

Conformal proton beam radiation therapy for prostate cancer: concepts and clinical results

Carl J. Rossi, Jr., MD | Loma Linda University Medical Center, Loma Linda, CA

In contrast to x-rays, protons have a low entrance dose, a well-defined high-dose plateau ("Bragg peak"), and no exit dose beyond the target tissue. These properties make them ideal for treating localized cancers in areas surrounded by dose-limiting normal structures. Their routine use required the creation of dedicated medical treatment centers which have only been in existence since the early 1990s. Protons have been successfully used in dose-escalation studies of organ-confined prostate cancer, with a recently published prospective randomized trial demonstrating an approximately 25% improvement in biochemical disease-free survival in the high-dose (79.2 Gy) arm, without a significant increase in moderate-to-severe treatment-related morbidity. Long-term treatment results from nonrandomized trials also demonstrate biochemical disease-free rates equivalent to other forms of therapy with minimal morbidity. Impending technical advances in proton beam treatment delivery (active beam scanning) will further enhance the dosimetric advantages of this unique form of radiation therapy.

Effective radiation therapy for prostate cancer, like virtually all other solid tumors treated by irradiation, depends on two factors: the ability to deliver a tumoricidal dose of radiation to the tumor while limiting the radiation dose to levels that the adjacent normal tissue can withstand with an acceptable risk of morbidity.¹ These aims are often mutually exclusive, and the radiation dose that is actually administered is frequently a compromise between what we would like to give to the tumor and what the normal tissues can tolerate. The impetus for virtually every significant technical advance in radiation treatment has been to improve the therapeutic ratio, or the difference in radiation dose between the tumor and normal tissues. This goal was first articulated in the early 20th century, but its realization awaited the development of three-dimensional (3D) imaging and fast computers that allow the radiation oncologist to more fully exploit our technical ability to define the anatomic relationship between the tumor and surrounding normal tissue.²⁻⁶

Most current radiation therapy techniques use x-rays, or photons. Whether emitted by a source outside of the body (external beam irradiation) or by implanted radioisotopes, x-rays have the same general physical properties: They are massless, chargeless units of energy. The lack of both mass and charge causes x-rays to be relatively sparse-

ly attenuated by human tissue and, hence, allows them to pass through the body, which is what makes them a useful diagnostic tool. Unfortunately, this same property makes x-rays a less than optimal form of radiation for therapy. It is possible with modern x-ray therapy techniques (such as intensity-modulated radiation therapy [IMRT]) to "sculpt" the beam so that the high-dose area is well confined to the target. Nevertheless, whenever one uses x-rays for treatment, irrespective of the delivery system employed, one inevitably irradiates tissue beyond the tumor volume. This so-called dose bath encompasses a considerable volume of normal tissue, which receives a low to moderate radiation dose. Although this dose is often dismissed as being clinically unimportant, such a characterization flies in the face of radiobiologic data, which admits of no known "threshold" dose below which tissue injury does not occur. The fact that radiation oncologists have striven relentlessly to decrease the radiation dose to normal tissue also calls this characterization into question.^{7,8}

Manuscript received September 27, 2006; accepted January 4, 2007.

Correspondence to: Carl J. Rossi, Jr., MD, Associate Professor, Department of Radiation Medicine, Loma Linda University Medical Center, 11234 Anderson Street, Loma Linda, CA 92354; telephone: 909-558-4257; fax: 909-558-4083; e-mail: crossi@llurm.org.

Commun Oncol 2007;4:235-240 © 2007 Elsevier Inc. All rights reserved.

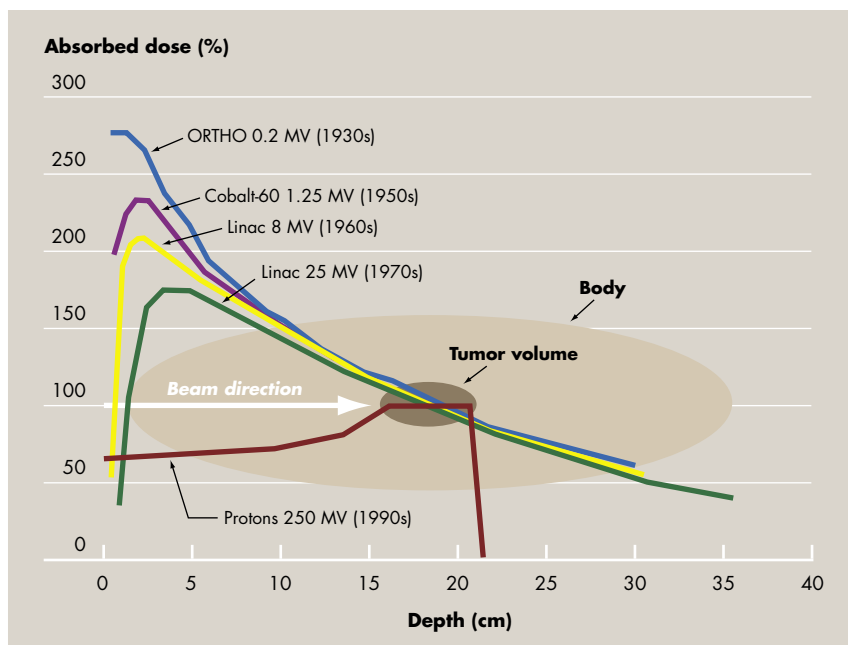


FIGURE 1 Dose distribution of protons versus x-rays.

Potential advantages of protons over photons

If one could devise a perfect radiation beam, therefore, it would deposit its entire dose in the target and deliver no radiation to the normal tissue. This is a physical impossibility with x-rays, but it can be approached with other forms of radiation, such as protons. Protons are relatively heavy, positively charged subatomic particles that are a component of the atomic nucleus. These properties are critically important because they change the way in which protons interact with human tissues. Unlike x-rays, protons stop within the body and therefore do not deliver any dose to tissues distal to the target area (Figure 1). In addition, the highest dose area of any proton beam is located not at a relatively shallow depth (as is the case with x-rays) but, rather, at the target itself. This phenomenon—named the Bragg peak after its discoverer—was one of the first major discoveries of modern high-energy physics.^{9–11}

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, and has the potential to produce a concomitant reduction in the risk of a normal tissue injury.^{14,15}

The potential advantages of protons over x-rays were first recognized by physicist Robert Wilson in his seminal 1946 paper,¹⁶ but for over 40 years their use was limited to physics laboratories that had the requisite synchrotron or cyclotron needed to accelerate protons to the extremely high velocities (approximately 50% to 60% of the speed of light) required for treatment in humans. The first proton beam treatment center designed from its inception as a medical treatment facility opened at Loma Linda University Medical Center (LLUMC) in 1990, with prostate cancer treatment commencing in October 1991.¹⁷ Currently, five clinical proton beam facilities treat prostate cancer in the

United States, and several additional centers are in either the construction or planning stage.

Before the clinical results of proton beam radiation therapy for prostate cancer are reviewed, one more crucial point must be made. Although the radiation doses given off by protons *outside* of the Bragg peak region are *far lower* than the doses emitted by x-rays, the biologic effects of protons on malignant (and normal) tissue *within* the Bragg peak region are essentially *identical* to the effects of x-rays.¹⁸ In other words, if a tumor receives a radiation dose of 80 Gy delivered with either protons or x-rays, the impact on the tumor cells will be identical; the only (and critically important) difference between the two modalities will be the dose delivered to the adjacent normal tissues. It also follows, therefore, that the expected tumor response to proton therapy will be similar to that achieved with x-rays. If the available data indicate that a given x-ray dose is effective in sterilizing a tumor, the identical proton dose will be equally effective.^{3,14}

Treatment planning and delivery

Proton beam radiation therapy for prostate cancer is an outpatient procedure. The extreme precision inherent in proton beams mandates that the patient be treated in a stable, reproducible position. The first step in the treatment planning process, therefore, is the fabrication of a customized full-body shell, or “pod,” which provides a stable frame of reference and minimizes patient movement. After the pod is constructed, it is used to encase the patient while he undergoes a thin-slice planning CT scan. The 3D data thus obtained are transferred to a dedicated planning system, wherein the prostate gland and critical adjacent normal structures are drawn on a slice-by-slice basis, and a series of tentative plans are created and analyzed with respect to tumor versus normal

tissue radiation dose. This planning involves the creation of patient-specific isodose plots, dose-volume histograms, and beam's-eye views.

The "typical" treatment plan consists of a left and right lateral beam pair, which allows maximal coverage of the prostate gland while delivering the minimal amount of radiation to the bladder and rectum (Figure 2). To further reduce the volume of these structures within the high-dose area, a water balloon is inserted into the patient's rectum prior to each treatment (and prior to the planning scan), and the patient is also encouraged to fill his bladder before each daily session. The computer planning system generates the data necessary to fabricate patient-specific apertures and tissue compensators (one set for every beam used). These devices are identified by unique bar codes, which must be verified before each treatment.

Immediately prior to each day's treatment, the patient's position is confirmed by first obtaining orthogonal radiographs, which are captured by an electronic portal imaging device and are electronically compared to a set of digitally reconstructed radiographs generated by the planning CT. A computer-based system then calculates what, if any, table movements are required to make the daily position correspond to the planning position; any such required movements are then made, and the patient is treated. Typically, 10 minutes is required for each session (including treatment). Since, in a multi-room facility, patients can be set up in several rooms simultaneously, a high-patient throughput (up to 150 patients per day) can be maintained.¹⁹

A typical course of proton beam radiation treatment lasts for 8–9 weeks. In general, patients' activities of daily living are unaffected by therapy, although common minor adverse effects include dysuria, nocturia, and urinary frequency and hesitancy. The most common late adverse effect is mild radiation proctitis, which occurs

in approximately 30% of patients. Radiation proctitis typically appears 9–12 months after treatment and continues intermittently (although it is often exacerbated by constipation) for up to 5 years post therapy.²⁰

Clinical results

Shipley and associates at Massachusetts General Hospital (MGH) were the first to use proton beam radiation therapy for prostate cancer, commencing in 1977. Utilizing an existing cyclotron at the nearby Harvard Cyclotron Laboratory, they initiated a phase I trial in which patients with clinical stage T3 and T4 tumors received a "boost" dose of protons directed at the prostate gland in conjunction with whole-pelvic x-ray therapy. The aim of the study was to deliver a higher dose of radiation to the gland than was possible with x-ray therapy alone, in the hope of improving local disease control.²¹

The success of this treatment (in terms of delivering the higher radiation dose safely) led to a subsequent randomized trial in which patients with advanced disease were randomly assigned to receive either 69 Gy of

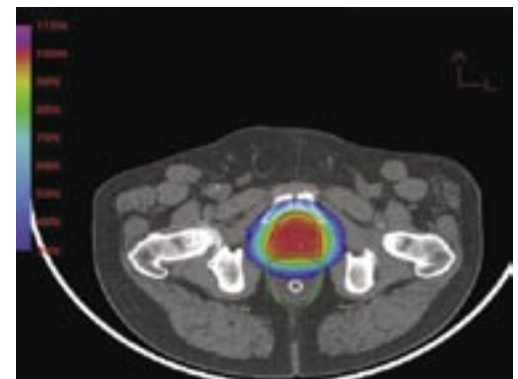


FIGURE 2 Conformal proton beam dose distribution.

x-ray therapy or 75.6 Gy given via a combination of x-rays and protons. (In this trial, conducted in the pre-prostate-specific antigen [PSA] era, advanced disease was defined as tumor which clinically or radiographically extended outside of the prostate gland to involve the seminal vesicles, bladder, or rectum. The study, reported in 1995, showed no survival advantage of high-dose therapy (nor, in retrospect, would one be expected in a subset of patients at such high risk of harboring micrometastatic disease at diagnosis).²² The study did, however, reveal a trend toward decreased

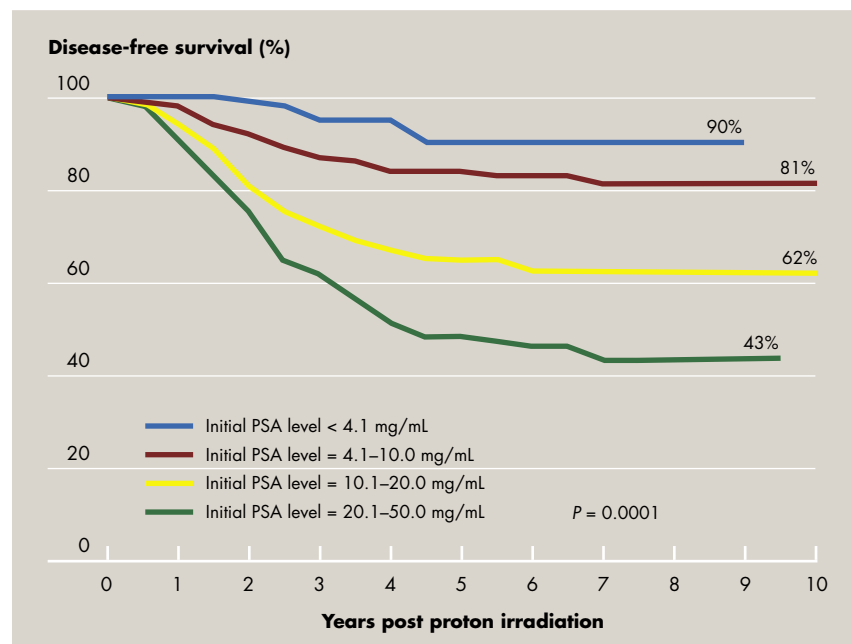


FIGURE 3 Effect of initial PSA level on 10-year disease-free survival rate. Adapted, with permission, from Shipley et al.²²

TABLE 1
Baseline characteristics of patients treated with proton beam therapy*

Characteristic	Number of patients
Stage	
1A/1B	35
1C	314
2A	291
2B	248
2C	283
3	50
Gleason score	
2-4	204
5-7	868
8-10	86
PSA level (mg/ml)	
≤ 4.0	106
4.1-10.0	606
10.1-20.0	339
> 20.0	133

PSA = prostate-specific antigen
* At Loma Linda University Medical Center from October 1994 to December 1997

local failure (assessed by post-treatment biopsy) in the high-dose treatment group, which reached statistical significance in patients with Gleason 8-10 tumors. Dose escalation was associated with an increased incidence of minor, self-limited RTOG (Radiation Therapy Oncology Group) grade 1 rectal bleeding, but moderate to severe rectal injury was extremely infrequent and was considered to be clinically acceptable.²²

The lack of a survival advantage seen in the high-dose arm of this trial has led some to erroneously conclude that protons are no better than x-rays. This perception reflects a misunderstanding of both the goals of this study and the radiobiologic properties of protons. The trial conducted by Shipley et al was *not* a study of protons versus x-rays; rather, it was a study of dose escalation in which protons were used to deliver the higher radiation dose. 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.

As mentioned above, physicians at the LLUMC began treating prostate cancer patients with protons in October 1991, and the results of this experience have been continuously updated. The most recent update, published in 2004,²³ involved 1,256 patients treated between October 1994 and December 1997. All of these patients received a total prostatic radiation dose of between 74 and 75 Gy, and none of them received adjuvant or neoadjuvant hormonal therapy or chemotherapy. Baseline characteristics of these patients are summarized in Table 1. The patients were assessed

weekly during treatment and at regular intervals thereafter. Biochemical disease-free survival and biochemical failure were defined according to the American Society for Therapeutic and Radiology Oncology Consensus Conference criteria; three successive > 10% increases in PSA level above a nadir value were considered evidence of biochemical failure. Acute and late treatment-related morbidity were graded according to the RTOG scoring system.

The results achieved with proton beam treatment at LLUMC are shown in Figure 3. Pretreatment Gleason score, PSA, and clinical stage were all statistically significant predictors of biochemical outcome.²³ A rough comparison of these data with surgical data from Johns Hopkins,²⁴ shown in Table 2, demonstrates that when patients are stratified by clinical stage and pretreatment PSA, the 10-year rates of biochemical no evidence of disease (bNED) survival achieved with surgery and proton beam therapy are essentially equal. Proton beam treatment was extremely well tolerated; the incidence of RTOG grade 3 or higher gastrointestinal or genitourinary morbidity was < 1%.

These favorable results from both

TABLE 2
Ten-year disease-free survival rates in patients with stage T1-T2 prostate cancer: proton beam therapy versus surgery

Pretreatment PSA level (ng/mL)	Radical prostatectomy at Johns Hopkins ²³ (n = 2,123)	Proton beam therapy (74-75 Gy) at LLUMC ²² (n = 1,102)
≤ 4.0	91%	92%
4.1-10.0	79%	81%
10.1-20.0	57%	64%
> 20.0	48%	53%

PSA = prostate-specific antigen; LLUMC = Loma Linda University Medical Center

TABLE 3
Late morbidity rates: Proton Radiation Oncology Group 95-09 trial

Assigned dose: RTOG toxicity grade:	70.2 Gy				79.2 Gy			
	1	2	3	4	1	2	3	4
Genitourinary toxicity	43%	18%	2%	0%	43%	20%	1%	0%
Gastrointestinal toxicity	36%	8%	1%	0%	43%	17%	1%	0%

RTOG = Radiation Therapy Oncology Group

LLUMC and MGH led to the initiation of a multi-institutional, 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. As shown in Figure 4, 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 (defined as a PSA level < 10 ng/mL, Gleason score ≤ 6, and stage T1c–T2a), who, by virtue of their potentially low disease burden, were felt by some not to require dose escalation. The employment of such highly conformal techniques resulted in no significant difference in late gastrointestinal or genitourinary morbidity between the two arms (Table 3).²⁵ The favorable outcomes achieved with high-dose therapy in this trial have led to its implementation as the current “standard” treatment for organ-confined prostate cancer at LLUMC, and similar equivalent radiation doses are being delivered at the other active proton therapy centers.

The improvement in bNED survival and lack of severe morbidity have raised the obvious question, would even higher doses achieve better results? In an attempt to answer this question, investigators at LLUMC and MGH initiated the American College of Radiology (ACR) trial, a phase II dose-escalation study up to a total radiation dose of 82 Gy. This trial closed to patient accrual in March 2006. Although it is too early to report any preliminary findings in

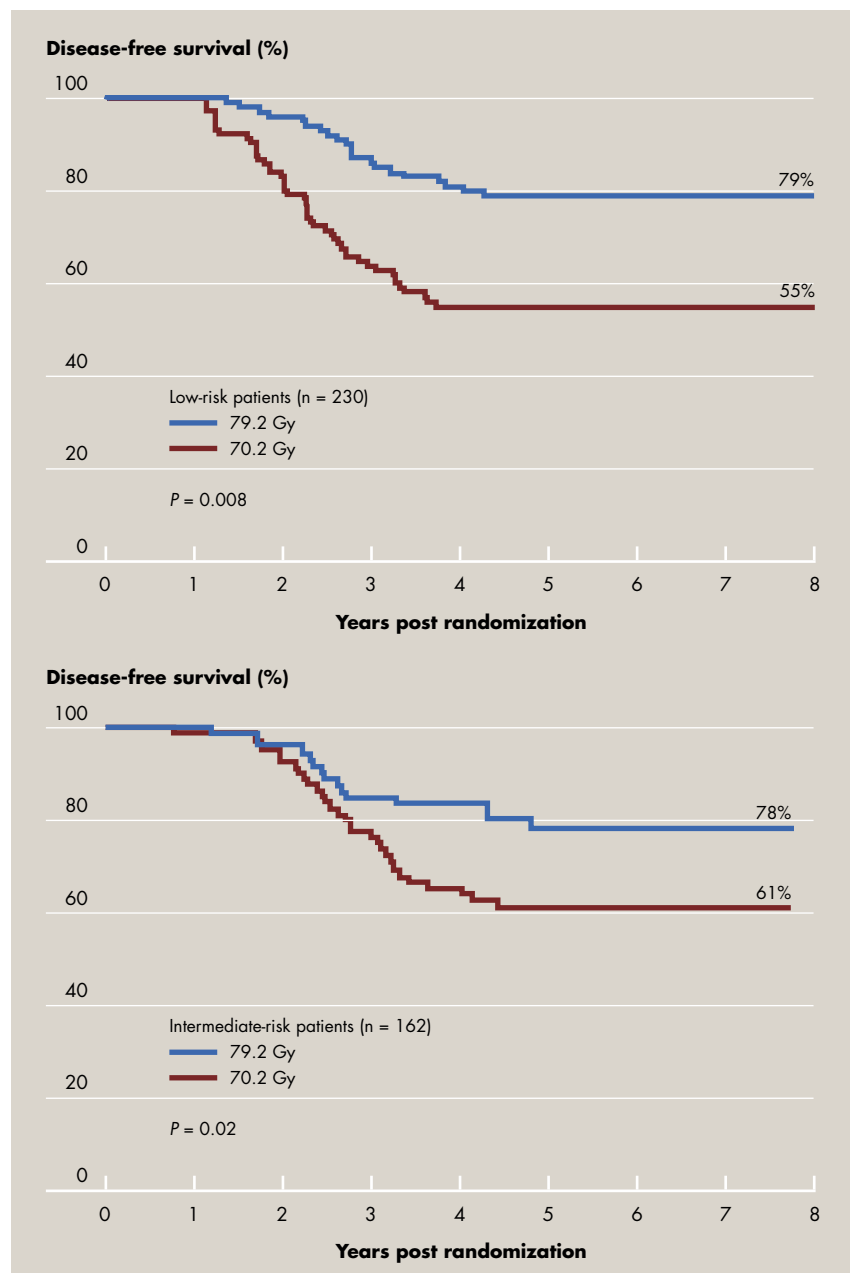


FIGURE 4 Proton Radiation Oncology Group 95-09 study: freedom from biochemical failure, as defined according to American Society for Therapeutic and Radiology Oncology Consensus Conference criteria. Low risk was defined as a prostate-specific antigen (PSA) level < 10 ng/mL, Gleason score ≤ 6, and stage T1c–T2a; intermediate risk was defined as a PSA level ≥ 10 ng/mL, Gleason score > 6, or stage T2b. Adapted, with permission, from Zielman et al.²⁵

terms of biochemical disease control or overall morbidity, acutely the treatment has been well tolerated.

Conclusion

Conformal proton beam therapy has clearly been shown to be a safe and ef-

fective treatment for prostate cancer. The unique physical properties of the proton beam allow for marked reductions in normal tissue radiation dose as compared with x-ray-based therapy and make further dose escalation feasible. The development and construc-

tion of dedicated medical treatment facilities have enabled this modality to progress from a laboratory curiosity to a mainstream therapy. The technology continues to evolve, with one development, active beam scanning, promising even further reductions in normal tissue radiation dose than are currently possible.²⁶ The available data support the routine use of conformal proton beam therapy in the treatment of patients with prostate cancer. As additional facilities become operational, an ever larger number of patients will be able to take advantage of this unique and precise form of noninvasive treatment.

References

- Rossi CJ Jr, Slater JD, Reves-Molyneux N, et al. Particle beam radiation therapy in prostate cancer: is there an advantage? *Semin Radiat Oncol* 1998;8:115-123.
- Suit HD, Goitein M. Dose-limiting tissues in relation to types and location of tumors: implications for efforts to improve radiation dose distributions. *Eur J Cancer* 1974;10:217-224.
- Austin-Seymour M, Urie M, Munzenrider J, et al. Considerations in fractionated proton radiation therapy: clinical potential and results. *Radiat Oncol* 1990;7:29-35.
- Suit HD, Goitein M, Munzenrider J, et al. Increased efficacy of radiation therapy by use of proton beam. *Strahlenther Onkol* 1990;166:40-44.
- Suit HD. Potential clinical gains by use of superior radiation dose distribution. NCI Proton Workshop. *Int J Radiat Oncol Biol Phys* 1992;22:233-234.
- Hanks GE, Leibel SA, Krall JM, Kramer S. Patterns of care studies: dose-response observations for local control of adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1985;11:153-157.
- Brenner DJ, Hall EJ, Curtis RE, Ron E. Prostate radiotherapy is associated with second cancers in many organs, not just the colorectum. *Gastroenterology* 2005;129:773-774; author's reply: 774-775.
- Fowler JF. What can we expect from dose escalation using proton beams? *Clin Oncol (R Coll Radiol)* 2003;15:S10-S15.
- Johansson B, Ridderheim M, Glimelius B. The potential of proton beam radiation therapy in prostate cancer, other urological cancers and gynaecological cancers. *Acta Oncol* 2005;44:890-895.
- Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol* 2005;44:850-861.
- Schulte RW, Slater JD, Rossi CJ Jr, Slater JM. Value and perspectives of proton radiation therapy for limited stage prostate cancer. *Strahlenther Onkol* 2000;176:3-8.
- Mock U, Bogner J, Georg D, Auberger T, Potter R. Comparative treatment planning on localized prostate carcinoma conformal photon- versus proton-based radiotherapy. *Strahlenther Onkol* 2005;181:448-455.
- Loeffler JS, Smith AR, Suit HD. The potential role of proton beams in radiation oncology. *Semin Oncol* 1997;24:686-695.
- Suit H, Goldberg S, Niemierko A, et al. Proton beams to replace photon beams in radical dose treatments. *Acta Oncol* 2003;42:800-808.
- Suit HD. Protons to replace photons in external beam radiation therapy? *Clin Oncol (R Coll Radiol)* 2003;15:S29-S31.
- Wilson RR. Radiological use of fast protons. *Radiology* 1946;47:487-491.
- Yonemoto LT, Slater JD, Rossi CJ Jr, et al. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. *Int J Radiat Oncol Biol Phys* 1997;37:21-29.
- Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002;53:407-421.
- Rossi CJ. Conformal proton beam therapy of prostate cancer—update on the Loma Linda University Medical Center experience. *Strahlenther Onkol* 1999;175(suppl 2):82-84.
- Slater JD, Yonemoto LT, Rossi CJ Jr, et al. Conformal proton therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1998;42:299-304.
- Shibley WU, Tepper JE, Prout GR Jr, et al. Proton radiation as boost therapy for localized prostatic carcinoma. *JAMA* 1979;241:1912-1915.
- Shibley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys* 1995;32:3-12.
- Slater JD, Rossi CJ Jr, Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys* 2004;59:348-352.
- Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28:555-565.
- Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294:1233-1239.
- Cella L, Lomax A, Miralbell R. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;49:217-223.

ABOUT THE AUTHOR

Affiliation: Dr. Rossi is Associate Professor, Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA.

Conflicts of interest: None disclosed.