Rationale for Particles

PTCOG 52
Educational Workshop

Stephen M. Hahn

June 3, 2013

PENN RADIATION ONCOLOGY
Penn Medicine

Disclosures

- **No conflicts to disclose**

http://www.med.upenn.edu/apps/my/index.php?_app_id=514c3d4ae8ab5&_display=1&_hist_id=1&_preserve[init_panel]=%2Fead_public%2Fmain&CEALID=

CA A Cancer Journal for Clinicians

Cancer Statistics, 2013

Rebecca Siegel, MPH1; Deepa Naishadham, MA, MS2;
Ahmedin Jemal, DVM, PhD3

Overall, cancer death rates have declined 20% from their peak in 1991 (215.1 per 100,000 population) to 2009 (173.1 per 100,000 population).

Death rates continue to decline for all 4 major cancer sites (lung, colorectum, breast, and prostate).

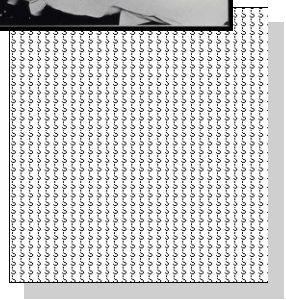
The reduction in overall cancer death rates since 1990 in men and 1991 in women translates to the avoidance of approximately 1.18 million deaths from cancer, with 152,900 of these deaths averted in 2009 alone.

CACancerJClin2013;63:11-30.VC 2013AmericanCancerSociety.

The Evolution of Radiation Therapy

1960's

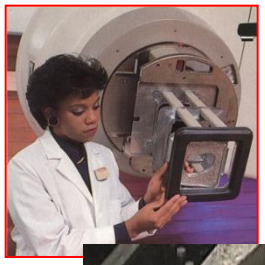
The First Clinac

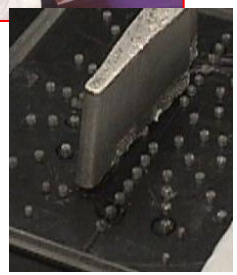


Standard Collimator

The linac reduced complications compared to Co60

1970's



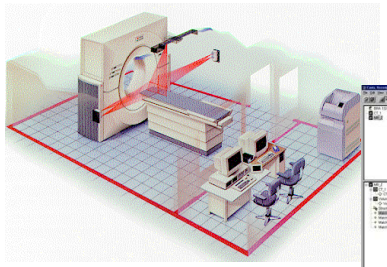


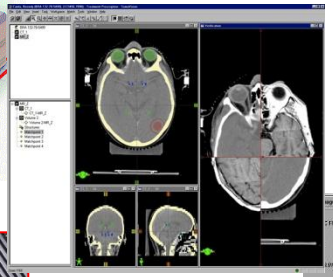
Cerrobend Blocking
Electron Blocking

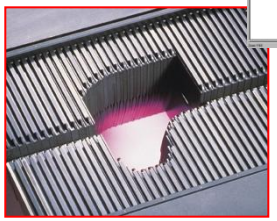
Blocks were used to reduce the dose to normal tissues

1980's

Computerized 3D CT Treatment Planning



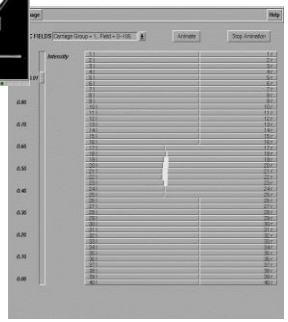




Multileaf Collimator

MLC leads to 3D conformal therapy which allows the first dose escalation trials.

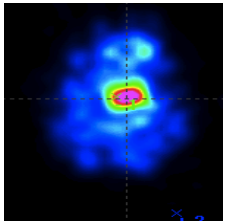
1990's



Dynamic MLC and IMRT

Computerized IMRT introduced which allowed escalation of dose and reduced compilations

2000's



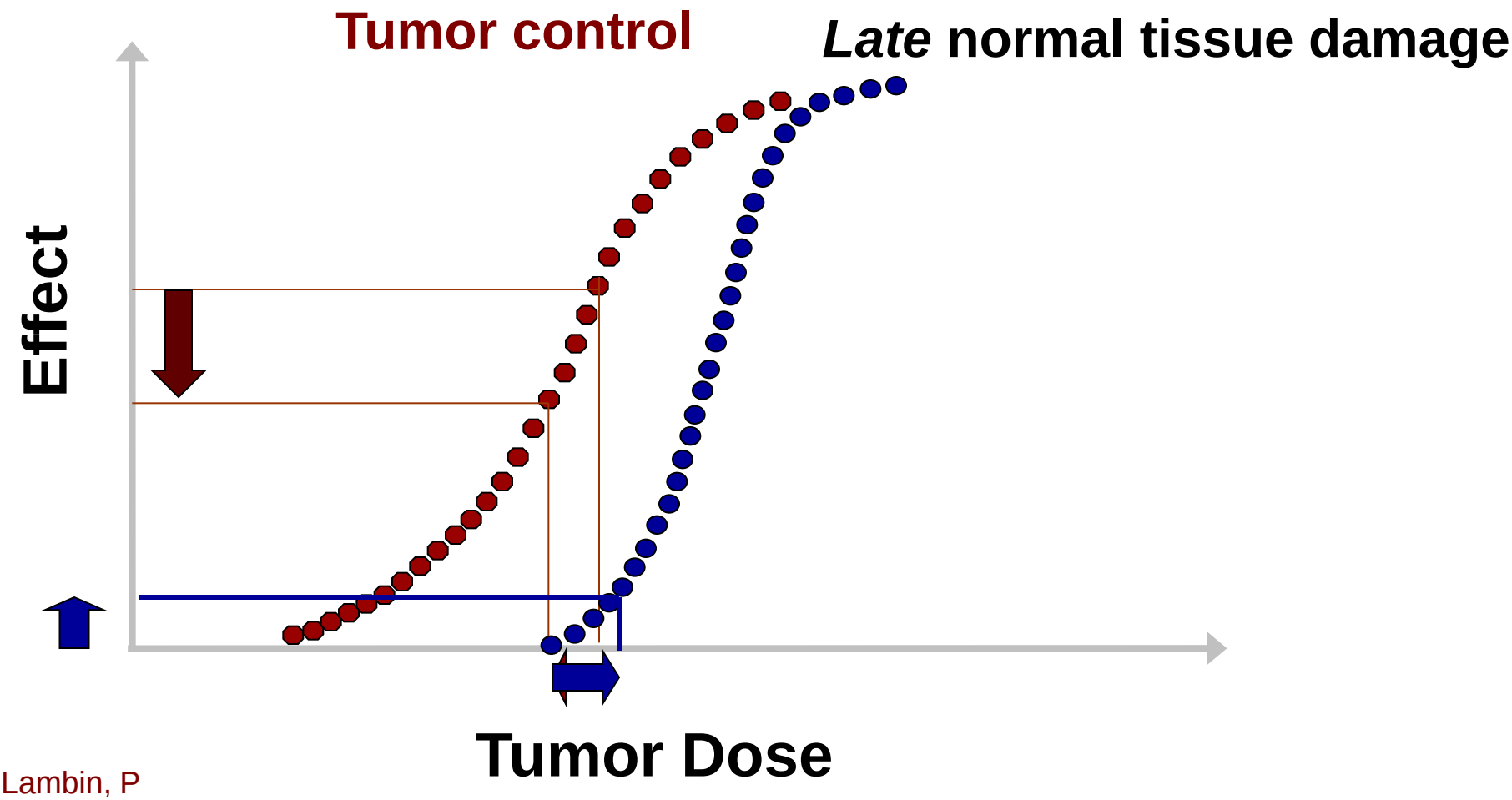
Functional Imaging

High resolution IMRT

IMRT Evolution evolves to smaller and smaller subfields and high resolution IMRT along with the introduction of new imaging technologies

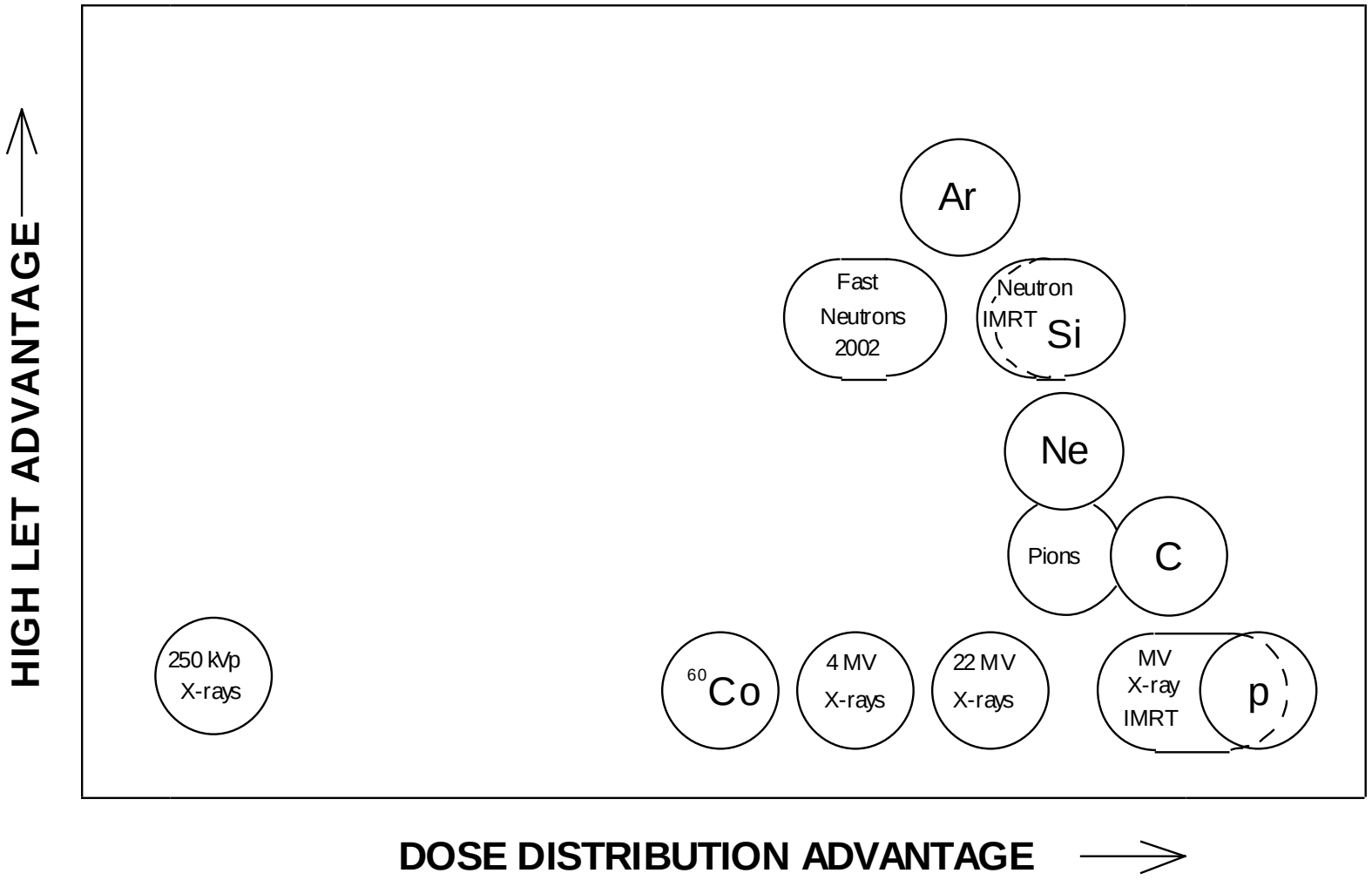
McKenna, WG

Effect of underdosage and overdosage



Lambin, P

Characteristics of Proton and Heavy Particle Therapy



Kohler, A

Relative Effects of Particle Therapy

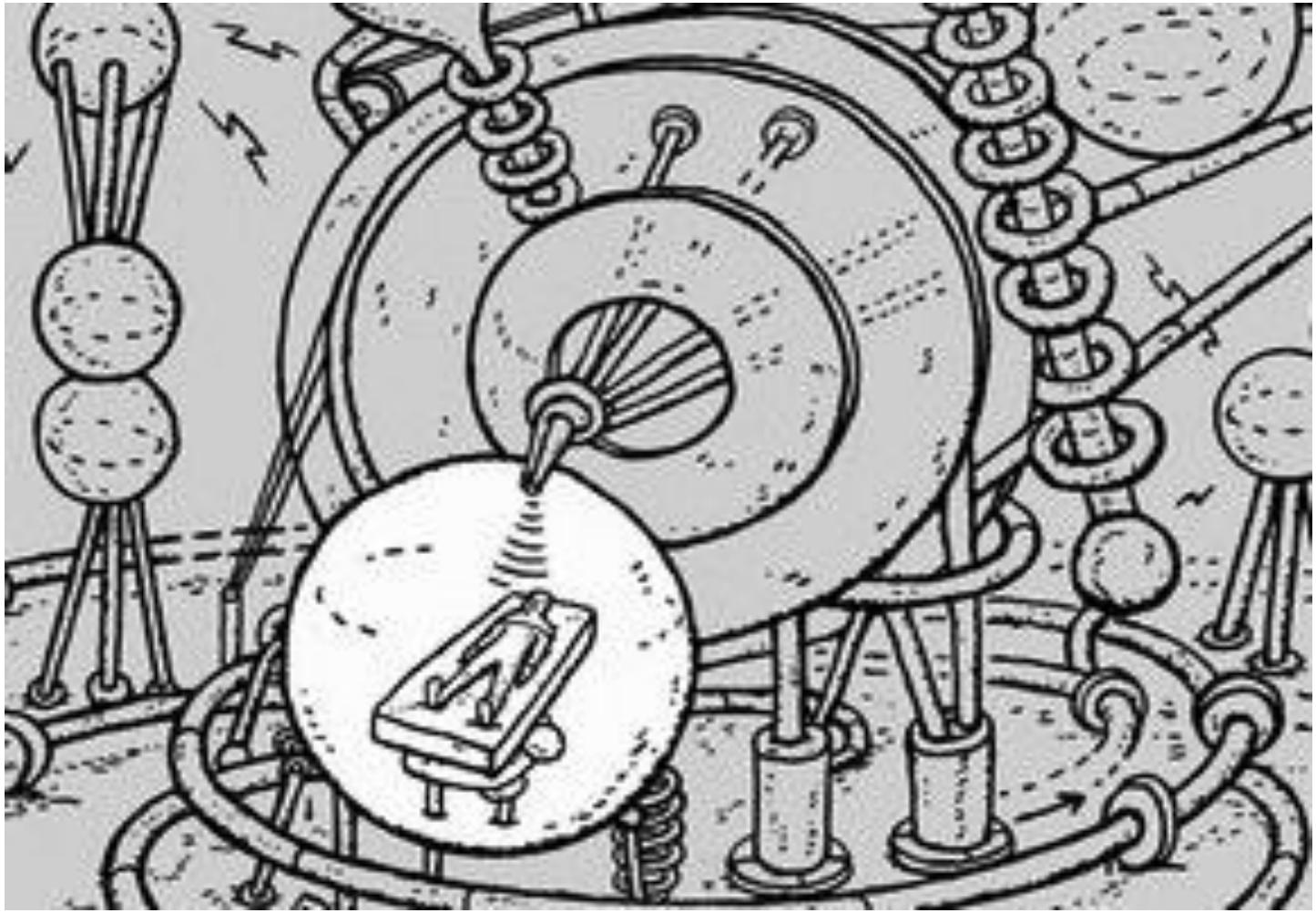
- Proton RBE is similar to photons & there is ample clinical experience providing reassurance to clinicians re: late effects
- Distribution advantages of heavy ion beams are similar to those of protons.
- Tail on Bragg peak due to ^{12}C break-up
- Improved Lateral Penumbra compared to protons
- Heavy ions are relatively high LET particles and may provide a biological (RBE) & clinical advantage
- RBE is dependent upon dose, biological system, dose rate, endpoints evaluated
- Higher RBE is only a therapeutic advantage for tumors if there is a therapeutic ratio with normal tissues

Summary - Rationale for Particles

- **Dose distribution – less normal tissue dose relative to the dose deposited in tumors. Dose conformality is key, however. The dose distribution advantage will be most critical in those clinical situations where toxicities are of greatest concern**
  - **Pediatrics**
  - **Combined modality setting**
  - **Proximity to critical structures**
  - **Second malignancies**
- **Biological advantage for some tumors with higher LET particles. Fractionation, dose, dose rate are key factors. The LET advantage will be important in**
  - **Hypoxic Tumors (oxygen effect)**
  - **Slowly growing tumors**

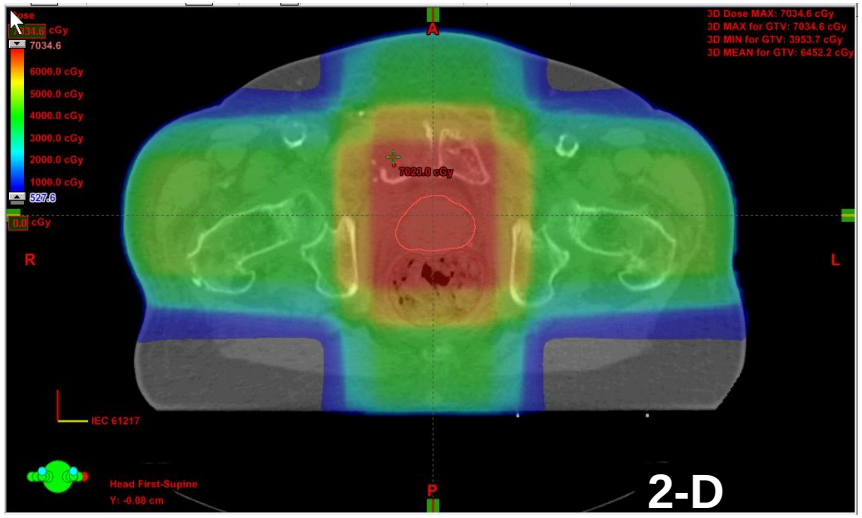
Summary - Rationale for Particles

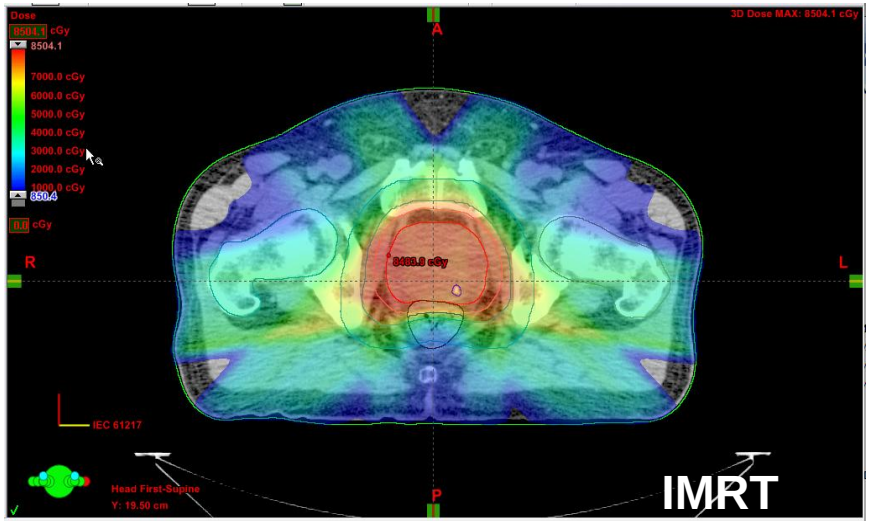
- **Higher Health Care Value**

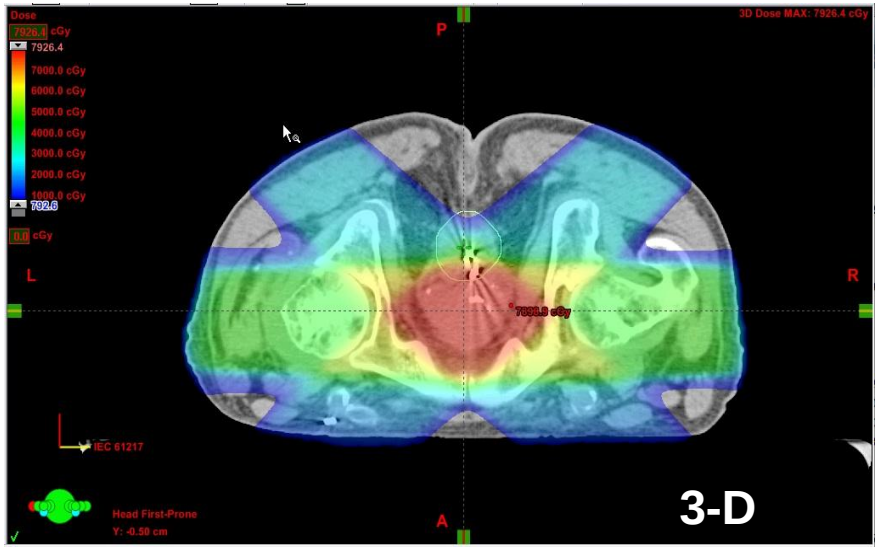


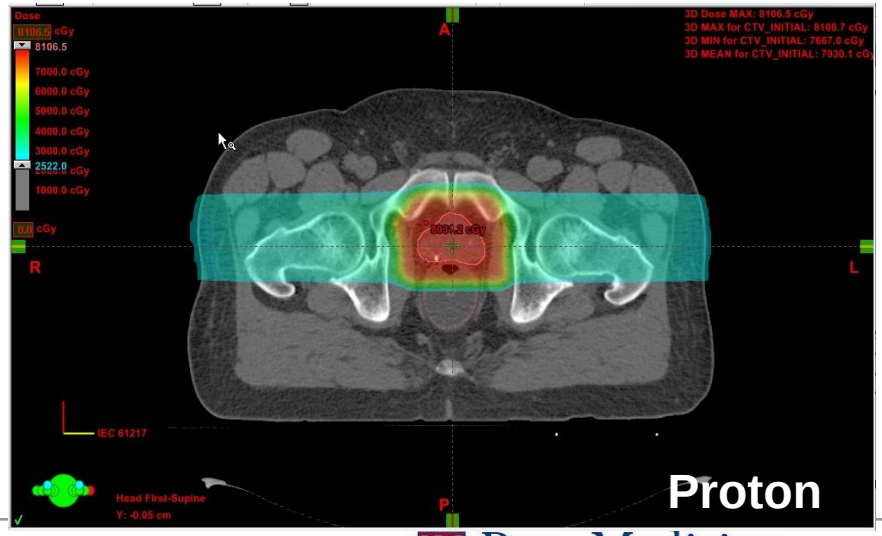
Emanuel and Pearson NYT January 2012

The Evolution of Conformal Radiotherapy





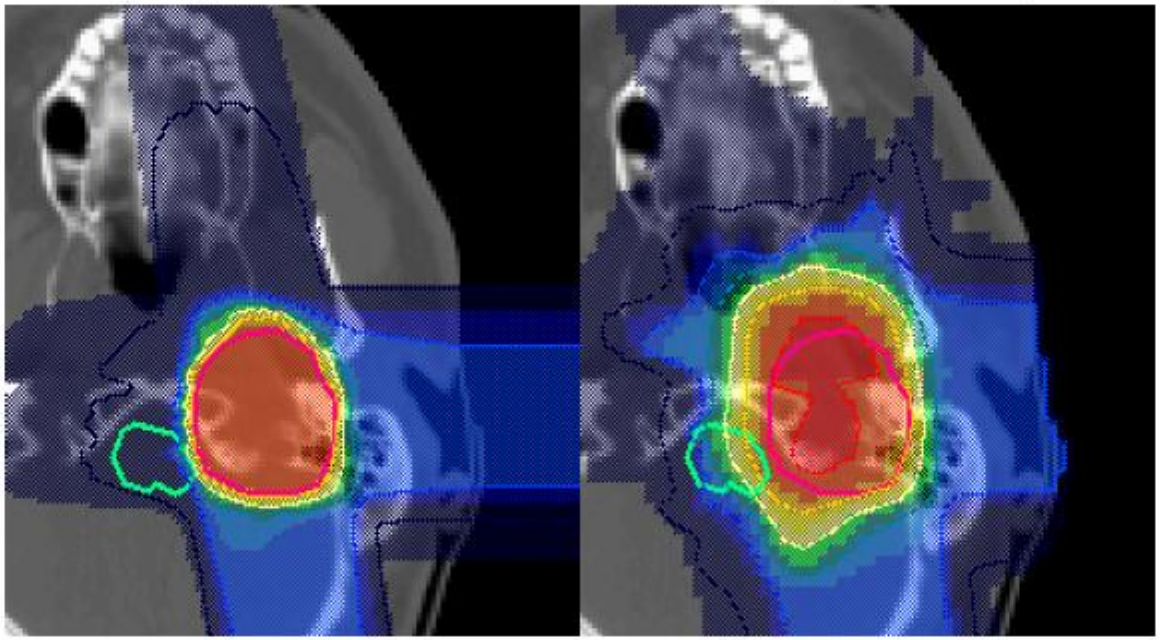




Comparison of Carbon Ions vs. Protons

C-12 (GSI)

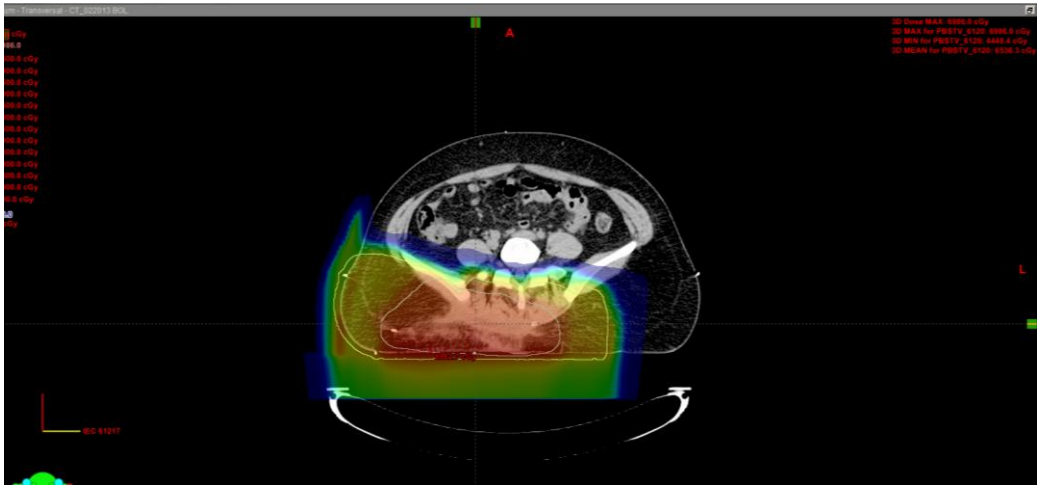
Protons (Capetown/SA)



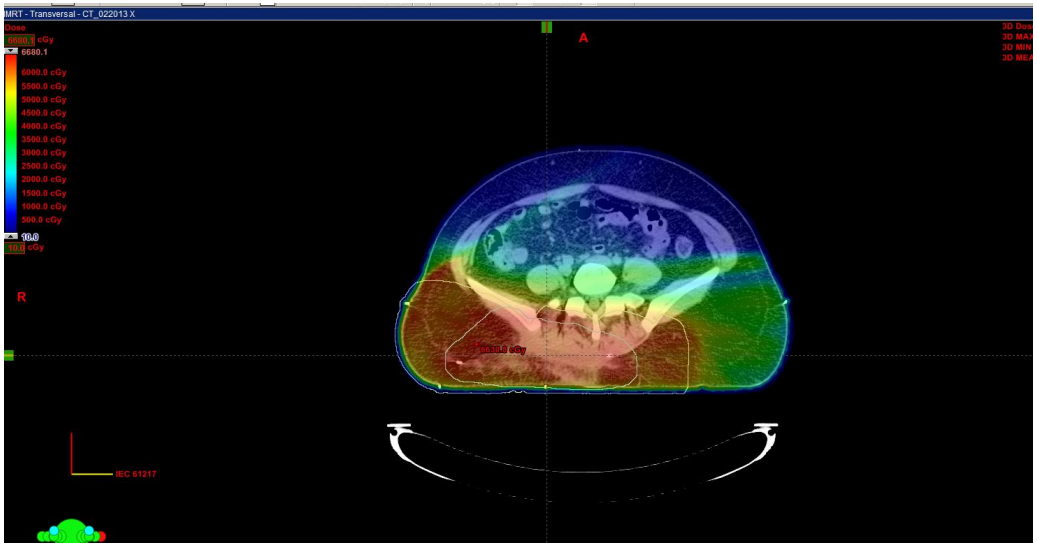
Advantage due to beam scanning and less lateral scattering

O.Jaekel et al. DKFZ

Proton Therapy in the Future – PBS on a Gantry



PBS



IMRT

47 year old woman with a desmoid tumor s/p multiple resections and positive Margins

Past & Current State – Particle Therapy

- There have been many patients treated with particle therapy
- > 11,000 patients treated with ion beams – Berkley which closed in 1992 and currently NRIS/Chiba, CNAO and GSI/HIT
- > 12,000 patients treated with fast neutrons – Seattle, Detroit, FermiLab, France, Belgium, & S. Africa
- >1,000 patients treated with pions - Los Alamos, PSI, TRIUMF
- > 4,000 patients treated with BNCT – BNL, MIT, Japan, Netherlands and Finland
- >90,000 patients treated with protons

PCTOG 2011

What are the Data For the Clinical Use of Particle Therapy?

- **Pediatric Malignancies – Protons based not on the existence of Level 1 data but the unarguable necessity for reducing integral dose**
- **Ocular Melanoma - Protons**
- **Skull Base and Spine Tumors - Protons**
- **Salivary Gland Tumors – neutrons**
- **Emerging proton data in the combined modality setting**
- **Current randomized trials in protons – locally advanced NSCLC & low/intermediate risk prostate cancer**

Second Malignancies

- MGH-Harvard Cyclotron Laboratory
- Matched retrospective cohort study of 1,450 HCL proton pts and photon cohort in SEER cancer registry.
- Matched 503 HCL proton patients with 1591 SEER patients
- Median f/u: 7.7 years (protons) and 6.1 years (photon)
- Median age 56 (protons) and 59 (photons)
- Second malignancy rates
  - 6.4% of proton patients (32 patients)
  - 12.8% of photon patients (203 patients)
- Photons are associated with a higher second malignancy risk
  - Hazard Ratio 2.73, 95% CI 1.87 to 3.98, p< 0.0001

Courtesy of H. Shih, MD

Chung et al. ASTRO 2008

Unanswered Questions

- **Ideal Fractionation with particle therapy and how does this differ between higher and lower LET therapies?**
- **RBE (and potentially normal tissue effects) is dependent upon LET but also dose, biological system, dose rate, endpoints evaluated**
- **It may be important to take advantage of the higher RBE of high LET radiation for tumor control but the effects on normal tissues may limit application.**
- **If hypofrationation is considered, it is probably important to limit the deposition of high LET radiation in normal tissues because the repair differences between tumor and normal tissue will likely be less important**
- **Therefore, motion management, onboard imaging, advanced imaging for tumor and normal tissue delineation become critical factors**
- **In the end, for clinicians, it is about the balance between tumor control and late normal tissue toxicities.**

Unanswered Questions

- What is the role of particle therapy in the treatment of hypoxic tumors?
- Patient selection is critical – the role of biomarkers
- Hypoxia imaging will likely be important
- We need to understand better the role of re-oxygenation
- There are emerging data which relate abnormalities in the tumor microenvironment to molecular events (signal transduction pathway activation)
- We will need to understand the molecular signatures of tumors that are associated with hypoxia
- We will also need to understand the molecular signatures of treatment and how that predicts for clinical outcome.

When Should We Use Particles?

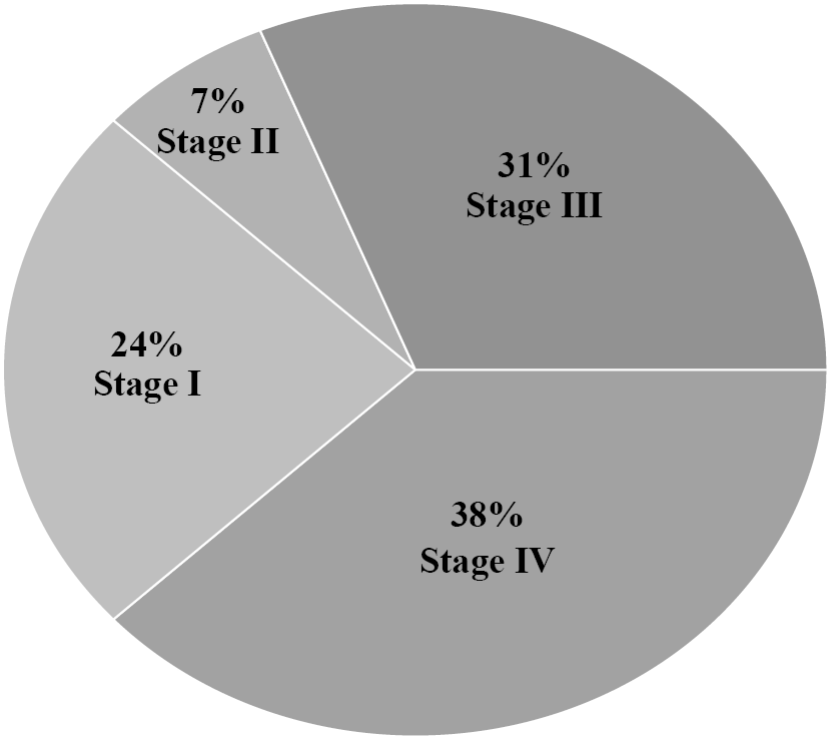
- Serious AE with x-rays
- Importance of surrounding normal tissue
- Improvements in local control are needed
- Late morbidity is an important issue
- Complex geometry
- Target volume large relative to normal tissue compartment
- Tumor biology factors – hypoxia, repair
  - Adapted from Zietman, Goiten, Tepper JCO 2010

Possible Clinical Situations for Particle Therapy

- Pediatric Malignancies
- Combined modality setting – dose avoidance
  - NSCLC
  - GI cancers
  - cervical cancer
- Hypofractionation
- Re-irradiation
- Tumors of the Brain, Spine & CNS
- Tumors of the Mediastinum
- Low grade or benign tumors
- Hypoxic & radio-'unresponsive' Tumors

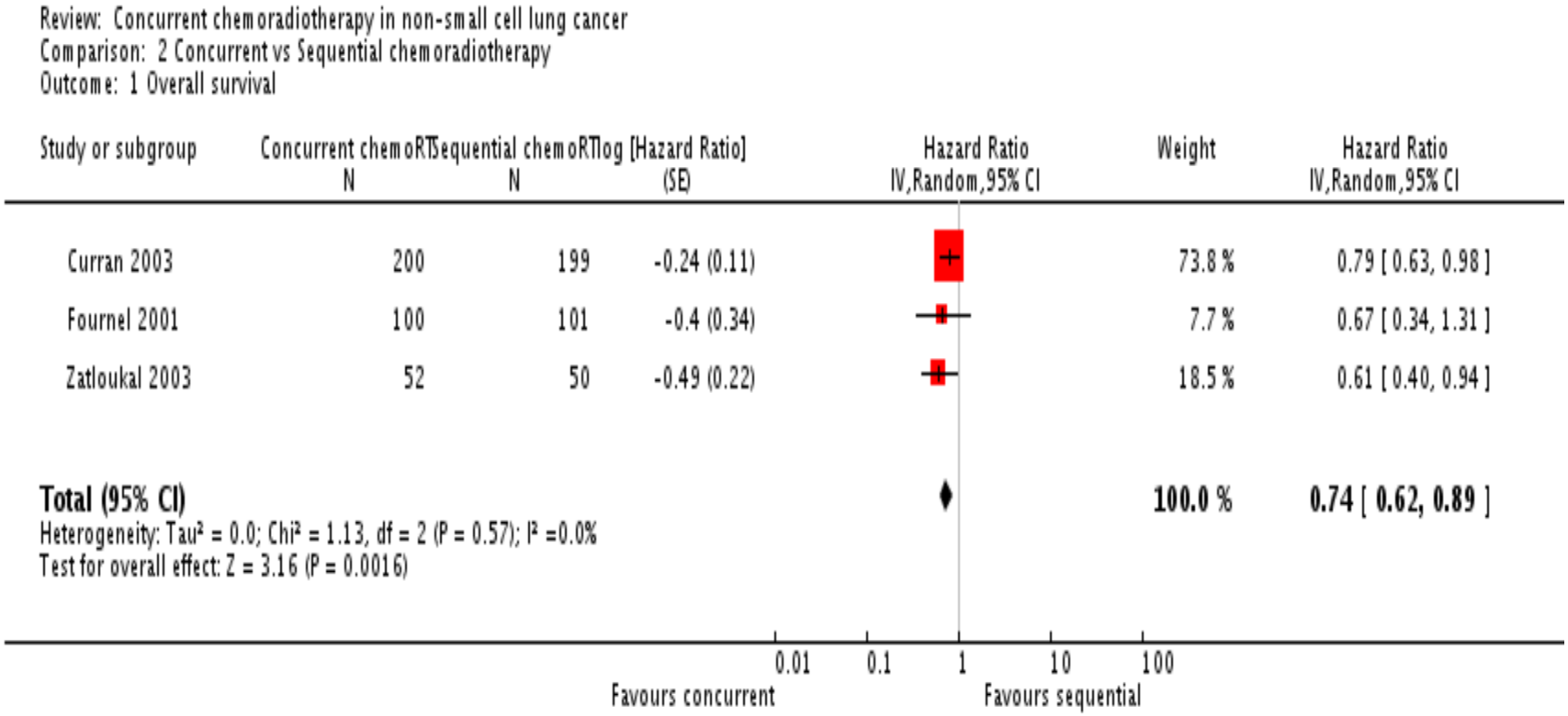
NSCLC - Advanced Disease is Common…

- **70% of NSCLC patients present with Stage III or IV disease**



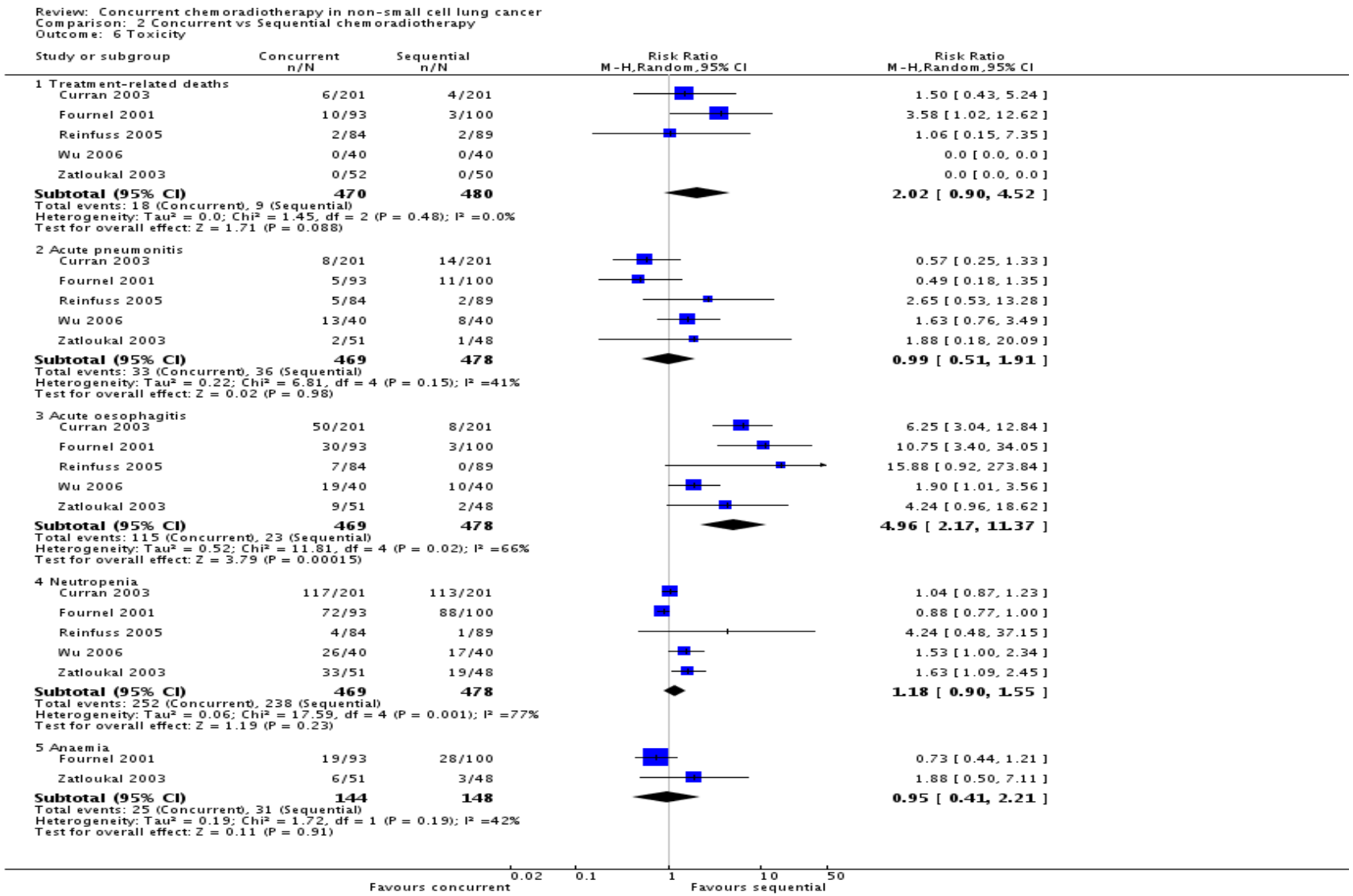
Chemoradiotherapy is the standard approach in many of these patients

Overall Survival Improved with Concurrent Chemoradiotherapy



Cochrane Database Syst Rev. 2010 Jun 16

Serious Toxicities Also Increased



RTOG 0617

A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer

Intergroup Participation:
RTOG, NCCTG, CALGB

Presented at the ASTRO Annual Meeting Plenary Session 2011

Slide courtesy of Jeff Bradley, MD and the RTOG

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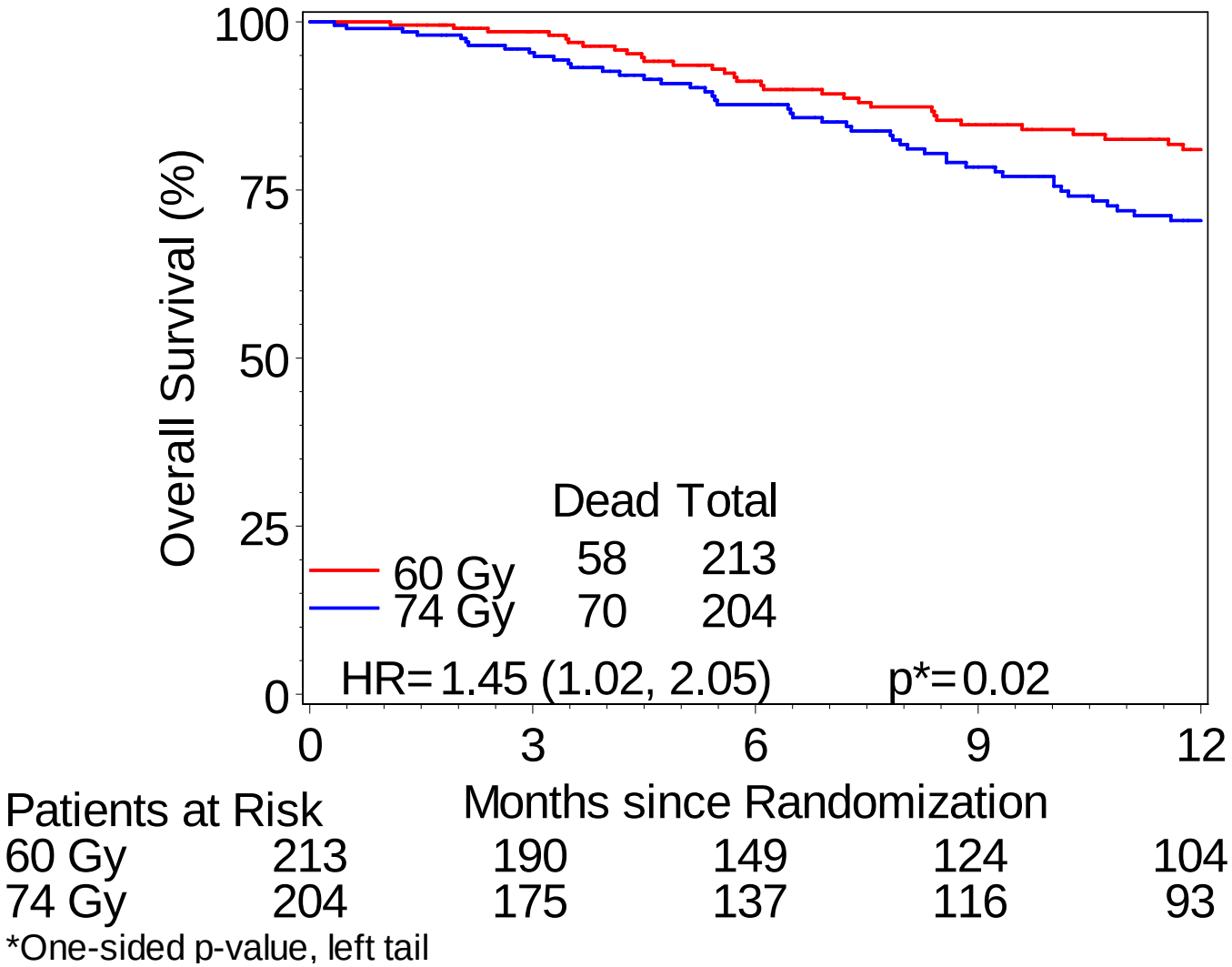
Schema

STRATIFY	RANDOMIZE	Concurrent Treatment	Consolidation Treatment
RT Technique 1. 3D-CRT 2. IMRT **Zubrod** 1. 0 2. 1 **PET Staging** 1. No 2. Yes **Histology** 1. Squamous 2. Non-Squamous		**Arm A** Concurrent chemotherapy* RT to **60 Gy**, 5 x per wk for 6 wks	Arm A Consolidation chemotherapy*
		Arm B Concurrent chemotherapy* RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm B Consolidation chemotherapy*
		Arm C Concurrent chemotherapy* and **Cetuximab** RT to **60 Gy**, 5 x per wk for 6 wks	Arm C Consolidation chemotherapy* and Cetuximab
		Arm D Concurrent chemotherapy* and **Cetuximab** RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel

Slide courtesy of Jeff Bradley, MD and the RTOG

Overall Survival 0617



*One-sided p-value, left tail

Slide courtesy of Jeff Bradley, MD and the RTOG

RTOG 0617

Definitely, Probably, or Possibly Related to Treatment (Using CTCAE Version 3.0)

September 2011	Standard Dose: 60 Gy (n=192) Grade			High Dose: 74 Gy (n=183) Grade		
	3	4	5	3	4	5
Worst non-hematologic	79 (41.1%)	14 (7.3%)	4 (2.1%)	85 (46.4%)	17 (9.3%)	8 (4.4%)
Worst overall	84 (43.8%)	45 (23.4%)	4 (2.1%)	78 (42.6%)	52 (28.4%)	8 (4.4%)

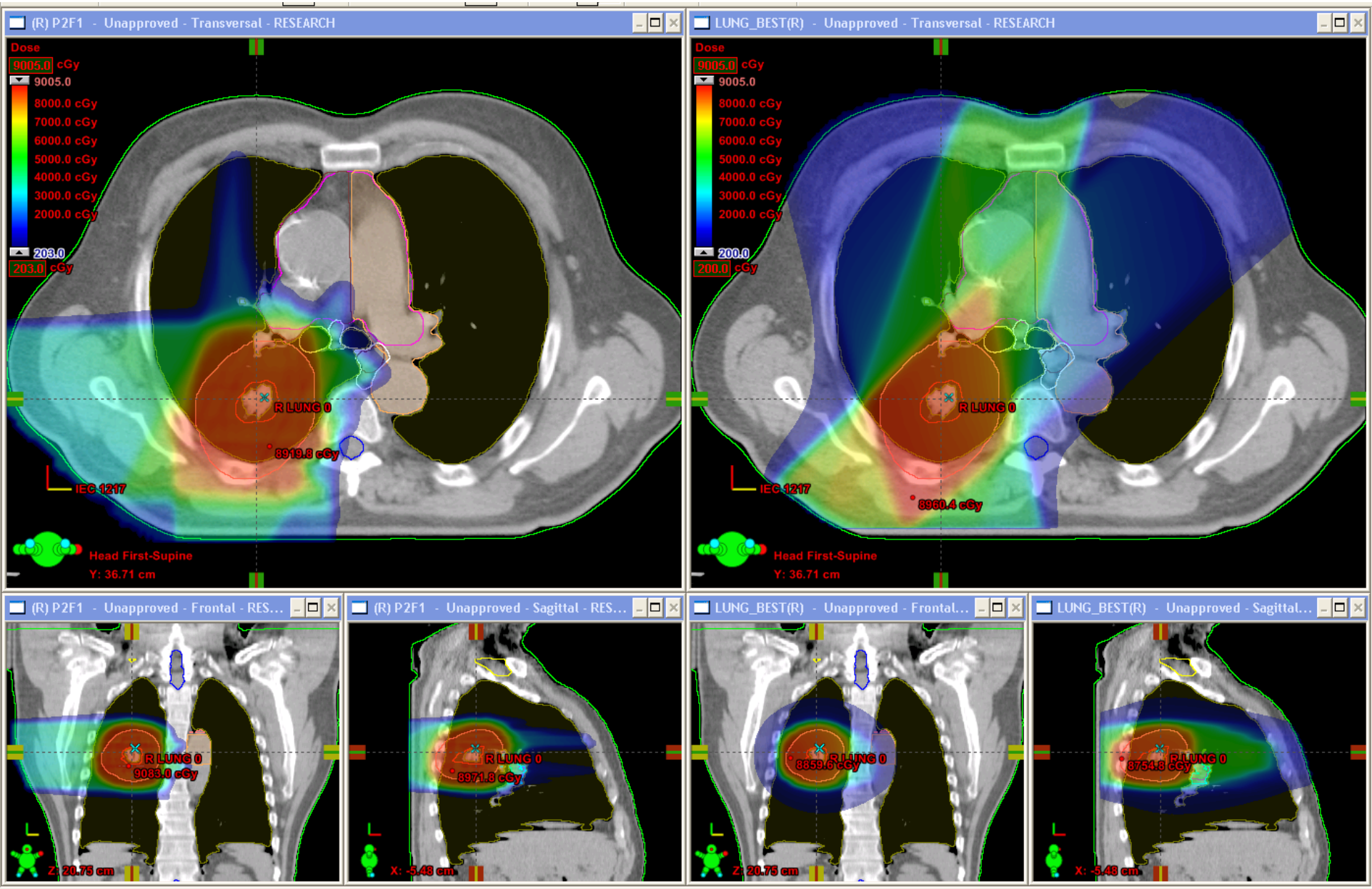
Grade 5 Events	(n=4)	(n=8)
-As scored by institution -No significant difference	2 Pulmonary 1 Thrombosis 1 Death NOS	2 Pulmonary 1 Thrombosis 1 Upper GI Hemorrhage 1 Pulmonary Hemorrhage 1 Pneumonia NOS 1 Esophageal 1 Death NOS

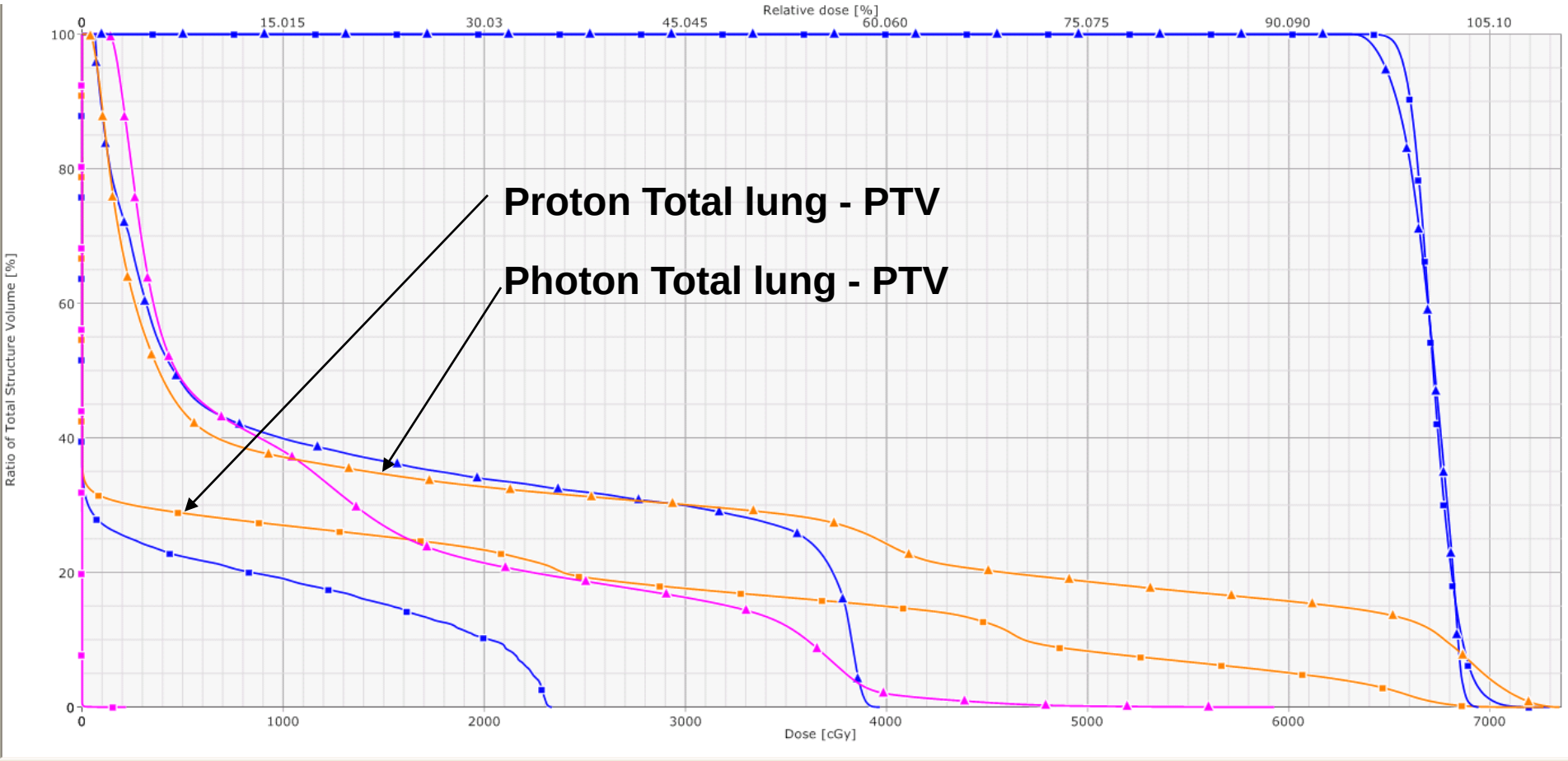
Slide courtesy of Jeff Bradley, MD and the RTOG

Lung Cancer

- Serious AE are a problem
- Sparing surrounding normal tissues is an important goal
- Improvements in local control are needed
- Complex geometry
- There appears to be a reasonable rationale for protons in lung cancer & some preliminary data suggesting a benefit

Adapted from Zeitman, Tepper, Goiten JCO


(R) P2F1 - Unapproved - Transversal - RESEARCH
Dose
9005.0 cGy
9005.0
8000.0 cGy
7000.0 cGy
6000.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
203.0
203.0 cGy
R LUNG 0
8919.8 cGy
IEC 1217
Head First-Supine
Y: 36.71 cm
LUNG_BEST(R) - Unapproved - Transversal - RESEARCH
Dose
9005.0 cGy
9005.0
8000.0 cGy
7000.0 cGy
6000.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
200.0
200.0 cGy
R LUNG 0
8960.4 cGy
IEC 1217
Head First-Supine
Y: 36.71 cm
(R) P2F1 - Unapproved - Frontal - RES...
R LUNG 0
9083.0 cGy
Z: 20.75 cm
(R) P2F1 - Unapproved - Sagittal - RES...
R LUNG 0
8971.8 cGy
X: -5.48 cm
LUNG_BEST(R) - Unapproved - Frontal...
R LUNG 0
8859.6 cGy
Z: 20.75 cm
LUNG_BEST(R) - Unapproved - Sagittal...
R LUNG 0
8754.8 cGy
X: -5.48 cm



Selection | Registration | Contouring | Field Setup | Plan Evaluation

Fields | Dose Prescription | Dose Statistics | Plan Sum

View	DVH Line	Structure	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	■	TOTAL LUNG -PTV	(R) 4D P3F PL	Training	2940.8	100.0	100.1	0.0	7272.8	1117.9
☑	▲	TOTAL LUNG -PTV	(R) INITIAL	RESEARCH	2940.8	100.0	100.0	37.2	7354.4	1982.2
☑	■	HEART	(R) 4D P3F PL	Training	235.7	100.0	100.0	0.0	227.3	0.4
☑	▲	HEART	(R) INITIAL	RESEARCH	235.7	100.0	100.0	131.5	5929.8	1184.2
☑	■	CORD	(R) 4D P3F PL	Training	40.4	100.0	100.4	0.0	2337.8	403.8
☑	▲	CORD	(R) INITIAL	RESEARCH	40.4	100.0	100.0	61.8	3972.4	1469.5
☑	■	C T V	(R) 4D P3F PL	Training	220.5	100.0	100.0	6344.3	7301.8	6727.4
☑	▲	C T V	(R) INITIAL	RESEARCH	220.5	100.0	100.0	6297.5	6949.3	6707.1
☐	■	newitv	(R) 4D P3F PL	Training						

Lung Cancer and Proton Therapy

- Consecutive patients enrolled in two IRB approved protocols at MDA Cancer Center 5/06-6/08
- 44 pts with Stage III NSCLC treated with 74 cGy, weekly carbo/paclitaxel
- Median F/U 19.7 mos; Median OS 29.4 mos
- Grade 3 esophagitis 5 pts (11%)
- Grade 3 pneumonitis 1 pt (2%)
- Local disease recurrence 4 pts (9%)

Chang JY et al Cancer Mar 22 2011

RTOG 1308

RTOG 1308

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

STRATIFY

Stage
1. II
2. IIIA
3. IIIB

GTV Volume
1. ≤ 130 cc
2. > 130 cc

Histology
1. Squamous
2. Non-Squamous

Neoadjuvant Chemo
1. No
2. Yes

RANDOMIZE

Arm 1: Photon dose—Higher achievable dose between 60-70 Gy, once daily plus platinum-based doublet chemotherapy*

Arm 2: Proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*

Both Arms: Consolidation chemotherapy x 2 is allowed*

Conclusions

- There has been a substantial increase in the technological complexity of radiotherapy driven by advances in computing power, imaging and more efficient methods for delivering radiation
- Particle therapies provide a potential benefit over conventional radiotherapy with respect to dose distribution and biological effectiveness – does this translate into clinical benefit?
- The dose distribution advantage will be most critical in those clinical situations where toxicities are of greatest concern: Pediatrics, Combined modality, Proximity to critical structures, second malignancies
- Biological advantage with higher LET particles: Hypoxic Tumors (oxygen effect), Slowly growing tumors

Penn Radiation Oncology

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

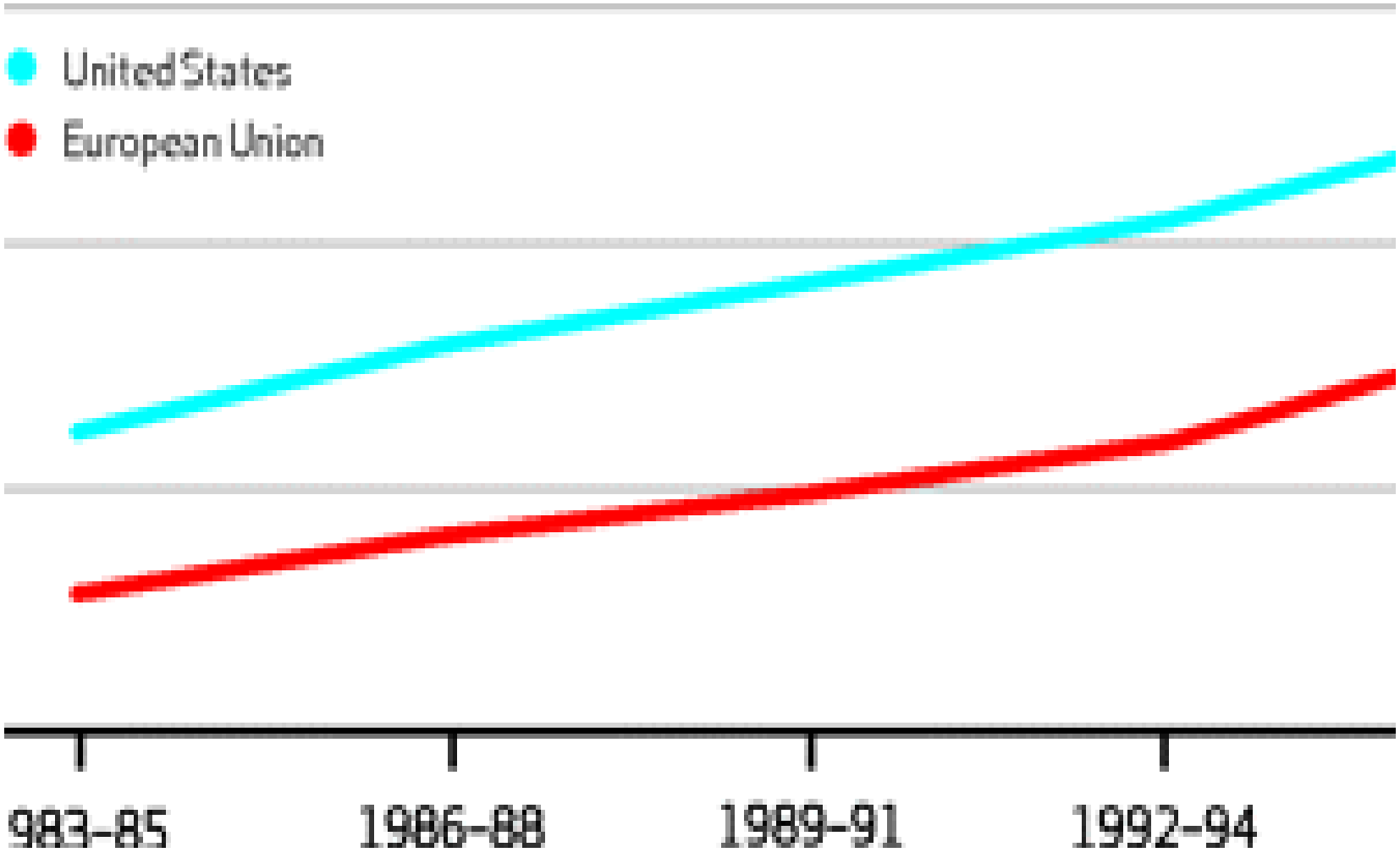
Thank You

The Value of Cancer Care Expenditures in the US

- **Philipson and colleagues University of Chicago**
- **Study to assess the value of cancer care expenditures in the US compared to the European Union**
- **Standard health services metrics were evaluated – value of additional years of life in dollar terms**

Philipson, T. et al Health Affairs, April 2012

Cost of Cancer Care Higher in the US



Philipson, T. et al Health Affairs, April 2012

The Value of Cancer Care Expenditures in the US

- **Cancer patients in US lived – 11.1 years vs. 9.3 years after diagnosis**
- **Extra years of life worth $598 Billion or $61,000 per cancer patient**
- **Value highest in prostate cancer & breast cancer patients**
- **US cancer care was more expensive but achieved better outcomes & therefore, the additional costs may be justified**

Philipson, T. et al Health Affairs, April 2012