Proton Therapy Insurance Appeals Strategy Guide

Guidelines, Articles & Examples to Assist You with Your Insurance Appeal

Information provided in this guide is effective as of July, 2015.
Check with your insurance carrier for their most recent information.

July 2015

Introduction

Most likely you have your health insurance through your place of employment, or hold an individual policy, or are Medicare eligible. Most large employers offer more than one plan from which to select. No matter how you obtained your health coverage, if you have not done so, take the time to thoroughly read your policy. If you are considering changing plans, do extensive research. Health insurance policies are **contracts** between you and the insurer. You **AGREE** to their terms and it only makes sense that you read and understand what you've agreed to. Many people select their policy based only on the fact that their current physician is in network. The rest of the policy may deny them many services but that seems secondary…until they need those services. Not every single instance is spelled out, but you should know what your options are. You may also want to ask your health care providers what their experiences have been with a specific carrier.

Keep in mind that your physicians have their own biases, but if you hear phrases such as "very difficult to get payment," or "one of the worst to get timely approval," give some serious thought about what you are signing up for.

If you are considering a Medicare supplement plan, find out if they are following Medicare guidelines. This is especially important when requesting coverage for proton treatment for prostate cancer. Traditional government Medicare (as of July, 2015) covers proton. However, some Medicare supplement plans do not and are not required to follow traditional Medicare guidelines.

Also remember, an insurer may "cover" proton therapy but that may not mean they cover it 100%. Some reimburse at 100% while some reimburse at 80% or lower of the usual and prevailing fee (U&P). U&P refers to the usual fee charged by the majority of providers in your geographic area. For example, if the 50 out of 60 physicians in your area charge $100 for a treatment, and 10 physicians charge $150 for the same treatment, the insurer will pay 80% of $100 irregardless of what the physician charges. The best thing you can do is take the time to read and understand your health insurance policy before you agree to it and before you need it.

So You Were Denied Proton Treatment – What Do You Do Next?
A Guide through the Appeal Process

You, or someone close to you, have been diagnosed with prostate cancer. After researching treatment options, the decision was made to receive proton beam radiation therapy. Now, in addition to the emotional upheaval, you find that your insurance company has denied you coverage. Understandably your first reaction is anger, fear and confusion.

The outline below is intended to help give you some strategies for successfully overturning denials. While it is becoming harder to overturn denials, about 30% who file an appeal and follow the BOB strategies eventually win, but too many people get frustrated and do not complete the appeals process and settle for other treatments. You may need to go through several appeal levels, including an external review, but continue to fight. The initial appeals are internal to your health plan and normally confirm the initial decision not to provide coverage for proton therapy. Fight the denial all the way, including external review. According to AARP, 45% all of denials are overturned in the external review process. Hire a lawyer if necessary. File a complaint with you state's Health Insurance Commissioner. Do not give up until all avenues are exhausted. You can win!

Here are the six points that are covered in this document:

1. Review your health benefits policy. Pay close attention to the appeals procedure section.
2. Be sure you understand the type of plan you have – is it an HMO, PPO, Indemnity, Medicare or Medicare supplement?
3. Determine why you were denied.
4. Enlist the help of your physician.
5. Gather documents that will help support your appeal.
6. Craft a professional appeal letter geared to refute the denial reason.

In addition, in this document you will find information on what to keep track of, how to fight specific denials, some overall tips and sample appeal letters that can act as a guideline.

Point 1: Review your health benefits policy.
Pay close attention to the appeals procedure section.

- Stay calm. Do not immediately call the insurer and demand they review. Review your policy to find out what the proper steps to take are when filing an appeal. Any review asked for and done is one less review option available. Make them count.

- Do not become adversarial or confrontational in your written and verbal communications. It's hard to accept but there really are people on the other end of the line, and they have feelings as well. Contrary to popular belief, the people who review appeals are medical people – appeals are first reviewed by RNs who then turn them over to MDs. The medical personnel are required to follow the company guidelines and calling them names won't change or help a thing.
- Do not request an appeal verbally. You are not providing the insurer with anything to review, so you can expect another denial and will have lost one level of appeal. The written file is what counts, so be sure everything that is communicated orally is also communicated in writing.
- How many appeal levels does your plan allow? Check your benefits handbook. If you don't have one, contact your benefits provider. They should be able to provide it to you. You need to know how your policy works so you can follow the appeal process exactly. If you decide to forgo the appeal process and have your appeal reviewed first by the legal judicial system, the appeal will most likely be thrown out because the process wasn't followed.
- The initial approval request is normally done by the facility as they need to provide diagnosis and treatment codes. If the initial request is denied, it is recommended you create and file appeals.

Point 2: Be sure you understand the type of plan you have. Do you have an HMO, PPO, Indemnity, Medicare or Medicare supplement?

- Who is the carrier? Is it an HMO, PPO, Indemnity, Medicare or Medicare supplement? The appeal process can vary depending on the type of plan. Typically, insurers are allowed 30 - 60 business days for an appeal. Most insurers take every day allowed under the terms of the plan. They know that most people get frustrated and stop. Their strategy is denial by delay. You can beat them if you persist.
- Does your company self-fund? This means that the employer hires the insurer to administer the plan. In those cases the employer may ask the insurer to cover something normally denied. It's frequently called an "Administrative Waiver." If this is the case, contact the benefits area of the employer and ask to discuss your situation with them. Be prepared to explain why proton treatment will benefit them in terms of less down time, less lost productivity, less medical expense to treat side effects. Ask if they will intervene with the insurer.
- Do you also have traditional Medicare? As of July, 2015, Medicare does not cover anything investigational/experimental. Medicare covers proton for prostate cancer at 80% of U&P. The Medicare bulletin detailing this is at the end of this document.

Point 3: Determine why you were denied.

- What is the denial reason? The appeal must be tailored to the reason. The most common reasons for denial of services are:
  - Services are not medically appropriate.
  - Services are considered experimental/investigational.
  - The service is a non-covered benefit.
  - The service requested is out of the network.

See details about strategies for fighting these denials at the end of the document.

- Was the denial received in writing? It is important to have the letter so the insurer can't say later on that your denial was in actuality based on something other than what you were told. As well, you know exactly what reason you need to refute in your appeal.

Point 4: Enlist the help of your physician.

- In many cases your physician can provide the medical documentation you need. Your physician can also discuss the denial with the health plan physician reviewer. This is known as a peer-to-peer review and may count as an appeal. The most important thing your physician can do is provide a detailed "Letter of Medical Necessity" to your insurer explaining why proton therapy is appropriate for you. Physician phone calls are usually not enough to change a decision.

Be cautious about having your physician do a verbal consult with your insurer. Many companies will view this as an appeal and without any documentation for them to review, they will frequently uphold their denial, and you may lose one appeal step.

Point 5: Gather documents that will help support your appeal. Do not refer to links without sending hard copy. It is *not up to the insurer* to look up your resources. Providing a hard copy will also make it harder for the insurer to say no information was provided.

- Do research on the Internet, in books, and through various cancer organizations. Keep hard copies of materials that support your position and submit them with your appeal. Share the information with your physician so that your physician has a sense of how important this is to you. Also, there is so much new information that no physician can keep up to date on all of it.

- Request the insurer provide YOU with a copy of the documentation they used to make their decision. Legally, they must provide it. The patient is not the only one who has to provide proof – it works both ways.
- Review the member resource list on the BOB organization site. Note the name, city and state of those who have had proton treatment covered by the same insurer. Include them in your appeal letter. If the member has an asterisk next to their name, they do not want their information shared. Please respect that. Once a precedent is set it's harder for the insurer to deny. *However, if the insurer changes their policy at contract renewal time, what they did before they may not do now. While that is their legal right, continue to go through the appeal process. It is better to try, and be denied, than to not try and find out later you could have won.*

Please be aware that the list of insurers on the BOB website and in Bob Marckini's book is accurate only at the date of printing. Also, contracts within an insurance company can vary state to state. The lists are meant as guidelines. Be certain to verify with your insurer as to their current status on approving proton. While the physician or facility normally checks eligibility, it is your responsibility to verify your coverage.

Point 6: Craft a professional appeal letter.

- Do you have any medical history/problems? If you have a history of previous cancer, abdominal/intestinal surgery, uncontrolled diabetes, seizures, heart conditions etc., this information can make it easier to resolve a "not medically necessary" appeal.
- Tailor the appeal letter to the denial reason. For example, if the denial is for investigational or experimental, include a copy of the traditional Medicare bulletin that outlines their decision to cover proton for prostate cancer. Medicare never pays for investigational/experimental. Commercial health insurance companies do not use the same definition of investigational or experimental that Medicare does. They basically define any treatment that is not the norm as investigational or experimental. They also sometimes rely on out of date reports from allegedly independent third parties such as ECRI or Hays. They are not obligated to seek out new information but are obligated to consider information that you, and particularly your physician, submits to them. Be sure that they have the most recent medical publications related to your situation. Some insurers who previously approved proton now deny stating it is investigational/experimental. Ask why it was once covered and considered approved treatment but now the insurer has reversed position. Ask for their internal documents detailing how and why the change was made.

- In the appeal letter, professionally let the insurer know that you will not go away and will pursue all avenues available, including external review and legal representation. The primary advantage of using a lawyer is that your lawyer will know how to be sure that the insurer is following their own rules and carefully document each step of the appeal process. Using an attorney is also likely to cause the insurer to take your case more seriously.
- Bring up the emotional/lifestyle issues involved. For example, BOB members are employed in careers representing all professions. Treatment that would have left them incontinent would have denied them the ability to continue in their jobs. These intangible elements have value.
- Discuss the high cost of treating side effects – and not only the medical supplies and devices. A man who is left impotent may have some psychological issues and require mental health intervention. This is costly for the insurer.

Remember you have a legal right to information the insurer uses to make decisions. While you have to provide proof that something isn't, for example, experimental, the insurer has to provide the proof of what they used to claim it *is* experimental.

If possible, make sure the letter is sent to a specific person - not just to the appeals department. Consider sending your appeal letter and documents via certified mail.

Keep track of the following:

Whenever you are dealing with an insurance company, it is advisable to take careful notes. Whether you have your treatment approved ahead of time or not, be sure you note the following:

- Document every phone call you make, as well as those made to you. Note the date, time, the phone number, extension, and department, and be certain to get the name and position of anyone you talk to. Get both first and last name, or first name and last initial of everyone you speak with.
- Write down exactly what you asked and what you were advised. Notes might appear as follows:

  3/10/2007. 9:30 AM EDT. Called United Healthcare Precert Department (document phone number). Spoke with Sue B. Advised proton treatment for prostate cancer is eligible and will be covered 100%. $10 copay will apply. Asked if an approval letter will be sent. Sue B. said it should go out 3/12/2011.

  Documentation of this type is invaluable if coverage is denied at a later date. You also now have a date for follow up. If you were promised a response and it is not received in a reasonable length of time, call back to verify all information you were given and verify when you will receive your letter.

- Keep copies of all written communication you send to the insurance company, hospitals, doctors, and keep copies of anything sent to you.
- No matter how frustrating the process seems, remember that anger, yelling, cursing, threatening and disrespect to those you speak with on the phone will not help get you the results you want. Customer Service Representatives are advised that they have the right to terminate a call if anyone becomes abusive on the phone. Stay calm and use respectful language. If you are unhappy with the quality of information you are receiving, ask to speak with a supervisor.

Hints for what to do when things go wrong:

When submitting an appeal, consider the following:

- Ask the health provider what guidelines they used to formulate the denial and request a copy is sent to you. You have a legal right to this documentation.
- Submit your appeal documentation stating clearly the reason for the requested service. Health providers make their coverage decisions partially based on the documentation you provide so it's in your best interest to provide complete information up front. The more factual, substantial information you can provide the better. Research on the Internet. Print out any information that supports your position. Keep copies of all medical documentation.
- Follow up with the health provider if they have not responded in a timely manner. Your benefits book will tell you what time frames are in effect. For example, most insurers have 30 days to respond to an appeal; however, time frames can vary so be sure to check your plan.
- Know the levels of internal appeal review available. If your appeal is not approved on the first try, request a second appeal, and create a new appeal that contains information from the first appeal as well as any additional information. Most plans also provide a third level of appeal. If all levels of appeal are overturned, consider filing with an Independent Review Board, Peer (physician to physician) Review, or to the State Insurance Commissioner. At this point you may or may not require a lawyer. Be persistent, factual, and adhere to all requests and requirements of the health plan.
- Do not bypass any step in the appeals process. If your first level appeal is denied, do not jump right to an independent reviewer. Most insurance regulations and even some independent review board mandates require the policy holder to first exhaust the internal appeal process with the insurance carrier. This is a prerequisite to getting an outside agency review or even, in some cases, winning in court.

- You may also consider discussing the denial with your company's benefit person/coordinator even if the plan is not self-funded. While it is not the usual practice for the employer to request a service be covered, it does happen.

Automatic Facility-Filed Appeals

Consider asking your proton facility what their policy is when they receive a denial after the initial request for approval is submitted. Some facilities will automatically file an appeal on your behalf without your knowledge. When a facility files an appeal, they normally do not provide any new documentation. Since the individual does not know the appeal is being filed, there is no opportunity to provide any additional information. If the individual has a past history of certain medical issues, that could be key to overturning the denial, as can work/personal lifestyles, etc. Most insurers are not educated about proton therapy and the facility most likely does not provide any educational documents. This boils down to an appeal that most likely will continue to be denied due to lack of any new, supportive documentation. *NOTE: Some insurers only allow one or two appeal levels which is problematic, since one level is now lost.*

Find out how the facility handles an initial denial, and if they provide any additional documentation to their appeal, such as recent findings on proton effectiveness, information on how proton works, how long it's been in use, and its advantages over other forms of treatment, cost analysis for the treatment of side effects from other treatments, background on your work and personal lifestyle that would be jeopardized due to side effects, etc. Ask if you are given the opportunity to give input to their appeal. You can ask about their policy during your initial discussions with the finance/insurance area of the facility. If you find that the appeal is basically a resubmission of the previous request, it is recommended advising the facility NOT to appeal on your behalf, and create the appeal yourself.

If the facility tells you that a letter from the physician stating that proton is medically necessary for you will be included in the appeal, ask if the letter will also state WHY it is medically necessary, and not just state that it is the opinion of the physician. Insurers want proof, not opinions.

Consult Approvals

Your request for a consult for proton treatment may be approved, but that doesn't mean that your proton treatment is covered. This may in fact *not* be the case. In many instances, insurers approve a consult for proton treatment when in fact they deny proton for prostate cancer.

Consults are considered information gathering appointments and when the consult is requested, treatment is not usually requested at the same time. This leads to misunderstanding and frustration.

If you receive an approval for your proton consult, make sure you understand exactly what it is that's been approved. Do not assume the treatment itself has been approved. Questioning why

a consult is approved but not the treatment will most likely be explained away with the statement that while proton is being denied, you are not being told you cannot have proton treatment. You can certainly go ahead with treatment, but you will pay for it.

Attention Veterans!

If you have prostate cancer, were in the services during the Vietnam War era and spent any time on the ground in Vietnam, file a disability claim with the VA or the Vietnam Veterans Association as soon as you receive your diagnosis. The VA recognizes the link between Agent Orange exposure and prostate cancer. They will provide a disability benefit starting the date you file your claim until 6 months post treatment. Your local VA or Vietnam Veteran's Association will guide you in the process.

This is a separate issue from your health plan insurance. Note that the VA does not pay for proton treatment. This is a disability benefit you have earned and should take advantage of if you qualify.

This also applies to veterans who were in Korea (on/near the DMZ in the late 60's) – they were also exposed to Agent Orange. If you were there then, contact your VA.

Proton Therapy Experimental?

If your health provider advises you that proton treatment for prostate cancer is "experimental," include the 10 year study and 15 year update that were released by Loma Linda. These document the success of proton treatment. Explain that traditional Medicare covers proton treatment. This is important as traditional Medicare does not cover any investigational or experimental treatments. Include a list of all facilities currently providing proton, and those in the planning stage. If the insurer previously covered proton, but is now denying coverage with the reason that proton is "experimental" or "investigational," bring it to their attention and ask for an explanation with documentation.

Surgery More Cost Effective?

Occasionally a health provider will deny proton treatment for prostate cancer saying surgery is more cost effective. Ask them to consider the TOTAL cost for prostatectomy – not just the hospital surgery and stay. The added cost of intensive post-operative treatment, which includes home supplies for wound and catheter care, multiple physicians visits, risk of infection and post-operative complications due to invasive procedures, continued purchases of home medical equipment for incontinence (diaper pads, bandages, antibiotic ointments, pain medications, oral antibiotics and others), potential cost for impotence treatment all combined with the emotional impact most likely eclipses the cost of proton treatment. If you have another medical condition that will require additional monitoring, medication adjustment or otherwise complicate surgery or post-operative recovery, such as a cardiac condition or limited mobility, ask them to factor that in as well. The cost of Home Health Care is expensive!

Medical Supplement Plan?

If you have a Medicare Supplement Plan and are denied proton, contact the Medicare Advocacy Group (can be found on the Internet). By law, Medicare plans must follow traditional Medicare guidelines; however, there are many complex issues at work so check to see if your plan is living up to and is required to follow legal guidelines.

Proton treatment is currently being used to treat the following:

Prostate Cancer

Lung Cancer
Early-stage, medically inoperable lung cancer

Breast Cancer

Ophthalmological Conditions
Malignant/benign tumors of the orbit
Ocular (uveal) melanoma

Benign Tumors
Acoustic neuroma
Arteriovenous malformation
Craniopharyngioma
Pituitary adenoma
Intracranial meningioma

Pediatric Malignancies
Medulloblastoma, craniospinal
Ependymoma
Pineal tumors
Astrocytoma
Retinoblastoma
Orbital rhabdomyosarcoma

Head and Neck Malignancies
Nasopharyngeal carcinoma
Paranasal sinus carcinoma
Oropharyngeal/parapharyngeal malignancies

Base of Skull Sarcomas
Chordoma and chondrosarcoma
Spinal Cord and Paraspinal Tumors
Paraspinal soft-tissue malignancies
Chordoma
Sarcoma subtypes

Gastrointestinal Malignancies
Carcinoma of the rectum
Pancreatic carcinoma
Hepatocelluar carcinoma

Genitourinary Cancer

Bladder carcinoma
Prostate malignancies

Common Reasons for Denying Coverage for Proton Beam Therapy

General Information: Proton beam therapy (PBT) has been around since the early 1950s, and has been used in a hospital setting at Loma Linda University Cancer Center (LLUCC) since 1990. Proton has been in use for almost 60 years. It was first used in Berkeley, California to treat cancer in the early 1950s, and to date, tens of thousands of patients have been treated with protons. The challenge is that there are only 17 proton therapy centers in the U.S. with a total of fewer than 40 treatment rooms. This compares to over 2,000 treatment centers with over 4,000 treatment centers for conventional photon (IMRT & 3D conformal) radiation and hundreds of surgery centers. Proton therapy is not yet common; but for most prostate cancer patients it is superior. Critics of proton therapy usually focus on the higher initial costs, which most people overstate, and the modest improvement in short term survivability (If it is you, no improvement in survivability is modest.) The critics ignore the substantially reduced long-term side effects, including both cancer recurrence and secondary cancer, and important quality of life issues.

Some members of the medical community have been slow to recognize the benefits, however, and PBT is only recently gaining wider acceptance as a practical choice for men diagnosed with prostate cancer. Getting provider approval for PBT depends in large part on the patient's type of health insurance, age, and state of residence. PPOs (Preferred Provider Organizations) are more likely to cover proton therapy than HMOs (Health Maintenance Organizations). Those eligible for traditional Medicare or TRICARE (the retired military health plan) may get approval for PBT. Some states have better appeal procedures than others. Most have independent review boards that have the power to overrule an insurance company's denial. The message that comes through the emails we've seen is: **Do not let the insurance company wear you down. Know your rights and keep at it until you win approval.**

Here are some of the more common reasons for denial of coverage:

1. Proton beam therapy is experimental (or investigational).

Proton beam therapy is not experimental or investigational. Proton treatment has been in use for almost 60 years. It was first used in Berkeley, California to treat cancer in the early 1950s, and to date, more than 60,000 people have been treated with protons. The means of delivery may change as techniques develop, but the therapy itself is established as efficacious, efficient, and preferred in light of the side effects associated with alternative therapies.

The efficacy of this treatment has been proven to the satisfaction of the FDA and has its stamp of approval. It is an approved treatment by traditional Medicare who does not cover anything experimental. There are more peer reviewed medical articles on proton therapy for prostate

cancer in the last decade than any other form of prostate cancer treatment. The criticism that there are no prospective, randomized clinical trials comparing proton therapy to other alternatives ignores the issue that is also true for the other forms of treatment as well.

Intended as an alternative to surgery and other forms of radiation, proton beam therapy is target-specific, delivers more radiation to the tumor, does minimal damage normal tissue and has minimal side effects. Loma Linda University Cancer Center, the first hospital-based proton therapy center, has treated more than 11,000 prostate cancer patients since 1990. LLUCC obtained initial FDA approval of the proton technology in 1988, and the FDA approved an upgraded version in 2000. Worldwide, more than 60,000 patients have been treated with proton therapy for cancer and many other diseases.

Several thousand prostate cancer patients have been treated successfully at **Loma Linda University Cancer Center** in Loma Linda, California since 1990. A proton beam therapy center is operational at the following:

1. Francis H. Burr Proton Therapy Center at Massachusetts General Hospital, Boston, MA (2003)
2. M.D. Anderson Cancer Center's Proton Center, Houston, TX (2006)
3. University of Florida Proton Therapy Institute, Jacksonville, FL (2006)
4. ProCure Proton Therapy Center, Oklahoma City, OK (2009)
5. CDH Proton Center, Chicago, IL (2010)
6. Hampton University Proton Therapy Institute, Hampton, VA (2010)
7. Roberts Proton Therapy Center at UPENN, Philadelphia, PA (2010)
8. ProCure Proton Therapy Center, NJ/MetroNY, Somerset, NJ (2012)
9. SCCA Proton Therapy, A ProCure Center, Seattle, WA (2013)
10. S. Lee Kling Proton Therapy Center at Barnes-Jewish Hospital, St. Louis, MO (2013)
11. Provision Center for Proton Therapy, Knoxville, TN (2014)
12. Scripps Proton Therapy Center, San Diego, CA (2014)
13. Willis-Knighton Health System, Sheveport, LA (2014)
14. Ackerman Cancer Center, Jacksonville, FL (2015)
15. Robert Wood Johnson University Hospital, NJ (2015)
16. UCSF Medical Center, Davis, CA (low energy system, treats only ocular tumors) (1994)

There are 23 proton treatment facilities outside the United States, with many more coming in the next few years.

Medicare (Bulletin 406, 3/31/97) [see text below] declared proton beam radiation therapy as non-investigational in 1997. The organization is conservative and does not cover procedures deemed "experimental."

2. Proton beam therapy is not medically necessary.

The definition of "medically necessary" is quite broad. The Code of Federal Regulations (CFR) defines "Medically or psychologically necessary" in part as follows: "The frequency, extent, and

types of medical services or supplies which represent appropriate medical care and that are generally accepted by qualified professionals to be reasonable and adequate for the diagnosis and treatment of illness…" [32 CFR 199.2(b)]

The key here is to get a "Letter of Medical Necessity" for proton beam therapy from your doctor. Your personal medical history is also vital to overturning this type of denial. Be sure to document any previous or ongoing medical issues such as cardiac disease, past surgeries, past cancer history, neurological issues and systemic diseases such as lupus, rhematoid arthritis, etc.

3. Proton beam therapy is outside the plan's medical network.

This may be the toughest type of claim to refute. One way is to show the benefits of proton beam therapy and note that there are no PBT facilities within the network. You can also point out that TRICARE (formerly CHAMPUS) regularly approves proton therapy, even though it has its own IMRT (Intensity Modulated Radiation Therapy) facilities.

If you are covered by one of the larger insurers that provide coverage nationwide or in multiple states, do some research to determine if they cover proton therapy at facilities that are in the specific network for that area. If they do, point out that you are being discriminated against as people fortunate enough to live in a network with an in-network proton provider facility can have proton treatment but you are being denied because of demographics.

4. Other treatment methods have the same effectiveness as proton beam therapy.

Proton therapy has a success rate at least equal to the so-called "Gold Standard" of radical prostatectomy (prostate surgery), without the need for an invasive procedure and with markedly fewer side effects. Medicare Bulletin 406 (below) describes the advantages of proton therapy over conventional (photon) radiation therapy. The Bulletin also contains policy statements which authorize the use of proton therapy for treatment of prostate malignancies.

On the following page, you will find a sample letter that was crafted by a BOB member and used to successfully overturn a denial. Following the first letter, you will find another sample letter crafted by a BOB member. These letters will give you a guideline to follow and a good sense of the thorough job you need to do.

Sample Letter #1

Name
Address
Phone Number

Insurance Company Name
Address
Date

VIA CERTIFIED MAIL #

Copies to:

RE: First Appeal to Notice of Coverage Denial, Reference Number

Dear Sir or Madam,

This is my first appeal to coverage denials dated for:

1. Out-Of-Network Services consisting of computed tomography guidance for placement of radiation therapy fields, from (list providers).
2. Out-Of-Network Services consisting of proton beam therapy from a non-participating provider requested by Dr. (name) for (date) and denied by (name of insurer and date of denial).

I am appealing (name of insurance company) coverage denial for the following reasons:

Reason 1: The denial was based on "an item or service that is commonly available from participating providers." The service is not commonly available from participating providers. There are no providers of proton beam therapy in (name of insurance company) network.

Reason 2: The treatment is medically necessary: prostate cancer progresses to cancer of the lymphatic system and/or bone cancer, and eventually, death. Conformal proton beam radiotherapy for prostate cancer is a therapy that has been FDA approved and has important differences from all other modalities of treatment for prostate cancer, which is especially important for my specific situation.

I am a full-time, self-employed consultant frequently required to meet clients in a professional capacity.

Reason 2:
(continued)

The possibility of fecal incontinence and/or urinary problems that result from other forms of treatment for prostate cancer would endanger my ability to conduct business activities and, consequently, earn a living. Conformal proton beam radiotherapy is extremely effective because of its ability to accurately target tumors while minimizing damage to the surrounding healthy tissues. For this reason, it is favored for treating certain kinds of tumors like those of the prostate. Because of the lower dose to healthy tissue, protons have fewer severe side effects than conventional radiation therapy, and studies have demonstrated equal and even superior long-range effectiveness.

Reason 3: (Name of insurance company) agreed proton therapy is a viable option. A (name of insurance company) medical director, Dr. (name) scheduled a peer-to-peer telephone review with my radiation oncologist, Dr. (name) on (date) to inquire about alternative therapies. Dr. (name) suggested that stereotactic radiosurgery might be a possible alternative, and if not, (name of insurance company) would consider approving proton beam therapy.

On (date), I spoke with (name of contact) at (area of contact's employment) seeking the name of an in-network stereotactic radiosurgery specialist and was provided the name of Dr. (name). I contacted Dr. (name) to discuss my specific medical needs. It was his opinion that stereotactic radiosurgery is not a viable treatment modality for my condition because the technology is relatively new and generally used only for head and neck cancers that are very close to other vital tissues.

Reason 4: Proton therapy is cost-effective. When the third party payers consider the cost for care from a broad perspective, the cost for treatment of adverse sequelae of the treatment must be considered. Reports from the United States and Europe reveal that proton therapy results in a lower incidence of acute and long-term adverse sequelae than in surgery and/orconventional radiation therapy.

Analysts have found that the increased costs for proton therapy are outweighed by the savings from a lower incidence of adverse treatment effects. In addition, patients treated with proton therapy report an improved quality of life, an immeasurable benefit. In the long term, proton therapy will prove to be a lower cost solution than conventional modalities for some cancers including prostate.

Reason 4:
(continued)

The clinical advantages of proton beam therapy include:

- Decreased hospitalization (no surgical hospital stay)
- Less bodily pain
- No anesthesia effects
- Decreased morbidity
- Decreased mortality
- Decreased radiation-related complications to healthy organs and tissues
- Fewer outpatient visits (higher doses are used)
- Fewer side effects in comparison to conventional photon therapy
- Avoidance of incontinence and/or impotence and cost of treatments for those conditions
- Higher probability of disease control

Therefore, proton therapy may be the lower overall expense for the payer, because there will not be payments for additional diagnostic services, care needed due to adverse sequelae of a treatment, ancillary services, and treatment of disease recurrence.

The (name of insurer), an affiliation of (name of insurer and area of coverage) included scientific background information in their recently-implemented (January 2006) policy regarding coverage of proton therapy (Hall EJ, Cox JD: Physical and biological basis of radiation therapy. In Radiation Oncology: Rationale, Technique, Results, 8th ed. Cox JD, Ang KK, Eds. St. Louis, Mosby, 2003, p. 3-62). The (name of insurer) notes proton therapy's low or zero incidence of Grade III or Grade IV gastrointestinal (GI) or genitourinary (GU) toxicity among patients with prostate cancer. For prostate cancer, Grade III GI toxicity includes rectal bleeding that requires transfusion and GU toxicity includes severe cystitis (that may require in-patient treatment). The treatment of such adverse side effects of traditional radiation therapy generates expenses for the third party payer and the patient beyond those of radiation treatment alone.

Reason 5: Proton therapy is unmatched by other treatment modalities. The challenge for a radiation oncologist is to find the treatment for each patient that offers the greatest chance of cure and the least chance of significant damage to normal tissue. The measure of the best treatment is the one with the highest therapeutic ratio, i.e., the ratio of the probability of tumor control to the probability of normal tissue damage.

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(date), Page 4

Reason 5:
(continued)

Proton therapy is more efficient and precise than conventional radiation therapy. Greater precision in radiation dose distribution results in improved therapeutic ratios and both increased disease control and better quality of life outcomes.

Proton therapy provides increased tumor control due to the proton beam's unique ability to increase the radiation dose delivered to the targeted tumor. Conventional radiation therapy is primarily delivered with the use of either photons (high energy x-rays) or electrons. They enter the body at relatively high energy and continue to dissipate energy as they pass through the patient's body, damaging tissue along their entire path. They deliver an unwanted dose to the healthy tissue surrounding the intended target. By contrast, protons enter the body at relatively lower energy and do less damage as they travel to the tumor site. Once they reach the tumor site, they can be "programmed" to stop. As they stop, they give off a burst of energy at the tumor site.

There is no exit dose. Protons therefore do less damage on the entrance dose, deliver the majority of their energy at the tumor site, and have no exit dose. Since protons cause less damage, physicians can be more aggressive by delivering higher doses of radiation to the tumor.

Higher doses of radiation are associated with a greater likelihood of tumor control/increased likelihood of eradication which in turn is associated with a lower incidence of disease recurrence. These statements are supported by published articles by Drs. Carl Rossi (Enclosure 1) and James Metz (Enclosures 2 and 3).

First Appeal to Notice of Coverage Denial, Reference Number 4004797
(date), Page 5

Reason 6: Proton therapy has been embraced and approved by the FDA, traditional Medicare, healthcare insurers throughout the United States and numerous BC/BS plans:

- Blue Cross / Blue Shield of Alabama
- Blue Cross / Blue Shield of CO
- BC/BS Federal Employees
- BC/BS of Florida
- BCBS Iowa
- BCBS of Illinois

- Blue Cross of Louisiana
- BC/BS of Michigan
- Blue Cross / Blue Shield of Minnesota
- BCBS of Nevada
- BCBS of New Mexico
- Blue Cross / Blue Shield of New York
- BC/BS of North Carolina
- Blue Cross / Blue Shield of Oregon
- BCBS of Western PA
- Blue Cross / Blue Shield of Texas
- Blue Cross/PORAC
- Empire Blue Cross/Blue Shield
- Horizon Blue Cross / Blue Shield
- PEEHIP of Alabama BC/BS
- Premara Blue Cross
- Regence Blue Cross / Blue Shield of Oregon
- Regency Blue Shield

I have stage T1C prostate cancer that is curative with proton therapy. Proton therapy provides the greatest opportunity to restore my health to pre-cancerous condition. (Name of insurance company) has complete documentation of my medical condition and recommendations from physicians to treat the condition with proton therapy.

Please let me know if any additional information will be helpful to my request. Thank you for your immediate attention to this matter.

Sincerely,

Enclosures:

1. Conformal Proton Beam Radiotherapy of Cancer, Carl J. Rossi, Jr. MD, Loma Linda University Medical Center
2. Differences between Protons and X-rays, James Metz, MD, The Abramson Cancer Center of the University of Pennsylvania
3. Reduced Normal Tissue Toxicity with Proton Therapy, James Metz, MD, The Abramson Cancer Center of the University of Pennsylvania

Enclosure 1

Conformal Proton Beam Radiotherapy of Cancer

Carl J. Rossi, Jr., MD
Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, California. *Originally Received March 4, 1995; Last Revised March 5, 1996.*

Introduction

This article is provided primarily for patients and family members in the hope that it will answer some of the most commonly asked questions about conformal proton beam radiotherapy, and to illustrate the usefulness of this form of radiation treatment in a variety of clinical situations. A separate article specifically addressing the use of this form of treatment for patients with prostate cancer is currently in development.

What is conformal proton beam radiotherapy?

Conformal proton beam radiotherapy (henceforth known as PBRT) is a form of external beam radiation treatment. "External beam" refers to the fact that the radiation is generated and administered by a machine outside of the patient's body, as opposed to implanted sources of radiation, which either temporarily or permanently place radioactive sources within a person's body. Other forms of external beam radiotherapy include x-ray therapy and cobalt-60 gamma-ray therapy.

"Conformal" means that it is possible to shape or "conform" the beam in three dimensions to "fit" the shape of the organ or tumor to be radiated, so that the majority of the radiation is administered to the organ or tumor and not to the surrounding, normal tissue. It is this unique ability to conform a proton beam to a specific tumor or target which sets PBRT apart from other forms of external beam radiotherapy.

Is PBRT a new or experimental therapy for cancer?

The answer to this question is an emphatic "no" on both counts. The ability of PBRT to be shaped to particular targets within the human body was recognized in the 1940s when cyclotrons ("atom smashers") were being developed. The first scientific paper discussing their potential use in cancer treatment was published in the *Journal of Radiology* in July 1946. The author of the paper was Robert Wilson, a world-renowned physicist who was involved in early cyclotron development at the Donner (later Lawrence) radiation laboratory of the University of California. In this paper, Dr Wilson discussed how a proton beam could be manipulated to deliver high doses of radiation to a small target while at the same time sparing surrounding tissues. As a direct outgrowth of this paper, scientists at the Harvard Cyclotron Laboratory and the Lawrence Berkeley Laboratory began to modify their research cyclotrons to permit human treatment. Initial treatments of intracranial sites began in the late 1950s. The results were so encouraging that, as the technology improved, modifications were made to existing machines to permit treatment of deep tumors in virtually any part of the body. Extensive studies were also carried out regarding the "radiobiology" of PBRT, or how protons interact with normal and malignant tissue. By the late 1980s, some 14,000 patients around the world had been treated with PBRT, and follow-up studies on some patients stretched back over 20 years.

Because of the significant number of patients treated, and the amount of follow-up data now available, it has become possible to assess the effectiveness of PBRT in cancer therapy. In virtually every tumor site examined, the higher tumor doses and lower normal tissue doses delivered by PBRT have been shown to improve local control and to reduce acute and late complications as compared with x-ray therapy. When the available data on PBRT was reviewed by the federal Medicare program and the National Cancer Institute in the early 1990s, it was decided that sufficient data existed to classify PBT as an accepted (i.e. non-experimental) treatment for any of a number of localized tumors and for treatment of intracranial aneurysms.

Loma Linda University and Harvard University are currently engaged in a series of studies sponsored by the National Cancer Institute to determine the "best" or optimal PBRT dose for certain cancers (such as prostate cancer and a variety of brain tumors). It is important to emphasize that these studies are not being done to see if PBRT is an effective therapy. This has already been established. What is being determined now is the optimal way to use this tool in the fight against cancer. Similar studies are performed all the time with other standard forms of cancer therapy such as chemotherapy and surgery.

Where in the US can I receive PBRT?

At the time of writing there are two facilities in the United States treating patients with protons on a regular basis. The older facility is the Massachusetts General Hospital/Harvard Cyclotron Laboratory, which has been operational since 1957. Currently, that facility is limited to treating less than 10 patients per day, and cannot routinely irradiate many deep tumors. To overcome

this problem, a new PBRT facility is being constructed at Massachusetts General Hospital. This new facility has been designed to treat up to 100 patients per day, and is scheduled to open in June 1998.

Loma Linda's PBRT center opened in 1990 and is now fully operational, with four rooms available for the treatment of patients and a fifth room for basic science research. The facility was designed to treat a maximum of approximately 100 patients per day and is currently averaging about 80 patient treatments per day.

Is PBRT ever combined with other forms of radiation therapy?

Conformal PBRT is often used in conjunction with x-ray therapy to "boost" the levels of radiation at sites of gross disease and to allow irradiation of a large volume of tissue at doses sufficient to sterilize microscopic cancer.

An example of this type of combination radiotherapy is available in the treatment of certain stages of prostate cancer. Depending on the amount of cancer within the gland, and the type of prostate cancer present, a patient may be at risk for harboring microscopic "nests" of prostate cancer cells within the pelvic lymph nodes. These nodes lie at some distance from the prostate, and will not be irradiated if conformal PBRT alone is delivered to the prostate gland. Similarly, the use of x-ray therapy alone will limit the total dose of radiation which can be given to the prostate because of the high doses which would be delivered to large amounts of normal tissue. The solution is to utilize conformal PBRT to treat the prostate gland and to follow this with x-ray therapy of the pelvic area to treat the lymph nodes. By giving some of the treatment with conformal PBRT, the total x-ray dose can be reduced substantially, thus reducing the risk of complications while simultaneously permitting treatment of potentially cancerous lymph nodes (which would be missed if x-rays were not used at all). An analogous situation is seen in the treatment of many head and neck cancers, when there is also a significant risk for lymph node involvement.

Why is there so much interest in using PBRT in prostate cancer?

The prostate gland lies deep within the pelvis and is surrounded by critical structures such as the bladder and the rectum. Cancer of the prostate is now the most common malignancy in males (excluding skin cancers). In 1996 it was estimated by the American Cancer Society that over 300,000 new cases of prostate cancer will be diagnosed and that as many as 41,400 patients will die of this disease.

There is abundant evidence in the medical literature to demonstrate that radiation therapy or surgery (radical prostatectomy) are effective treatments for this disease. It has also been demonstrated that the ability of radiation therapy to control prostate cancer is highly dependent upon the total dose of radiation which is delivered. Higher doses equate to a higher degree of disease control. However, with normal external beam x-ray therapy alone (including

three-dimensional conformal x-ray therapy) a point of diminishing returns is reached beyond which further dose escalation begins to cause unacceptable side effects.

This risk of unacceptable side effects can be reduced by using conformal PBRT for some or all of the treatment by virtue of the tissue-sparing capabilities of PBRT on normal tissue as compared to external beam x-radiation. You may remember that a proton beam has a well defined high-dose area which can be manipulated to surround an irregularly shaped target (like the prostate gland) and thus give comparatively low doses of protons to the nearby normal tissues. In the treatment of prostate cancer, this tissue-sparing capability allows for reductions in the dose of radiation which may be delivered to the bladder and the rectal area while permitting the necessary high doses to be delivered to the prostate. The outcome is a reduced risk of radiation damage to the bladder and the rectal area — one of the major risks associated with conventional x-radiation therapy for prostate cancer.

How is PBRT planned and delivered?

It is impossible to deliver PBRT precisely without having (1) a three-dimensional reconstruction of the target organ or tumor and its relationship to the surrounding structures and (2) a reproducible treatment position to minimize movement errors (sometimes referred to as a "geographic miss").

The three-dimensional data are usually obtained by performing a computed tomography (CT) scan through the region of interest (chest, pelvis, etc.) with "slices" being taken at 3-5 mm intervals. Before the CT scan is performed, some type of immobilization device is constructed for the patient so that it is easy to reconstruct the patient's precise position each day during treatment. A typical immobilization device is a full-body "pod" constructed of a form-fitting foam liner surrounded by a rigid plastic (PVC) shell. For treatment of brain tumors, a custom-manufactured mask is utilized. The CT scan is obtained with the patient lying in the immobilization device so that the thickness of the immobilizing materials can be taken into account during the PBRT planning process.

Once the "pod" has been manufactured and the CT scan is complete, the treating physician sits down at a computer workstation and traces on the computer screen the tumor or organ to be irradiated and the surrounding normal tissue slice by slice. Next, a team of physicists and dosimetrists creates a proton beam treatment plan by generating a series of proton beams which are carefully designed to enter the patient at a variety of angles and by calculating the radiation dose being given to the tumor or target organ and the normal surrounding tissues. This plan is reviewed by the treating physician and, once approved, is electronically transferred to a series of automated machines which create the appropriate apertures and tissue compensating filters needed to turn the computer-generated plan into a treatment reality. All of these devices are calibrated by the physics support staff before the patient's first treatment to ensure that the planning and process of actual beam creation has been accomplished correctly.

What happens in the treatment room?

After changing into a gown, the patient enters the treatment room and lies down in the "pod" or puts on the mask. By utilizing a number of laser beams, the patient and the "pod" are moved to a position which is customarily within half a centimeter of the calculated optimal position. To further refine the patient's position, a series of low-power diagnostic radiographs are then taken. Distances from various bone landmarks to the "isocenter" are measured on these films each day and compared to identical measurements made on computer-generated films based on the planning CT scan. Usually, it is necessary to move the "pod" a few millimeters to make the daily position conform exactly with the ideal treatment position. These measurements and movements are performed by radiation therapy technologists and verified by a physician before each treatment.

After any necessary movements have been made, the treatment devices unique to each patient are loaded into the beam-line. All of these devices are identified by an individual bar-code which must be scanned by a laser scanner (similar to those you might see at a supermarket) before the computer will permit a treatment to take place. The purpose of this system is to minimize any risk that a particular patient might be treated with another patient's unique set of apertures and compensating filters.

At this point, the technologists and the physician retire to a control room located outside each treatment room and initiate the treatment. Protons enter the room as a series of discrete "spills" or "pulses" which (like x-rays) cannot be either seen or felt. Once the prescribed radiation dose has been delivered, the computer shuts off the proton beam, the technologists re-enter the room, and the patient gets out from the "pod" and changes back out of the gown.

Other cancers (and benign conditions) treated with PBRT

The following is a current list of the cancers and other benign conditions (listed by body site) which are currently being treated at Loma Linda using PBRT, either alone or in combination with x-ray therapy:

- Brain and head/neck
  - Astrocytoma
  - Meningioma
  - Acoustic neuroma
  - Ocular melanoma
  - Subfovealneurovascularization
  - Intracranial arteriovenous malformations
  - Brain metastases
  - Multiple head and neck sites (e.g., nasopharynx, tonsil, base of tongue, paranasal Sinuses, etc.)

- Spinal cord
  - Cordomas, including those involving the base of the skull
  - Chondrosarcomas

- Chest
  - Medically inoperable non-small-cell lung cancer (usually stage I or stage II tumors which have not metastasized to any other site in patient's whose general health makes removal of the lung impossible)

- Abdomen
  - Hepatocellular carcinoma
  - Liver metastasis (usually solitary)
  - Pancreatic cancer
  - Retroperitoneal sarcomas

- Pelvis
  - Prostate cancer
  - Cervical cancer
  - Sacral cordomas

We are in the process of performing improvements to the synchrotron and the proton beam transport system to allow treatment of large fields such as those required to breast cancer and Hodgkin's disease. We anticipate that this capability will exist by the end of 1997.

Enclosure 2

Differences between Protons and X-rays

James Metz, MD
The Abramson Cancer Center of the University of Pennsylvania

The main difference between protons and x-rays is based on the physical properties of the beam itself. Protons are large particles with a positive charge that penetrate matter to a finite depth based on the energy of the beam. X-rays are electromagnetic waves that have no mass or charge and are able to penetrate completely through tissue while losing some energy. These physical properties have a significant bearing on the treatment of patients.

The depth of treatment in tissue for protons is related to a quantity known as the Bragg Peak. This is due to a buildup of dose in the final few millimeters of the proton range. The depth of the Bragg Peak is dependent on the energy of the beam; with increasing energy, the Bragg Peak is located deeper in tissue. On the following page, Figure 1 shows the Bragg Peak. As you can see, the entrance dose is relatively low, but as the beam penetrates deeper in tissue, there is a sharp rise in dose deposited. This is followed by a rapid stop in dose deposition. The beam stops at this point. Thus no tissue is treated beyond the Bragg Peak.

This peak needs to be "spread out" to fit the width of the target to be clinically useful. Thus a special wheel, called a modulator, is placed in the beam to spread out the Bragg Peak to the desired size. Figure 2 shows a spread out Bragg Peak. Figure 3 shows the relationship between an unmodulated Bragg Peak, modulated spread out Bragg Peak, and standard x-rays.

Extensive studies have been performed to determine the biologic differences between protons and x-rays. A standard measure called the relative biologic effect (RBE) is used to compare the biologic effects of various radiation sources. A RBE of 1 is seen for standard x-rays. Neutrons have a much higher RBE of 3. It turns out protons can be thought of exactly the same as x-rays in terms of its biologic effects because the calculated RBE is 1.1. Another measure of effect in biologic systems is the oxygen enhancement ratio (OER). Again, there is no difference in OER between protons and standard x-rays. The bottom line is that the only difference between protons and standard x-rays lies in the physical properties of the beam and not the biologic effects in tissue.

Figure 1:

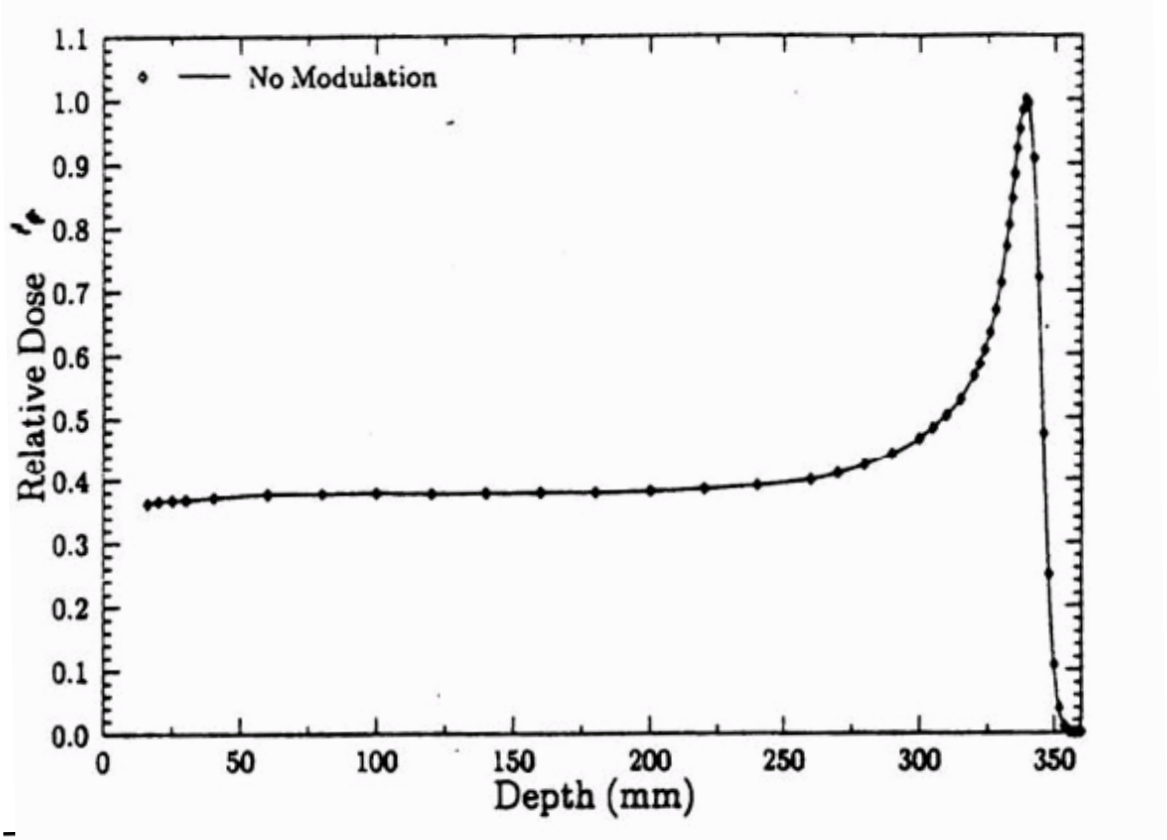


Figure 2:

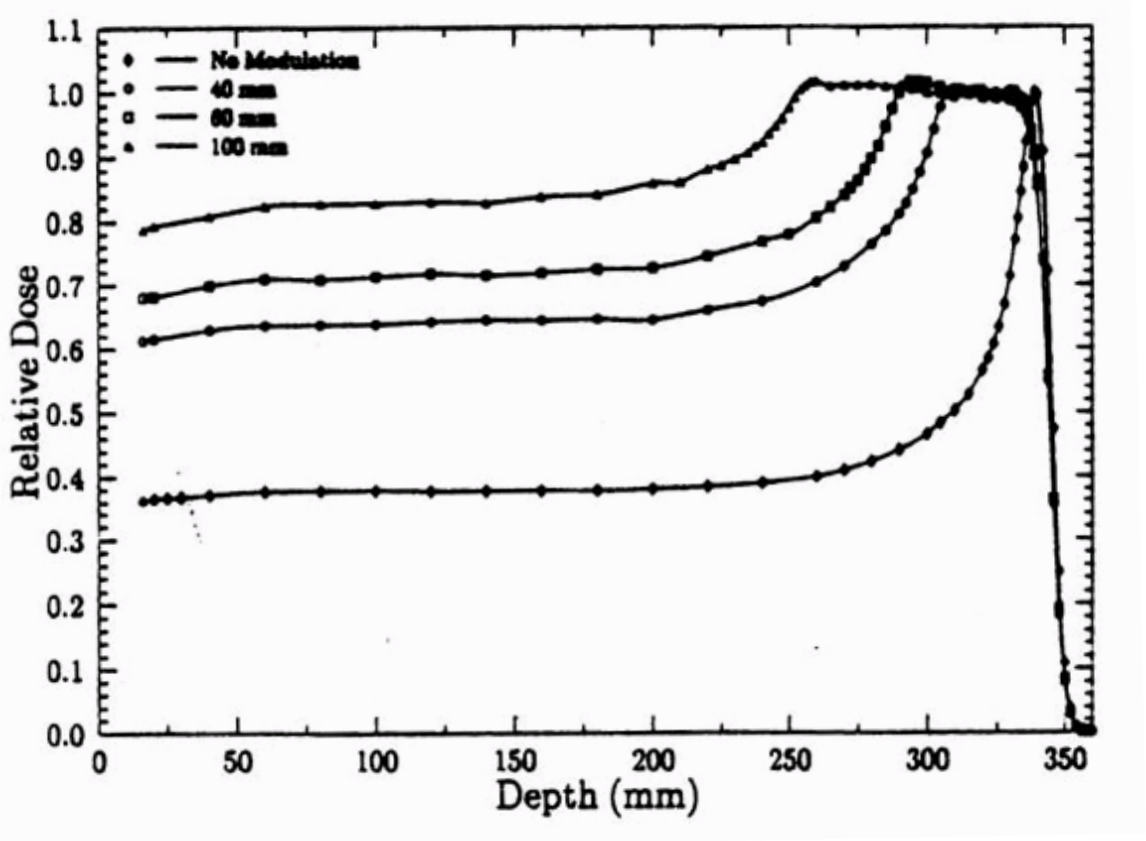
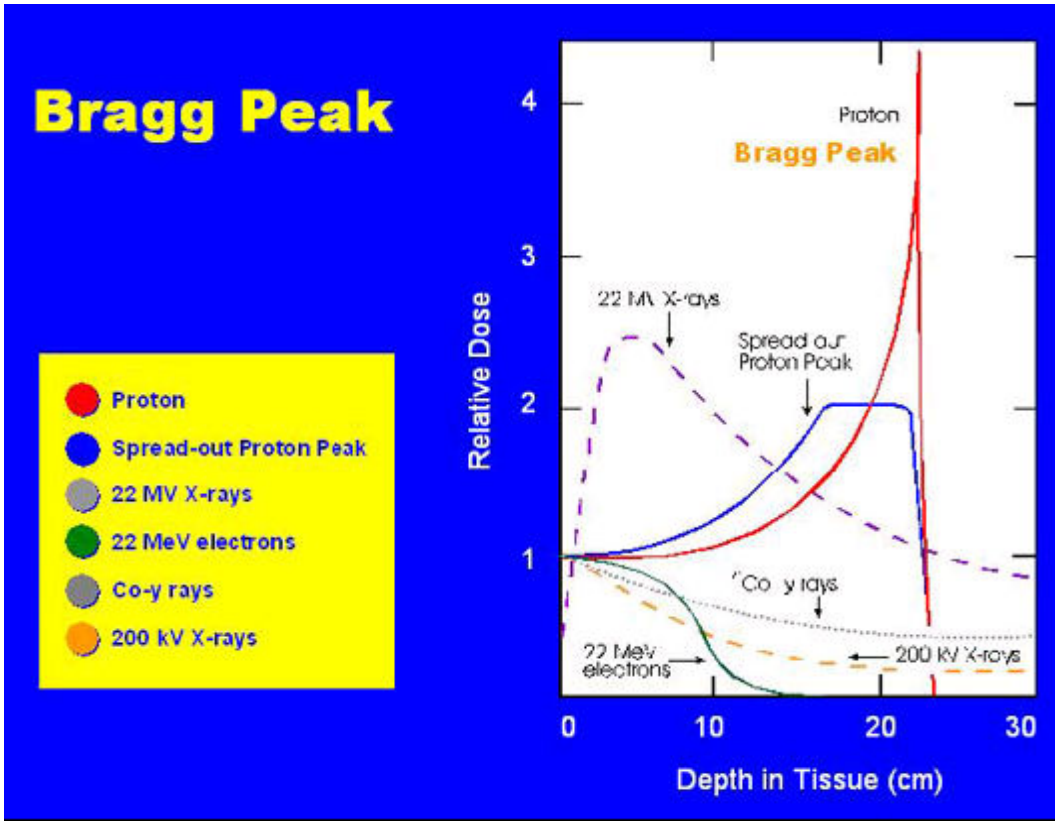


Figure 3:



Enclosure 3

Reduced Normal Tissue Toxicity with Proton Therapy

James Metz, MD
The Abramson Cancer Center of the University of Pennsylvania
Posting Date: April 28, 2002; Last Modified: June 29, 2006.

Proton beams offer highly significant advantages over x-rays in the sparing of normal tissues. This is due to the physical characteristics of the proton beam compared to x-rays. X-rays are electromagnetic waves and are highly penetrating, and will deliver dose throughout any volume of tissue irradiated, regardless of thickness. Thus x-rays always deliver substantial doses of irradiation both anterior and posterior to any tumor volume.

Furthermore, even for the most energetic x-ray beams available for practice, the depth at which the maximum dose of radiation is delivered (Dmax) ranges from as little 0.5 cm to a maximum of 3 cm depending on the energy utilized. Because a tumor is almost always located deeper than these ranges, a higher dose is invariably delivered to the normal tissues anterior to the tumor, and the tumor is always treated in the region of the beam where the energy deposition is falling off. To some extent, this can be overcome by bringing in beams from multiple directions, centered on the tumor, allowing the dose to sum within the tumor volume. However, since the beam travels throughout the entire thickness of the body, all normal tissues from the entrance area to the exit of the beam will be affected.

Unlike with x-rays, the absorbed dose of a proton beam increases very gradually with increasing depth and then suddenly rises to a peak at the end of a proton range. This is known as the Bragg Peak (Dmax of a proton beam). A proton beam can be directed so that the Bragg Peak occurs precisely within the tumor volume, something that can almost never be done with x-rays. The dose around the tumor volume is much less than the tumor itself, thus sparing the normal tissue in this area. The dose immediately beyond the Bragg Peak of a proton beam is essentially, zero which allows for the sparing of all normal tissues beyond the tumor volume. Side effects, both acute and long-term, typically seen with x-ray therapy can thus be markedly reduced with proton beams due to the sparing normal tissues that are situated around the tumor. These considerations are directly related to the physical characteristics of the proton beam, and require no demonstration or study. However, data are available from clinical series that support them. It should be remembered that the available clinical data are somewhat limited, because clinical proton beam facilities are only now being developed.

A number of published studies have documented the clinical advantages of proton beams, and shown decreased normal tissue toxicity, compared to conventional photons (x-rays). Numerous sites within the body have been shown to be more effectively treated with proton beam therapy. By limiting the dose to normal structures, higher doses can safely be delivered to the tumor itself. This should result in higher local control and ultimately increased survival while minimizing side effects of therapy. The following is a review of the currently available literature comparing the toxicity of conventional photon and proton beams:

Prostate Cancer

A significant proportion of patients treated in radiation oncology centers have prostate cancer. Side effects of treatment generally include gastrointestinal (GI) and genitourinary (GU) damage. Large numbers of patients experience urinary frequency and diarrhea during treatment, and long term, may suffer from impotence, incontinence, rectal fibrosis and bleeding, and extensive bowel fibrosis. These side effects may cause a reduction in the quality of life and result in delays of atypical radiation therapy treatment course. Tables 3 and 4 compare the acute and long-term complications of localized prostate cancer treated with protons, conventional x-rays, and radical prostatectomy, respectively. Figure 4 shows the reduction of normal tissue exposed to radiation with protons compared to photons (x-rays).

Table 3: Acute complications associated with the treatment of prostate cancer

Acute Toxicity	**Protons**	**Conventional Radiotherapy (Photons)**	**Prostatectomy**
≥ Grade 2 GU toxicity (frequency, nocturia, dysuria)	0%	28%	N/A
≥ Grade 2 GI toxicity (diarrhea, rectal/abd pain)	0%	35%	N/A
Either GU or GI morbidity	0%	53%	N/A
Hospitalization	None	None	5-7 days
Absence from work	None	None	4-6 weeks
Death	0%	0%	0.3%
Pulmonary embolism/ DVT	0%	0%	2.6%
Myocardial infarction or arrhythmia's	0%	0%	1.4%
Wound Complications	None	None	1.3%
Lymphocele	None	None	0.6%
Surgical Rectal Injury	N/A	N/A	1.5%

Table 4: Long-term complications associated with the treatment of prostate cancer

Chronic Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostatectomy
Impotence	30%	60%	60%
Incontinence requiring a pad	< 1%	1.5%	32%
Bladder Neck contracture	0%	3%	8%
Chronic Cystitis	0.4%	5%	N/A
Grade 3 GU toxicity	0.3%	2%	36%
Grade 3 GI toxicity	0%	7%	N/A
Rectal stricture	0%	0.5%	N/A

Lung Cancer

Lung cancer is the most common malignancy seen in men and women in the United States, and a very substantial source of all cancer mortality. A significant percentage of lung cancer patients are treated with radiation therapy at some point during the course of their disease. Since many of these patients have poor lung function due to years of smoking tobacco, preservation of functioning lung tissue is paramount. The destruction of lung tissue by conventional radiation techniques limits the delivery of potentially curative doses of radiation therapy. Tables 5 and 6 compare the acute and long-term complications of lung cancer patients treated with protons versus conventional x-rays.

Table 5: Acute complications associated with the treatment of lung cancer

Acute Side Effects	Protons	Conventional Radiotherapy (Photons)
Nausea/Vomiting	0%	30%
Dyspnea	0%	16%
Esophagitis	<5%	31%
Fatigue	<5%	23%
> 5 lb. weight loss	0%	34%

Table 6: Long-term complications associated with the treatment of lung cancer

Chronic Side Effects	Protons	Conventional Radiotherapy (Photons)
Lung Fibrosis by CT scan	33%	85%
Normal Lung Destroyed	8%	29%
Lung injury ≥ Score 2	0%	62%
Decreased pulmonary function testing (VC, FEV_1, diffusion capacity)	0%	20%
Dyspnea	0%	32%
≥ Grade 2 Esophagitis/Stricture	0%	10%
≥ Grade 2 Pneumonitis	5%	15%
Cardiac Complications	0%	7%

The doses of radiation utilized in the treatment of esophageal cancer are similarly limited due to the normal tissues within the radiation treatment portal. The spinal cord, heart, and lungs can receive significant doses due to the location of the esophagus. Comparative treatment plans for esophageal cancer show advantages similar to those noted in tables 5 and 6 in using protons instead of conventional x-rays.

Head and Neck Cancer

The morbidity associated with the treatment of head and neck cancer with protons and conventional photons has been reviewed at various institutions. Specifically, cancers of the paranasal sinuses, tonsillar region, and nasopharynx have been evaluated. In each of these cancers, proton therapy should result in an improvement of local control with a reduction in the morbidity associated with conventional photon treatment. There has been a significant reduction in the rates of blindness seen in the treatment of paranasal sinus tumors as shown in Table 7.

Also, comparative plans for the treatment of tonsillar and nasopharyngeal cancer revealed proton beam therapy can deliver higher doses of to the tumor volumes with significantly reduced radiation to the salivary glands and mandible than can photon beam irradiation. This results in a decreased incidence of xerostomia and radionecrosis of the mandible as demonstrated in Table 7.

It should be noted that essentially 100% of all patients treated for head and neck cancer with x-rays will experience severe xerostomia (dry mouth), which although it may not be life threatening, severely impairs quality of life. Many of these patients are for example unable to eat in a restaurant since they may require their food to be pureed or specially prepared for

them to be able to eat it. It is these sorts of poor quality of life outcomes that are very inadequately measured in current cancer statistics where the only measure of outcome is survival. Patients may be alive, but at considerable personal cost. This complication, xerostomia, is the sort of complication that is totally unavoidable with x-rays because of their through and through penetrating nature requiring us to treat both parotid glands even for well lateralized lesions, and which can be totally avoided with protons because of their lack of an "exit" dose. Given a choice of cure with or without xerostomia patients will make an obvious choice of protons over conventional x-rays.

Table 7: Major side effects associated with treatment of head and neck cancer

Side Effect	**Protons N=200***	**Conventional Radiotherapy (Photons) N=501****
Blindness (maxillary sinus tumors)	2%	15%
Xerostomia (Dry mouth)	< 5% (with protons alone)	100%
Dysphagia	12 %	100% 80% require liquid nutrition
Require PEG for nutrition	0%	30%

Pediatric Tumors

The treatment of pediatric tumors with proton therapy also provides a unique opportunity to significantly reduce the acute and long-term complications associated with conventional radiation therapy. The pediatric population is exquisitely sensitive to the effects of radiation therapy. Long-term sequelae including growth abnormalities, second malignancies, neurologic complications, cardiac and pulmonary toxicities, and infertility may all be reduced with the use of proton therapy. X-ray therapy causes effects on the hearts and lungs of pediatric patients, again due to the problem of "exit" dose. Proton beams should be able to entirely avoid these complications since the uninvolved normal structures can be totally avoided.

Well-recognized side effects of conventional photon irradiation of the brains of young children include neuropsychologic and intellectual deficits. The side effects vary directly with the volume of brain tissue irradiated and the dose of radiation delivered. By decreasing both the volume and dose of radiation to normal brain tissue through the use of protons, these side effects should be reduced. Table 8 outlines the reduced toxicity associated with proton therapy compared to conventional radiotherapy in pediatric patients.

Table 8: Complications associated with cranial spinal irradiation in pediatrics

Side Effect	Protons	Conventional Radiotherapy (Photons)
Restrictive Lung Disease	0%	60%
Reduced exercise capacity	0%	75%
Abnormal EKG's	0%	31%
Growth abnormality-Vertebral body receiving significant dose	20%	100%
IQ drop of 10 points at 6 yrs	1.6%	28.5%
Risk of IQ score < 90	15%	25%

Pancreatic Cancer

Comparative treatment planning performed at the Hospital of the University of Pennsylvania for the treatment of pancreatic cancer shows significant reductions in dose to normal structures. The tolerance of normal tissues has prevented effective dose escalation for this malignancy.

Table 9 shows how protons can significantly reduce the dose to normal tissues and allow for dose escalation.

Table 9: Comparison between X-ray and proton doses for pancreatic cancer

Structure	X-ray Dose (Gy)	Proton Dose (Gy)	Dose Reduction	p-value
Spinal Cord	27	6	78%	.003
Liver	22	10	55%	.061
Right Kidney	14	8	43%	.059
Left Kidney	11	3	73%	.025

Considering the experience to date, proton therapy offers important advantages over x-rays. There is no question that proton therapy results in a significant reduction in treatment related morbidity when compared to x-ray treatments. Because of this reduction in normal tissue toxicity, dose escalation studies are currently under investigation. This should further increase the local control, and ultimately survival, while minimizing treatment induced complications. Almost any site in the body may benefit from the use of protons compared to x-rays when normal tissue toxicity is analyzed.

Tumor Control with Proton Therapy

As more patients are treated with proton therapy, long term results on various sites of disease will be reported. When the same dose and fractionation regimens are used for x-rays and protons, there are similar cure rates. It is clear continued research is necessary to establish the optimum doses and fractionation of treatment for specific tumors using protons. Because protons can significantly reduce the side effects of treatment as noted above, studies on escalation of dose are ongoing. For many sites, increasing the dose of radiation therapy to the tumor may increase the ultimate cure rates. The following data are from sites already evaluated with proton therapy.

One of the most difficult areas to treat in the human body is a tumor that arises in the base of skull region. Damage to normal structures such as the brainstem, brain, cranial nerves, and optic chiasm can cause significant morbidity, thus limiting standard treatments. Surgical resection of this area is typically incomplete. Postoperative x-ray therapy achieves local control in only 35-40% of patients. It has been shown substantially higher doses of radiation therapy can be delivered with proton therapy. By delivering a median dose of 68.5 Gy with protons (typical Xray dose= 54 Gy), significant improvements have been made in both local control and survival with these tumors. The 5-year local control rates for proton therapy are 91% for chondrosarcomas and 65% for chordomas. The 5 year overall survival rates range from 62%-88%. Proton therapy has become the standard of care for tumors of the skull base. Uveal melanomas have historically resulted in loss of vision from the tumor or from the treatment, which consists of surgical removal of the eye. Over 2500 patients have been treated with proton therapy for uveal melanoma. The typical dose is 70 Gy over 5 treatments. The 5-year local control with protons is reported at 96%. The eye retention rate is 90% while the metastases free survival is 80%.

Loma Linda University Medical Center has treated over 1,000 patients with prostate cancer using proton therapy. Using doses comparable to standard x-ray treatments they have shown significant reductions in side effects as noted above. They have currently devised dose escalation studies to find the maximum dose that can be safely delivered with protons to the prostate gland.

Until the maximum dose is reached, final improvements in survival will not be known. However, the initial results reported based on PSA level with a very modest elevation of dose to 75 Gy are encouraging.

Table 10: Tumor control based on PSA at time of diagnosis

PSA Level	Proton Therapy	Conformal x-ray therapy	Radical Prostatectomy
< 4	100%	91%	92%
4-10	89%	69%	83%
10-20	72%	62%	56%
>20	57%	38%	45%

Unfortunately, some patients experience a local recurrence of their cancer after treatment with radiation therapy. Only a minority of patients is curable after a recurrence because the normal tissues can not tolerate significant doses of additional radiation. Because protons can spare normal tissues, many patients that were not previously considered treatable again with x-rays may be treated with protons. This may further increase the cure rates in some specific malignancies.

Any site treated in the body with standard x-rays is a reasonable target for proton therapy. The physical characteristics of the proton beam will allow markedly decreased dose to normal structures. Not only can malignancies be treated, but also there is currently significant interest in the treatment of a number of benign diseases. This includes functionally abnormal areas that can be safely ablated by protons for diseases such as seizures, Parkinson's disease, arteriovenous malformations, macular degeneration, and severe rheumatologic conditions.

There is also interest in evaluating protons for the prevention of coronary artery restenosis after angioplasty and prevention of stenosis of peripheral vascular shunts that are created in patients requiring dialysis. There are some preliminary data available on the treatment of macular degeneration. This is the leading cause of adult onset blindness in the United States. It is caused by the growth of blood vessels in the back of the eye, which are fragile and bleed. Current treatments include laser ablation, photodynamic therapy, standard x-ray therapy, and anti-angiogenic agents.

Unfortunately, none of these treatments have been extraordinarily successful for most patients. Proton therapy offers the opportunity to safely deliver a much higher dose of radiation in a single treatment to the vessels in the back of the eye then is possible with standard x-rays. There are very encouraging preliminary studies from Loma Linda University Medical Center where over 200 patients have been treated with a single fraction of 14 Gy. The lesion control is 95% with either improvement in vision or no worsening of vision. Side effects are very mild and seen in <10% of patients

Sample Letter #2

To: Member Appeals

From:

Date:

Subject: Pre-Service, Second-Level Grievance/Medical Necessity Appeal (File Ref: XXXX)

Review Committee:

This is my second appeal to coverage denials dated and for:

1. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and;
2. Proton beam therapy treatment at the University of Florida Proton Therapy Institute.

In the letter dated, the initial denial was upheld for the following reasons:

"The committee's findings: The requested proton beam therapy is considered experimental or investigative. Review of the available published material concerning proton beam radiation therapy shows there is no convincing evidence that treatment results are superior to photon beam therapy (conformal radiation). There is limited clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer."

"The committee's conclusion: After reviewing all of the above information, the committee determined that the requested treatment of proton beam therapy is experimental and investigational based on the available scientific literature. Therefore, denial remains upheld as contract benefit exclusion. In addition, the request to go out of network for evaluation for this therapy is not medically necessary because this therapy is considered experimental/investigational."

My Clinical Information

- (Age): diagnosed with prostate cancer in (year)
- Underwent a biopsy of the prostate secondary to elevated PSA levels (2.9)
- Biopsy was positive for Gleason 6 adenocarcinoma in 2 of 12 samples

Appeal Outline & Summary

I am appealing (name of insurance provider) coverage denial for proton beam therapy for the following reasons:

1) Proton beam therapy for prostate cancer is neither experimental nor investigational

a) Proton beam therapy (PBT) is generally recognized by the medical community, as clearly demonstrated by Reliable Evidence, as effective and appropriate for the treatment of prostate cancer. PBT is of proven benefit for the treatment of prostate cancer. Reliable Evidence exists that PBT for prostate cancer has a definite positive effect on health outcomes. Reliable Evidence exists that *over time*, proton beam therapy leads to improvement in health outcomes (i.e. the beneficial effects outweigh any harmful effects)

i) FDA approved; Medicare Policy (1997): PBT non-experimental, non-investigational
   (1) **Medicare Bulletin 406** (April 13, 1997), "Proton Beam Radiation Therapy"

ii) The Loma Linda Experience: PBT effective and appropriate for prostate cancer
   (1) **Slater, Jerry D., et al.** 2004. Proton Therapy for Prostate Cancer: The Initial Loma Linda University Experience*. International Journal for Radiation Oncology*, pp. Vol. 59 No. 2 pp. 348-352.
   (2) **Slater, Jerry D.** 2006. Clinical Applications of Proton Radiation Treatment at Loma Linda University: Review of a Fifteen-year Experience. *Technology in Cancer Research and Treatment.* April 2006, Vol. 5, Number 2.
   (3) **Rossi Jr., Carl J.** 2007. Conformal Proton Beam Radiation Therapy of Prostate Cancer. *Prostate Cancer Communication.* March 2007, Vol. 23, Number 1.

iii) Insurers have determined PBT to be non-experimental and non-investigational, including (name of insurer)

2) Reliable Evidence clearly demonstrates that proton beam therapy for prostate cancer is at least as effective in improving health outcomes as established technology. Moreover, there is convincing evidence that treatment results from PBT are *superior* to photon beam therapy (conformal radiation)

a) **Metz, James.** 2006. Reduced Normal Tissue Toxicity with Proton Therapy. *OncoLink*. Abramson Cancer Center of the University of Pennsylvania (June 29, 2006).
b) **Vargas, Carlos, et al.** 2008. Dose-Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer. March 1, 2008, *International Journal of Radiation Oncology*, pp. Vol. 70 Issue 3 pp. 744-751.

c) **Chung CS, et al** "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *Int J RadiatOncolBiolPhys* 2008; 72(1 Suppl):S8. Abstract 17.
d) **Cella, L., et al.** 2001. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. International Journal of Radiation Oncology, Biology, Physics. (January 1, 2001); 49(1): 217-23.
e) Levin WP, et al. Proton Beam Therapy. *British Journal of Cancer* Vol. 93: 849-54, 2005.
f) **Zietman, Anthony L, et al.** Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.

3) There is *sufficient* clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer. It is *not generally* recognized by Reliable Evidence or the medical community that additional study on proton beam therapy's safety and efficacy for the treatment of prostate cancer is recommended. Reliable Evidence shows that the prevailing opinion among experts regarding proton beam therapy is that *studies <u>or</u> clinical trials* have determined its maximum tolerated dose, its toxicity, its safety, its efficacy or its efficacy as compared with a standard means of treatment for prostate cancer.

i) RCTs comparing proton therapy to photon beam therapy in treatment of prostate cancer are unnecessary and may be unethical.

(1) **Buckner, C.D.** 2002. Intensity Modulated Radiation Therapy (IMRT). *Current Topics in Oncology 2002.*
(2) **Suit, Herman, et al.,** 2008. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 2008;86(2):148-53.
(3) **Goitein, Michael & Cox, James D.** 2008. Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, Vol. 26: No. 2 (2008) p. 175.

ii) Many more proton therapy centers are now available and under construction, at premier medical institutions, *because it is generally recognized by the medical community that proton beam therapy's safety and efficacy have been established*.

Proton Beam Therapy (PBT) for Prostate Cancer is neither Experimental nor Investigational

PBT is generally recognized by the medical community, as clearly demonstrated by Reliable Evidence, as effective and appropriate for the treatment of prostate cancer. PBT is of proven benefit for the treatment of prostate cancer. Reliable Evidence exists that PBT for prostate cancer has a definite positive effect on health outcomes.

PBT has been in use for over 40 years, since treatments began at Harvard University in 1961. The therapy is well-established as efficacious, efficient, and preferred in light of the side effects of standard treatments. In the last 50 years, more than 60,000 patients have been treated world-wide using PBT. More than 300 peer-reviewed articles have documented the clinical efficacy of PBT in a wide variety of cancers including eye, lung, pediatric, gastrointestinal, head and neck, sarcoma, and brain tumors as well as prostate cancer.

There is virtually no debate in the scientific literature regarding the effectiveness of PBT to treat prostate cancer. PBT is considered a reasonable and necessary form of treatment:

- Scientific data show that PBT is well recognized as an effective way to treat many cancers, including prostate cancer.
- PBT's inherent characteristics allow the physician to maximize the dose to the target while minimizing the dose to normal tissues outside the target. This is important because normal-tissue irradiation is the major limitation in tumor control.
- The ability to minimize dose to normal tissues allows for higher doses to be given to target volumes, thus promoting increasing rates of tumor control even as no increase occurs in rates of treatment-related toxicity. (RuthitaFike, CEO, Loma Linda University Medical Center).

FDA approved; Medicare Policy 1997: PBT is non-experimental, non-investigational

PBT is FDA approved. In 1997, more than ten years ago, Medicare concluded that PBT for prostate cancer was neither experimental nor investigational:

> "Policy: Proton Beam Radiation Therapy for treatment of Prostate Cancer will no longer be considered investigational. Proton beam radiation therapy is non-investigational in the treatment of malignancies. Proton beam therapy may be medically necessary for the treatment of:
>
> - Intraocular melanomas
> - Pituitary neoplasms
> - Small arteriovenous malformations
> - CNS lesions
> - Head and neck malignancies
> - Prostate malignancies
>
> Benefits will be provided when services are considered medically reasonable and necessary to treat the prostate cancer. Treatment with PBT should consider the characteristic absorption in a specified target volume and location that would likely result in superior clinical outcomes as compared to conventional (photons) or electron-beam radiotherapy." Medicare Bulletin 406 (April 13, 1997) attached on page 77 of this document.

The Loma Linda Experience: PBT is effective and appropriate for prostate cancer. Reliable Evidence exists that *over time*, PBT leads to improvement in health outcomes (i.e. the beneficial effects outweigh any harmful effects)

> **Slater, Jerry D., et al.** 2004. Proton Therapy for Prostate Cancer: The Initial Loma Linda University Experience*. International Journal for Radiation Oncology*, pp. Vol. 59 No. 2 pp. 348-352.
>
> **Conclusion:** "Conformal proton beam radiation therapy for prostate cancer can achieve excellent biochemical freedom-from-relapse rates with minimal treatment-related morbidity at the doses reported" (352).
>
> **Slater, Jerry D.** 2006. Clinical Applications of Proton Radiation Treatment at Loma Linda University: Review of a Fifteen-year Experience. *Technology in Cancer Research and Treatment.*April 2006, Vol. 5, Number 2.
>
> "Proton radiation therapy has been used at Loma Linda University Medical Center*for 15 years*. Our cumulative experience has confirmed that protons are a superb tool for delivering conformal radiation treatments, enabling delivery of effective doses of radiation and sparing normal tissues from radiation exposure" (81).
>
> **Rossi Jr., Carl J.** 2007. Conformal Proton Beam Radiation Therapy of Prostate Cancer. *Prostate Cancer Communication.* March 2007, Vol. 23, Number 1.
>
> Conclusion: "Conformal proton beam therapy has clearly been shown to be a safe and effective treatment for prostate cancer. The unique physical properties of the proton beam allow for marked reductions in normal tissue radiation dose as compared with x-ray-based therapy and make further dose escalation feasible. The development and construction of dedicated medical treatment facilities have enabled this modality to progress from a laboratory curiosity to a mainstream therapy." (239-240)

Insurers have determined PBT to be non-experimental and non-investigational, including (name of insurer).

In addition to the FDA and Medicare, healthcare insurers throughout the United States have embraced PBT as non-experimental and non-investigational in the treatment of prostate cancer. "Proton therapy has an established history of reimbursement by Medicare and private healthcare payers. More than 150 insurance carriers, including Medicare, cover proton therapy" (MD Anderson Proton Cancer Center). Below is a *partial list* of the more than 150 insurers, including (name of insurer), that do not consider PBT experimental or investigational. Following the list are the names of two men who were approved by (name of insurer) for proton beam therapy for prostate cancer, without appeal.

Anthem Blue Cross
http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a053258.htm

Blue Cross Blue Shield of Florida
http://mcgs.bcbsfl.com/

Empire Blue Cross Policy
http://www.empireblue.com/provider/noapplication/f2/s5/t9/pw_ad084931.pdf

MountainState Blue Cross Blue Shield
http://www.msbcbs.com/medpolicy/R-18-003.html

Regence
http://blue.regence.com/trgmedpol/medicine/med49.html

Cigna
http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0252_coveragepositioncriteria_proton_beam_therapy_for_prostate_cancer.pdf

Blue Cross Blue Shield of North Carolina
http://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/charged_particle_radiotherapy.pdf

Highmark Blue Shield
https://www.highmarkblueshield.com/pdf_file/prn/hbs-prn-8-05.pdf

(Name of insurer) PPO plan does not cover experimental or investigational procedures. Yet at least two men were approved for PBT without appeals. The first has been approved for treatment at (name of facility) beginning (date), and has already completed pre-treatment consultations/preparations at the site:

Name
Home: XXXXXXXX
Cell: XXXXXXX
Email: XXXXXXX

The second was treated at (name of facility) in (date) and was also approved by (name of insurer), without appeal, and with a PPO plan that excludes experimental/investigational treatments from coverage:

Name
Home: XXXXXXXX
Cell: XXXXXXX
Email: XXXXXXX

Conclusion: (Name of insurer) has already determined that there is sufficient Reliable Evidence in the scientific literature to approve PBT for prostate cancer as neither experimental nor investigational. Since this is fundamentally a question of evidence in the "available scientific literature," there is no scientific basis for proton therapy policy differences between the (name of insurer) PPO plan and the (name of insurer) HMO.

Based on the Reliable Evidence presented above, the first-level appeal committee incorrectly concluded that "the requested treatment of proton beam therapy is experimental and investigtaional based on the available scientific literature.

Reliable Evidence clearly demonstrates that proton beam therapy for prostate cancer is at least as effective in improving health outcomes as established technology. Moreover, there is *convincing* evidence that treatment results from PBT are *superior* to photon beam therapy (conformal radiation).

PBT has clear advantages over photon therapy when treating prostate cancer. PBT reduces the exposure and damage caused by radiation therapy to surrounding healthy tissue. Unlike photons, which scatter when entering the body and thus deliver the majority of their radiation in normal tissues upstream from the target volume, protons deliver their maximum radiation to the prostate. The physical properties of protons (i.e. mass, positive charge) allow them to scatter much less when entering tissue. Protons thus have a low entrance dose relative to the target, with the maximum dose occurring at a predetermined point, the Bragg Peak. This peak can be adjusted to conform precisely to the target volume and can be stopped within 2-3 mm of that volume. Hence there is no exit dose of radiation into normal tissues (see Levin, WP et. al., Proton Beam Therapy.) This phenomenon is not possible with photons; all individual photon beams deliver not only the greater part of their dose to normal tissues as they enter the body, but also irradiate normal tissues "downstream"from the target volume. (RuthitaFike, CEO, Loma Linda University Medical Center)

PBT, as compared to IMRT, reduces the amount of harmful radiation to normal tissue

Radiation harms human cells. Data suggest that higher radiation doses to cells result in higher risks of cell death. No dose is considered "safe." Therefore, the radiation oncologist seeks to irradiate normal cells as little as possible, and to avoid such radiation whenever possible. A major advantage of PBT over other forms of radiation therapy is its ability to minimize radiation exposure to normal cells, not only because of reduced scatter and the Bragg Peak phenomenon, but also because PBT can deliver a highly conformal dose to the target volume with relatively few radiation portals. The result is a greater volume of normal tissues not exposed to any dose of radiation, and a minimal dose delivered to normal tissues that are exposed.

Advancements in conventional radiation therapy such as intensity-modulated radiation therapy (IMRT) use computerized x-ray accelerators to deliver radiation to the target volume with greater precision than traditional photon radiation allows. Some have claimed that IMRT is as effective as PBT. IMRT delivers radiation to the target via several portals — often many more than are used in standard x-ray therapy. IMRT uses computer assistance to vary the position of the portals and intensity of the beam, thus enabling it to reduce the dose to selected normal tissues near the target while still delivering a high dose to the target cells. The price paid for this target-volume conformality, however, is a larger volume of normal tissues exposed to radiation. In fact, the cumulative dose throughout this volume (the volume integral dose) is higher with IMRT than with standard photon radiation. The dose to most of the tissues in this larger volume is relatively low (albeit IMRT can have significantly more hot spots than are seen with protons or other forms of x-ray delivery), but it remains to be seen whether the greater volume exposed to radiation eventuates in long-term sequelae.

Thus, while both PBT and IMRT are effective in treating prostate cancer, PBT can be distinguished from IMRT based on both the volume of normal tissue treated by the radiation and the amount of radiation exposure to normal tissue. With the IMRT approach, instead of a single volume of normal tissue receiving a high dose of radiation, multiple areas of normal tissue are exposed to lower doses of radiation. This exposure still can lead to a second malignancy or other unwanted side effects to the normal tissue, which may take years, perhaps decades, to develop. The end result is that patients receiving IMRT are exposed to two to three times more radiation to normal tissue than with PBT. (RuthitaFike, CEO, Loma Linda University Medical Center)

PBT allows increased total doses of radiation per course of treatment

Because PBT minimizes both the dose delivered to normal tissues and the volume of normal tissues receiving radiation, PBT can provide dose escalation, while not harming normal tissues, in ways that photon radiation — whether delivered by IMRT or otherwise — does not permit. It is *generally agreed* among radiation oncologists that higher total doses increase the likelihood of disease control for most solid cancers, and in the case of localized prostate cancer, it has been demonstrated that an increased radiation dose delivered to the prostate decreases the chances of a recurrence (DeWeese, Theodore & Song, Danny Y. Radiation Dose Escalation as Treatment for Clinically Localized Prostate Cancer: Is More Really Better? *JAMA*, Vol. 294: No. 10 (2005) p. 1275). A study performed by researchers at Massachusetts General Hospital and Loma Linda University found that treating men with clinically localized prostate cancer with a high-dose combination therapy of conventional radiation along with PBT instead of just a conventional dose of external radiation therapy led to the patients being more likely to be free from increased prostate-specific-antigen (PSA) levels 5 years later, and less likely to have locally persistent disease (see **Zietman, Anthony L, et al.** Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.)

Dose escalation with photon radiation, even with modern methods such as IMRT, is difficult to achieve because increasing the dose to the target volume also will increase the scattered and "downstream" dose to normal tissues. In contrast, because PBT can localize the dose to the target volume and minimize exposure to normal tissue, higher doses can be delivered without significantly increasing the toxicity and harmful side effects of the radiation (see **Slater, Jerry D. et. al.** 2004). Therefore, a major benefit of PBT over photon radiation is the ability to increase the total dose administered per course of treatment. (RuthitaFike, CEO, Loma Linda University Medical Center)

Conclusion: PBT is effective in treating prostate cancer and protects normal tissues to a greater extent than is possible with photon irradiation.

Documentation

> **Metz, James.** 2006. Reduced Normal Tissue Toxicity with Proton Therapy. *OncoLink*. Abramson Cancer Center of the University of Pennsylvania (June 29, 2006).
>
> "Proton beams offer highly significant advantages over x-rays in the sparing of normal tissues. This is due to the physical characteristics of the proton beam compared to x-rays."

"A significant proportion of patients treated in radiation oncology centers have prostate cancer. Side effects of treatment generally include gastrointestinal (GI) and genitourinary (GU) damage. Large numbers of patients experience urinary frequency and diarrhea during treatment, and long term, may suffer impotence, incontinence, rectal fibrosis and bleeding, and extensive bowel fibrosis. These side effects may cause a reduction in the quality of life and result in delays of a typical radiation therapy treatment course. Tables 3 and 4 compare the acute and long-term complications of localized prostate cancer treated with protons, conventional x-rays, and radical prostatectomy, respectively."

Table 3:

Acute complications associated with the treatment of prostate cancer Acute Toxicity	**Protons**	**Conventional Radiotherapy (Photons)**	**Prostatectomy**
> Grade 2 GU toxicity (frequency, nocturia, dysuria)	0%	28%	N/A
> Grade 2 GI toxicity (diarrhea, rectal/abd pain)	0%	35%	N/A
Either GU or GI morbidity	0%	53%	N/A
Hospitalization	None	None	5-7 days
Absence from work	None	None	4-6 weeks
Death	0%	0%	0.3%

Pulmonary embolism / DVT	0%	0%	2.6%
Myocardial infarction or arrhythmias	0%	0%	1.4%
Wound complications	None	None	1.3%
Lymphocele	None	None	0.6%
Surgical rectal injury	N/A	N/A	1.5%

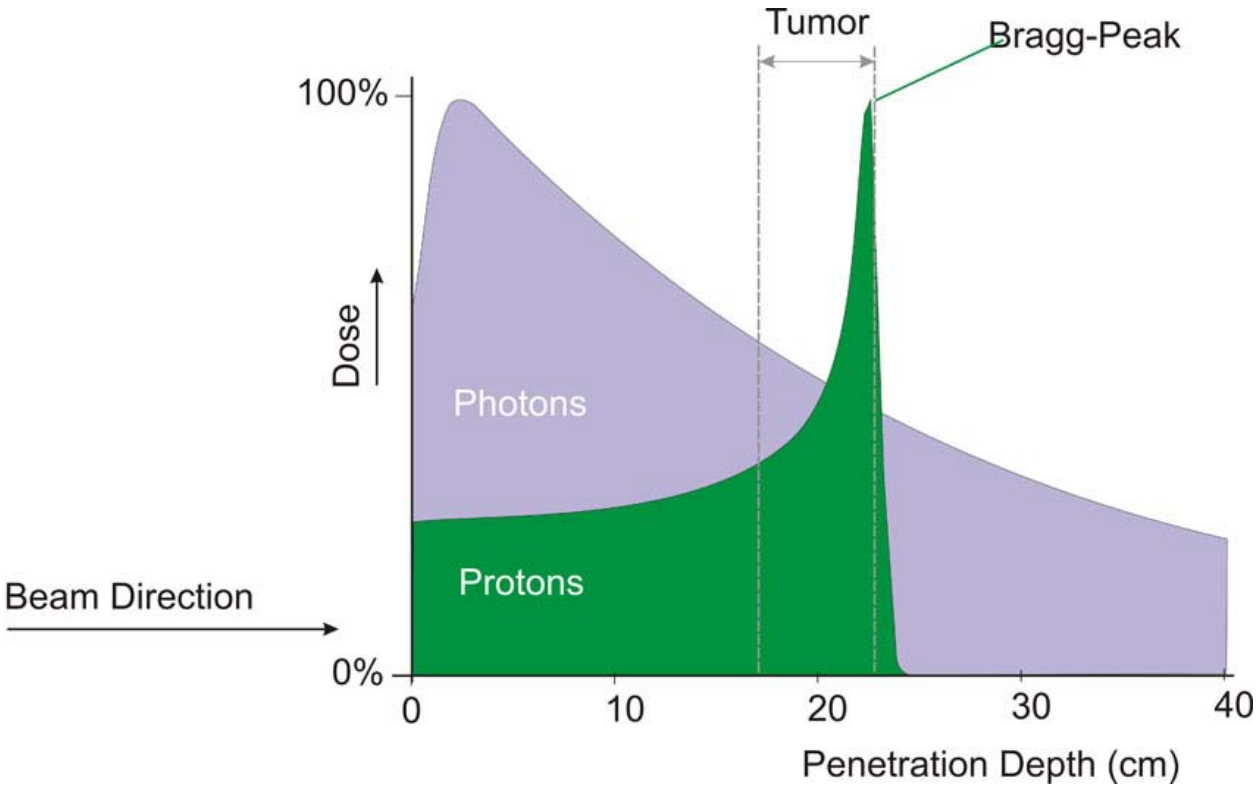
Source: Reduced Normal tissue Toxicity With Proton Therapy; June 29, 2006; James Metz, MD – Assistant Professor of Radiation Oncology, The Abramson Cancer Center of the University of Pennsylvania

Table 4:

Long-term complications associated with the treatment of prostate cancer Chronic Toxicity	**Protons**	**Conventional Radiotherapy (Photons)**	**Prostatectomy**
Impotence	30%	60%	60%
Incontinence requiring a pad	< 1%	1.5%	32%
Bladder Neck contracture	0%	3%	8%
Chronic Cystitis	0.4%	5%	N/A
Grade 3 GU toxicity Severe frequency q 1 hr dysuria	0.3%	2%	36%
Grade 3 GI toxicity rectal bleeding requiring transfusion severe pain (>70 Gy)	0%	7%	N/A
Rectal stricture	0%	0.5%	N/A

Source: Reduced Normal tissue Toxicity With Proton Therapy; June 29, 2006; James Metz, MD – Assistant Professor of Radiation Oncology, The Abramson Cancer Center of the University of Pennsylvania

The Figure below shows the reduction of normal tissue exposed to radiation with protons compared to photons (x-rays):



A study from the University of Florida Proton Therapy Institute (UFPTI) (Vargas, Carlos, et al, March 2008, IJROBP) compared PBT and IMRT plans for prostate cancer. This study demonstrated significant reductions in the volume of rectal tissue receiving doses from 10 Gy to 80 Gy.

> **Vargas, Carlos, et al.** 2008. Dose-Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer.March 1, 2008, *International Journal of Radiation Oncology*, pp. Vol. 70 Issue 3 pp. 744-751.
>
> **"Conclusion:** The results of our study have shown that proton radiotherapy dose delivery characteristics can be optimized to improve results seen with IMRT. The dose-sparing advantage was larger for the rectum, although the mean bladder doses were also decreased significantly. The PTV coverage was excellent with better homogeneity than with IMRT."
>
> **Chung CS, et al** "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *In the Journal of Radiation Oncology, Biology, Physics*. 2008; 72(1 Suppl):S8. Abstract 17.

"**Conclusion:** The results of our preliminary analysis indicate that the use of proton radiation therapy is associated with a significantly lower risk of a second malignancy compared to photon radiation therapy."

Cella, L., et al. 2001. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*. (January 1, 2001); 49(1): 217-23.

"Conclusion: Both IM x-ray and proton beams were able to optimize the dose distribution and comply with the goal of delivering the highest dose to the target while reducing the risk of severe morbidity to acceptable levels. The main advantage compared to IM X-rays was that IM protons succeeded in significantly reducing the low-to-medium dose to the non-target tissues and achieved a small improvement in planning target volume (PTV) dose heterogeneity."

Levin WP, et al. Proton Beam Therapy. *British Journal of Cancer* Vol. 93: 849-54, 2005.

"**Conclusions:** As discussed, the main benefit of proton therapy over photon beam radiotherapy is the absence of exit dose, which offers the opportunity for highly conformal dose distributions, while simultaneously irradiating less normal tissue. This technology therefore reduces irradiation to normal tissue, while permitting dose escalation to levels not achievable with standard techniques. Dose escalation with protons has been shown in a randomised clinical trial for prostate cancer to improve local tumour control; clinical experience with proton radiotherapy in phase II studies in other anatomic locations suggests that dose escalation in other sites results in improved local control."

The Zeitman study accrued patients from 1996-99 and increased radiotherapy doses from 70.2 Gy to 79.2 Gy. In both dose groups, the initial 50.4 Gy was delivered with X-rays; following the X-ray treatment a proton boost was given of 19.8 Gy for a total dose of 70.2 Gy in the low radiation dose group or 28.8 Gy for a total dose of 79.2 Gy in the high radiation dose group. Thus approximately 28% of the total radiation dose was delivered with protons in the low dose treatment group and 36% with protons in the high dose group. This trial demonstrated a significantly lower risk of PSA failure rate with the higher radiation dose in both the intermediate risk prostate cancer patients, and, for the first time, in low risk prostate cancer patients. The 97% cure rate reported in low risk prostate cancer patients treated with the higher dose on the Zeitman trial has not been surpassed in any other randomized trial of radiation or other treatment modality in low risk prostate cancer. The rather compelling results of the study demonstrate that proton therapy is an extremely effective treatment for patients with localized prostate cancer. (Stuart Klein, Executive Director, University of Florida Proton Therapy Institute)

Zietman, Anthony L, et al. Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.

"**Conclusions:** Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity."

Summary: "A salient shortcoming of photon radiation therapy for prostatic carcinoma is the damage to the urethra, rectum, and bladder that often arises when doses sufficiently high to control prostate cancer are delivered. Dose-volume relationships indicate, for example, that rectal bleeding occurs when the irradiation dose exceeds 70 Gy and the volume of return included is high (>25%) (see **Storey, M.R., et al.,** Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *International Journal of Radiation Oncology, Biology, Physics*.2000 Oct 1;48(3):635-42.) Conversely, insufficient dose results in local failure and recurrence. The proton beam offers a delivery mechanism to administer the same qualitative ionizing radiation to the volume of interest, but to a much higher total dose. This heightens the chance of achieving biochemical as well as clinical disease-free control while avoiding the complications that interrupt and prevent delivery of a sufficient dose with photon beams. Proton beam therapy also avoids the large volume of normal pelvic tissues irradiated to low doses with IMRT." (*Additional Supporting Documentation Regarding Proton Therapy Services*)

Based on the Reliable Evidence presented on the previous page, the first level appeal committee incorrectly concluded that "published material concerning proton beam radiation therapy shows there is no convincing evidence that treatment results are superior to photon beam."

There is sufficient clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer.

It is *notgenerally* recognized by Reliable Evidence or the medical community that additional study on proton beam therapy's safety and efficacy for the treatment of prostate cancer is recommended. Reliable Evidence shows that the prevailing opinion among experts regarding proton beam therapy is that *studies or clinical trials* have determined its maximum tolerated dose, its toxicity, its safety, its efficacy or its efficacy as compared with a standard means of treatment for prostate cancer.

Randomized Phase III Clinical Trials (RCTs) comparing proton therapy to photon beam therapy in treatment of prostate cancer are unnecessary and may be unethical.

A randomized phase III clinical trial is unnecessary to prove the benefits of PBT for the treatment of prostate cancer. The benefits have already been documented. If PBT is at least as

effective as conventional or IMRT photon irradiation in treating prostate cancer, and reduces radiation exposure to healthy surrounding cells, the simple conclusion is that PBT has a beneficial role in the treatment of prostate cancer. The medical community has responded with a flurry of recently completed and planned proton beam therapy centers.

There are several reasons why there have not yet been any phase III trials comparing conventional photon radiation to PBT. One is that some in the field do not find any scientific need or benefit to conducting such phase III trials. (See **Suit, Herman et. al.,** Should Positive Phase III Clinical Trial Data Be Required before Proton Beam Therapy is More Widely Adopted? No. *Radiotherapy and Oncology*. Vol. 86 (2008) pp. 152-153). Another is that, in the judgment of some, conducting a phase III randomized clinical trial would be unethical. Given the demonstrated facts that dose distributions of proton beam therapy are superior to x-rays (photons), that proton therapy delivers two to three times less energy to normal, healthy tissue outside the prostate, that tissue response per unit does between protons and x-rays is virtually identical, and that radiation damages normal tissues, there are real ethical questions about whether RCTs comparing proton therapy to photon beam therapy in treatment of prostate cancer should be pursued. (See **Goitein, Michael & Cox, James D.** Should Randomized Clinical Trials Be Required for Proton Radiotherapy?, *Journal of Clinical Oncology*. Vol. 26: No. 2 (2008) p. 175).

Ethical concerns arise from the fact that the major clinical difference between modern photon irradiation (IMRT) and PBT lies in the volume of normal tissue exposed to radiation. The main point of a comparative trial would be to determine whether (if one assumes the same total dose delivered to the target volume) the difference in volume integral dose results in detectable clinical differences—presumably in side effects and second malignancies—over time. In order to conduct such a clinical trial, the study must be approved by institutional review boards, which are charged with ensuring that human research subjects are not harmed. Yet, a phase III study comparing photons to protons would require researchers to expose patients in the photon therapy group to normal-tissue radiation. Since there is overwhelming evidence that all radiation is harmful, how could one ethically design a study wherein half of the participants would be receiving two to three times more radiation to normal tissue with no expected clinical benefit? It would certainly be difficult to find patients willing to participate in such a study and to find an institutional review board willing to approve such an experiment. (see **Suit, Herman et. al.,** Should Positive Phase III Clinical Trial Data Be Required Before Proton Beam Therapy Is More Widely Adopted? No. *Radiotherapy and Oncology*, Vol. 86 (2008) pp. 149, 152-153)

A Double Standard

It is worth noting that, just as there have been no phase III trials comparing conventional photon radiation to PBT, there have been no phase III trials comparing conventional photon radiation to IMRT. Most proposals for a phase III trial call for a comparison between IMRT and PBT, on the assumption that IMRT is the most advanced form of photon radiation. Given the greater volume integral dose associated with IMRT, however, such an assumption may be

premature. For this reason, as well as the demonstrated effectiveness of PBT in treating prostate cancer, the lack of phase III studies comparing IMRT to PBT is not an appropriate basis to deny coverage. (RuthitaFike, CEO, LomaLindaUniversityMedicalCenter)

In the field of radiation therapy, proton therapy is not unique in offering limited comparative evidence of one technology's superiority over another. For example, there is little, if any, direct clinical evidence proving the superiority of IMRT over conformal three dimensional radiation therapy for the treatment of prostate cancer. Yet IMRT is a widely available technology that is offered by the vast majority of radiotherapy facilities.

"The current state of the art treatment modality, Intensity Modulated Radiation Therapy (IMRT), was widely adopted without comparative trials based on the same type of surrogate dose distribution modeling that supports the case for proton therapy. We believe that conducting randomized comparative clinical trials would do unnecessary harm to patients as this would expose the normal tissues to needlessly high levels of radiation. While we agree that clinical research on proton therapy needs to continue, the existence of well established surrogate models and published data has already been established. Therefore, we believe the development of comparative evidence through randomized clinical trials is an unnecessary and expensive undertaking." (Robert L. Foote, MD; Professor of Radiation Oncology, Mayo Clinic)

> **Buckner, C.D.** 2002. Intensity Modulated Radiation Therapy (IMRT). *Current Topics in Oncology, 2002.*
>
> "What is the data to support the use of IMRT over 3D-CRT? There have been no published randomized controlled trials comparing IMRT to 3D-CRT. The extended use of and enthusiasm for this technology rests on observations of phase II trials and simulation results where radiation to normal tissue was calculated to be less than for 3D-CRT under the same circumstances. Since this technology has apparently replaced 3D-CRT, it is unlikely that randomized trials will be performed in the future" (1-2).
>
> "Summary: At the present time, it appears that IMRT will or has replaced 3D-CRT for the treatment of cancers where these are the appropriate choices. It is unlikely that there will be any significant number of formal randomized trials to confirm the superiority of IMRT over other technologies. Most major radiation oncology centers believe this technique to be superior and have already invested heavily in this technology." (4)
>
> **Suit, Herman, et al.,** 2008.Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 2008;86(2):148-53.
>
> **"CONCLUSIONS:** Proton therapy provides superior distributions of low LET radiation dose relative to that by photon therapy for treatment of a large

proportion of tumor/normal tissue situations. Our assessment is that there is no medical rationale for clinical trials of protons as they deliver lower biologically effective doses to non-target tissue than do photons for a specified dose and dose distribution to the target. Based on present knowledge, there will be some gain for patients treated by proton beam techniques. This is so even though quantitation of the clinical gain is less secure than the quantitation of reduction in physical dose. Were proton therapy less expensive than X-ray therapy, there would be no interest in conducting phase III trails."

Goitein, Michael & Cox, James D. 2008. Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, Vol. 26: No. 2 (2008) p. 175.

"It is therefore hard to imagine how any objective person could avoid the conclusion that there is, at the very least, a high probability that protons can provide superior therapy to that possible with x-rays in almost all circumstances. It is primarily for this reason that the practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays." (175)

Many more proton beam therapy centers are now available and under construction, at premier medical institutions, because it is generally recognized by the medical community that proton beam therapy's safety and efficacy have been established.

Recent long-term reports of treatment history and results have generated a rapid proliferation of planned "Centers of Excellence" and primary medical institutions that are investing in the facilities to administer the Proton Beam Therapy. In 2005, there were only three primary proton beam medical facilities in the U.S. There are now five such centers with fully operational proton facilities that are currently treating cancer patients in a hospital environment: Loma Linda University Medical Center (LLUMC) at Loma Linda, California; Massachusetts General Hospital (MGH) in Boston; Midwest Proton Radiotherapy Institute at Indiana University, Bloomington; the M. D. Anderson Cancer Center in Houston, Texas; and the University of Florida Proton Therapy Institute at Jacksonville, Florida.

As of March 2008, the LLUMCProtonCenter had treated well over 12,000 cancer patients with many types of cancer disease. More than half of these (approximately 65%) were treated for prostate cancer. The Texas and Florida centers have been in operation since mid-2006. There are minor variations at the different locations, depending on the facilities and doctors. However, the daily use of protons in the hospital environment has been proven (at LLUMC and the other active proton centers), and proton treatment protocols are well established.

Highlighting the growing recognition, progress, and degree of potential for proton beam treatment, there are several new centers either under construction or in the advanced planning stage within the U. S., most requiring an investment of $120 million to $200 million.

The University of Pennsylvania is building a large facility near Philadelphia, which is being partly funded by The Dept. of Defense in partnership with WalterReedArmyHospital. Construction of this facility is on schedule and proceeding. The cyclotron, built by IBA of Belgium, arrived in Philadelphia January 29, 2008.

Construction is in progress on a private, for-profit ProtonCenter in Oklahoma City that is planned to open in 2009. It is being built by ProCure Inc., the developers of the Bloomington, Indiana facility. Construction is well underway; the cyclotron was delivered in May 2008. HamptonUniversity in Hampton, Virginia, is planning a $183 million facility that is scheduled to open in 2010, and will treat approximately 125 patients daily (over 2,000 patients per year). The Seattle Cancer Care Alliance is planning a $120 million center in Seattle, Washington. A Letter of Intent was signed in February 2008; this facility will probably be on-line in late 2010 or 2011. In October 2006 NorthernIllinoisUniversity announced plans to build a world-class cancer treatment and research center in Chicago that will provide state-of-the-art proton therapy. The facility will be known as the Northern Illinois Proton Treatment and ResearchCenter. CentralDuPageHospital of Winfield, Illinois, a suburb of Chicago, is also pursuing development of a proton center.

ProCure Inc. is also planning a new proton center in south Florida, near Boca Raton. “The 58,000-square-foot center will be located in Broward or Palm Beach County with site selection near completion. The facility will be able to treat as many as 1,500 patients a year.” Barnes-Jewish Hospital in St. Louis, Missouri; Broward General at Ft. Lauderdale, and Orlando Regional at Orlando, Florida, are planning smaller units ($20 million; see reference to MIT proton development below) to be brought on-line in 2009 and later. There are about fourteen others in the proposed, pre-planning, or design stage in the U. S. and worldwide. Experts foresee up to 100 U.S. proton centers within the next few decades. (Fuller C. Jones, ProtonBeamCenters for Cancer Treatment: A Status Summary Update – July 2008)

Based on the Reliable Evidence presented above, the first-level appeal committee incorrectly concluded that there is a need for additional “clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer.”

Overall Conclusion

In light of the Reliable Evidence provided above and in the attached documents, I hereby request that Keystone Health Plan East approve for me the following:

1. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and;
2. Proton beam therapy treatment at the University of Florida Proton Therapy Institute.

Sincerely,

Response to (name of physician)
Peer Review Report
Date

In his Peer Review Report of (date), Dr. (name) concludes that "The requested treatment is experimental and investigational based on the available scientific literature." While I have addressed this conclusion in the accompanying document, Dr. (name) makes a number of specific claims and suggestions that require a rebuttal.

The document opens with the ominous statement that "only limited comparative clinical data are present and considerable concern has been aroused." Again, the accompanying document thoroughly establishes the efficacy of proton beam therapy and explicitly addresses the issue of clinical data, but *who* exactly has expressed "considerable concern" and about what?

Any new treatment will have its critics, and they will come primarily from the ranks of those practicing the conventional, competing treatment options. It is easy to say, "more studies need to be done", especially when proton beam therapy, with new centers springing up everywhere, is poised to revolutionize cancer treatment and make some conventional treatments obsolete – in large part because of its ability to limit side effects and preserve quality of life. There are almost no post-treatment prostate cancer patients expressing "considerable concern" about their choice of proton beam therapy, because as a lot they are overwhelmingly satisfied with the results. The attached **Patient Testimonials**, addressed to XXXXXX, are just a sampling.

As for the "potential additional risk for secondary malignancies" with proton beam therapy, a 2008 study turned the tables on photon radiation. C.S.Chung et al. conclude that **"the use of proton radiation therapy is associated with a significantly lower risk of a second malignancy compared to photon radiation therapy."** Not only does this study deflate the "considerable concern" about proton therapy, it is more evidence that proton therapy is superior to conventional photon radiation. This abstract and accompanying text are included among the attached references (Chung CS, et al "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *Int J Radiation Oncology BiolPhys* 2008; 72(1 Suppl):S8. Abstract 17).

Dr. (name) goes on to reference D'Amico et al. in *Campbell-Walsh Urology* (9th edition), which is many years out-of-date in its status report on proton treatment facilities. It mentions only one free-standing facility, Loma Linda Medical Center, and suggests that proton therapy is an experimental treatment associated with physics labs. In fact, there are now nine such free-standing centers in existence in the United States alone, there are others around the world, and many more are nearing completion and in development: "In 2005, there were only three primary proton therapy medical facilities in the U.S. There are now five such centers with fully operational proton facilities that are currently treating cancer patients in a hospital environment: Loma Linda University Medical Center (LLUMC) at Loma Linda, California; Massachusetts General Hospital (MGH) in Boston; Midwest Proton Radiotherapy Institute at

Indiana University, Bloomington; the M. D. Anderson Cancer Center in Houston, Texas; and the University of Florida Proton Therapy Institute at Jacksonville, Florida" (from the accompanying documentation).

The Peer Review Report concludes with an unattributed three-sentence quotation that implies proton beam therapy is currently not safe: (sic) The same technical advances that allow delivery of improved photon therapy (conformal radiation) must be used by particle beam specialists. In time, it may be possible to deliver particle beams safely…" This passage is also from D'Amico et al.'s article in *Campbell-Walsh Urology* [I checked], and this conclusion is as out-of-date as their status report on proton beam therapy facilities. Proton therapy has already been established as safe and efficacious in the treatment of prostate cancer.

With all due respect to Dr. (name) and others, it is evident – and even understandable – that not all urologists are up-to-date on the status of proton therapy as a safe, legitimate, superior, and preferable option for the treatment of prostate cancer. Dr. (name) is a surgeon who has specialized in nerve grafting during radical prostatectomy (see his article titled, "Bilateral nerve grafting during radical retropubic prostatectomy: Extended follow-up"). He is not a radiation oncologist and is perhaps not in the best position to evaluate this relatively new form of treatment. Taken together, this rebuttal and the accompanying documents provide a much more thorough, up-to-date assessment of proton beam therapy's efficacy and superiority over other available options for the treatment of prostate cancer.

In light of the Reliable Evidence provided above and in the attached documents, I request that (name of insurer) approve for me the following:

3. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and
4. Proton beam therapy treatment at the University of Florida Proton Therapy Institute

Sincerely,

References

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Goitein, Michael & Cox, James D. 2008. Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, Vol. 26: No. 2 (2008) p. 175.

University of Florida Proton Therapy Institute
Additional Supporting Documentation Regarding Proton Therapy Services. Jacksonville, FL.

Medicare Bulletin 406

April 13, 1997

Proton Beam Radiation Therapy

Subject: Local Medical Review Policy-Proton Beam Radiation Therapy

This Medicare policy will be retroactive for services performed on or after June 27, 1996.

Description

Protons are one of several types of subatomic particles that have been used by the radiation oncologist in the treatment of malignancy. The biologic activity resulting from proton beams is identical to other forms of radiation therapy, i.e. these charged particles interact with electrons in the target tissue to produce ionization. The ionization affects the replicating ability of the cells. While these cells have some ability to repair themselves, a cancer cell's ability to repair itself is usually inferior to normal cells. This permits selective cell destruction.

The major advantage of protons over conventional radiation therapy is that the characteristic energy distribution of protons can be deposited in tissue volumes designated by the physician in a three-dimensional pattern. This superior control and precision allows the radiation oncologist to significantly increase the dose to the tumor target while minimizing the dose (and radiation-induced complications) to healthy surrounding tissue.

Policy

Proton beam radiation therapy for treatment of prostate cancer will no longer be considered investigational. Proton beam radiation therapy is non-investigational in the treatment of malignancies. Proton beam therapy may be medically necessary for the treatment of:

- Intraocular melanomas.
- Pituitary neoplasms.
- Small arteriovenous malformations.
- CNS lesions.
- Head and neck malignancies.
- Prostate malignancies.

Benefits will be provided when services are considered medically reasonable and necessary to treat the prostate cancer. Treatment with proton beam radiation therapy should consider the characteristic absorption in a specified target volume and location that would likely result in superior clinical outcomes as compared to conventional (photons) or electron beam radiotherapy.

Appendix

These documents can be found on the following pages (beginning on pg. 57)

1. Science Daily: Proton Therapy Lowers Chance of Later Cancers, Study Suggests, 11/22/08

2. Dr. Andrew Lee of M.D. Anderson Cancer Center Responds to Wall Street Journal Article of 8/5/09

3. Journal of Clinical Oncology: Randomized Trial Comparing Conventional-Dose With High-Dose Conformal Radiation Therapy in Early-Stage Adenocarcinoma of the Prostate: Long-Term Results From Proton Radiation Oncology Group/American College of Radiology 95-09

4. The Promise of Proton Therapy is Two-fold—Less toxicity and higher cure rates than achievable with X-ray therapy

5. PAACT, Inc: Prostate Cancer Communication Newsletter 3/2007: Conformal Proton Beam Radiation Therapy of Prostate Cancer by Carl J. Rossi, MD, Associate Professor, Radiation Medicine, Loma Linda University Medical Center

ScienceDaily
Your source for the latest research news

Proton Therapy Lowers Chance of Later Cancers, Study Suggests

ScienceDaily (Sep. 22, 2008) — Patients who are treated with proton therapy (a specialized type of external beam radiation therapy using protons rather than X-rays to treat cancer) decreases the risk of patients developing a secondary cancer by two-fold, compared to being treated with standard photon radiation treatment, according to a first-of-its-kind study.

This study contradicts recent theories that have suggested that proton radiation might actually increase — instead of decrease — the incidence of secondary cancers because of what is called scatter radiation. When proton radiation is delivered, neutrons are produced by nuclear interactions and are therefore scattered as a result.

"This study could have a substantial impact on the care of patients," Nancy Tarbell, M.D., senior author of the study and a radiation oncologist at the Massachusetts General Hospital in Boston, said. "Since cancer patients are surviving for longer periods of time, side effects of therapy are becoming increasingly important for doctors to consider when developing treatment plans. Since this is a retrospective study, however, we will need additional studies to further prove this hypothesis."

Photon radiation is the standard external beam radiation therapy treatment, while proton radiation is a more targeted form of external beam radiation which delivers less radiation to bordering normal structures. During external beam radiation therapy, a beam of radiation is directed through the skin to the cancer and the immediate surrounding area in order to destroy the main tumor and any nearby cancer
cells.

The retrospective cohort study matched 503 patients who underwent Harvard Cyclotron proton radiation treatment with 1,591 patients treated with photon radiation therapy from the Surveillance, Epidemiology, and End Results (SEER) cancer registry from 1974 to 2001. According to the study, 6.4 percent of patients who underwent proton therapy developed a secondary cancer while 12.8 percent of patients who had photon treatment developed another type of cancer.

The abstract, "Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy," was presented September 22, 2008, at the American Society for Therapeutic Radiology and Oncology's 50th Annual Meeting in Boston.

Web address:
http://www.sciencedaily.com/releases/2008/09/080922122421.htm

Adapted from materials provided by American Society for Therapeutic Radiology and Oncology, via EurekAlert!, a service of AAAS.

Letter to Wall Street Journal from Dr. Andrew Lee

Dr. Andrew Lee of M.D. Anderson Cancer Center Responds to Wall Street Journal Article / Aug. 5, 2009

The use of proton therapy for prostate cancer is well studied and the largest randomized study looking at high-dose external beam radiation therapy published in the U.S. actually used proton therapy.

The cancer control rates with the higher doses of proton therapy in this study were >91%, which exceeds even the best single institution retrospective experiences. (JAMA 2005 with correction 2008).

If a drug had a >90% cure rate in cancer, it would be adopted without question but we are facing an uphill political battle due to the perception of cost.

What's more interesting is that the patient reported quality of life between the low dose and high dose arms were not significantly different when proton therapy was used (ASCO 2007). No similar data exists for other radiation modalities.

We've also published an analysis comparing IMRT vs. Protons in prostate cancer and the potential impact on 2nd radiation-associated malignancies.

We found that proton therapy may decrease the rates of 2nd radiogenic cancers by up to 30-40% compared to IMRT. (Fontenot et al. IJROBP 2009).

This is corroborated by the clinical experience at Mass General: When they reviewed their 2nd cancer rates with protons, it was significantly lower than the national average with x-rays, and interestingly, **the patients who received proton therapy alone (not mixed x-rays and protons) had no 2nd malignancies.** (C.Chung ASTRO 2007)

Proton therapy is not only useful for the "rare" cancers (e.g. children), it also has a long clinical track record treating the number one cancer killer in the America….lung cancer.

There have been many clinical papers showing the benefit of proton therapy for this disease not only in terms of control rates but also decreasing treatment-related toxicity.

We also are currently conducting a randomized trial comparing IMRT vs. Protons in locally-advanced lung cancer.

There is also an issue of how fast these centers can actually be built. These centers are labor intensive and take time…even if everything goes correctly, I would estimate only ~3 centers could be built every 5 years. Furthermore, even if we had 20 proton centers in the U.S. we

would still only have the capacity to treat <3% of all the patients that need radiation therapy.

In terms of the fiscal impact to the U.S. healthcare expenditure, that's a "drop in the bucket".

Our center and others like us are working tirelessly to improve the state of cancer therapy for our patients with these tumors as well as others. Unfortunately the lay-press has not been supportive in that effort and has compounded the obstacles we face.

I work 12-16 hours a day and my salary (which is fixed) is <30-40% of my counterparts in private practice (including some who work for Uro-rad type IMRT practices).

No radiation therapy center (academic or community-based) will remain viable without treating certain common cancers (e.g. prostate and breast)….that's reality…I'm not saying that makes it "right", but we are trying to make a difference in many different cancers.

Just to clarify: As you know there are "charged" dollars and "reimbursed" dollars. If you look at Medicare reimbursement rates for IMRT vs. Proton Therapy (including image-guidance) for 8-weeks of prostate cancer treatment it's about $24K vs. $39K.

While proton therapy is more expensive…trust me…we spend a lot more time & effort to ensure that it's done right compared to most IMRT-based practices, and I think our patient-satisfaction rates would speak for themselves.

So while it might be more expensive, it's a good value.

Surgery is a viable option for many men, but carries an increased risk of urinary leakage and diminishment in erectile dysfunction compared to radiation (New England Journal of Med 2008).

Furthermore, a portion of these men will require post-operative radiation for positive surgical margins or extra-prostatic extension.

I hope these comments were somewhat useful and thank you for your time and interest.

Please do not hesitate to contact me with any additional questions.

Best regards, Andrew

Andrew K. Lee, MD, MPH
Associate Professor
Director, Proton Therapy Center
Department of Radiation Oncology
M.D. Anderson Cancer Center

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial Comparing Conventional-Dose With High-Dose Conformal Radiation Therapy in Early-Stage Adenocarcinoma of the Prostate: Long-Term Results From Proton Radiation Oncology Group/American College of Radiology 95-09

Anthony L. Zietman, Kyounghwa Bae, Jerry D. Slater, William U. Shipley, Jason A. Efstathiou, John J. Coen, David A. Bush, Margie Lunt, Daphna Y. Spiegel, Rafi Skowronski, B. Rodney Jabola, and Carl J. Rossi

See accompanying editorial doi: 10.1200/JCO.2009.26.5579

From the Loma Linda University Medical Center, Loma Linda, CA; Massachusetts General Hospital, Harvard Medical School, Boston, MA; and Radiation Therapy Oncology Group, American College of Radiology, Philadelphia, PA.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Anthony L. Zietman, MD, Department of Radiation Oncology, Cox 3, Massachusetts General Hospital, Boston MA 02114, e-mail: azietman@partners.org.

0732-183X/10/2809-1/$20.00

DOI: 10.1200/JCO.2009.25.8475

ABSTRACT

Purpose
To test the hypothesis that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes.

Patients and Methods
Men with T1b-T2b prostate cancer and prostate-specific antigen ≤ 15 ng/mL were randomly assigned to a total dose of either 70.2 Gray equivalents (GyE; conventional) or 79.2 GyE (high). No patient received androgen suppression therapy with radiation. Local failure (LF), biochemical failure (BF), and overall survival (OS) were outcomes.

Results
A total of 393 men were randomly assigned, and median follow-up was 8.9 years. Men receiving high-dose radiation therapy were significantly less likely to have LF, with a hazard ratio of 0.57. The 10-year American Society for Therapeutic Radiology and Oncology BF rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy ($P < .0001$). This difference held when only those with low-risk disease (n = 227; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose ($P < .0001$). There was a strong trend in the same direction for the intermediate-risk patients (n = 144; 37% of total; 42.1% *v* 30.4%, $P = .06$). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional dose compared with 6% after high dose ($P = .047$). There remains no difference in OS rates between the treatment arms (78.4% *v* 83.4%; $P = .41$). Two percent of patients in both arms experienced late grade ≥ 3 genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade ≥ 3 GI toxicity.

Conclusion
This randomized controlled trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose versus conventional-dose radiation. This was achieved without an increase in grade ≥ 3 late urinary or rectal morbidity.

J Clin Oncol 28. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The majority of cases of prostate cancer now diagnosed in the United States are detected at an early stage, and external-beam radiation is one of the principal treatment options.[1] There is concern that conventional-dose radiation therapy does not eradicate prostate cancer in a significant proportion of patients, with a resultant increase in prostate-specific antigen (PSA), need for secondary treatment, and ultimately clinical recurrence.[2,3] Increasing the radiation dose delivered may increase the probability of local tumor control but carries a risk of greater side effects unless the volume of normal tissue treated along with the tumor can be reduced. In the 1990s, a number of computed tomography (CT) –based techniques became available to deliver radiation more accurately. These are collectively known as conformal therapy and include three-dimensional conformal photon beam, intensity-modulated photon beam, and proton beam.

Several phase III studies have now demonstrated a consistent improvement in tumor control using radiation dose escalation,[4-6] but only one has reported with long follow-up.[6] This study focused on men with more advanced disease, men who now represent only a minority of the patients seen in contemporary US practice.

Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09 was a randomized trial that used the technology of proton beam to conformally increase the radiation dose to the prostate. The study looked primarily at patients with the common presentation of low- and intermediate-risk disease. It compared conventional-dose radiation (70.2 Gy) with high-dose radiation (79.2 Gy) and was first reported with 5-year follow-up.[7] At that time it showed an advantage to dose escalation for low-risk patients without any increase in serious late rectal or urinary morbidity. It is recognized that prostate cancer failure and late normal tissue toxicity can occur well beyond the 5-year time point and that a more complete understanding of the benefits or hazards of dose escalation can only come from additional follow-up.[8,9] This report with long-term follow-up provides more definitive conclusions.

PATIENTS AND METHODS

Study Schema

This randomized controlled trial was designed to compare two different radiation doses delivered by conformal techniques. Patients were stratified at random assignment to ensure balanced groups with respect to serum PSA (< 4 ng/mL *v* 4 to 15 ng/mL) and for nodal status (Nx *v* N0).

All patients received conformal photon (x-ray) therapy to a fixed dose of 50.4 Gy. The difference between the arms was in the boost dose, which was delivered using proton beam (Fig 1). The unique physical characteristics of this beam allow the treatment of tumors with considerable sparing of normal tissues.[10,11] The boost dose was either 19.8 Gy or 28.8 Gy, for total doses of either 70.2 Gy (conventional dose) or 79.2 Gy (high dose). All patients received their radiation without the administration of any concurrent or adjuvant hormonal therapy.

Study Objective

The primary objective was to determine whether local failure (LF) at 5 years in the high-dose arm was reduced compared with the conventional-dose arm. The secondary objectives were biochemical failure (BF) defined by the American Society for Therapeutic Radiology and Oncology Consensus definition (ASTRO BF), BF by Phoenix definition (Phoenix BF), overall survival (OS), and genitourinary (GU) and GI toxicity.

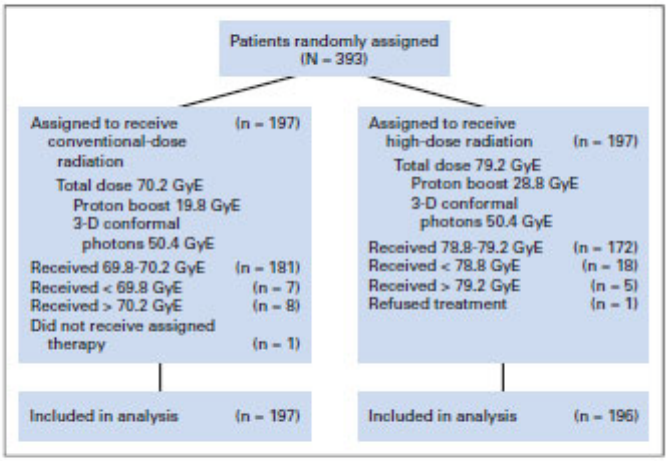

Fig 1. CONSORT diagram. GyE, Gray equivalents.

Patient Eligibility and Follow-Up

Eligible patients with early-stage adenocarcinoma of the prostate, as defined by criteria available in 1995, were offered entry onto this trial: T1b-T2b (1992 American Joint Committee on Cancer criteria) tumors, serum PSA of ≤ 15 ng/mL, and no evidence of metastatic disease by both bone scan (if PSA > 10 ng/mL or T2b or Gleason ≥ 7) and abdominopelvic CT scan. There was no exclusion from entry on the basis of Gleason grade.

All participants gave informed consent, and the study had the approval of the institutional review board at both participating institutions and at the ACR. For LF, prostate rebiopsy was recommended for men whose postradiation PSA either did not decrease to 1 ng/mL by 2 years or increased above that level at some subsequent point. It was, however, recognized that it is difficult to encourage elderly men to undergo rebiopsy, and thus a biochemical surrogate for local control would be required.[12] All patients were seen every 3 months for the first year, every 6 months to 5 years, and annually after that.

Radiation Treatment

Conformal radiation therapy was given in two phases:

Phase I. In phase I, conformal proton beams were used to treat the prostate alone. The proton beam dose was corrected to a photon equivalent using a radiobiologic effectiveness ratio of 1.1. Dose is thus expressed as Gray equivalent (GyE). Either 19.8 GyE or 28.8 GyE was given, depending on random assignment, in either 11 or 16 1.8-GyE fractions. The clinical target volume was the prostate with a 5-mm margin. Planning was performed using three-dimensional CT-based techniques. Patient position and beam arrangement differed according to local experience. At Loma Linda University Medical Center, patients were treated supine using opposed lateral 250-MV proton beams. At Massachusetts General Hospital, patients were in the lithotomy position using a single 160-MV perineal proton beam.

Phase II. All men, regardless of trial arm, received 50.4 Gy delivered with photons in 1.8-Gy fractions to the prostate and seminal vesicles. Patients were treated supine using a combination of four high-energy (10 to 23 MV) beams (anterior, posterior, right lateral, and left lateral). The clinical target volume included the prostate and seminal vesicles, with a margin of 10 mm.

Patient immobilization and treatment target imaging. Patients were immobilized daily using casts of thermal setting plastic or body foam. During proton treatments, a balloon was inserted into the rectum and inflated with 25 to 50 mL of saline as described previously.[11,13] This immobilized the prostate and displaced the posterior rectal wall from the beam path. Daily portal images were performed throughout the first phase of treatment and weekly during the second phase.

Design

This study required 390 eligible patients to detect a 20% increase in the proportion of men free from LF at 5 years with at least 80% statistical power.

Study End Points

LF. The failure event was defined as either: (1) a failure to achieve a complete response of palpable disease to protocol therapy, (2) a positive biopsy (backdated to date of equivocal disease), (3) clinical evidence of progression, or (4) PSA greater than 1 ng/mL more than 2 years after the completion of radiation therapy.[12]

BF by ASTRO Consensus. The failure event is the earlier one of the following two: (1) Three successive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last nonincreasing value (PSA nadir), or (2) initiation of salvage therapy.[14]

BF by Phoenix Consensus. The failure event is defined as the PSA value ≥ PSA nadir + 2 ng/mL after radiation therapy.[15]

OS. The failure event is defined as death due to any cause.

Toxicity. Acute and late GU and GI toxicities were scored using the Radiation Therapy Oncology Group (RTOG) criteria.[16] This is a 0 to 5 scale in which lower scores equate with fewer symptoms.

Statistical Methods

χ^2 test statistics were used to compare pretreatment characteristics of cases. Time to failure was measured from the date of random assignment to the

date of a failure event. The Kaplan-Meier method[17] was used to estimate the OS, and the log-rank test[18] was used to test the difference between the treatments or categories in the univariate analysis. The cumulative incidence method[19] was used to estimate the LF rate and two BF rates, and Gray's test[20] was used to test the difference between the treatments or categories in the univariate analysis. A Cox proportional hazards regression model [21] was used for OS, and Fine and Gray's regression model [22] was used for LF and the two different BFs. Unadjusted and adjusted hazard ratios were calculated for all covariates using either Cox proportional hazards model or Fine and Gray's regression model with associated 95% CIs and *P* values. All outcomes were modeled using multivariate proportional hazards regression with the following covariates: Treatment arm (70.2 GyE [reference level {RL}] *v* 79.2 GyE), age (continuous), PSA (< 4 [RL] *v* 4 to 15 ng/mL]), Gleason score (2 to 6 [RL] *v* 7 *v* 8 to 10), and clinical stage (T1b or T1c [RL] *v* T2a or T2b). The patients were divided into three risk groups: low risk (T1-2a, PSA < 10 ng/mL, and Gleason ≤ 6), intermediate risk (PSA 10 to 15 ng/mL or Gleason 7 or T2b), and high risk (Gleason 8 to 10). All statistical tests were two-sided, and a *P* value less than .05 was considered statistically significant.

RESULTS

A total of 393 patients were enrolled at two centers: Loma Linda University Medical Center and the Massachusetts General Hospital. Three hundred ninety-one patients were eligible: one withdrew consent and one refused to participate after random assignment. Patients were randomly assigned by the ACR on protocol 95-09 of the PROG between January 1996 and December 1999. In total, only two patients underwent a formal node sampling. Median follow-up for surviving patients was 8.9 years (range, 0.8 to 12.5 years). A median of 10 PSA values were available per patient. Table 1 shows that distribution of patients by pretreatment and prognostic factors were balanced between the two arms (*P* values > .05).

There were 227 patients (58%) in the low-risk group, 144 patients (37%) in the intermediate-risk group, and 17 patients (4%) in the high-risk group.

Table 1. Pretreatment Characteristics

Characteristic	Assigned Dose: 70.2 GyE (n = 196) No.	%	79.2 GyE (n = 195) No.	%
Age, years				
45-59	43	22	34	17
60-69	92	47	106	54
70-79	61	31	55	28
≥ 80	1	0.5	0	
Median	67		66	
Range	45-91		47-78	
Race				
White	175	89	178	91
Hispanic	4	2	7	3
Black	12	6	5	3
Other	5	3	5	3
PSA, ng/mL				
< 5	54	28	47	24
5 to < 10	114	58	119	61
10-15	28	14	29	15
Median	6.3		6.2	
Range	1.24-14.68		0.67-14.30	
Karnofsky performance status				
80	8	4	9	5
90	52	27	47	24
100	136	69	139	71
Combined Gleason				
2-6	148	75	147	75
7	29	15	30	15
8-10	18	9	15	8
Unknown	1	1	3	2
T stage				
T1b	1	1	0	
T1c	120	61	120	61
T2a	43	22	50	26
T2b	32	16	25	13
N stage				
N0	0		2	1
NX	196	100	193	99
Risk groups*				
Low	111	57	116	59
Intermediate	75	38	69	35
High	10	5	7	4
Not classified	0		3	2

Abbreviations: GyE, Gray equivalents; PSA, prostate-specific antigen.
*Risk groups according to D'Amico et al.[23]

Radiation Dose Delivered

Of the 197 patients randomly assigned to 70.2 GyE, 180 patients (92%) received this dose (Fig 1). Seven patients (3.6%) received lower doses, and eight patients (4.0%) received higher doses. One patient refused treatment. Of the 196 patients assigned to 79.2 GyE, 172 patients (88.2%) received this dose, five patients (2.5%) received higher doses, and 18 patients (9.2%) received lower doses. Of these, only two patients received lower doses because of toxicity. Four patients received lower doses because of new medical issues; others did so for a mixture of anxiety, refusal to accept random assignment to the higher dose, and convenience.

LF

There was a statistically significant difference in LF rate between the two arms. Men treated with 79.2 GyE were less likely to have LF than those treated with 70.2 GyE, with a hazard ratio of 0.57 ($P < .0001$; 95% CI, 0.43 to 0.74). This result held when adjusted for other covariates. There was a statistically significant difference in LF for the low-risk group and the intermediate-risk group ($P = .01$ and .002, respectively).

BF

In the conventional-dose arm, 81.0% had a PSA nadir of less than 1.0 ng/mL, and 44.7% had a nadir less than 0.5 ng/mL. In the high-dose arm, these proportions were 86.6% and 59.8%, respectively. The difference between the nadirs less than 0.5 ng/mL was significant ($P = .003$). Median time to nadir was 28.0 months after conventional-dose and 39.6 months after high-dose radiation.

The 10-year ASTRO BF rates were 32.3% (95% CI, 25.7% to 39.0%) for the conventional dose arm and 16.7% (95% CI, 10.8% to 22.7%) for the high-dose arm ($P = .0001$; Fig 2A). This difference held when only those with low-risk disease were examined: 10-year ASTRO BF rate was 28.2% (95% CI, 19.4% to 37.1%) in the conventional-dose arm and only 7.1% (95% CI, 2.3% to 11.9%) in the high-dose arm ($P < .0001$; Fig 3A). There was a strong trend in the same direction for the smaller group of 144 intermediate-risk patients: 42.1% (95% CI,

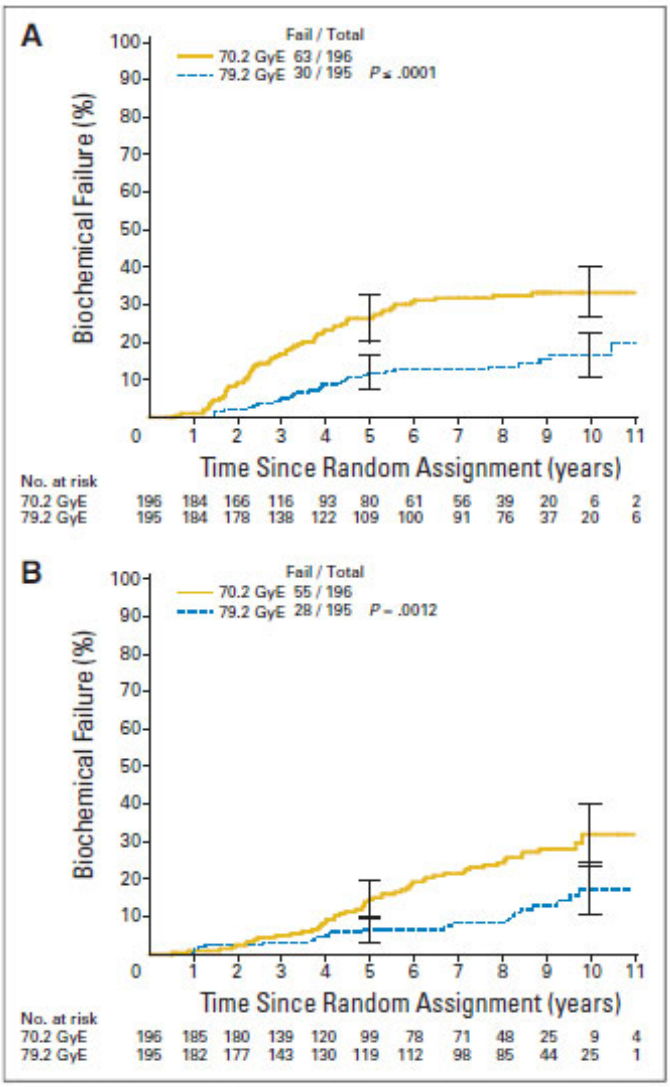

Fig 2. Biochemical failure after either conventional-dose or high-dose conformal radiation therapy. (A) Biochemical failure by American Society for Therapeutic Radiology and Oncology consensus.[14] (B) Biochemical failure by Phoenix criteria.[15] GyE, Gray equivalents.

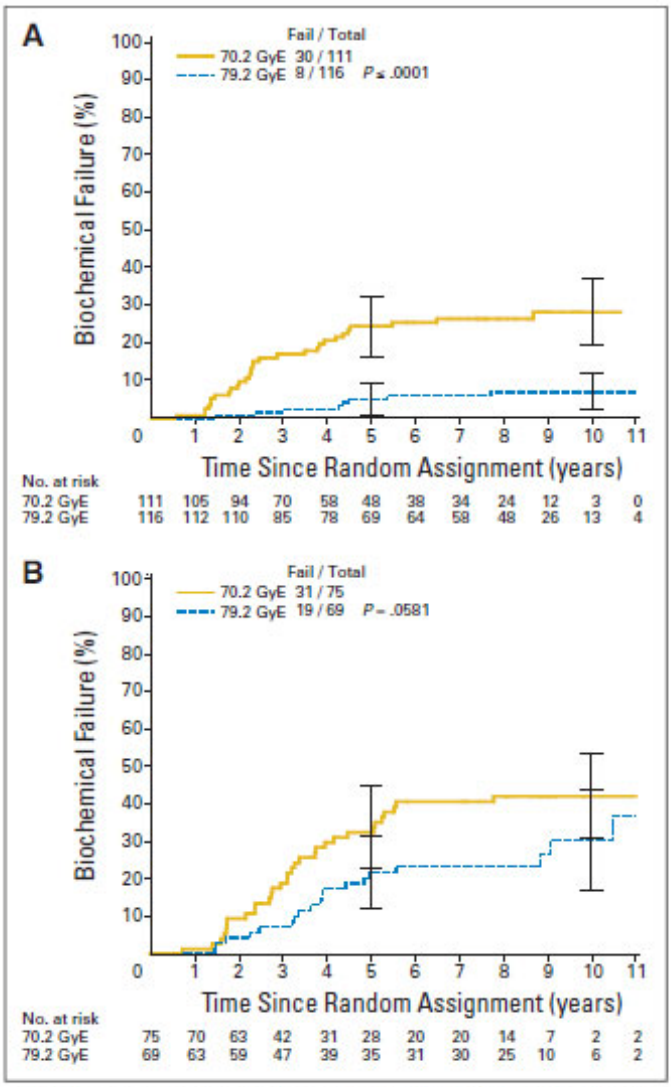

Fig 3. Biochemical failure by American Society for Therapeutic Radiology and Oncology Consensus definition after either conventional-dose or high-dose conformal radiation therapy. (A) Biochemical failure for the low-risk group; (B) biochemical failure for the intermediate-risk group. GyE, Gray equivalents.

30.6% to 53.5%) versus 30.4% (95% CI, 17.1% to 43.6%; $P = .06$; Fig 3B). The hazard ratios after adjusting for other covariates show the same results (hazard ratio was 0.22 [95% CI, 0.1 to 0.5] for the low-risk group and 0.58 [95% CI, 0.3 to 1.0] for intermediate-risk group). The smaller numbers in the intermediate-risk group limited the power to observe a significant difference in that group to only 54%. Because backdating used in the ASTRO definition of BF may affect the timing and rate of failure,[14] it has been superseded since PROG-9509 was initiated by the Phoenix Consensus definition.[15] The differences in Phoenix BF between the arms were similarly highly significant (Fig 2B). At 10 years, the Phoenix BF rates were 32.0% (95% CI, 23.8% to 40.2%) versus 17.4% (95% CI, 10.5% to 24.3%) for conventional- and high-dose radiation, respectively ($P < .001$). In the conventional-dose arm, 22 patients have received secondary treatment with androgen deprivation compared with 11 patients in the high-dose arm ($P = .47$). Treatment was started at the discretion of the physician and usually for an increasing PSA.

OS

At this time, there is no difference in the overall survival rates between the treatment arms (78.4% and 83.4%; $P = .41$). There were 34 deaths in the conventional-dose arm (four related to prostate cancer) and 27 deaths in the high-dose arm (two related to prostate cancer).

Toxicity

Table 2 shows morbidity associated with treatment and randomization group. Only 3% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute GU toxicity of RTOG grade ≥ 3. Fifty-four percent and 62% of conventional-dose and high-dose patients, respectively, experienced grade 2 acute GU toxicity. The proportions for grade 2 or worse acute GI toxicity were 45% and 64%, respectively. So far, only 2% of patients in both arms have experienced late GU toxicity of RTOG grade ≥ 3, and 1% have experienced late GI toxicity of grade ≥ 3. For late grade ≥ 2 GU

Table 2. Acute and Late GU and GI Toxicity

	Assigned Dose																
	70.2 GyE (n = 196)								79.2 GyE (n = 195)								
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4		
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P*
Acute																	
GU	72	37	100	51	5	3	0	0	56	29	117	60	4	2	1	1	.0745
GI	76	39	87*	44	2	1	0	0	50	26	123*	63	2	1	0	0	.0006*
Late																	
GU	82	42	44	22	4	2	0	0	88	45	52	27	3	2	0	0	.7934
GI	68	35	25	13	0	0	0	0	79	41	46	24	2	1	0	0	.0895

Abbreviations: GU, genitourinary; GyE, Gray equivalents.
*Testing grade 1 versus others using χ^2 test.

toxicity, these proportions were 25% and 29% ($P = .79$), respectively, and for grade ≥ 2 GI toxicity, these proportions were 13% and 24%, respectively ($P = .09$).

DISCUSSION

This randomized trial shows that when men with early-stage prostate cancer are treated with high-dose rather than conventional-dose external radiation therapy, they are more likely to be free from an increasing PSA 10 years later and less likely to have required additional cancer therapy. It also shows that when highly conformal radiation techniques are used, dose escalation to 79.2 Gy can be safely achieved without an increase in serious (grade ≥ 3) acute or late morbidity. This study therefore provides Level 1 evidence to justify trends already well established in the United States toward conformal technology and higher doses in early-stage disease.

In 1995, when this trial was designed, early-stage disease was largely defined by T stage and PSA. Since then, predictive risk groups have been developed. The lowest risk are those with T1-2a tumors, Gleason grades of ≤ 6, and PSA of less than 10 ng/mL.[23] Such patients comprised 227 (58%) of 393 of those entered onto this trial. Intermediate-risk men comprised the majority of the remainder. The long-term advantage to higher radiation dose was clearer for those with low-risk disease than it was for those with higher risk, and this represents the novel finding of the trial. The greater advantage for the low-risk group perhaps reflects the fact that these men are more likely to have locally confined disease and thus are more likely to benefit from an improved local therapy.

Median follow-up was 8.9 years, and this, therefore, represents one of only two prospective studies in the literature documenting long-term outcome after conventional-dose or high-dose radiation in the contemporary era. It is also the only such study in which proton beam has been used. It demonstrates that conventional-dose radiation is already sufficient to render the majority of men with low-risk prostate cancer free but that this proportion may be increased even further with dose escalation. The choice of dose may therefore be made by the physician based on other patient considerations, such as life expectancy and concern about normal tissue injury. Although there was no survival advantage shown in this study, it may be presumed that those who have persistent disease as indicated by an increasing PSA are at greater risk of requiring additional therapy and ultimately of a prostate cancer death. Of the three other randomized trials examining this issue, all have shown a similar advantage to higher doses of radiation.[4-6] Two of these trials allowed the additional use of androgen deprivation therapy, which confounds the interpretation of radiation efficacy, and neither reports follow-up beyond 5 years.[4,5] The only other radiation monotherapy trial has reported 10-year data, but it concentrated on patients with higher-risk disease.[6] It too showed that improvements in freedom from PSA failure are associated with a reduction in the risk of having recurrent disease, requiring future salvage therapies, and dying from disease.

It is most likely that the improvement in biochemical disease-free outcome seen in this trial is due to improved local control, and this was suggested by the reduced hazard rate using a biochemical surrogate. Prostate rebiopsy would have been more definitive but, although this was encouraged, it was not done routinely for two reasons. First, interpretation of prostate biopsies in the first 3 post-treatment years is unreliable.[24] Second, it is ethically difficult to recommend routine prostate rebiopsy, an uncomfortable procedure, when the results are unlikely to influence subsequent management.

The randomized trials of radiation dose reported by Kuban et al,[6] Al-Mamgani et al,[5] and Dearnaley et al[4] all showed higher levels of late rectal morbidity, particularly bleeding, in the higher dose arms at 5 years. We have also seen a small increase in grade ≥ 2 rectal morbidity in the high-dose arm of our trial, though not grade ≥ 3. Surprisingly, a cross-sectional survey of long-term survivors on this study using a more sensitive quality-of-life instrument did not detect more morbidity than the physician-reported morbidity scales used.[25] Satisfaction scores were equal and high in both arms of the trial, even when physician-reported morbidity was present. This implies that patients adapt well with time to chronic morbidity such that this becomes a new "normality." Questions regarding sexual function were asked, but these are now recognized to be so prone to bias that the available data have not been presented here.

Although this trial strongly validates the use of proton beam as effective therapy, it was not designed to test whether this modality is more or less efficacious than other conformal techniques or, for that matter, brachytherapy or surgery. Nor does it justify using doses above 79 Gy outside a clinical trial.

In summary, this randomized, controlled trial shows a significant and durable advantage to high-dose over conventional-dose conformal radiation in terms of freedom from BF for men with low- and intermediate-risk prostate cancer. This advantage was achieved without any associated increase in either acute or late severe urinary or rectal morbidity by the use of highly conformal radiation techniques that included three-dimensional photon and proton beams.

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FROM RESEARCH TO PRACTICE

The Promise of Proton Therapy is Two-fold—

Less toxicity and higher cure rates than achievable with X-ray therapy

by Nancy Price Mendenhall, MD

Benefits of Proton Therapy

In most cancers requiring radiation therapy, proton therapy can produce better radiation dose distributions with respect to cancer and normal tissue than techniques employing X-rays. A better radiation dose distribution is more important in some clinical situations than others. When considering possible benefits of proton therapy, it is useful to consider the therapeutic ratio likely with other radiation therapy treatment options first—i.e., the probability that other radiation options will control the tumor without causing toxicity.

In some cancers, proton therapy is the only treatment option, offering hope for cure without unacceptable toxicity. Examples in this category include chordomas and chondrosarcomas occurring at the base of the skull. Because of proximity to critical structures such as the brainstem and optic nerves, surgery alone is rarely successful and sufficient radiation doses to destroy these tumors usually cannot be given with X-ray therapy. However, clinical researchers at Harvard have reported excellent long-term disease control with minimal toxicity with proton therapy.[1-3]

In a second group of cancers, other treatment options are available, but the therapeutic ratio of these other options leaves room for improvement in either tumor control or normal tissue toxicity. In these cases, clinical or dosimetric data suggest an important and likely measurable benefit of proton therapy. One example is melanomas of the eye, which can be treated with surgical removal of the entire eye, radiation with a cobalt plaque, or proton therapy. Large clinical trials from the U.S. and England show similar survival rates among the three treatment options, but better long-term preservation of vision with proton therapy.[4]

A second example is pediatric tumors, in which even low radiation doses to normal tissues cause measurable effects on neurocognitive function, muscle and bone growth, endocrine function, etc., so any savings in normal tissue exposure from proton therapy is likely to produce measurable benefits.

A third example in this category is early stage prostate cancer where there is room for measurable improvement in disease control, but not at the price of additional toxicity.[5] The improved dose distribution achieved with proton therapy was used to test the concept of radiation dose escalation as a means of decreasing tumor recurrence.[5] Prostate cancer patients were randomized to receive proton therapy to two different doses after initial treatment with conventional radiation therapy. Patients receiving the higher dose with protons had only half the number of PSA tumor recurrences as those receiving the lower dose, but no increase in toxicity because of the avoidance of normal tissue possible with proton therapy.

In a third group of cancers, the therapeutic ratio with conventional irradiation is high, and the dosimetry benefits from proton therapy may not translate into measurable clinical improvements. An example may be early stage breast cancer treated with breast conserving surgery and conventional radiation therapy, where both the local recurrence and toxicity rates are very low.

Proton therapy has now been used with success in prostate cancer, eye tumors, sarcomas, base of skull tumors, brain, lung, head and neck, gastrointestinal, and pediatric cancers.

How Proton Therapy Is Delivered

Protons are generated from water that has been de-ionized. Water is comprised of two atoms of hydrogen and one atom of oxygen. When an electric current passes through water, the water undergoes electrolysis and is broken into its parts, hydrogen and oxygen, both components of the air we breathe. The hydrogen is then injected into the cyclotron, where high heat creates a plasma state in which electrons can be stripped away from single hydrogen atoms by an electric field, creating a stream of protons.

The cyclotron, which may weigh 440,000 pounds, accelerates protons to increasing speeds by alternating electromagnetic forces (see Figure 1. Proton Beam Therapy Blueprint). Once the acceleration of the protons reaches the

University of Florida Proton Therapy Institute (UFPTI) is a three-story facility of approximately 98,000 square feet. Within UFPTI is a conventional radiation therapy suite with three treatment vaults; a simulation suite including an MRI, a CT scanner, and a PET/CT scanner for tumor localization and treatment planning; the proton therapy suite; space for future bench research, as well as faculty and staff offices.

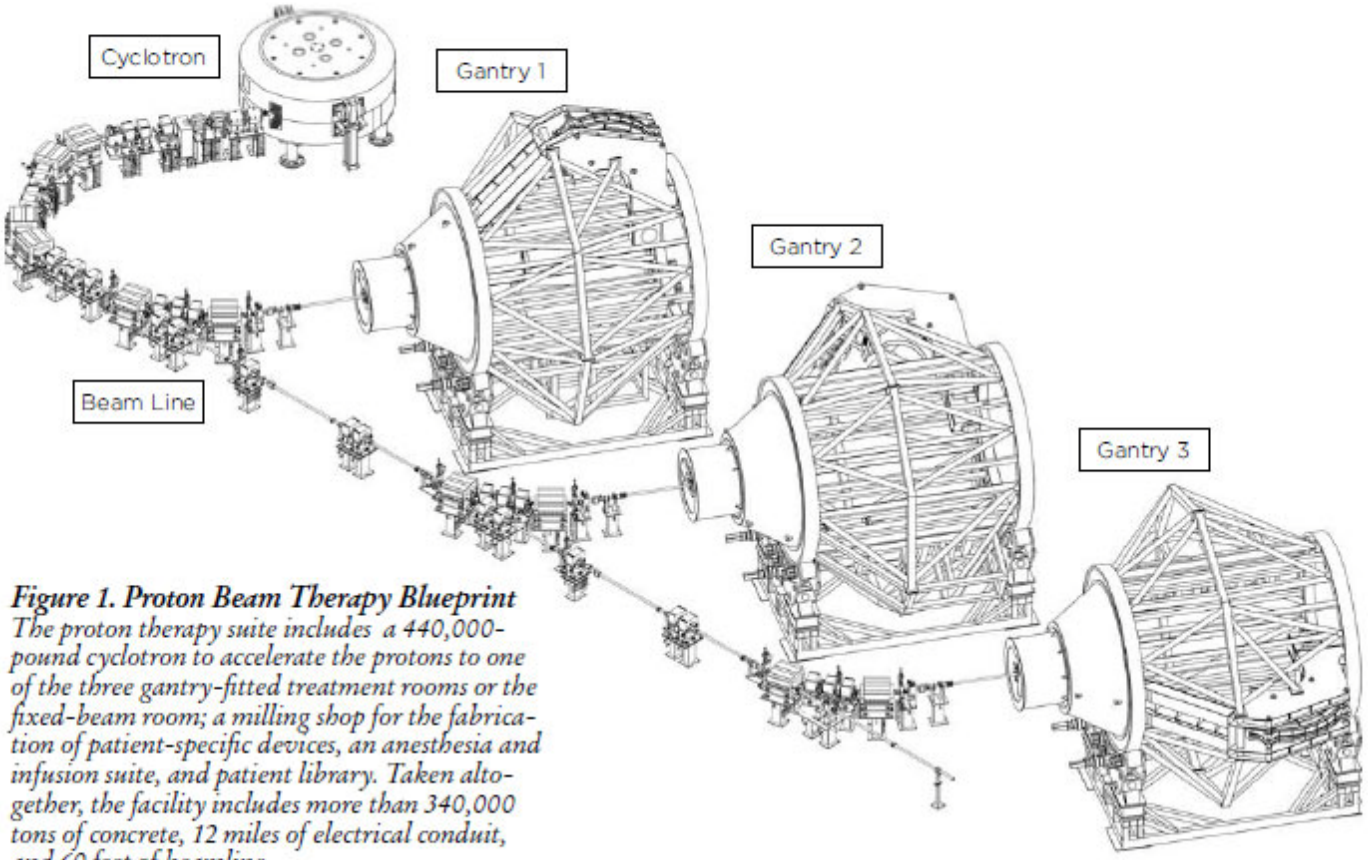

Figure 1. Proton Beam Therapy Blueprint
The proton therapy suite includes a 440,000-pound cyclotron to accelerate the protons to one of the three gantry-fitted treatment rooms or the fixed-beam room; a milling shop for the fabrication of patient-specific devices, an anesthesia and infusion suite, and patient library. Taken altogether, the facility includes more than 340,000 tons of concrete, 12 miles of electrical conduit, and 60 feet of beamline.

desired energy (230 MeV to 250 MeV), magnets are used to direct the protons into a beam line that carries the protons into treatment rooms. The protons may be directed into a fixed horizontal or vertical beam line or into a 360-degree rotational gantry that can deliver the beam of protons to a target from any angle. The gantries tend to be large, requiring up to three stories of space and weighing up to 100,000 pounds. The patient is positioned on either a treatment table or in a treatment chair to receive treatment. Modern treatment tables have up to six degrees of freedom facilitating submillimeter precision in patient alignment.

Proton Therapy vs. Conventional Radiation Therapy

A true comparison between these two technologies will measure four important areas: clinical outcomes, consistency in quality assurance, cost, and availability.

Although more than 40,000 patients worldwide have been treated with proton therapy, much of the experience has been in research facilities suitable for treating only a few rare tumors. Limited capacity for proton therapy in clinically dedicated facilities has prevented large-scale trials of proton therapy, but available data suggest that improved radiation dose distribution will translate into clinical advantages over other forms of radiation therapy in most cancers, where outcomes with conventional radiation therapy leave room for improvement.

The more radiation dose distributions are restricted to the actual targets, the more demanding the quality assurance measures. The treatment process with proton therapy requires onsite high-resolution imaging to define the three-dimensional target volume, highly sophisticated computerized treatment planning software, specialized patient immobilization devices, strategies to decrease movement of organs within the body during treatment, and submillimeter precision in patient positioning and beam guidance. The added precision requires additional physics and engineering personnel for technical support.

The cost of proton therapy is somewhat more than the cost of conventional radiation therapy, related to more expensive equipment and technical personnel required for treatment and equipment maintenance. With respect to capital cost, the price for a proton therapy facility that could treat 150 patients a day could be up to 10 times the cost of a conventional therapy facility with similar capacity. Proton therapy facilities are built to last a minimum of 30 years, however, while conventional linear accelerators require replacement after 7 to 10 years. Proton facilities also carry somewhat higher operational costs related to the level of expertise required for treatment planning, quality assurance, machine operation, and maintenance. Despite the higher initial costs of proton therapy, if proton therapy fulfills the promise of decreasing recurrence rates and toxicity rates, then its long-term cost may actually prove less than conventional radiation therapy. Medicare and most national health insurance companies provide coverage for their policyholders.

Since opening in August 2006, the University of Florida Proton Therapy Institute has delivered more than 4,000 proton therapy treatments. At UFPTI there are ongoing trials in a variety of head and neck cancers, brain tumors,

pediatric malignancies, prostate cancer, and bone and soft tissue sarcomas.

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How Proton Therapy Works

Protons are subatomic particles considered by scientists for decades to be one of three basic building blocks of matter. Protons and neutrons make up the nucleus or center of atoms, while electrons, which have a negative charge, circle in orbit around the positively charged nucleus. Protons are 1,800 times more massive than electrons and have a positive charge, while neutrons are slightly heavier than protons and have no charge. Physicists have discovered even smaller particles, but it is the number of protons in the nucleus that distinguishes different types of matter. For example, oxygen is an element comprised of atoms which have eight protons, eight neutrons, and eight electrons, whereas hydrogen, another element in air, is comprised of atoms with only one proton, one electron and no neutrons.

Radiation therapy destroys cancer cells by causing chemical reactions known as ionizations, which lead to cell damage and ultimately to cell death. These chemical reactions occur when an electron is ejected from its orbit around a nucleus, either when the energy from an X-ray is absorbed or the electron is hit by a particle such as a proton. The atom then has fewer electrons than protons, and thus becomes a positively charged ion. The electron attaches to another atom or molecule which then becomes a negatively charged and highly active ion. This interaction occurs in both cancer cells and normal tissue cells, so radiation can kill cancer cells but also cause damage to normal tissues.

Most therapeutic radiation today is given with X-rays generated by linear accelerators. When X-rays pass through tissue there is a characteristic pattern of energy absorption, which is most intense between 1 and 5 cm below the skin surface (see Figure 2), but continues with most of the radiation exiting from the patient.

The process in proton radiation is similar: when protons collide with atoms, ionizations occur leading to cell damage or death. However, unlike X-rays, protons can travel only a finite distance, because they have mass. The faster protons are accelerated, the farther they travel. As they enter tissue, they collide with occasional atoms. Because they are relatively heavy compared with electrons, they lose a small amount of energy and slow with each collision, in contrast to X-rays which are completely absorbed on collision. Just before the protons reach the end of their range, they deposit the majority of their energy. This peak of energy deposition is called a Bragg peak (see Figure 3).

The important therapeutic difference between X-rays and protons is related to the difference in the pattern of energy (or radiation dose) deposition, (see Figure 2). In general, an X-ray beam is like a bullet, which passes through a patient, leaving a track of damage from entrance to exit that is most intense just below the skin surface. A proton beam loses much less dose as it enters tissue, then deposits a very high relative dose just before it stops. Since the protons stop, there is no exit dose. The depth protons travel in tissue is directly correlated with their speed, so by accelerating protons to a specific energy, one can set the precise depth at which most of the radiation energy will be deposited. In contrast to X-rays, a proton beam is like a firecracker which can be set to go off exactly at the tumor.

Because, most of the energy with X-rays is actually deposited in normal tissues the X-ray beam encounters before reaching the tumor and in tissues the X-rays pass through as they exit the patient, there is much more radiation inadvertently given to normal tissues with conventional X-ray therapy than with proton therapy. This

Figure 2. X-Ray and Proton Dose Distribution

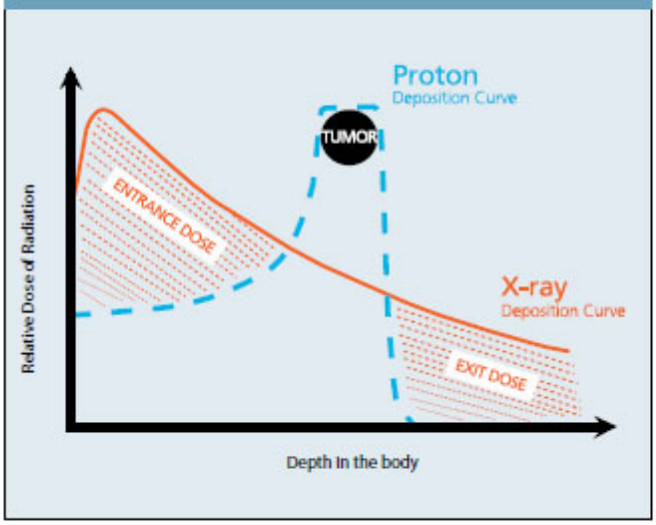
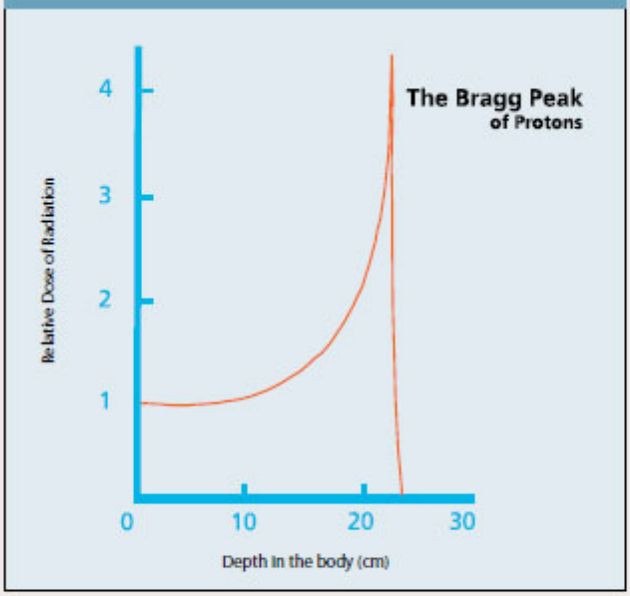


Figure 3. Bragg Peak of Protons



means there is generally a higher risk of damage to normal tissues with X-rays than with protons, so the use of proton therapy is likely to significantly reduce the risk of treatment complications. As a result of normal tissue at risk, the radiation dose that is given to the tumor is often compromised to avoid normal tissue injury.

The choice of radiation dose is usually a compromise between the ideal dose to eradicate a tumor and a dose that is unlikely to cause particular complications in normal tissues around the tumor. Because less damage is done to normal tissues with protons, it will be possible to deliver higher doses to tumors, likely resulting in higher cure rates. So the therapeutic promise of proton therapy is two fold: higher cure rates and fewer complications.

A Brief History of Proton Beam Therapy

Proton therapy, a type of radiation treatment for cancer, is generating much interest across the U.S., as well as in Europe and Asia. Although proton therapy was first used for patient care in 1954, it was not until 1991 that the first proton facility dedicated to patient care opened at Loma Linda University Medical Center in California. Another decade went by before the second such facility in the U.S. opened in 2001 at the Massachusetts General Hospital. In 2004, the Midwest Proton Therapy Institute in Bloomington, Indiana adapted an extant research cyclotron to clinical usage. In 2006, $100-million-plus proton therapy centers opened at the M. D. Anderson Cancer Center in Houston and the University of Florida in Jacksonville. Across the world, only 23 cancer centers offer proton therapy, some with technical limitations that preclude treatment of certain types of cancers. Recently a number of other major academic and community cancer centers have announced intentions to build proton therapy facilities.

The recent increased interest in proton therapy is related to recognition of the applicability of proton therapy to many kinds of cancers and the demonstration of an economically feasible method of proton treatment deliverable in the clinical setting. In 1991, Loma Linda University opened the first clinically dedicated proton therapy facility with the development of a rotational gantry similar to those used in conventional X-ray therapy systems, which permitted proton delivery from any direction, significantly increasing the applicability of this modality. Over the next decade, the feasibility of using proton therapy in a variety of malignancies was demonstrated by Loma Linda University Medical Center and other facilities outside the U.S.

This more general experience complemented the excellent outcomes already documented in rare tumors such as melanomas of the eye and chordomas at the base of the skull that had been treated in research centers around the world, including Massachusetts General Hospital. The *JAMA* 2005 publication of a randomized controlled trial conducted by Loma Linda University Medical Center and Massachusetts General Hospital comparing two dose levels in prostate cancer treated with proton therapy highlighted the utility of protons for prostate cancer, the most common malignancy in the U.S., and proved the promise of proton therapy as a means of dose escalation to achieve higher cancer control rates without added toxicity.[5]

Meanwhile, in the background, the rapid proliferation of 3-D conformal radiation therapy, and subsequently IMRT, during the last decade set the stage for the development of a technical infrastructure to support proton therapy, which likewise relies on precise knowledge of the size, shape, and whereabouts of the tumor and more intensive physics engineering and technical support for treatment planning and delivery than necessary in conventional radiation therapy.

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A NOTE OF THANKS FROM THE EDITOR

On behalf of the PAACT staff we would like to thank our members, advocates, professionals, donors, sponsors, corporates, and foundations that participated in the large fund raising effort that took place during December, 2006. As noted in our March financial statement you will find the year end report for 2006. Total revenues at $202,644.97, total expenses for the year at $192,753.60. Because of your generosity we had our second largest December since 1993 with donations topping out at $66,050.03. The overall result is that 2006 total revenues finished $9,891.37 ahead of total expenditures. Congratulations and thank you to each and every one of you, we could not have done it without you.

CONFORMAL PROTON BEAM RADIATION THERAPY OF PROSTATE CANCER

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Introduction

External beam radiation therapy is one of the commonly employed curative treatments for prostate cancer. The term "External Beam," refers to the fact that the radiation used for treatment is generated by a machine which is external to the body. This distinguishes external beam radiation from brachytherapy, in which small radioactive sources are actually inserted into the prostate gland. With few exceptions, "External Beam" implies treatment with x-rays for it is x-ray therapy which has been the mainstay of radiation treatment since its inception in the late 19th century.

Over the last fifteen years, a new type of external beam radiation therapy, proton beam radiation therapy, has become available at a few select centers in the United States and abroad. This treatment employs subatomic particles to deliver high doses of radiation to a variety of cancers, including prostate cancer[1]. The rationale and desire to treat with protons is based on their physical superiority to x-rays. Simply put, a proton beam will stop at some point within the body, while x-rays will not. From a clinical standpoint, this unique aspect of proton beam radiation allows the radiation on-

cologist to reduce the normal tissue radiation dose to levels which are not possible with any type of x-ray therapy (including Intensity-Modulated Radiation Therapy and Tomotherapy) while simultaneously escalating the radiation dose to the target tumor. In the following paragraphs, I will briefly illustrate the physical differences between protons and x-rays, discuss the history of their use in prostate cancer treatment, and cover clinical results to date.

The Differences Between Protons and X-Rays

In order to understand the potential advantages of proton beam radiation therapy, it is necessary to delve somewhat into the fundamental physics of x-rays and protons and their interactions with human tissue. X-rays are, essentially, high energy forms of visible light. X-rays are massless, and do not possess an electric charge. Because of this, they are highly penetrating and it is indeed their ability to penetrate the human body which makes them such useful diagnostic tools. As an x-ray beam enters the human body, the energy of the beam is rather slowly dissipated by interacting with bone and soft tissue. However, there is typically some energy which passes completely through the body. If the goal is diagnosis, this is a useful property because it is the x-ray energy which leaves the body that can be captured and analyzed to provide a picture of the internal organs along the beam's path. However, what is desirable in diagnosis is not necessarily desirable in therapy because that same beam is delivering radiation to everything within its path, be it normal tissue or tumor. Again, this is true of all types of x-ray therapy including IMRT - while with IMRT we can vary the intensity of the beam so that the dose rate as the beam passes through particularly critical normal tissues may be low, what we cannot do, and what is indeed impossible to do, is to get that x-ray beam to stop within the body. IMRT in fact represents the latest in a series of elegant compromises between the radiation dose we want to give to the tumor and that which the normal tissue will tolerate - it reduces the volume of normal tissue receiving a high radiation dose at the expense of increasing the volume of normal tissue receiving low to moderate radiation doses. What would be ideal, from a treatment standpoint, would be a form of radiation which would deliver zero dose to the tissues in front of the target, 100% dose to the target, and zero dose beyond the target and this ideal is and always will be an impossibility with x-rays[2-5].

It is, however, far more achievable with protons. A proton is a subatomic particle with a discreet mass and an electric charge, and these two properties radi-

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cally influence the proton-human tissue interaction. When a beam of high-energy protons enters the human body, the radiation dose delivered to tissues proximal (in front of) the target is low, because at that point the protons are still traveling with a high velocity and therefore have very little interaction with the tissue they are passing through. By attenuating the beam so that the protons are brought to a stop as they pass through the target (this is accomplished by passing the beam through a series of patient-specific anatomic compensators before the beam enters the patient) the radiation dose to the target is maximized, and since the protons (by virtue of exhausting their kinetic energy) come to rest just beyond the distal (far) edge of the target, the "exit" dose is zero. From a practical standpoint, the "integral dose" (total dose to normal tissue) in a proton beam treatment plan for prostate cancer is three to five times less than that which is common when sophisticated x-ray therapy plans (utilizing IMRT) are employed. Again, this reduction in normal tissue dose means that the radiation dose given to the tumor can be increased with relative safety, and indeed the benefits of such dose-escalation in early stage prostate cancer will be discussed shortly[6, 7].

Like many medical breakthroughs, the potential superiority of protons over x-rays, and their utility in radiation therapy, was recognized not by a physician, but by a scientist from another discipline. Physicist Robert R. Wilson, then a professor at Cornell University (and later the founding director of the Department Of Energy's Fermi National Accelerator Laboratory, one of the world's premier physics research institutions) had the insight to propose, in a seminal 1946 paper{Wilson, 1946 #4749} their use in cancer treatment. However, again like many other ideas, their routine use required the development and maturation of other technologies before the theoretical advantages of protons could be exploited in clinical medicine.

Early Clinical Work

Although initial treatments of intracranial cancers began in the late 1950's, proton beam radiotherapy of prostate cancer commenced in 1977, when Dr. William Shipley and colleagues at the Harvard Medical School began a study in which patients with advanced prostate cancer received some of their radiation treatment via a proton beam "boost" delivered in the hope that by giving a higher dose of radiation than was possible at the time with the x-ray therapy equipment then in existence, they may improve the control rates of such advanced tumors without creating unacceptable side effects. Since at that time dedicated proton beam medical treatment facilities did not exist, the patients were treated in Cambridge at the Harvard Cyclotron Laboratory, utilizing a machine which was primarily employed in high energy physics research. The initial results of what was in effect a toxicity trial were published in 1979 and demonstrated that the technique could be performed in safety and with acceptable side effects{Shipley, 1979 #4739}.

These encouraging results led to a larger trial, in which again patients with locally advanced bulky prostate cancer (stage T3 and T4 disease) were randomly assigned to receive either a) a radiation dose of 67.5 Gy to the prostate, delivered entirely with x-rays or b) a total dose of 75.6 Gy, delivered with a combination of x-rays and protons, the latter being incorporated to "boost" the radiation dose to the prostate. Because of the limited number of patients who could be accommodated on the Harvard Cyclotron, patient accrual was slow and in fact, over a period of over a decade, just over two hundred patents were enrolled and treated on the trial.

The results of the trial were published in 1995[8]. Although the overall survival was no different between the two treatment groups (primarily because of the high rates of metastatic failure in both groups, which was a consequence of the advanced stage of the patients at diagnosis), the incidence of local (i.e., prostate) failure was lower in the high dose group, and this trend was most significant in those patients with the highest grade tumors (Gleason 8-10). This finding led credence to the concept of dose-escalation as a means of improving prostate tumor control, and directly led to the eventual creation of a clinical trial to test this hypothesis.

Development of Hospital-Based Proton Beam Treatment Facilities

Although the aforementioned physical advantages of protons over x-rays are easy to demonstrate, their use in clinical medicine was limited by the lack of treatment centers dedicated to their use in a medical, not laboratory, setting. Why was this so? Because in order to accelerate protons to the velocities necessary for human treatment (roughly one-half of the speed

of light) one must construct purpose built "Atom-Smashers" (either a cyclotron or synchrotron) that are far more complex in their construction, operation, and maintenance than the linear accelerators used for x-ray therapy. Until 1990 such equipment was exclusively found in the realm of high-energy physics, and in laboratories like the Harvard Cyclotron Lab and the Los Alamos National Laboratory. It was felt by most experts that protons would forever remain an esoteric curiosity, reserved for treatment of only the toughest tumors (like those abutting the spinal cord), and would never be employed in mainstream clinical radiation oncology. One of the few radiation oncologists who refused to accept this "fact" was Dr. James Slater, then chairman of the department of Radiation Medicine at Loma Linda University Medical Center. Dr. Slater believed that the physical superiority of protons could best be demonstrated and exploited if they could be used in a clinical setting like a hospital or, in other words, in the same environment in which x-ray therapy is routinely administered. In the early 1980's he founded a working group with the Fermi National Accelerator Laboratory and the Argonne National Laboratory which was dedicated to designing and constructing a hospital-based proton beam treatment center[9]. Construction began at Loma Linda in April 1988, and the first patient (a nurse with an ocular melanoma) was treated in October 1990. At the time of its construction the Loma Linda University conformal proton beam treatment center was the single most expensive medical device ever built, at a cost (including research and development) of $120 million. The facility contained four patient treatment rooms and was designed to eventually treat up to 150 patients per day (in contrast, recall that over a ten-year period, only 100-odd prostate patients were treated at the Harvard Cyclotron Laboratory) .

Proton Beam Radiation Therapy of Prostate Cancer – The Loma Linda Experience

Conformal proton beam treatment of prostate cancer commenced on October 8th, 1991 and has continued uninterrupted since that date. The primary goals of therapy have been to improve local disease control (via dose-escalation) while simultaneously limiting treatment-related side effects to an acceptable level. Currently, a "typical" treatment course for early-stage prostate cancer (T1b-T2b disease) is to irradiate the prostate to a total radiation dose of between 79-81 Gy (=7,900-8,100 rads), with treatment taking place daily, five days per week, over a period of nine weeks. Precision therapy requires a reproducible patient position, so the first phase of each patient's treatment planning process consists of the construction of a customized full-body immobilization device, or "pod," which is in effect a Styrofoam and fiberglass shell that conforms to the patient's body contours and ensures a stable frame of reference for daily treatment. Before the CT planning scan, and before each day's treatment, a water balloon is inserted into the rectum and inflated with 120ml of water. This serves to minimize prostate motion by pushing the gland anterioraly against the pubic bone and also displaces the majority of the rectum from the proton radiation field, protecting this vital organ by reducing the volume of rectal tissue which receives any radiation dose. A thin slice CT planning scan of the pelvis is performed to create in effect a 3-dimensional model of the patient's pelvic anatomy. This data is critical in designing the patient-specific devices which attenuate the proton beam so that it delivers its maximal radiation dose within, and not outside of, the prostate.

On treatment days, the patient arrives at the facility and changes into the inevitable gown. His pod is retrieved from a storage area and locked to the treatment table. The patient is placed in his pod and the rectal balloon is inserted and inflated. Correct patient position is then checked daily by obtaining two low-power orthogonal (at 90 degree angles to each other) x-rays; the images are captured by a digital imaging device and compared (via computer) to similar images created at the time of treatment planning. The "difference" between the daily position (if any) and the "ideal" position is adjusted by moving the treatment couch in the appropriate directions, the therapy personnel leave the room, and treatment is delivered. Prostate patients are typically treated in fifteen minute time slots, with the majority of that time being utilized to verify correct daily positioning.

In general, treatment is well tolerated. There are no physical restrictions placed on the patient during treatment and, in fact, exercise is encouraged. Common side effects include feelings of urinary frequency and urgency; these symptoms commence during the first two weeks of treatment and are usually of the "annoyance" variety. If necessary, they can be managed with over-the-counter medications like ibuprofen. Since, unlike x-ray therapy, the small intestine is not irradiated, diarrhea is not typically an issue and in fact constipation (from the rectal balloon in-

sertions) is a relatively common occurrence. During the last few weeks of treatment it is also common to notice some redness of the skin over the proton beam entrance path; this is due to the slight amount of radiation dose deposited in the skin as the protons enter the body.

Following the completion of treatment, patients are followed via methods identical to those employed in x-ray therapy and surgery i.e., regular PSA determinations and physical examinations, with additional tests (bone scan, re-biopsy, etc.) being obtained should circumstances warrant. Treatment-related side effects are scored using the Radiation Therapy Oncology Group's (RTOG) morbidity scoring system, with data on side effects being gathered from patient interviews, patient-completed questionnaires, and review of outside records.

Results of treatment have been published in numerous peer-reviewed medical journals. Currently, the most comprehensive review of long-term results from Loma Linda was published in the International Journal of Radiation Oncology, Biology, and Physics in 2004. This paper focused on 1,256 patients with stages T1-T3 prostate cancer, all of whom were treated between October 1991 and December 1997, and none of whom received any adjuvant hormonal therapy. The radiation dose employed was 74-75 Gy (our institutional standard at the time, based on the Harvard experience), and the median follow-up was sixty-three months. Biochemical disease-free survival (as defined by PSA-based criteria) was 95% in patients with pre-treatment PSA's of < 4.1 , 85% for PSA of 4.1-10.0, 65% for PSA of 10.1-20.0, and 48% for PSA's of 20.1-50.0. These numbers compare favorably with a similar group of patients (stratified by pre-treatment PSA, Gleason Score, and clinical stage) who underwent radical prostatectomy at Johns Hopkins[10]. The five and ten year incidence of moderate to severe Genitourinary and Gastrointestinal morbidity was 1%. This series represents one of the largest groups of individuals treated with a three-dimensional conformal proton beam technique treated at the same institution and demonstrates that the treatment is well tolerated and capable of producing biochemical disease-free survival rates equivalent to those achieved with other treatment methods[11].

The PROG-9509 Randomized Trial

One of the bedrock tenants of radiation oncology is that increasing the radiation dose to a tumor will increase the probability of sterilizing the tumor and, hence (if the disease has not already metastasized) the probability of cure. It will be recalled that the original Harvard randomized trial demonstrated that those patients who received the higher radiation dose were less likely to experience progression of disease within the prostate gland. Because of the advanced stage of the patients in the Harvard trial, improving local control did not equate to improved cure, but the data suggested that if dose-escalation was performed in patients who had early stage disease and hence a low chance of having already developed metastasis, those patients receiving a higher dose may be more likely to be cured.

It was to test just this hypothesis that in 1996 physicians at Loma Linda University and Harvard instituted a prospective, randomized trial, known as the PROG (for Proton Radiation Oncology Group) 9509 trial. Patients enrolling in this trial were randomly assigned to receive a total radiation dose of either 70.2 or 79.2 Gy, with the former dose chosen to represent the "standard" radiation dose then prevailing in radiation oncology. Between 1996 and 2000, some 393 patients were enrolled and have been followed continuously ever since. PROG 9509 was the first multi-institution prospective randomized trial of dose escalation ever performed in prostate cancer, and its success is a tribute to those brave and generous patients who were willing to participate in a clinical study.

The results of the PROG 9509 trial were published in the Journal of the American Medical Association in 2005[12]. The data strongly confirms the hypothesis that dose-escalation reduces biochemical failure (rising PSA, which is a surrogate for disease recurrence) in early stage disease. The advantage of dose-escalation was seen amongst all patient subgroups and was strongly statistically significant. It equates to an approximately 20-30% reduced risk of biochemical failure at five years in the high-dose group, and it is highly likely that this difference between groups will increase with further follow-up. Equally importantly, the increase in radiation dose was not associated with an increase in moderate to severe treatment related morbidity - in fact, the incidence of moderate or greater long term side effects was <1% in both groups. As a consequence of this trial, the new "standard" radiation dose for early stage disease at LLUMC and the other proton centers is now equal to

the "high dose" arm of the 9509 trial, and a further dose-escalation study (to 82 Gy) has recently been completed.

Protons VS IMRT

One of the most recent technological advances in x-ray therapy has been the development of Intensity Modulated Radiation Therapy (IMRT). In IMRT, a computer-controlled linear accelerator is used to treat a tumor, like prostate cancer, with a multitude (the typical plan utilizes seven to fourteen beams) of individually shaped x-ray beams. In order to protect normal tissue, the intensity of the beams is adjusted dynamically by placing within the beam an absorbing material (typically made of Tungsten or some other high-density metal) so that when a particular beam path traverses large amounts of normal tissue the beam intensity is decreased. This type of treatment will produce a high-dose region which nicely surrounds the prostate but (and this is an important point regarding the difference between proton therapy and IMRT treatment) at the expense of increasing the amount of normal tissue which receives low to moderate radiation doses. The reason for this gets back to the aforementioned physical differences between protons and x-rays. IMRT is still fundamentally x-ray based therapy, and while one can change the intensity of the beam, what one cannot do (for it is a physical impossibility to do so) is to get an x-ray beam to stop at some point in space.

Patients and colleagues routinely tell me that IMRT has made protons unnecessary because with IMRT we can achieve high dose distributions that in some cases are similar to those achievable with protons. When I point out that the integral dose (total dose to normal tissue) is 3-5 times less with protons than when IMRT is used, they will often dismiss this low-dose radiation as being unimportant because it is not likely to cause any clinically identifiable problems. I consider this argument flawed because of the following points:

1. Virtually every advance in radiation treatment technology since the inception of radiation therapy has been directed at the goal of reducing any radiation dose to normal tissue to the greatest extent technologically possible. IMRT reverses this trend because it exposes large amounts of normal tissue to low-dose radiation.
2. Our knowledge of radiation-induced organ injury is based primarily on analyzing the volume of that organ which receives a high radiation dose. Our understanding of the effect of treating a large volume of a normal organ to a low dose is very limited, and the long term effects of such exposure are poorly understood.
3. The only absolutely safe dose of radiation that we know of is zero. Therefore, anything we can do technologically to limit as much normal tissue to zero dose will always be desirable and advantageous to the patient.

Conformal proton beam radiation represents the future of external beam radiation therapy. In terms of technological development it is presently in what I would consider to be the first generation of development. As accelerator technology matures, and active scanned proton beams become a reality (this latter development is nearing its introduction into clinical oncology and is already available at one center in Europe) the disparity between what can be achieved with protons and what one must accept with x-rays (including IMRT) will only become greater[13-15].

The Future

Conformal proton beam radiation therapy of prostate cancer is now available at five institutions in the United States (Loma Linda, Harvard, MD Anderson Cancer Center, University of Florida, Indiana University) with several other facilities either under construction or in the planning stages. Ongoing clinical research will focus primarily on further dose-escalation and on a concept known as hypofractionation, in which higher than "standard" daily radiation doses are given so as to deliver the same equivalent total radiation dose to the prostate over, say three to four weeks as would typically be given over nine weeks. Another concept under active investigation is that of intra-prostatic boosting, in which areas within the prostate gland containing identifiable tumor (as delineated by endo-rectal MRI or PET) will receive even higher doses of radiation than the remainder of the gland.

Conclusion

Conformal proton beam radiation therapy of prostate cancer is safe and effective, and can produce biochemical disease-free survivals which are comparable to other treatment methods. The physical characteristics of protons guarantee that for any given treatment

plan they will always result in a lower total radiation dose to normal tissue than can be achieved with any form of x-ray therapy, which over a century's worth of clinical experience in radiation oncology has been shown to always be beneficial to the patient. This technology continues to evolve and impending advances in proton beam treatment delivery will serve to further improve our ability to irradiate the prostate to high doses while simultaneously minimizing normal tissue toxicity.

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WHAT THE HECK HAS BEEN GOING ON IN MY WORLD-PART 14!!!

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Let me see if I get this straight. Michigan loses to Ohio State on a controversial call (for those of you who missed it, there was a helmet hit by Shawn Crable from Michigan on Troy Smith from Ohio State and I believe Mr. Smith got a small boo boo from the hit, so they threw a flag) and gets beat in the Rose Bowl by 2 touchdowns from that school out West where the players apparently get cold hard cash for playing on the team (am I bitter about this game or what). Also, just when you think it could not get any worse, Ohio State gets the Astroturf kicked out of them by Florida in the National Championship Game (no, I do not need my cranium examined, I may hate Ohio State when they play Michigan but otherwise I am always the Big Ten fan - all the way baby)! These are dark days my friends. I know that you are thinking that these are only football games and not life or death, but this does not help my pain, which is so bad! How bad is my pain? It hurts more than a 7-foot Urologist with large hands doing a rectal exam with the entire hand - that is how bad it hurt me (rim shot please).

81) Men on androgen deprivation therapy (ADT) for prostate cancer are simply not getting enough calcium and vitamin D in their diet and/or from supplements, and these two supplements alone could protect them potentially from numerous serious side effects.

(References: Orsola A, Planas J, Salvador C, et al. J Urol 175(4): page 41, abstract 130, April, 2006. & Kincade MC, Derweesh IH, Malcolm J, et al. J Urol 175(4): page 41, abstract 128, 2006.)

This was a nice lifestyle study from Barcelona, Spain. A total of 372 prostate cancer patients treated by surgery (106 patients) or taking androgen deprivation therapy (ADT, 266 patients) were a part of this study. Daily calcium intake was calculated after a dietary interview was completed at the time of bone mineral density (BMD) screening with a Dual-Energy X-ray Absorptiometry (DEXA) at the lumbar spine and hip. DEXA is the gold standard for diagnosing osteoporosis in the U.S. and most other countries in women and men. The median age of this group was approximately 70 years old, the average Gleason score was between 6 and 7 (6.8), and the average PSA at diagnosis was 9.8 ng/ml and 75.1 at the time of the beginning of ADT. Out of all of these men the following DEXA results indicated:

-183 men had osteoporosis
-132 men had osteopenia
-57 men had a normal bone mineral density (BMD)

The usual recommendation, at least minimally for men this age, is to get 1,000 mg of calcium per day,

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Proton Beam Radiation Therapy

Subject: Local Medical Review Policy-Proton Beam Radiation Therapy

This Medicare policy will be retroactive for services performed on or after June 27, 1996.

Description

Protons are one of several types of subatomic particles that have been used by the radiation oncologist in the treatment of malignancy. The biologic activity resulting from proton beams is identical to other forms of radiation therapy, i.e. these charged particles interact with electrons in the target tissue to produce ionization. The ionization affects the replicating ability of the cells. While these cells have some ability to repair themselves, a cancer cell's ability to repair itself is usually inferior to normal cells. This permits selective cell destruction.

The major advantage of protons over conventional radiation therapy is that the characteristic energy distribution of protons can be deposited in tissue volumes designated by the physician in a three-dimensional pattern. This superior control and precision allows the radiation oncologist to significantly increase the dose to the tumor target while minimizing the dose (and radiation-induced complications) to healthy surrounding tissue.

Policy

Proton Beam Radiation Therapy for treatment of Prostate Cancer will no longer be considered investigational. Proton-beam radiation therapy is non-investigational in the treatment of malignancies. Proton-beam therapy may be medically necessary for the treatment of:

- Intraocular melanomas.
- Pituitary neoplasms.
- Small arteriovenous malformations.
- CNS lesions.
- Head and neck malignancies.
- Prostate malignancies.

Benefits will be provided when services are considered medically reasonable and necessary to treat the Prostate Cancer. Treatment with proton-beam radiation therapy should consider the characteristic absorption in a specified target volume and location that would likely result in superior clinical outcomes as compared to conventional (photons) or electron-beam radiotherapy.