Preliminary Evaluation of Bone Marrow Suppression in Locally advanced NSCLC patients treated with Concurrent Chemotherapy and Proton Therapy (PBT) or IMRT

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Background

- Standard of care for locally advanced NSCLC is concurrent CT/XRT
- These patients are at risk of BM toxicity which can lead to
  - Interrupt or lower dose of CT or XRT
  - Hospitalizations
  - Need for Growth Factors to avoid treatment interruption
  - Reduce QOL

Bone Marrow Distribution

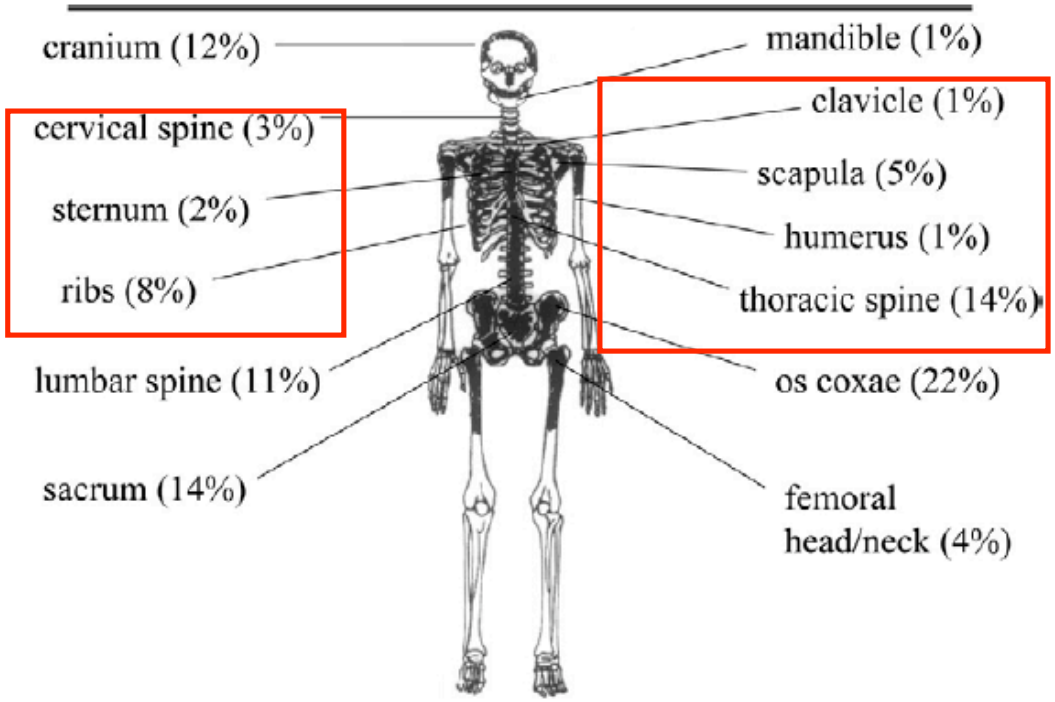


Fig. 1. Distribution of bone marrow in an adult. Adapted, with permission, from Ellis *et al.* (14) and Mauch *et al.* (19).

Thorax - Thoracic Spine + Ribs + Clavicle + Sternum = 25% of BM reserve

Part of these areas are included in the treatment volume, especially for patients with locally advanced disease

Hypothesis

- Proton Beam Therapy (PBT) compared to photons shows lower exit dose and lower integral dose
- This may translate into lower BM toxicity in patients treated with concurrent CT and PBT

Objective

- To compare BM toxicity in patients with locally advanced NSCLC treated with concurrent CT and either PBT vs. IMRT

METHODS

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

Methods: Criteria

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

Methods: Toxicity

- Common Terminology Criteria (CTC) version 3.0 was used to grade toxicity
- Acute toxicity
- Time Frame: from start of XRT to 2 months months after completion of XRT treatment
  - Hemoglobin
  - Platelets
  - WBC/Neutrophils/Lymphocytes
  - Fatigue

Methods: Toxicity

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

BLOOD/BONE MARROW Page 1 of 1

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death

Methods: Toxicity

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

CONSTITUTIONAL SYMPTOMS						Page 1 of 2
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—

ADL: Activity of Daily Life

Patient Characteristics

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

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	Most patient had stage III disease
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%)**

Most common concurrent regiment was Carbo/Taxol

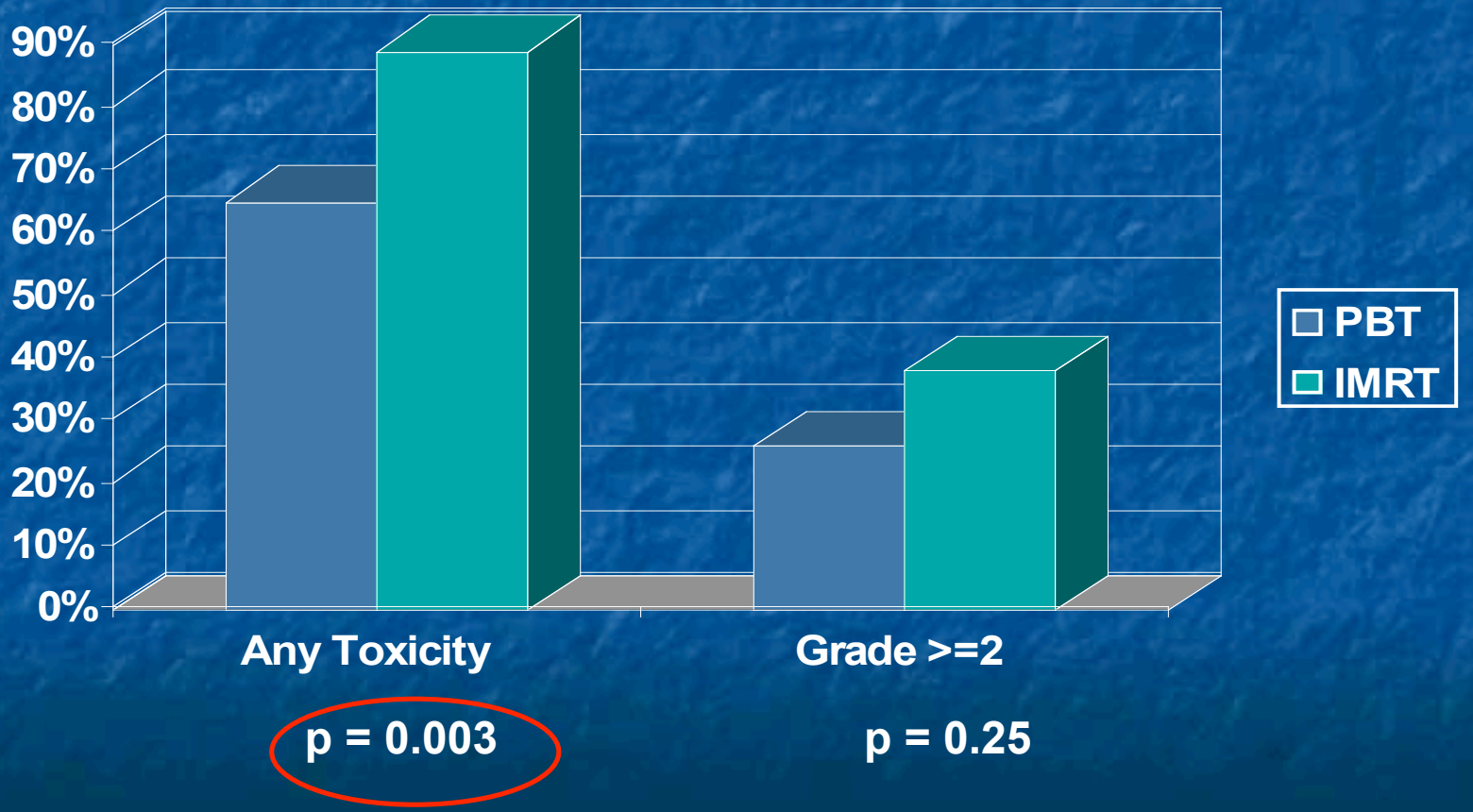
Mean and Range Baseline Hematologic Values for PBT and IMRT Patients

	PBT	IMRT	P-value
Hemoglobin	**13.3 (10.0-16.0)**	**12.5 (8.8-15.6)**	**0.01**
Platelets	**290.7 (66-640)**	**384.8 (247-703)**	**0.25**
Neutrophils	**5.7 (1.6-12.5)**	**6.5 (2.2-121.4)**	**0.35**
Absolute Lymphocytes	**1.4 (0.5-2.9)**	**1.7 (0.3-3.8)**	**0.11**
White Blood Count	**7.9 (3.1-12.7)**	**9.0 (3.1-26.9)**	**0.32**

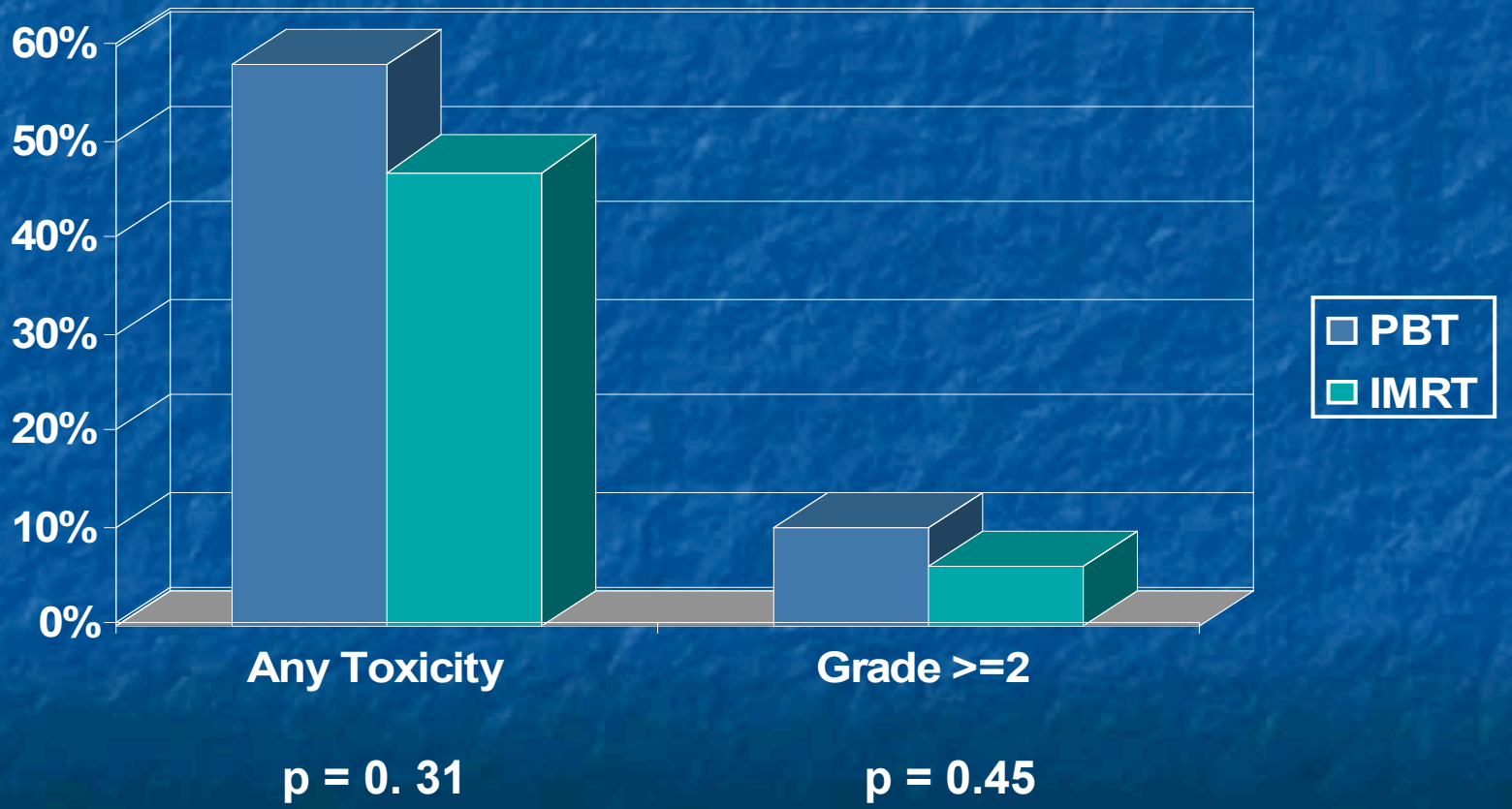
Results

	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)	

Hemoglobin Toxicity
PBT versus IMRT Patients



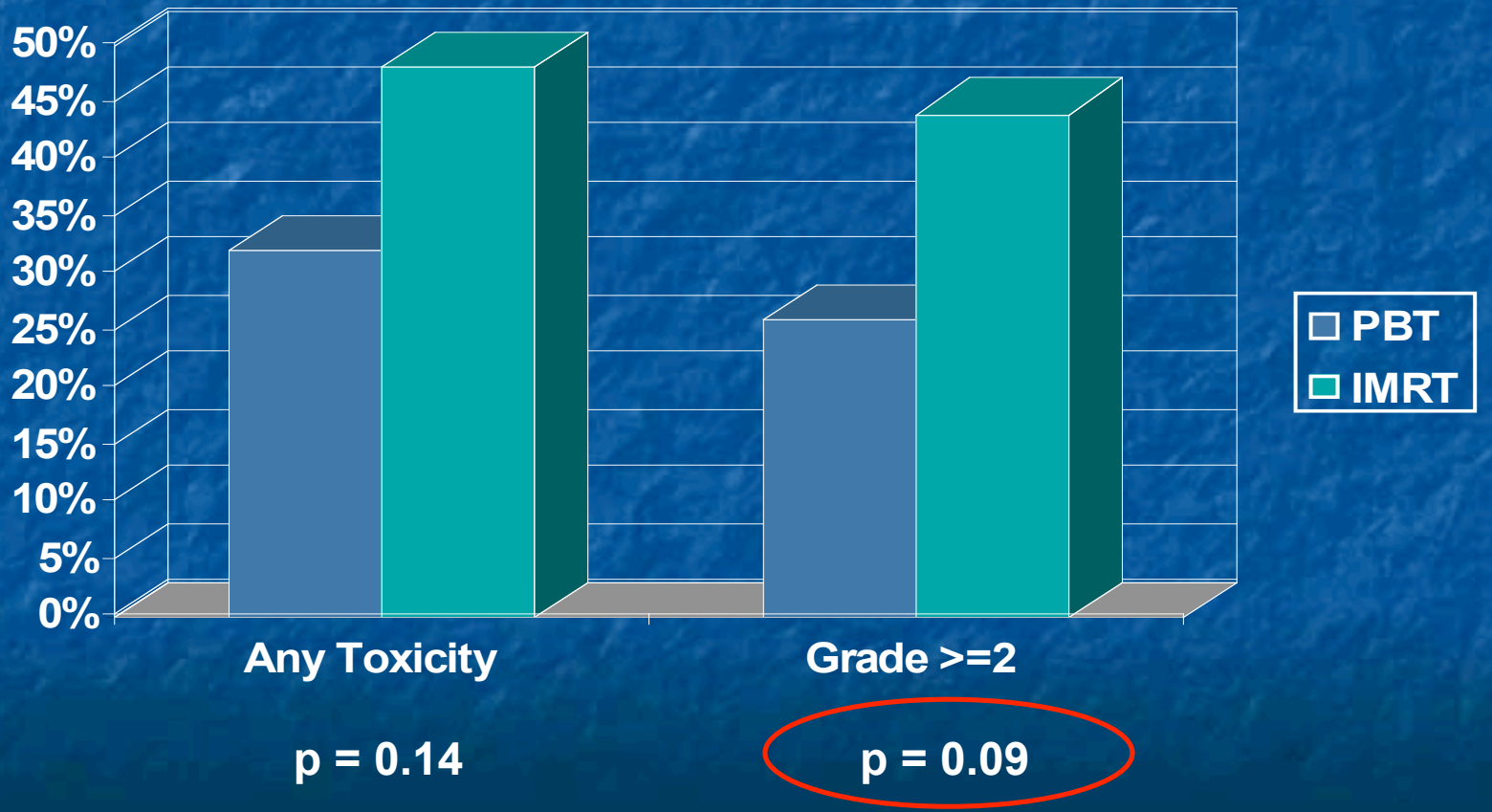
Platelet Toxicity
PBT versus IMRT Patients



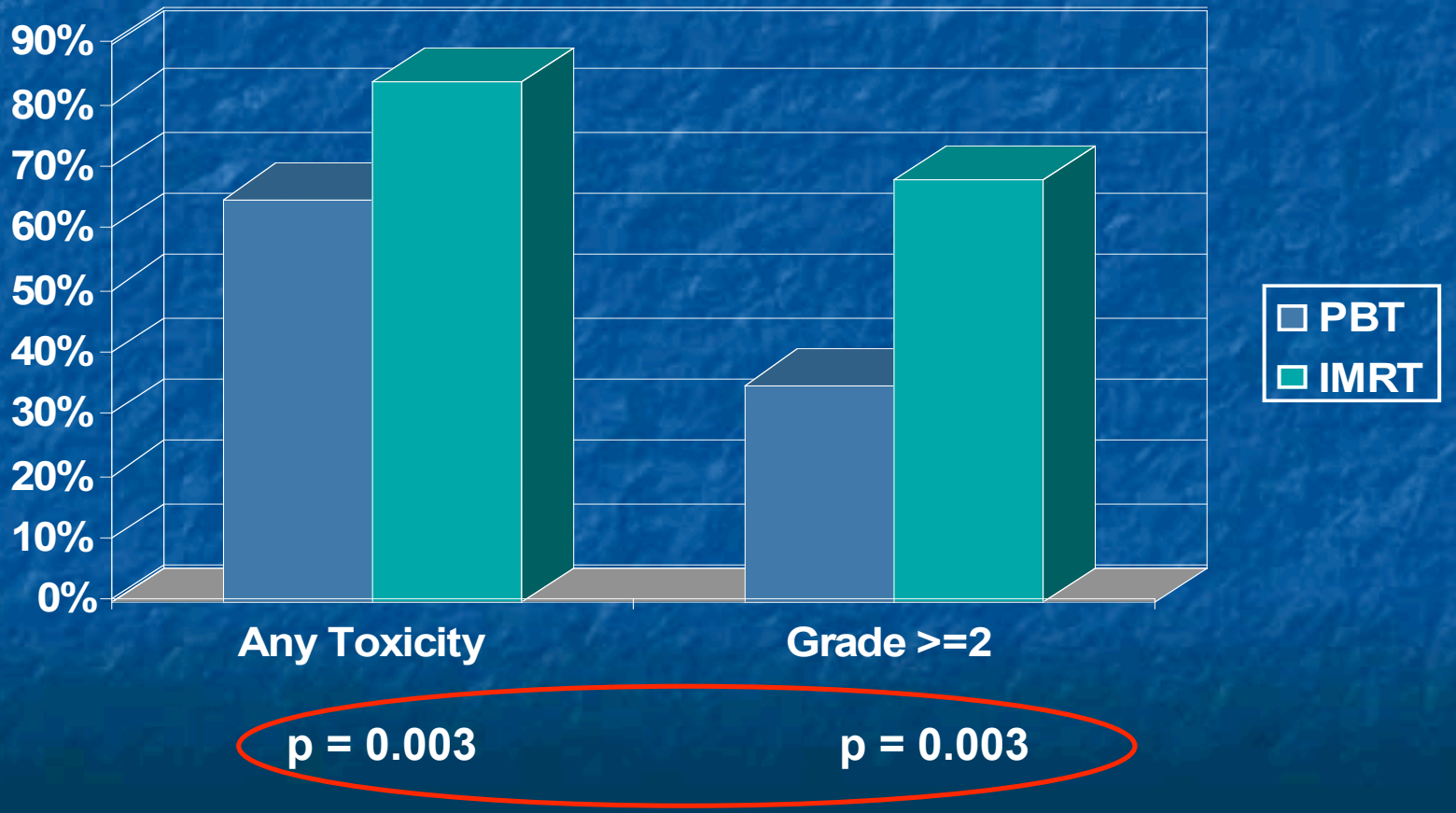
p = 0. 31

p = 0.45

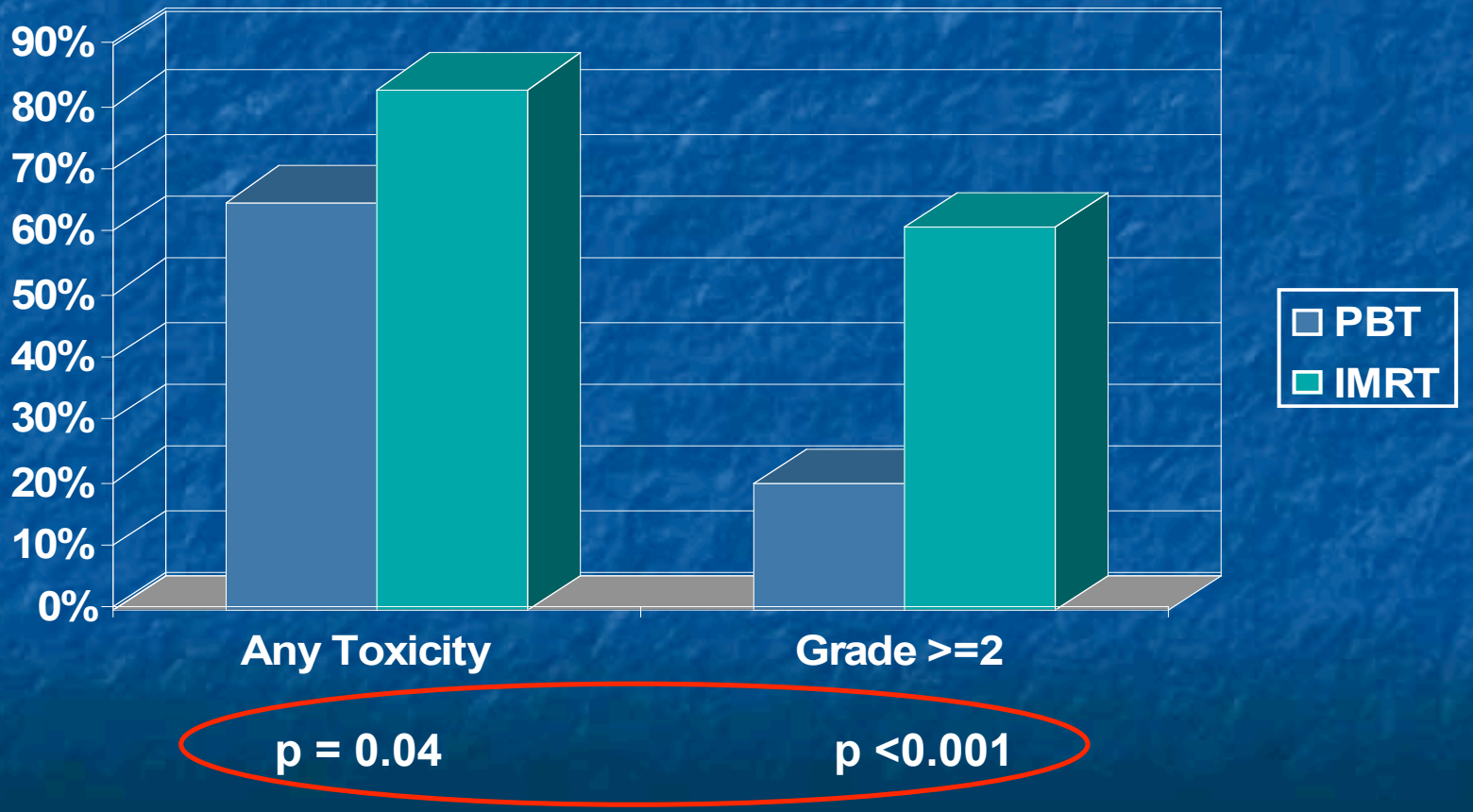
Neutrophil Toxicity
PBT versus IMRT Patients



WBC Toxicity
PBT versus IMRT Patients



Fatigue Toxicity
PBT versus IMRT Patients



Tumor Volume and BM toxicity

GTV (cc)	N	N (%) of ≥2 Grade Hemoglobin Events	P value	N (%) of ≥2 Grade Platelets Events	P value
≤ 100	PBT = 22 IMRT = 9	16 (72.7) 7 (87.5)	0.40	6 (36.4) 8 (75.0)	0.06
≤ 200	PBT = 28 IMRT = 30	8 (28.6) 8 (27.6)	0.93	11(39.3) 21(75.0)	0.007
≤ 300	PBT = 29 IMRT = 43	8 (27.6) 13 (30.0)	0.76	11 (37.9) 29 (70.7)	0.006
≤ 400	PBT = 30 IMRT = 48	8 (26.7) 13 (37.7)	0.35	11(36.7) 33 (73.3)	0.002
≤ 500	PBT = 31 IMRT = 56	8 (26.7) 20 (37.7)	0.31	11(35.5) 29 (69.1)	0.004

Tumor Volume and BM toxicity

GTV (cc)	N	N(%) of ≥2 Grade Neutrophil Events	P value	N(%) of ≥2 Grade WBC Events	P value	% of ≥2 Grade Abs. Lymphocyte Events	P value
<=100	PBT = 22 IMRT = 9	7(31.8) 4(44.4)	0.51	2(9.1) 1(11.1)	0.85	13(61.9) 6(85.7)	0.24
<=200	PBT = 28 IMRT = 30	8(28.6) 13(44.8)	0.20	2(7.1) 2(6.7)	0.94	18(64.3) 25(89.3)	0.03
<=300	PBT = 29 IMRT = 43	8(27.6) 17(40.5)	0.26	3(10.3) 2(4.7)	0.35	18(62.1) 38(92.7)	0.002
<=400	PBT = 30 IMRT = 48	8(26.7) 21(45.7)	0.10	3(7.5) 2(4.3)	0.52	19(63.3) 42(93.3)	0.001
<=500	PBT = 31 IMRT = 56	8(26.7) 25(47.2)	0.07	3(9.7) 3(5.6)	0.48	20(64.5) 47(92.2)	0.002

Limitations

- Retrospective Study
- Data on blood transfusions, growth factors, treatment break for chemo, or dose reduction in chemo not available for all patients
  - Data is being collected

Conclusions

- In patients with locally advanced NSCLC treated with PBT or IMRT with concurrent CT, our preliminary evaluation shows that:
  - PBT significantly reduced any Hgb. toxicity compared to IMRT.
  - PBT significantly reduced frequency of fatigue compared to IMRT.
  - PBT significantly reduced any and grade $\geq$2 WBC toxicity compared to IMRT.
  - PBT and IMRT showed no difference in grade $\geq$2 platelet toxicity.
  - Breakdown by tumor size showed that PTB significantly reduced grade$\geq$2 Plt. & Lymph. toxicities compared to IMRT.

Future

- Prospective Randomized Study

  3DCRT vs. IMRT vs. PTB

  has been activated and accruing patients with stage III NSCLC
- All patients get concurrent chemotherapy for this study
- Target :168 patients
- Endpoint : Comparison of NTCP

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