Impact of technology on Radiation Oncology

AAPM Symposium

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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

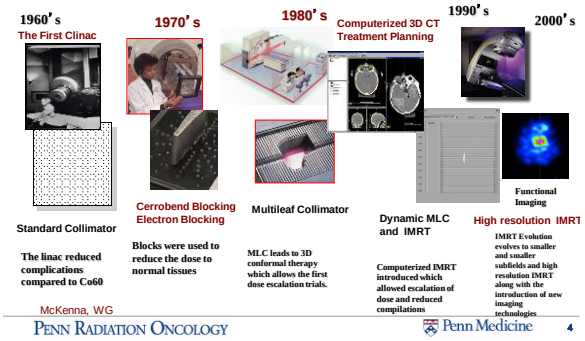
Overall, cancer death rates have declined 20% from their peak in 1991 (215.1 per 100,000 population) to 2009 (173.1 per 100,000 population).

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.

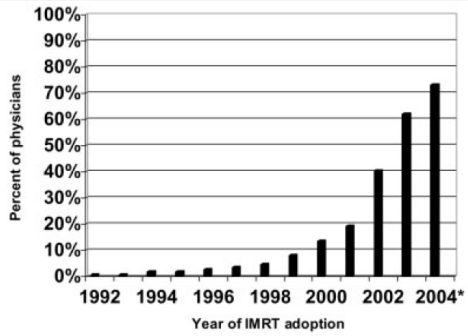
CACancerJClin2013;63:11-30.VC 2013AmericanCancerSociety.

Are We At the Limits of What Technology Can Offer our patients?



McKenna, WG

IMRT Cumulative Adoption



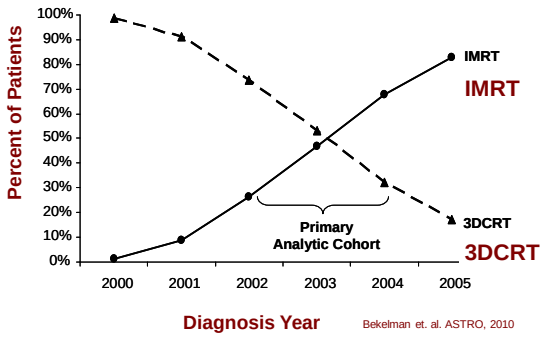
Mell et al, Cancer 2005

Study Aim

- **To test the hypothesis that IMRT compared to CRT is associated with fewer post-treatment complications in elderly men with non-metastatic prostate cancer**

Bekelman et. al. ASTRO, 2010

Use of IMRT for Men with Non-Metastatic Prostate Cancer



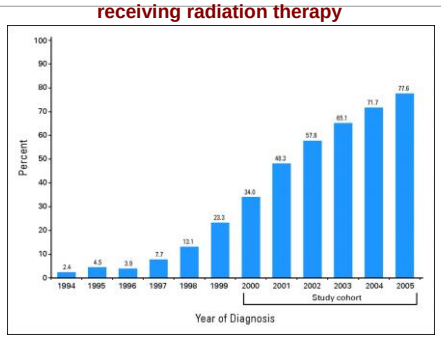
Bekelman et. al. ASTRO, 2010

Conclusions

- **IMRT associated with moderate reduction in**
  - composite measure of bowel complications, and
  - specific complications of proctitis/hemorrhage
- **IMRT not significantly associated with reduction in urinary complications**
- **Erectile complications involving invasive procedures rare in both treatment groups**
  - IMRT associated with a moderate increase in new diagnoses of impotence compared to CRT

Bekelman et. al. ASTRO, 2010

3D simulation by year of diagnosis among patients receiving radiation therapy



Chen A B et al. JCO 2011;29:2305-2311

JOURNAL OF CLINICAL ONCOLOGY

Survival Outcomes for NSCLC patients after adoption of CT-Based Simulation

- Planning studies suggest that CT simulation improves the therapeutic ratio
- SEER-Medicare data 2000-2005 analyzed by Cox models & propensity score analysis
- CT simulation use increased from 2.4% (1994) to 34% (2000) & 77.6% (2005)
- CT simulation associated with a lower risk of death – hazard ratio 0.77

– Chen AB et al J Clin Oncol 29(17) 2011

The Impact of Image Guidance

- Evaluation of multiple image-based modalities for image-guided radiation therapy (IGRT) of prostate carcinoma: A prospective study

Essa Mayyas[1], Indrin J. Chetty[1], Mikhail Chetvertkov[1], Ning Wen[1], Toni Neicu[1], Teamor Nurushev[1], Lei Ren[1], Mei Lu[2], Hans Stricker[3], Deepak Pradhan[1], Benjamin Movsas[1], and Mohamed A. Elshaikh[1]

- Evaluated four 3D US, kV planar images, CBCT, & implanted electromagnetic transponders to assess inter- and intrafraction localization errors during intensity-modulated radiation therapy based treatment of prostate cancer
- Twenty-seven prostate cancer patients were enrolled in a prospective IRB-approved study and treated to a total dose of 75.6 Gy (1.8 Gy/fraction). Overall, 1100 fractions were evaluated.

The Impact of Image Guidance

- Analysis of interfraction setup errors were comparable (within 3–4 mm) among the 4 imaging modalities
- Evaluated four 3D US, kV planar images, CBCT, & implanted electromagnetic transponders to assess inter- and intrafraction localization errors during intensity-modulated radiation therapy based treatment of prostate cancer
- Interfraction planning margins, relative to setup based on skin marks, were generally within the 10 mm prostate-to-planning target volume margin
- With image guidance, interfraction residual planning margins were reduced to approximately less than 4 mm.

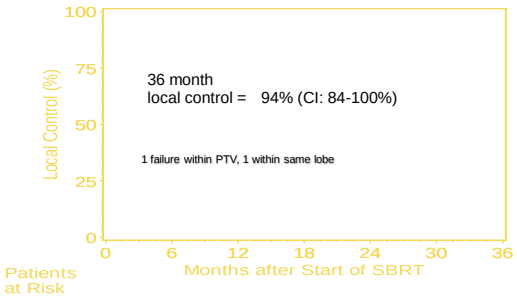
Mayyas, E et al. Med. Phys. **40**, 041707 (2013)

Stereotactic Body Radiation Therapy

- Not a machine, but a type of radiation delivery.
- ***Stereotactic*** = precise positioning of the target volume in 3 dimensions.
- Has become synonymous with high dose per fraction.
- Enabled by imaging & advances in delivery systems

J. Bradley, 2013

RTOG 0236: Local Control



Timmerman et al.: JAMA 2010

Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer

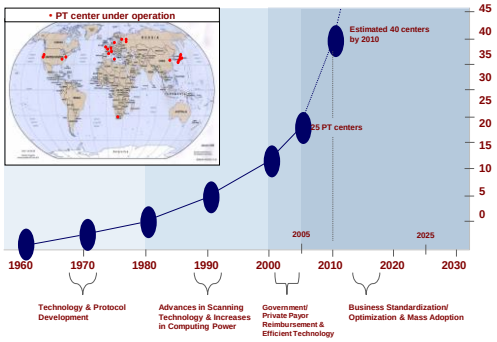
J. Martin Brown , David J. Brenner , David J. Carlson

International Journal of Radiation Oncology Biology Physics Volume 85, Issue 5 2013 1159 - 1160

"Thus the higher TCPs for SBRT can be fully explained by the much higher tumor BEDs delivered. For NSCLC, then, it follows that there is no need to invoke a "new biology" to explain the high tumor control rates."

"The old paradigm, that successful radiation therapy involves putting as much dose into the tumor while depositing as little dose as possible to surrounding normal tissue, seems to remain unchanged. Stereotactic body radiation therapy of NSCLC has taken this to its logical extreme, with dose distributions that are so good that normal tissue sequelae play a much smaller role in determining the maximum tumor dose that can be delivered."

Proton Therapy Worldwide…

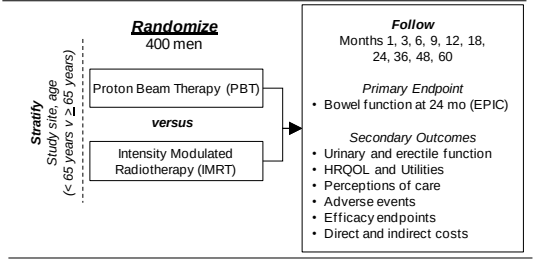


Summary - Rationale for Particles

- **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**

Phase III Randomized Clinical Trial of Proton Therapy vs IMRT

Study Schema



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

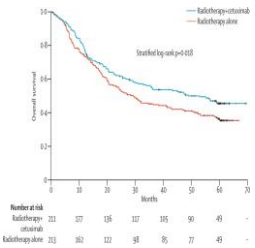
RANDOMIZE

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*

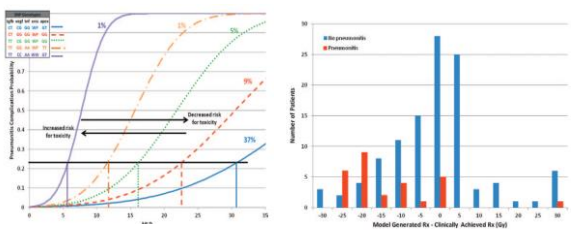
The Promise of Molecularly Targeted Therapy and Radiation



	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	62 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35 (16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

Bonner JA et al. Lancet Oncol 2010; 11: 21–28

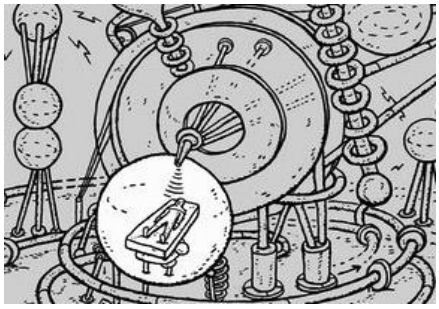
Prescribing Radiation Dose to Lung Cancer Patients Based on Personalized Toxicity Estimates



Vinogradskiy et al., JTO, 7(11), 2012
Slide courtesy of Xing Liao, MD
MDACC

Valuation of High Technology

- Higher Health Care Value



Emanuel and Pearson NYT January 2012

Challenges

- How do we demonstrate the benefit of proton therapy and other high technology (HT) treatments?
- The theoretical benefits are significant
- Yet, cost containment pressures are real
- Technological changes are rapid and high technology therapies tomorrow are likely to look different from those today
- Value = benefit divided by cost
- The difficulties in assessing cost effectiveness

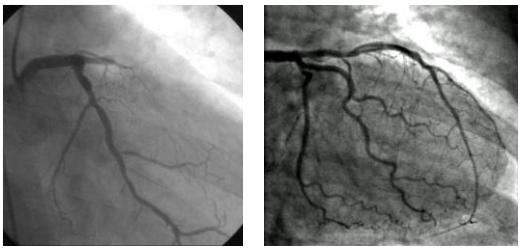
Comparative Effectiveness

The essence of comparative effectiveness research (CER) is to understand what health interventions work, for which patients, and under what conditions

In the US, attention has focused on radiotherapy technological advances, including IMRT, proton therapy, and SBRT, that have been quickly adopted with few studies investigating whether they represent an incremental improvement in patient outcomes, the defining evaluation threshold of CER.

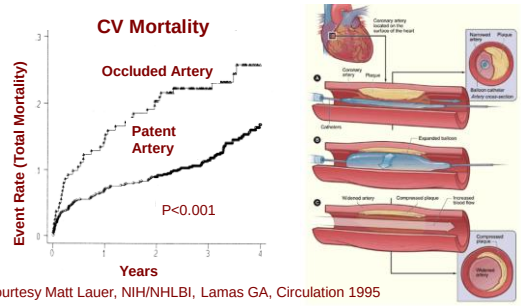
Bekelman, Shah & Hahn. PRO 2011

Coronary Intervention for Persistent Occlusion after Myocardial Infarction



Courtesy Matt Lauer, NIH/NHLBI

Coronary Intervention for Persistent Occlusion after Myocardial Infarction

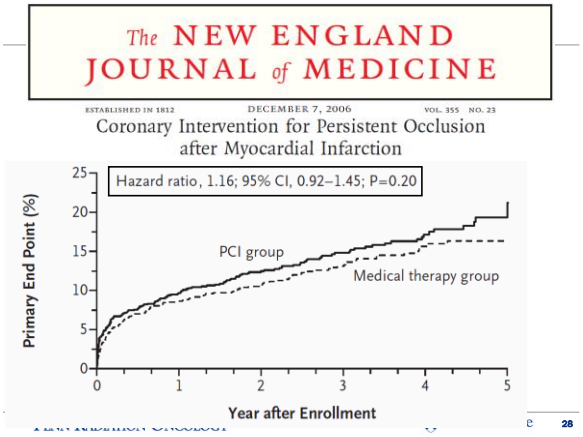


Courtesy Matt Lauer, NIH/NHLBI, Lamas GA, Circulation 1995

Coronary Intervention for Persistent Occlusion after Myocardial Infarction

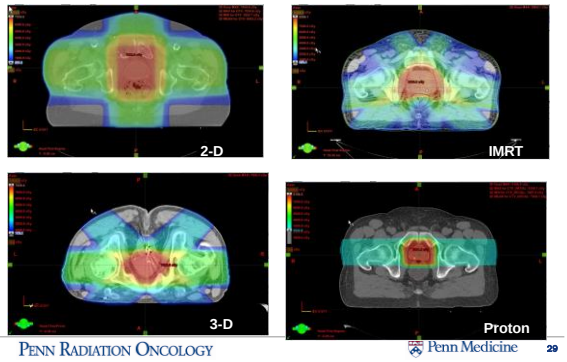
"Many doctors were so convinced of the value of this procedure…that they thought it would be unethical to assign any patients to the control group, which would get all the best medicines for this condition but not the artery-reopening procedure."

- **Boston Globe, December 9, 2006**

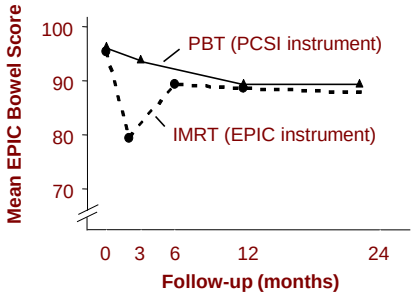


The Evolution of Conformal Radiotherapy

Localized Prostate Cancer



Are Protons Better?



Gray PJ, et al. Cancer 119:1729, 2013

Are Protons Better?

Proton Versus Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity

James B. Yu, Pamela R. Soulos, Jeph Herrin, Laura D. Cramer, Arnold L. Potosky, Kenneth B. Roberts, Cary P. Gross

Manuscript received May 15, 2012; revised September 24, 2012; accepted September 25, 2012.

Correspondence to: James B.Yu, MD, Yale University School of Medicine, Department of Therapeutic Radiology, 40 Park St, LL511-SMILOW, New Haven,

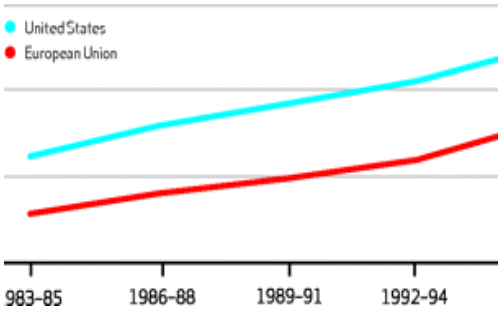
Although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment.
J Natl Cancer Inst 2013;105:25–32

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

While we cannot afford to pay for expensive therapies that provide little benefit to patients, we also cannot afford to stifle evidence development for innovative treatments that may lead to better health outcomes.

SOURCE: Bekelman and Hahn, 2014, in review

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
- IMRT, Image guidance, CT simulation, SBRT, and particle therapies have shown benefit to patients in defined situations
- It is unlikely that we have reached the limits of what high technologies can offer patients
- The intersection of biology and physics will also likely yield additional advances in therapy and imaging
- Is the cumulative effect of incremental advances of high technology greater than that observed with each individual therapy & if so, how do we justify the cost?

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Thank You