- From: [Insuree]- - - 8/16/09
Board of Trustees - - - - - - - - -
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Portland, OR 972 - - - - - - - - - - -
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Dear Trustees:

This letter and accompanying information is my request for review (or appeal) of denial of coverage for proton radiation therapy for prostate cancer. In [Ins. Co.]'s February 25, 2009 letter denying coverage there was a reference to an earlier notification of denial. I wish to make it clear that I received no issuance of denial from [Ins. Co.] prior to this letter.

The letter specified that of the criteria listed in the 3rd paragraph, it had been determined that the "medical necessity" of proton therapy had not been established (4th paragraph). The letter provided a list of five criteria which must be met in order to meet their definition of "medical necessity." The letter also included a Peer Specialty Review (PSR)—said to be the basis for denial—but gave no explanation as to how the Review pertained to the medical-necessity criteria.

My attorney at the time asked for more information about how the denial decision was made, and in a subsequent letter received April 3, 2009, [Ins. Co.] 1) singled out two of the five medical-necessity criteria as not having been met, 2) confirmed the information given in the Peer Specialty Review as its "explanation of the medical or clinical judgment for the determination of medical necessity," but 3) again supplied no information as to how the Review pertained to the medical-necessity criteria.

[Ins. Co.] refused to identify the Peer Specialty Reviewer. In a phone call, [Ins. Co.] would only say he/she was a U.S. radiation oncologist who had written a book. I was not able to check credentials, nor identify potential biases. As is known anecdotally and through professional study[a], prostate cancer treatment providers are known for recommending treatment in their specialty. I was not able to discern if this held true in this instance.

Regardless, I do understand that [Ins. Co.]'s decision to deny coverage was based on the application of information given in the Peer Review to medical-necessity Criteria #s 1 and 5, and further understand from the Review and the Feb. 25, 2009 denial letter that [Ins. Co.] is making a comparison between protons and "more common forms of radiation therapy," particularly 3D-CRT and IMRT, so that is how I've focused my appeal.

This letter will show that

- the PSR does not support denial relative to medical-necessity Criteria #s 1 and 5,
- references cited by the Peer Reviewer actually speak favorably of proton therapy,
- the dose distribution characteristics of protons are different enough from photons to constitute a "level of service" than cannot be provided with photons, and
- studies bear witness to protons' tissue-sparing dosimetric benefits, in the form of lower risk of side effects compared to photons.

I therefore request coverage of proton radiation therapy for prostate cancer treatment.

To help you to navigate this letter, the Table of Contents provides an overview, while highlights are covered on pages 4-21. Appendices flesh out topics already addressed.

Thank you for your consideration,

[Insuree]

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Appendices

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Note: References within this letter are cited alphabetically. Numerical references within quotes remain as they appear in that reference. Numerical references are not further listed here.

A Quality-of-Life Decision

I was diagnosed with prostate cancer in October of 2008 following nine months of documented rising PSA. The biopsy showed Gleason 6, with a two-thirds chance the malignancy was confined to the prostate. There was a 30% chance it had spread to the margins just outside the prostate, 4% to the seminal vesicles and 1% to the lymph nodes.

As a relatively young man (age 57), employed, active, and expecting to live at least another 25 years,[b] beyond treating the cancer, quality of life was paramount in my choice of treatment. Since organs affecting bowel, bladder, and sexual function are adjacent to the prostate, these are frequently affected by treatment. The literature shows a wide disparity between post-treatment side effects depending on selected treatment. These can have a large impact on long-term quality of life (as well as costs).

From a quality-of-life study after prostate cancer treatment by David F. Penson, MD, MPH:

> Given the lack of unequivocal survival data clearly favoring one treatment over another for localized prostate cancer, patients strongly consider quality-of-life effects when choosing treatment for this common malignancy.[c]

Physician Consultations

Physician consultations played a large part in my choice-of-treatment decision.

1. My first appointment was with my urologist, [Urologist #1], in October of 2009 who recommended cryosurgery—his specialty. He said I would be left impotent as a result of the treatment but that there were ways to address that. Being a man of 56, I felt impotence was an unacceptable consequence, if other more satisfactory treatments could be found. [Urologist #1] also said there was time to consider my options and enjoy the holidays.

2. My second appointment was with [Urologist #2] in November who warned against radiation—he was seeing long-term problems with impotence, bladder and rectum issues. I brought up proton radiation therapy. [Urologist #2] said there was less likelihood of side effects with protons, and that he'd had four patients travel to Loma Linda for the treatment whom he'd subsequently seen for as long as five years, none exhibiting side effects. He said that if I had not been doing research into proton therapy, he would be recommending prostatectomy. There was potential to save one nerve, and *if* that were successful, the chance of impotence was lowered to 30%. The incontinence risk was similar to cryosurgery at 5%. He also suggested robotic surgery and cryosurgery as options.

3. My final consultation was with Dr. Bush, radiation oncologist at Loma Linda University Medical Center who explained about the ability of protons to target the prostate more accurately than x-rays (photons) with less exposure to the bladder and surrounding tissues. He said the cure rate between radiation and surgery was the same. He said bladder and rectal damage were rare, but that mild symptoms such as urinary frequency and urgency were common during treatment, typically abating a few months after treatment. Erectile dysfunction was at 20-30%. Finally, he explained that the target area would include an additional margin to capture the 30% possibility that the cancer had spread to areas immediately outside the prostate.

4. Following the research and consultations, I checked back with my primary physician, Dr. Inkeles, who first noticed my rising PSA, and made the recommendation for proton treatment. (See Appendix 2.)

Based on research, my consultation with Dr. Bush, and the warning from [Urologist #2], I chose proton therapy to treat my prostate cancer:

a) Similar rate of cure compared to prostatectomy;
b) Lowest incidence of side effects;
c) Margins are treated as well.

Proton Introduction

Protons are a kind of radiation which perform very differently in the body than x-rays, or photons, thus providing a different "level of service." Protons are characterized by their ability to release a majority of their dose at a prescribed target (the "Bragg peak"), as opposed to photons which release radiation along their entire path through the body. Photons thus irradiate more non-target tissue than protons.

From an article by Jerry D. Slater reviewing 15 years' experience at LLUMC:

> Proton radiation is a heavy-charged-particle radiotherapeutic modality that is perhaps best known for the ability it provides radiation oncologists to design and deliver highly conformal treatments to intended target volumes. This conformability is related to the intrinsic characteristics of accelerated protons; they deposit little radiation as they enter the patient's body and proceed to the target; they deposit the bulk of their ionizing energy in the targeted volume, followed by a sharp fall-off (the Bragg peak); and they do not irradiate tissue distal to the target. These features provide radiation oncologists with the opportunity to deliver higher radiation doses to the target, with the potential of increased tumor control, as well as significantly reduced integral volume dose to the normal tissues and, consequently, few radiation-related side effects.[d]

Delivery technique spreads out the proton beam to create a "spread-out Bragg peak," shown here compared to photons and explained by Alfred R. Smith, Ph.D., Professor at the M.D. Anderson Cancer Center:

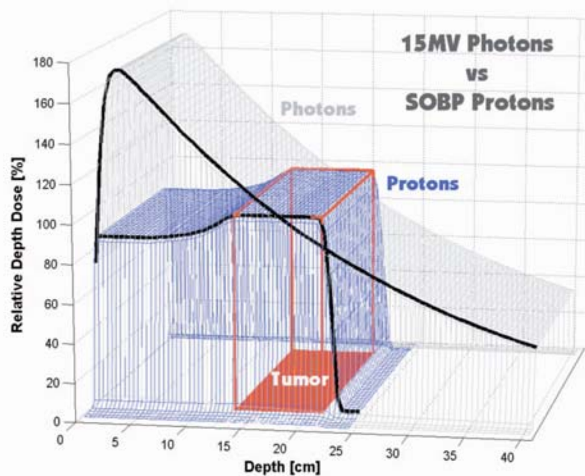

FIG. 1. *Comparison between the depth dose curves for 15 MV photons and a proton spread-out-Bragg peak (SOBP). A "target volume" is shown in red. Shown also in red lines is an "ideal dose distribution" for the target volume, which provides uniform, maximum dose to the target volume and zero dose outside the target volume. The proton dose distribution approaches the ideal case to a much greater extent than does the photon dose distribution. Notably, the proton dose stops abruptly distal to the target volume and delivers less dose to the region proximal to the target volume.* [e]

Illustration and caption: Alfred R. Smith. Vision 20/20: Proton therapy. Med. Phys. February 2009;36(2):556-568.

From a review of proton literature by Olsen et al.:

> In front of the Bragg-peak, the dose level is modest as compared to photon beams; beyond the Bragg-peak the dose falls practically to zero. By choosing appropriate proton beam energies, the depth of the Bragg-peak can be adjusted according to the depth and extent of the target volume. Hence, excellent conformality can be achieved compared to conventional or intensity modulated radiotherapy.[f]

From an article by Carl J. Rossi, Jr., MD, LLUMC:

> The Bragg peak and associated superior dosimetry have profound implications in radiation therapy. In practical terms, the "integral dose" (defined as the radiation dose to normal tissue) is always lower with protons than with any x-ray–based treatment delivery system.[12,13] In the case of prostate cancer, treatment with proton beams reduces the integral dose by a factor of three to five as compared with IMRT…[g]

Dose photos from Trofimov et al.[h] (the 4th reference cited in the Peer Specialty Review) show the difference between photons and protons. IMRT (a) is delivered from numerous directions creating a prescribed cumulative dose at the target. However in so doing, a large amount of non-target tissue is subjected to lower dose radiation. Protons (b) & (c) are delivered from 2 directions, thereby minimizing exposure to non-target tissues. The two paths of radiation do not build up dose in non-target tissues the same way as photons because of the Bragg peak falloff in which little-to-no radiation is deposited on the far side of the prescribed target. (Note: Sources say IMPT (c) is not yet being provided in the US.)

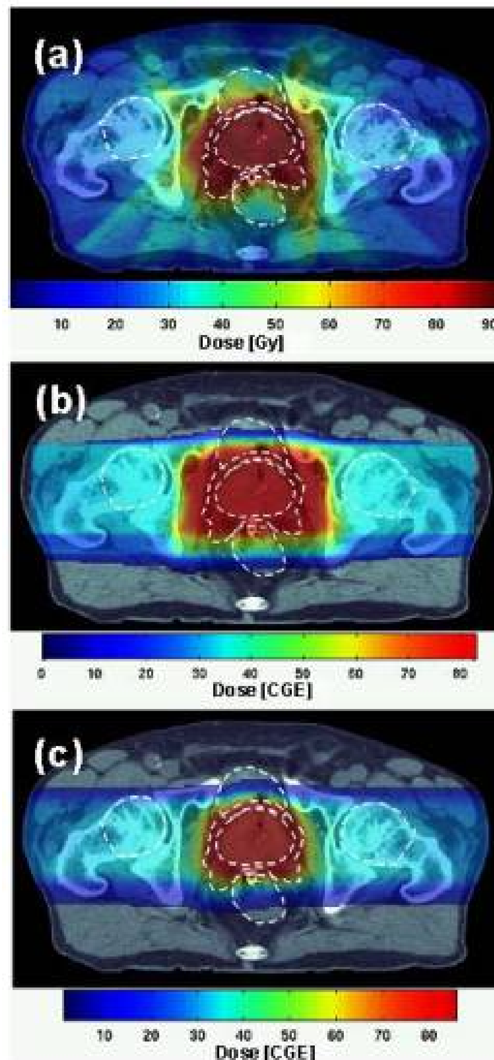

Figure 2

Patient 1: dose distribution in the transversal isocenter section from (a) IMRT, (b) 3D-CPT and (c) IMPT plans. Dashed white lines show the contours of the prostate, PTV1, rectum, bladder and femoral heads.[h]

Images, right, and caption, above: Trofimov et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. International Journal Radiation Oncology Biology Physics. 2007 Oct 1;69(2):444–453.

See Appendix 3 for more proton information and Appendix 2 for Dr. Bush's letter with a history of protons.

Clinical Superiority

“Is proton beam radiation a clinically superior treatment compared to external beam radiation?” –[Ins. Co.]’s question to Peer Specialty Reviewer.

Answer: “Clinical superiority” is not mentioned as a requirement in [Ins. Co.]’s criteria to establish medical necessity. The Review thus does not respond relative to the criteria. Furthermore, any rationale which links the Review to Criteria #s 1 and 5 was left unexplained. And yet, this Review was reiterated as the reason for denial of coverage in [Ins. Co.]’s April 3, 2009 letter. The problem with this disjunct between Review and criteria is further discussed in the opening paragraphs of the sections on Criteria #s 1 and 5. At any rate, other peers disagree with [Ins. Co.]’s Reviewer’s opinion.

From Smith: “Clinical data strongly support the conclusion that proton therapy is superior to conventional radiation therapy in a number of disease sites.” [e]

From a dose-volume comparison between protons and IMRT by Vargas et al.: “…proton radiotherapy dose delivery characteristics can be optimized to improve the results seen with IMRT.” [i]

Goitein and Cox (respectively Harvard Medical School, Dept. of Radiation Oncology; and M.D. Anderson Cancer Center, Div. of Radiation Oncology) find it “…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.” [j]

These assertions are borne out in further studies, as shown throughout this letter.

Available Literature

The Peer Reviewer found evidence to be lacking in comparing three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and proton therapy. But there are numerous clinical studies, comparisons, and discussions available. In fact, a 2007 review mentioned *1894* references meeting selected proton search criteria.[f]

Reviewing the voluminous published data is daunting. It was helpful to look at those studies which reviewed and analyzed categories of studies. Excerpts from these, as well as from other documents, are presented throughout this appeal letter.

Cited in Physician Peer Review

With the huge amount of information available, how were the four references cited in the Review selected? The latest reference was published in October of 2007. There was more than a year’s worth of literature after this. Was it considered by the Reviewer?

1st Reference

The first reference (Proton therapy in clinical practice: Current clinical evidence[k]) is a review of literature which briefly discussed studies which are not relevant to comparing protons to photons, and overlooked all other proton studies. This review provided no 3D-CRT, IMRT, nor other photon information from which to conclude these modalities are equitable to protons.

2nd Reference

This essay (The Titanic and the Iceberg: Prostate proton therapy and health care economics[l]) questioned protons' ability to meaningfully escalate dose in tumor control, and if so, then its economic utility. However, it overlooked the other side of the coin—the increased safety brought about by the Bragg peak and the associated savings, as well as other points. (See the section on costs later in this letter.)

The article contradicted itself: "apart from some comparative planning studies, there is no proof that it is superior to its alternatives." Aside from this being wrong, *there are* those planning studies. They cannot be dismissed and they consistently show protons to be superior. Dose distribution benefits are becoming more evident. Risk of secondary malignancies and morbidities are lower with protons. (See the relevant sections.)

The article, in referring to the Konski study[m], actually supports proton therapy as being cost effective for a man my age. (See the costs section.)

Author Zietman summed up the proton/photon conflict in his mind saying, "What then matters more, a low dose to the pelvis [photons] or a higher dose to the hips [protons]—more rectal or bladder cancers or more hip fractures?" He offered no support in the article for these fears, however, subsequently LLUMC went on record refuting the charge of proton-caused hip fractures[n] and Chung et al.[o] has shown a higher incidence of secondary malignancies with photons. (See the relevant sections.) Thus, we have an answer to both Zietman's and [Ins. Co.]'s question. Protons are superior due to their organ-sparing dosimetric advantage.

3rd Reference

The third reference (Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial[p]) did not compare photons to protons directly—a point already noted and discounted in the Peer Review. However, numerous reviews and analyses point to this and another trial as evidence of the benefit of protons' ability to safely escalate dose. (See the section on biochemical failure.)

This trial produced the highest rate of freedom from biochemical failure in the high-dose proton boost arm of the trial. (See the section on biochemical failure.)

4th Reference

The fourth reference (Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: A treatment planning comparison [h]) found favorably for protons in terms of mean dose reduction to the rectum and bladder (26% and 20% respectively) as well as for most specified ranges. This study in its conclusion noted a dose-reduction benefit relative to men younger than age 65, or any age due to secondary malignancies:

> …protons irradiated substantially smaller volumes in the range up to 30 Gy. Since more than 70% of all prostate cancers in the United States are diagnosed in males over age 65, the benefit of the integral dose reduction with protons may not be as appreciable as in younger age groups. However, recent reports of the increased risks of secondary malignancies in the older population, after prostate cancer radiotherapy ([35], [36], [37]), indicate that the dose reduction may be practical in that demographic group as well.[h]

The study also noted the reduction of lower dose volumes with protons:

> Dose to healthy tissues in the range lower than 50% of the target tissues was substantially lower with proton therapy…In the lower dose range, the rectal V30

> was reduced with protons vs. IMRT between 16% (Patient 8) and 53% (Patient 2).[h]

Lower and medium dose range reductions from protons in non-target tissues are proving to be important in reducing side effects. (See Appendix 7.)

Randomized Controlled Trials

The Peer Reviewer noted there were no trials comparing protons to 3D-CRT or IMRT. It must be obvious that this cuts both ways. [Ins. Co.]'s citing of Criterion #5 in its decision of denial, means it ([Ins. Co.]) has declared that 3D-CRT and IMRT provide the same "level of service" and are as safe as protons. But no information was provided to support the contention. Is this more than an omission? Without those trials, *is there any evidence at all?* Furthermore, if RCTs are a requirement of coverage, then IMRT also fails [Ins. Co.]'s test. Where is the trial which showed IMRT's superiority over 3D-CRT, thus approving *its* coverage? Why are protons held to a different standard?

A number of prostate cancer therapies are in use without having undergone RCTs. From a systematic review of the literature by Wilt et al:

> Primary androgen deprivation, cryotherapy, brachytherapy, intensity-modulated radiation therapy, proton-beam radiation therapy, and laparoscopic and robotic-assisted radical prostatectomy have not been evaluated in randomized trials, despite their widespread use.[q]

Furthermore, many professionals feel that proton/photon RCTs should not be performed.

From Smith:

> There is an ongoing discussion in the radiation oncology community regarding the appropriateness of prospective, randomized clinical trails comparing protons with photons. The basic argument is that the dose distributions of protons will always be superior to those for photons when both modalities are optimized and one cannot justify randomized clinical trials of protons vs. photons because there would not be equipoise between the two arms of the trial.[25,26] [e]

From the Rossi article:

> Performing, as some have advocated, a randomized trial of protons versus x-rays would, in my opinion, be scientifically and ethically questionable. As long as the radiation doses delivered to the target area in the two arms of such a trial were equal, the only "difference" to the patient would be the amount of radiation that his normal tissues would receive. Since over a century's worth of experimental and clinical experience has conclusively demonstrated that giving a lower radiation dose to normal tissue is always in the patient's best interest, I do not believe that exposing half of the patients in such a trial to three to five times more radiation dose than the other participants receive would be justifiable.[g]

Goitein and Cox:

> …we find it totally unacceptable to insist on what we judge to be unethical RCTs purely to establish the financial cost-effectiveness of an admittedly better technology—nor would patients, if fully informed, consent to participate in such studies.[j]

See Appendix 4 for more on proton/IMRT RCTS.

Medical Necessity Criterion #1

> *Appropriate as to place and level of care in amount, duration and frequency for treatment of the condition.*

The citing of this decision criterion is confusing. Since Criteria #s 2 and 3 were found acceptable, it's clear [Ins. Co.] recognizes proton therapy as an accepted treatment for prostate cancer.

Peer Specialty Review does not support denial decision

The Peer Specialty Review does not support [Ins. Co.]'s denial on this basis. Inappropriateness of this therapy is not raised in any way. If the Reviewer felt proton therapy were not appropriate, he/she had an ethical obligation to say so. None of the references cited in the PSR say protons are inappropriate for treating prostate cancer. They all speak to the contrary:

Cited in the Peer Specialty Review:

1st Reference [k]

Brada et al.: "The promising sites where Protons may offer the potential advantage of more localized treatment…initially include some head and neck tumors and pelvic tumors, particularly prostate cancer."

2nd Reference [l]

Zietman: "…there is certainly a growing body of evidence confirming clinical efficacy [of using protons for prostate cancer treatment]…" and "PBT is…a legitimate form of external radiation for prostate cancer…"

3rd Reference [p]

Zietman et al.: This study showed using protons to escalate dose to the prostate lowered risk of biochemical failure without increasing grade 3 GU or GI morbidity.

4th Reference [h]

Trofimov et al.: In this study comparing proton plans to IMRT plans, all patients were ultimately treated with protons. Clearly their doctors felt it appropriate.

The literature recognizes appropriateness

Place— Loma Linda University Medical Center, Department of Radiation Medicine in Loma Linda, California is the closest facility offering proton therapy. Proton therapy is a unique "level of service" (Criterion #5) which cannot be provided at facilities other than proton facilities. The choice of this location, operating since 1991 to the public, was appropriate.

Wilt et al. referred to LLUMC as a "center of excellence" in the proton portion of their review of prostate cancer treatments:

> Several nonrandomized reports from 1 center of excellence provided clinical outcomes after combined proton beam and photon radiation therapy (53–57). Between 86% and 97% (54, 57) of men were free of disease at the end of follow-up… [q]

Slater wrote specifically of LLUMC's experience with proton therapy in 2006:

> 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.[d]

There is nothing in the benefits booklet to indicate any relevant restrictions on location/travel for treatment, etc. The only mention speaks to limiting *charges* relative to the geographic area, but not to limiting *location* of treatment. Given that proton therapy's geographic area constitutes half a dozen locations across the country, perhaps [Ins. Co.] should compare the relative costs at these facilities and cover an amount consistent with the least costly.

Level of care in amount, duration, and frequency— Over 8000 prostate patients have been treated with protons at LLUMC.[n] I received high-dose therapy as prescribed by Dr. Bush. Literature shows this to be both effective and routine.[r]

> …higher radiation doses for patients with clinically localized prostate cancer are now considered standard of care [r]

My treating physician at Loma Linda, Dr. Bush, prepared a letter for your consideration in which he addressed appropriateness and medical necessity in detail. Furthermore, my primary physician in McMinnville, Oregon, Dr. Inkeles, recommended proton therapy, also terming it "medically necessary," (See Appendix 2 for both these letters.)

Insurance Coverage

Proton therapy is already accepted by most insurance companies. (See Appendix 5)

BlueCross/Blue Shield of Texas, Illinois, New Mexico, and Oklahoma recently reviewed and renewed their approval policy of proton therapy for prostate cancer. Their criteria included peer-reviewed scientific literature. A copy of a letter which briefly explains the decision is included in Appendix 5. "…although the evidence supporting proton beam therapy for prostate cancer is still emerging, it is sufficient..."

For these reasons, I contend this criterion does not apply to denial of coverage.

Medical Necessity Criterion #5

> *The least costly of the available supplies or level of service which can be safely provided to the member. This means, for example, that care rendered in a hospital inpatient setting or by a nurse in the patient's home is not medically necessary if it could have been provided in a less expensive setting, such as an Extended Care/Skilled Nursing Facility, without harm to the patient.*

This is a complex criterion, the key terms of which are *least costly, level of service, safely provided,* and *without harm to the patient.* A covered therapy is either a different level of service, the safer of two therapies which provide the same level of service, or the least costly of two therapies which provide both the same level of service and degree of safety.

However, because [Ins. Co.] covers IMRT, which is more expensive than 3D-CRT, it is clear that a modality need not be the least costly. The alternative would be that IMRT is the safer, a

contention in dispute (see the section on secondary malignancies), or that the two are considered different "levels of service" which would, of course, mean that protons are, as well.

Data show proton therapy provides a reduction in the risk of biochemical failure, secondary malignancies, and morbidities over IMRT and 3D-CRT. Theoretical harms about stray-neutrons, and hip fractures have been disputed or eliminated. Proton therapy is the safest radiation modality. Finally, under the decision information supplied by [Ins. Co.], proton therapy is cost effective for a man my age. (See the relevant sections.)

Level of Service/Safety/Harm*—Denial under Criterion #5 is not well supported by the Peer Specialty Review*

[Ins. Co.] has provided no evidence to place photons at the same level of service as protons. Furthermore, most of the cited references are favorable toward protons in their respective topics. Where potential harms were raised, subsequent literature has refuted them.

Cited in the Peer Specialty Review:

1st Reference [k]

Brada et al.: This review of selected clinical evidence noted the improved tumor control with proton boosts. A proton-created neutron concern was mentioned which has since been refuted in subsequent studies. (See the neutron section.)

2nd Reference [l]

Zietman: The best this essay could do to challenge protons was to say that photons "have narrowed the gap" while admitting "Undoubtedly, theoretical advantages still exist [with protons]." The article contorted the results of the Trofimov study (the 4th cited reference[h]) when it downplayed protons' "substantially lower" low-dose volumes versus IMRT and instead took issue with the high-dose volumes which are only "a little larger" with protons versus IMRT. Trofimov's Figure 6 (b) and (e), below, illustrates why the emphasis is misplaced. The dose difference in the low-dose range is substantial; the higher dose difference is small. (See Appendix 7 for the importance of low-dose volume reduction.) Two potential harms were mentioned without any corresponding support—hip fractures and ED. However, hip fracture harms have been disputed and ED is lower with protons than photons. (See the relative sections.)

3rd Reference [p]

Zietman et al.: This study of high-dose proton boosts showed the classic benefit of using protons to escalate dose: There was a lowered risk of biochemical failure without a corresponding increase in grade 3 GU or GI morbidity. (A reported increase in grade 2 GI morbidity in the high-dose arm has been superseded by a long-term quality-of-life questionnaire showing no difference between the two arms.[s])

Results for this study were subsequently corrected to show even better freedom from biochemical failure (FFBF) than initially reported, including possibly the highest rate for any prostate cancer treatment modality.[t]

4th Reference [h]

Trofimov et al.: This comparative planning study between IMRT and protons was overall favorable toward protons, showing a significant decrease in dose to the bladder and rectum in the low-to-medium dose range, compared to IMRT which performed better for the bladder in the high-dose range. Rectal volumes in the high dose range were similar between the two modalities. Trofimov's Figure 7 (b) and (e) illustrates this comparison. Protons also significantly lowered the average dose to both the bladder and rectum.

Figure and caption: Trofimov et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. International Journal Radiation Oncology Biology Physics. 2007 Oct 1;69(2):444–453.

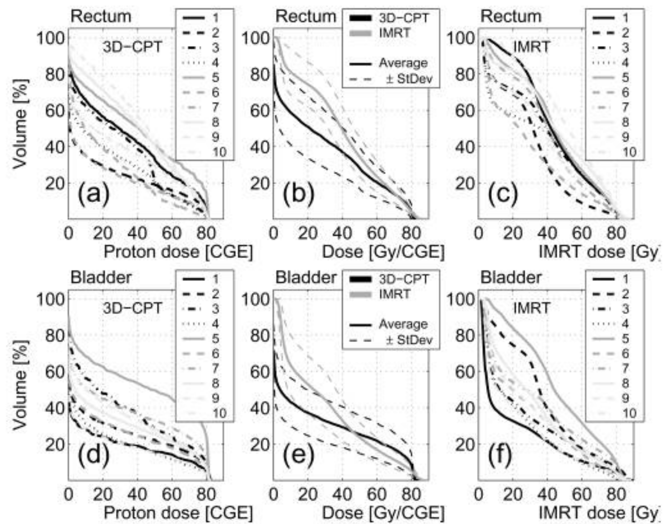

***Figure 7** Dose-volume histograms for the rectum (a-c) and bladder (d-f). Individual DVH from ten 3D-CPT and IMRT plans are shown in (a, d) and (c, f), respectively. Plots (b) and (e) show curves obtained by averaging, over the irradiated volume, of the DVH from 10 plans, as well as one-standard-deviation variability bounds (dashed lines).* [h]

Lower and intermediate dose rectal sparing is proving to be important. (See Appendix 7.) The study noted the benefit of integral dose reduction in relation to secondary cancer risk. This study downplayed the neutron concern mentioned in the 1st reference.

Literature & other documentation support approval

"level of service" — protons irradiate significantly smaller volumes of non-target tissues than photons

As shown in the Proton Introduction section, accompanying Appendices 3 and 8, and the 4th reference cited in the Peer Review, [h] protons have significant advantages over photons in the sparing of healthy tissues. Furthermore, this is not merely a different product, or "level of service," but a higher one. Planning studies by-and-large support protons' dose-deposition superiority over photons. [f,h,i,u,v]

In a 2007 analysis, Palm and Johansson reviewed treatment planning studies and compared dose distributions and impacts between external beam radiation modalities. They found protons improved dose distribution while substantially decreasing radiation to organs at risk:

> The data consistently shows that proton beam therapy substantially decreases the OAR [organs at risk] average dose compared to the other two techniques [conventional radiotherapy and IMRT]. It is also clear that protons provide an improved dose distribution in non-target tissues compared to conventional radiotherapy and IMRT...For large OARs and OARs of mainly parallel structure proton beam therapy can offer significant tissue sparing, likely preserving the organ function or at least significantly reducing the risk for damage…This review clearly demonstrate that a more favorable dose distribution in OARs and non-target tissue can be achieved using proton beam therapy compared to IMRT, which may reduce the risk for normal tissue complications and secondary malignancies. [w]

"safely provided" *— reduced risk of side effects*

The Peer Review said dose-planning studies have given mixed results, but this was not found to be the case. (See Appendix 8 and throughout this letter.) Radiation is more safely provided with protons. As Dr. Bush put in his April 7, 2009 letter (Appendix 2):

> The benefits of high-dose treatment include improvement in biochemical freedom from relapse as compared with lower doses of radiation therapy, while the precision by which protons can be delivered has been shown to reduce the incidence of significant acute and late treatment-related complications as compared with x-ray therapy.

Biochemical Failure

In efforts to exploit protons' ability to target tumors with higher doses while having less impact on surrounding tissues, two RCTs [p,x] compared proton boosts following photon radiation treatments. Both studies found a significant reduction in biochemical failure in the higher dose groups. These trials are repeatedly cited for the ability of protons to increase dose, and correspondingly increase freedom from biochemical failure, while minimizing radiation increase to OARs as compared to photons.

One of these trials[p] (the third reference mentioned in the Peer Review) looked at clinically localized prostate cancer and reported favorably for the high-dose arm. For low-risk disease the 5-year freedom from biochemical failure was 97.3% in the high-dose group. According to research by Dr. Paul Morgan in his recent successful appeal for insurance coverage [y] *this 97.3% rate has not been surpassed in literature for any prostate cancer treatment*:

> 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) [y]

Levin et al. gave the credit to protons: "Importantly, dose escalation was achieved with protons, without any comparable increase in significant or late radiation morbidity." [z]

Olsen et al.[f] reviewed the other RCT [x] which looked at advanced prostate cancer, and commented on the significant results of the proton-boost arm which also showed improved biological control: "…an improved local control in patients with poorly differentiated tumors was observed; 19% vs 85% local tumor control at 8 years in the low dose group and high dose group, respectively." The review went on to say, "Clearly the two randomized clinical trials offer some evidence on the clinical implications of dose escalation using proton irradiation." [f]

I was treated to high-dose radiation. The reason this can be safely done is the precise reason proton therapy is a superior treatment—it can be used for higher dose which has been shown to limit recurrence, without a corresponding increase in exposure to OARs compared to photons, thus limiting an increase in complications.

See Appendix 6 for more information on these two trials.

Secondary Malignancies

It has long been theorized that protons' ability, via the Bragg peak, to deliver more radiation to a specified target vs. photons' radiation delivery along its entire path, meant that non-target tissues and organs receive less radiation with protons resulting in reduced side effects and secondary cancers. New studies are bearing this out.

In a review of different radiation techniques James A. Purdy explained how IMRT increases radiation to normal tissues and why it's a concern: "Followill et al. (1997a and b) early on in the IMRT era expressed concern that the move from 2DRT/3DCRT to IMRT may result in an increased rate of secondary malignancies because of the significantly larger number of monitor units (MUs) required to deliver a comparable prescribed dose." And "… compared to 2DRT [2-dimensional radiation therapy] and 3DCRT, IMRT requires a significantly larger number of MUs to deliver a comparable prescribed dose, which results in an increase in the whole body dose as a result of leakage and scattered radiation." Purdy finishes the proton portion of his review saying, "Proton and IMRT show similar improved coverage for target volumes, but PBT [proton beam therapy] results in less dose to the normal tissues." [aa]

Following on the heels of Purdy's review is an exciting recent retrospective study by Chung, et al.[o] showing the difference in secondary malignancies between protons and photons. Comparing 503 proton patients to 1591 photon patients the study found, after an average of 7.7 and 6.1 years respectively, that *only half the number of proton patients had developed a secondary malignancy compared to the photon patients at 6.4% vs. 12.8% respectively.* "…Proton radiation therapy is associated with a significantly lower risk of a secondary malignancy compared to photon radiation therapy." [o]

A 2009 risk study by Fontenot et al. similarly found:

> Proton therapy reduced the risk of an SMN [secondary malignant neoplasm] by 26% to 39% compared with IMRT…This reduction was attributed to the substantial sparing of the rectum and bladder from exposure to the therapeutic beam by the proton therapy plan.[u]

Levin et al. finish the thought:

> [IMRT] requires increasing the volume of normal tissue that is irradiated (i.e. a higher integral dose); hence, one of the concerns of IMRT is that, over time, this exposure of more tissue to low-dose radiation will cause a second malignancy or other unwanted late normal tissue effect.[z]

Finally, in their review of treatment planning studies, Palm and Johansson noted that when comparing conventional radiation to IMRT, "Hall and Wuu [47] estimated that IMRT would increase the incidence of second malignancies by a factor of two compared to conventional radiotherapy." [w]

It appears IMRT could be the external beam modality carrying the greatest risk of secondary cancers.

See Appendix 8 on superior dose distribution for more information.

GU and GI Morbidity

Morbidity is a serious consideration with any prostate cancer treatment. The reduction in dose to non-target tissues from protons reduces these side effects as well as secondary malignancies. Talcott et al. in a study of post-treatment side effects makes a typical comment regarding prostate cancer therapies.

"Urinary incontinence increased sharply after RP, while bowel problems and urinary irritation/obstruction rose after EBRT and BT. Sexual dysfunction increased in all patients, particularly after radical prostatectomy, and nerve-sparing surgical technique had little apparent benefit." [bb]

Lips et al.[cc] in the course of their 2008 IMRT study, compared acute and late toxicity results of previous studies of 3D-CRT and IMRT (their Table 3).[cc] Note that the Zietman trial,[p] the only trial in the table to use proton boosts to achieve high dose, shows the best performance in the 3D-CRT category in grades 3 and 4.

Table 3: Acute and late toxicity from different studies

Authors	Acute toxicity						Late toxicity					
	GU (%) Grade			GI (%) Grade			GU (%) Grade			GI (%) Grade		
	2	3	4	2	3	4	2	3	4	2	3	4
3D-conformal radiotherapy												
Storey, 2000 [18], Pollack 2002 [2]	24	4	1	43	0	0	10	3	-	19	7	-
Beckendorf, 2004 [15]	30	7	-	28	2	-	-	-	-	-	-	-
Michalski, 2005 [16]	41	3	0	41	3	0	17	4	0	18	2	1
Zietman, 2005 [3]	49	1	1	57	0	0	20	1	0	17	1	0
Peeters, 2005/2006 [1,17]	42	13	0	47	4	0	26	13	-	27	5	-
Intensity-modulated radiotherapy												
Zelefsky, 2002/2006 [8,11]	28	0.1	0	5	0	0	9	3	0	2	0.1	0
De Meerleer, 2004/2007 [7,10]	36	7	0	29	0	0	19	3	0	17	1	0
Teh, 2005 [23]	35	0	0	6	0	0	-	-	-	7	2	0
Skala, 2007 [9]	-	-	-	-	-	-	9	1	-	3	1	-
Current study	47	3	0	30	0	0	21	4	0.3	9	1	0.3

Abbreviations: GU = genitourinary; GI = gastrointestinal; - = toxicity rate not available.
Table: Lips IM, Dehnad H, van Gils CH, et al. High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. Radiation Oncology. Published: 21 May 2008. 3:15.

Compare these findings to results of protons studies compiled for this letter:

Protons														
Study	Year	#Pts.	Acute						Late					
			GU (%) grade			GI (%) grade			GU (%) grade			GI (%) grade		
			2	3	4	2	3	4	2	3	4	2	3	4
Schulte et al.[dd]	2000	911							5.4	0	0	3.5	0	0
Slater et al.[ee]	1999	319							5	0	0	6	0	0
Hara [ff]	2004	16	6	0	0	0	0	0						
Mayahara [gg]	2007	287	39	1	0	0	0	0						

The comparison shows protons outperforming photons. Protons are better in acute GI, and late GU morbidity. Protons also appear to be leading in acute grade-3 GU and late grades 2 and 3 GI.

Olsen et al.[f] and Wilt et al.[q] more thoroughly reviewed the literature in their respective analyses and found similar results. Wilt summarized their findings in a table juxtaposed with IMRT. That portion of the table is reproduced here:

Table 1[q] **Summary of Evidence on the Comparative Effectiveness and Harms of Therapies for Localized Prostate Cancer***

Comparison [Reference]	Level of Evidence	Conclusion
------ *[break]* ------		
Harms		
------ *[break]* ------		
Emerging technologies		
------ *[break]* ------		
Proton-beam radiation therapy [53, 55, 57]	Low	<1% had gastrointestinal and urinary toxicity
IMRT [51]	Low	Rates: grade 2 acute gastrointestinal toxicity, 4%; rectal bleeding, 2% to 10%; grade 2 acute urinary toxicity, 30%; late toxicity, <20%

* ADT = androgen deprivation therapy; EBRT = external-beam radiation therapy; IMRT = intensity-modulated radiation therapy; PSA = prostate-specific antigen; RCT = randomized, controlled trial; RP = radical prostatectomy; SPCG-4 = Scandinavian Prostate Cancer Group Study No. 4; VACURG = Veterans Administration Cooperative Urological Research Group; WW = watchful waiting.

Dr. James Metz at the Abramson Cancer Center provided a side-by-side comparison between protons, conventional radiation, and prostatectomy in his Tables 3 and 4, again showing similar results. [hh] See Appendix 9 for the comparisons.

Dr. Bush notes in his letter (see Appendix 2) reduced morbidity of protons over photons:

> Our data on 645 gentlemen treated with conformal proton beam radiotherapy at LLUMC between December, 1991 and December, 1995 demonstrates an equivalent biochemical freedom from relapse rate at five years to similar (stratified by pre-treatment PSA) patients treated with Radical Prostatectomy, and a lower incidence of moderate to severe bladder and rectal toxicity than is reported when conformal x-ray therapy alone is administered to equivalent total radiation doses. [11,14]

Erectile Dysfunction

Erectile dysfunction as a result of treatment for prostate cancer is high. There is an expectation that this is an unavoidable risk, if not consequence. Wilt et al., in their review of nearly 500 studies, reported "Erectile dysfunction occurred frequently after all treatments (radical prostatectomy, 58%; radiation therapy, 43%; androgen deprivation, 86%)." [q] The review further called out the impotence rate with nerve-sparing prostatectomy at 5-60%, cryosurgery at 40-100%, and ultrasonagraphy 2-53% in Table 1.[q] Talcott is even more depressing: "Roughly two thirds of prostate cancer patients undergoing primary treatment experience severe erectile dysfunction, regardless of modality." [ii] A review by Burnett et al.[jj] (which did not include protons) gave similarly high risks:

> Database extraction from 31 articles, in which results for at least 50 patients were reported, yielded ranges of rates for complete erectile dysfunction, partial erectile function and intact erectile function that were 26% to 100%, 16% to 48% and 9% to 86% for radical prostatectomy, 8% to 85%, 21% to 47% and 36% to 63% for external beam radiation, and 14% to 61%, 21% and 18% for interstitial radiation, respectively.[jj]

A 2002 analysis of literature on the topic by Robinson et al. made the comment, "The potential loss of erectile function is a major consideration for prostate cancer patients when assessing their treatment options." [kk]

Additional studies confirm patients undergoing photon radiation, including IMRT, are at high risk for erectile dysfunction. These photon studies show a *range of ED from 36-76%:*

> Two years after EBRT, 35 of the 96 patients [36%] had developed ED.[ll]
>
> At 2 years after RT, 10 patients (35.7%) reported new-onset erectile dysfunction and were unable to attain firm enough erections to have intercourse.[mm]
>
> Of the 51 patients, 12 remained potent [24%], 22 had reduced potency [43%], and 17 were impotent [33%] at 2 years [after conformal radiotherapy (CFRT)].[nn]
>
> The median follow-up was 36.8 months [following IMRT]… Eight of 32 patients (25%) had no post-treatment ED…32 (9%) had mild post-treatment ED…five of 32 (16%) had mild to moderate ED…five of 32 (16%) had moderate ED…and 11 of 32 (34%) had severe post-treatment ED…[oo]
>
> Among patients who were potent before intensity modulated radiation therapy, erectile dysfunction developed in 49%.[pp]

Comparing these results to my initial consultation with Dr. Bush—20-30% risk of erectile dysfunction with protons, and Table 4 from Dr. Metz's article [hh]—30% impotence risk (Appendix 9), shows protons offer a lower risk of erectile dysfunction.

Patient reported proton ED is even less. Bob Marckini, author and co-founder of the Brotherhood of the Balloon, an organization dedicated to proton education and awareness recently polled the membership, receiving an overwhelming response he claims as 20% of men who have been treated with protons for prostate cancer. Responses indicate lower general morbidity for protons. From the organization's June newsletter:

> To date, 1,591 members have responded. That's 55% of those with e-mail addresses, 41% of our entire membership, and almost 20% of all the men who have been treated with proton therapy for prostate cancer … a pretty good representation. We received an additional 64 surveys via postal mail that have also been entered into the system…In summary, the overwhelming majority reported no changes in urinary, bowel or sexual function; *94% said the quality of their lives was as good as, or better than before treatment;* 99% said, in retrospect, they made the best treatment decision for themselves; 97% said they would make the same decision again; 98% rated their treatment experience as outstanding; 99% said they would recommend proton therapy for prostate cancer to others; and 95% were confident their prostate cancer was in remission as a result of their proton therapy. [qq] [Emphasis added.]

"without harm to the patient" *— harms refuted*

Criterion #5 presents an example showing that the less-expensive of an equivalent "level of service" is covered providing it can be delivered "without harm to the patient."

It has been shown in this letter that protons have a lower risk of side effects than photons. That means that even if a decision is made which declares that protons and photons provide the same "level of service," it remains that photons still carry a higher risk of harm to the patient.

Theoretical proton-caused harms were raised in several of the references cited in the Peer Specialty Review.

Neutrons

A neutron concern was raised in the 1st reference [k] cited by the Peer Specialty Review. However, research is showing the concern unfounded. A study by Zacharatou Jarlskog found "…the

neutron dose lateral to the field is smaller than the reported scattered photon doses in a typical intensity-modulated photon treatment.” [rr]

In a study of radiation leakage, Moyers et al. reported:

> These new results confirm that the dose equivalents received by patients outside the primary proton field from primary particles that leak through the nozzle are below the accepted standards for x-ray and electron beams…At the center of a patient for a whole course of treatment, the dose equivalent is comparable to that delivered by a single whole-body XCT scan.[ss]

Hip Injury

The 2nd reference [l] cited in the Peer Review mentioned a hip fracture concern associated with protons but provided no basis for the allegation. There was no way to check on this. Regardless, Slater and Schulte responded based on 15 years’ experience:

> … at Loma Linda, in over 8,000 prostate patients treated with lateral beams that do go through the hip, the long-term sequelae from this have been minimal, if any, with over 15 years of follow-up.[n]

***Costs**—Denial under Criterion #5 is not supported by the Peer Specialty Review*

The Peer Specialty Review opinion provided no information on costs. The references cited by the PSR do not provide any comparative information of radiation modalities from which a conclusion could be drawn supporting denial under Criterion #5.

Cited in the Peer Specialty Review:

1st Reference [k]

Brada et al.: This review of clinical evidence provided no comparative information on costs from which to conclude denial based on Criterion #5.

2nd Reference [l]

Zietman: In terms of costs this essay also provided no specific, useful information comparing radiation types. Furthermore, in discussing the Konski study,[m] it actually supported proton therapy for a man of my age.

3rd Reference [p]

Zietman et al.: This study of high-dose proton boosts did not address costs.

4th Reference [h]

Trofimov et al.: This comparative planning study of IMRT and protons also did not address costs.

Literature & other documentation support approval under the costs aspect of Criterion #5

This letter shows, through the professional literature, how proton therapy provides better biochemical control through a more-safely-delivered modality. The data show protons provide a significant reduction in the risk of secondary malignancies and other side effects over IMRT and

3D-CRT. This meets the safety/level-of-service requirement of Criterion #5. The cost consideration of Criterion #5 is not relevant.

However, this costs section is included because the 2nd reference [l] cited in the Peer Review referenced a portion of the Konski study [m] relative to economic effectiveness and acceptability.

A study by Pijls-Johannesma et al.[tt] reviewed costs studies and pointed out the need to take a broader view of the impact of treatment on costs down the line. Regarding Konski they felt that certain analyses were lacking, and further commented that the impact of protons' lower incidence of side effects was not being taken into account in figuring costs:

> Konski et al. [29] did not take toxicity into account and it was assumed that the utilities for IMRT and proton therapy were similar (0.9). It is questionable if this assumption is justified, since the late toxicity grade seems to be lower after proton therapy as compared to photon treatment [3]. [tt]

The study went on to point out the long-term cost-savings and quality-of-life benefits of proton therapy, and explained that previous literature of proton costs had not made a study of this:

> It is expected that in the long run, due to a decrease in the absorbed integral dose, fewer secondary cancers will be induced. Also, due to the expected decrease in side effects and increase in tumor control probability (TCP), it is expected that long-term costs will decrease as a result of less hospitalization, less palliative care and improved quality of life. Therefore, it would be interesting to determine the probability of local tumor recurrence, treatment-related morbidity at different toxicity levels and the time of appearance of the morbidity and the frequency of G II [grade 2] progressing to G III after 5 or 10 years and then to G IV at 10-30 years. To our knowledge, none of the published studies on the cost-effectiveness mentioned in this paper give insight in the above. [tt]

Consistent with this line of reasoning is a 2006 pre-Konski study by Wilson et al.[uu] (which did not include proton therapy) emphasizing the need to consider long-term consequences of prostate cancer treatments:

> Our data demonstrate that prostate-related costs per person are substantial and sustained over time and that short-term treatment cost comparisons most commonly found in the literature do not truly reflect the cost of treatment choices over the long-term.[2,6] [uu]

It is not only the lower incidence of complications associated with proton therapy which improves cost and quality of life. Bellizzi et al.[vv] examined the impact of fear of recurrence and treatment-specific side-effects in men with prostate cancer and found improved health when these were reduced:

> …improved FOR [fear of recurrence] (P<0.01) and improved bowel function (P<0.01) significantly predicted better mental health scores, whereas higher number of post-treatment symptoms (P<0.01) was correlated with worse mental health…For physical health, improved urinary bother (P<0.01) and fewer number of post-treatment general symptoms (P<0.01) were associated with better physical health. As for FOR, there seems to be a marginally significant trend, such that improved FOR was related to better physical health (P<0.06).[vv]

In other words, understanding that a treatment, such as proton therapy, is superior in these aspects will improve health (and therefore lower health-care costs). We know now that protons significantly reduce the risk of complications over other modalities.

Age

The Konski study, despite being fraught with problems, does make this point: “This analysis showed that proton beam therapy becomes cost effective, under the conditions used to inform the model, the longer the time frame (15 years or greater) for the analysis.” [m] This portion of the study was discussed by the 2nd reference[l] cited in the Peer Review.

Given that my life expectancy is nearly 30 years,[b] odds are that proton therapy is a cost-effective treatment according to this reference.

The contributions proton therapy is expected to give over the course of the rest of my life compared to other therapies—reduced side effects, lower incidence of secondary malignancies, higher quality of life—will go toward reducing the long-term cost of my treatment. [Ins. Co.] could have been facing a higher likelihood of paying for treatment of long-term complications such as impotence, incontinence, biological recurrence, or secondary cancer, which could include surgery, chemotherapy, or possibly the highest cost of all, hormonal therapy. [uu]

Conclusion

This letter shows that proton therapy offers greater freedom from biological failure compared with other external beam modalities, and lowers risks relative to side effects.

- Proton therapy is an appropriate treatment for prostate cancer, according to the Peer Specialty Review.
- Protons lower the risk of secondary cancers by 50% over photons.
- Protons lower risks of morbidities compared to photons.
- Cost effectiveness of proton therapy is achieved relative to the standard supplied by [Ins. Co.]. This was the only cost information given and it was reiterated in the April 3, 2009 letter that the PSR was the information upon which [Ins. Co.] relied for its decision.

[Ins. Co.] has misplaced the emphasis in Criterion #5. There is no argument that IMRT irradiates more normal, non-target tissues than proton therapy, and that increased radiation in any instance raises questions of safety. IMRT, then, should bear the requirement to show that it is as safe as protons. Goitein and Cox put this well:

> We doubt that many of us, while healthy, would agree to receive, for example, 25 Gy to a large fraction of our brain or abdomen in exchange for some thousands of dollars, with no known or credibly hypothesized medical benefit. If we would not, how can we ask our sick patients to do so? Once proton beam therapy has become clinically available, is not the burden of proof on conventional x-ray therapy? Should not its advocates have to demonstrate that the cost savings achieved by using xrays are not accompanied by undesirable additional morbidity? Do the users of x-ray therapy have the evidence to support such a claim? [j]

Fortunately, it is not necessary here to quantify tradeoffs in cost savings vs. increased medical benefits. There is not a specific benchmark to meet. The requirement is to show that there is that additional benefit with proton therapy. That has been done and, thus, coverage should be granted.

Appendix 1 — Acronyms & Terms

2DRT: Two-dimensional radiation therapy

3D-CPT: Three-dimensional conformal proton therapy

3D-CRT: Three-dimensional conformal radiation therapy

ADT: Androgen deprivation therapy

ASTRO: American Society for Radiation Oncology

Biochemical failure: Three successive post-treatment PSA increases of 10% or more as defined according to the American Society for Therapeutic and Radiology Oncology Consensus Conference criteria

bNED: Biochemical no evidence of disease

BT: Brachytherapy

CGE: Radiation units of measure—Cobalt Gray Equivalent (protons)

Conventional radiation—catch-all term of radiation types which includes 3D-CRT and often IMRT, but not protons (at present)

DVH: Dose-volume histogram

E: Stray radiation

EBRT: External beam radiation therapy

ED: Erectile dysfunction

EUD: Equivalent uniform dose

FOR: Fear of recurrence

FU: Follow-up

GI: Gastrointestinal

GTV: Gross tumor volume

GU: Genitourinary

Gy, Gye: Radiation units of measure—Gray (photons)

IMPT: Intensity modulated proton therapy

IMRT: Intensity modulated radiation therapy

Integral dose: Volume of irradiated normal, or non-target, tissue

LLUMC: Loma Linda University Medical Center

MGH: Massachusetts General Hospital

OARs: Organs at risk

PBR: Proton beam radiation (various acronyms used)

PBT: Proton beam therapy

PT: Proton therapy

Photon or x-ray: Generally interchangeable terms which include 3D-CRT & IMRT

PSA: Prostate-specific antigen (value typically determined by blood test)

PSR: Peer Specialty Review, physician review

PTV: Planning target volume

RP: Radical prostatectomy

RT: Radiation therapy

RTOG: Radiation Therapy Oncology Group rating system for morbidity severity

SMN: Secondary malignant neoplasm

X-ray: same as photon

Morbidity: Relating to side effects—typically GU, GI, ED

Toxicity: Relating to side effects—typically GU, GI, ED

V_n: Volume of tissue receiving "n" amount of Gy

Appendix 2 — Physician Letters

LOMA LINDA UNIVERSITY MEDICAL CENTER

DEPARTMENT OF RADIATION MEDICINE

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April 7, 2009

SUBJECT: Letter of Medical Necessity for Conformal Proton Beam Radiation for Treatment of Prostate Cancer

RE: Sanchez, Jose – MR #06197264

To Whom It May Concern:

[Insuree] is a gentleman who was recently diagnosed and treated for early stage adenocarcinoma of the prostate. The treatment options for such a case would be either radical surgery (to radical prostatectomy) radiation therapy. Long-term comparisons between the methods indicate that they give an essential equal chance of freedom from disease; with radiation therapy having a much lower incidence of engendering several complications then is seen with surgery.

[Insuree] chose treatment for his cancer with conformal proton beam radiation therapy. This is a form of external beam radiation, which utilizes protons, as opposed to x-rays, to deliver high dose precision radiation therapy to the prostate. The benefits of high dose treatment include improvement in biochemical freedom from relapse as compared with lower doses of radiation therapy, while the precision by which protons can be delivered has been shown to reduce the incidence of significant acute and late treatment-related complications as compared with x-ray therapy. Some additional background information regarding the use of conformal proton beam radiation therapy in the treatment of prostate cancer is given below.

The two currently available forms of potentially curative treatment for organ-confined prostate are either definitive radiation therapy or radical prostatectomy[4, 5, 6, 7]. There have been multiple retrospective trials performed over the last 20 years comparing these two modalities with comparisons beginning in the "pre" PSA era and continuing into the era of PSA determination. To date, the preponderance of retrospective evidence indicates that definitive radiation therapy and radical prostatectomy give essentially equivalent local disease control and overall survival. This contention is backed up by consensus statements from the National Institutes of Health and National Cancer Institute[6,7]. The primary difference between the two modalities are the potential

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complications which are associated with each procedure, and it is the responsible physician's duty to present the pros and cons of either procedure to a patient and let him decide which procedure He wishes to undergo based upon his personal preference and desires in terms of maintaining quality of life.

The "modern era" of definitive radiation therapy for prostate cancer began in the mid 1950's with the pioneering work of Dr. Bagshaw at Stanford University Medical Center. The advent of Cobalt 60 treatment units allowed for the first time delivery of reasonable radiation doses to the prostate while at the same time not delivering inordinate amounts of radiation to surrounding organs. In fact, it has been this desire to reduce the amount of radiation given to normal tissue which has been the impetus for every significant advancement in radiation therapy since its inception in 1895[2]. As megavoltage linear accelerators became widely available in the late 1970s and early 1980s, further reductions in normal tissue dose were made possible by the superior dose deposition characteristics of these high energy beams as compared to Cobalt 60 gamma rays. The linear accelerator has become widely accepted as a method of delivering external beam treatment for prostate cancer solely because it reduces the dose of radiation given to normal tissue, not because it is "superior" at curing prostate cancer as compared to its Cobalt 60 predecessor[2, 10, 12]. In fact, there has never been a randomized trial performed that demonstrates an improvement in local disease control between Cobalt 60 photons and the megavoltage photons produced by a linear accelerator. This is an important point to keep in mind when considering a discussion of the merits of conformal external beam radiation therapy delivered with proton beams.

The utility of proton beam radiation in treating deep seated tumors was recognized by Dr. Robert Wilson of the Lawrence Berkley Laboratory in the mid 1940s, and the concept was first published by him in the Journal of Radiology in July 1946[1]. Protons differ from x-rays of any energy solely in their dose deposition[1, 2, 11, 13, 14, 16]. Since the proton is a relatively heavy charged particle, it interacts with human tissue in a fashion different than that of an x-ray. Specifically, a proton beam has a relatively low entrance dose, a well-defined high dose region (known as the Bragg peak) and no exit dose. This is in contrast to x-rays of any energy, which have a high dose point usually within 2-3 cm of the skin surface, and exponential decay of dose through and beyond the target volume. The radiobiological effects of protons in their high dose region (Bragg peak) and megavoltage photons are essentially identical[1, 2]. In other words, a dose of 7000 rad of proton will have an identical effect on a tumor of any particular type as is seen with 7000 rad of x-ray. This equivalence was established by radiobiological experiments, which took place in the early 1950s and has been confirmed in numerous experimental studies and in over 15,000 patient treatments to date. However, since the proton beam Bragg peak is so tightly defined, the dose of radiation given to surrounding normal tissue is reduced by several orders of magnitude as compared with megavoltage x-rays[1, 2, 11, 13, 14, 16]. It is this reduction of normal tissue dose with its attendant decrease in the potential for acute and long-term complications that make protons an ideal modality for treating a deep-seated tumor. This is analogous to the aforementioned development of linear accelerators for treating deep tumors, but the normal tissue dose is reduced by a factor of 50-250% (as compared to Cobalt 60) when protons are used as compared to only 10-15% when a linear accelerator is used[1, 2].

The benefits in term of reduction in acute and late complications and in terms of clinical and biochemical disease control, of conformal radiation therapy techniques has been well established in the medical literature[4, 5, 7, 9, 10]. In locally advanced prostate cancer, the results of a phase III randomized trial between "standard" non-conformal x-ray and x-ray followed by a conformal proton beam boost demonstrate an improvement in local disease control in those patients whom had high grade prostatic tumors[13, 14]. In early prostate cancer the results are much more striking with single institution reports from the Memorial Sloan Kettering Cancer Center, the Fox Chase Cancer Center, and Loma Linda University Medical Center, demonstrating improvements in local disease control and significant reductions in acute and long term morbidity when conformal radiation approaches are performed[4, 5, 14]. Our data on 645 gentlemen treated with conformal proton beam radiotherapy at LLUMC between December, 1991 and December, 1995 demonstrates an equivalent biochemical freedom from relapse rate at five years to similar (stratified by pre-treatment PSA) patients treated with Radical Prostatectomy, and a lower incidence of moderate to severe bladder and rectal toxicity than is reported when conformal x-ray therapy alone is administered to equivalent total radiation
doses[11, 14]. A similar experience is seen in the Brachytherapy literature in which temporary or permanent interstitial radiation sources are placed within the prostate gland to give a conformal radiation boost to the prostate. It is notable that all the above approaches (with the exclusion of the Massachusetts General Hospital conformal proton beam study) utilized either complex multiple megavoltage x-ray beams planned and delivered by computer or invasive procedures where Brachytherapy sources are placed within the body to achieve a conformal radiation dose. These complex arrangements are necessary because an x-ray beam cannot be stopped at some point within the patient's body and inevitably gives radiation beyond the prostatic target. In contrast, a dose distribution superior to any conformal x-ray or interstitial Brachytherapy plan can be achieved by a relatively simple 2-3 field conformal proton beam technique which is simpler and in many cases less expensive to plan and deliver than a laborious multi-field external beam x-ray or interstitial Brachytherapy techniques.

The National Cancer Institute has reviewed data from the Loma Linda University Medical Center and the Massachusetts General Hospital regarding the use of proton beam radiation in the treatment of localized prostate cancer. As a result of this review, the NCI is currently sponsoring a phase III dose randomization trial designed to determine whether or not there is any additional benefit to further dose escalation via conformal radiation technique[15]. In other words, the purpose of this study is simply to determine the optimum dose of radiation for organ-confined prostate cancer. It is <u>not</u> a study to determine efficacy of treatment as this has already been determined by prior published phase I and phase II trials. The "standard" external beam treatment regimen in this trial is a combination of conformal proton beam boost plus conformal x-rays to a dose of 7020 cGy. The "investigational" arm of this trial is the same treatment given to a total dose of 7920 cGy. The inclusion of a conformal proton beam "boost" in the "standard" arm of this trial is Prima Facie evidence that, in the opinion of the NCI, conformal proton radiation is considered a standard form of treatment of early prostate cancer. This logically follows from the well established fact that protons and x-rays are radiobiologically equivalent in

their high dose region and that the advantage to using conformal proton radiation lies in its superior ability to reduce normal tissue radiation dose as compared with an x-ray beam[17].

In summation the development of new radiation modalities and new treatment delivery methods to reduce normal tissue dose is a hallmark of all significant advances in radiation oncology[1, 2, 11]. The benefit of conformal treatment technique has been well established in both early and locally advanced prostate cancer. Proton beams represent the "ultimate" form of conformal treatment delivery because of their superior dose deposition characteristics. Since their radiobiologic properties are virtually identical to those to high energy x-rays they can be prescribed and administered in a fashion identical to that of x-ray therapy without having the attendant high normal tissue doses inevitably delivered with conventional x-ray therapy. The NCI has included a conformal proton beam boost in the "standard of care" arm of a current phase III trial for treatment of early prostate cancer. Published data from the Massachusetts General Hospital and from LLUMC demonstrate that conformal proton beam boosts can be given with minimal and acceptable acute and long term morbidity, particularly when techniques are utilized which minimize the radiation dose given to the anterior rectal wall[3, 13, 14, 16, 17]. The efficacy of conformal proton beam radiation in treating localized cancer of any type has been demonstrated in over 15,000 patients since the mid 1950s[1, 2, 13, 14, 16].

I would be happy to answer any questions you might have regarding the above and I can be reached at (909) 558-4280.

Sincerely,

David A. Bush, M.D.
Department of Radiation Medicine

DAB/uhh

References:

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All

Fax:

Physicians Medical Center
254 NE Norton Lane
McMinnville Oregon 97128
(503)472-6161
(503)434-6290 fax

March 20, 2009

To Whom it may concern,

I have recommened that [Insuree] complete Proton Radiation Therapy by David A Bush, MD in Loma Linda, CA.

I believe this to be medically necessary in his treatment of prostate cancer. If you have any questions, I can be reached at 503-472-6161

Stephen B. Inkeles, MD

Appendix 3 — Additional Proton Descriptions

From an article by Metz:

> 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. [hh]

Appendix 4 — The Ethical Issue of Proton/Photon RCTs

In an article from the BOB Tales July, 2009 newsletter,[ww] Bob Marckini included an excerpt from a letter by **Ruthita Fike**, CEO of LLUMC, to the Center for Medicare and Medicaid Services discussing the issues with performing proton randomized trials:

> There are several reasons why there have not 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. (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. (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)
>
> The latter opinion arises 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. Hence, 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, among other things, that human research subjects are not harmed. (45 C.F.R. § 46.116) 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, if not impossible, to find patients willing to participate in such a study and to find an institutional review board willing to approve such an experiment. (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)
>
> 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, one presumes, that IMRT is merely 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 eliminate Medicare coverage for either IMRT or PBT. Both technologies are still maturing.

Appendix 5 — Other Insurance Coverers

Information on this page was kindly provided by Bob Marckini who maintains the Brotherhood of the Balloon (protonbob.com) informational website:

INSURANCE PLANS THAT HAVE APPROVED PROTON BEAM THERAPY (PBT):

AARP
Aetna
Aetna US HealthCare
AFLAC
Aid Ass'n for Lutherans
Alberta Blue Cross
Alberta Government Health Plan
Amer. Family
American Association of Lutherans
American Medical Security
American National, Galveston
Anthem BC/BS
Anthem Blue Cross / Blue Shield of Indiana
Bankers Life
Benefit Assistance
BC/BS
Blue Cross / Blue Shield of Alabama
Blue Cross / Blue Shield of California
Blue Cross / Blue Shield of CO
BC/BS Federal Employees
BC/BS of Florida
BCBS Iowa
BCBS of Illinois
Blue Cross of Louisiana
CARE FIRST Maryland Blue Cross / Blue Shield
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
California Care
CHAMPUS (now TRICARE)
Christian Fidelity Life Ins. Co.
CIGNA
Cityhss
Continental
Country Life
Delta Pilots Medical Plan
Empire Blue Cross/Blue Shield
Equitable Life & Casualty
Firefighters Local
First Choice
Freedom Life
G.I.C. (Unicare)
GEHA
German DKV
GHI
Golden Rule
Government Employees Hospital Assoc.
Government of Ontario CA
Great West
Group Health Co-op
Group Health Co-op of Puget Sound
Harrington Benefits
Hartford
HCF
Health Net
Health Partners
Healthspring
Heritage Health Plans PPO
Horizon Blue Cross / Blue Shield
Humana W. of KY
KPS Business Basic
Lifewise
Lifewise Health Plan of Washington
Loma Linda Medical Group
Mail Handlers
MDIPA
Med Care
Medica
Medica Choice MN
Medicaid
Medi-Cal
Medical Mutual
Medical Mutual of Ohio
Medicare
Montana Unified School Trust
Monumental
Mutual of Omaha
Nat. Auto. Sprinkler
National States
Nationwide
Nevada Care
N. Tex Healthcare
ODS Health Plan
ODS Of Oregon
Officers Union
P.E.R.S. Care
PacifiCare
Partners
PEEHIP of Alabama BC/BS
PEIA Acordia
Physicians Mutual
Primecare for Life
Pioneer Life
Premara Blue Cross
Presbyterian Senior Health Care
Prudential
Regence BlueShield of Idaho
Regence Blue Cross / Blue Shield of Oregon
Regency Blue Shield
Rio Grande Employees Hospital Assn.
Risk Management
Rocky Mountain HMO
SAG
Scott & White Health Plan
Secure Horizons
Starmark
Sterling Option 1
TRICARE (Military health plan, formerly CHAMPUS)
Trigon (Now Anthem Blue Cross and Blue Shield)
TROA Mediplus
TRS Care
Tufts HMO
Unicare
Uniform (WA state)
Union Pacific Emp. Health Assoc.
United American
United Health Care
Univera
UPREHS
USAA
Value Health
Wausaw
Zuric

BlueCross BlueShield
of Illinois
A Division of Health Care Service Corporation, a Mutual Legal Reserve Company, an Independent Licensee of the Blue Cross and Blue Shield Association

P.O. Box 1364
Chicago, IL 60690-1364

June 1, 2009

Luke Warner Mizell
1624 Banks St.
Houston, TX 77006

Re: Health Care Service Corporation (HCSC) Medical Policy on proton beam therapy for prostate cancer.

Dear Mr. Mizell:

Thank you for your letter of 05/16/09, regarding the proposed change in the HCSC medical policy relating to the use of proton beam therapy for treatment of prostate cancer.

HCSC has established a committee of medical directors to review HCSC's medical policy. The Medical Policy Medical Directors (MPMD), as the committee is called, reviews HCSC's medical policies on a periodic basis. The MPMD represent the Blue Cross and Blue Shield Plans of Texas, Illinois, New Mexico and Oklahoma. The medical policies are based on research that provides evidence of scientific merit for a particular medical technology. Technology determinations used in medical policies are based in part on criteria developed by the Blue Cross Blue Shield Association's Technology Evaluation Center (TEC). They are also based on data from the peer-reviewed scientific literature, from criteria developed by specialty societies and from guidelines adopted by other health care organizations. Medical policies are used as guidelines for coverage determinations in health care benefit programs, unless otherwise indicated. It is important to note that medical policies are not a guarantee of benefit coverage under any particular health benefit plan. In the event of a conflict between the medical policy and the terms of the member's health benefit plan, the terms of the benefit plan will govern.

The MPMD has undertaken another review of the use of proton beam therapy for the treatment of prostate cancer. Based upon that review the committee has concluded that although the evidence supporting proton beam therapy for prostate cancer is still emerging, it is sufficient to justify making no change in the HCSC coverage position at this time. The current policy (THE801.023) will remain in force and prostate cancer will remain an approved indication for proton beam therapy.
Thank you once again for sharing your interest in HCSC and its medical policies.

Sincerely,

Paul B Handel, M.D.
Senior Vice President, Chief Medical Officer
Health Care Service Corporation

Appendix 6 — Two Randomized Controlled Trials

(See section on Biochemical Failure.)

Rossi described the LLUMC/MGH trial, calling it a success in terms of increased bNED survival while holding the line on morbidity:

> …a multi-institutional [LLUMC and MGH], phase III, prospective, randomized trial (the Proton Radiation Oncology Group [PROG] 95-09 study), which was designed to test the hypothesis that dose escalation from 70.2 to 79.2 Gy via conformal proton beam therapy would result in a demonstrable difference in bNED survival without engendering unacceptable morbidity. Between 1996 and 2000, 393 patients were randomized at the two institutions, and these patients have been followed for a mean of 5 years. To date, the published data have completely validated the underlying hypothesis…dose escalation has resulted in approximately a 20%–30% improvement in 5-year bNED survival. Increased bNED survival was seen even among patients at low risk…The employment of such highly conformal techniques resulted in no significant difference in late gastrointestinal or genitourinary morbidity between the two arms…[g]

Actual results are impressive showing more than a 50% improvement in the risk of failure in the high-dose arm:

> The proportions of men free from biochemical failure at 5 years were 78.8%…for conventional-dose and 91.3%…for high-dose therapy (P<.001), a 59% reduction in the risk of failure.[t]

Talcott et al. confirmed, in a long-term survey, no difference in patient-perceived morbidities between the low and high-dose arms of the trial:

> We attempted to survey all surviving patients using the validated Prostate Cancer Symptom Indexes (PCSI), which measures urinary, bowel and sexual dysfunction… We found no differences in mean scale scores for urinary incontinence and obstruction/irritation, bowel problems and sexual dysfunction… These patient-reported results, the most sensitive indicator of treatment-related toxicity, indicate that increased doses of highly conformal radiation therapy sufficient to improve the control of clinically localized prostate cancer do not cause significantly increased morbidity.[s]

Appendix 7 — Low and Medium Dose Volume Reduction Relationship to Lowered GI Morbidity

Studies are noting a correlation between protons' lower volume of non-target tissue radiated in the low and medium dose range and rectal health. A planning study comparing protons to photons by Mock et.al.[v] found significant dose reductions with protons to OARs over 3D-CRT and IMRT and discussed the relationship of reduced medium-dose range, in particular, to rectal bleeding:

> …the present, as well as other studies, have shown that improvements in dose delivery to OARs can be achieved with this treatment option [19]. The main advantage of proton beams compared to photon beams is in the significant reduction in the low to medium dose range for all analyzed non-target tissue types. Consequently, proton-based-treatment-planning techniques showed mean dose reductions almost in all analyzed OARs…v
>
> …the clinical relevance of intermediate dose levels is also supported by several studies. In the results published by Fiorino et al. [10], the incidence of late rectal bleeding was significantly correlated with the percentage of rectal volume receiving dose levels >50-65 Gy but not in the dose region between 70-75 Gy. Jackson et al. [16] compared rectal wall DVHs of bleeding versus nonbleeding patients and found the largest difference in the DVH shape in the 40- to 50Gy region, while relatively small differences were found in the high dose region between 70-75 Gy. Skwarchuk et al. [30] analyzed dosimetric parameters associated with late rectal toxicity > grade 2 and found the following factors to be predictive of rectal bleeding: small rectal volumes, maximum dose to the rectal wall and enclosure of the outer rectal contour by the 50% isodose line. These results show that even doses < 50 Gy may have an impact on the risk of developing treatment-related side effects. Within this context proton plans clearly show an advantage over both the conformal and the IMRT photon plans. [v] [Emphasis added.]

Indeed, Mock's conclusion seems to be borne out in the Japanese study of acute morbidity by Mayahara et al. [gg] which found only 2% of proton patients developed acute Grade 1 GI symptoms. There were no instances of higher acute GI grades exhibited. This is in sharp contrast to the Lips et al. comparisons of 3D-CRT and IMRT acute GI results.[cc] (See the section on GU and GI morbidity.) Mayahara suggested the non-target tissue-sparing benefits of protons was relevant:

> [Mock] concluded that main advantage of proton therapy is the significant reduction in the low to medium dose range of the rectum and bladder compared with 3D-CRT and IMRT (46). The clinical importance of intermediate dose levels has been reported by several analyses of late rectal toxicity. Fiorino et al. (47) found that the incidence of late rectal bleeding correlated significantly with the percentage of rectal volume receiving dose levels of 50-65 Gy. Jackson et el. (48) showed that the volumes of the rectum receiving intermediate doses (40-50 Gy) could play a role in predicting rectal complications. They speculated that when high-dose regions are surrounded by extensive volumes receiving intermediate doses, the ability to aid in the repair of central injury could be inhibited (the so-called dose-bath effect) (48). The low incidence of acute GI morbidity with proton therapy could also be explained by the reduction on the volume of the rectum receiving a low to medium dose range. [gg]

Note: A moderate increase in rectal bleeding was found in the two RCTs previously mentioned.[p,x] However, Olsen et al. [f] addressed this in a review suggesting it was the result of positioning of a small portion of patients which did not take advantage of the Bragg peak for rectal shielding.

Appendix 8 — Proton's Superior Dose Distribution

A review by Olsen et al summed up protons' potential benefit in reducing secondary malignancies:

> A number of treatment plan comparison studies have demonstrated that proton irradiation offers a far better conformality as compared to conventional and other conformal irradiation techniques [2-6]…Results from dose-planning proton therapy studies have raised the question as to whether the improved dose confinement in proton therapy may reduce the risk of secondary malignancies. In contrast to photon intensity-modulated-radiation-therapy (IMRT), where large volumes of healthy tissue are irradiated, proton irradiation is associated with smaller irradiated volumes of normal tissues [2-8] [f]

A dose-volume plan comparison by Vargas, et al., between protons and IMRT found mean proton dose reductions of 59% and 35% for rectal and bladder, respectively, over IMRT. "Compared with IMRT, proton therapy reduced the dose to the dose-limiting normal structures while maintaining excellent planning target volume coverage." [i]

> RESULTS: All rectal and rectal wall volumes treated to 10-80 GE (percentage of volume receiving 10-80 GE [V(10)-V(80)]) were significantly lower with proton therapy ($p < 0.05$). The rectal V(50) was reduced from 31.3% +/- 4.1% with IMRT to 14.6% +/- 3.0% with proton therapy for a relative improvement of 53.4% and an absolute benefit of 16.7% ($p < 0.001$). The mean rectal dose decreased 59% with proton therapy ($p < 0.001$). For the bladder and bladder wall, proton therapy produced significantly smaller volumes treated to doses of 10-35 GE ($p < 0.05$) with a nonsignificant advantage demonstrated for the volume receiving < or =60 GE. The bladder V(30) was reduced with proton therapy for a relative improvement of 35.3% and an absolute benefit of 15.1% ($p = 0.02$). The mean bladder dose decreased 35% with proton therapy ($p = 0.002$). CONCLUSION: Compared with IMRT, proton therapy reduced the dose to the dose-limiting normal structures while maintaining excellent planning target volume coverage.[i]

Mock, et.al. compared treatment plans between 3D-CRT, IMRT and proton therapy, finding "Both the 3-D conformal and the IMRT photon treatment technique resulted in increased mean doses (~ 40–80%) for OARs when compared to protons. With both photon techniques non-target tissue volumes were irradiated to higher doses (mean dose difference ≥ 70%) compared to proton-beam radiotherapy." [v]

From Levin: "In general, a set of proton fields achieves significant dose reduction to uninvolved normal tissues compared to a matched set of photons fields." [z]

From Smith:

> Many treatment planning studies have been published [10,11,12,13,14] all of which had the general conclusion that, when photon and proton treatment plans with comparable complexity are compared, protons provided superior dose distributions. …In particular, the integral dose in the proton treatment plans was two to three times less than the integral dose in the photon plans. [14] [e]

Appendix 9 — Reduced Morbidities

Tables from James Metz, MD: [hh]

Table 3. Acute complications associated with the treatment of prostate cancer [hh]

Acute Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostat-ectomy
≥ 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 [hh]

Chronic Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostat-ectomy
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

Appendix 10 — References

Some of these references might require membership to access. Please advise if I can be of assistance.

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