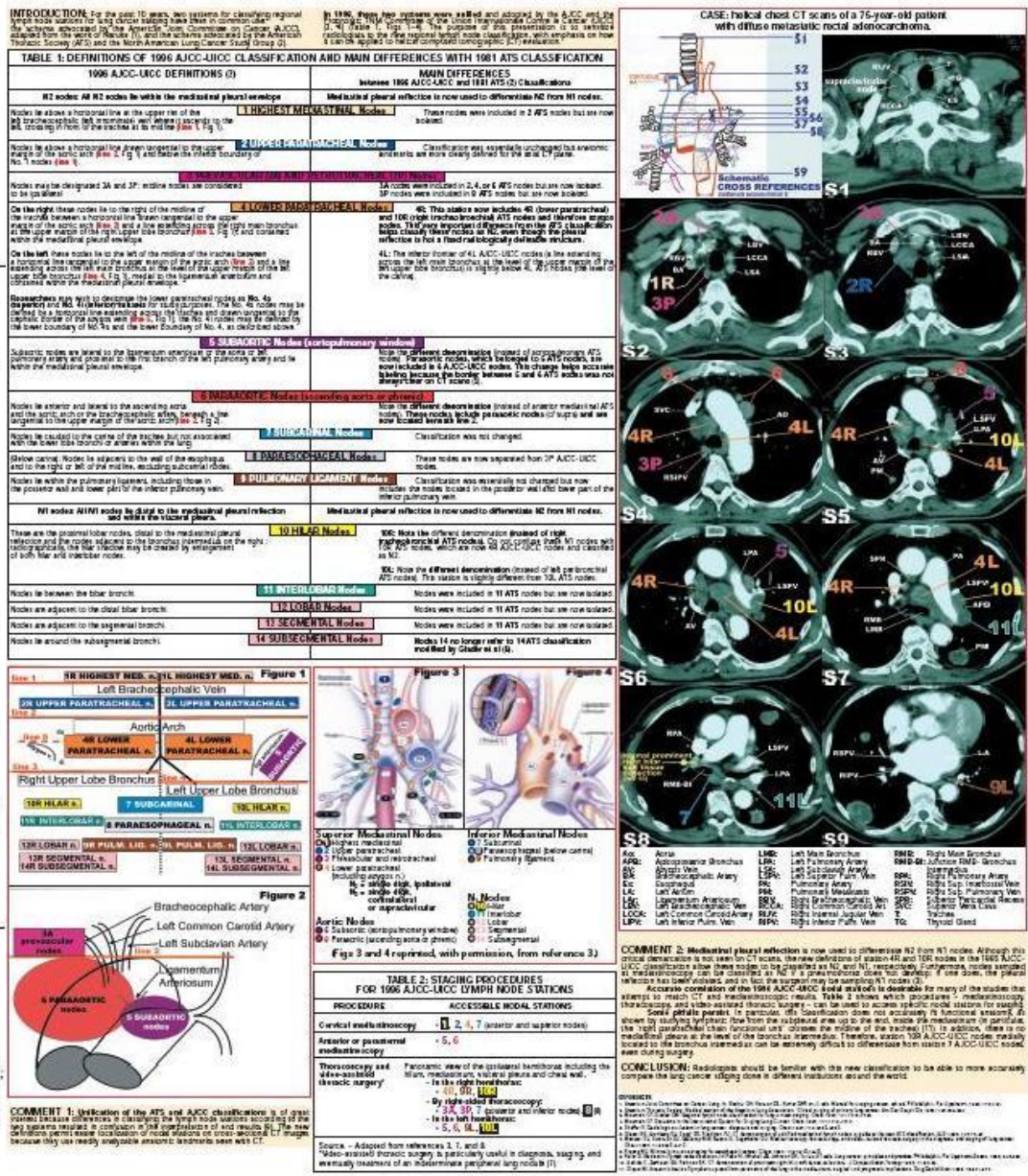
RadioGraphics 1999; Volume 19

*RSNA, 1999



RT-Planning - Defining the GTV

Cross Sectional Anatomy - Suggested Paper

Cross-sectional Nodal Atlas: A Tool for the Definition of Clinical Target Volumes in Three-dimensional Radiation Therapy Planning[1]

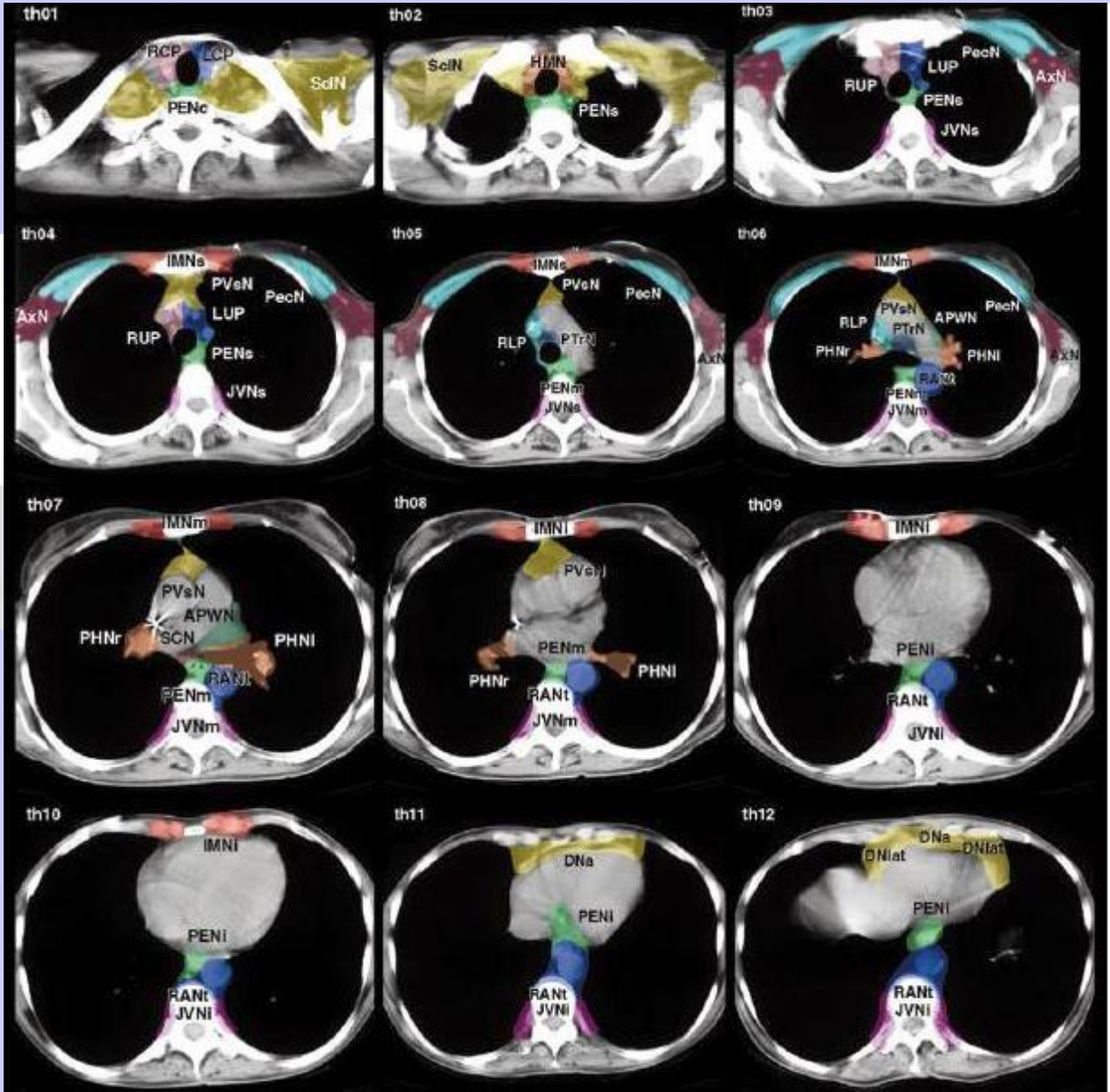
Virtual three-dimensional clinical target volume definition requires the identification of areas suspected of containing microscopic disease (frequently related to nodal stations) on a set of computed tomographic (CT) images, rather than the traditional approach based on anatomic landmarks. This atlas displays the clinically relevant nodal stations and their correlation with normal lymphatic pathways on a set of CT images.

Rafael Martinez-Monge, MD
Patrick S. Fernandes, MD
Nilendu Gupta, PhD
Reinhard Gahbauer, MD

Index terms:
Computed tomography (CT), three-dimensional, 99.12917, 99.92
Lymphatic system, 99.12917, 99.92
Special reports
Treatment planning, 99.92

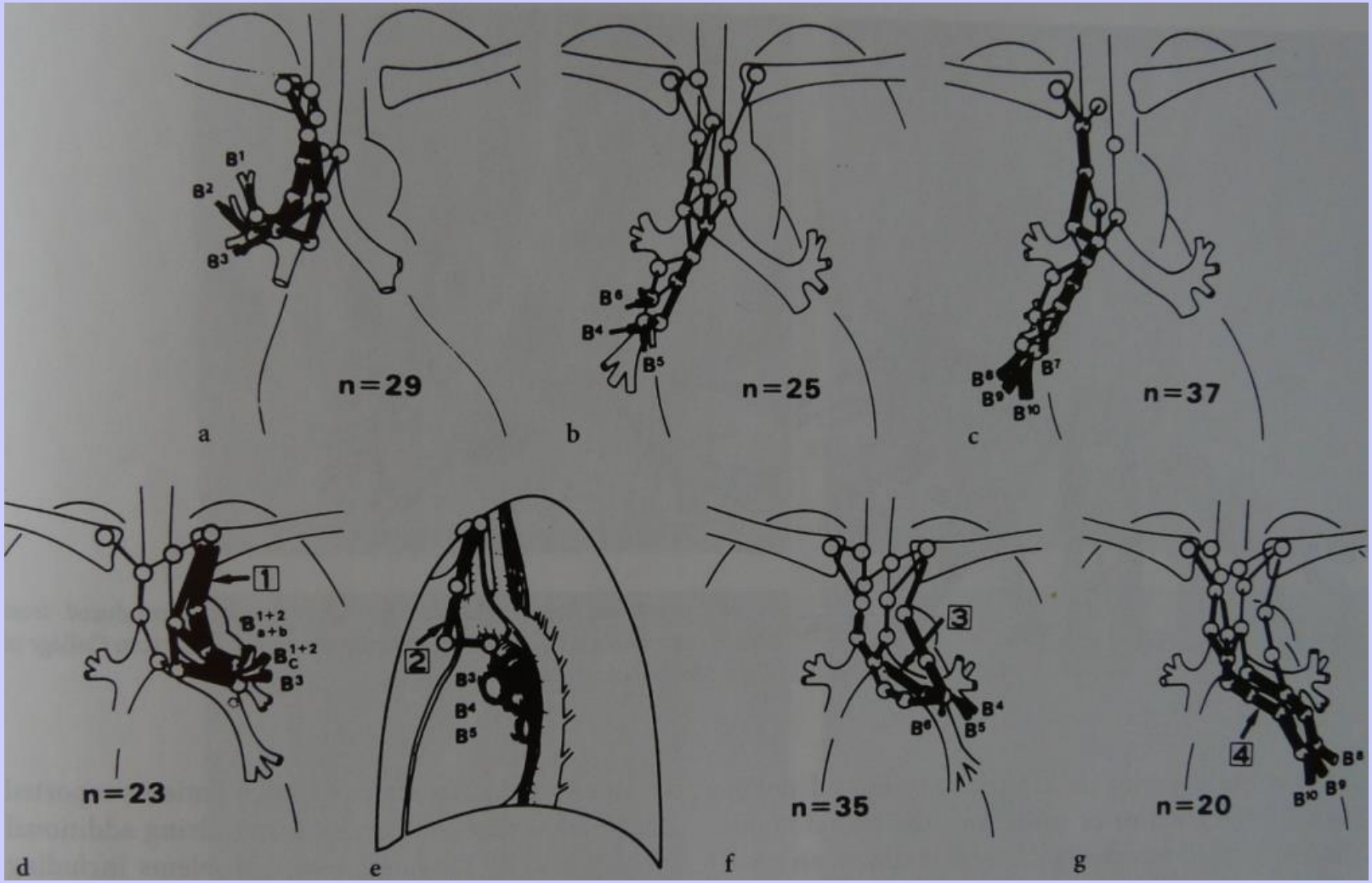
Radiology 1999; 211:815–828

Abbreviations:
CTV = clinical target volume
GTV = gross tumor volume
3D = three-dimensional



RT-Planning – Defining the GTV

Knowledge of lymphatic drainage according to localisation of PT (Hata 1990)



RT-Planning – Defining the GTV

Integrating PET

Value of PET for PT:
Atelectasis – reduction of irradiated volume

Value of PET for LN staging:
Sensitivity 79%
Specificity 91%
Negative predictive value 95%
Positive predictive value 80%
(hot spots still require verification)

Value of PET for Metastases:
metastases detected in10-15% of surgical candidates

RT-Planning – Defining the GTV

Impact of PET on RT planning

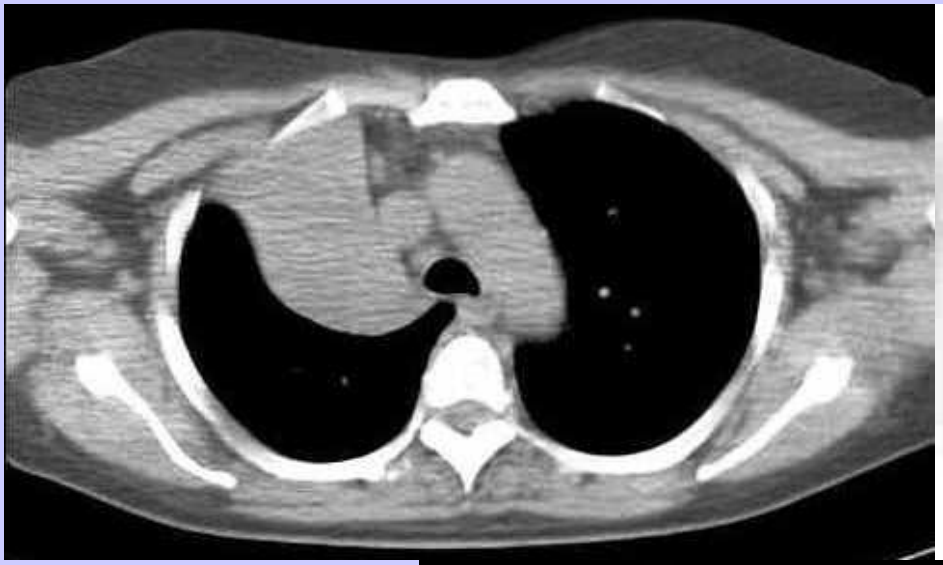
PTV increased in 64% (detected nodes)
decreased in 36% (exclusion of atelectasis)
(Erdi 2002)

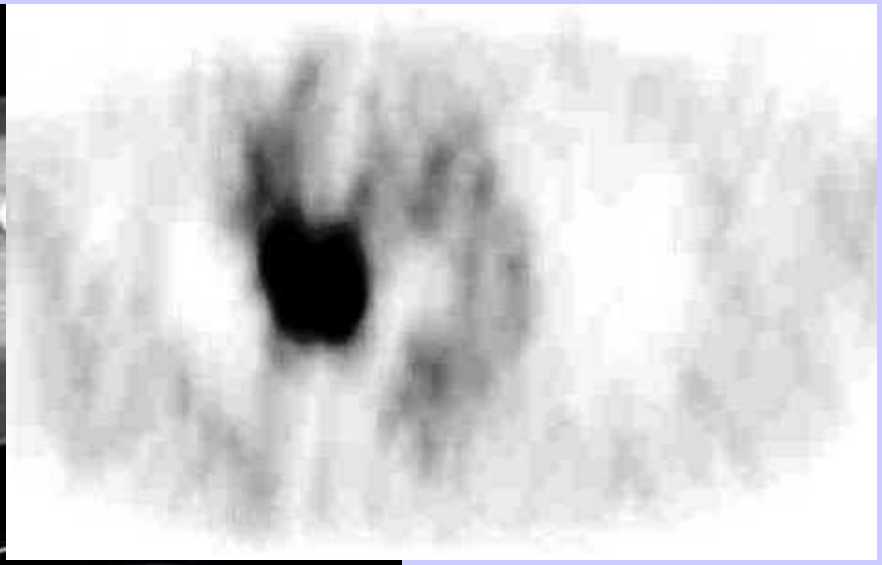
Average reduction of PTV by 29%
Average reduction of V_{20} by 27%
(Vanuytsel 2000)

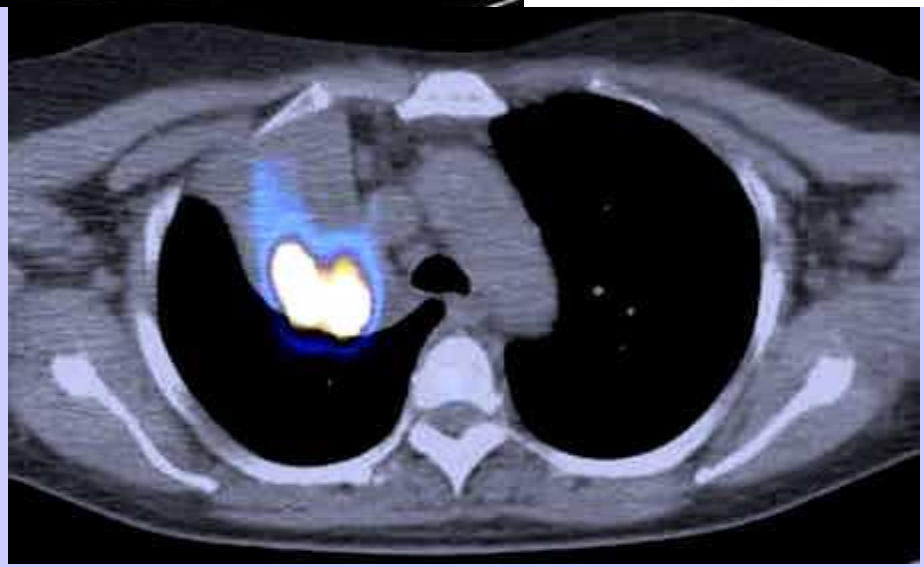
Interobserver variability reduced:
mean ratio of GTV without PET: 2.31
mean ratio of GTV with PET: 1.56
(Caldwell 2001)

RT-Planning – Defining the GTV

Impact of PET: Atelectasis

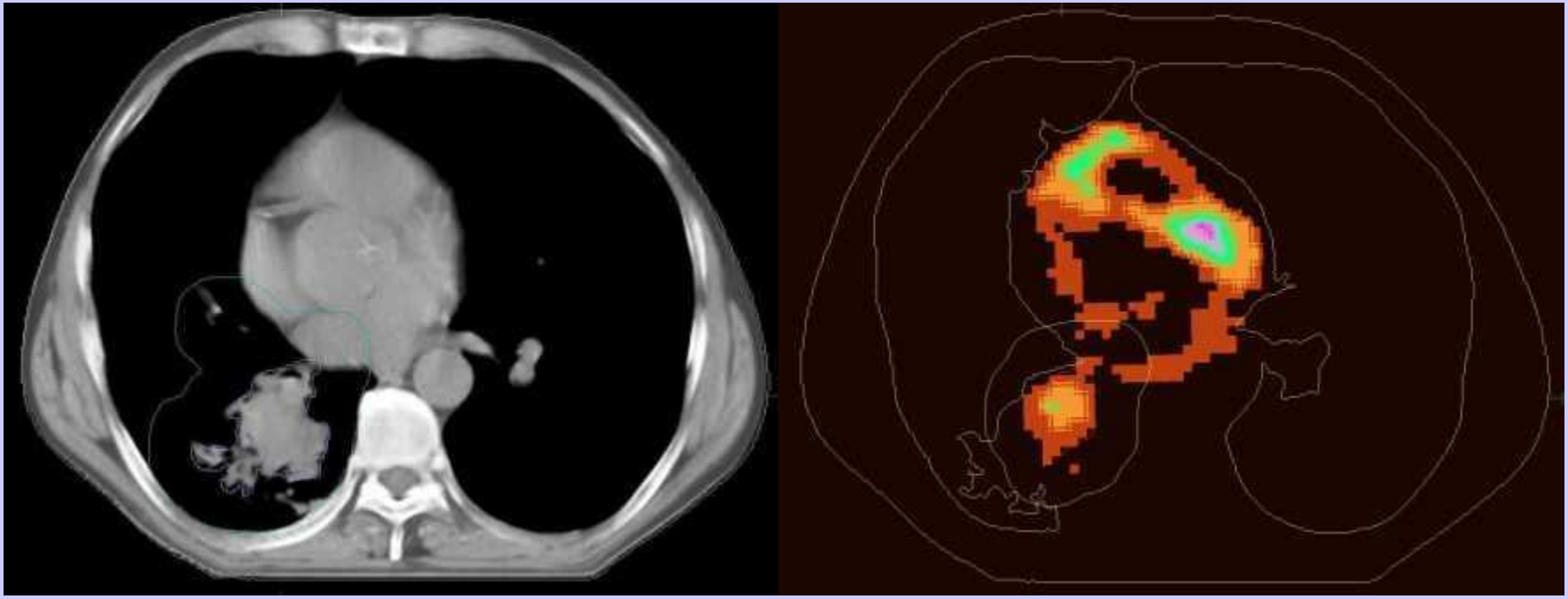






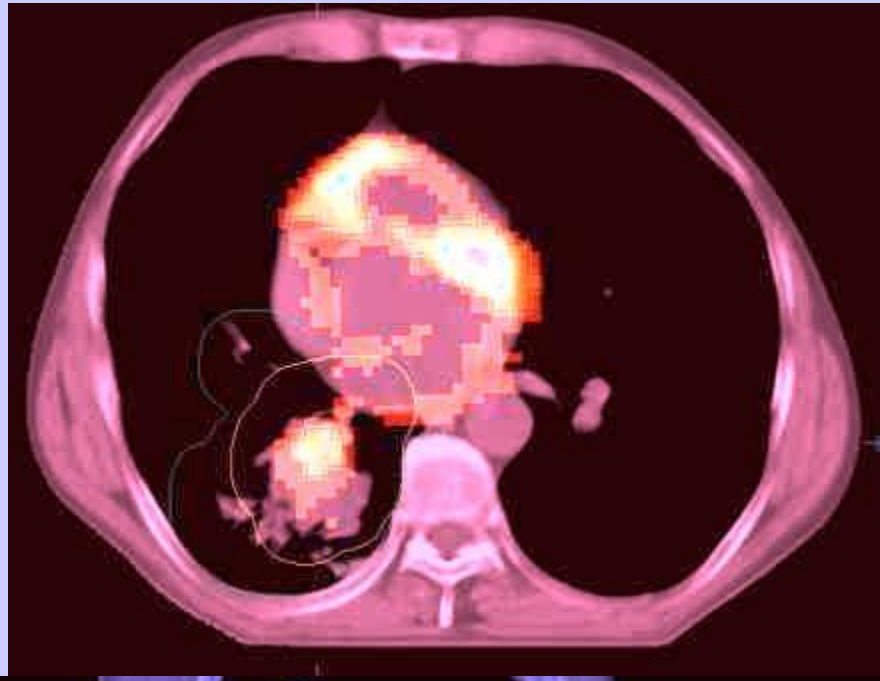
RT-Planning – Defining the GTV

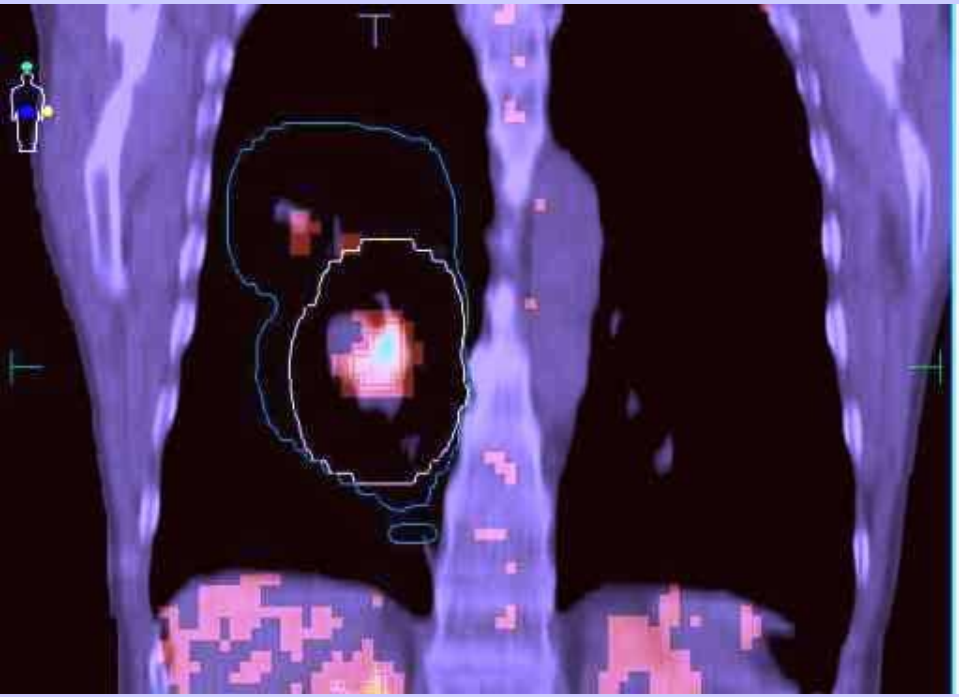
Impact of PET: PTV

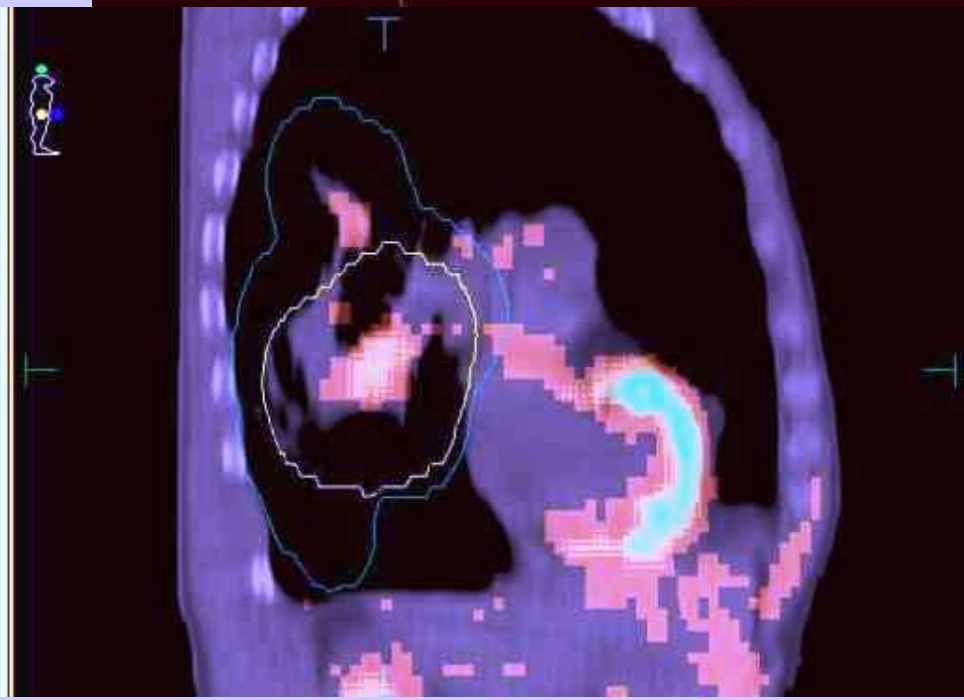


RT-Planning – Defining the GTV

Impact of PET: PTV

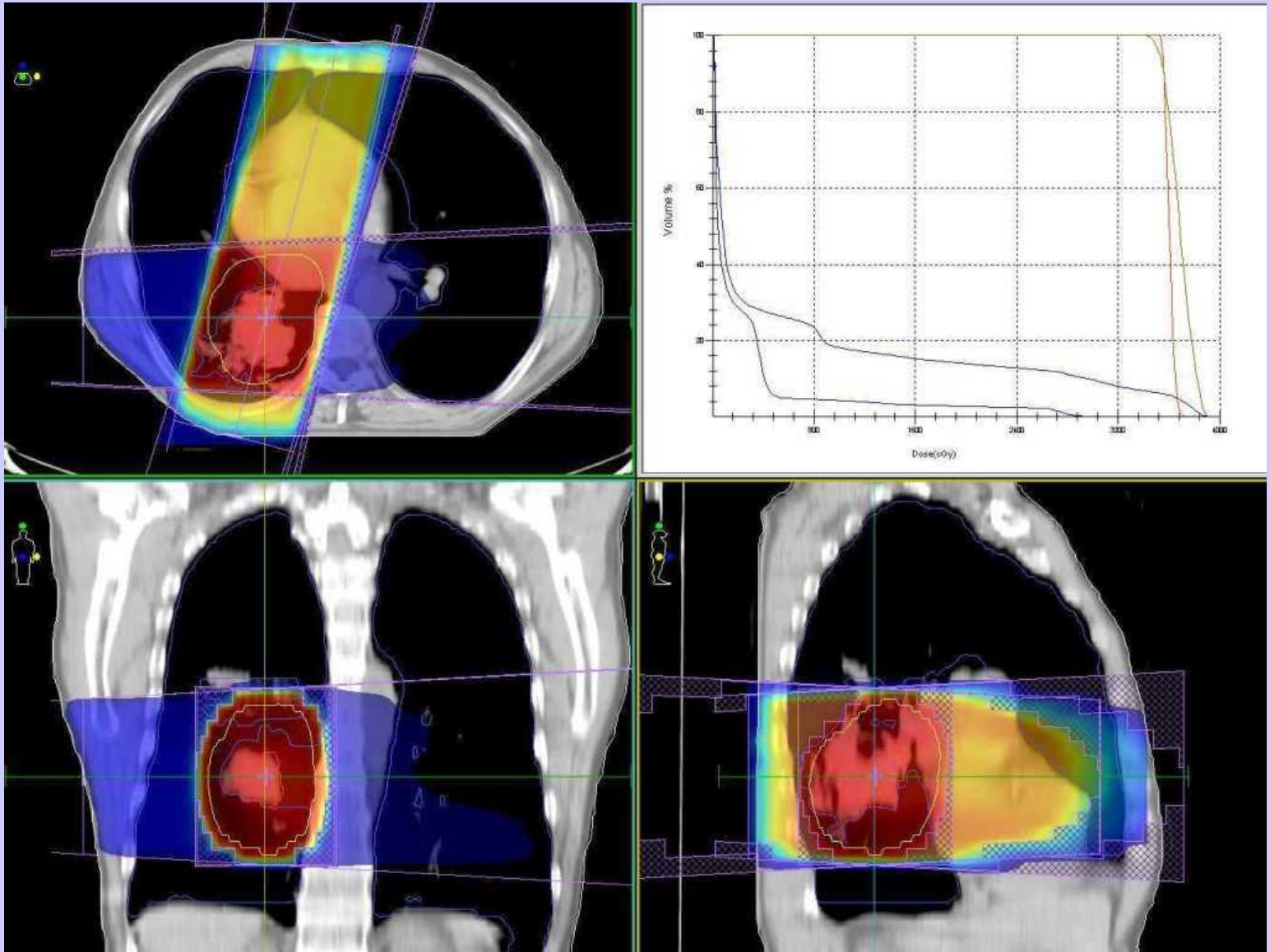






RT-Planning – Defining the GTV

Impact of PET: PTV – RT Plan



RT-Planning – Defining the GTV

Limiting factors of PET

-Resolution 4-8mm (depending on scanner and institution)

-Registration errors (esp. with software based fusion)

-Threshold value (SUV) individually to be determined

Summary:

PET is a promising complementary tool in RT planning of NSCLC. Its value for staging has been established and preliminary reports suggest that it may lead to more consistent definition of GTV in RT planning. However, it is still not clear, whether this will translate into better survival.

RT-Planning – Defining the CTV

1. Margin around primary tumour (microscopic spread)

Histopathologic quantification of subclinical cancer around the grossly visible primary (Giraud 2000):

Microscopic extension	**Adeno**	**Squamos**
mean value	2.69mm	1.48mm
5mm margin covers:	80%	91%
margin to cover 95%	**8mm**	**6mm**

This data could also be used for IMRT planning:

-define constraint for GTV (dose escalation to primary)
-define constraint for subclinical disease (less dose)

-increase therapeutic index

RT-Planning – Defining the CTV

2. Subclinical lymph nodes (ENI)

-high risk of nodal spread in lung cancer
-but value of ENI is not proven

Reasons against ENI:

-less than 20% locally controlled 1y after RT with conventional dose (Arriagada 1991)
-need for more intense treatment to gross tumour
-large volumes prevent dose escalation (normal tissue tolerance)
-small primary tumor and small total tumor volume predictive (Basaki 2006, RTOG 93-11 2008)
-modern chemotherapy regimens may lead to better control of microscopic disease

RT-Planning – Defining the CTV

2. Subclinical lymph nodes (ENI)

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 120–126, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.06.029

CLINICAL INVESTIGATION **Lung**

LONG-TERM RESULTS OF HIGH-DOSE CONFORMAL RADIOTHERAPY FOR PATIENTS WITH MEDICALLY INOPERABLE T1–3N0 NON–SMALL-CELL LUNG CANCER: IS LOW INCIDENCE OF REGIONAL FAILURE DUE TO INCIDENTAL NODAL IRRADIATION?

MING CHEN, M.D., M.S.,* JAMES A. HAYMAN, M.D.,* RANDALL K. TEN HAKEN, PH.D.,* DANIEL TATRO, R.T.P., C.M.D.,* SHANELI FERNANDO, M.D.,† AND FENG-MING KONG, M.D., PH.D.*†

*Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI; and †Department of Radiation Oncology, Veterans Administration Medical Center, Ann Arbor, MI

Purpose: To report the results of high-dose conformal irradiation and examine incidental nodal irradiation and nodal failure in patients with inoperable early-stage non–small-cell lung cancer (NSCLC).

Methods and Materials: This analysis included patients with inoperable CT-staged T1–3N0M0 NSCLC treated on our prospective dose-escalation trial. Patients were treated with radiation alone (total dose, 63–102.9 Gy in 2.1-Gy daily fractions) with a three-dimensional conformal technique without intentional nodal irradiation. Bilateral highest mediastinal and upper/lower paratracheal, prevascular and retrotracheal, sub- and para-aortic, subcarinal, paraesophageal, and ipsilateral hilar regions were delineated individually. Nodal failure and doses of incidental irradiation were studied.

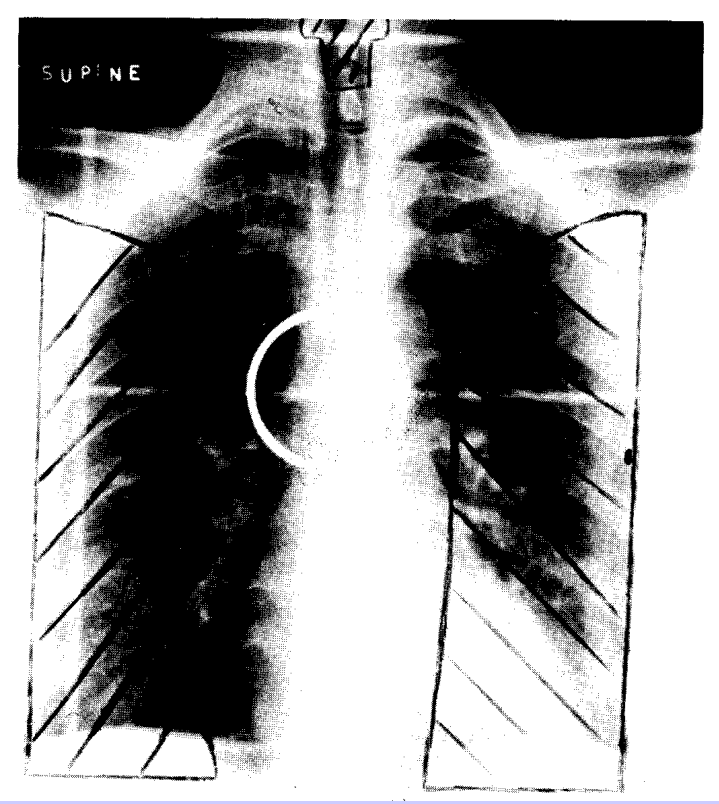
Results: The potential median follow-up was 104 months. For patients who completed protocol treatment, median survival was 31 months. The actuarial overall survival rate was 86%, 61%, 43%, and 21% and the cause-specific survival rate was 89%, 70%, 53%, and 35% at 1, 2, 3, and 5 years, respectively. Weight loss ($p = 0.008$) and radiation dose in Gy ($p = 0.013$) were significantly associated with overall survival. In only 22% and 13% of patients examined did ipsilateral hilar and paratracheal (and subaortic for left-sided tumor) nodal regions receive a dose of ≥40 Gy, respectively. Less than 10% of all other nodal regions received a dose of ≥40 Gy. No patients failed initially at nodal sites.

Conclusions: Radiation dose is positively associated with overall survival in patients with medically inoperable T1–3N0 NSCLC, though long-term results remain poor. The nodal failure rate is low and does not seem to be due to high-dose incidental irradiation. © 2006 Elsevier Inc.

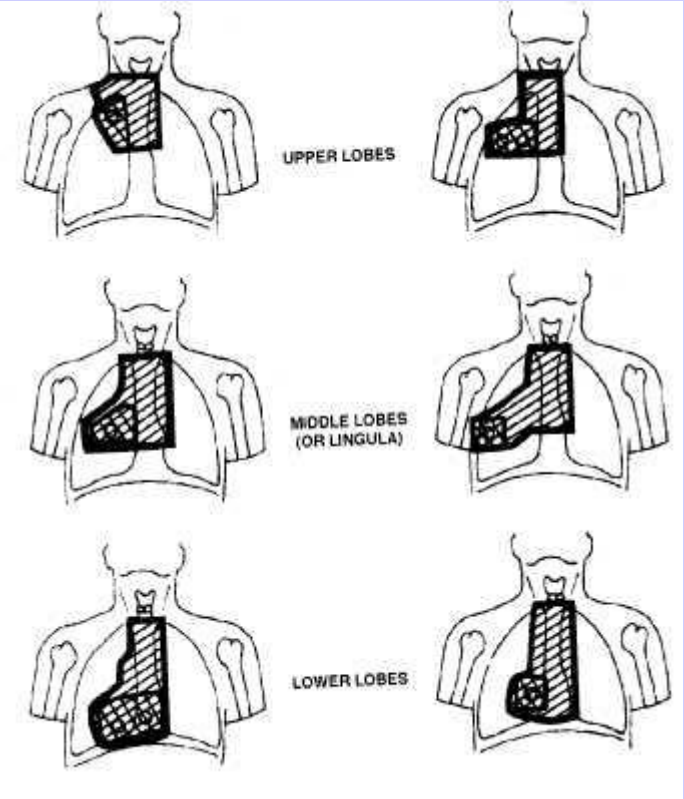
RT-Planning – Defining the CTV

2. Subclinical lymph nodes (ENI)

From large ....



“Old“ Standard …

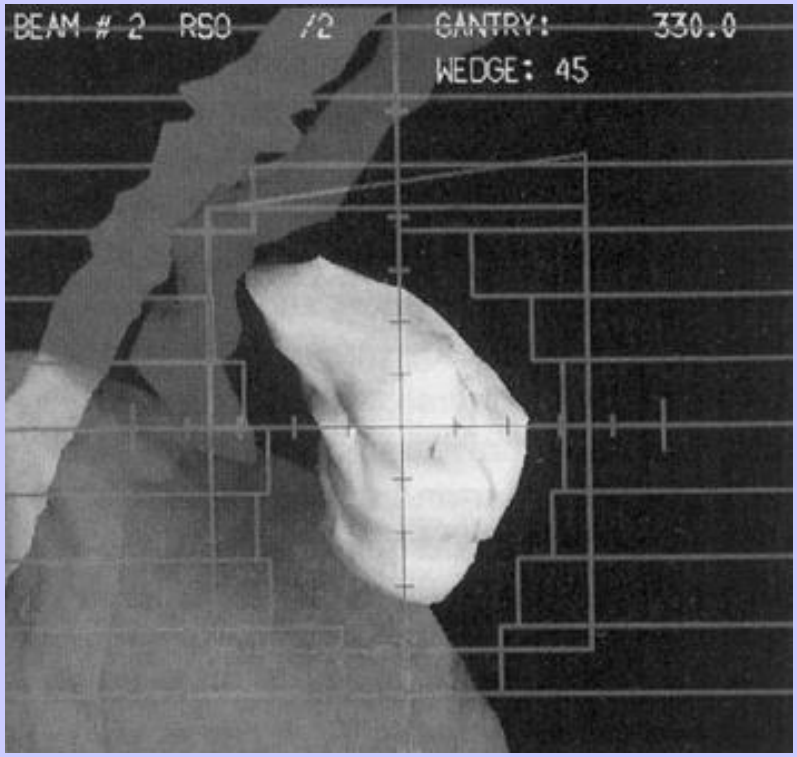


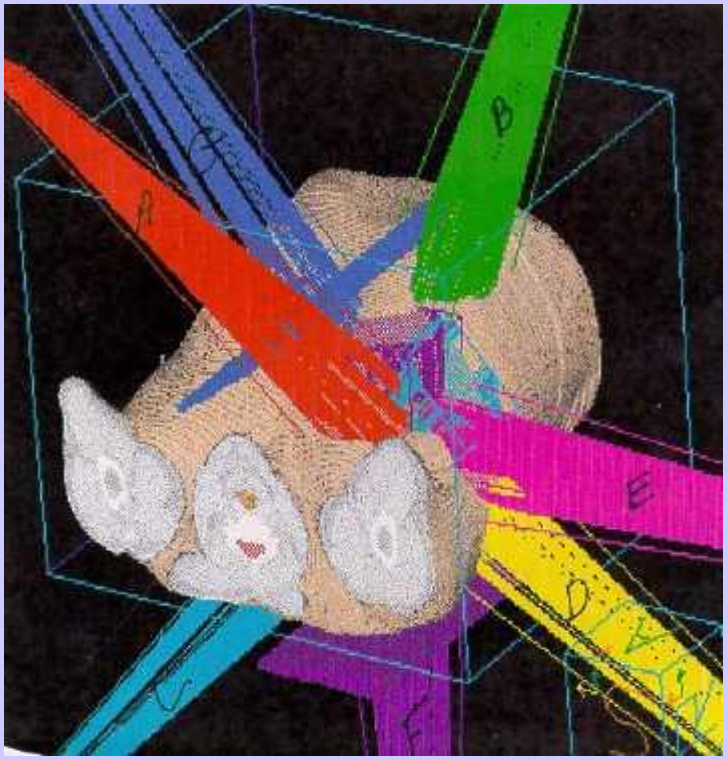
(Perez 1997)

RT-Planning – Defining the CTV

2. Subclinical lymph nodes (ENI)

.... to small !





…“New“ Trend

(IMRT 2007)

RT-Planning – Defining the PTV

ICRU recommendations

CTV ...

+ Internal Margin (Internal Target Volume)
  variations in position, size and shape of CTV

(internal reference system
attached to the patient)

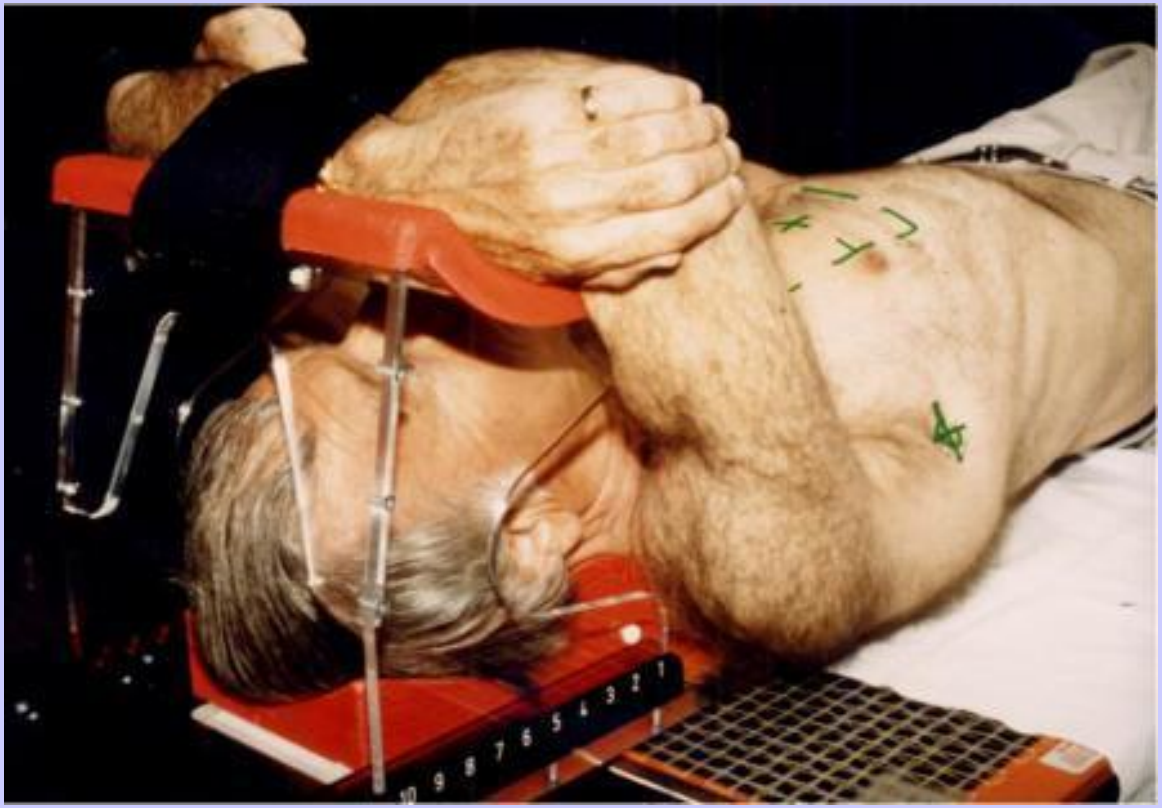
+ Set-up Margin
  variations in relation patient - beam

(external reference system
attached to machine)

RT-Planning – Defining the PTV

Reducing set-up uncertainty:

-Tattoos (instead of skin markers)
-Custom immobilisation devices

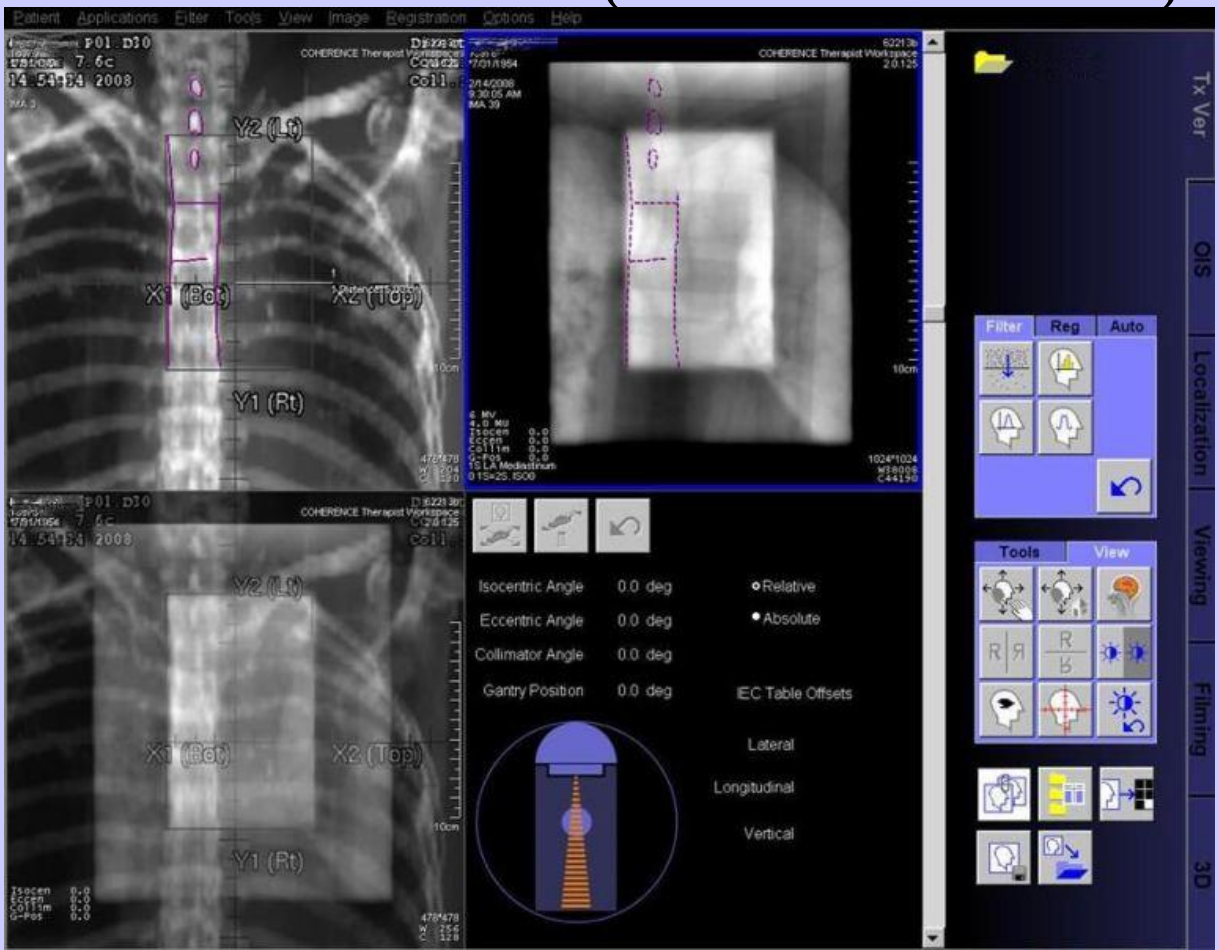


RT-Planning – Defining the PTV

Reducing set-up uncertainty:

-Daily EPID: -matching DRR - EPI

-distinguish between systematic (needs correction) and random error (no correction needed)



RT-Planning – Defining the PTV

Reducing respiration induced errors:

-Breath - hold
- -Voluntary (Deep Inspiration Breath Hold)
- -Forced (Active Breathing Control)

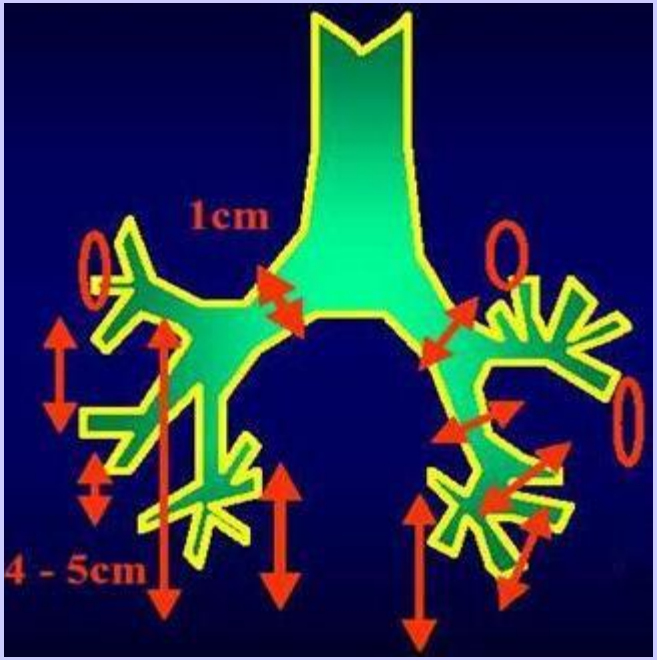
-CT scanning
- -Slow scanning
- -Respiration correlated CT
- -Gating

RT-Planning – Defining the PTV

Reducing respiration induced errors:

Size of movement dependent on:
- tumour location in the lung
- fixation to adjacent structures
- lung capacity and oxygenation
- patient fixation and anxiety

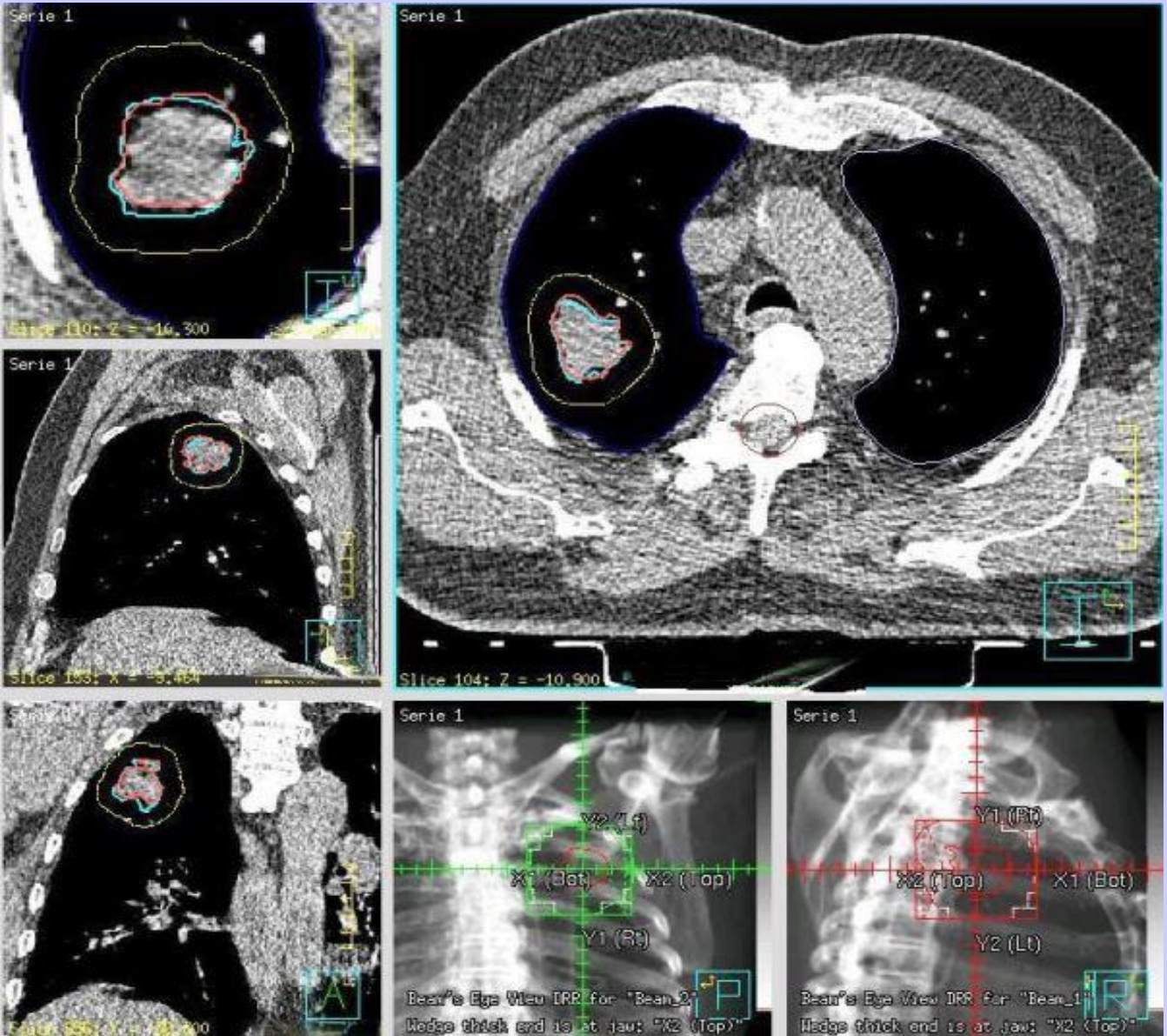
Average movement in normal breathing:
- Upper lobe 0 - **0.5**cm
- Lower lobe 1.5 - **4.0**cm
- Middle lobe 0.5 - **2.5**cm
- Hilum 1.0 - **1.5**cm



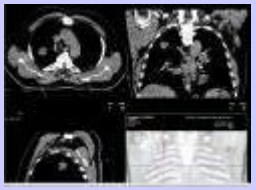
Steppenwoolde 2004

RT-Planning – Defining the PTV

Reducing respiration induced errors:



Gated CT normally reduces the margin PTV - CTV (compared to using published data):



RT-Planning – Defining the PTV

Drawing PTV in gated planning CT:

-Define GTV/CTV for inspiration and expiration phase
-Give a margin of 0.5 - 1cm in all directions (setup uncertainty)

Closing Words:

DON'T use dose escalation and highly conformal techniques such as IMRT for lung cancer until tumour motion can be taken into account !

In the meantime ...

-Outline GTV as best as possible
-Construct CTV based on the literature
-Construct PTV based on measured tumour motion and known setup uncertainty.