Protons or Photons for Prostate Cancer: The Case for Equipoise

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Disclosures

- I have never used protons
- Duke is exploring protons
- I was trained in Gainesville
Proton beam is an excellent treatment for prostate cancer...

..as are active surveillance, radical prostatectomy, IMRT and brachytherapy.
Goitein and Cox

1) Depth dose superior; entrance and exit
2) All relevant differences are physical; biology doesn’t matter
3) Severity of tissue injury increases with dose

“These points are not contested... they are demonstrated facts.”
Goitein and Cox

“..the practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays.”

They have lost equipoise.

JCO 26:175, 2008
Goitein and Cox

1) Depth dose superior; entrance and exit (Physics)
2) All relevant differences are physical; biology doesn’t matter (Biology)
3) Severity of tissue injury increases with dose (Clinical Oncology)

Contesting the Uncontested!
Ernest Rutherford
Physics of Protons

Is it really this simple?
Physics of Protons

Uncertainties:

- CT approximation
- Tissue inhomogeneities
- Accelerator energy
- Scattering system
- Compensator density

Distal margin is uncertain
Physics of Protons

The inherent uncertainties of the proton beam dose should lead to an increase in PTV for proton therapy.

\[ PTV_{prot} > PTV_{phot} \]
“The great advantage that protons have of stopping at a well-defined depth within the patient is also a source of difficulty.”

“...the perception that proton technology is mature is wrong.”

Goitein, IJROBP 70:654, 2008
Physics of Protons

I reserve the right to be skeptical of any study/report if these uncertainties are not considered.

Protons are not photons!
Herman D. Suit
Biology of Protons

RBE increases beyond peak!

Robertson, Cancer 35: 1664, 1975
Biology of Protons

“..there is a local “hot region” over the terminal few millimeters of the SOBP and an extension of the biologically effective range. This needs to be considered in treatment planning, particularly for single field plans or for an end of range in or close to a critical structure.”

Paganetti, IJROBP 53:407, 2002
“For SOBP proton beams, variations in RBE with dose, target characteristics, and position appear to be in the range of 10-15% or less. Effective dose (RBE times physical dose) may appreciably impact treatment outcome.”

Gerweck and Paganetti
“Proton and Charged Particle Radiotherapy”, 2008
Goitein and Cox:

“Radiation delivered to normal tissues causes damage to them, just as it does to tumors, and the severity of that damage increases with increasing dose.”
Clinical Oncology

DVH comparisons:

- Dependent on planner
- Dependent on TPS
- $\text{PTV}_{\text{prot}} > \text{PTV}_{\text{phot}}$
- $\text{RBE}$ increase beyond peak
DVH comparisons

IMRT can do better; push the constraints!

PTV_{prot} = PTV_{phot}

Rectum

Vargas, IJROBP 70:744, 2008
DVH comparisons

UF

Rectum

MGH

IMRT

Proton

Vargas, IJROBP 70:744, 2008

Trofimov, IJROBP 69:444, 2007
The proton therapy plan was better at sparing the rectum at doses of less than 50 Gy. However, above 50 Gy, IMRT was better at sparing the rectum.

Zhang IJROBP 67:620, 2007
We must be very careful about the use of DVH to argue for superiority; clinical results in patients should always matter more than any surrogate.
DVH comparisons

Brachytherapy always wins!!
1) Depth dose superior; entrance and exit
2) All relevant differences are physical; biology doesn’t matter
3) Severity of tissue injury increases with dose

“These points are not contested... they are demonstrated facts.”

It’s not that simple.....
Protons or Photons for Prostate Cancer: Do We Need a Randomized Trial?
Proton Propaganda

A randomized trial has demonstrated that the higher total dose made possible by protons results in a higher biochemical disease-survival rate, with no increase in radiation-related complications. Loma Linda Website, accessed 3/19/08

This unique characteristic gives proton therapy the ability to deposit a radiation dose in a precise manner and thus minimize damage to the surrounding normal tissue. This leads to better cancer control with fewer side effects. MD Anderson website, accessed 3/19/08

“We have patients who get treated in the morning and play golf in the afternoon.”  
Jim Cox, The Economist 3/8/08
Superiority?

- Postmenopausal HRT
- Bare-metal coronary stents
- Megadose anti-oxidants
- BMT in breast cancer
- Swan-Ganz catheters
- Gabapentin in bipolar
- Erythropoietin
- Rofecoxib

Emanuel, JAMA 297:2131, 2007
A Possible Way Out

• Registry study
• HRQOL endpoint
• Patient-reported

Clinicians don’t gather data!
“...given that protons are a limited and expensive resource, it is important to identify the indications for which protons would probably have the greatest advantage—presumably largely for situations in which current therapies are inadequate.”

Goitein and Cox JCO, 2008 epub 4/28/08