THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

Image-Guided Proton Therapy in Non-small Cell Lung Cancer (NSCLC)

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Thoracic Radiation Oncology

Objectives:

1. Introduce proton therapy in NSCLC

2. Discuss impact and management of intra- and inter- fraction tumor motion and anatomy change in proton treatment planning and delivery

3. Review undergoing proton therapy clinical trials in NSCLC

4. Discuss proposed clinical studies

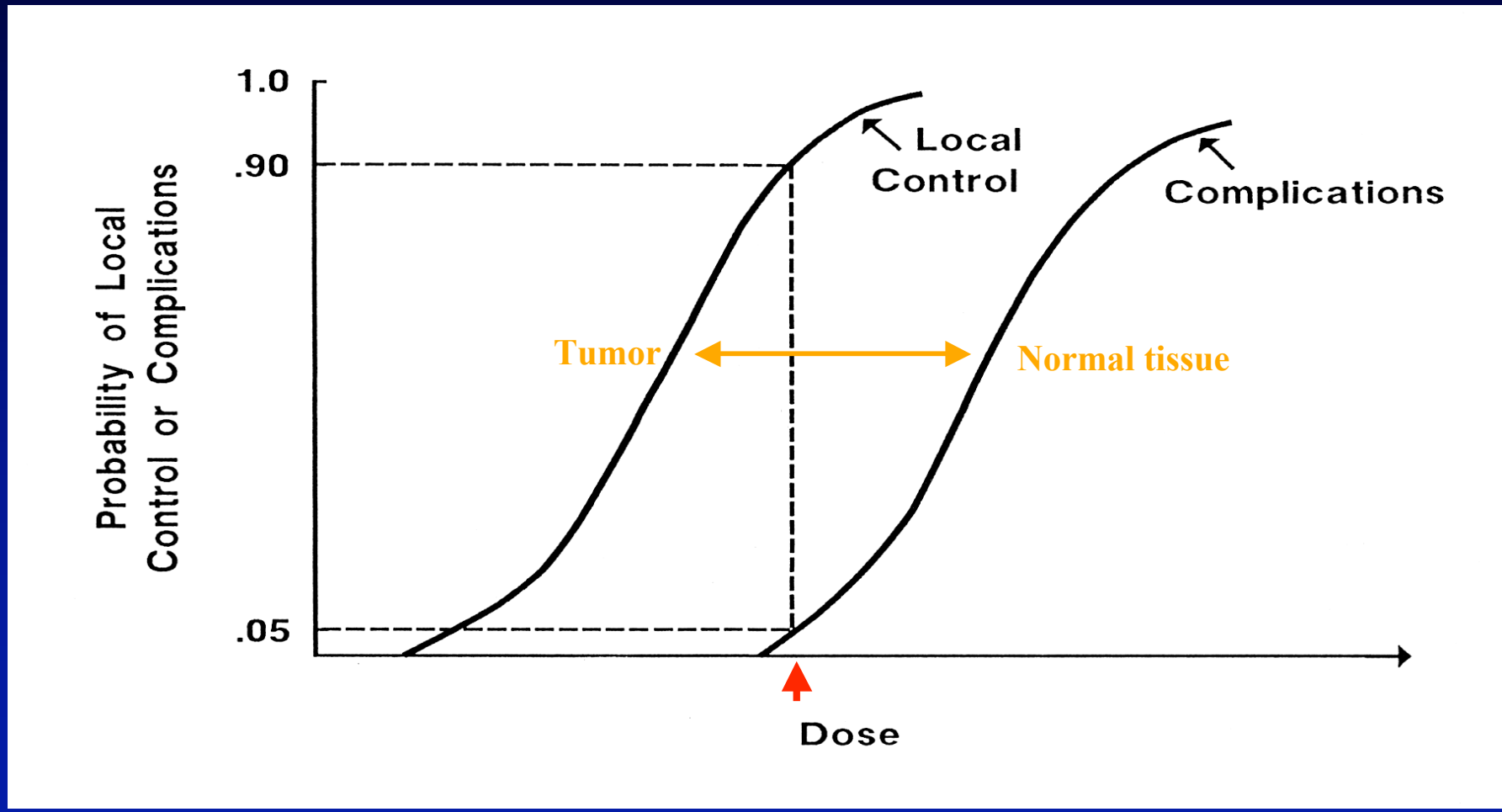
Lung Cancer Basic Factors

- No. 1 cancer killer
- 161,840 patients will die in 2008
  - Higher than prostate, breast, colon/rectum, pancreas cancers combined
- 1 patient dies every 3 min in US
- Overall 5 year survival 15%
- Local control: about <50% with standard photon dose (60 to 66 Gy)

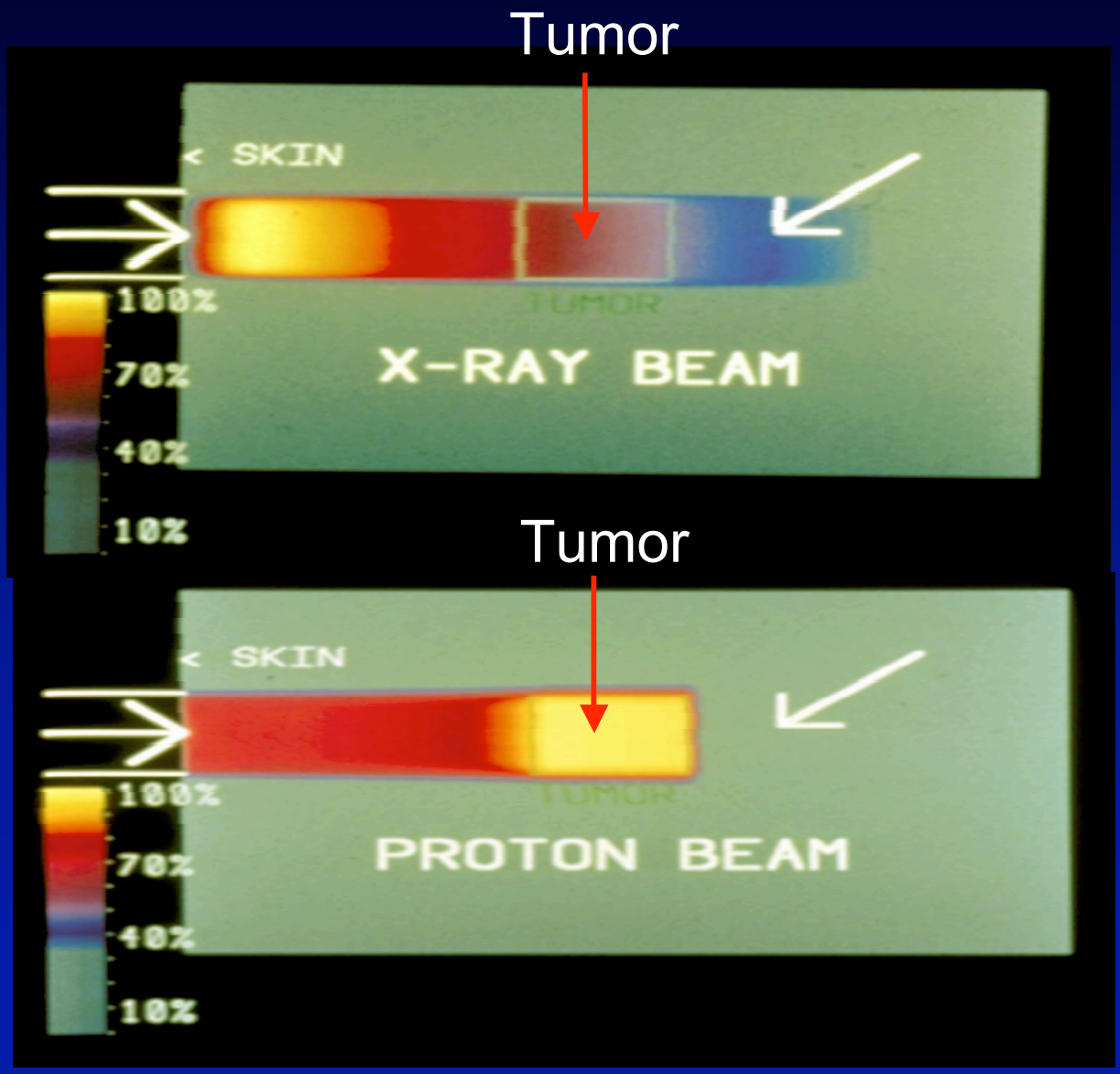
- Changes are needed!

Proton Therapy in lung cancer:

Improves therapeutic ratio
and allows dose escalation/acceleration



Spread Out Bragg Peak (SOBP)

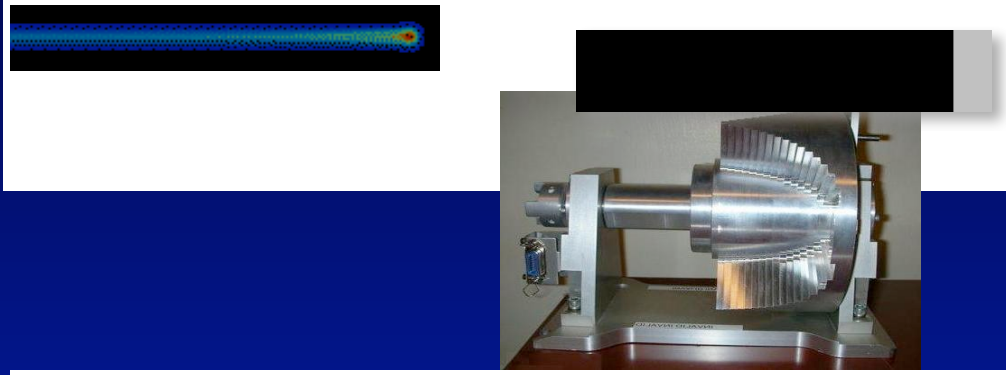


Proton delivery:

1. Passive Scattering Proton Therapy (PSPT)

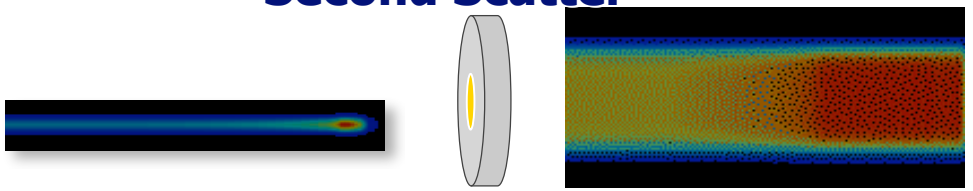
Movie.7

Rotating Modulating Wheel



Movie.8

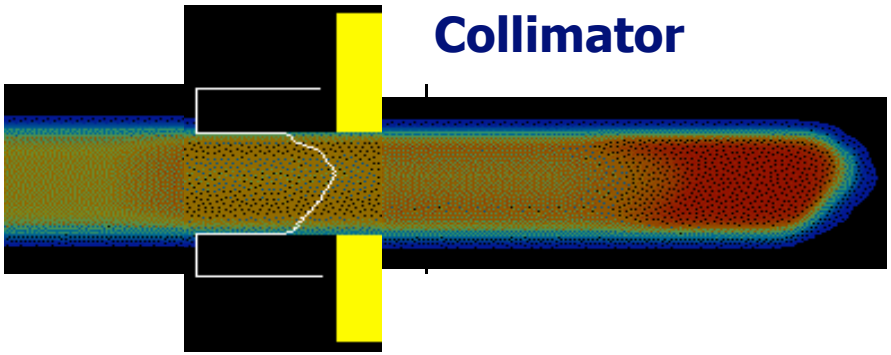
Second Scatter

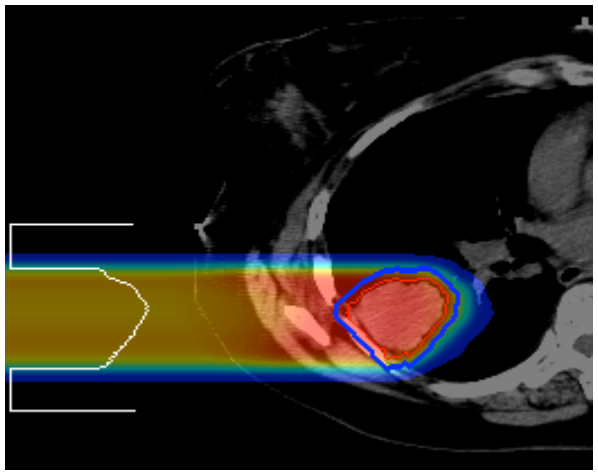


Spread Out Bragg Peak (SOBP)

Compensator

Collimator



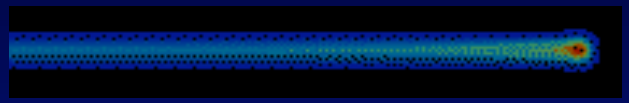


Target

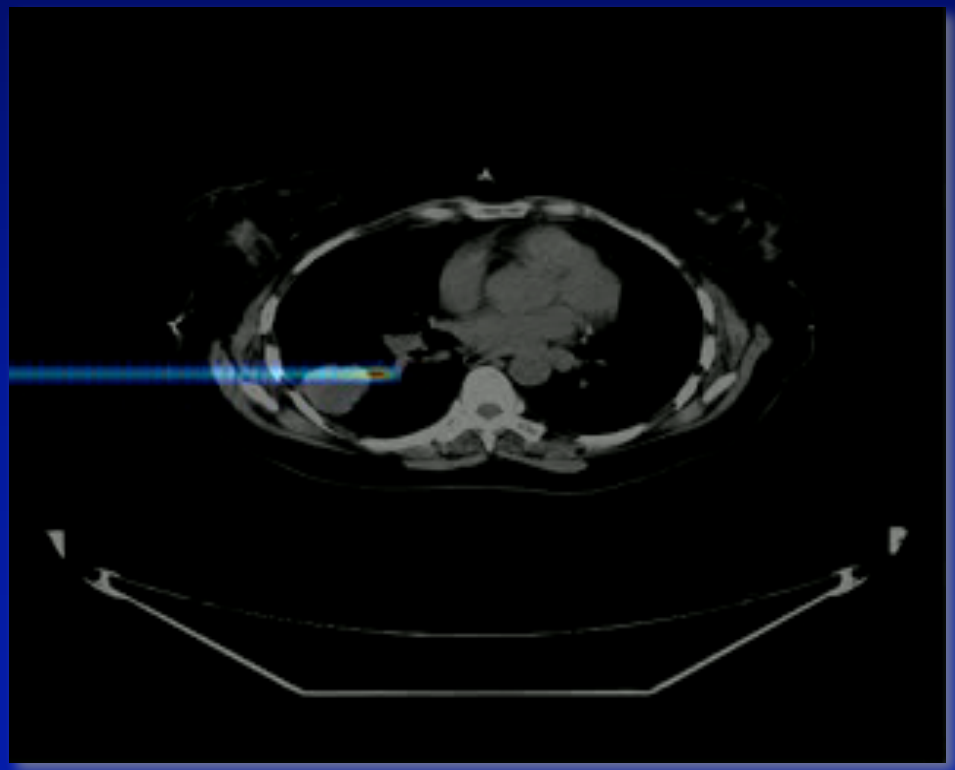
(Yoshikazu Tsunashima)

Proton Delivery:

2. Spot scanning (Intensity-modulated proton therapy, IMPT)

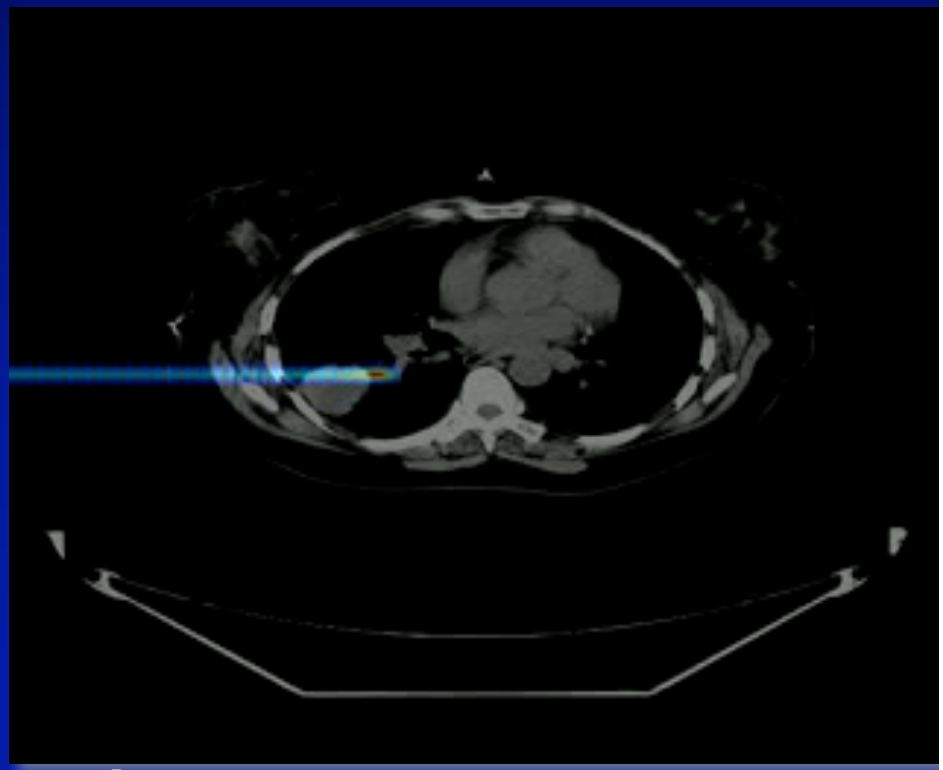


Cumulative dose



Movie.9

Spot position

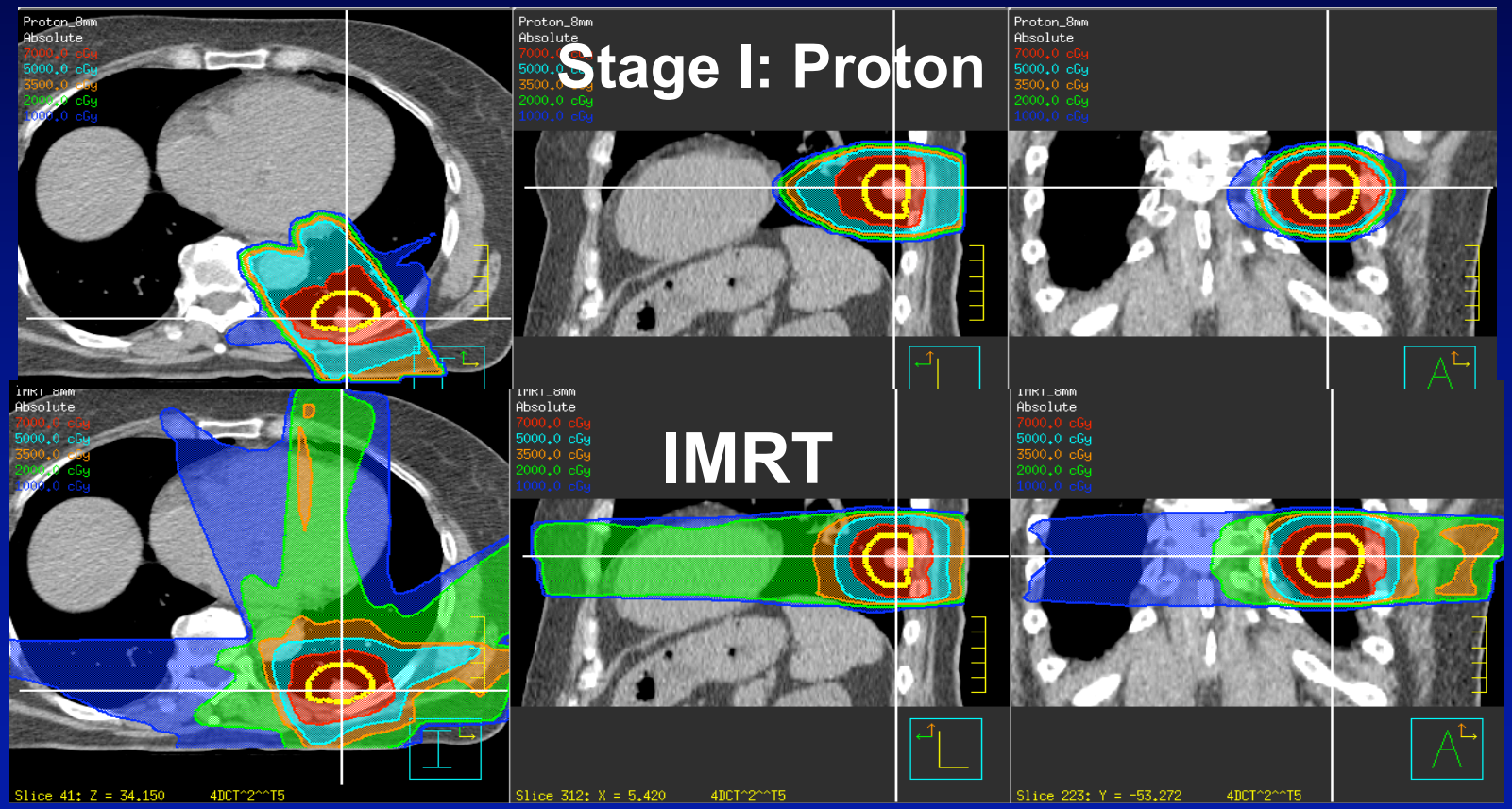


Movie.10

(Yoshikazu Tsunashima)

PSPT:
Reduce normal tissue dose compared with 3-DCRT and IMRT

10-20% absolute improvement in lung V5 and V10
33-61% absolute improvement in non-target integral dose

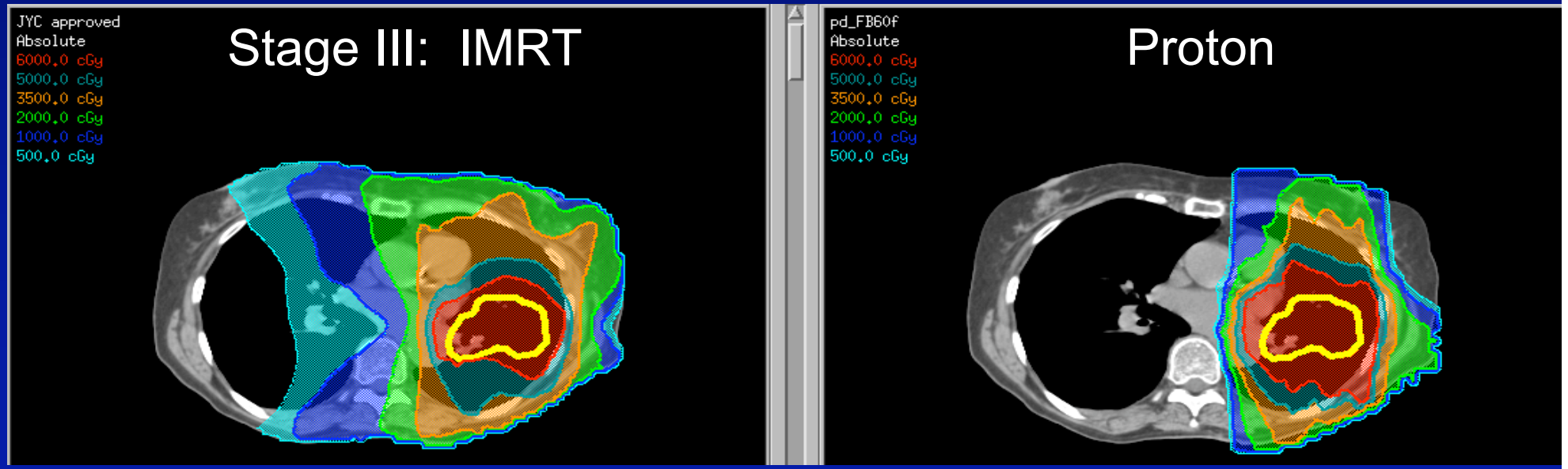


Chang et al: Int J Rad Onc Bio Phys 65:1087-96, 2006

PSPT:
Dose escalation of PSPT in NSCLC:

87.5 CGE in stage I
74 CGE in stage III
DVH showed: spares more normal tissues compared with 3-DCRT or IMRT using 60 Gy

(Chang et al: Int J Rad Onc Bio Phys 65:1087-96, 2006)



IMPT:

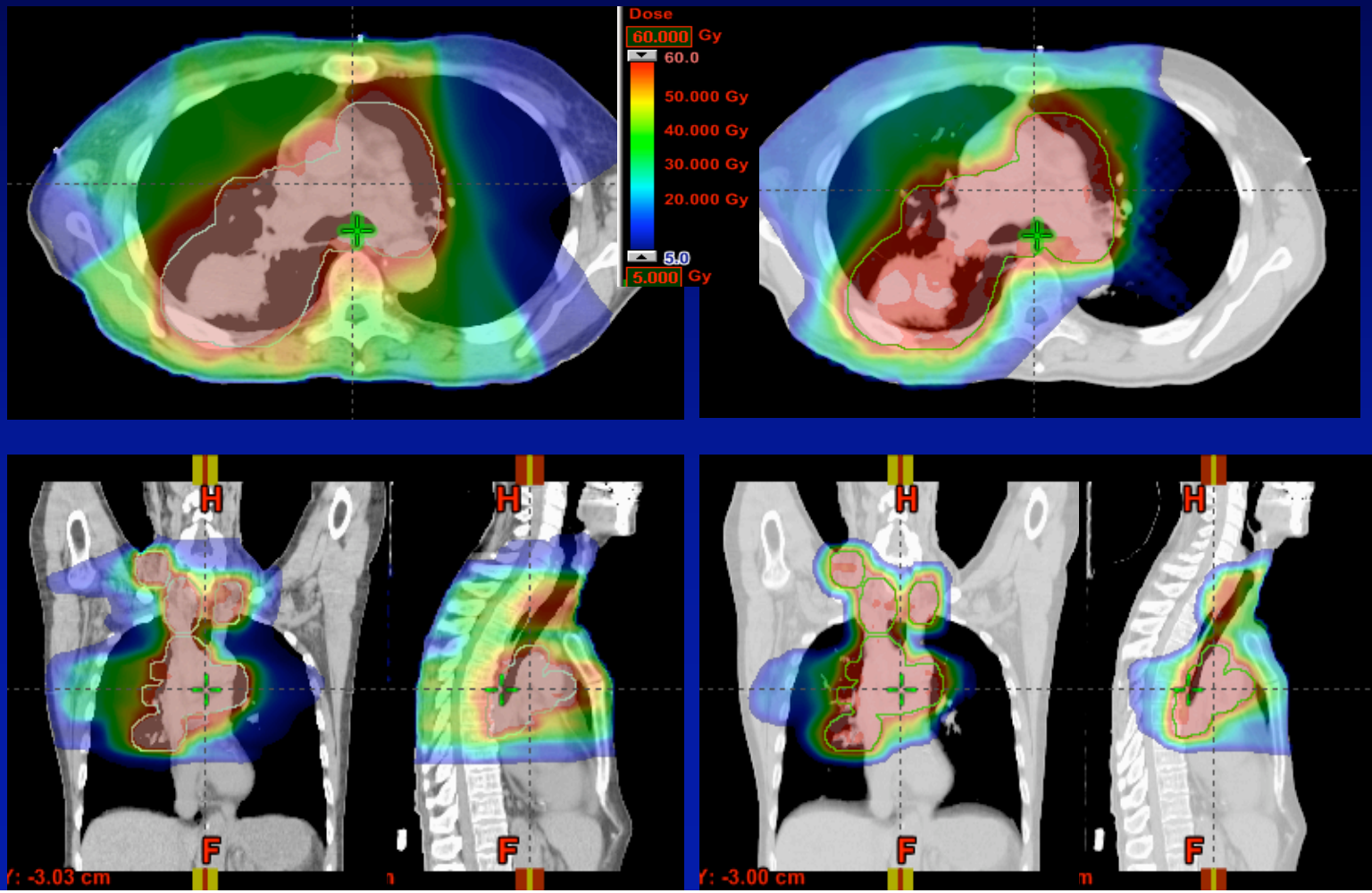
Reduces the normal tissue dose compared with IMRT in stage IIIB NSCLC

13-22% absolute improvement in lung V5 and V10

(Chang et al: PTCOG 47, poster 39)

IMRT

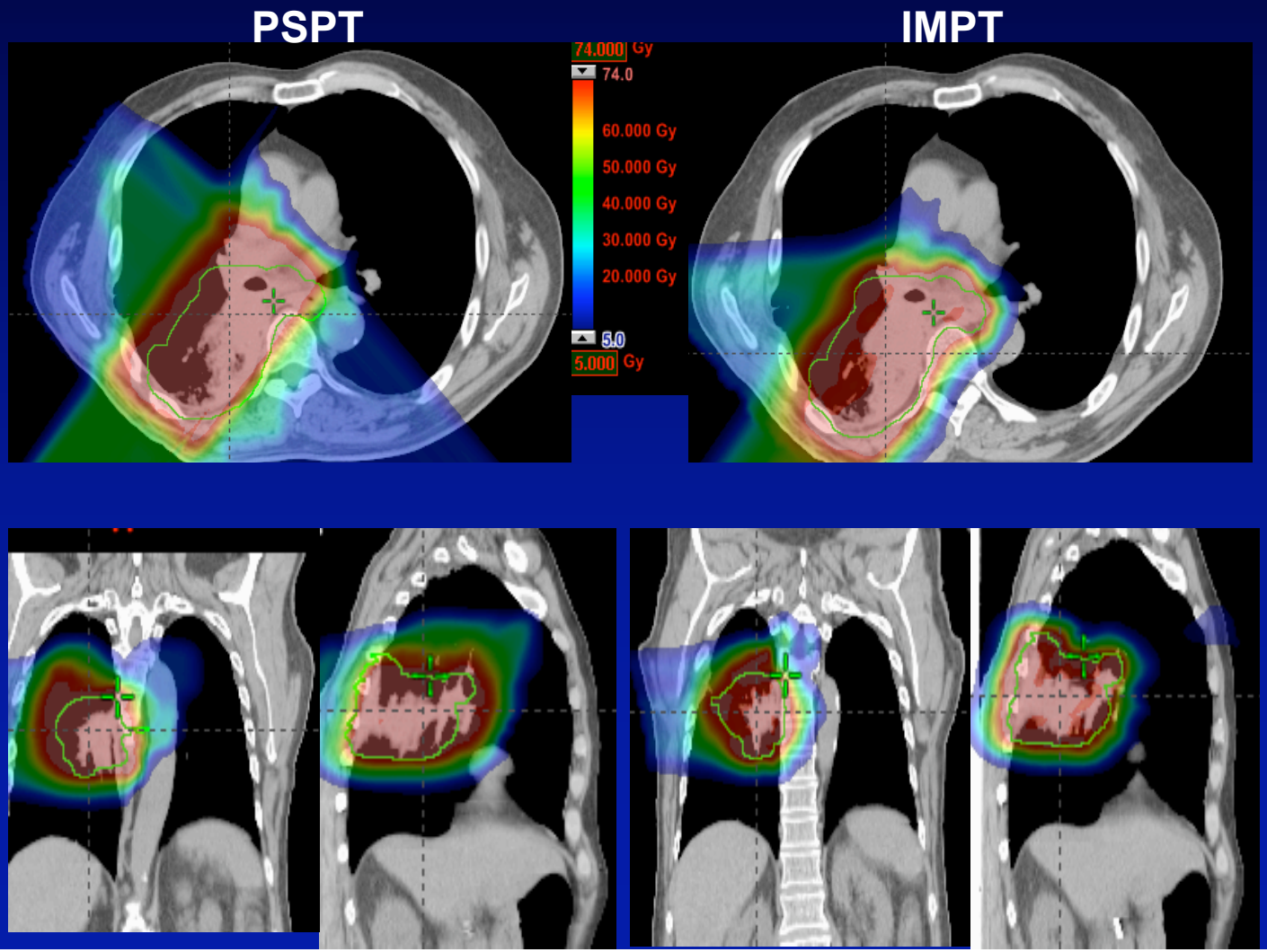
IMPT



IMPT:

Improves normal tissue sparing compared with PSPT and allows further dose escalation

5-10% absolute improvement in lung V5 and V10
(Chang et al: PTCOG 47, poster 39)



Chang et al: JTO 3:177, 2008

T50

T0

ITV

PTV

IGTV:
Path of gross
tumor motion

50%: move 0.5 to 1 cm
10%: move > 1 cm

Lung cancer moves

Proton radiotherapy margins for motion and other uncertainty

Aperture Margin 10 mm alone (50-90% proton penumbra)

Border smoothing margin 10 mm

Smearing margin:

$$Smearing\ m\arg in = \sqrt{(IM + SM)^2 + [0.03 \times (distal\ CTV\ depth + compensator\ thickness)]^2}$$

DM = 0.035 XCTV distal depth + 3 mm

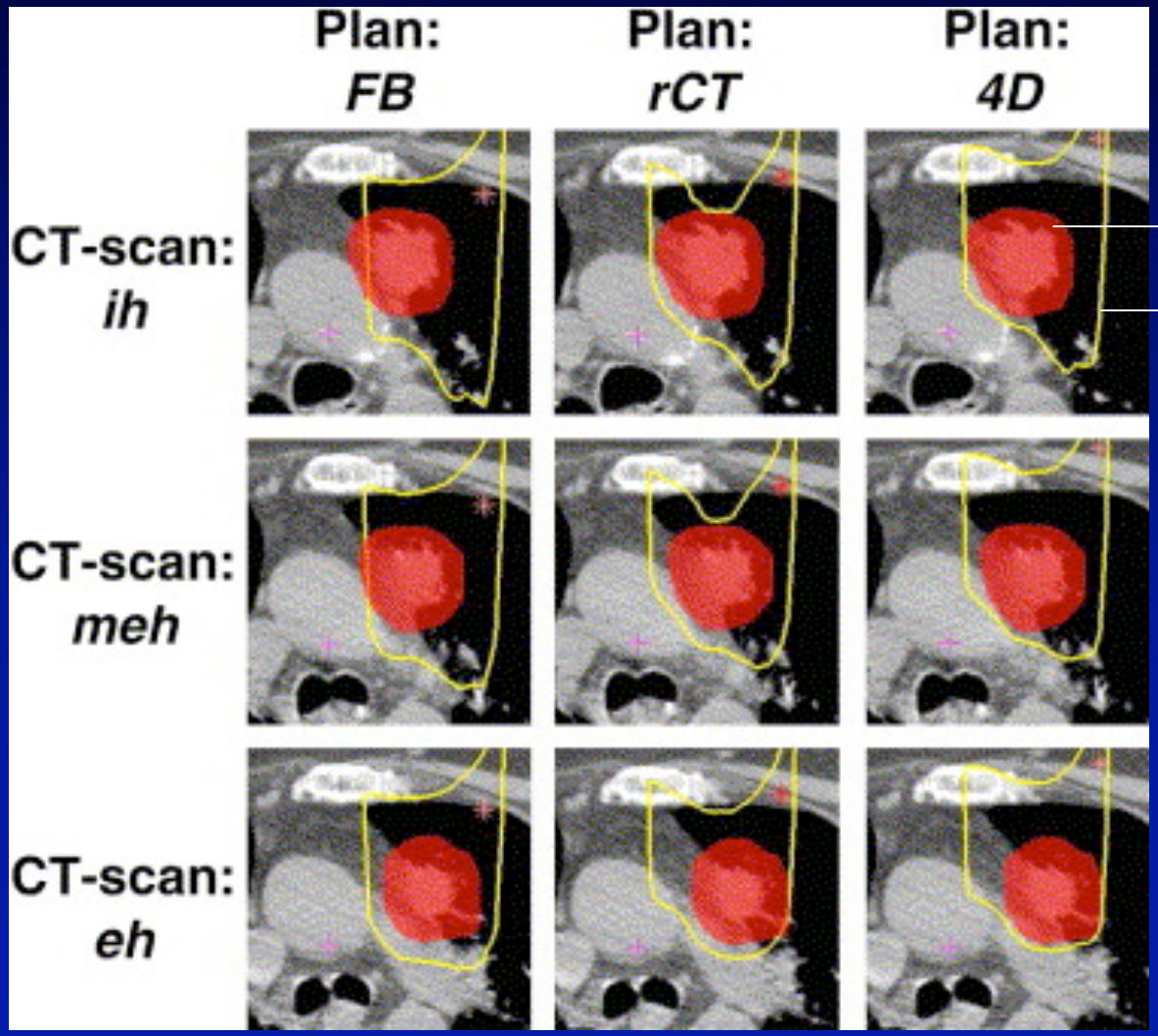
PM = 0.035 X CTV proximal depth + 3 mm

(Moyers et al: Int J Rad Onc Bio Phy 49:1429-38, 2001)

Intra-fraction tumor motion:

4-D CT planning guarantees delivery of prescribed dose and spare more normal tissue

(Engelman et al: Int J Rad Onc Bio Phy 64:1589-95, 2006)



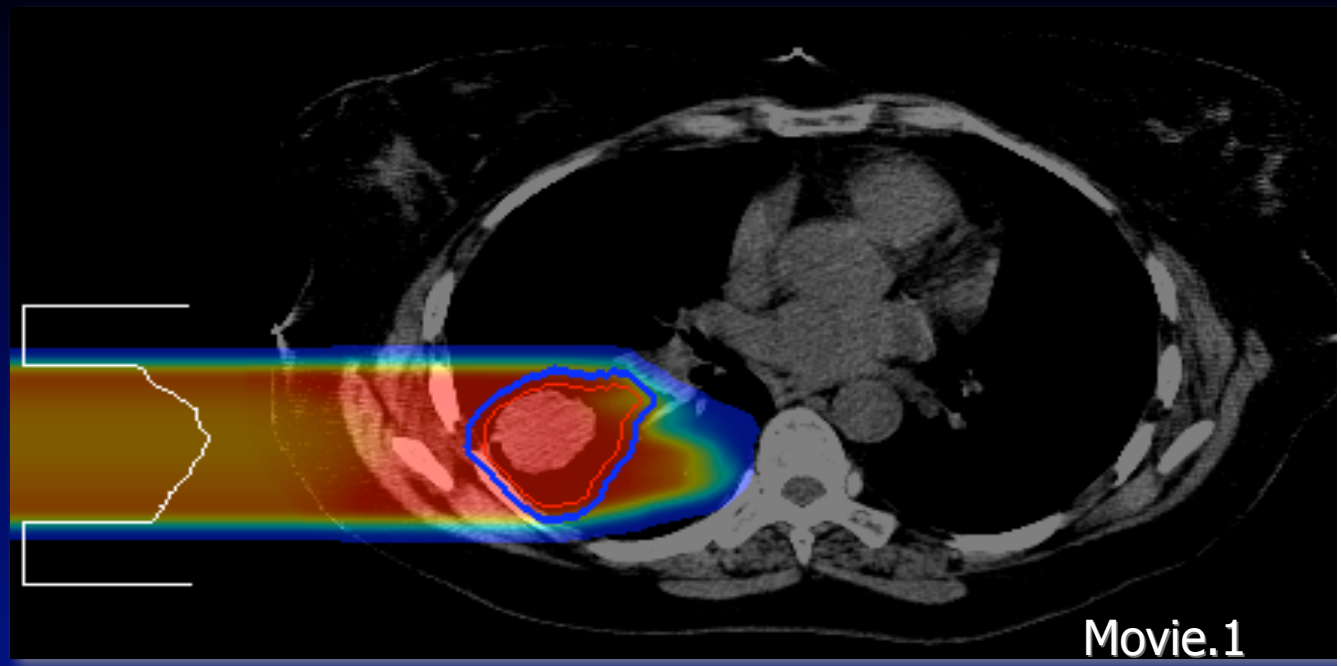
•4D Proton Plans

Non gating

Free breathing

0~10 % phase

GTV from MIP

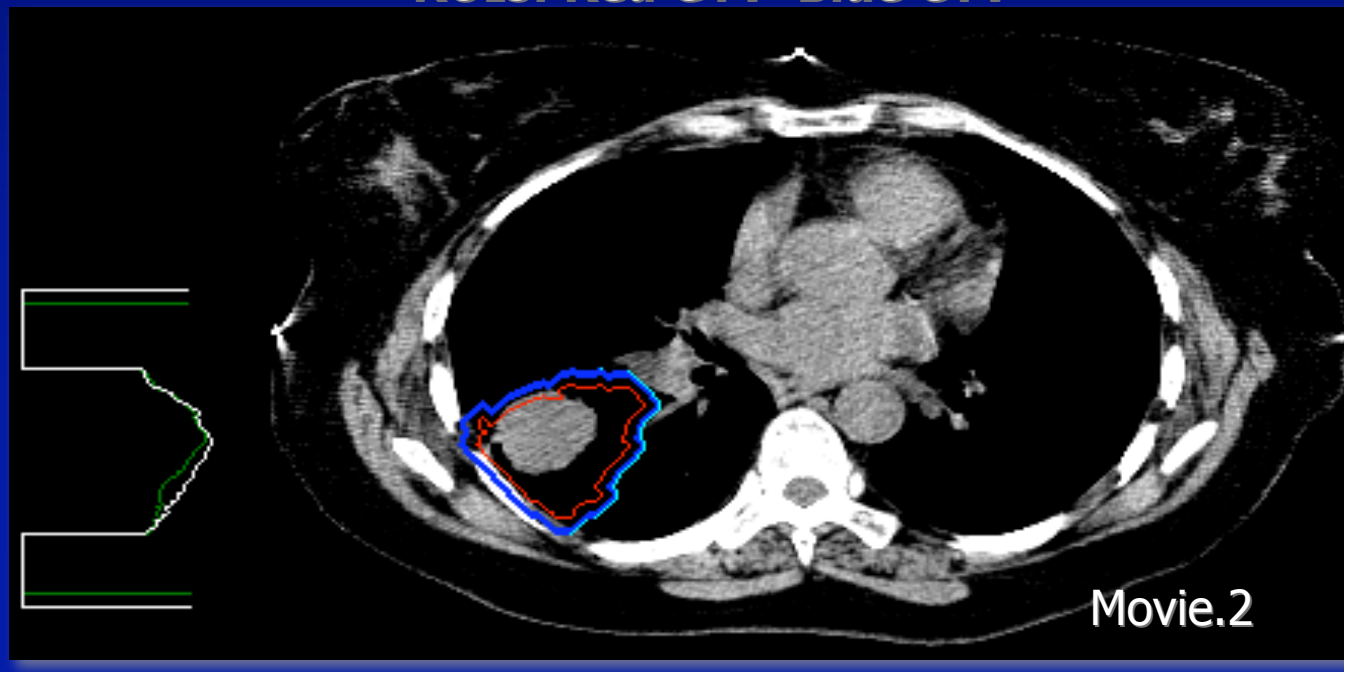


ROIs: Red GTV Blue CTV

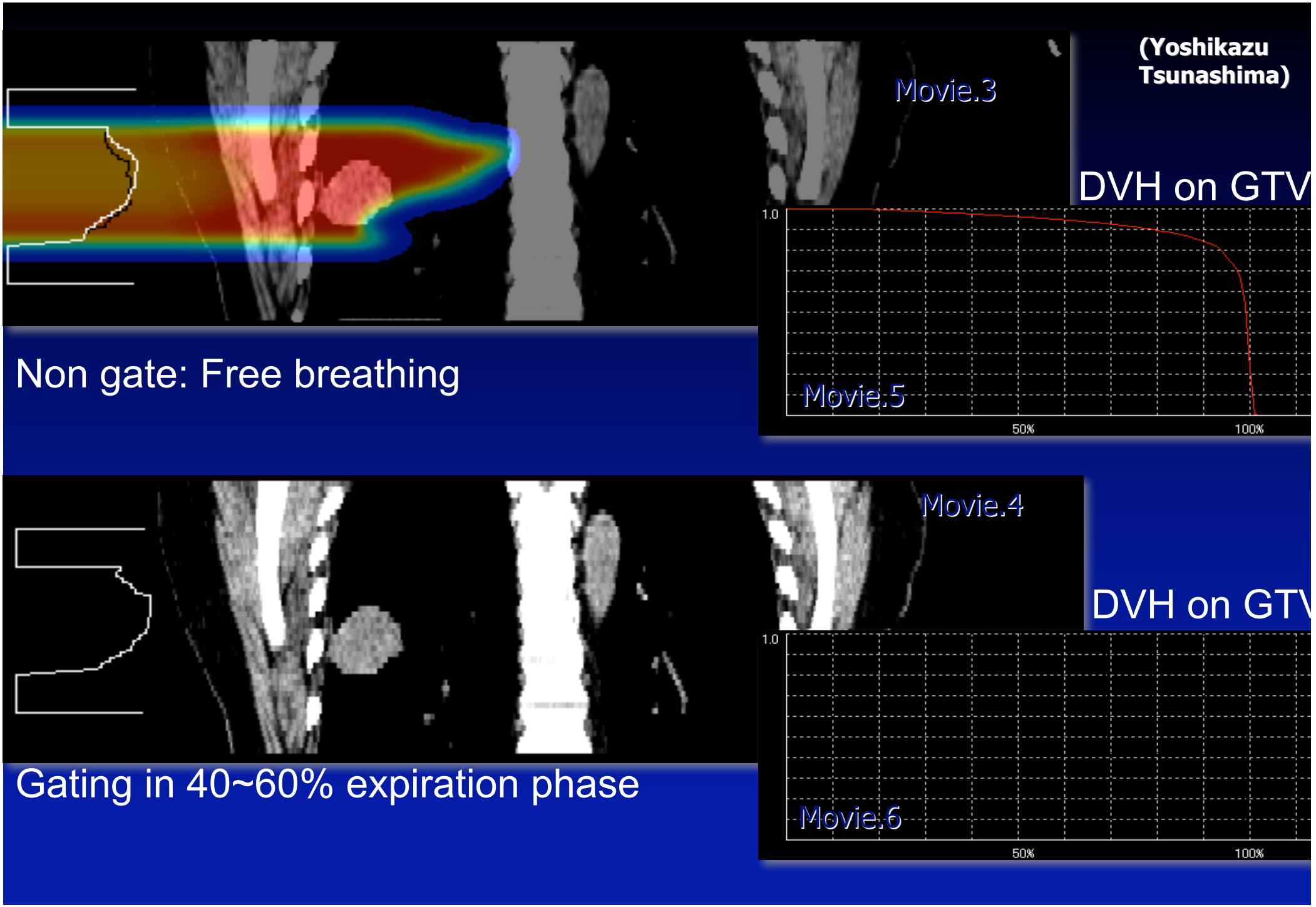
Gating

40~60% expiration phase

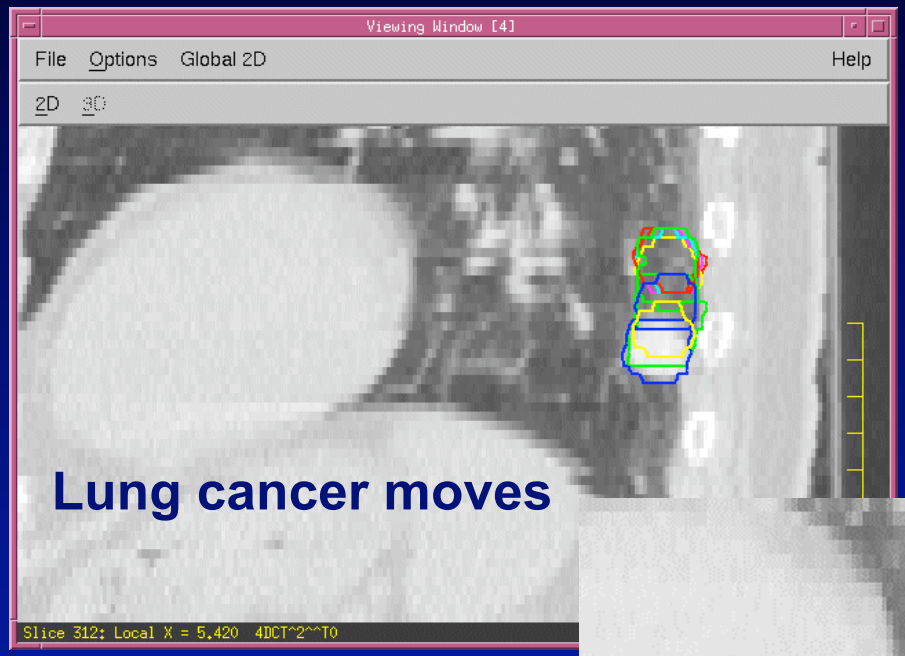
GTV from $MIP_{40\text{-}60}$



(Yoshikazu Tsunashima)

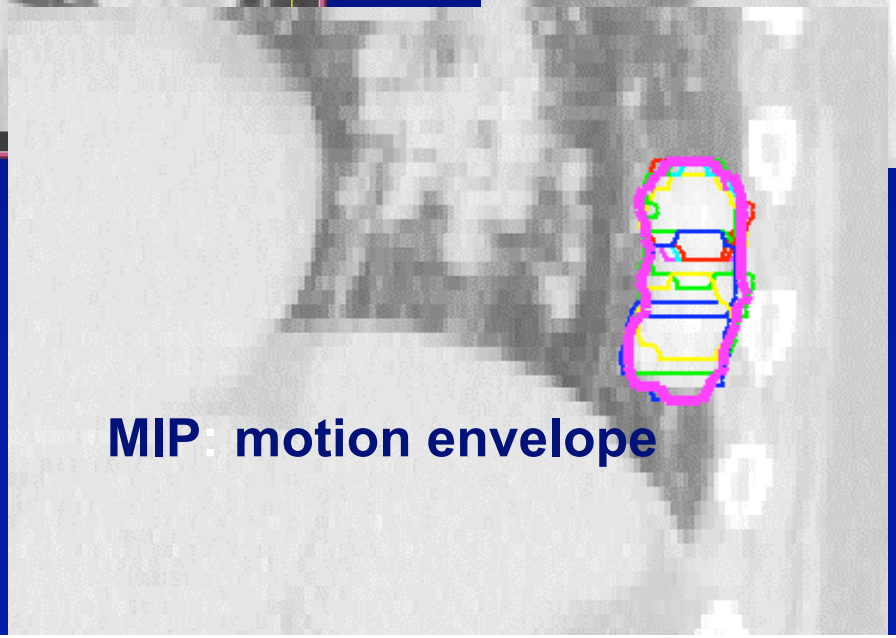

(Yoshikazu Tsunashima)
Movie.3
DVH on GTV
1.0
Movie.5
50%
100%
Non gate: Free breathing
Movie.4
DVH on GTV
1.0
Movie.6
50%
100%
Gating in 40~60% expiration phase

4-D CT-based simulation: individualized ITV approach



Lung cancer moves

"Average" CT

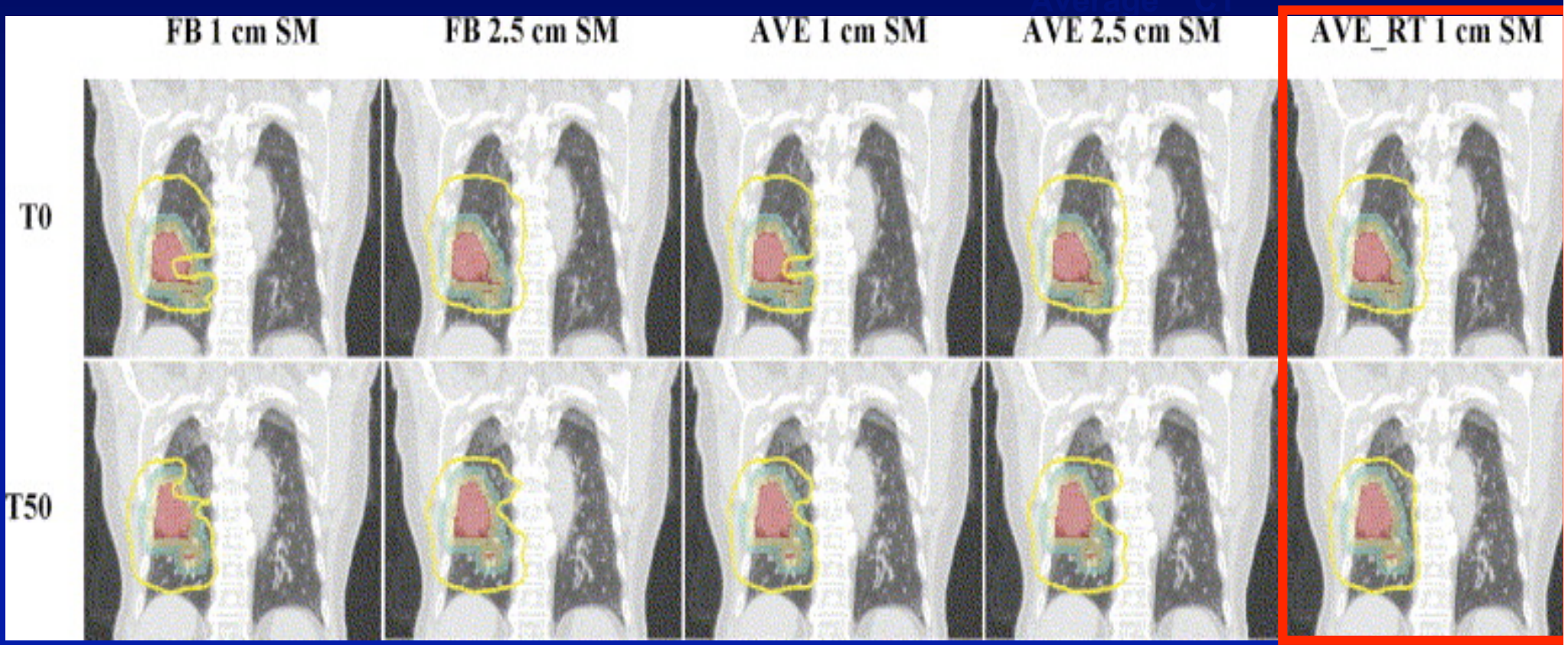


MIP: motion envelope

4-D CT-based proton planning: ITV approach

(Kang, et al: Int. J. Rad. Oncol. Bio. Phys. 67:906, 2007)

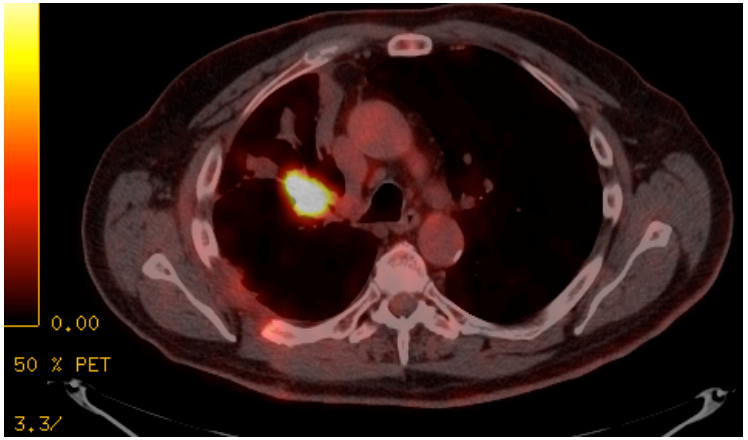
MIP density replaces IGTV in average CT data base for compensator design and dose calculation achieved the best overall target coverage and critical structure sparing



4-D CT-based ITV approach proton treatment planning

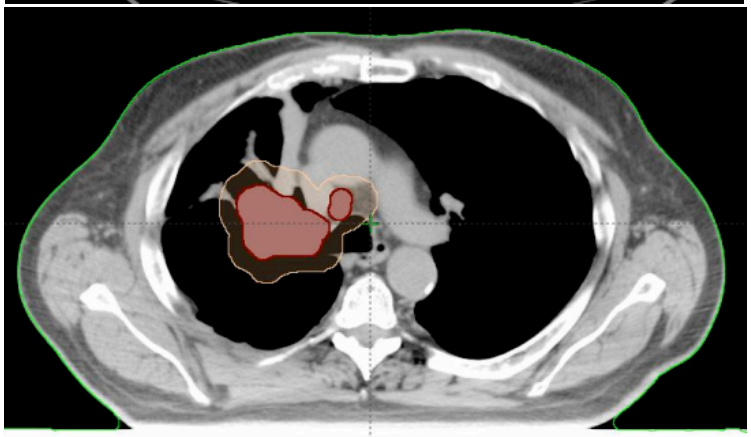
A.

PET



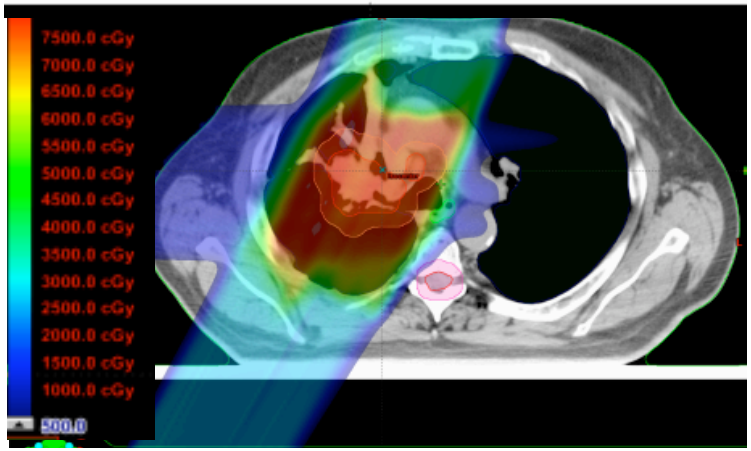
B.

MIP density replaces IGTV in average CT data set



C.

Isodose distribution in average CT



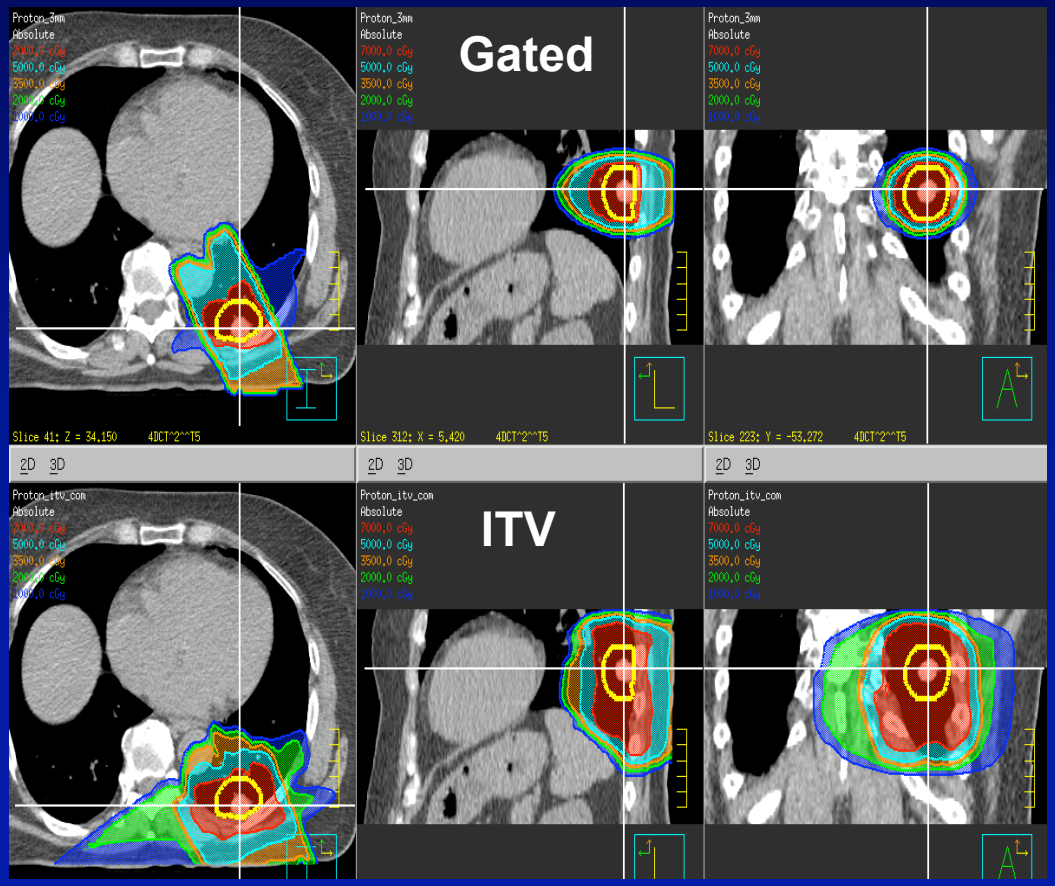
Chang et al: IGRT in lung cancer 2007

Respiratory gated proton therapy

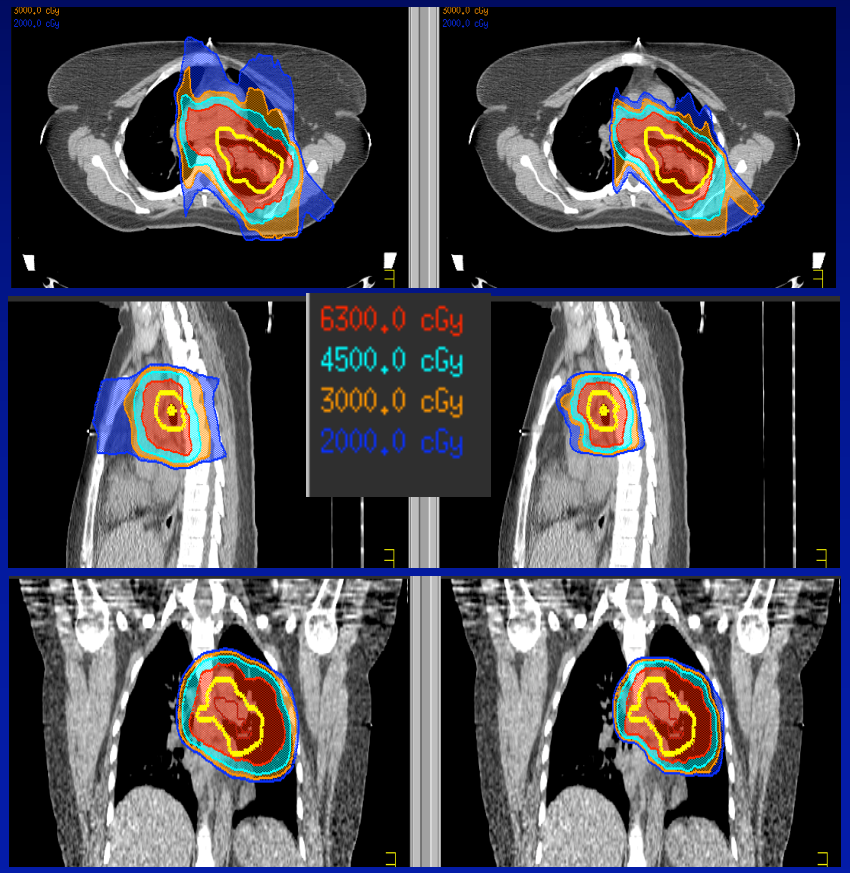
(Chang et al, PTCOG 2006)

6% absolute improvement in lung V5, V10 and V20

Stage I NSCLC

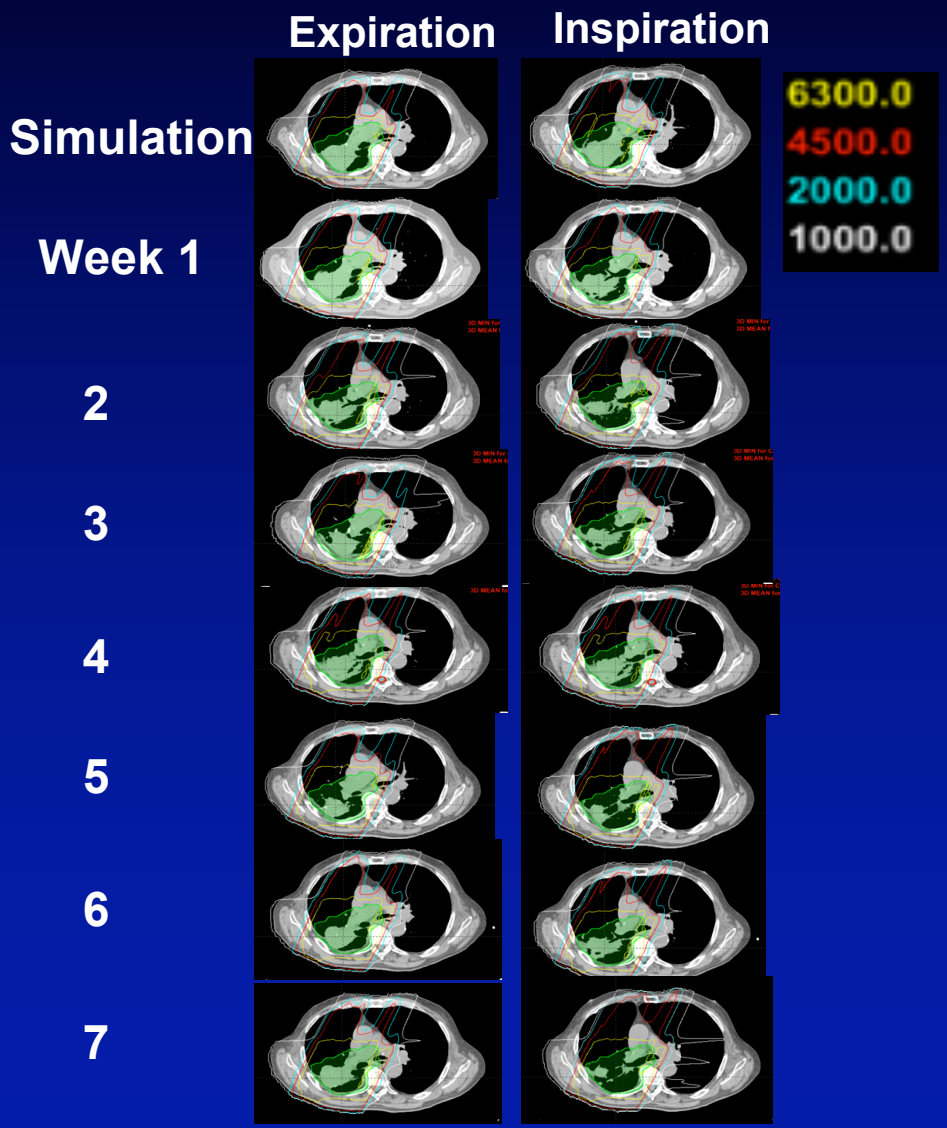


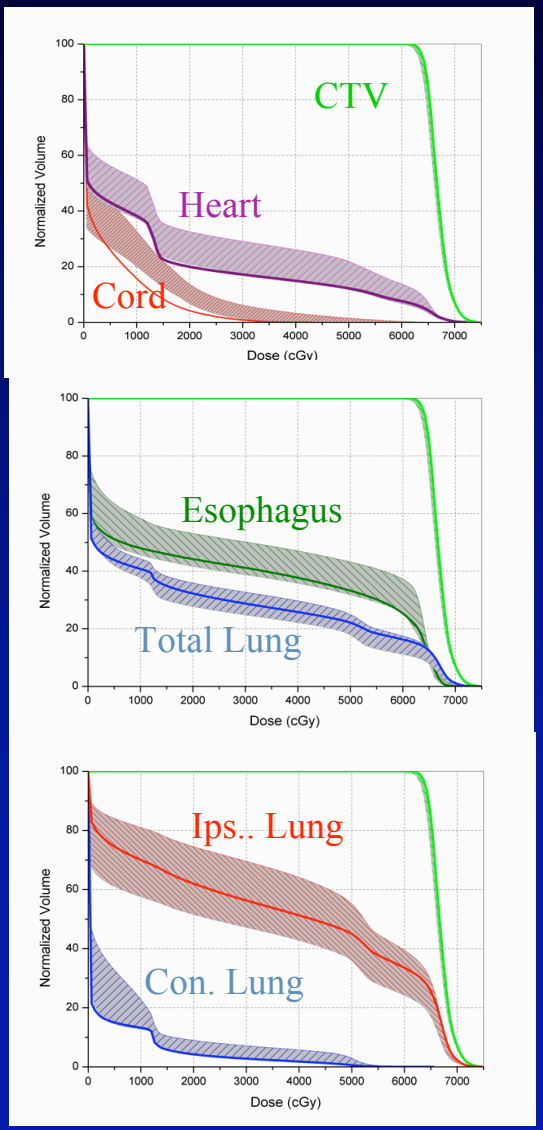
Stage III NSCLC



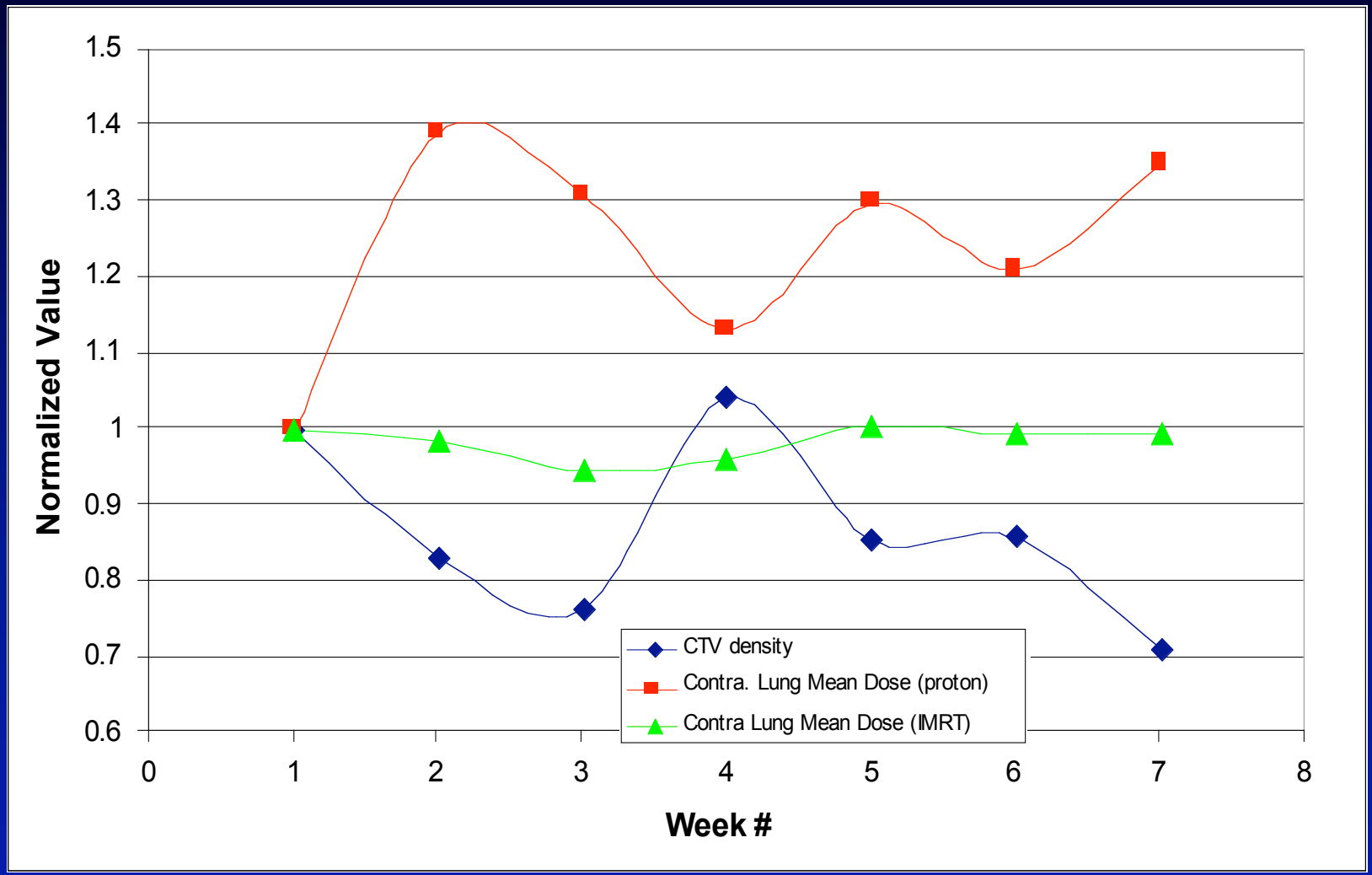
Inter-fraction tumor motion and anatomy changes: A typical case

(Hui et al: Int J Rad Onc Biol Phy. 2008 in press)





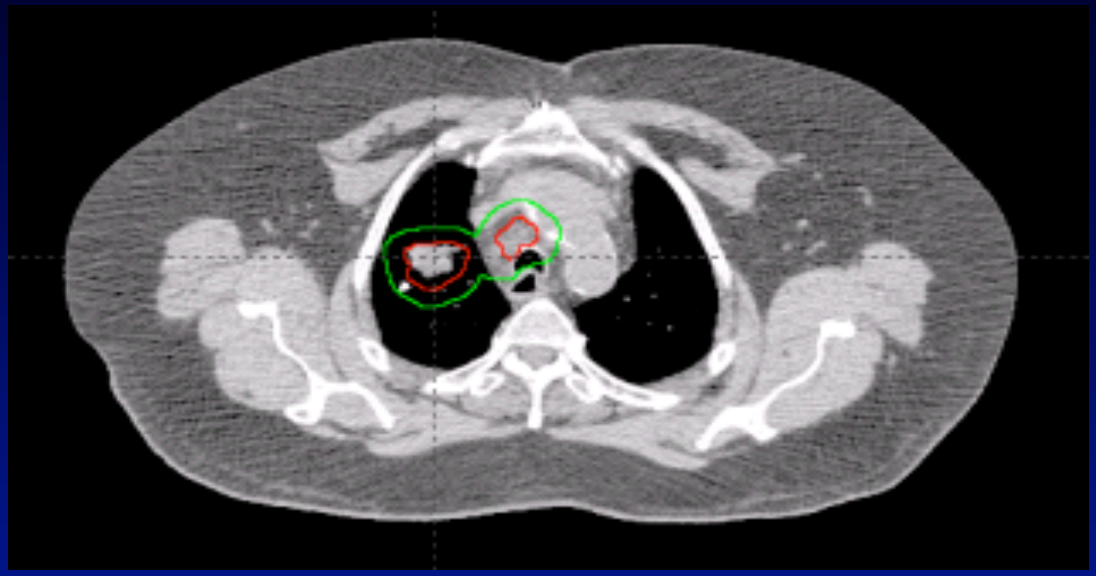
CTV density change correlated with increased contra-lateral lung mean dose over 7 weeks of RT in proton but not IMRT



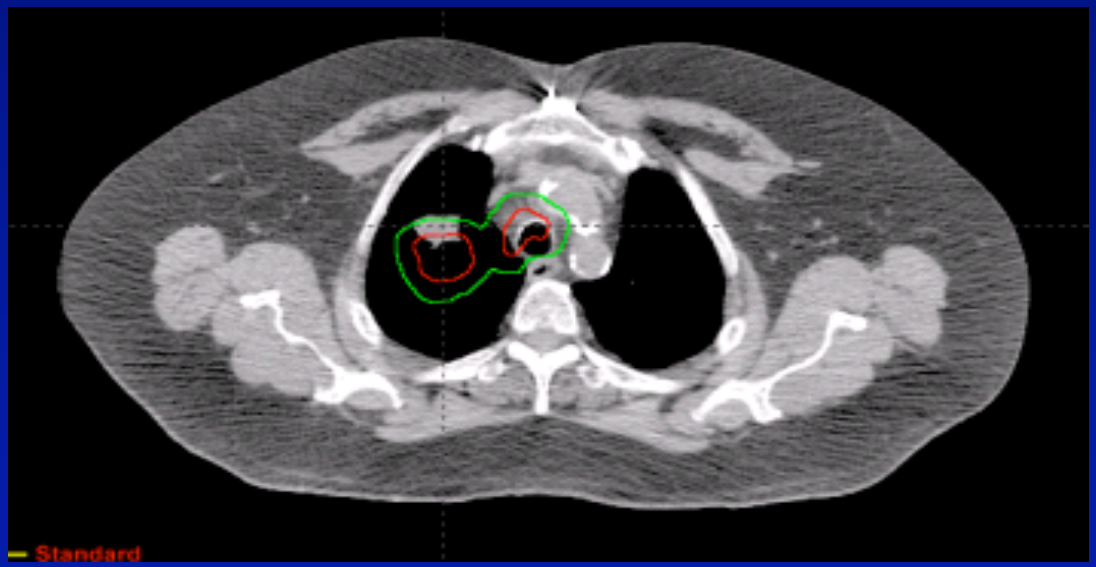
(Hui et al: Int J Rad Onc Biol Phy. 2008 in press)

Inter-fraction anatomy/motion change
A extreme case

Week 1

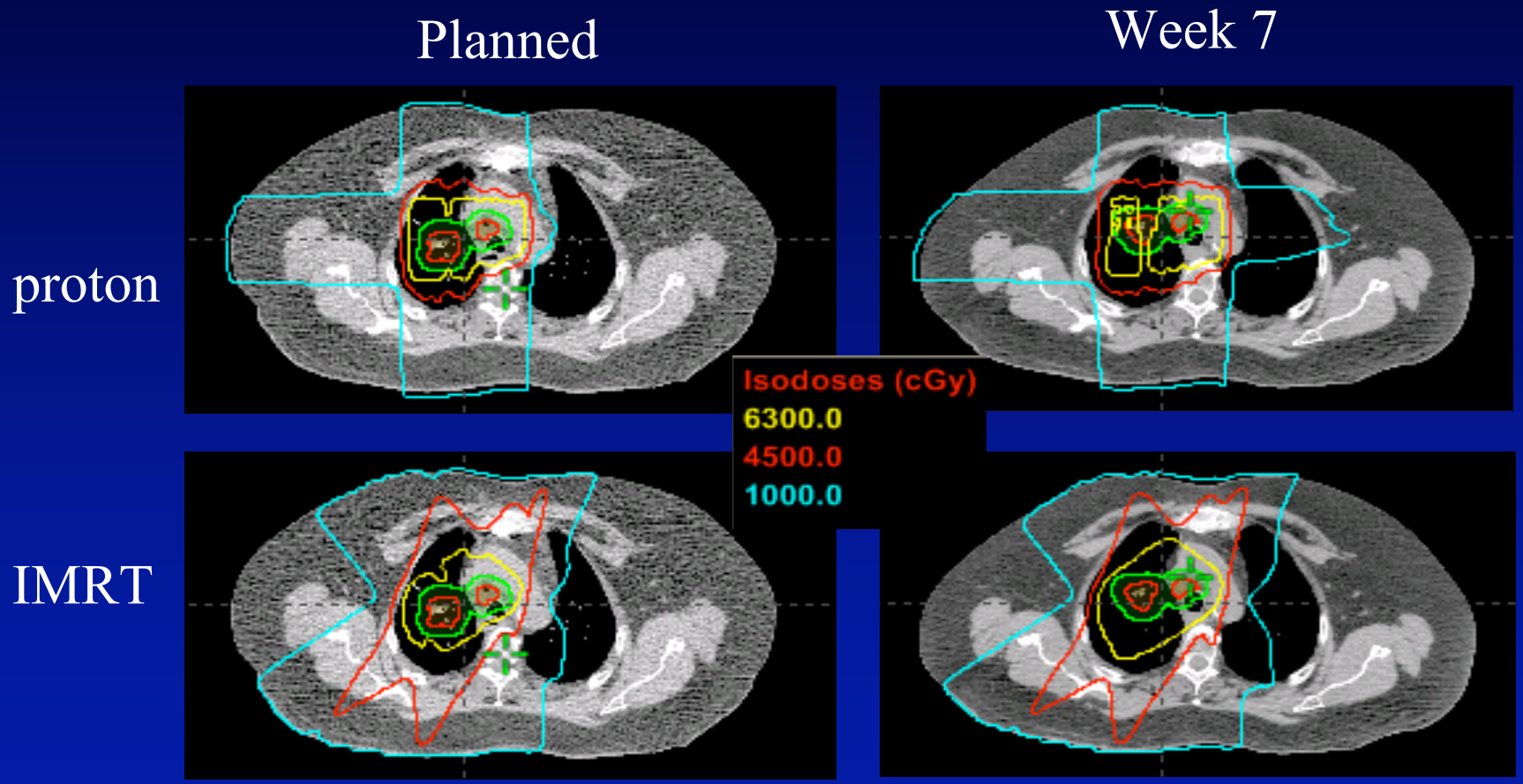


Week 7



(Hui et al: Int J Rad Onc Biol Phy. 2008 in press)

CTV coverage drops from 99% to 92.3% with proton but not in IMRT

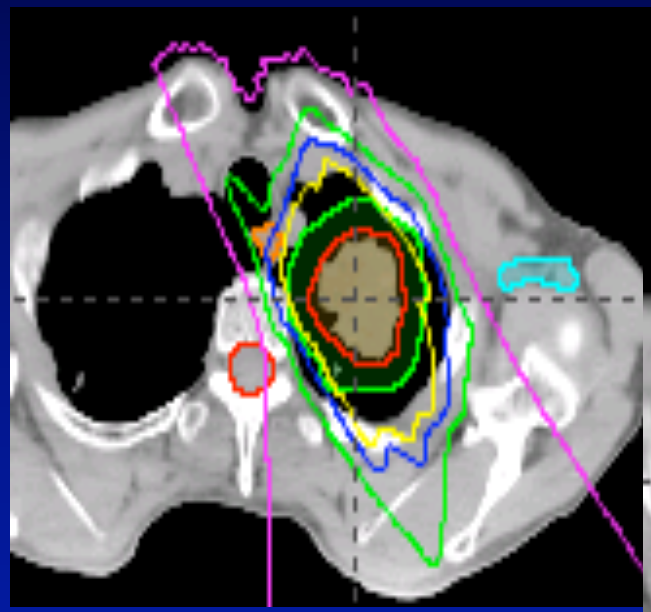


(Hui et al: Int J Rad Onc Biol Phy. 2008 in press)

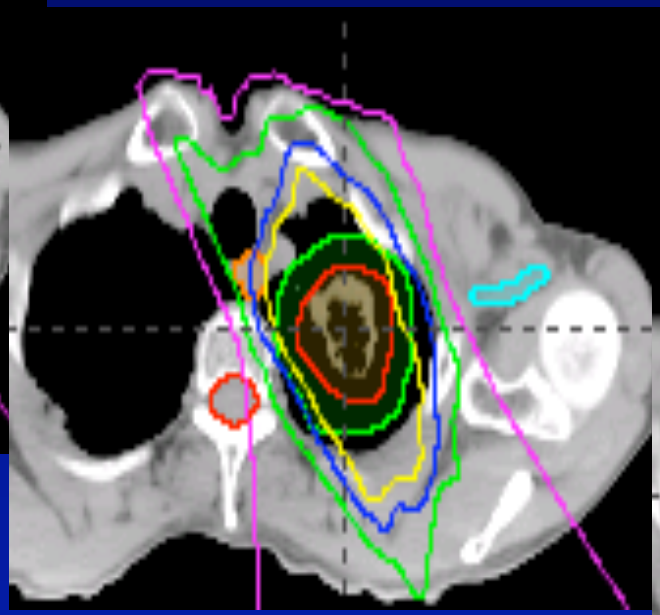
Adapted proton therapy

87.5 CGE in T2N0M0 NSCLC

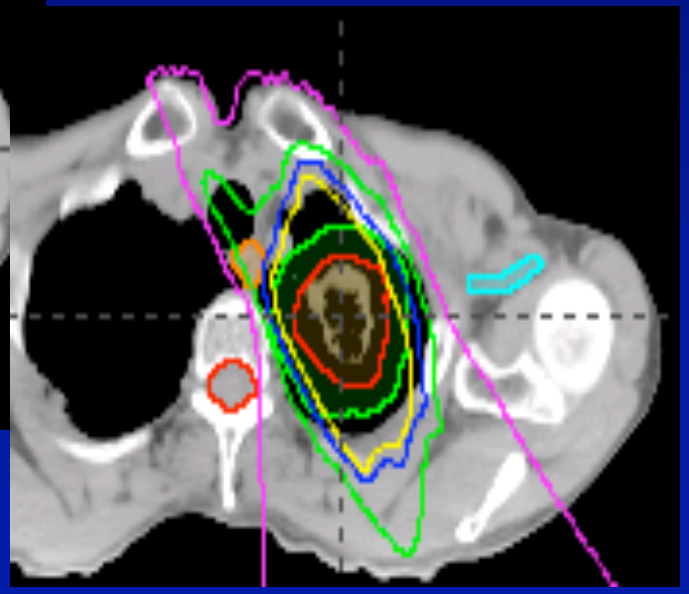
Initial plan



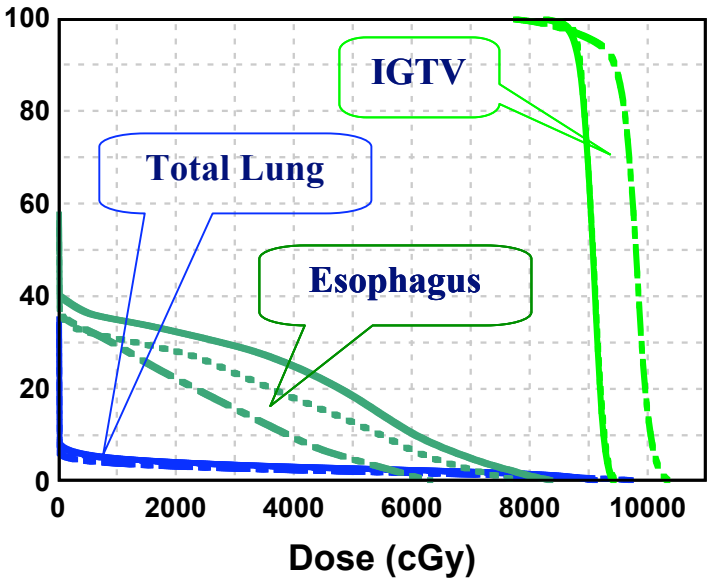
Initial plan recalculated based on CT after 5 wks TX

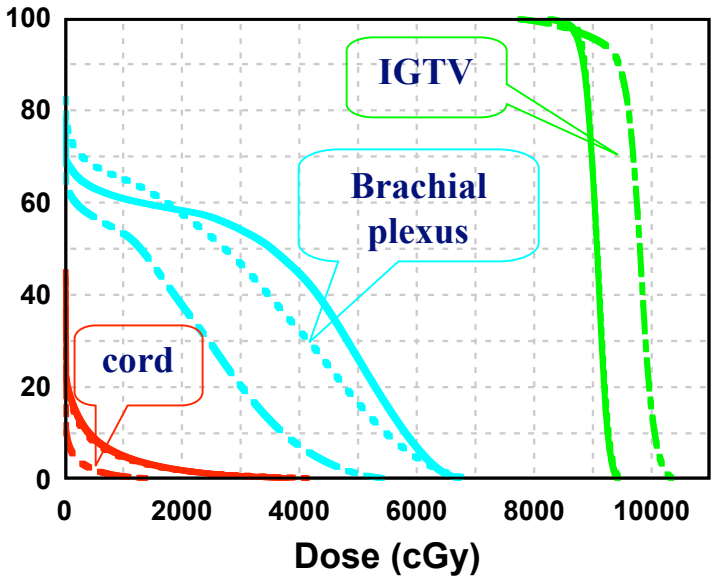


Re-plan based on CT after 5 wks TX



Adapted proton therapy





Dashed line: Initial plan

Solid line: Initial plan recalculated based on CT taken after 5-weeks of proton therapy

Dot-dashed line: re-plan

Adapted proton radiotherap

A.

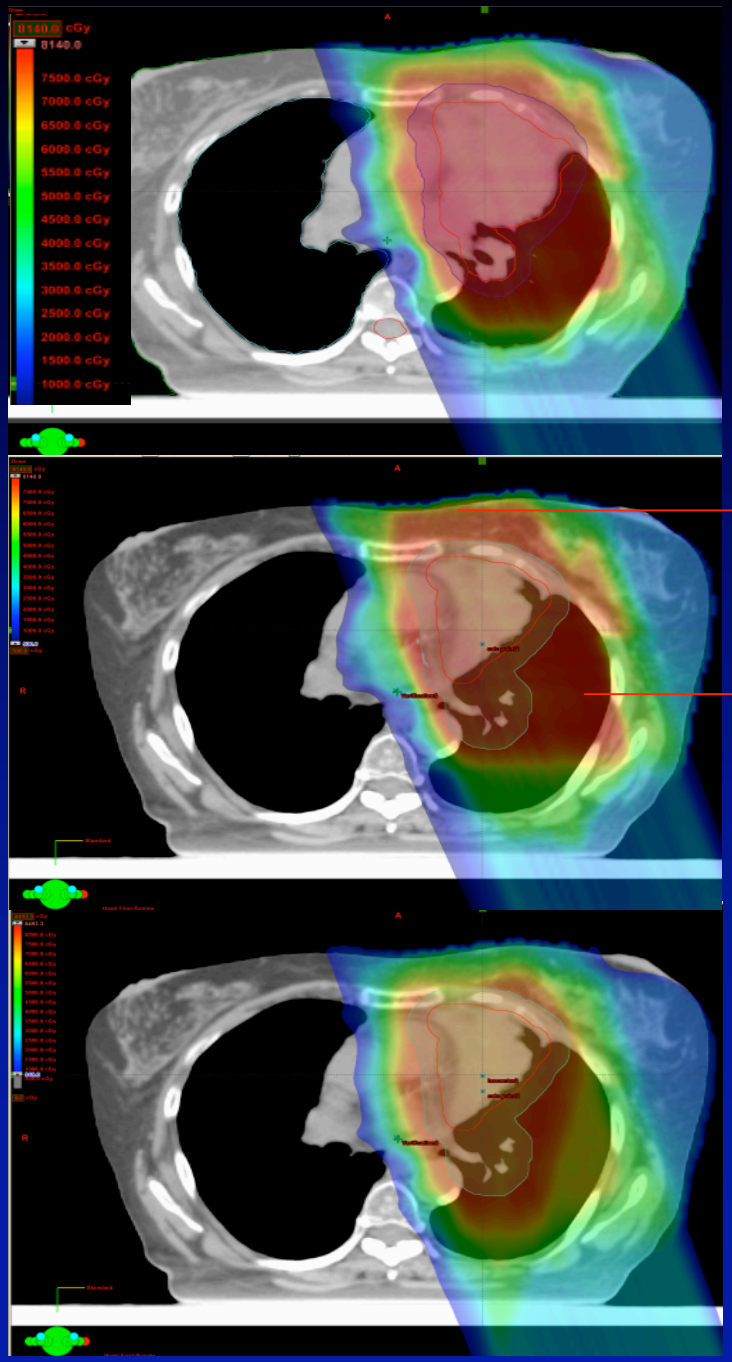
Simulation

B.

3 weeks later

C.

Adapted plan



74 CGE with Carb/Taxol in Stage III NSCLC

Chang et al: IGRT in lung cancer 2007

Proton therapy clinical studies in NSCLC

(Bush 1999, 2004, Shioyama 2003, Nihei 2006, Hata 2007)

Total of 5 published series (n=215), mainly stage I NSCLC. No concurrent chemo

1. Dose: range 45 to 94 CGE in 7 to 32 Fx

2. Issues:
   - Wide range of disease stage
   - Tumor motion: no 4-D CT
   - Wide range of dose and fractionation
   - Dose may not be adequate in some studies

3. Toxicities appear reduced.
   Data in stage Ia with BED > 100 CGE comparable to surgery

Ongoing Proton clinical protocols for NSCLC in MDACC

1. Phase II escalated/accelerated proton radiotherapy for medically inoperable centrally located T1N0M0 or any location of T2N0M0 and selective T3N0M0 (chest all) (stage I-II) NSCLC

87.5 CGE with 2.5 CGE/F
15/23 pts enrolled.

Dermatitis: grade III: 15%
Pneumonitis Grade II: 6.7%, no grade III
No esophagitis

2. Phase II concurrent proton and chemotherapy in inoperable stage III NSCLC

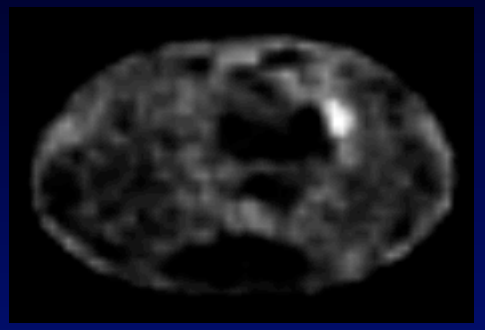
74 CGE with 2 CGE/F
32/56 pts enrolled:

Acute esophagitis: grade II: 25%, grade III: 6%
Dermatitis: grade III: 9%
Pneumonitis Grade II: 19%, no grade III

Proton therapy (87.5 CGE) in central stage I NSCLC

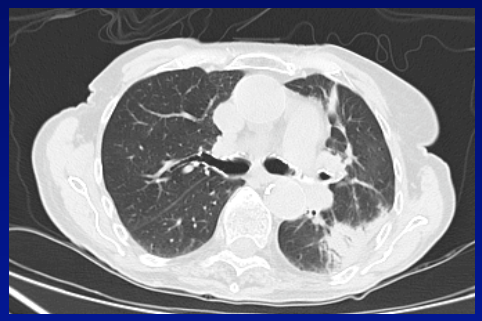
A.

B.

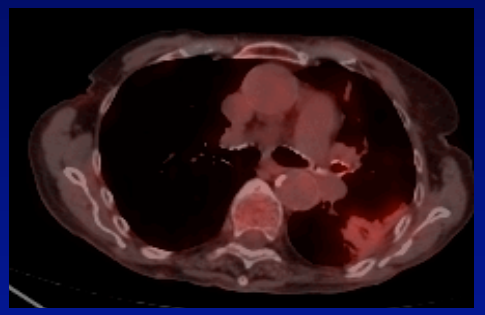


Before Proton

C.

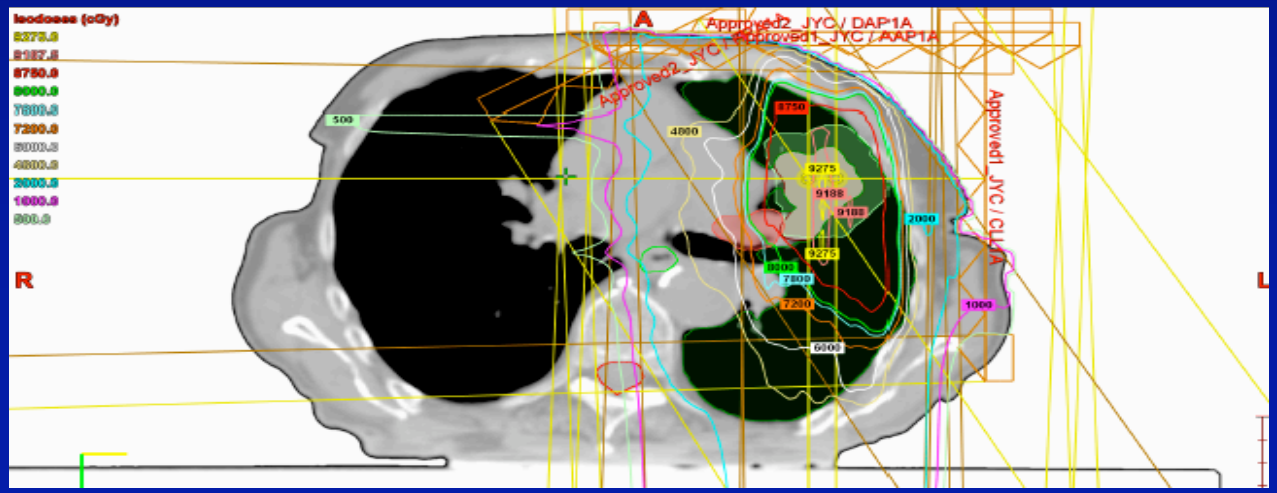


D.



After Proton

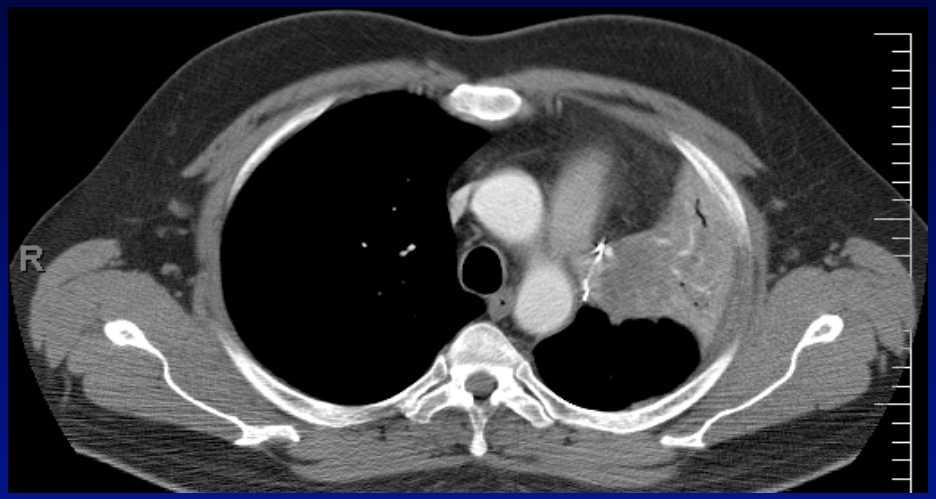
E.

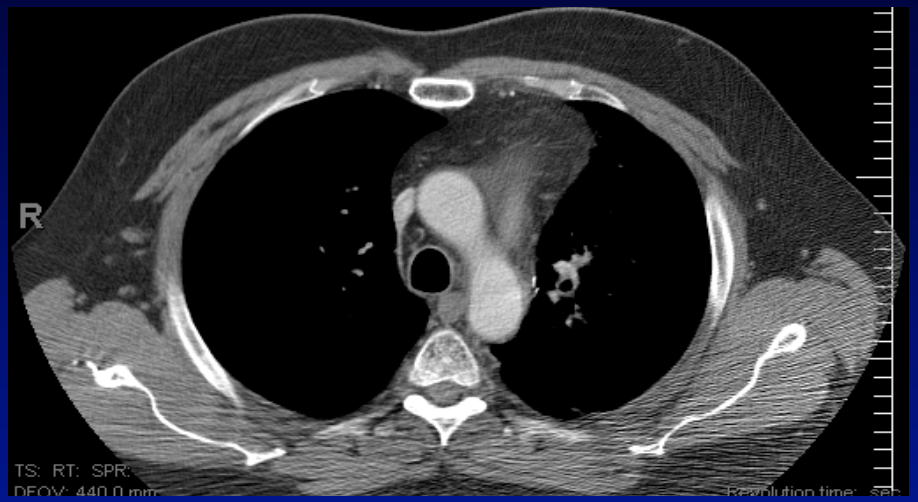


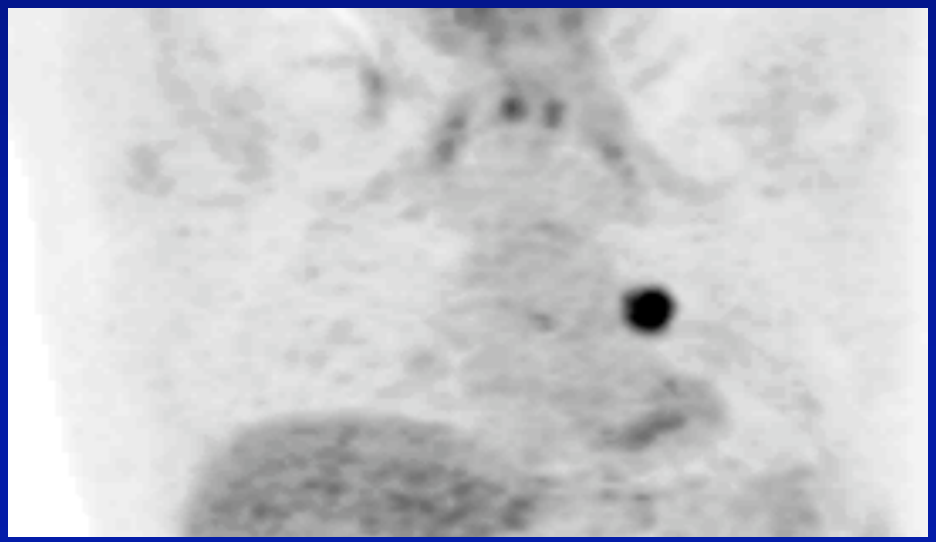
Stage IIIA NSCLC treated with 74 CGE proton and chemotherapy

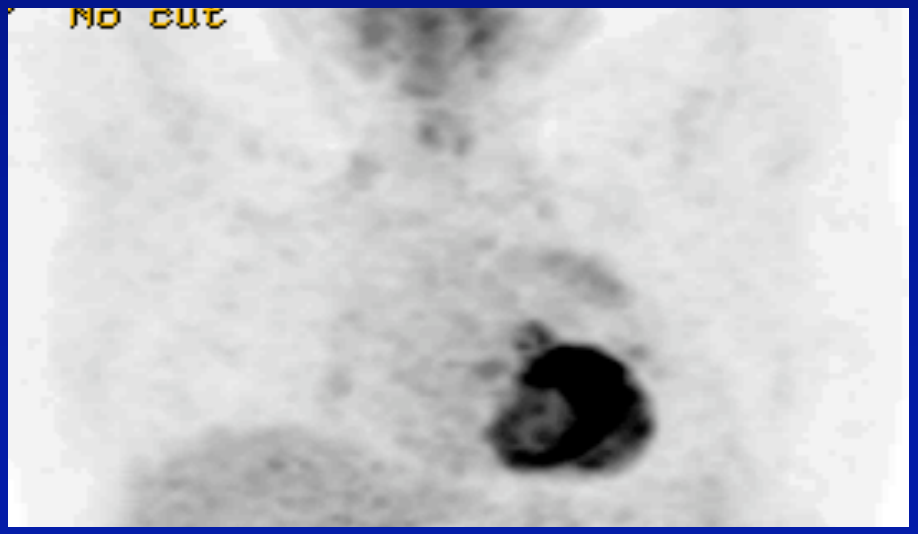
Before proton RT

6 months after







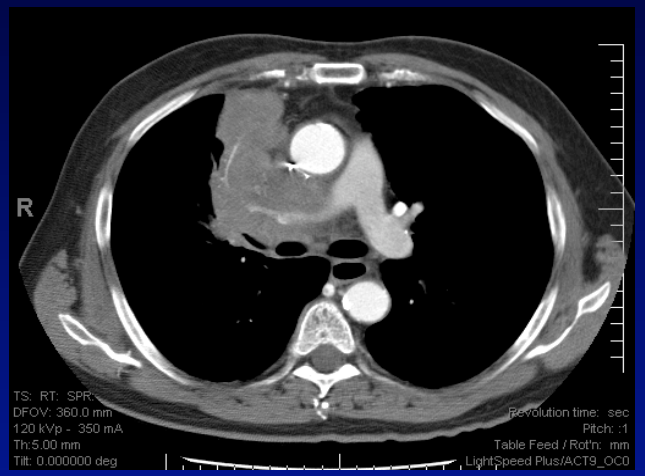


Stage IIIB NSCLC treated with 74 CGE proton and chemotherapy

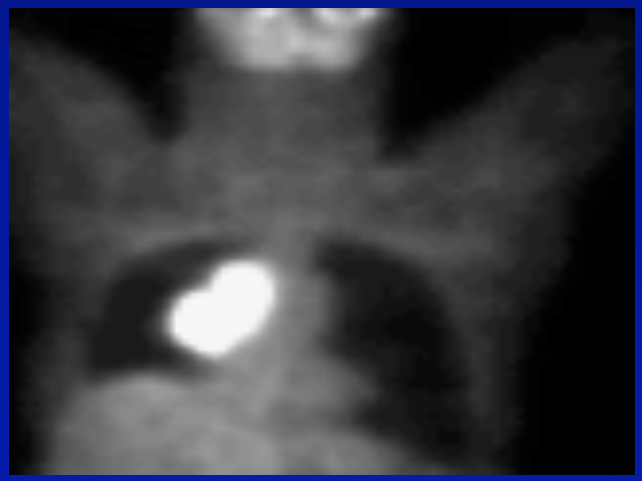
Before proton therapy

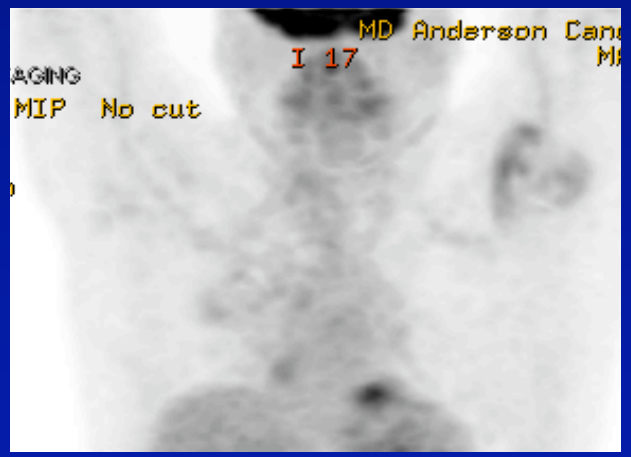
One year After therapy

CT



PET





Proposed phase II adaptively randomized clinical trials to compare proton to photon therapy (MDACC and MGH)

1. Proton therapy (87.5 CGE with 2.5 CGE/F) vs photon therapy (84 Gy with 2.15 Gy/F) in centrally located T1 or T2 stage I NSCLC
2. Proton therapy (74 CGE with 2 CGE/F) vs photon IMRT therapy (74 Gy with 2 Gy/F) with concurrent chemotherapy in stage III NSCLC

Proposed phase I clinical trials to escalate/accelerate proton therapy:

1. IMPT simultaneous integrated boost (SIB) dose escalation to IGTV with concurrent chemotherapy in stage II/III NSCLC
2. Hypofractionated stereotactic body proton therapy in centrally located T1 or T2 stage I NSCLC

Conclusions:

- Proton therapy may reduce toxicity and allow for dose escalation/acceleration in NSCLC
- 4-D based treatment planning is crucial and adapted treatment is indicated in selective patients
- Further optimizing proton therapy and clinical trials are needed.

Acknowledgements

- Radiation Oncology

- James D. Cox, MD
- Ritsuko Komaki, MD
- Zhongxing Liao, MD
- M. Kara Bucci, MD
- Melenda Jeter, MD
- Mary McAleer, MD, PhD
- Michael O'reilly, MD, PhD
- Samir Sejpal, MD
- All thoracic and PTC dosimetrists and therapists and clinical and research staff

- Thoracic Surgery

- Jack A. Roth, MD
- Stephen Swisher, MD
- All thoracic surgeons

- Radiation Physics

- Radhe Mohan, PhD
- Lei Dong, PhD
- Xiaodong Zhang, PhD
- Michael Gillin, PhD
- Richard Amos, MS
- George Starkschall, PhD
- Zhouguang Hui, MD
- Peter Balter, PhD
- Yoshikazu Tsunashima
- Ronald Zhu, PhD
- Bijan Arjomandy, PhD
- Mary Martel, hD
- All Thoracic and PTC Medical Physicist

- Thoracic Medical Oncology

- Frank Fossella, MD
- All Thoracic Medical Oncologists

Thank You!