Dose escalation for NSCLC using conformal RT: 3D and IMRT.

Hasan Murshed

Take home message

Preliminary data shows CRT technique in NSCLC

- allows dose escalation to an unprecedented level
- maintaining cancer control
- keeping acceptable morbidity in pts.

Case presentation

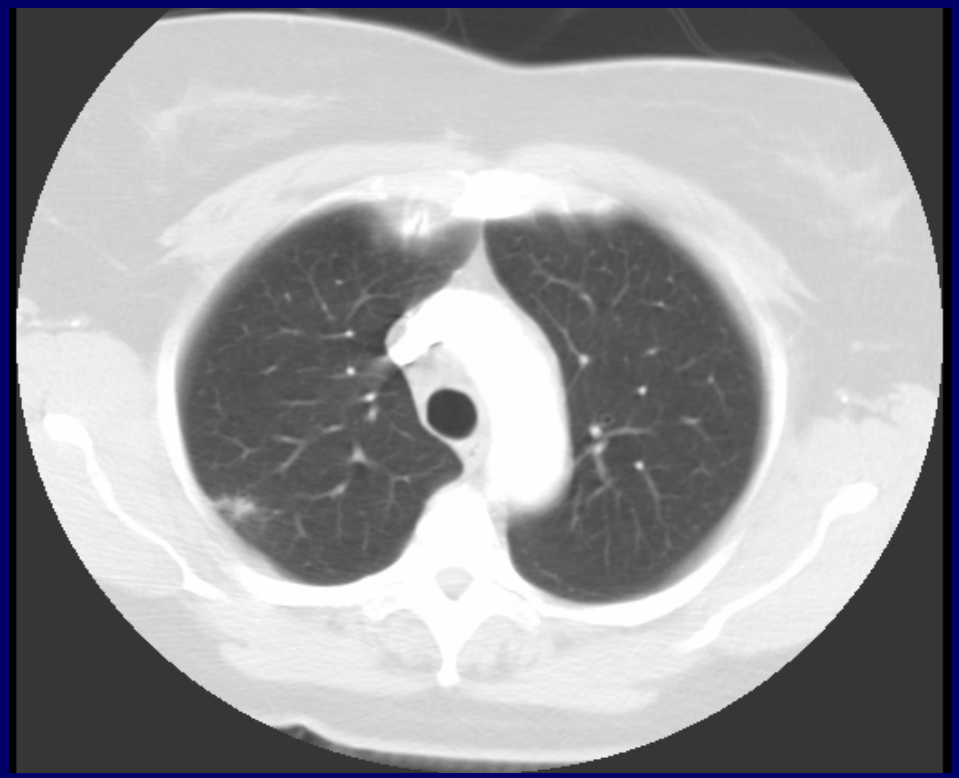
- 58 yow
- 12/01
  - single episode of hemoptysis, mild SOB,
  - no wt. loss/cough/sputum, PS 1.
  - CXR + mass in rt lung.
  - CT chest RUL nodular density/mediast/lt paratracheal/subcarinal LN.

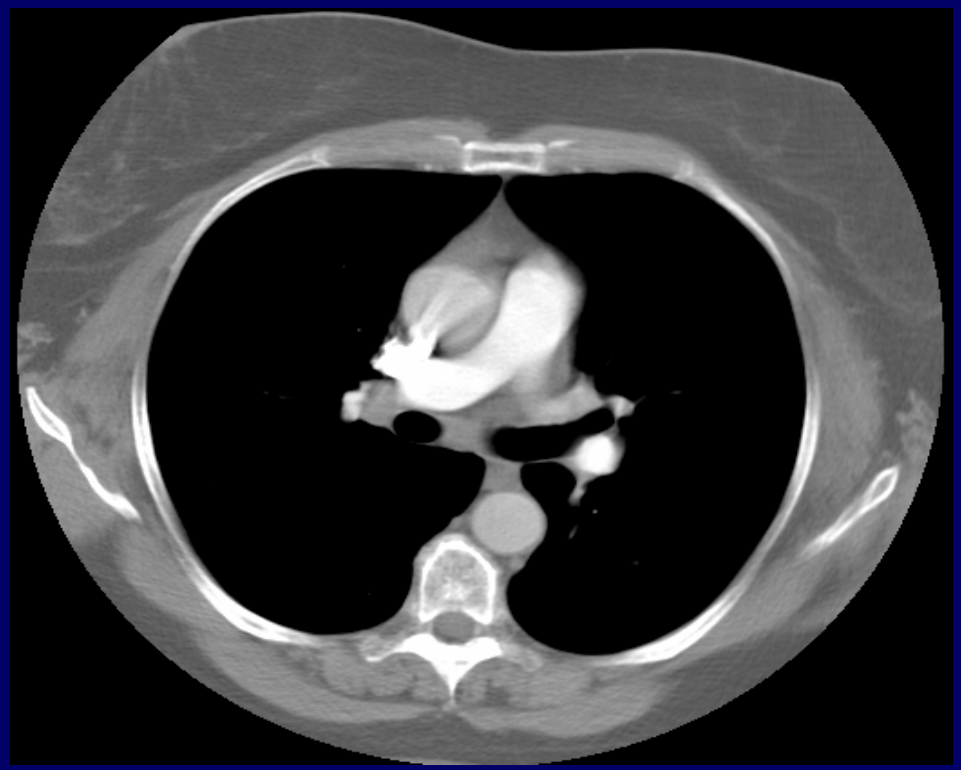
Case presentation

- 12/01
  - bronch showed RUL friable tumor and endobronchial rt main bronchus lesion.
  - bx + adenoca.
- 01/02
  - MRI brain -, BS -, no PET available.

Case presentation

- CT chest on 2/02, after 2 cycles of chemo.



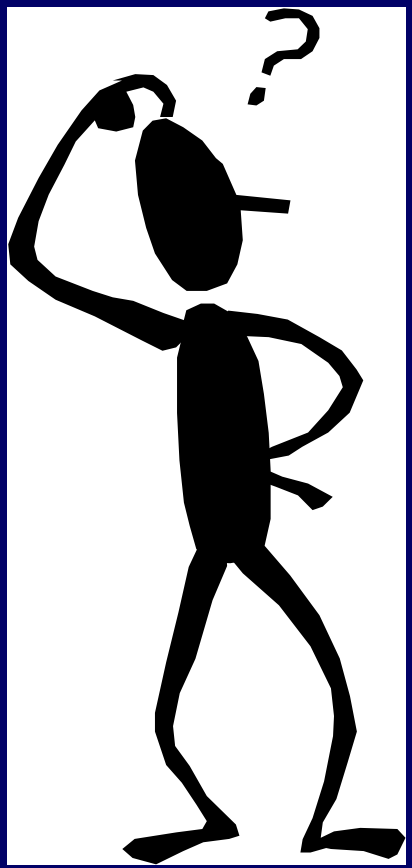


Case presentation

Diagnosis

- RUL locally advanced non-small cell cancer
- Adenoca
- T1N3M0, stage IIIB.

Questions



- Prognosis of this LANSCLC pt.
- Management of this pt.
- Role of IMRT for dose escalation in this pt.

Arriagada R et al 1991

- 353 pts with LANSCLC randomized to RT vs ChemoRT.
- RT dose 250 cGy to 65 Gy
  - AP/PA included tumor, hilar/medias/Sclav LN to 40 Gy
  - Opp lats included tumor, hilar/medias LN to 15 Gy
  - Opp obliq included tumor, hilar/medias LN to 10 Gy
- Chemo was given in sequence, neoadjuvant/adjuvanrt
  - Vindesine 1.5 mg/m2 on d1, 2
  - Cyclophosphamide 200 mg/m2 on d2, 3, 4
  - CDDP 100 mg/m2 on d2
  - Lomustine 50 mg/m2 on d2, 25 mg/m2 on d3

Int J Radiation Oncol Biol Phys: 20 (6), 1183-90, 1991

Arriagada R et al 1991

- F/U done via imaging and **bx of primary** to determine final response.
- Rslts: mean f/u 40 m.

	CR @ 3m	LC @ 1yr	DM @ 2y	OS @ 2y	MS
	(%)	(%)	(%)	(%)	(months)
RT alone	20	17	67	14	10
ChemoRT	16	15	45	21	12
p value			< 0.001	0.08	

Int J Radiation Oncol Biol Phys: 20 (6), 1183-90, 1991

Arriagada R et al 1991

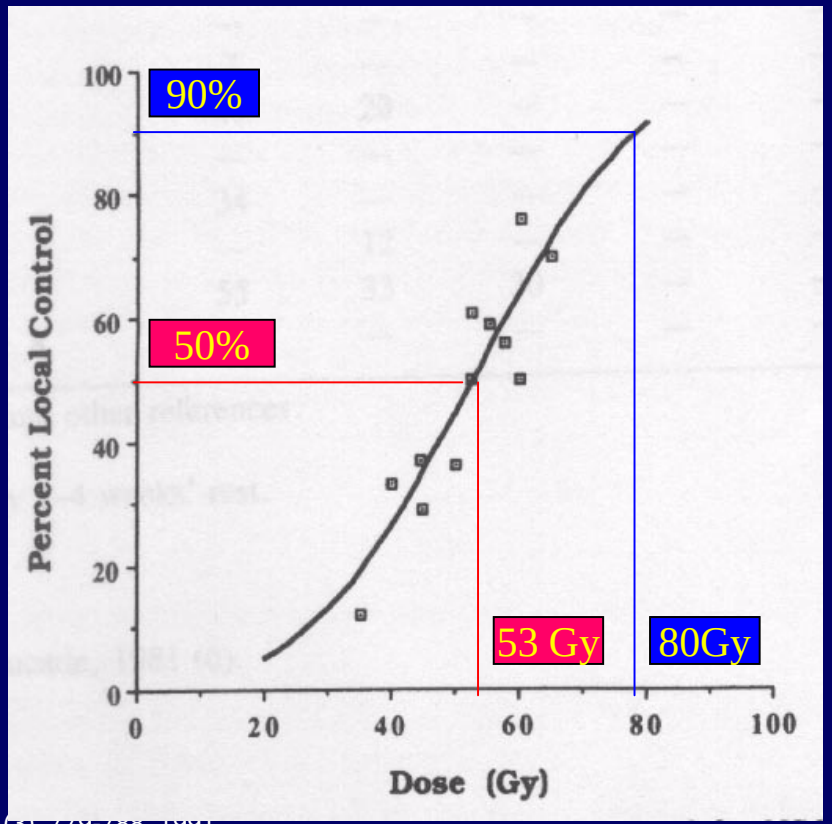
Conclusions

- RT of 65 Gy is ineffective for LC in NSCLC.
- LC remains a significant problem, survival will not improve until LC improves.
- Decrease in DM did not improve OS.

Int J Radiation Oncol Biol Phys: 20 (6), 1183-90, 1991

Vijayakumar S et al 1991

- Correlation between dose and LC for NSCLC from published data.
- Increasing RT dose improves LC.



Int J Radiation Oncol Biol Phys: 21 (3), 779-788, 1991

To summarize

- Improved LC needed to improve OS in NSCLC.
- NSCLC has a dose response and can be optimized with dose escalation.

Means to improve LC/OS

Higher RT dose

conformal RT technique

altered fractionation

Trimodality therapy

CT and RT followed by surgery

Addition of CT to RT

sequential, concurrent

better CT

Gene therapy

3D CRT

- 3D, computer-generated reconstruction of tumor volume and surrounding critical normal structures from direct CT/MRI data in preparation for noncoplanar/coplanar RT therapy.
    - Improves target delineation.
    - Assess RT dose to normal structure surrounding target.
    - Is a dose escalation tool.

Graham MV et al 1999

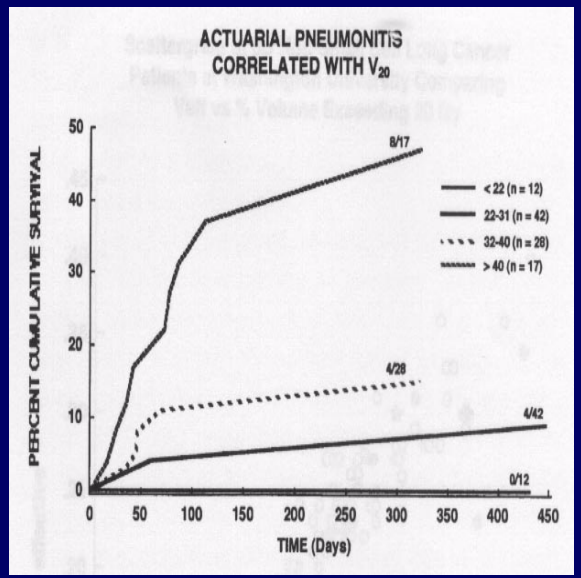
- 99 pts with NSCLC T3/T4, N2/N3 treated with 3DCRT, retrospectively analyzed.
  - GTV = gross dz, LN > 1 cm
  - CTV = GTV+7-10 mm
  - PTV1 = CTV+7-10 mm, PTV2 = GTV+7-10 mm
  - RT dose PTV1 = 50 Gy, PTV2 = boosted to 70 Gy.
  - Attempt to cover PTV in 95%, lung correction done.
- Almost half of the pts received chemo.
- Clinical pneumonitis correlated with DVH of total lung.

Int J Radiation Oncol Biol Phys: 45 (2), 323-3290, 1999

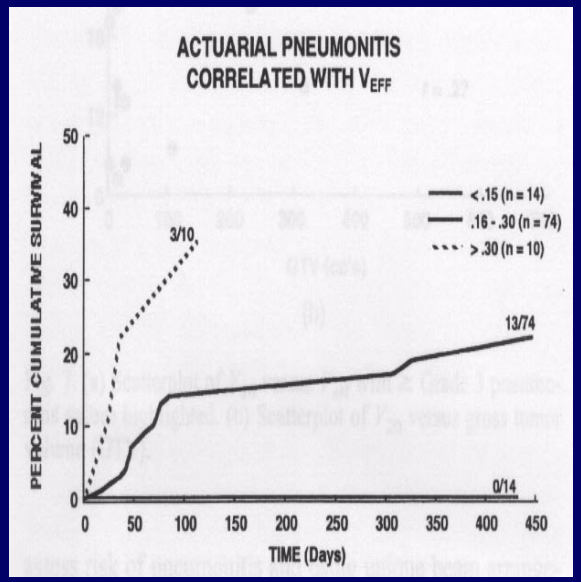
Graham M et al 1999

- Results: significant factors predicting pneumonitis.

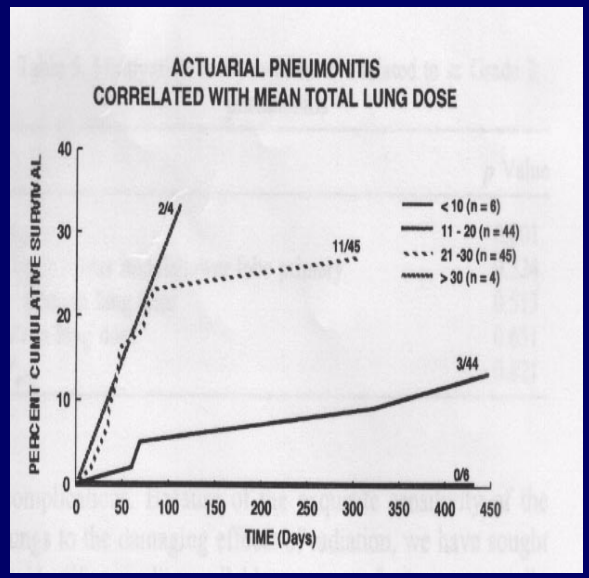
V20



Veff



lung mean dose



Int J Radiation Oncol Biol Phys: 45 (2), 323-329, 1999

Graham M et al 1999

- Results: in multivariate only V20 significant.

	Pneumonitis		
V20	gr 2	gr 3-5	fatal
(%)	(%)	(%)	(total pt)
< 22	0	0	
22-31	8	8	
32-40	13	5	1
> 40	19	23	3

- Concl:
  - Strong correlation between V20 and severity of pneumonitis.
  - V20 is a useful parameter to evaluate pneumonitis.
  - Can be used to stratify pts for dose escalation.

Int J Radiation Oncol Biol Phys: 45 (2), 323-329, 1999

Hayman JA et al 2001

Dose Escalation in Non–Small-Cell Lung Cancer Using Three-Dimensional Conformal Radiation Therapy: Update of a Phase I Trial

By James A. Hayman, Mary K. Martel, Randall K. Ten Haken, Daniel P. Normolle, Robert F. Todd III, J. Fred Littles, Molly A. Sullivan, Peter W. Possert, Andrew T. Turrisi, and Allen S. Lichter

Purpose: **High-dose radiation may improve outcomes in non–small-cell lung cancer (NSCLC). By using three-dimensional conformal radiation therapy and limiting the target volume, we hypothesized that the dose could be safely escalated.**

Materials and Methods: **A standard phase I design**

locally recurrent disease. Twenty-five received chemotherapy, and 63 were assessable for escalation. All bins were escalated at least twice. Although grade 2 radiation pneumonitis occurred in five patients, grade 3 radiation pneumonitis occurred in only two. The maximum-tolerated dose was only established for the larg-

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Phase I dose escalation trial for medically inoperable stage I, II, stage III, recurrent NSCLC pts using 3DCRT.
- Five bins created based on normal lung volume (Veff) irradiated.
- Dose levels within bins were chosen based on estimated risk of radiation pneumonitis by NTCP.

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Pts were enrolled 3 at a time
  - if 1/3 pt developed gr 3 pneumonitis, 3 more enrolled
  - if 2/3 pt developed gr 3 pneumonitis, accrual stopped.

- Target volume included primary tumor, LN $\geq$ 1 cm.

- Gr 3 radiation pneumonitis chosen as primary end point, other end points patterns of first failure, PFS, OS.

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

Table 1. Revised Dose-Escalation Schema Using V_{eff} Based on Both Lungs and New Parameters

	V_{eff} Bins (Gy)				
NTCP (%)	1 (0-0.12)	2 (> 0.12-0.18)	3 (> 0.18-0.24)	4 (> 0.24-0.31)	5 (> 0.31-0.40)
1	84	69.3			
2	92.4	75.6			
3	102.9	84	65.1		
5		92.4	69.3	63	
7		102.9	75.6	65.1	
10			84	69.3	63
14			92.4	75.6	65.1
20				84	69.3
28				92.4	75.6
38					84

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Radiation therapy
  - Pt supine, alpha cradle, breathing freely, CTsim, fluoroscope.
  - GTV = gross dz, LN ≥ 1 cm, CTV = GTV+0.5 cm, PTV = CTV+0.5 cm±0.5 cm for respiration.
  - 2-7 noncoplaner static 3D CRT fields, PTV covered by 95% IDL, 2.1 Gy/fx 5fx/wk, 6-25 MV photons, lung correction.
  - Uninvolved nodal region were not included.

- Spinal cord = 50 Gy, esophagus = 1/3 to 65, 72, 80 Gy, heart = 1/3 to 65 Gy, whole to 40 Gy, total lung Veff ≤ 40%

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Chemotherapy
  - Initially pts did not receive any chemo.
  - After 1996 pts with stage III, recurrent dz received neoadjuvant chemo.
  - CDDP 100 mg/m2 d1, 29, Vinorelbine 25 mg/m2 d1, 8, 15, 22, 29.

- RT to start at day 50.

Journal of Clinical Oncology 19, 127-136, 2001

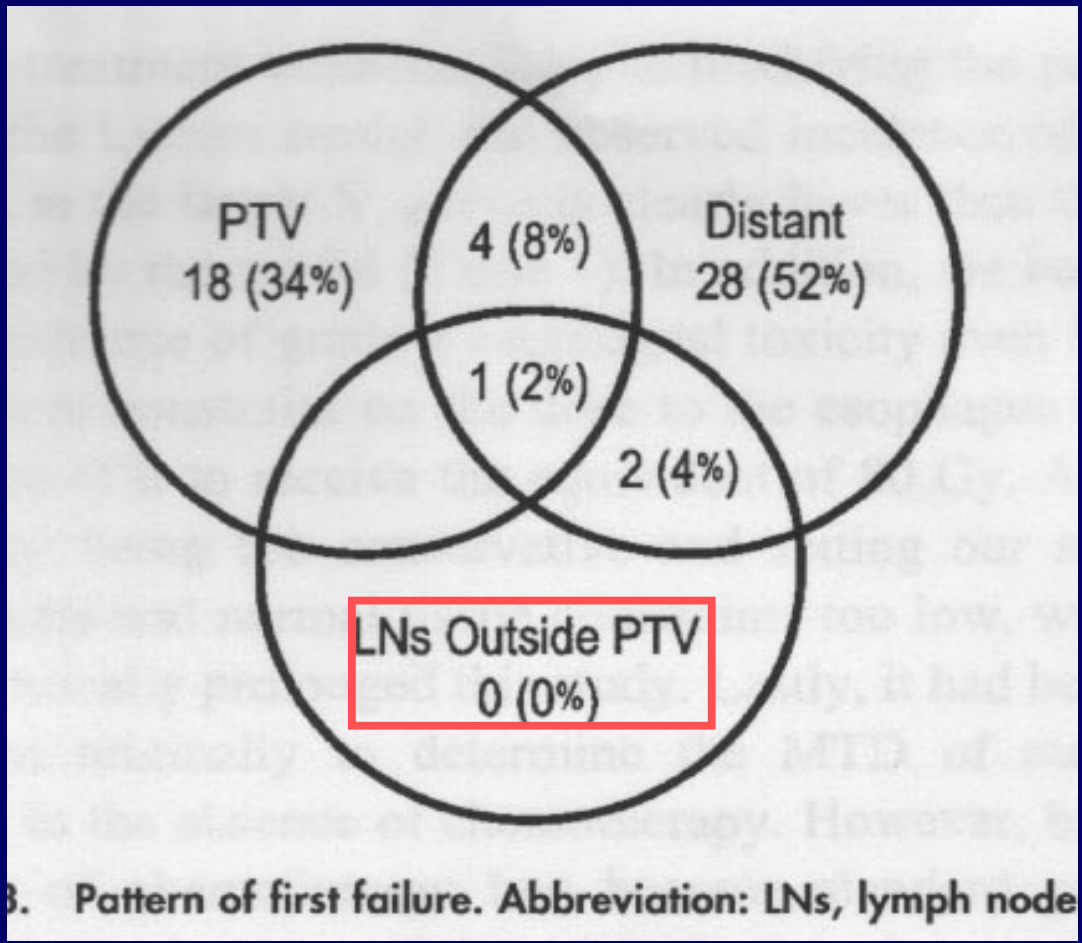
Hayman JA et al 2001

- Results: 104 pts enrolled, 81 completed RT, 63 evaluable for dose escalation.

	V_{eff} Bins									
	1 (0-0.12)		2 (> 0.12-0.18)		3 (> 0.18-0.24)		4 (> 0.24-0.31)		5 (> 0.31-0.40)	
NTCP (%)	Dose (Gy)	No. of Patients of Total	Dose (Gy)	No. of Patients of Total	Dose (Gy)	No. of Patients of Total	Dose (Gy)	No. of Patients of Total	Dose (Gy)	No. of Patients of Total
1	84	4/4	69.3	3/4						
2	92.4	5/5	75.6	4/4						
3	102.9*	1/2	84	8/8	65.1	5/6				
5			92.4	3/3	69.3	3/4	63	1/1		
7			102.9*	0/1	75.6	5/8	65.1	3/6		
10					84*	0/4	69.3	6/8	63	4/5
14					92.4		75.6*	1/3	65.1†	3/6
20							84		69.3	4/10
28							92.4		75.6	
38									84	

Hayman JA et al 2001

- Results:
- Median F/U 9.4 m (range 2 - 57 m)
- Patterns of initial failure



3. Pattern of first failure. Abbreviation: LNs, lymph node

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Survival results:

	MS	2 yr PFS	2 yr OS
This study	(months)	(%)	(%)
All pts	18	17	40
Stage I, II	20	24	49
Stage III, recr	16	12	36
Other studies			
CALGB 8433	14		
RTOG 9410	17		

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

- Radiation toxicity

Gr 3 skin reaction –	1 pt
Gr 3 nausea -	1 pt
Gr 2 pneumonitis -	5 pt
Gr 3 pneumonitis -	2 pt
Gr 3 pulmo fibrosis -	1 pt
Fatal pulmo hemor -	2 pt
Gr 3 esophagitis -	6 pt
Gr 4 esophagitis -	1 pt

Chemo toxicity

Gr 3 nausea -	2 pt
Gr 3 hemato -	4 pt
Fatal -	1 pt

Journal of Clinical Oncology 19, 127-136, 2001

Hayman JA et al 2001

Conclusions:

- Not treating elective LNs did not increase nodal failures or compromise the survival of pts.
- Except large Veff bin, MTD for other bins has not been reached.
- Dose escalation to an unprecedented level in NSCLC pts has been accomplished safely using 3DCRT.

Journal of Clinical Oncology 19, 127-136, 2001

F/U case presentation

- Treatment at MDA
  - 01/02 - started chemo with CarboTaxol x3 cy.
  - 03/02 - started concurrent chemoRT
  - 3D CRT dose 180 cGy to 63 Gy, 6 MV AP/PA to 36 Gy, 6/18 MV LAO/RPO to 27 Gy.
  - GTV = primary+LN $\geq$ 1 cm, CTV = GTV+8 mm, PTV = CTV+8-12 mm.
  - Cord = 38 Gy, esophagus = 1/3 to 54 Gy, heart = 1/3 to 55 Gy, total lung $\geq$ 20 Gy to $\leq$ 40% volume.

F/U case presentation

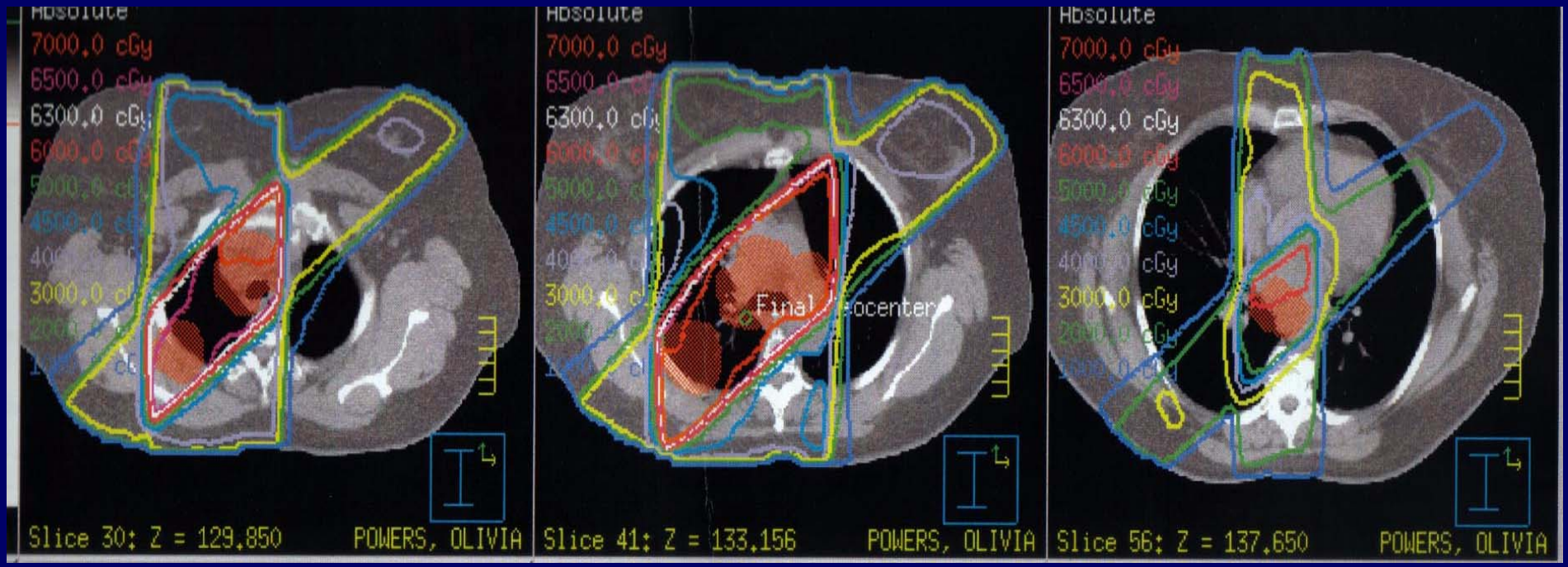
- Concurrent chemo CarboTaxol x2 cy
  - Taxol 50 mg/m2
  - Carbo AUC 2.

- 05/02 - COT, during RT gr 2 nausea, gr 2 esophagitis, treated with compazine and hydrocodone.

- 09/02 - last f/u no evidence of dz, PS 1, working fulltime, CT chest post RT changes.

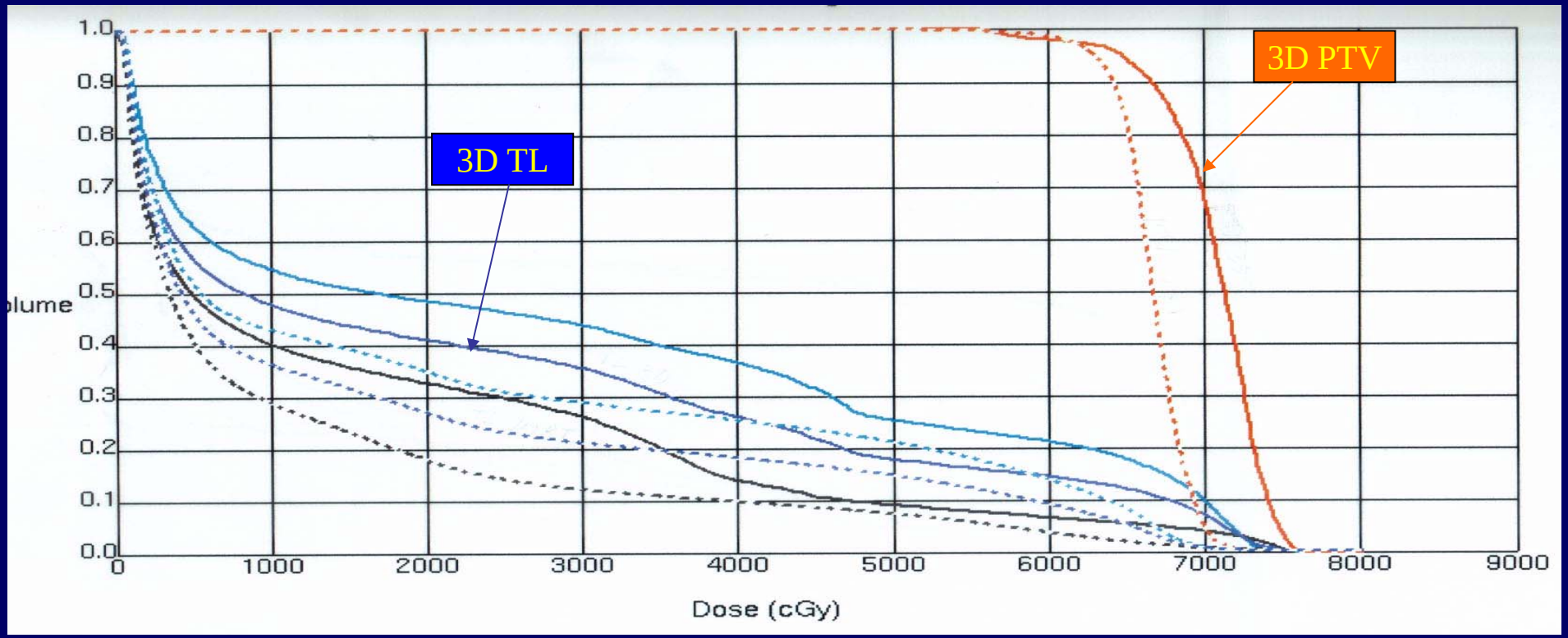
F/U case presentation

- 3D isodose plots



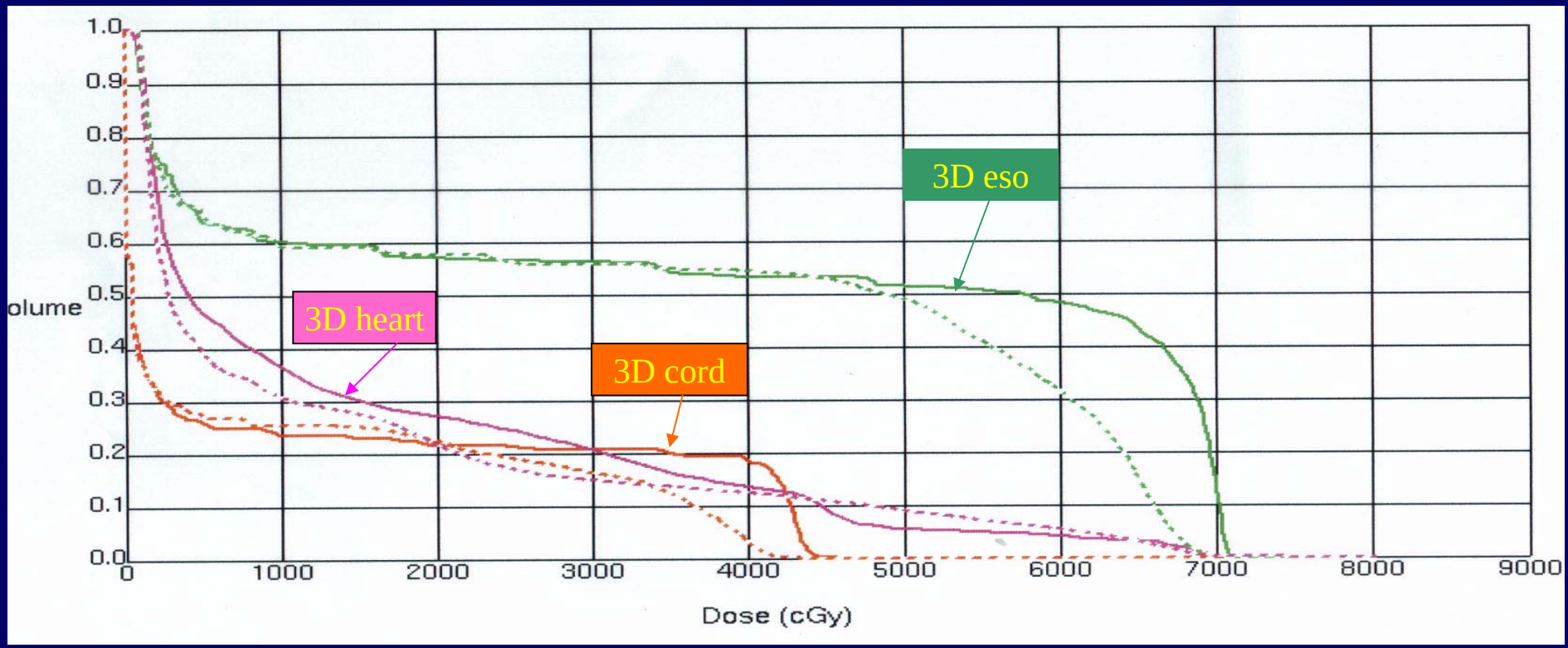
F/U case presentation

- 3D DVH



F/U case presentation

- 3D DVH



IMRT

- IMRT combines two advance concepts to deliver 3D conformal radiation
  - inverse treatment planning with computer optimization
  - computer controlled intensity modulation of the radiation beam.
- Potential advantages
  - to create multiple targets
  - multiple critical avoidance
  - new accelerated fractionation scheme.
- Has potential in radiation oncology in the the 21st century
  - Used to spare critical structures allowing dose escalation in NSCLC pts.

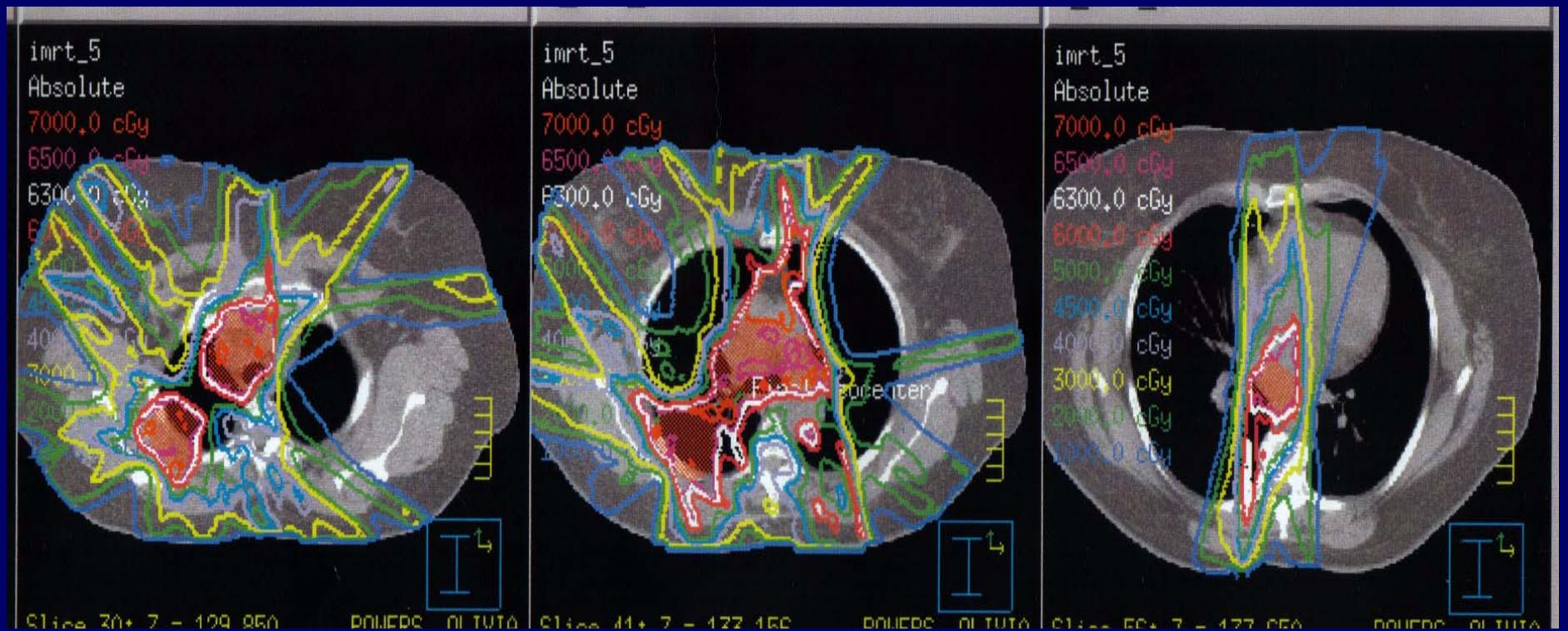
F/U case presentation/IMRT

- Post treatment IMRT planning
  - 180 cGy to 63 Gy in 35 fxs
  - 9 equispaced fields
  - GTV, CTV, PTV same as 3D planning
  - PTV with 95%, all constrains remain the same as 3D planning
  - 6 MV photons, Lung correction done

- ADAC Pinnacle planning system
  - gradient technique for optimization
  - convolution technique for dose calculation

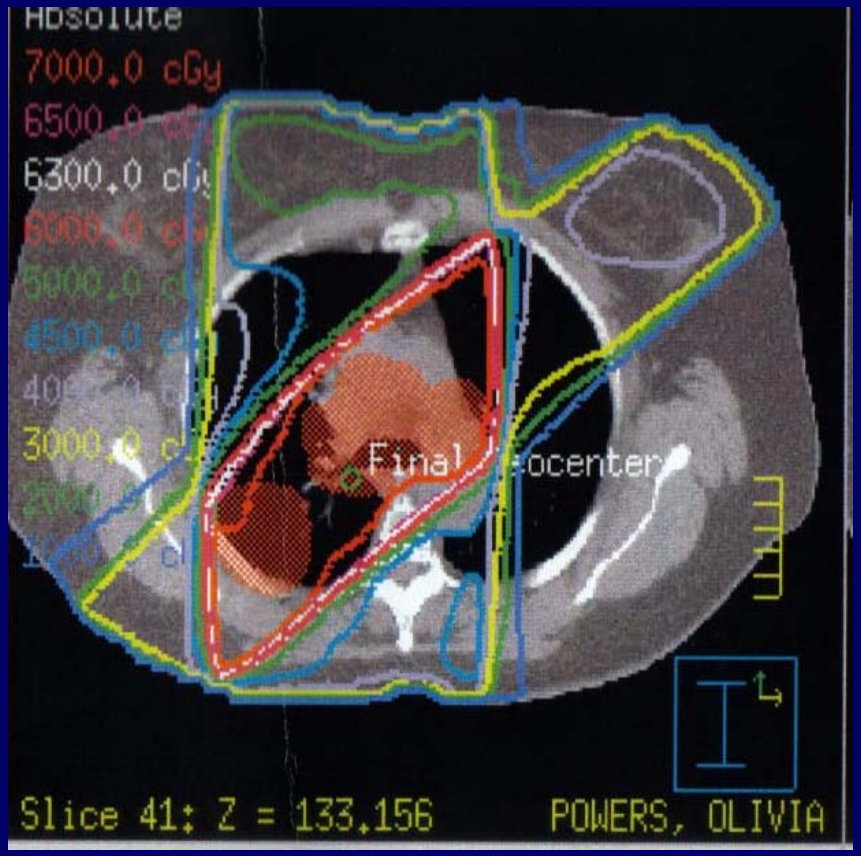
F/U case presentation/IMRT

- IMRT isodose plots

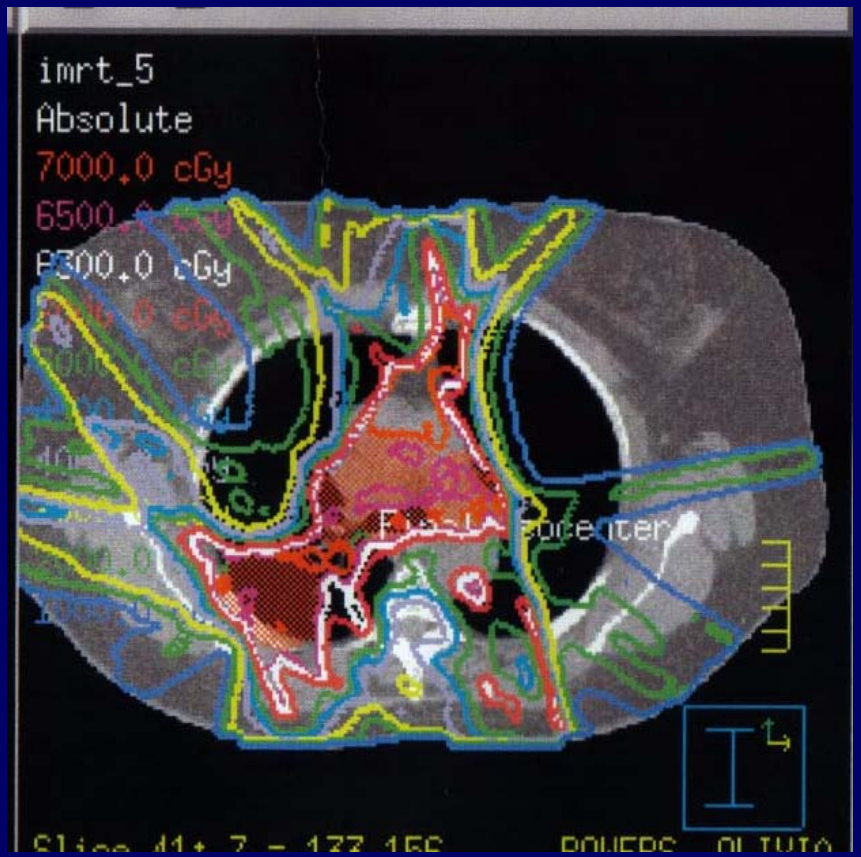


F/U case presentation/IMRT

- 3D

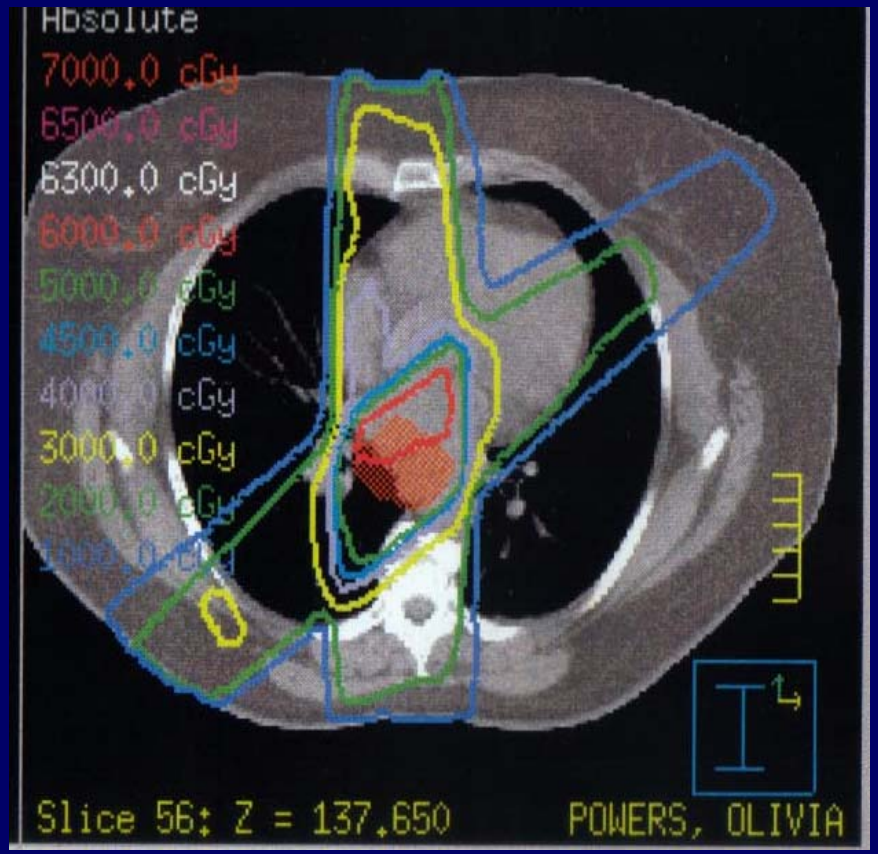


IMRT

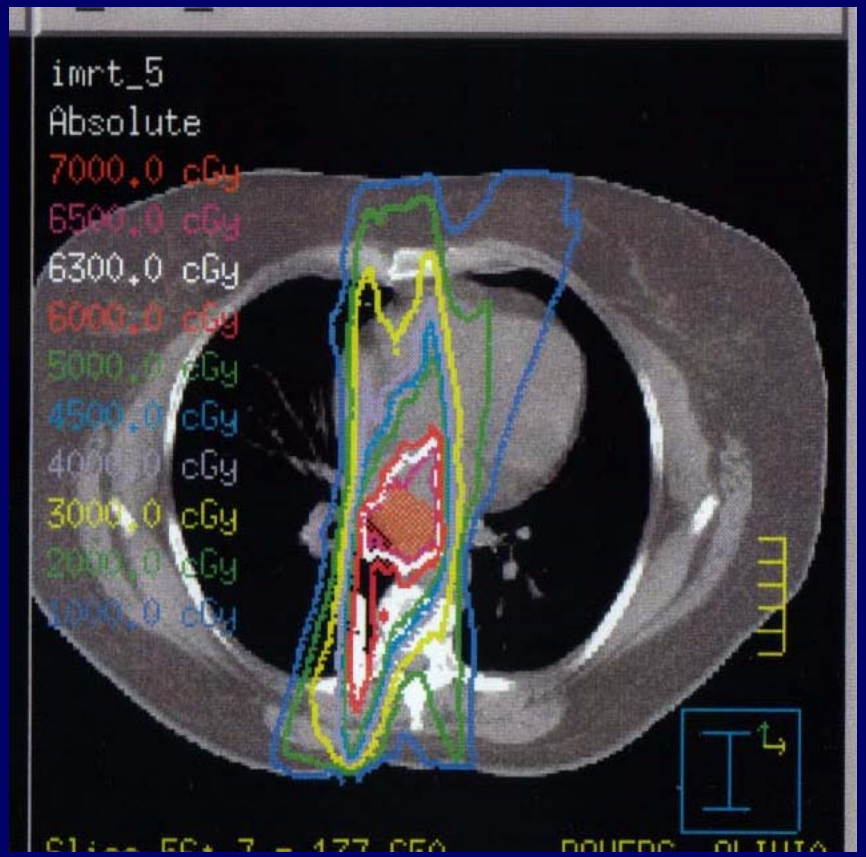


F/U case presentation/IMRT

- 3D

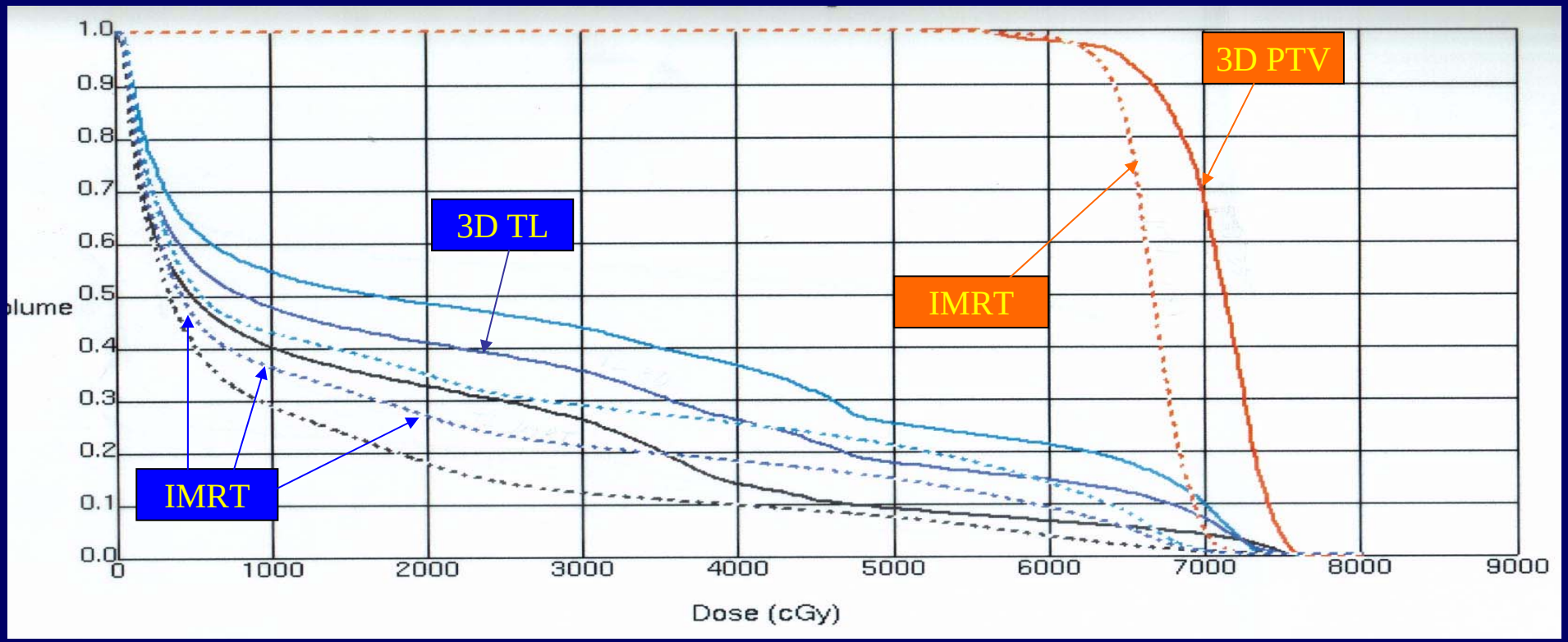


IMRT



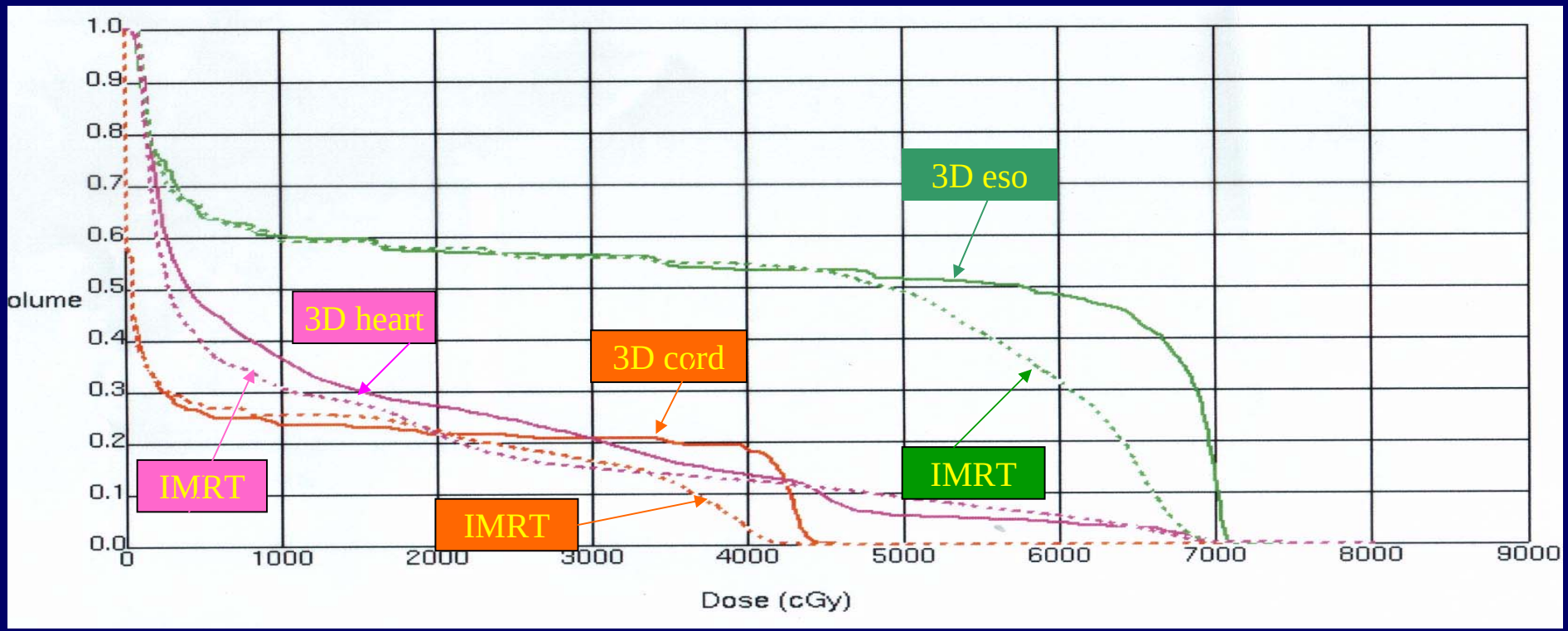
F/U case presentation/IMRT

- 3D/IMRT DVH



F/U case presentation/IMRT

- 3D/IMRT DVH



F/U case presentation/IMRT

- Dosimetric parameters 3D vs IMRT.

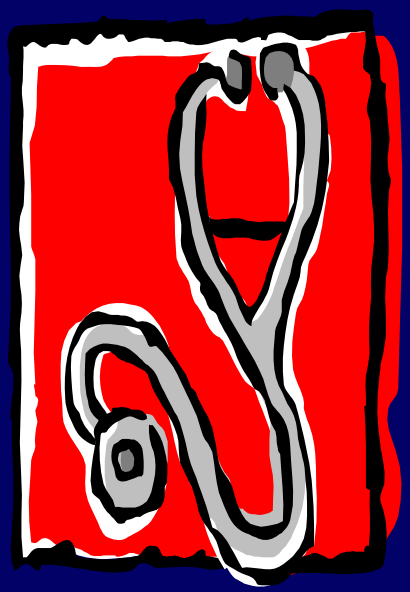
Parameters	3D CRT	IMRT
Conf index	1.75	1.67
Het index	1.09	1.15
% TL @ 5 Gy	56	46
% TL @ 10 Gy	48	37
% TL @ 20 Gy	41	28
Veff @ 20 Gy (%)	66	58
Mean dose (Gy)	17.98	16.48
% eso @ 45 Gy	100	53
% heart @ 40 Gy	3.9	8
% cord @ 45 Gy	0.4	0.6
max cord dose	4880	5040

Conclusions

- 3D CRT allowed unprecedented dose escalation to more than 100 Gy in NSCLC pts with lower than expected morbidity.

- However, MTD for most pts has not been reached yet.

Conclusions



- Preliminary data from dose escalation in NSCLC shows encouraging local control and promising survival.

Conclusions

- IMRT planning would have placed this pt in a lower V20 level
  - would reduce risk of pneumonitis
  - allowed dose escalation

- IMRT is a superior dose escalation tool.

Conclusions

- MDA IMRT lung project in two stages
  - Preclinical dosimetric evaluation - 40 pts
    - V20 – reduction in 100% pts
    - V5 – reduction in 75% pts
  - Clinical implementation of IMRT - protocol
    - organ motion – gating, active breath control
    - small dose to large lung volume – better algorithm

Future/RTOG 9311

A PHASE I/II DOSE ESCALATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY IN PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER

SCHEMA

All patients must have a completed 3D plan prior to entering this protocol

Group 1* < 25%	Dose level 1:	70.9 Gy/33 fx/7-8 wks *(closed 1/8/98)*
	Dose level 2:	77.4 Gy/36 fx/7-8 wks *(closed 9/23/98)*
	Dose level 3:	83.8 Gy/39 fx/8-9 wks *(closed 12/20/99)*
	Dose level 4:	90.3 Gy/42 fx 9-10 wks *(opened 12/20/99)*
Group 2* 25%- < 37%	Dose level 5:	70.9 Gy/33 fx/7-8 wks *(closed 6/14/99)*
	Dose level 6:	77.4 Gy/36 fx/7-8 wks *(opened 6/14/99)*
	Dose level 7:	83.8 Gy/39 fx/8-9 wks
Group 3*+ ≥ 37%	Dose level 8:	64.5 Gy/30 fx/6-7 wk *(closed 7/1/99)*
	Dose level 9:	70.9 Gy/33 fx/7-8 wks
	Dose level 10:	77.4 Gy/36 fx/7-8 wks

+ Group 3 closed to accrual 7/1/99 for all dose levels.

Future/RTOG L0117

RTOG L-0117

A PHASE I/II DOSE INTENSIFICATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY AND CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER

SCHEMA

Schema A			Schema B		
Arm	**RT***	**Chemo****	**Arm**	**RT***	**Chemo****
1	75.25 Gy/35 fx *(2.15 Gy per fraction)*	A	2	75.25 Gy/35 fx *(2.15 Gy per fraction)*	B
3	84.0 Gy/35 fx *(2.4 Gy per fraction)*	A	4	84.0 Gy/35 fx *(2.4 Gy per fraction)*	B
5	79.5 Gy/30 fx *(2.65 Gy per fraction)*	A	6	79.5 Gy/30 fx *(2.65 Gy per fraction)*	B
7	75 Gy/25 fx *(3.0 Gy per fraction)*	A	8	75 Gy/25 fx *(3.0 Gy per fraction)*	B

* All prescription doses are at the ICRU-50 Reference Point

** Chemotherapy: concurrent beginning day 1 with RT

Schema A: Paclitaxel 50 mg/m^2, over 1 hour, days 1, 8, 15, 22, 29, 36, 43
Followed by Carboplatin AUC=2, over 30 minutes, days 1, 8, 15, 22, 29, 36, 43

Schema B: Paclitaxel 135 mg/m^2, over 3 hours, days 1, 22, 43
Followed by Carboplatin AUC=5, over 30 minutes, days 1, 22, 43

Happy New Year.