THE UNIVERSITY OF TEXAS M. D. ANDERSON CANCER CENTER

Comments Regarding CMS *Potential* NCD for Prostate Patients

National Coverage Determination for Proton Beam Therapy

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

Steve Phurrough, MD, MPA
Centers for Medicare and Medicaid Services
Director of Coverage and Analysis Group
Mailstop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244

RE: Comment Period for the CMS Potential National Coverage Determination for Proton Beam Therapy and Prostate Cancer. The contents of this paper strongly support coverage for proton beam therapy inclusive of prostate cancer. **If under your leadership a creation of** a **National Coverage Determination is required, we would like to offer our assistance and explicit use of this white paper in development or review.**

Dear Dr. Phurrough,

On behalf of my colleagues at The University of Texas M. D. Anderson Cancer Center, I wish to offer the following comments in response to the sufficiency of medical evidence regarding Proton Beam Radiation Therapy for prostate cancer. The Proton Therapy Center at the U.T. M.D. Anderson Cancer Center has treated to date more than 800 patients with this very effective modality, and we appreciate greatly the opportunity to post comments supporting its benefits including prostate cancer. This document will outline the clinical effectiveness of proton beam therapy by citing clinical references and treatment rationale, thus demonstrating that Medicare coverage of proton beam therapy is appropriate inclusive of prostate cancer.

BACKGROUND AND OVERVIEW

Radiation therapy controls cancer. At high doses, radiation can kill any cancer. However, at high doses radiation will also kill any tissue. Much of the history of radiation therapy is read as a search for a dose distribution and a treatment regimen to neutralize cancer while sparing normal tissues. Proton therapy is a form of external beam radiation therapy, but since it involves particles, the dose can be deposited over a specified range. More importantly, protons can stop in tissue and deposit no dose beyond the target whereas photons (x-rays) continue to deposit radiation dose to healthy tissue beyond the tumor (APPENDIX I**).** This unique ability allows higher radiation doses to be deposited to a discrete tumor volume while minimizing exposure to surrounding tissues. Proton beams' unique ability and greater precision enables the radiation oncologist to deliver higher radiation doses to neutralize cancers while sparing normal tissues to a greater extent than is possible with photon beams.

Currently, five fully operational, clinically-based, proton beam therapy facilities exist in the United States and fifteen more exist in other countries.

The clinical benefits of proton beam therapy over conventional radiation therapy for prostate cancer can be summarized as follows:

1. Increased tumor control, due to proton beam therapy's ability to increase the radiation dose administered to the targeted tumor;

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

2. Reduced occurrence of treatment-related tissue damage and other side effects, because of the precision of dose delivery and the resulting limited amount of radiation delivered to healthy tissues adjacent to the tumor site;

3. Potential increase in the daily dose of radiation being delivered to the tumor thereby reducing the number of daily treatments a patient requires.

Prostate cancer is the most common non-cutaneous cancer affecting men in the United States. The American Cancer Society projects the annual incidence is expected to climb to 300,000 cases per year in the next 10 years. Treatment methods typically used for prostate cancer include surgery, radioactive seed implants, and external-beam radiation therapy, each used exclusively or in combination. Clinical control rates of cancers that are restricted within the gland are fairly high even two decades after radiation treatment. When cancer is spread outside the gland, however, the risk of recurrence is much higher - up to 28% 10 years after treatment and greater than 35% 20 years after treatment.[1]

Unfortunately, traditional treatment options are often associated with undesirable sequelae. Surgery can result in more severe patient-reported changes in urinary incontinence and impotence than external beam radiation therapy. [2] More data is emerging that cancer control rates and functional outcomes depend on the experience and skill of the urologist. Radical prostatectomy may have a learning curve beyond the first 250 cases that may actually impact cancer control. [3] This may be acceptable if you are the 251st patient, but what about the first 250 men? Photon (i.e. X-ray) beam radiation therapy typically involves total prostate irradiation, with the attendant risks of irradiating surrounding organs. These risks are accentuated by the fact that control of prostate cancer is radiation dose-dependent. The likelihood of disease control is greater as the total delivered dose is greater, but the likelihood of undesirable sequelae also increases with dose when conventional radiation is employed. Rectal bleeding has been identified as one of the side effects of external-beam photon radiation treatment. [4] Brachytherapy also is a potentially effective modality but has been shown to carry a higher risk of urinary irritative side effects (e.g. frequency, hesitancy, dribbling, painful urination) and toxicity. [2,5,6]

PROTON THERAPY AND INTENSITY MODULATED RADIATION THERAPY (IMRT)

Advances in external beam radiation therapy (e.g. IMRT) have made this a more attractive option, however, traditional x-ray (photons) therapy, even when using intensity modulated radiation therapy (IMRT), requires 5-8 different beam angles in order to achieve reasonably conformal dose distributions around the prostate target. While this may result in a high radiation dose to the prostate, it also results in the delivery of low and intermediate radiation doses to a relatively large volume of the pelvis. The clinical implications of this are uncertain, but large tissue volumes exposed to low radiation doses may place a patient at increased risk for developing radiation-associated second malignancies later in life as well as other potential late side effects. (Appendix II**)**.

We are not aware of any published mature prospective trials that have examined intensity modulated radiation therapy (IMRT) with x-rays for prostate cancer. The published IMRT reports to date have largely been single institution retrospective experiences, which are subject to multiple biasing factors and reporting errors, and these should not be considered the equivalent of even non-randomized prospective studies. In fact, proton

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

therapy for prostate cancer has been used for nearly 20 years to treat over 5,000 men, which is longer than the experience with IMRT.
If one looks at the data from prospective trials in the United States, the randomized trial from Loma Linda and Massachusetts General Hospital [7] that used protons has yielded the best prostate cancer control rates (>95% disease control rates for Gleason 6 prostate cancer) compared to any other published prospective study using any external beam radiation therapy modality. The findings of this randomized control study published in 2005 (and corrected in 2008) seem to have been neglected by the "Hayes Directory."

Prostate cancer patients want to be cured of their disease, but they also are interested in preserving their quality of life, no matter what their age. Proton therapy affords them an opportunity to do both.

CLINICAL RATIONALE FOR OUR RECOMMENDATION AND SUPPORT

The relative merits of particle radiation therapy for carcinoma of the prostate have been evaluated in multiple prior studies. [1,8,9,10,11,12]

One of the largest clinical experiences with proton therapy in the treatment of prostate cancer was reported by investigators at Loma Linda University Medical Center.[13] They analyzed the results of 1255 men with prostate cancer treated with either combination x-rays and protons (n=731) or protons alone (n=524) to a dose of approximately 75 Gray-Equivalents (GyE) between 1991 and 1997. With a median follow-up greater than 5 years (and ranging out over 10 years), they reported excellent 5-year PSA control rates of 75%. As expected, the outcomes were dependent upon the initial presenting clinical factors. Patients presenting with PSA values of 4ng/ml or less had 90% PSA failure-free survival at 5 years. Furthermore, the treatment-related toxicity in this study was extremely low with Radiation Therapy Oncology Group (RTOG) grade 3 toxicity rates of <2% for either gastro-intestinal or genitourinary events. Notably, the dose of radiation used in this study was considerably higher than what was considered standard at the time. One must also consider that this study represented one of the first comprehensive reports from a reasonably modern clinical facility dedicated to patient care.

Many of the earlier studies from other institutions involved treatment at physics research facilities that were subsequently modified to treat patients. [1] There were a number of limitations to these treatment units that led clinicians to utilize sub-optimal treatment techniques that have been subsequently abandoned. Furthermore, these studies were performed in the pre-PSA era and included more advanced disease (perhaps even some men with occult distant metastases) than is typically seen today. These older studies also suffered the inherent limitations of the times (e.g. poor CT-imaging, antiquated hardware, and less sophisticated treatment planning software). The relevance of any study performed beyond the last 10-15 years to treatments performed in the past decade is limited and using such studies for comparison may not be prudent.

The excellent control rates seen in the Loma Linda report may not be surprising given the results of prospective randomized dose-escalation trial performed at M.D. Anderson Cancer Center with photons (i.e. x-rays).[14,15] The investigators randomized 305 men with T1-T3 prostate cancer to either 70 GyE or 78 GyE with conformal x-rays. As expected there was a significant improvement in PSA failure-free survival for the high dose arm (64% vs. 70% at 6 years). However, this clinical benefit came at the cost of higher rectal toxicity in the high dose arm at 26% compared to 12% in the standard dose arm. Rectal toxicity was dependent on which arm the patient received but also on the volume of rectum receiving at least 70 GyE.[16] Furthermore, a follow-up study indicated that patients treated on the high dose arm suffered inferior quality of life compared to the standard-

dose patients in terms of bowel-related factors.[17] This study represented the first randomized trial in the U.S. that showed a significant disease-control benefit to higher radiation doses in prostate cancer.

The second randomized dose-escalation randomized trial was performed by investigators at Massachusetts General Hospital and Loma Linda University Medical Center.[7,18] They randomized 393 men with localized prostate cancer to either 70.2 GyE or 79.2 GyE with a combination of protons followed by x-rays (both arms received the same dose of x-rays). The overall doses and techniques were similar to those used in the M.D. Anderson study with the exception of the use of proton therapy. The initial report published in 2005 had a gross error in the method used to calculate biochemical failure that was subsequently corrected in 2008. Analogous to the M.D. Anderson trial, the higher dose arm fared better with 5-year biochemical control rate of 91.3% compared to 78.8% for the conventional dose patients ($p<0.001$). This represented a dramatic 59% reduction in the risk of failure. (If a drug were to achieve these results, then it would be approved without question.) Furthermore, patients with more favorable low risk features had an impressive **97.3%** disease control rate with higher doses of protons compared to 82.6% in the conventional dose arm (a risk reduction of 84%, $p<0.001$). This was the first randomized study to show a benefit to higher doses of radiation for lower risk patients.

Equally impressive were the low toxicity rates seen in this study. Specifically, the conventional-dose arm had a 9% rate of grade 2-3 gastro-intestinal (GI) morbidity at 5 years and the high-dose arm had a 18% GI morbidity rate. While more GI toxicity was seen with higher doses of protons than with conventional doses, the absolute rate was still significantly lower than those seen in the M.D. Anderson trial with x-rays alone. Unlike the M.D. Anderson trial, patients treated on the proton randomized study enjoyed a similar level of quality of life with respect to bowel parameters whether they received high- or low-dose protons. [19]

Modification of the proton beam characteristics and incident-beam portal can further improve the results. A strong correlation between rectal bleeding and the position of the portal for the proton beam has been identified. [20,21] Investigators have observed that if more than 40% of the anterior rectum absorbed radiation of 75 GyE or more, rectal bleeding occurred. [20,21] The conformability of the proton beam permits delivery of a high dose to the prostate while keeping low the dose to the anterior rectum.

While no formal clinical comparison between IMRT and protons has been performed, dosimetric comparative studies have indicated that protons allow more dose-sparing to normal tissue (e.g. rectum, bladder, and whole pelvis) compared to IMRT. [22]

Therefore, if one examines the mature prospective randomized data published in the U.S., the use of protons afforded patients the highest cancer control rates with the fewest side effects while maintaining their quality of life compared to any other external beam modality. We are not implying that other modalities are not effective or do not have benefits, but the majority of these therapies (including IMRT) have not been held to the rigors of a randomized-control trial. Single institution retrospective experiences should not be compared to even non-randomized prospective data and certainly not to a randomized prospective study. If decisions are made on the basis of retrospective data and popular opinion while ignoring randomized evidence, then we are entering onto a slippery slope.

Furthermore, similar to the technologic advances seen in the past decade for x-ray therapy, proton therapy has benefited from profound improvements in treatment units, imaging, patient immobilization, computer software, and perhaps most importantly in the knowledge-base of its users. The full potential of proton therapy to treat cancer patients is only beginning to be realized with significant advances projected in the near future.

THE UNIVERSITY OF TEXAS M. D. ANDERSON CANCER CENTER

Comments Regarding CMS *Potential* NCD for Prostate Patients

National Coverage Determination for Proton Beam Therapy

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

SUMMARY

A salient shortcoming of photon radiation therapy for prostatic carcinoma is the damage to the urethra, rectum, and bladder that often arises when doses sufficiently high to control prostate cancer are delivered. Dose-volume relationships indicate, for example, that rectal bleeding occurs when the irradiation dose is between 60 and 75 GyE. Conversely, insufficient dose results in local failure and recurrence. The proton beam offers a delivery mechanism to administer the same qualitative ionizing radiation to the volume of interest, but to a higher total dose. This improves the chance of achieving biochemical as well as clinical disease-free control while avoiding the complications and untoward side effects that limit the delivery of a sufficient dose with photon beams.

CONCLUSION

We believe that the contents of this paper strongly support coverage for proton beam therapy inclusive of prostate cancer.

- Authoritative evidence demonstrates that the benefits of proton beam therapy far outweigh its reasonably anticipated risks, which have proved to be minor;

- The literature is clear that proton beam therapy can be efficacious in any clinical situation in which photon radiation is used. That hardly means, however, that it is an equivalent technology. The technology is markedly different and provides superior clinical effectiveness and benefits, more favorable health outcomes, and fewer or less significant adverse side effects for patients; and

- As an alternative or replacement for a currently covered service (i.e., other forms of radiation therapy and surgical intervention), proton beam therapy has been demonstrated to be superior in terms of disease control and has resulted in fewer or less significant adverse side effects. The precise conformability of the proton beam enables this combination of capabilities to be realized.

Please find attached a reference list of published papers as well as the actual papers for your very close consideration.

If you have any questions please feel free to contact me at 713-563-2300, or you may contact Robin Famiglietti, Division Administrator, at 713-563-2327.

Respectfully submitted on behalf of U.T. M.D. Anderson Cancer Center,

James D. Cox, M.D., FACR
Professor and Head
Division of Radiation Oncology

Cc: Robin Famiglietti

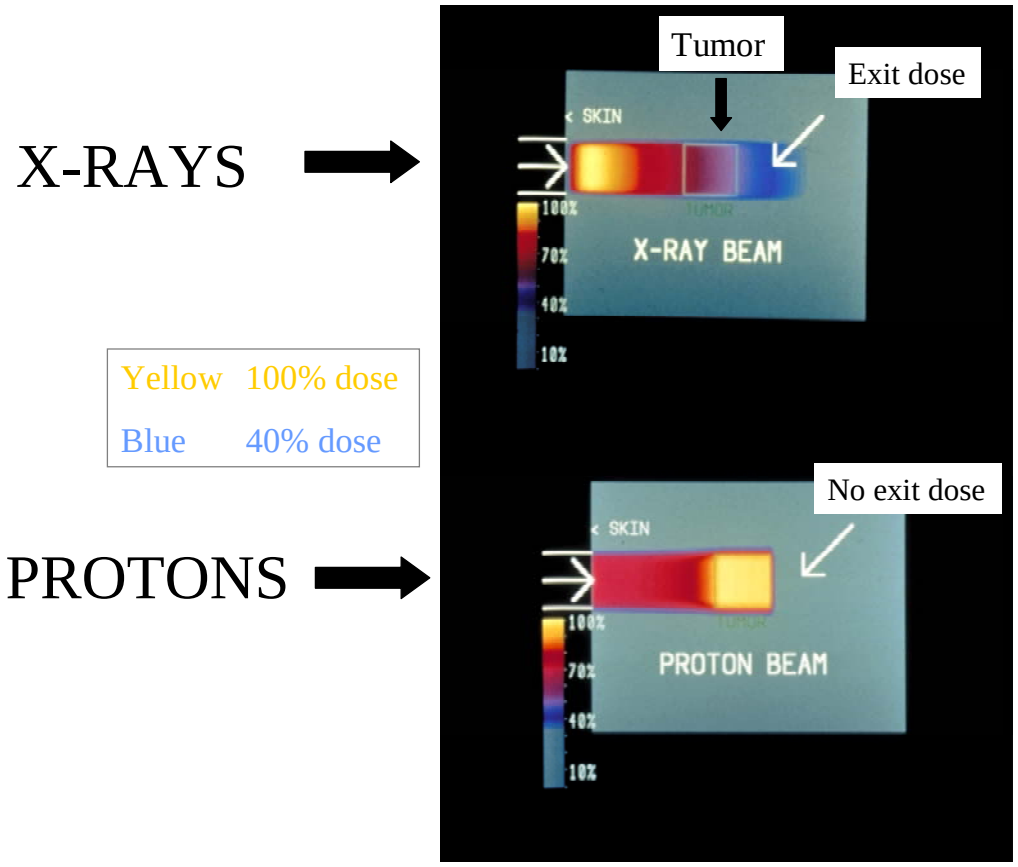
Attachments
Appendices

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

APPENDIX I

X-ray vs. Proton beam (note high dose before and after target with x-rays)



Multiple studies have shown that higher radiation doses are needed for maximal efficacy in prostate cancer therapy. This may lead to increased treatment-related side effects if special radiation therapy planning and techniques are not employed. X-ray therapy (i.e. photon therapy) may provide good disease control but requires more radiation exposure to a larger area of the pelvis, which may have long-term implications as previously mentioned. *(Figure courtesy of Loma Linda Cancer Center)*

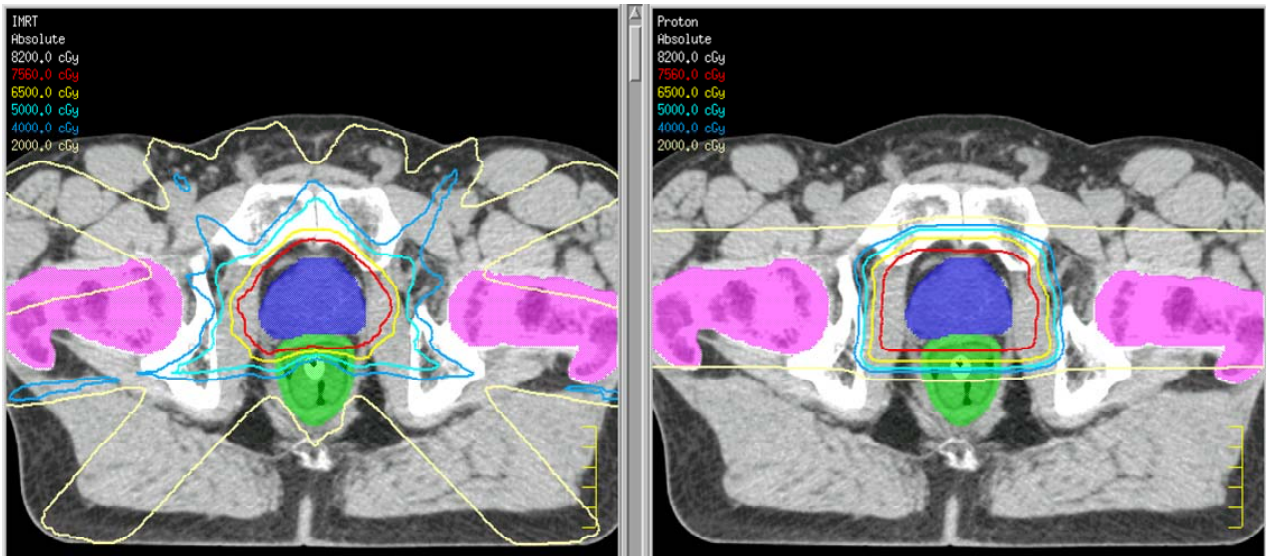
To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

APPENDIX II

IMRT vs. Proton plan (Prostate is blue and rectum is green)

IMRT (x-rays) Protons

8 fields 2 fields



Red is high radiation dose
Blue & beige are lower doses

This difference may be particularly profound in younger patients as some radiation-related events may occur after many years. Dose-escalation proton therapy for definitive local treatment has a high success rate, compact dose-distribution and low side effect profile.

There was an abstract presented at the 2008 American Society of Clinical Oncology annual meeting that evaluated the health-related quality of life (HRQOL) of patients on this proton study and found that the high dose patients enjoyed a similar level of quality of life compared to the low dose patients when it came to rectal-bowel parameters. This seems to indicate that proton therapy allows higher doses without compromising HRQOL.

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

BIBLIOGRAPHY

1. Shipley 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 [see comments]. *Int J Radiation Oncol Biol Phys*. 1995; 32(1): 3-12.

2. Sanda MG et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 358:1250-61, 2008.

3. Klein EA et al. Surgeon experience is strongly associated with biochemical recurrence after radical prostatectomy for all preoperative risk categories. *J Urology* 179:2212-6, 2008.

4. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. *Br J Radiol*. 1973;46:529-537.

5. Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperitoneal I-125 implantation for Stage T1-T2 prostatic carcinoma. *J Clin Oncol.* 1996: 14:449-454.

6. Wallner K, Roy J, Harrison L. Dosimetry guidelines to minimize urethral and rectal morbidity following transperitoneal I-125 prostate brachytherapy. *Int J Radiation Oncol Biol Phys*. 1995;32:465-472.

7. Zietman AL et al. Correction: Inaccurate Analysis and Results in a Study of Radiation Therapy in Adenocarcinoma of the Prostate. *JAMA* 299:898-900, 2008.

8. Duttenhaver JR, Shipley WU, Perrone TL. Protons or megavoltage x-rays as boost therapy for patients irradiated for localized prostate carcinoma: an early phase I-II comparison. *Cancer*. 1983;51:1599.

9. Rossi CJ, Slater JD, Reyes-Molyneux, NJ et al. Particle beam radiation therapy in prostate cancer: is there an advantage? *Semin Rad Oncol.* 1998;8(2):115-123.

10. The Treatment of Prostate Cancer: An Overview, The Prostate Cancer InfoLink, http://comed.com/Prostate/TreatmentOverview.html, October 6, 1998.

11. Yonemoto LT, Slater JD, Rossi CJ, Antoine JE, Loredo L, Archambeau JO, Schulte RW, Miller DW, Teichman SL, Slater JM. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. *Int J Radiation Oncol Biol Phys*. 1997;37(1):21-29.

12. Zietman A, Coen J, Shipley W, Willett C, Efird J. Radical radiation therapy in the management of prostatic adenocarcinoma: the initial prostate specific antigen value as a predictor of treatment outcome. *J Urology* 1994;151:640-645.

13. Slater JD et al. Proton therapy for prostate cancer: The initial Loma Linda University Experience. *Int J Radiation Oncol Biol Phys*. 59:348-352, 2004.

14. Pollack A et al. Preliminary Results of a Randomized Radiotherapy Dose-Escalation Study Comparing 70 Gy With 78 Gy for Prostate Cancer. *J Clin Oncol* 18:3904-3911, 2000.

15. Pollack A et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiation Oncol Biol Phys*. 53:1097-1105, 2002.

16. Storey MR et al. Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. *Int J Radiaiont Oncol Biol Phys.* 48:635-642, 2000.

17. Little DJ et al. Quality-of-life questionnaire results 2 and 3 years after radiotherapy for prostate cancer in a randomized dose-escalation study. *J Urology* 62:707-713, 2003.

18. Zietman AL et al. Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate: A Randomized Controlled Trial. *JAMA* 294:1233-1239, 2005.

19. Talcott JA et al. Long-term quality of life after conventional-dose versus high-dose radiation for prostate cancer: Results from a randomized trial (PROG 95-09). *J Clin Oncol* 26:#5058, 2008.

20. Slater JD, Rossi CJ, Yonemoto LT, Reyes-Molyneux NJ, Bush DA, Antoine JE, Miller DW, Teichman SL, Slater JM. Conformal proton therapy for early stage prostate cancer. *J Urology* 1999; 53: 978-84.

21. Slater JD, Yonemoto LT, Rossi CJ, Reyes-Molyneux NJ, Bush DA, Antoine JE, Loredo LN, Schulte RWM, Teichman SL, Slater JM. Conformal Proton Therapy for Prostate Carcinoma. *Int J Radiation Oncol Biol Phys.* 1998;42(2):299-304.

22. Vargas C et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiation Oncol Biol Phys.* 62:1297-1308, 2005.

ADDITIONAL REFERENCES

Berry RJ. Therapeutic uses of x-rays. *Int J Radiation Oncol Biol Phys* 1987; 51(5): 873-895.

Cancer facts and figures 1998: graphical data. *American Cancer Society home page:* http://www.cancer.org/statistics/cff98/graphicaldata.html, October 20, 1998, pp 1-18.

Cancer Fact Sheet. *Avicenna Systems Corporation home page:* www.avicenna.com/scripts/thr.dll, October 3, 1998, pp. 1-2.

Cancer treatment fact sheet. *American Cancer Society home page:* http://www3.cancer.org/cancerinfo/gen_main_cont.asp?st=tr, September 29, 1998, pp. 1-2

Chemotherapy fact sheet. *American Cancer Society home page*, http://www.canceranswers.com/chemotherapy.html, October 5, 1998, pp. 1-2.

Conditions Treated at the Proton Treatment Center, Loma Linda University Medical Center, http://www.llu.edu/proton/patient/sites.html, October 2, 1998.

Data on file, ZA Consulting/Health Evolutions.

Hewitt HB. Rationalizing radiotherapy: Some historical aspects of the endeavor. *Brit J Radiol*. 1973; 46: 917-926.

Hormonal therapy fact sheet. *American Cancer Society home page:* http://www3.cancer.org/cancerinfo/hormone.html, October 5, 1998, pp. 1.

How is cancer treated? *PhRMA home page:* http://www.phrma.org/guides/cancer/cancer5.html, October 5, 1998, pp. 1-2.

Kaplan HS. Basic principles in radiation oncology. *Cancer* 1977; 39:689-693.

Karim AB, Kralendonk JH, Njo KH, Tabak JM, Elsenaar WH, van Balen AT. Ethmoid and Iowski S, Reinfuss M, Skoyszewski J. The evaluation of radiotherapy after incomplete surgery in patients with carcinoma of the maxillary sinus. *Int J Radiation Oncol Biol Phys*. 1985;11(3):505-9.

Loeffler JS. Massachusetts General Hospital, Harvard Cyclotron Laboratory. Proton Radiation Therapy Research. Progress Report. October 1, 1996 to September 31,1997.

McLeod ME, Creighton RE, Humphreys RP. Anaesthesia for cerebral arteriovenous malformations in children. *Can Anaesthe Soc J.* 1982;29:299-305.

Nahum AE, Dearnaley DP, Steel GG. Prospects for proton-beam radiotherapy. *Eur J Cancer* 1994; 30A(10): 1577-83.

Nicholson J, DeVoe, D. Applications of proton beam therapy. *Radiol Tech.* 1996; 67(5): 439-41.

Pollack A, Zagars GK. External beam radiotherapy for stage T1/T2 prostate cancer: how does it stack up? *J Urology.* 1998;51:258-264.

Rubin P, McDonald S, Qazi R, eds. *Clinical Oncology: A multidisciplinary approach for physicians and students*. 7th ed. Rochester, NY: WB Saunders Company; 1993.

Slater JM, Archambeau JO, Miller DW, Notarus MI. The proton treatment center at Loma Linda University Medical Center: Rationale for and description of its development. *Int J Radiation Oncol Biol Phys.* 1992; 22(2): 383-389.

Slater JM, Neilsen IR, Chu WT, Carlsen EN, Chrispens JE. Radiotherapy treatment planning ultrasound-sonic graph pen-computer system. *Cancer* 1974; 34: 96-100.

To: CMS – Through: James D. Cox MD, Professor and Head - Division of Radiation Oncology

Statistics. *American Cancer Society home page:* http://www3.cancer.org/cancerinfo, July 6, 2001, pp. 1.

Suit HD. Local control and patient survival. *Int J Radiaiont Oncol Biol Phys* 1992; 23(3): 653-60.

Suit HD, Miralbell R. Potential impact of improvements in radiation therapy on quality of life and survival. *Int J Radiation Oncol Biol Phys.* 1989; 16(4): 891-895**.**

Suit H, Urie M. Proton beams in radiation therapy. *J Natl Cancer Inst.* 1992 Feb 5; 84(3): 155-64.

Thorton AF, Laramore GE. Particle Radiation Therapy. In press.

Wijnmaalen A, Helle PA, Koper PC, Jansen PP, Hanssens PE, Boeken, Kruger CG, VanPutten WL. Muscle invasive bladder cancer treated by transurethral resection, followed by external beam radiation and interstitial iridium-192. *Int J Radiation Oncol Biol Phys* 1997; 39(5): 1043-1052.)

Wilson, RR. Radiological use of fast protons. *Radiol*. 1996; 47, 487-491.

York T, Schneider R, Friedmann A, et al. Proton radiotherapy fro orbital rhabdomyosarcoma: clinical outcome and a dosimetric comparison with photons. *Int J Radiation Oncol Biol Phys.* 2005; 63(4): 1161-1168.

Zietman, A.L. et al., Radiation Dose Escalation as Treatment for Clinically Localized Prostate Cancer: Is More Really Better? *JAMA* 2005 Sep 14; 294(10): 1274-6.

Zink SR, Lyman JT, Castro JR, Chen GT, Collier JM, Saunders WM. Treatment planning study for carcinoma of the esophagus: helium ions versus photons. *Int J Radiation Oncol Biol Phys.* 1988; 14(5): 993-1000.