External Beam Radiation and Proton Therapy for Prostate Cancer

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Introduction

External beam radiation and proton beam radiation have been used since the late 1960s to treat prostate cancer.[1] Because of improvements in both technologies they are now considered acceptable options for patients who are looking for an almost entirely non-invasive approach to their cancer. For reasons related to medical economics, external beam radiation facilities are far more common than proton therapy centers, of the order of 1,000 to one. Technology related to improvements in external beam delivery has progressed faster in the realm of adaptive image guided treatment, computer modulation and optimization of the radiation beam.

History

Soon after the discovery of radioactive substances in the late 1800s physicians in the US and Europe worked to apply the new radioactive technology to cancers that were near the patient's surface such as skin cancers and breast cancer. In a little known case from the US, Hugh Hampton Young, the former chairman of the Johns Hopkins Medical School and the urologist who is most credited with being the father of the prostatectomy, used a rod of highly refined radium applied transrectally to the posterior prostate to make large, symptomatic and incurable prostate tumors shrink during several applications. (See Figure 1) Well before the modern understanding of DNA and cellular biology, Dr. Young in 1916 learned through experience on many patients that he needed to give his total radiation dose of many applications or fractions, in order to lower the incidence of side effects.[3-5]

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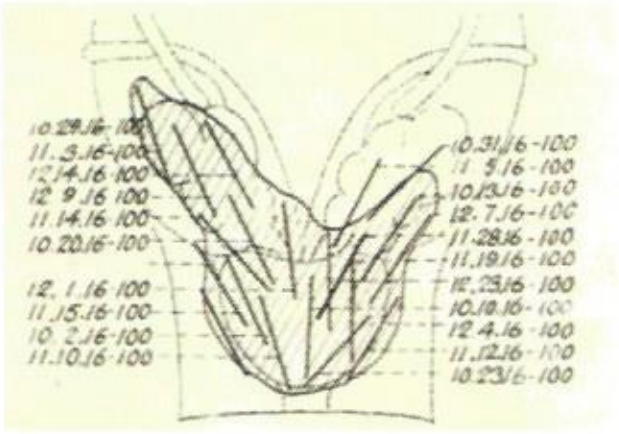
Figure 1.
A diagram of a transrectal treatment using refined radium to treat the prostate by Hugh Hampton Young in JAMA 1916.



Evolutions of Technology

The advance in radiation oncology that has propelled the field to the forefront of prostate oncology came in the 1950s when thoughtful clinicians at the Stanford Medical School and London's Hammersmith Hospital turned their interest to nuclear physics and their research accelerator facilities. By close collaboration, these research accelerators were turned toward human tumors and the ability to cure deep seated cancers was discovered. (Figure 2) During the 1960s Varian Associates, now Varian Medical Systems (Palo Alto, CA), developed and successfully commercialized the medical linear accelerator which has become an essential tool in the care of most cancer patients. The modern linear accelerator now has the ability to treat in several different energies of both photon and electron particles. The treatments are now delivered using dynamic radiation beams that can modulate the energy/penetrance of the beam from multiple angles or even through a dynamic moving arc of radiation. Additionally, the modern linear accelerator now fully integrates advanced CT imaging technology in real time to verify that the prostate is being precisely located before and during the treatment. In terms of numbers, there are several thousand linear accelerators in use throughout the world and a multiplicity of venders. Amongst all cancer patients, approximately 60 percent will require radiation therapy as a component of their care; among prostate tumor, especially the life threatening high risk cancers,

Figure 2.
Henry Kaplan at Stanford University standing next to an early model linear accelerator in 1950. Attribution to the NCI image library (www.cancer.gov) 2014.

radiation therapy has become the standard modality of treatment either after an attempted total resection of the prostate gland or as a standalone definitive treatment. (Figure 3)

Radiobiology and its Clinical Implications:

Radiation therapy produced by a beam has a well-known mechanism of action. Whether it is a photon, electron, proton or neutron the accelerated particle produces numerous DNA injuries when it interacts with DNA. Because of the ubiquity of photon radiation, its biophysical chemistry is well-described. A typical NCCN recommended course of radiation for prostate cancer advises that the gland receive a radiation dose in excess of 80 Gray (Gy). Historically that dose has been very well tolerated dose rate of between 1.8 Gy and 2.0 Gy a day. We have understood

Figure 3.
Adapted from the treatment algorithm for High and Very High Risk Prostate Cancer from NCCN Version 2.2014.

High Risk – T3a or Gleason 8-10 or PSA >20	
Initial Therapy –	Radiation Therapy+Androgen Deprivation (2-3 years)(category 1)
Initial Therapy –	Radical Prostatectomy + Pelvic Lymph Node Dissection followed by radiation therapy for adverse features
Very High Risk – T3b or T4	
Initial Therapy –	Radiation Therapy+Androgen Deprivation (2-3 years)(category 1)
Initial Therapy –	Radical Prostatectomy and Pelvic Lymph Node Dissection in patients without fixation followed by radiation therapy.
Initial Therapy –	Androgen Deprivation in selected patients who are not candidates for definitive therapy.

since the mid-1980s that with every Gray of radiation, any given cell in the path of the radiotherapy undergoes 40 double strand DNA breaks, 500 to 1,000 single strand DNA breaks and 1,000 to 2,000 base damages. We also know that most of this damage is repaired by the cellular repair apparatus within 30 minutes, but it takes at least four to six hours for greater than 99 percent of the damage to be repaired, hence the rationale for the daily radiation fraction.[6] The actual therapeutic target for radiation therapy is the DNA double strand break of the cancer cell; the accumulation of double strand breaks within the cancer cell leads to its eventual inability to successfully multiply and continue to grow. This pathway to senescence has significant clinical consequences, because most solid tumor cells don't actually die right after the application of radiation, but rather die when they attempt to divide, therefore slow growing tumors can appear to clinically or radiologically linger for an inordinately long time after the completion of therapy. For prostate cancer this means that it is not uncommon for the PSA, a dependable surrogate for prostate cancer tumor burden, to remain relatively elevated for up to two years following therapy as the cancer cells slowly move toward their division and eventual demise.

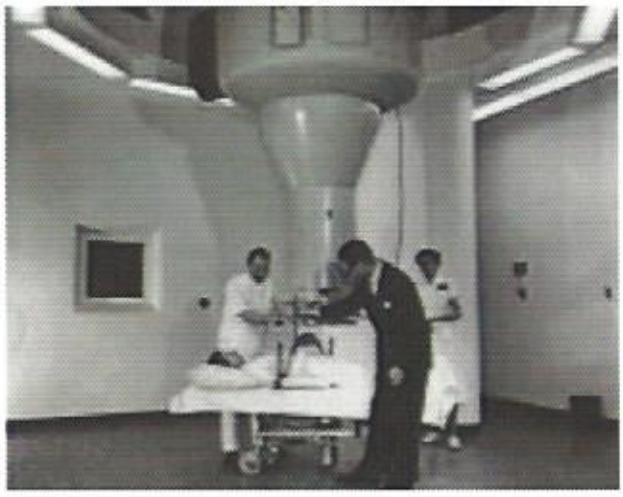
Dose Escalation and its limits:

Theoretically one should always be able to give enough radiation in order to achieve a cure every time. Prior to the 1990s it was very technically difficult to safely give the en-

tire prostate gland a dose in excess of 70 Gy; once this was achieved at several institutions the cure rate of radiation for prostate cancers in general terms rose from approximately 30 to 40 percent in the long term to 70 to 80 percent.[7] It is important to remember when viewing older radiation therapy results that this was a time which predated the extensive risk stratification and the diagnostic work-up that is applied today to prostate cancers. The PSA was a relatively new test and the Gleason scoring system was in its infancy. The barrier of 70 Gy was broken for most institution by the implementation of some form of three dimensional planning based on images of the prostate obtained through a CT scanner. Prior to this advancement, radiation oncologists used bony anatomy on plain X-ray films to define boxes of radiation which had a high probability of containing the prostate gland (and rectum, bladder, pelvic bones and penile tissues). (Figure 4) There were technical differences between the attention each practitioner paid to patient care that were meaningful for successful outcomes such as the use of rectal contrast and urethrograms, but for the most part it was an inexact science and radiation dose was freely deposited to all of the associated structures of the prostate such as the penile bulb, bladder, rectum and sigmoid; tissues which are known to have significant long terms damage in the dose range of 50 to 60 Gy.[6]

At forward looking institutions such as the Memorial Sloan Kettering Cancer Center and Fox Chase Cancer Center in the US, practitioners pushed the limits of the 70 Gy dose and found minimal gains in efficacy relative to the leap seen clinically from 65 Gy to 70 Gy. Doses as high as 86.4 Gy have been described, but the field as a whole has settled on doses in the 75.6 to 81 Gy region for low risk cancers and doses greater than 80 Gy for intermediate and high risk cancers.[7-9] Because these series are from expert high volume centers there are critiques of patient selection biases, but there are so many reported dose escalation experiences it is reasonable to sum up the efficacy of moving from 70 to 80 Gy as a five to 10 percent improvement in long term efficacy. There is a comparable dose escalation experience amongst the proton centers experience with prostate cancer which have reported similar results to the photon experience with far fewer patients.[10-12]

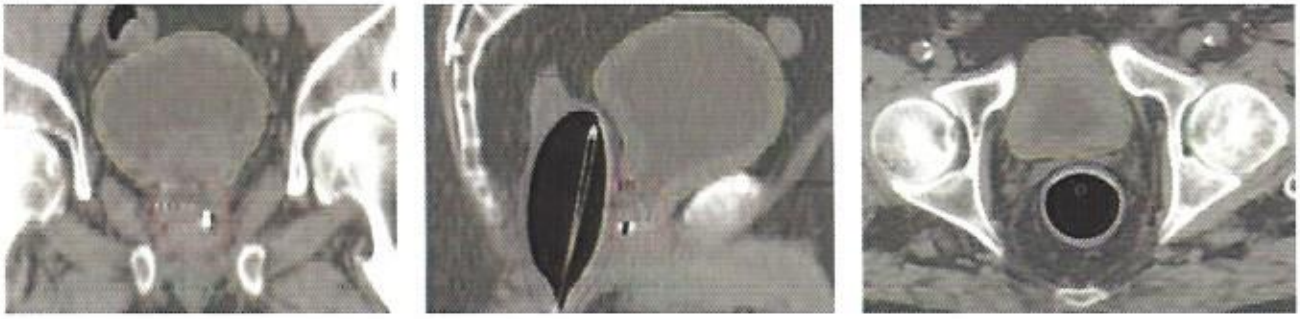
Figure 4.
Historical Limitations of Radiation Oncology, from the NCI image library (www.cancer.gov).



Stereotactic Body Radiotherapy

Stereotactic body radiosurgery is a phrase that formerly had a very specific meaning in the field of radiation oncology because of the limitations of the older generations of

Figure 5.
A prostate patient optimized for image guided intensity modulated treatment with gold markers placed, MRI guided penile bulb identification, a filled bladder as per protocol, and a rectal balloon.



linear accelerators. For most radiation oncologists today, it has come to mean giving a curative dose of radiation with a modern linear accelerator with advanced image guidance during a course of five fractions of radiation or less. In the past, before the advances in integrated imaging, stereotaxis was achieved by more elaborate means such as correlation of image sets obtained through free standing MRI and CT units with an external frame of reference which allowed for registration of a coordinate system from the imaging set to the linear accelerator room. In the late 1990s the meaning of stereotactic body radiosurgery was equated to "cyberknife" technology. A cyberknife was a small linear accelerator which took an x-ray prior to delivering its radiation dose and was moved around the patient and the radiation room via a robotic arm. The cyberknife was capable of giving x-ray image guided treatments by delivering small beamlets during the course of 40 to 60 minutes. When the beamlets were summed up a very high total dose could be delivered. Today, most linear accelerators are able to give these treatments in a matter of minutes.

In terms of efficacy, there have been no head to head comparisons of Stereotactic Body Radiation Therapy (SBRT) versus Intensity Modulated Radiation Therapy (IMRT), but there have been numerous aggregated reports.[13-16] Because prostate cancer is slow growing and can recur several years after treatment, the relatively short duration of the reported experiences with SBRT has been its main impediment to widespread adoption. The other issue that has been a major concern for radiation oncologists is that giving such large fractions to what is often a benign disease may cause long-term problems, like those when a similar wave of "short" radiation treatments were given to patients in the 1980s. The late effects did not manifest in the first five years after treatment and when they did manifest they continued to worsen during the ensuing decades.[17] It is also important to note that SBRT is not considered acceptable treatment for intermediate and high risk patients out of concern that the most dangerous parts of the prostate tumor are the cancer cells that have extended to the periphery of the gland. These cells that are starting to move beyond the gland into the body might be missed by the radiosurgeon's very close margin approach to treatment. Even as recently as July 2014, the US based study group RTOG which is responsible for dose escalation trials using cyberknife or linear accelerator based radiosurgery advised considerable caution in its use for prostate cancer.[18] It had been found that among 91 patients enrolled in dose escalation trials from 2006 to 2011 in phase 1 and 2 protocols that five of the six patients treated to the highest dose level, 50 Gy, required a colostomy to manage their high grade rectal toxicity.

Radiation in Addition to Surgery or a Seed Implant

As above, radiation above 70 Gy is considered efficacious for prostate tumors as a single treatment modality. Before radiation was considered both a safe and effective technique additional strategies that employed radiation were developed. External beam radiation above approximately 40 and below 50 Gy can be given to relatively large parts of the body, such as the entire pelvis, with the ability to kill micro-cancer metastases from several cancer types without damaging the treated area.[19-21] Based on trials, adjuvant external beam radiation following surgery has become the standard of care when high risk features are identified after the surgery within the pathology specimen or a rising PSA (Table 1).

Based on long-term follow-up of large numbers of patients, the combination of prostate seed implant and moderate external beam radiation has been shown to be a very effective and well tolerated treatment for intermediate and high risk cancers. Recently, Memorial Sloan Kettering published its experience with "seeds plus external beam radiation" versus their institutions experience with giving 86.4 Gy of radiation to the prostate.[22] The seven year actuarial PSA relapse-free survival rates were 81.4 percent versus 92 percent ($p<0.001$), and the distant metastases-free survival rates were 93.0 percent versus 97.2 percent ($p=0.04$). Most of these patients were treated without daily image guidance, the use of a full bladder or a rectal balloon. See Figure 6 for a view at modern prostate positioning for IMRT and IGRT to greater than 80 Gy.

Table 1.
Adapted from Indications for Post-prostatectomy Radiation Therapy from NCCN Version 2.2014

Indications for Adjuvant Radiation
Adverse pathological features found at surgery
Detectable PSA
No evidence of dissemination
pT3 disease
Positive Surgical Margins
Gleasons 8-10
Seminal Vesicle Involvement
Indications for Salvage Radiation
Rising PSA after surgery to begin prior to the PSA becoming 1 ng/ml or greater.

Proton Beam Radiation

Proton beam radiation has become more available as academic institutions have become more comfortable forming public private business partnerships in order to overcome their considerable cost of construction and maintenance.[23] A proton is a positively charged particle that is 1,800 times the size of an electron. Because of its size it must be accelerated using a considerably larger energy investment than an electron or photon (a photon has the physical behavior of both a very small particle and a wave).[24] Proton beams have a significant theoretical dosimetric advantage over traditional photon based treatments. The proton, because it is so relatively large, interacts much more vigorously with the body's tissues as it enters from the aperture of the beam. When the proton particle has reached its therapeutic depth it stops and deposits all of its residual energy at that level thereby creating a large peak of dose delivery at a very specific depth. For decades this technology has been used by the two much older proton therapy programs to treat rare pediatric and adult tumors. The Loma Linda facility published its long term results for prostate cancer in 2004.[10] Between October 1991 and December 1997 1,255 patients were treated; at five and eight years 75 percent and 73 percent were without disease recurrence. The Proton Research Oncology Group found at the five year median follow-up that 61.4 percent and 80.4 percent of patients were treated to either 70.2 Gy, and 79.2 Gy were without evidence of recurrence.[25] The Proton Research group investigators reported finding a serious statistical error in their initial report and later republished their results with the finding that the five year FFBF had actually been 78.8 percent versus 91.3 percent.[26,27] The group at the University of Florida in Gainesville published their experience with 211 patients treated with protons between doses of 78 Gy and 82 Gy using concomitant docetaxel for high risk patients. At two years of follow-up they found that 99 percent of their intermediate and high risk patients were without biochemical failure. An update of their series in March 2014 found that 99 percent (low risk cancer), 99 percent (intermediate risk cancer) and 76 percent (high risk cancer) were free from biochemical or clinical progression.[28,29]

Comparison of Proton Therapy and Photon base IMRT and IGRT

A recent JAMA article reported a meaningful population based comparison between patients treated with modern IMRT and proton therapy. The researchers found no difference in the treatment groups between the incidence of erectile dysfunction, incontinence or hip fractures. It was found, however, that the group treated with protons in the university setting were found to have a statistically higher incidence of gastrointestinal morbidity and were subsequently found to also undergo gastrointestinal procedures at a higher rate than patients treated in the community with IMRT. In statistical terms, patients treated with protons had an absolute risk of gastrointestinal morbidity of 17.8 per 100 person-years versus 12.2: RR, 0.66; 95 percent CI, 0.55-0.79.[30] Researchers from Yale School of Medicine reported in the Journal of the National Cancer Institute in 2013 an analysis of 27,647 Medicare beneficiaries treated for prostate cancer that the median Medicare reimbursement for proton therapy was $32,428 versus $18,575 for IMRT, but that there was no difference in gastrointestinal or other toxicity, calling into question the medico-economic justification for the differential in cost to the health care system.[31] These findings reinforced a report from 2003 which had similar findings in comparing the quality of life differences between IMRT and proton therapy.[32] Of note, a recent review article from researchers at the Mayo Clinic in Scottsdale Arizona, reported that the older passive scatter beam technology used by all operational US-based proton facilities may become obsolete when pencil beam proton beam therapy becomes available. These facilities should be able to deliver an IMRT type dose distribution using protons but at present no such data exists.[33]

Conclusion

The advances in radiation technology for prostate cancer treatment are impressive and have dramatically improved treatment outcomes for patients over the past several decades. The field continues to evolve at an impressive rate and the future appears to offer continued innovation in this important field. ✣

References

1. Kaplan HS. Historic milestones in radiobiology and radiation therapy. *Semin Oncol* 1979; 6: 479–89.
2. Cox J. "UF Proton Therapy Institute in Jacksonville rakes in patients – and profits" Florida Times Union 2011; April 21
3. Connell PP1, Hellman S. Advances in radiotherapy and implications for the next century: a historical perspective. *Cancer Res.* 2009 Jan 15;69(2):383-92
4. Aronowitz JN. Dawn of prostate brachytherapy: 1915-1930. *Int J Radiat Oncol Biol Phys.* 2002 Nov 1;54(3):712-8.
5. Young, H.H., The use of radium in cancer of the prostate and bladder: A presentation of new instruments and new methods of use. *JAMA*, 1917. 68: p. 1174–1177.
6. Hall E. Radiobiology for the Radiologist. Philadelphia, PA: Lippincott Williams & Wilkins 2012. DNA Chapters 4, 7, 8, 10.
7. Pahlajani N, Ruth KJ, Buyyounouski MK, Chen DY, Horwitz EM, Hanks GE, Price RA, Pollack A. Radiotherapy doses of 80 Gy and higher are associated with lower mortality in men with Gleason score 8 to 10 prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012 Apr 1;82(5):1949-56.
8. Beckendorf V, Guerif S, Le Prisé E, Cosset JM, Bougnoux A, Chauvet B, Salem N, Chapet O, Bourdain S, Bachaud JM, Maingon P, Hannoun-Levi JM, Malissard L, Simon JM, Pommier P, Hay M, Dubray B, Lagrange JL, Luporsi E, Bey P. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys.* 2011 Jul 15;80(4):1056-63
9. Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y, Hunt M, Greenstein S, Amols H. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. *Int J Radiat Oncol Biol Phys.* 2008 Jun 1;71(2):330-7.
10. 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.
11. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol.* 2010;28:1106–1111.
12. Mendenhall NP, Li Z, Hoppe BS, et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82:213–221.
13. Boike TP, Lotan Y, Cho LC, Brindle J, DeRose P, Xie XJ, Yan J, Foster R, Pistenmaa D, Perkins A, Cooley S, Timmerman R. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol.* 2011 May 20;29(15):2020-6.
14. Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, Hanscom HN, Laing S, Kim JS, Lei S, Batipps GP, Kowalczyk K, Bandi G, Pahira J, McGeagh KG, Collins BT, Krishnan P, Dawson NA, Taylor KL, Dritschilo A, Lynch JH, Collins SP. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol.* 2013 Mar 13;8:58.
15. King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC Jr. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* 2009 Mar 15;73(4):1043-8.
16. Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urol.* 2010 Feb 1;10:1.
17. Andreassen CN, Alsner J, Overgaard M, Sørensen FB, Overgaard J. Risk of radiation-induced subcutaneous fibrosis in relation to single nucleotide polymorphisms in TGFB1, SOD2, XRCC1, XRCC3, APEX and ATM--a study based on DNA from formalin fixed paraffin embedded tissue samples. *Int J Radiat Biol.* 2006 Aug;82(8):577-86.
18. Kim DW, Cho LC, Straka C, Christie A, Lotan Y, Pistenmaa D, Kavanagh BD, Nanda A, Kueplian P, Brindle J, Cooley S, Perkins A, Raben D, Xie XJ, Timmerman RD. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2014 Jul 1;89(3):509-17.

19. Kunos CA, Sherertz TM. Long-Term Disease Control with Triapine-Based Radiochemotherapy for Patients with Stage IB2-IIIB Cervical Cancer. *Front Oncol.* 2014 Jul 24;4:184.

20. Joye I, Haustermans K. Early and late toxicity of radiotherapy for rectal cancer. *Recent Results Cancer Res.* 2014;203:189-201.

21. Roach M 3rd, DeSilvio M, Valicenti R, Grignon D, Asbell SO, Lawton C, Thomas CR Jr, Shipley WU. Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. *Int J Radiat Oncol Biol Phys.* 2006 Nov 1;66(3):647-53.

22. Spratt DE, Zumsteg ZS, Ghadjar P, Kollmeier MA, Pei X, Cohen G, Polkinghorn W, Yamada Y, Zelefsky MJ. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. *BJU Int.* 2013 Oct 15. doi: 10.1111/bju.12514.

23. Konski A, Speier W, Hanlon A, et al. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol.* 2007;25:3603–3608.

24. Vargas C, Fryer A, Mahajan C, et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:744–751.

25. 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;294:1233-9.

26. Zietman AL. Correction: Inaccurate analysis and results in a study of radiation therapy in adenocarcinoma of the prostate. *JAMA.* 2008;299:898-9

27. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol.* 2010;28:1106–1111.

28. Mendenhall NP, Li Z, Hoppe BS, Marcus RB Jr, Mendenhall WM, Nichols RC, Morris CG, Williams CR, Costa J, Henderson R. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012 Jan 1;82(1):213-21.

29. Mendenhall NP, Li Z, Hoppe BS, et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82:213–221.

30. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA.* 2012;307:1611–1620.

31. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst.* 2013;105:25–32.

32. Gray PJ, Paly JJ, Yeap BY, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. *Cancer.* 2003;119:1729–1735.

33. Wisenbaugh ES, Andrews PE, Ferrigni RG, Schild SE, Keole SR, Wong WW, Vora SA. Proton beam therapy for localized prostate cancer 101: basics, controversies, and facts. *Rev Urol.* 2014;16(2):67-75.