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MD ANDERSON
CANCER CENTER
Making Cancer History™

Clinical Aspects of Proton Therapy in Lung Cancer

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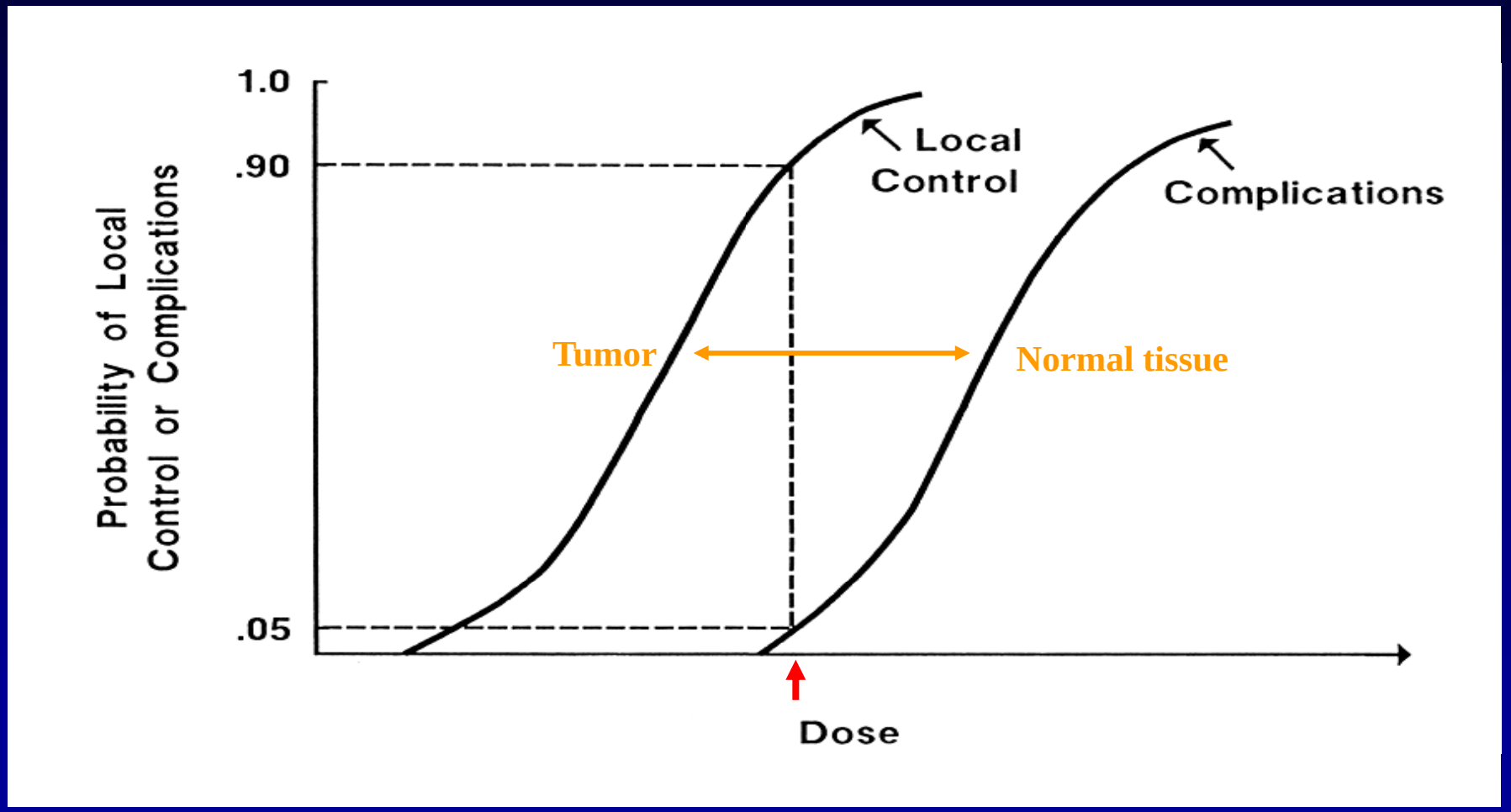
Lung Cancer Basic Factors

- No. 1 cancer killer
- 161,840 patients died in 2008
  - Higher than prostate, breast, colon/rectum, and pancreas cancers combined
- 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?



Virtual Clinical Studies in NSCLC:

1. PSPT compared with 3-D CRT and IMRT
2. IMPT compared with IMRT
3. IMPT compared with PSPT

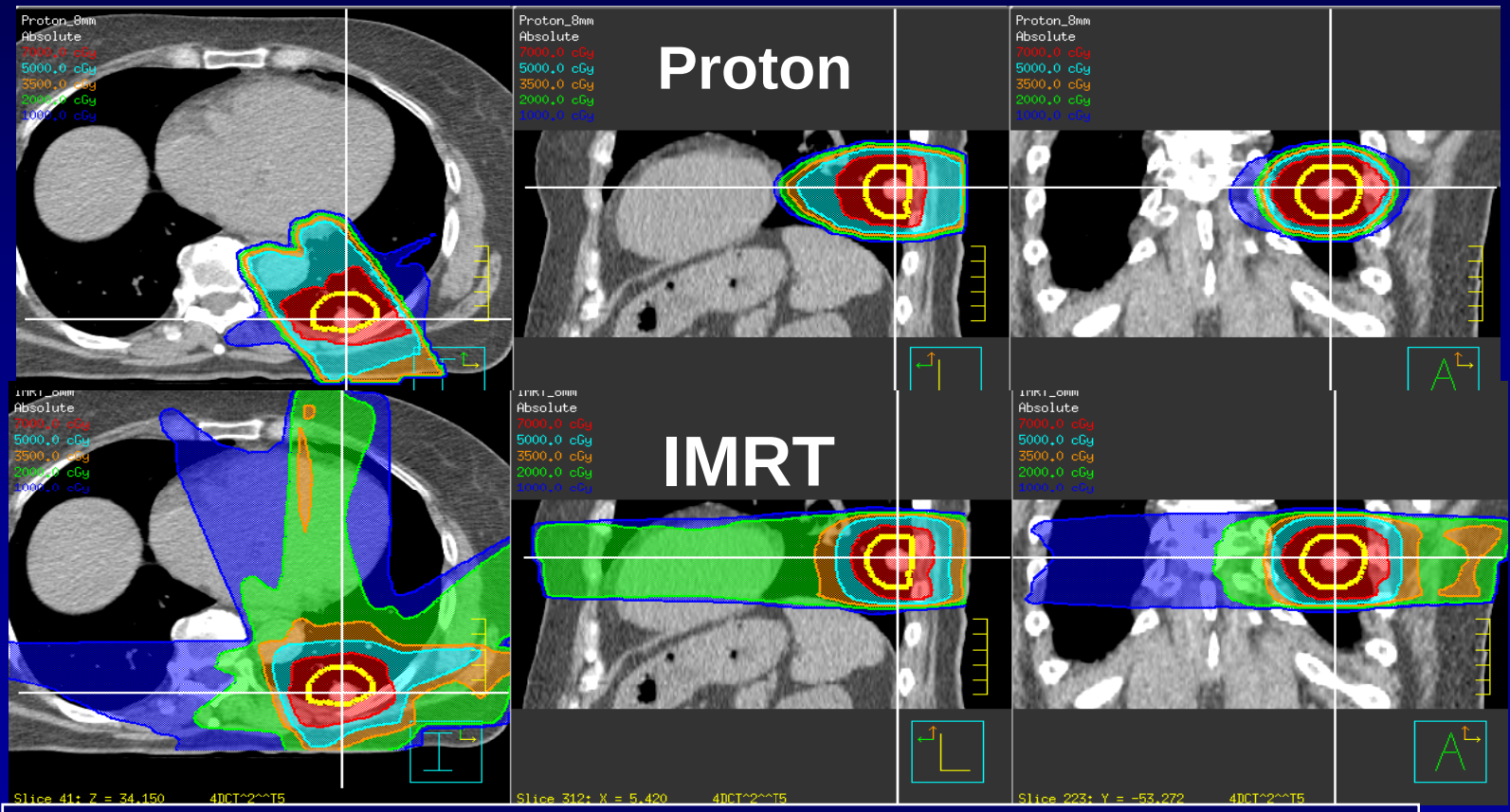
PSPT reduces normal tissue dose compared with 3-DCRT/IMRT

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)

Stage I

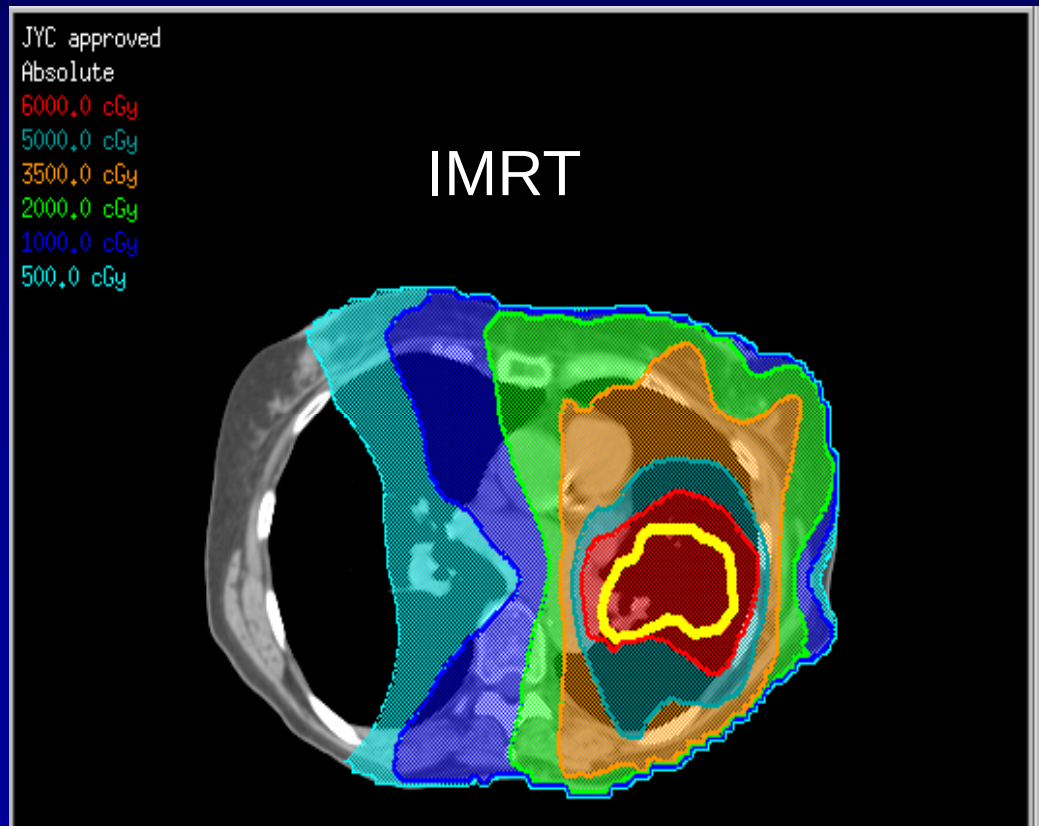


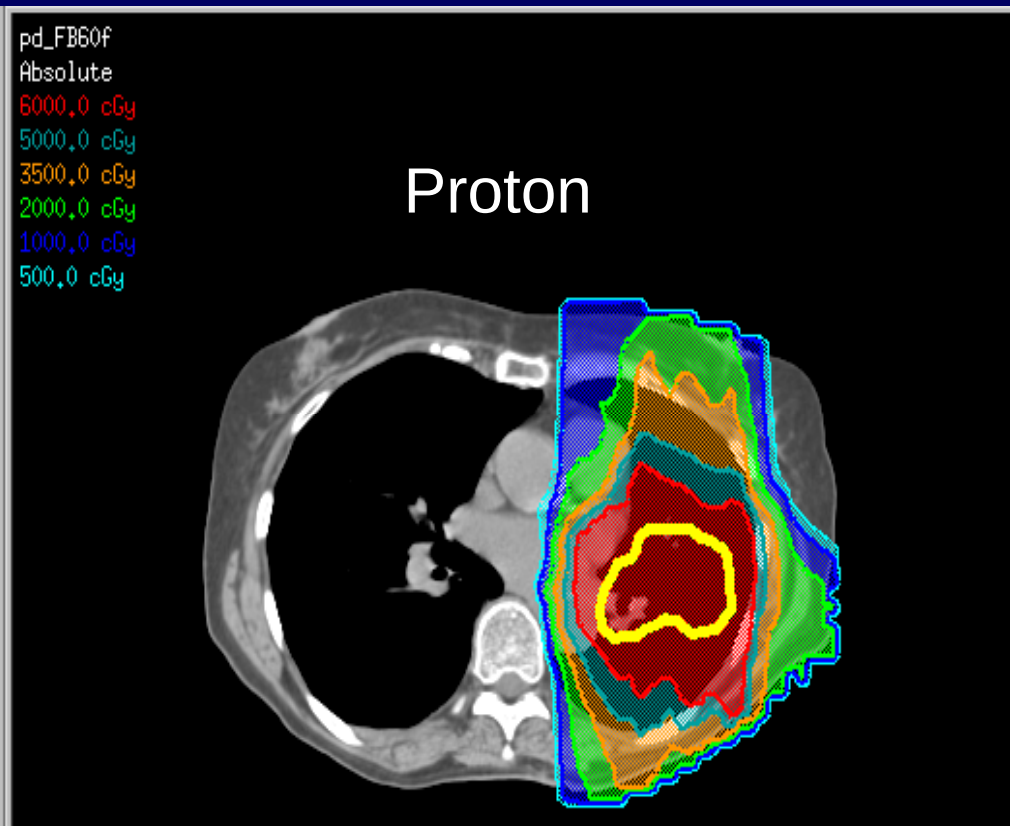
PSPT dose escalation still spares more normal tissues

Proton 87.5 CGE vs photon 60 GY in stage I
Proton 74 CGE vs photon 60 Gy in stage III

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

Stage III



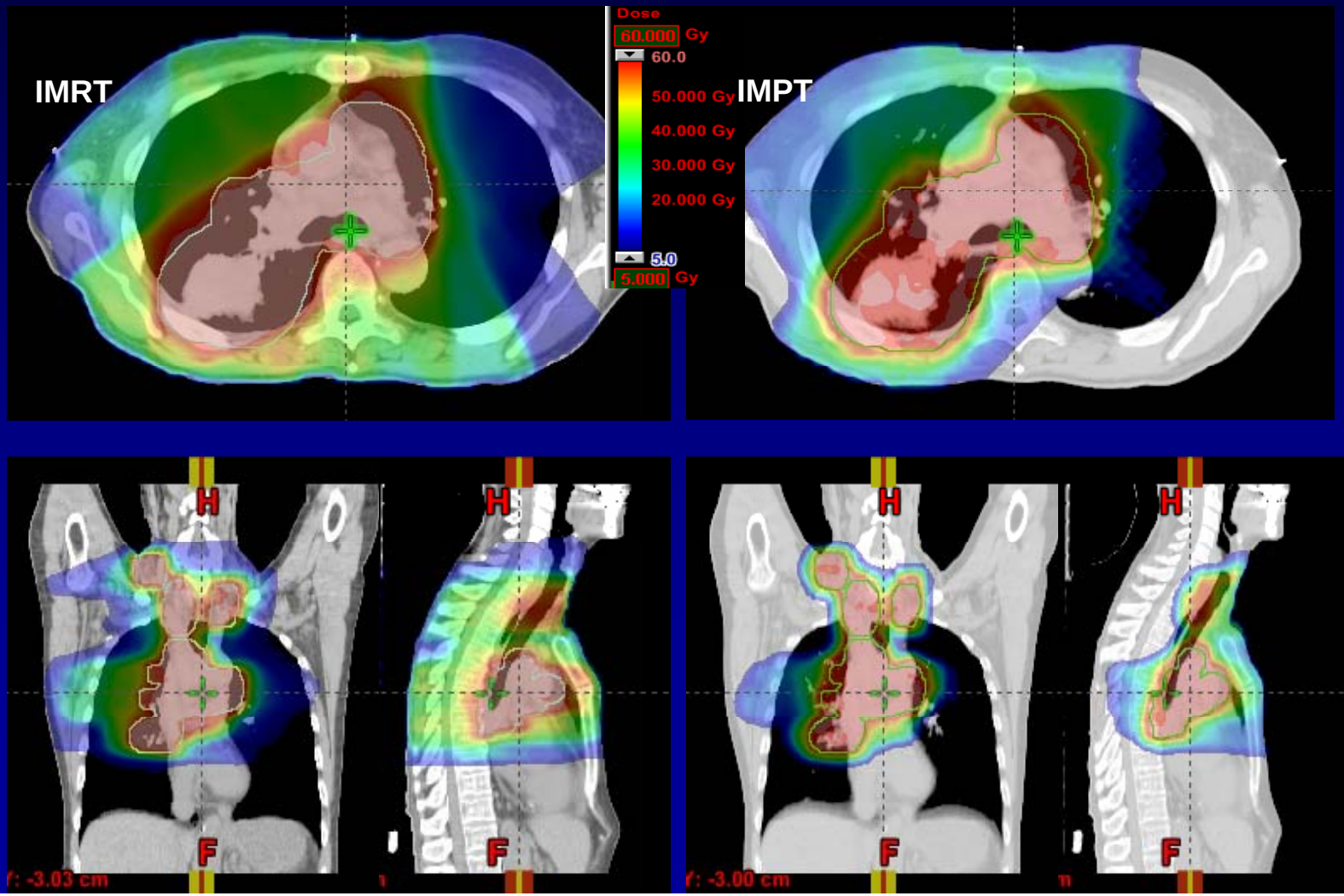


IMPT reduces normal tissue dose compared with IMRT in stage IIIB NSCLC

Absolute improvement in lung: V5: 22% V10: 13%

IMPT allows individualized radical radiotherapy to dose of 74 Gy to 84 Gy

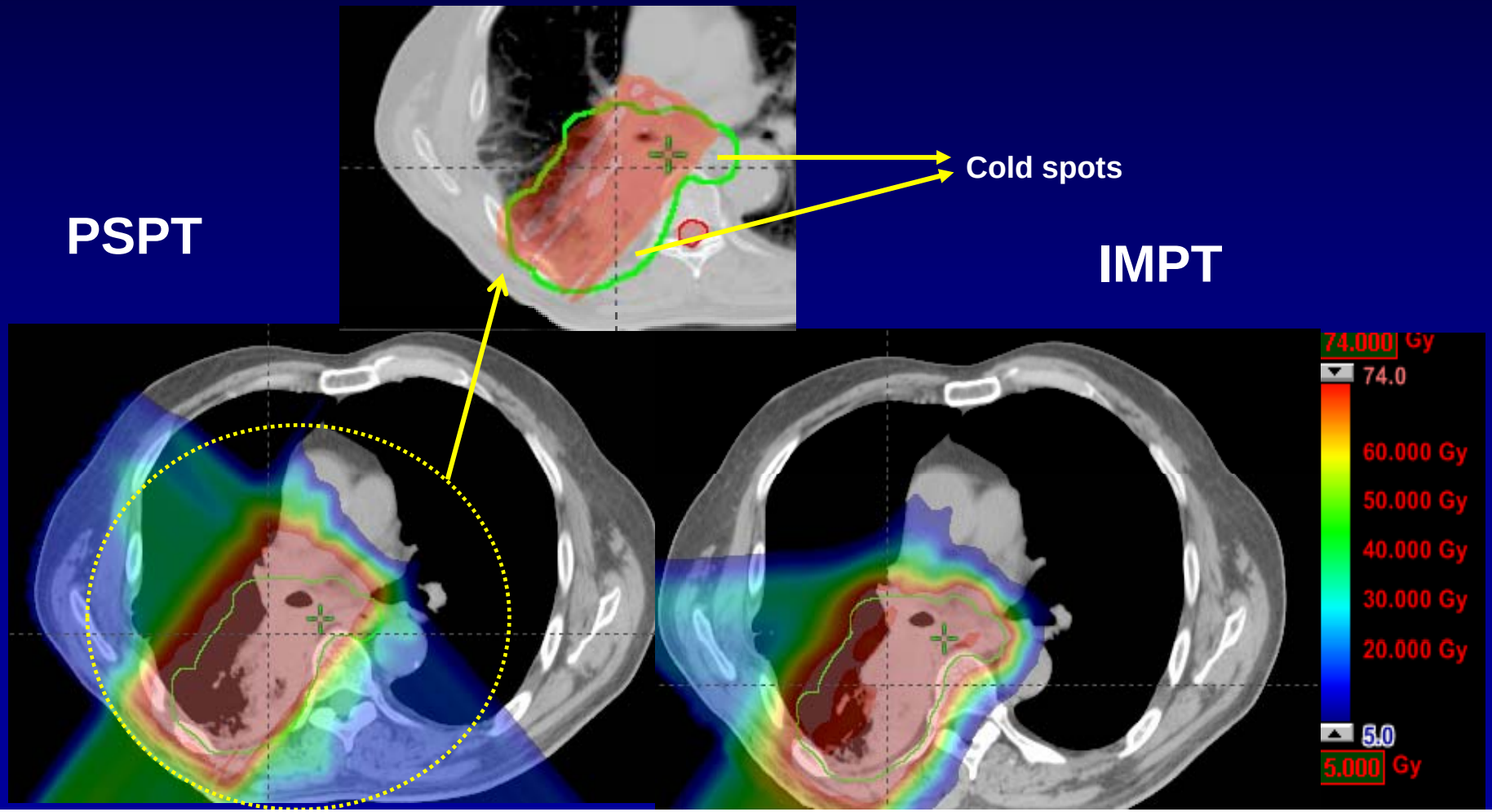
(Zhang and Chang et al: int J Rad Onc Bio Phy 2009, in press)



IMPT improves normal tissue sparing and target coverage compared with PSPT in complicated anatomy and allows further dose escalation

>5% absolute improvement in lung V5 and V10

(Zhang and Chang et al: int J Rad Onc Bio Phy 2009, in press)



Chang et al: JTO 3:177, 2008

T50
(Gating)

GTV

T0
(BH)

ITV

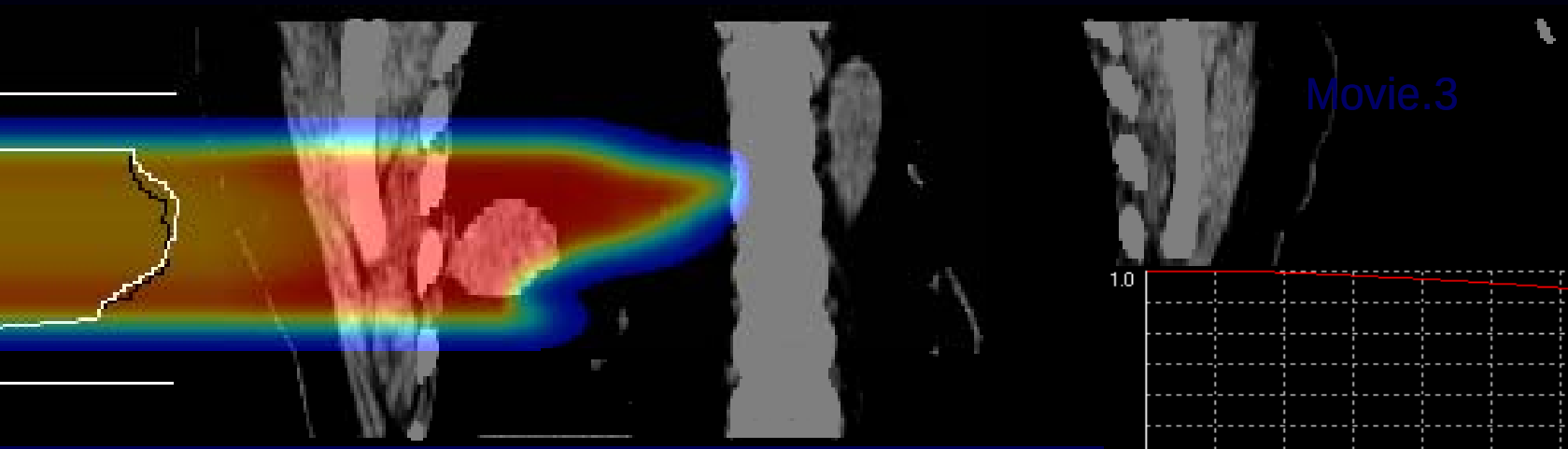
PTV

IGTV:
Path of gross tumor motion

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

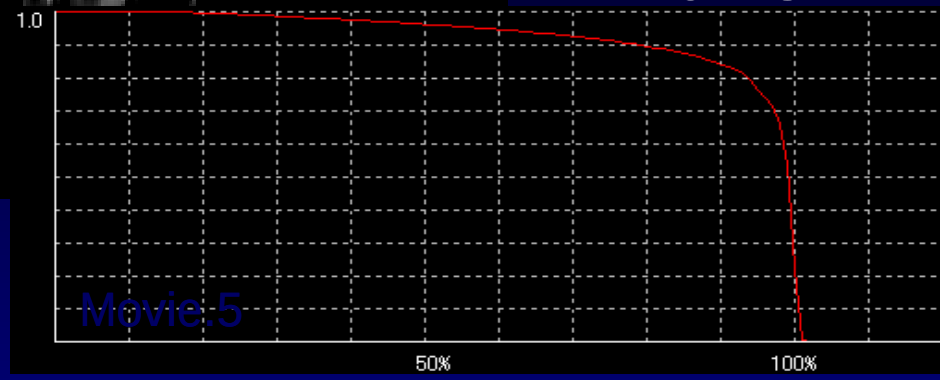
Lung Cancer Moves

(Yoshikazu Tsunashima)



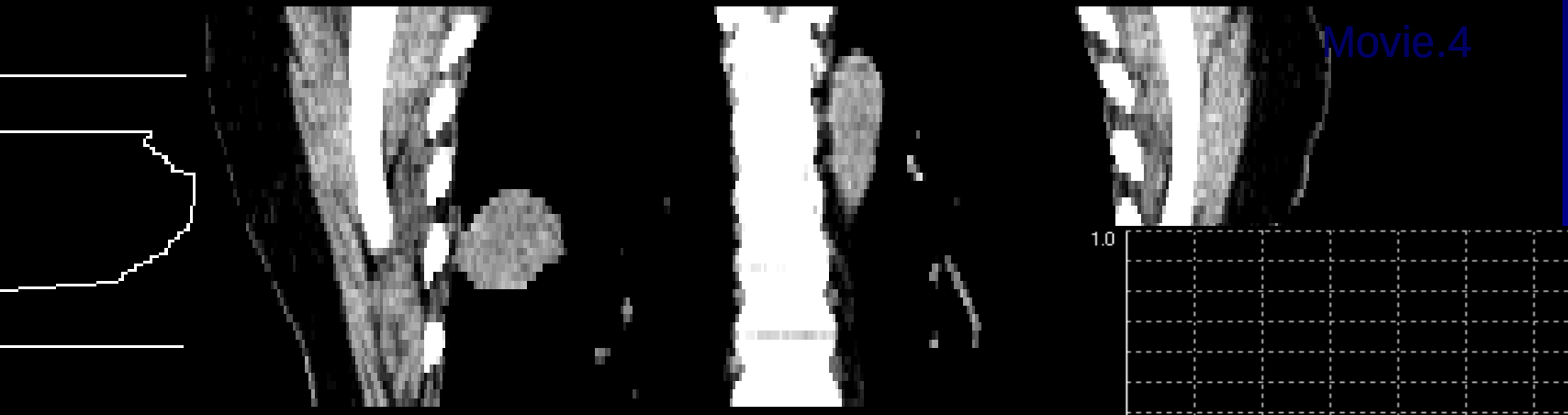
Movie.3

DVH on GTV



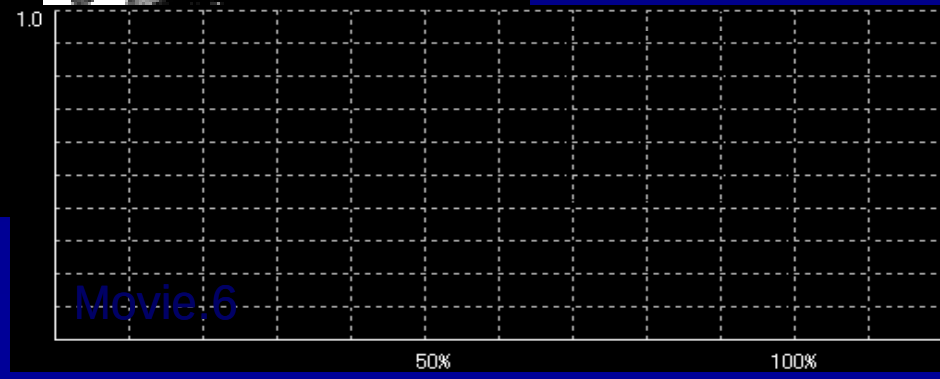
Movie.5

Non gate: Free breathing



Movie.4

DVH on GTV

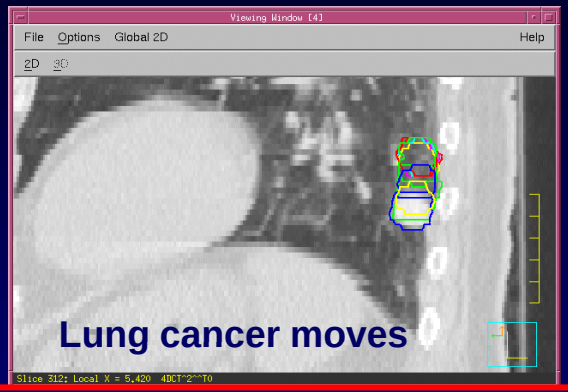


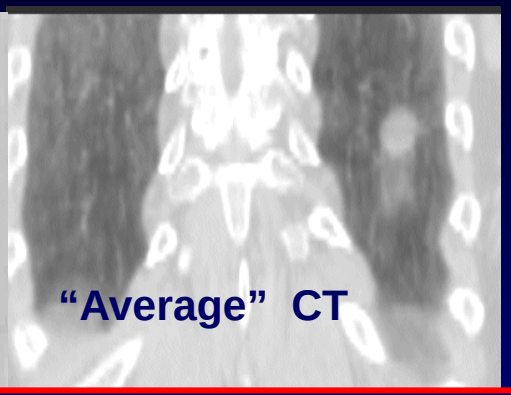
Movie.6

Gating in 40~60% expiration phase

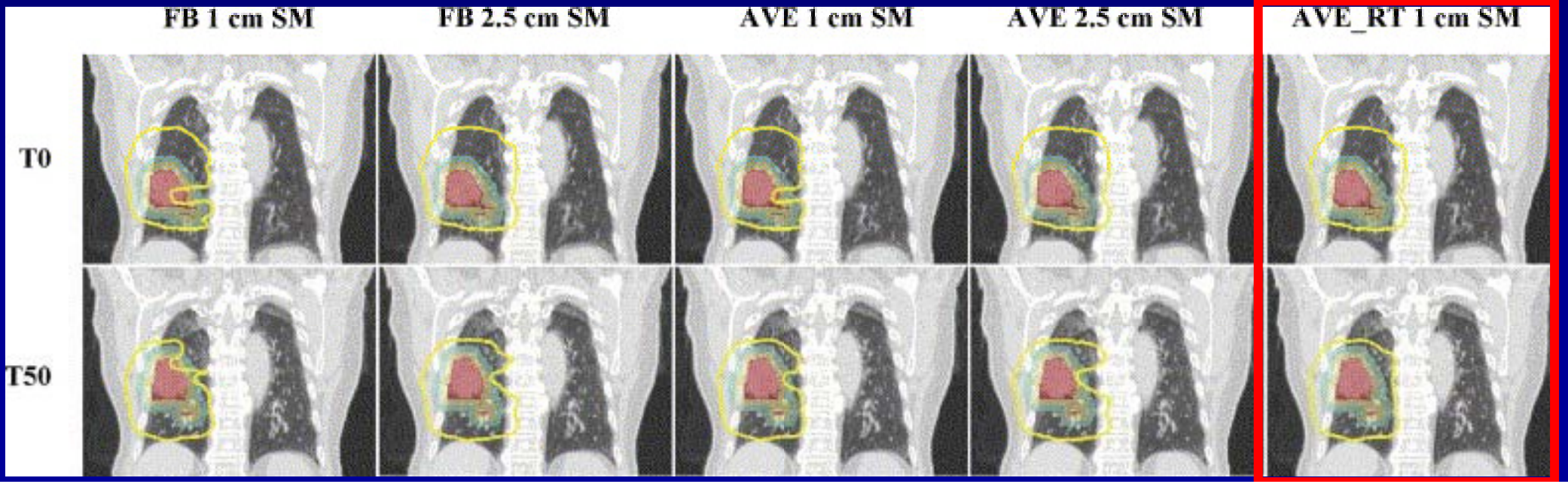
Intra-fraction motion:
4-D CT-based proton planning: ITV approach

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





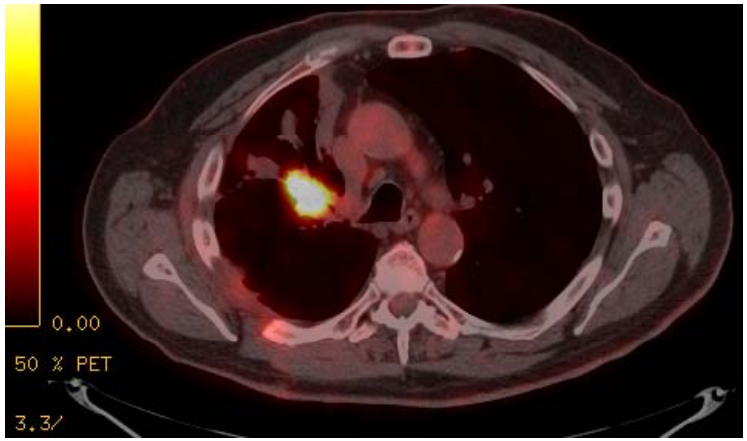
MIP density replaces IGTV in average CT data base for compensator design and dose calculation achieved the best overall target coverage and critical structure sparing



4-D CT-based ITV approach for proton treatment planning

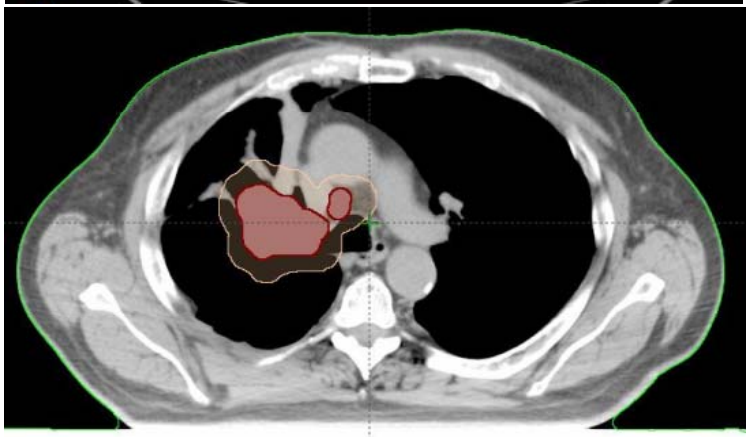
A.

PET



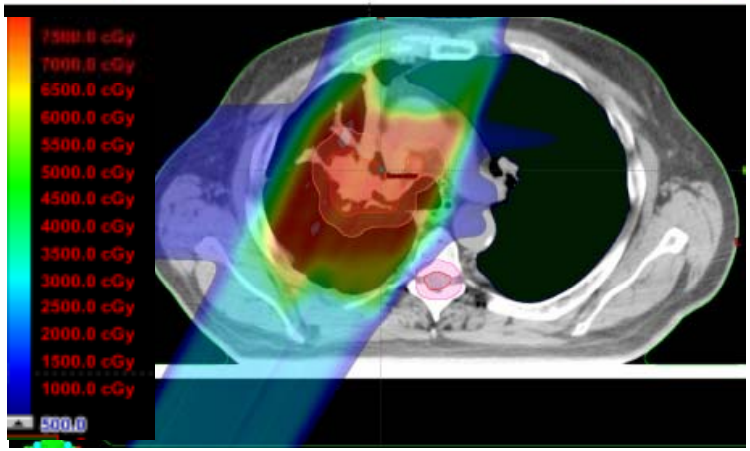
B.

MIP density replaces IGTV in average CT data set



C.

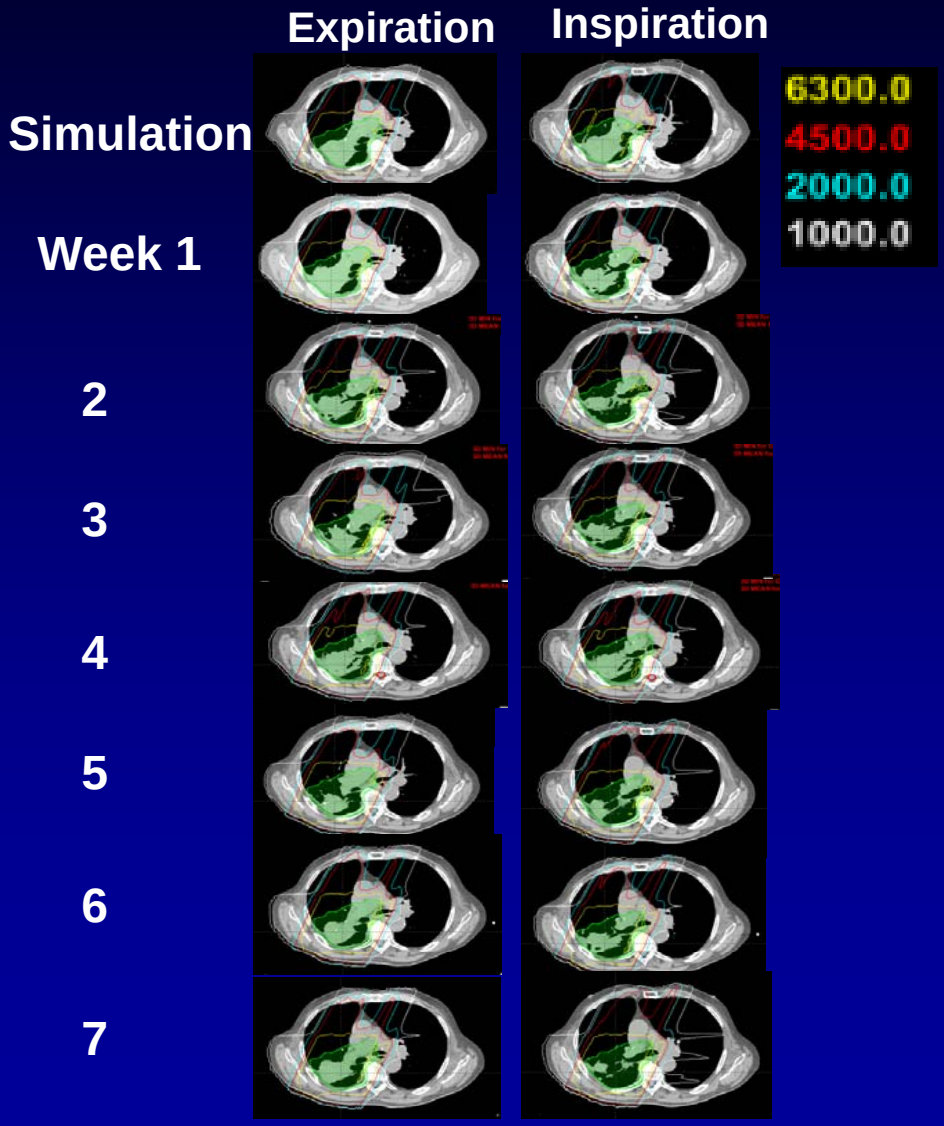
Isodose distribution in average CT

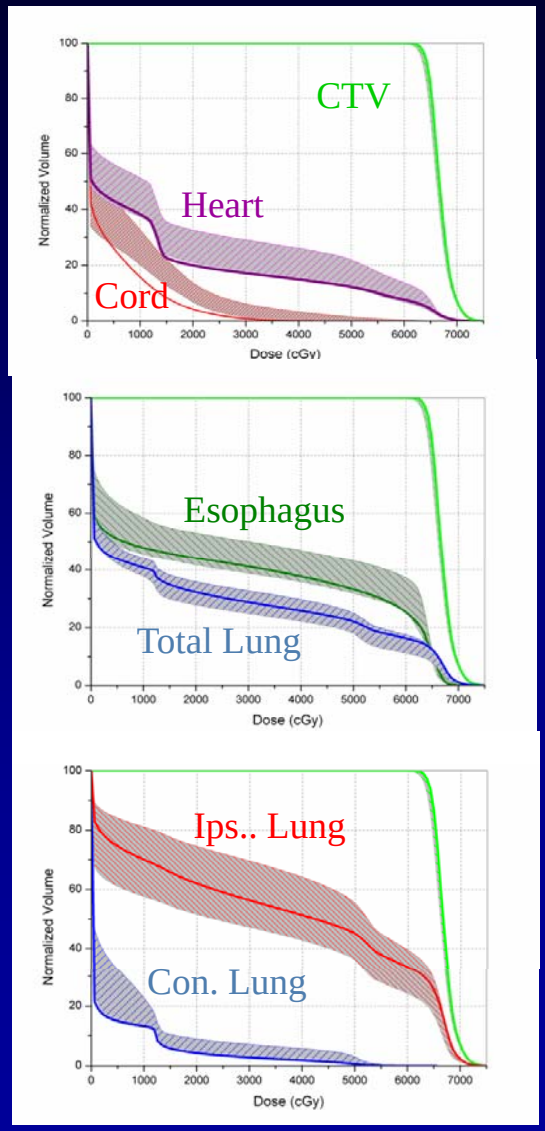


Chang et al: IGRT in lung cancer 2007

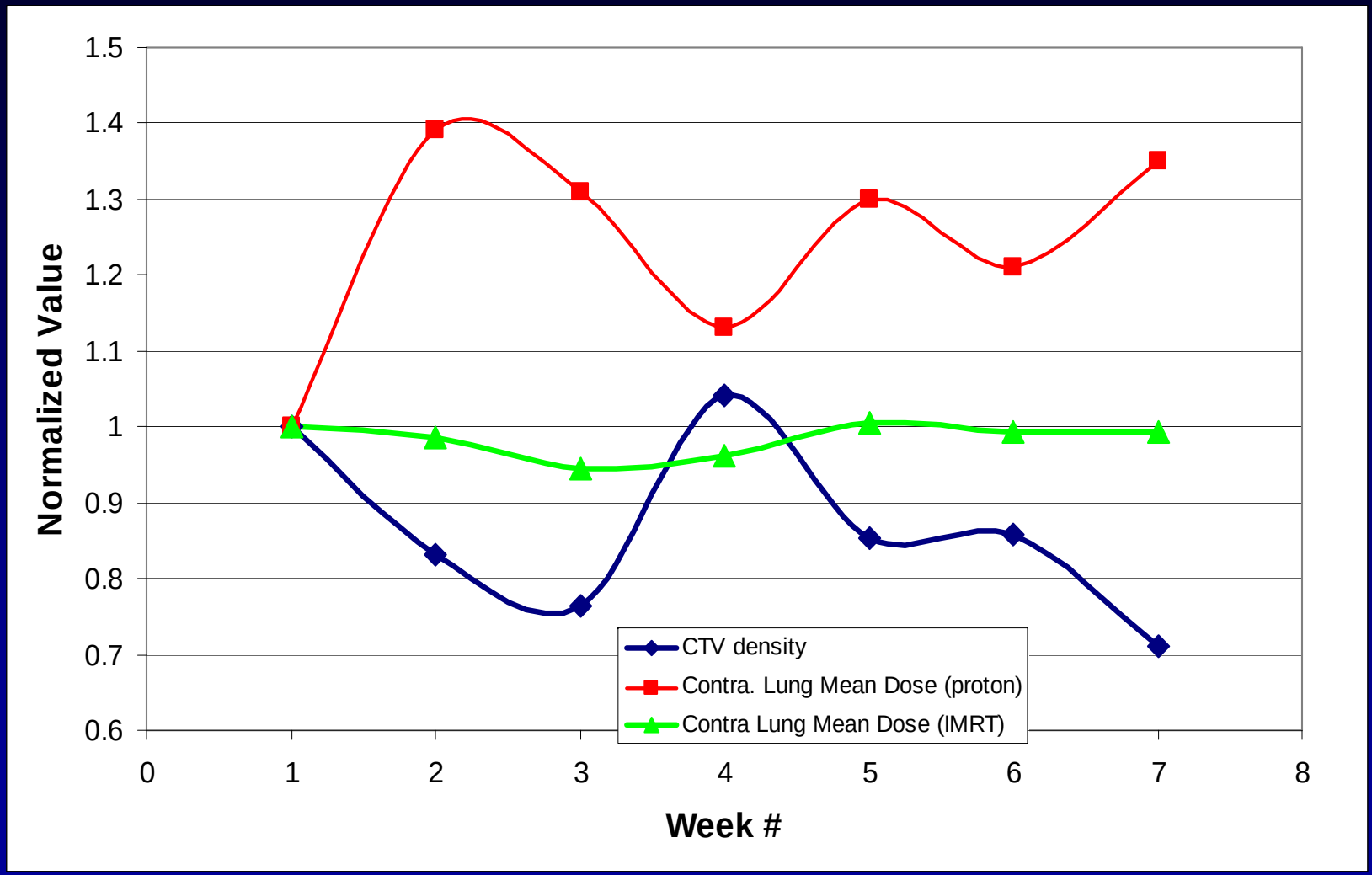
Inter-fraction motion and anatomy changes: A typical case

(Hui and Chang et al: Int J Rad Onc Biol Phy. 72:1385, 2008)





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

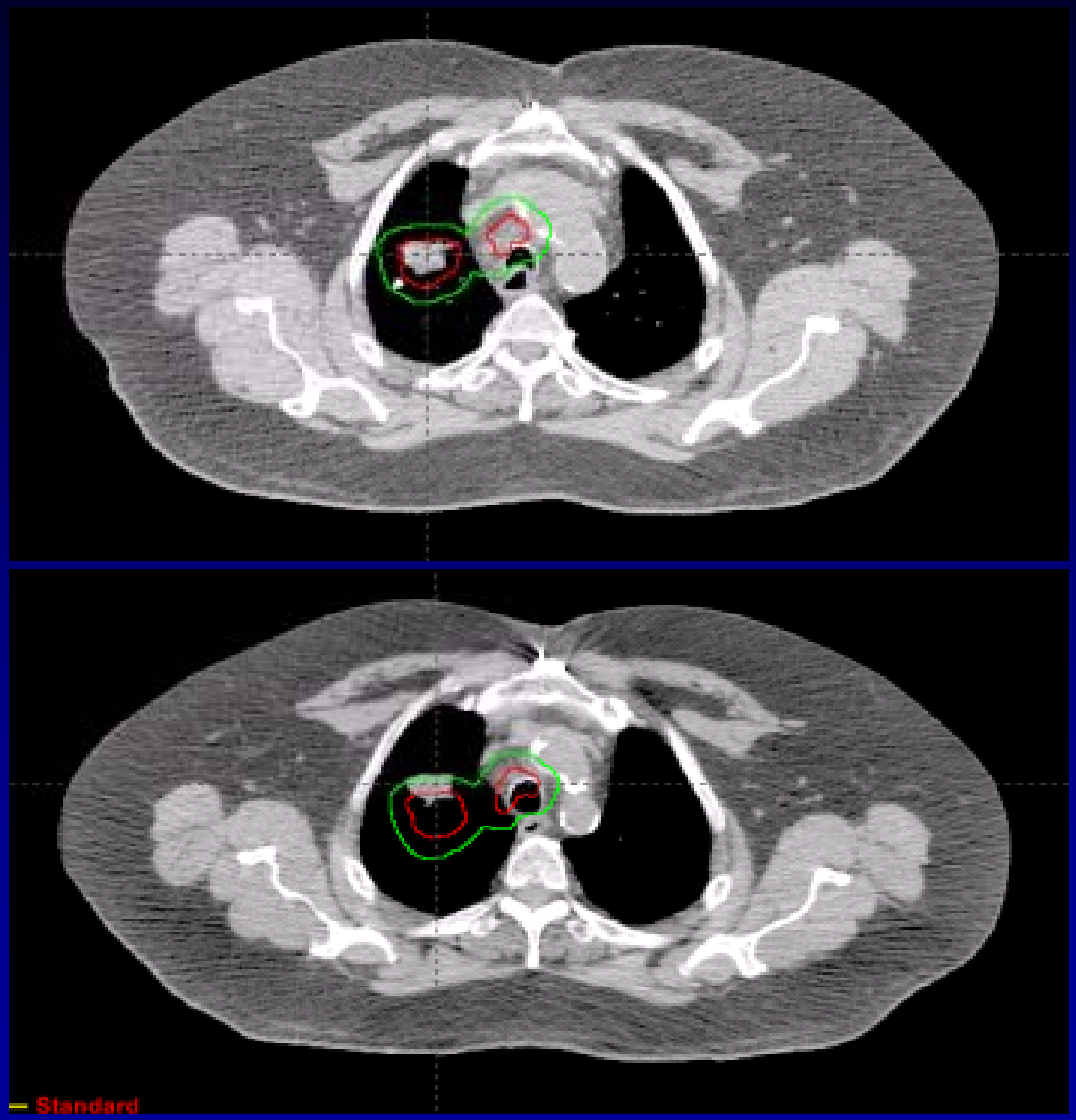


(Hui and Chang et al: Int J Rad Onc Biol Phy. 72:1385, 2008)

Inter-fraction anatomy/motion change
A extreme case

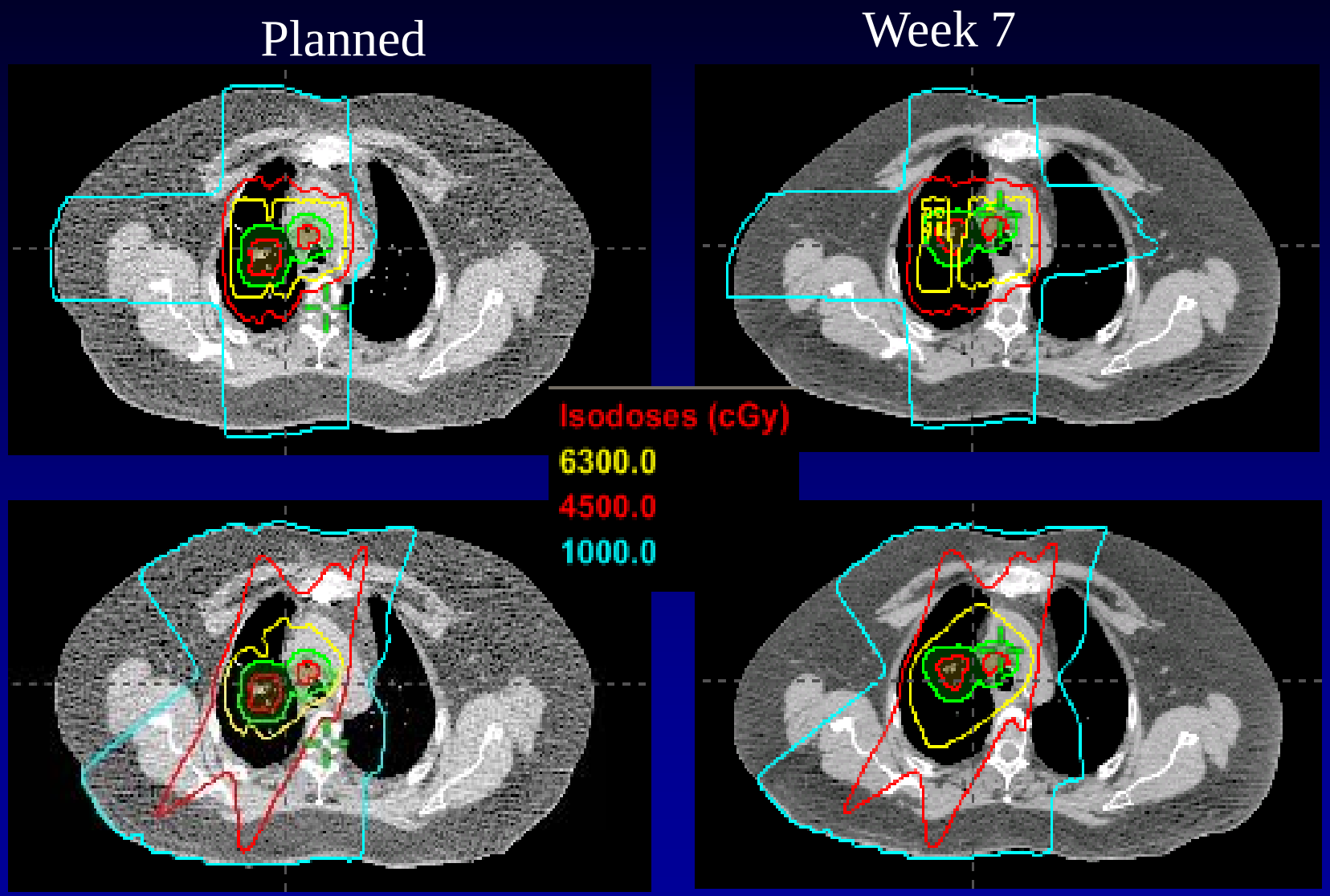
Week 1

Week 7



(Hui and Chang et al: Int J Rad Onc Biol Phy. 72:1385, 2008)

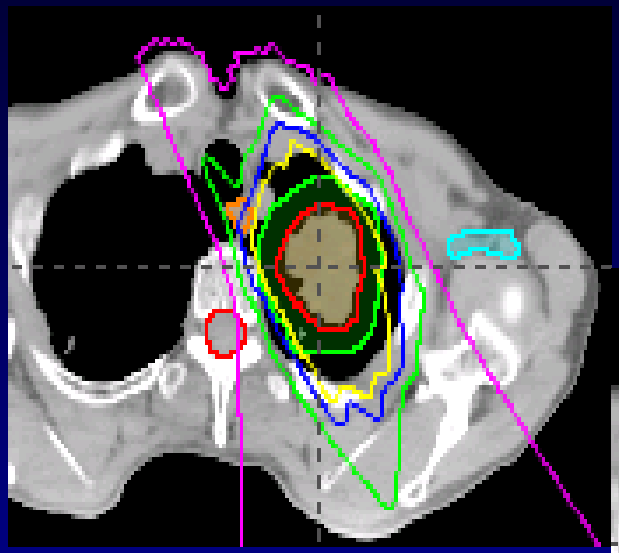
CTV coverage drops from 99% to 92.3% with proton but not in IMRT



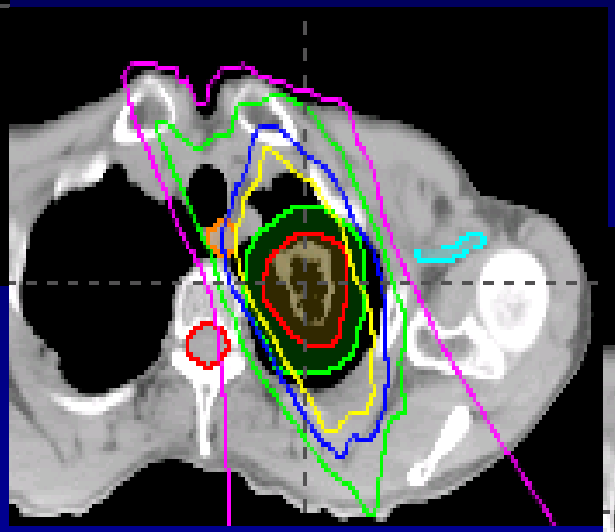
(Hui and Chang et al: Int J Rad Onc Biol Phy. 72:1385, 2008)

Adapted proton therapy

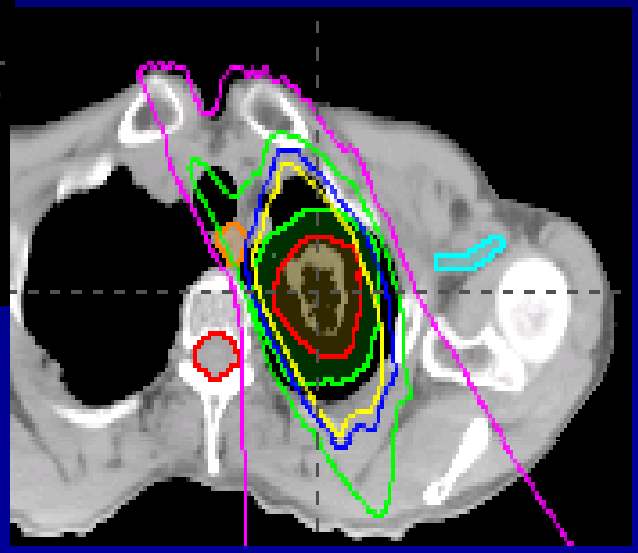
Initial plan



Initial plan recalculated based on CT after 5 wks TX

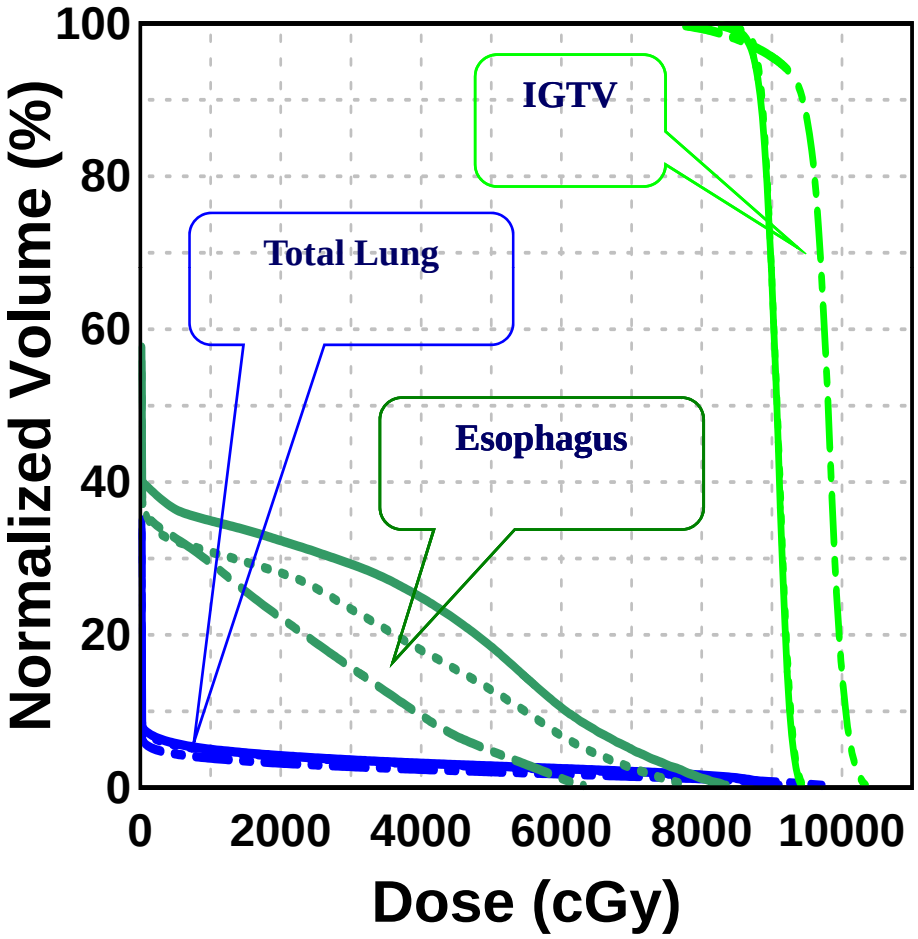


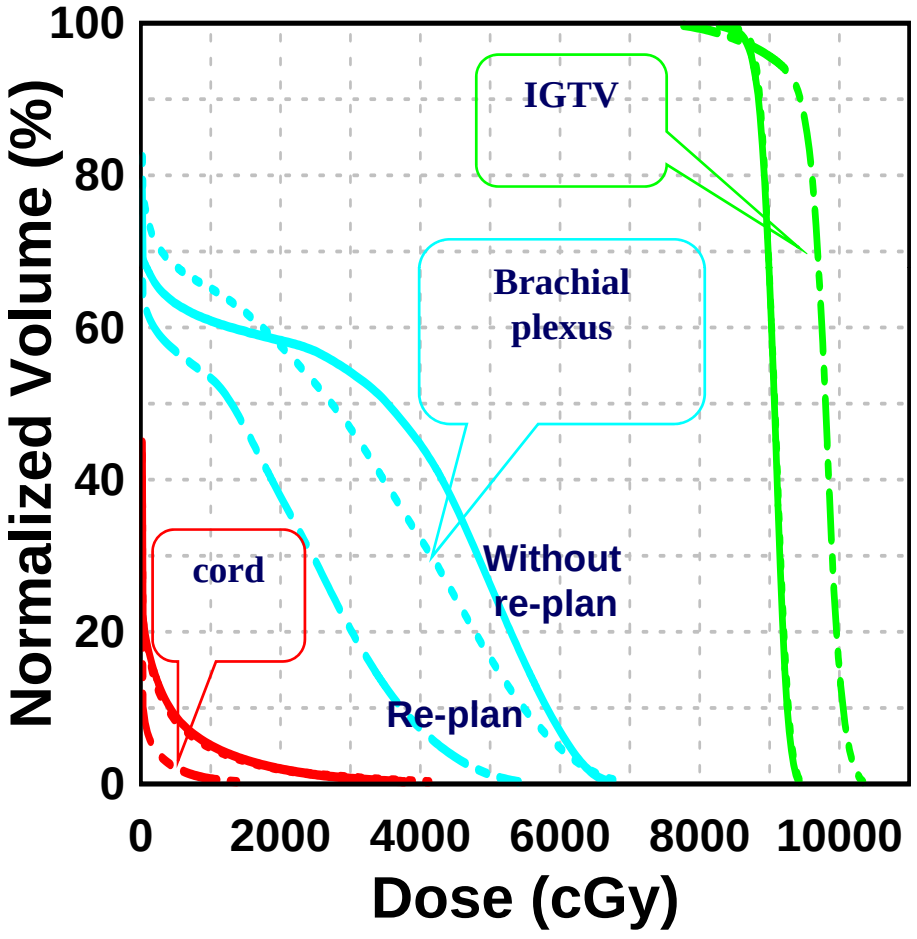
Re-plan based on CT after 5 wks TX



(Hui and Chang et al: Int J Rad Onc Biol Phy. 72:1385, 2008)

Adapted proton therapy



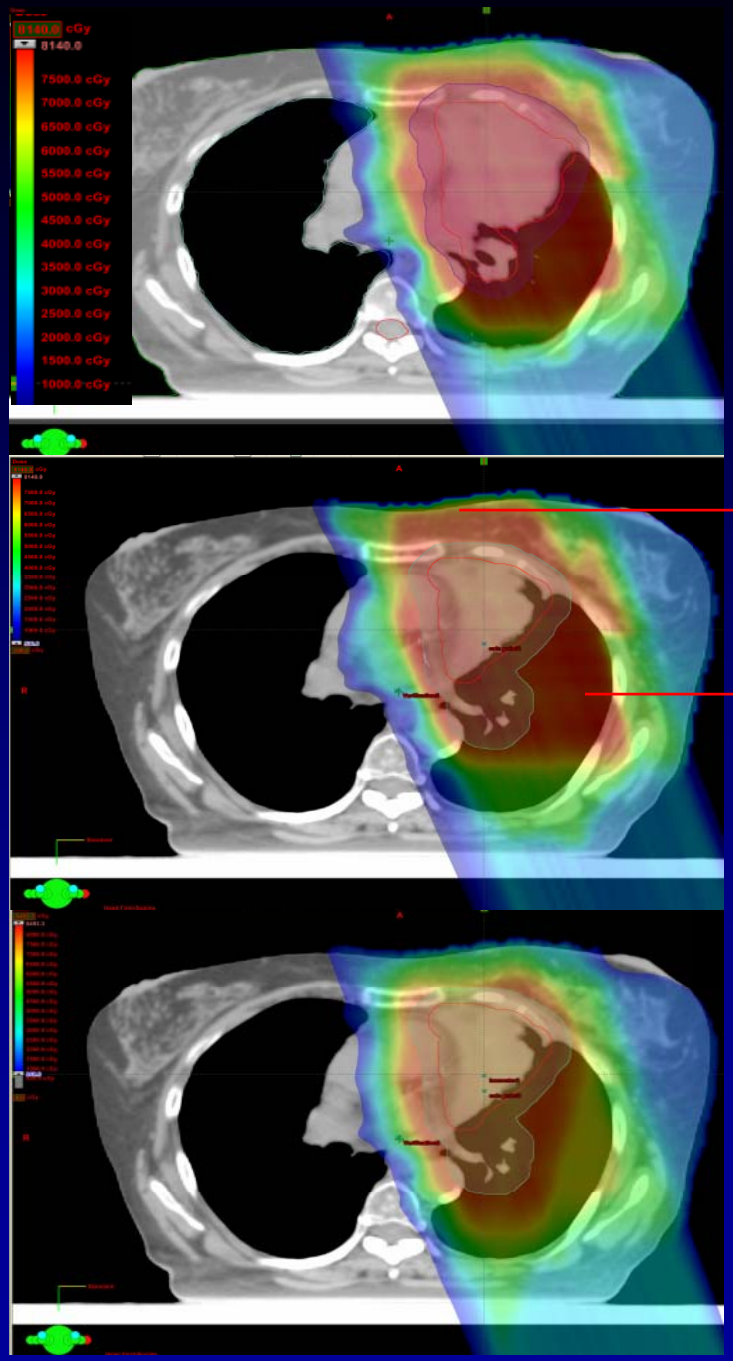


Adapted proton therapy

A.

B.

C.



Hot skin dose

Hot lung dose

Chang et al: IGRT in lung cancer 2007

Published and Undergoing Proton Therapy Clinical Studies in NSCLC

Published 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 appears reduced.
   Data in stage Ia with BED > 100 CGE achieved superior result comparable to surgery

Phase I/II escalated/accelerated proton therapy in early stage NSCLC

(Chang et al: IASLC 2009, supported by PO1 grant)

Eligibility:

Medically inoperable centrally located T1 or any location of T2 and selective T3N0M0 (chest all) (stage I-II)

Primary objectives:

Local control and toxicity

Proton Dose:

87.5 CGE with 2.5 CGE/F

Phase I/II escalated/accelerated proton therapy in early stage NSCLC

(Chang et al: IASLC 2009, supported by PO1 grant)

Preliminary Results:

20/40 pts enrolled.
Median F/U 16.5 months (range 5-24.1 months)

Toxicity:

No grade 4 or 5 toxicity, only grade 3 toxicity is dermatitis
Grade 2 pneumonitis: 7%
Grade 2 esophagitis: 7%

Tumor control:

Rates of local control: 93%
Regional lymph node failure 7%,
Distant metastasis 20% .

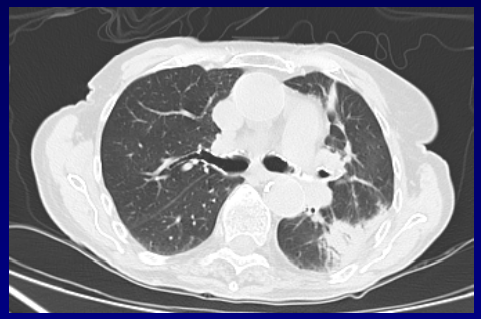
Proton therapy (87.5 CGE) in central stage I NSCLC

A.

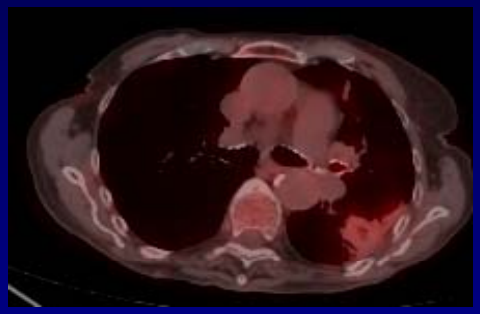
B.

Before Proton

C.

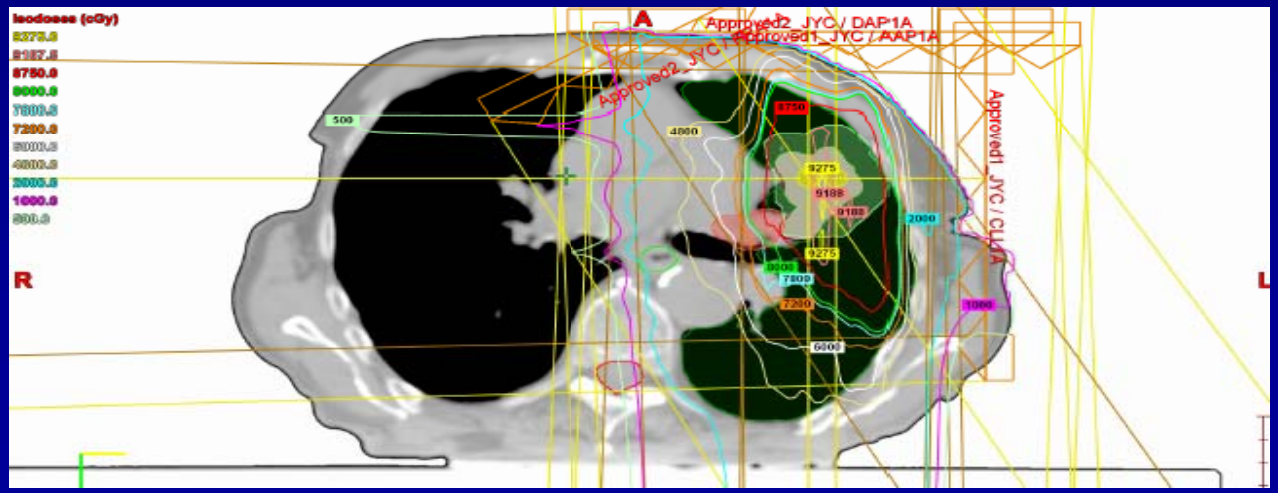


D.



After Proton

E.



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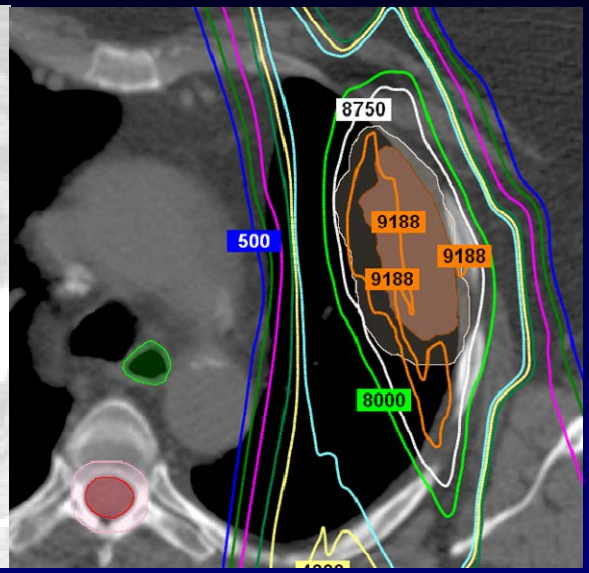
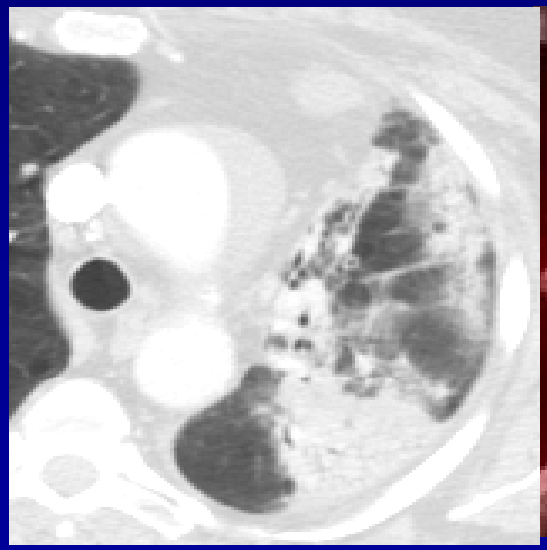
Local recurrence after 87.5 CGE proton therapy in T2 adenocarcinoma

Pre-RT

Proton TX

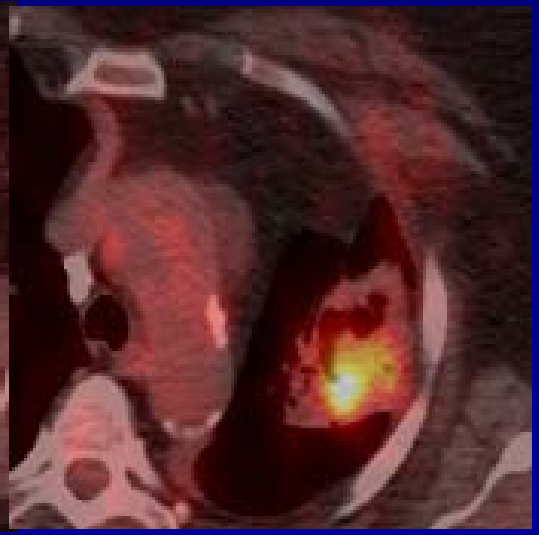


3 months



6 months/Bx

9 months after chemo



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Phase II dose escalated proton/chemo therapy for stage III NSCLC

(Chang et al: ASTRO 2009, supported by PO1 grant)

Eligibility:

Inoperable extensive stage III NSCLC

Primary objectives:

Survival and toxicity

Proton Dose:

74 CGE with 2 CGE/F with concurrent Carb/Taxol

Phase II dose escalated proton/chemo TX for stage III NSCLC

(Chang et al: ASTRO 2009, supported by PO1 grant)

Preliminary Results:

47/65 pts enrolled. 30 pts with median F/U 16 months (range 7-26 months)
Median overall survival has not been reached.

Toxicity:

- No grade 4 or 5 toxicity.
- Grade 3 adverse effect:
- Dermatitis (13.3%)
- Esophagitis (6.7%, compared with 20% in 63 Gy IMRT)
- Pneumonitis (3.3%, compared with 10% in 63 Gy IMRT)

Tumor Control:

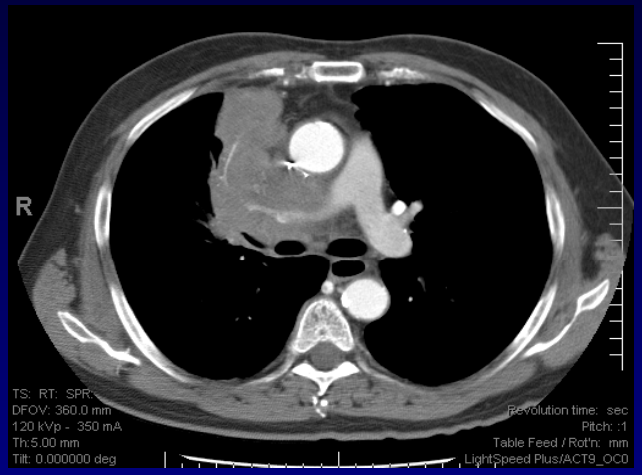
- Isolated local failure within PTV: 13.3%
- Regional lymph nodes recurrence outside PTV: 13.3%
- Distant metastasis: 20%;
- Distant metastasis + local/regional failure: 16.7%.

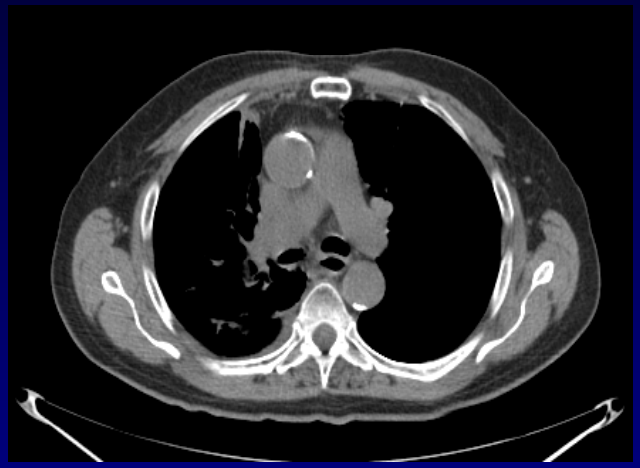
Stage IIIB NSCLC treated with 74 CGE proton and chemotherapy

Before proton therapy

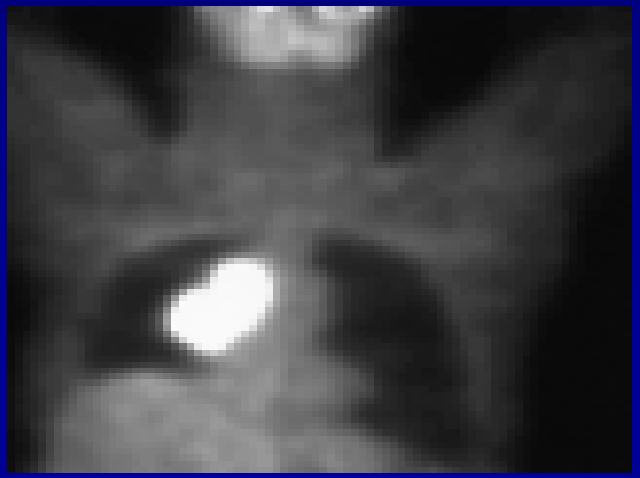
One year After therapy

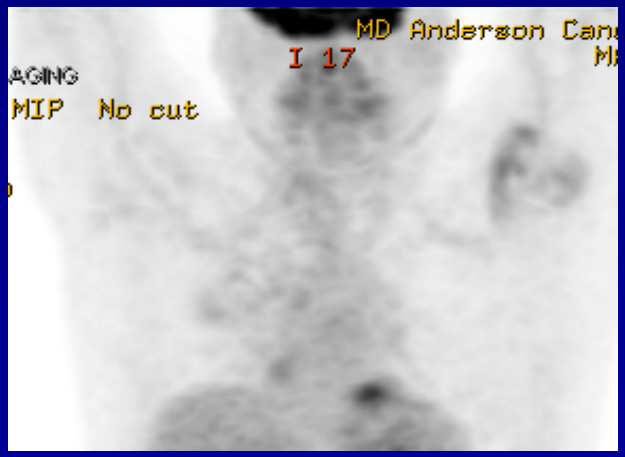
CT





PET





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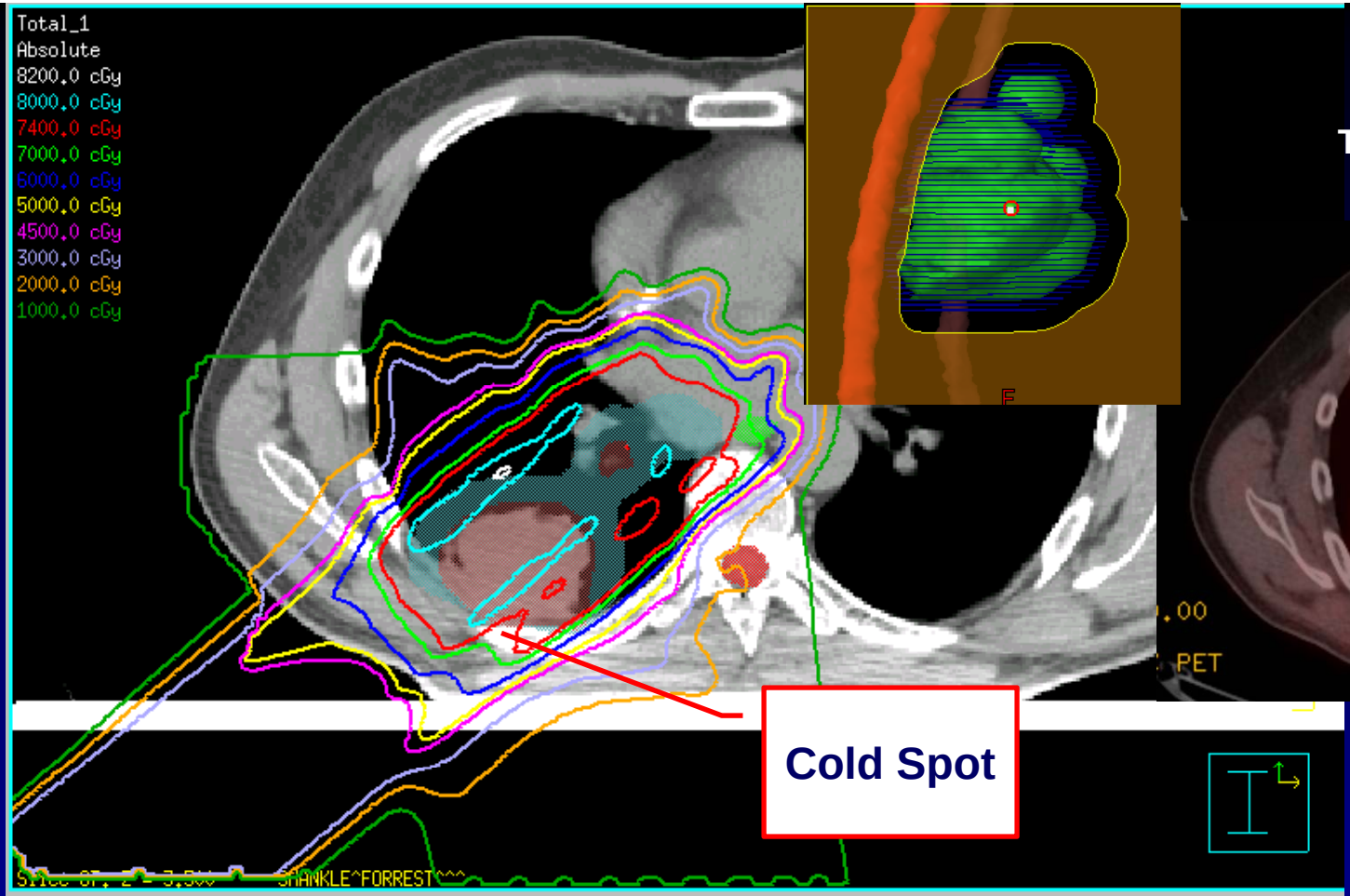

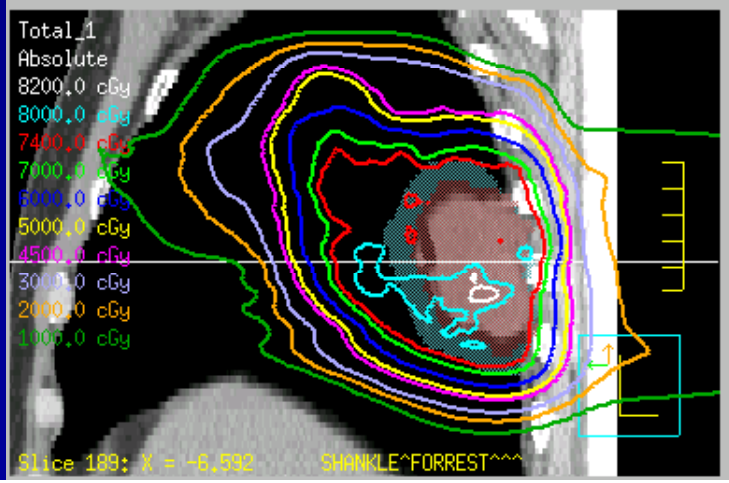

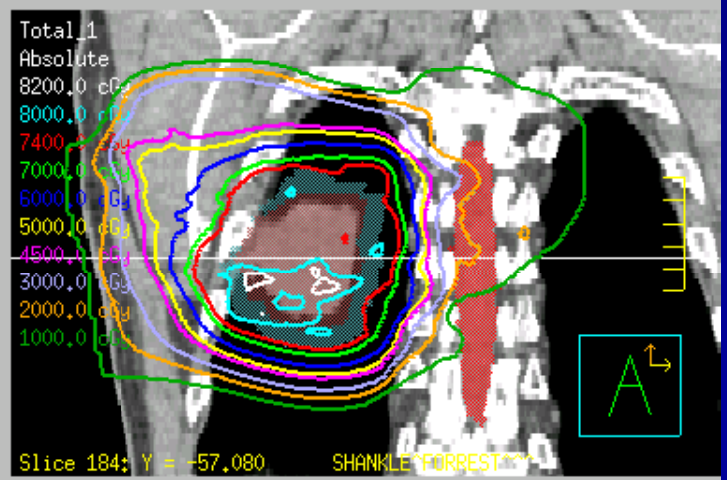

PSPT with cold spot

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Which is better: Proton or IMRT

MDACC/MGH PO1 grant:

Phase II adaptive randomization:

- **Proton therapy v.s. IMRT**

Eligibility: **Stage III NSCLC**

Dose: **74 Gy with concurrent Carb/Taxol in both arms**

Primary objectives: **Grade 3 pneumonitis and local control**

CONCLUSIONS:

- **Proton therapy reduces toxicity and allows 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 is needed**

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- Xiaodong Zhang, PhD
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- Ron. Zhu, PhD
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MGH

Radiation Oncology

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Thank you

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