PRELIMINARY EVALUATION OF TREATMENT-RELATED PNEUMONITIS (TRP) BY PROTON BEAM RADIOTHERAPY (PBT) COMPARED TO IMRT IN PATIENTS WITH LOCALLY ADVANCED NSCLC TREATED WITH CONCURRENT CT

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Background

- MDACC retrospective study of locally advanced NSCLC treated w/ CT/XRT (IMRT or 3DCRT)

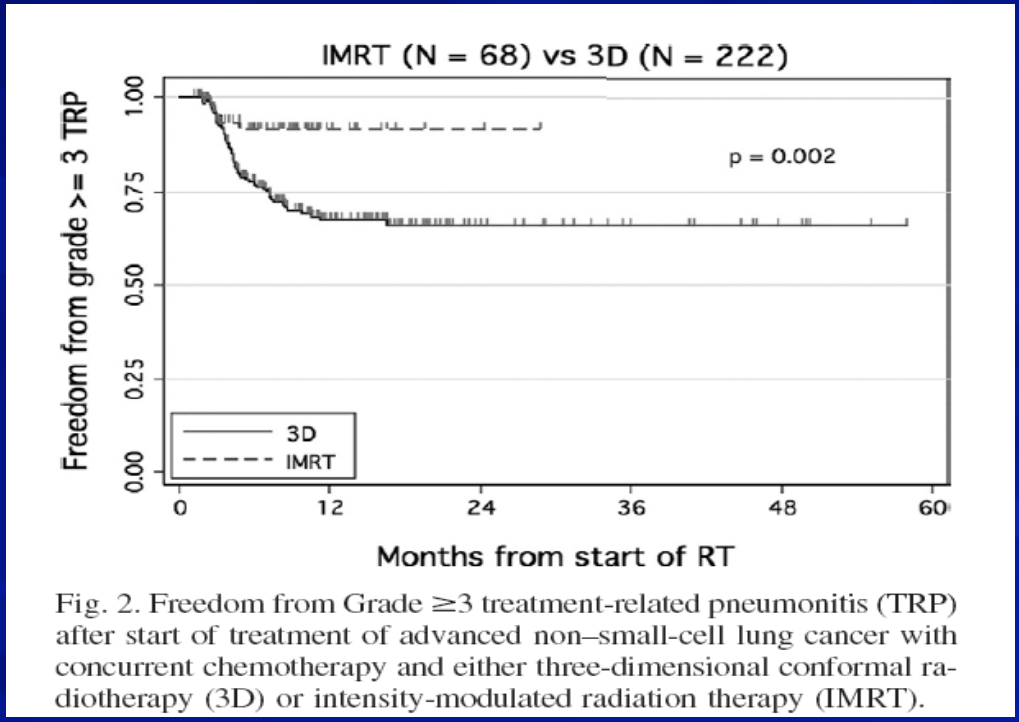


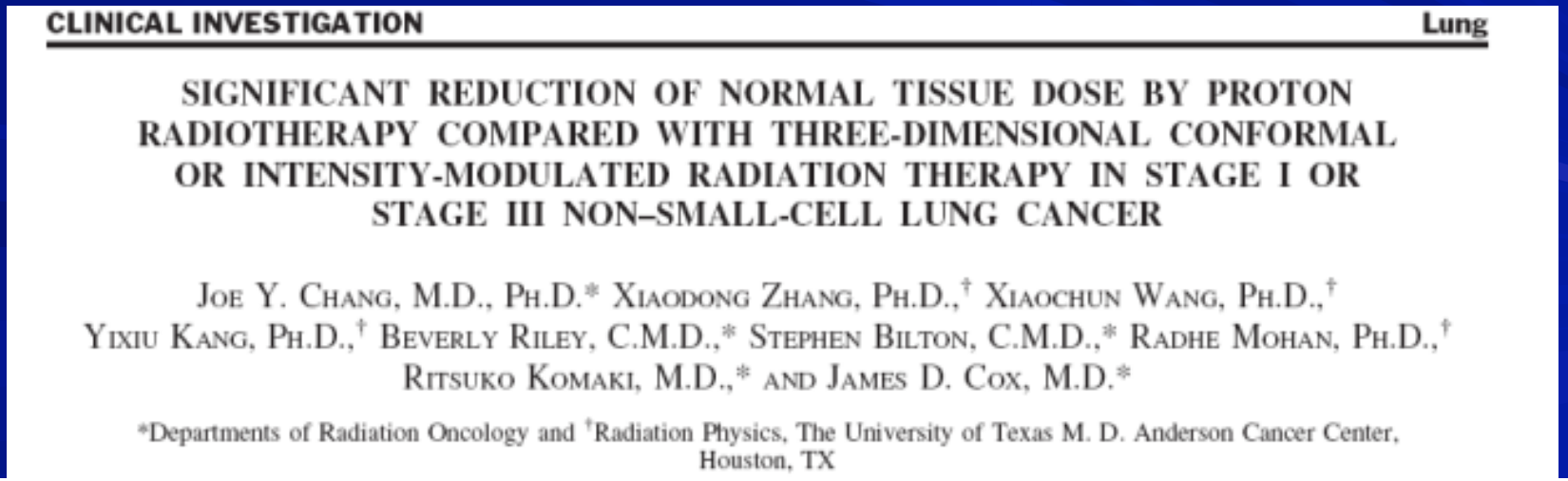
Fig. 2. Freedom from Grade ≥3 treatment-related pneumonitis (TRP) after start of treatment of advanced non–small-cell lung cancer with concurrent chemotherapy and either three-dimensional conformal radiotherapy (3D) or intensity-modulated radiation therapy (IMRT).

Yum,S et al. IJROBP 2007

At median f/up time of 9 months in both arms Grade =>3 TRP at 12 mo is 8% in IMRT arm and 32 % in 3D-CRT arm

Background

- Proton Beam Therapy (PBT) compared to photons
  - Lower exit dose
  - Lower integral dose
- Dosimetric reduction of dose to critical structures
- Dosimetric study by Chang et al… (*2007*)
- 10% to 20% absolute improvement in lung DVH for tx plans with Proton therapy compared to 3D-CRT or IMRT



CLINICAL INVESTIGATION Lung

SIGNIFICANT REDUCTION OF NORMAL TISSUE DOSE BY PROTON RADIOTHERAPY COMPARED WITH THREE-DIMENSIONAL CONFORMAL OR INTENSITY-MODULATED RADIATION THERAPY IN STAGE I OR STAGE III NON–SMALL-CELL LUNG CANCER

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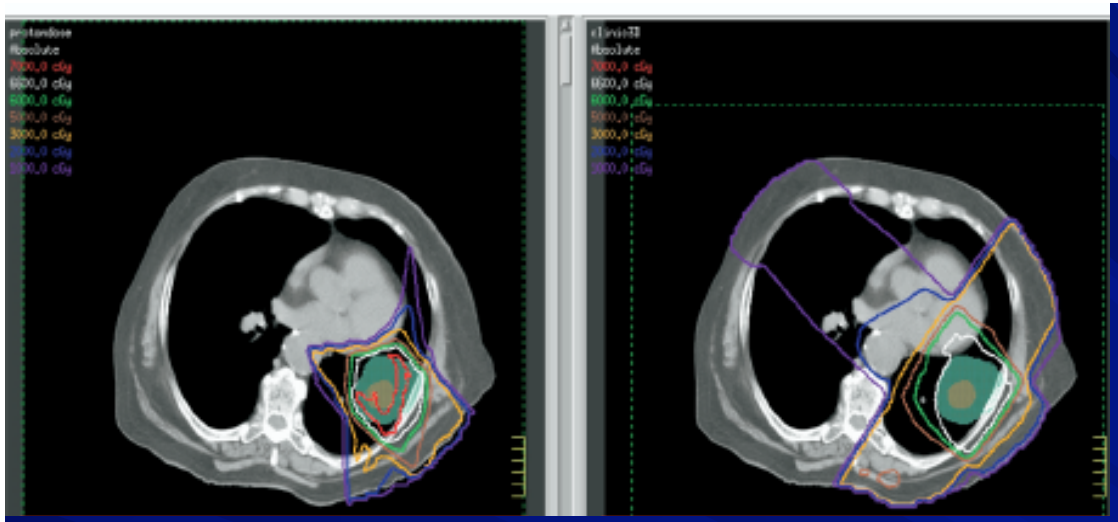


Proton Plan

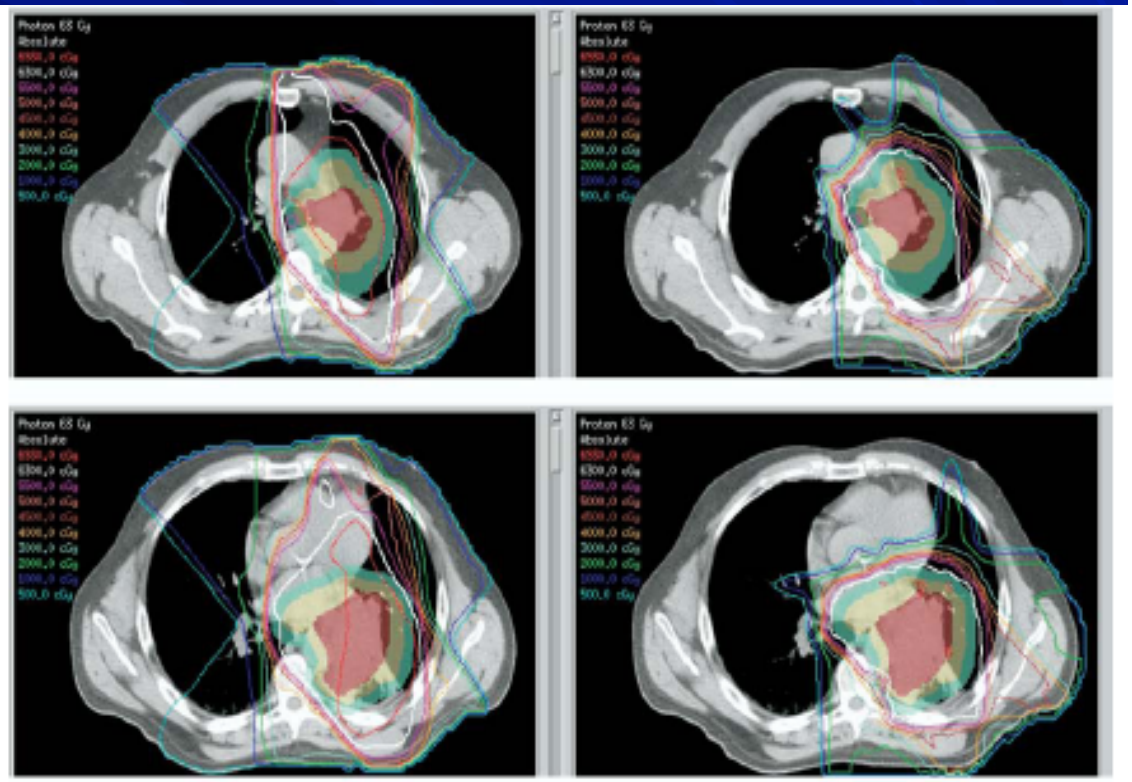
Photon Plan

Stage III NSCLC

Stage I NSCLC

Photon Plan

Proton Plan



Objectives

- Clinically evaluate incidence of treatment related pneumonitis (TRP) in:
  - Patients with locally advanced NSCLC who received concurrent CT with XRT (Proton Beam Therapy (PBT) or IMRT

Methods

- Retrospective Study
- From 2002 to 2007
- 106 patients identified
- PBT: 31 patients (2005-2007)
- IMRT: 75 patients (2002-2007)
- All patients after 2004 had treatment planning with 4D CT

Methods: Criteria

- Inclusion Criteria:
  - Concurrent Chemotherapy
  - No history of prior major thoracic RT
  - Dose >= 60 Gy (CGE for protons)
- Excluded
  - IMRT + 3D-CRT or IMRT + PBT

Methods: Toxicity

- Common Terminology Criteria (CTC) version 3.0 was used to grade toxicity

PULMONARY/UPPER RESPIRATORY						Page 3 of 4
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						

Patient Characteristics	PBT + Concurrent CT (N=31)	IMRT + Concurrent CT (N=75)	p-value
Gender			*0.857*
Male	20	47	
Female	11	28	
Age			*0.096*
Median (Range)	64.4 (45-78)	62 (38-82)	
Wt Loss			*0.118*
<5 %	25	49	
>= 5%	6	26	
Prior Malignancy			*0.001*
Yes	14	10	
No	17	65	

Tumor Characteristics	PBT + Concurrent CT (N=31)	IMRT + Concurrent CT (N=75)	p-value
Histology			*0.001*
Squamous	19	20	
Non-squamous	12	55	
Clinical Stage			*0.061*
IIB	1	4	
IIIA	10	15	
IIIB	11	42	
IV	2	9	
Recurrence	8	5	
Tumor Location			*0.413*
Left Lung	13	25	
Right Lung	18	47	
Mediastinum	0	3	

Chemotherapy Regimen

	PBT N = 31	IMRT N = 75
Induction CT	13 (42%)	37 (49%)
Concurrent CT	31	75
Carbo + Taxol	19 (61%)	42 (56%)
Cis + Taxol	6	4
Carbo + Etop	4	8
Cis + Etop	0	2
Other	2	19
Adjuvant CT	8 (26%)	18 (25%)

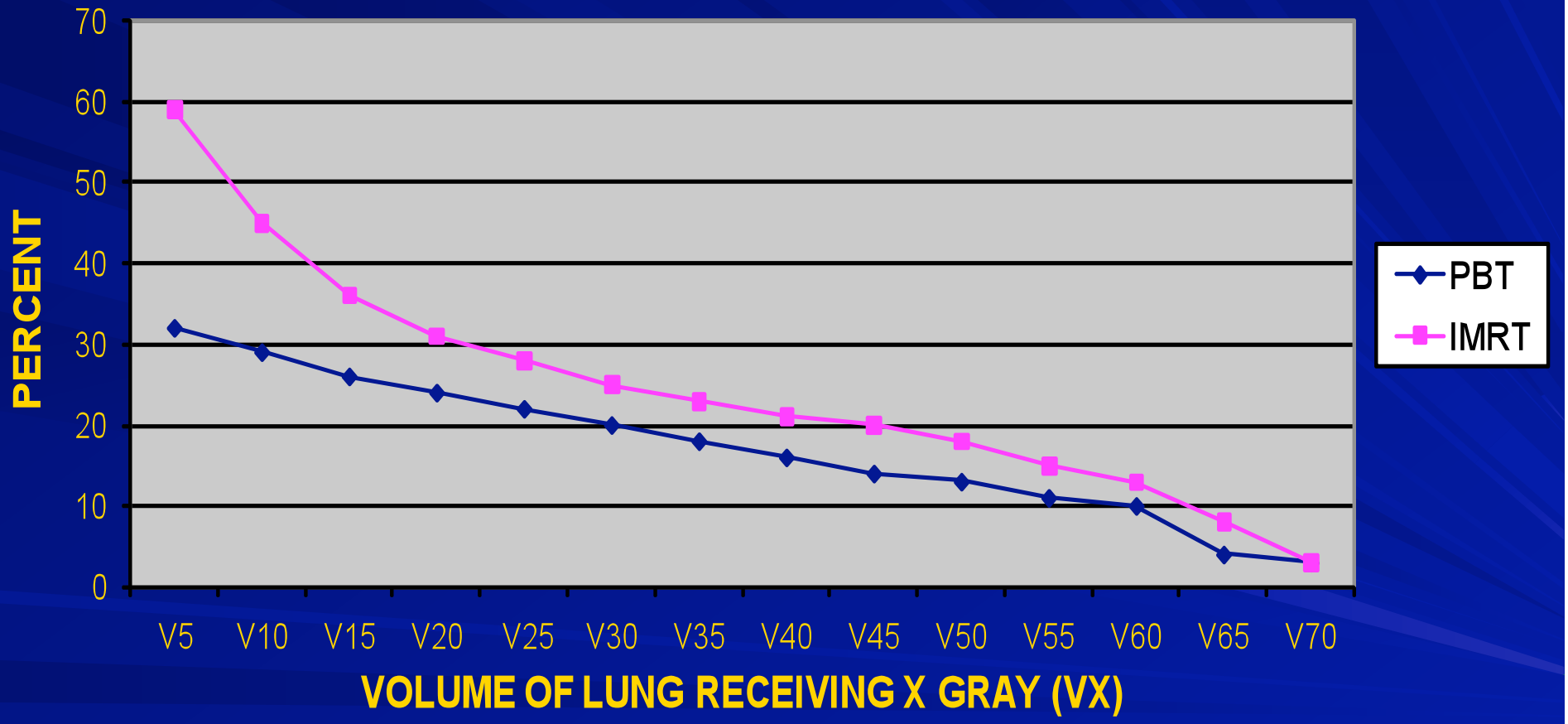
Results

	PBT	IMRT	p value
Median f/up Range	9.5 mo (range, 1.6 -16.1)	9.8 mo (range 1.4 – 32.3)	
Median KPS	80	80	
Median GTV volume	93.6 ml (range, 13 – 431 ml)	247.7 ml (range, 21 - 818 ml)	*<.0001*
Median Dose	74 CGE (range, 63 – 74 CGE) <on protocol>	63 Gy (range, 60 -76 Gy)	

Dosimetric Results

Mean V (dose)*	PBT	IMRT	p value
V5	**32**	**59**	***0.0001***
V10	**29**	**45**	***0.0001***
V15	26	36	*0.0006*
V20	**24**	**31**	***0.005***
V30	20	25	0.02
V40	16	21	0.009
V50	13	18	0.010
V60	10	13	0.07
V70	3	3	0.45

VOLUME OF NORMAL LUNG RECEIVING A RELATIVE DOSE FOR PBT VS IMRT



PBT reduced amount of normal lung receiving 5Gy – 65 Gy

Clinical Results

Incidence of Pneumonitis	PBT	IMRT	p value
Grade 1	12 (39%)	28 (37%)	*0.38*
Grade 2	6 (19%)	18 (24%)	
Grade =>3	0	7 (9.3%)	

Tumor Volume and TRP

GTV (cc)	N	=>2 TRP Events (%)	P value	V20%	P value
<=100	**PBT = 22** IMRT = 9	2 (9.1) 3 (33.3)	0.10	21 29	0.124
<=200	**PBT = 28** IMRT = 30	5 (17.9) 10 (33.3)	0.18	23 30	0.023
<=300	**PBT = 29** IMRT = 43	5 (17.2) 16 (37.2)	0.07	24 32	0.002
<=400	**PBT = 30** IMRT = 48	6 (20.0) 19 (39.6)	0.07	24 32	0.004
<=500	**PBT = 31** IMRT = 56	6 (19.4) 20 (35.7)	0.11	24 32	0.007

Summary of Results

- Compared to IMRT, PBT significantly reduced amount of normal lung receiving 5Gy – 65 Gy.
- Absolute Reductions
  - V5 of 30%
  - V10 of 15%
  - V20 of 7%
- Grade 2 – 5 TRP (*p=0.15*)
  - IMRT: 33%
  - PBT: 19.4%
- No patients treated with PBT experienced Grade >= 3 TRP compared to 9.3% with IMRT (*p = 0.078*)
- Analysis by GTV size: Trend towards decrease incidence of TRP in PBT arm compared to IMRT

Conclusions

- In patients with locally advanced NSCLC treated with PBT or IMRT with concurrent CT, preliminary evaluation shows that:
  - PBT appears to reduce frequency of TRP despite a higher total cumulative dose when compared to IMRT
- Longer follow up time and more patients are needed to confirm these results

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