Progress in 3D Conformal Radiation Treatment of Prostate Cancer

Gerald E. Hanks

From the Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

Correspondence to: Gerald E. Hanks, MD, Department of Radiation Oncology, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111. Tel: +1 215 72 82 940. Fax: +1 215 72 82 868. E-Mail:GE_Hanks@fccc.edu

Acta Oncologica Suppl. 13, pp. 69–74, 1999

The development of 3D conformal radiation is reviewed and the proof given of three key hypotheses that result in improved patient results. The Fox Chase outcomes from 3D CRT show 7- and 8-year biochemical freedom of disease rates of 72% for all patients, 84% for PSA < 10 ng/ml, 73% for PSA 10–19.9 ng/ml and 37% for PSA > 20 ng/ml. Dose responses by pretreatment PSA level grouping show steep slopes for patients with PSA > 10 ng/ml. Dose response is also demonstrated for 'favorable' and 'unfavorable' prognostic subgroupings of the classic three pretreatment PSA groups. A matched pair analysis of high-dose 3D CRT versus low-dose 3D CRT shows on multivariate analysis a significant advantage in freedom from distant metastasis. A similar matched comparison of high-dose 3D CRT with low-dose 3D CRT patients and low-dose conventional technique patients shows a significant advantage in distant metastasis, cause-specific survival and overall survival for the high-dose group. Future studies including those using biochemical endpoints to direct differential dose distributions are discussed.

The decade of the nineties has witnessed a revolution in treatment planning, target identification, and dose delivery in prostate cancer.

Identification of the target in three dimensions by CT technology has allowed conformation of the treatment beam to the target contour and the use of beam's eye view conformed beams. This technology results in the irradiation of a minimum shell of normal tissue around the target.

The conceptual change from standard portal-directed treatment to patient-specific target conformed beams in prostate cancer was finally made in the late 1980s and this has been followed by an explosion of progress. The ICRU Report 50 played a major role in disseminating this conceptual change (1).

In this communication, I will briefly review the development of three-dimensional conformal radiation technique (3D CRT), present some interesting new results from our program, and suggest the future this field may follow.

THE PAST

In the 1960s, Takahashi and Umegaki first developed conformal therapy and this work was expanded by Matsuda, Abe, and others (2–4). In 1987, Abe developed the first CT simulator with a diagnostic CT linked to a 3D planning system. The next major development in this technology was the Picker ACQSIM; the first unit was installed at Fox Chase Cancer Center in 1993, and about 240 are installed world-wide at present.

In 1987 investigators at the University of Michigan were the first to treat patients with 3D CRT in the USA (5). Lichter et al. developed beam arrangements, physics-related technology and initiated a dose-escalation study in patients with Stage C cancer (6–9).

Memorial Sloan Kettering investigators including Fuks, Leibel, Ling, Kucher, Hunt, Mohan and others treated their first patient in late 1988. They have continued to study dose escalation, the use of adjuvant hormone treatment, and have developed intensity-modulated treatment technology (10–16).

The program at the Fox Chase Cancer Center began in March 1989. Hanks et al. led the program and proved the need for immobilization, conducted a dose-escalation study, modeled morbidity and established the first dose-response functions for cure and morbidity in prostate cancer (17–27).

The National Cancer Institute funded a group of nine institutions to begin a multi-institution dose-escalation study in 1994 (University of California, San Francisco, Fox Chase Cancer Center, University of Miami, Washington University, University of North Carolina, Duke University, University of Michigan, University of Washington, University of Chicago). The Quality Assurance Center was awarded to Washington University where Purdy and oth-

ers have developed very comprehensive systems for information exchange and quality assurance in 3D CRT of prostate cancer and for other sites as part of the RTOG QA center.

The development of local area networks (LAN) was also important in conjunction with the use of real-time portal imaging. In Canada, Shalev et al. played an important role and the first all-digital radiation oncology department came into operation at Fox Chase in 1994 (28, 29).

Three key hypotheses

Three key hypotheses have been evaluated and proven by studies conducted over the past 10 years.

The first hypothesis was that more accurate identification and targeting of the cancer would improve local control without an increase in dose. Corn et al. have shown an improved 12-month PSA response for conformal patients compared with those on conventional treatment at Fox Chase. With prostate only irradiation, 76% of 3D CRT patients achieved a PSA of less than 1.5 ng/ml at 12 months' follow-up compared with 55% for those receiving conventional treatment ($p = < 0.02$) (30). It is likely that this improvement was due in part to better targeting.

The second hypothesis predicts a decrease in acute and late morbidity resulting from a reduction in the volume of normal tissue included in the beam. Hanks et al. have shown a reduction in acute grade 2 GI and GU symptoms from 57% for patients treated with conventional techniques to 35% for those treated with 3D CRT techniques ($p = 0.0001$) (31). The hypothesis has also been proven for late serious complications (18). The 5-year RTOG scale grade 3, 4 gastrointestinal complications observed at 70 to 80 Gy were less than 1% in the experience of both the Fox Chase Cancer Center and the Memorial Sloan Kettering Cancer Center (16, 18). These low rates are considerably below the USA national average observed at 65–70 Gy or the reports of RTOG prospective clinical trials (32, 33).

The third hypothesis predicts that an increase in the cure of prostate cancer will accompany the higher doses allowed by 3D CRT. This is proven by our dose-response studies, where a 20%–40% advantage in 5-year biochemical freedom from disease (bNED) rate is observed when patients treated with 3D CRT and ~ 76 Gy are compared with those treated with 3D CRT and ~ 70 Gy (18, 27). Several other institutions have confirmed these observations (34, 35).

THE PRESENT

General results

We have treated 848 patients with 3D CRT alone by the Fox Chase 4-field technique between March 1989 and December 1997. Outcomes in these patients are shown in Figs. 1 and 2. In Fig. 1 we show the bNED status for all patients treated with 3D CRT alone; the 5-year and 8-year

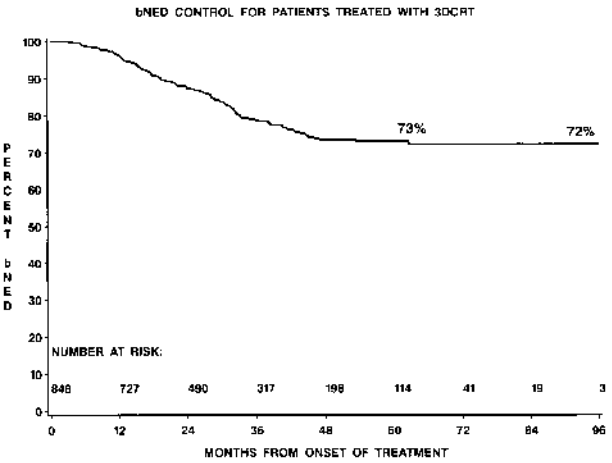

Fig. 1. Actuarial plot of all patients treated with 3D CRT alone.

biochemical freedom from disease by the ASTRO consensus definition is 73% and 72%. This plot includes patients with all Gleason scores and all pretreatment PSA levels.

Fig. 2 shows bNED results for the 3 PSA groupings of < 10 ng/ml, 10 to 19.9 ng/ml, and $20+$ ng/ml treated with 3D CRT alone, including, again, all stages and grades of cancer. Five-year rates are 85%, 73%, and 37%, respectively, and the 8-year rate for the PSA < 10 ng/ml group is 84%.

Dose-escalation results

Our dose-escalation studies have enabled us to look within the individual PSA groupings of patients to find that outcome depends on dose based on pretreatment prognostic indicators when the pretreatment PSA groupings are subdivided into favorable and unfavorable subgroups, and these are compared with the dose-response functions shown in Fig. 3 for our basic PSA groups. The favorable subgroup includes patients who have T1 or T2A and

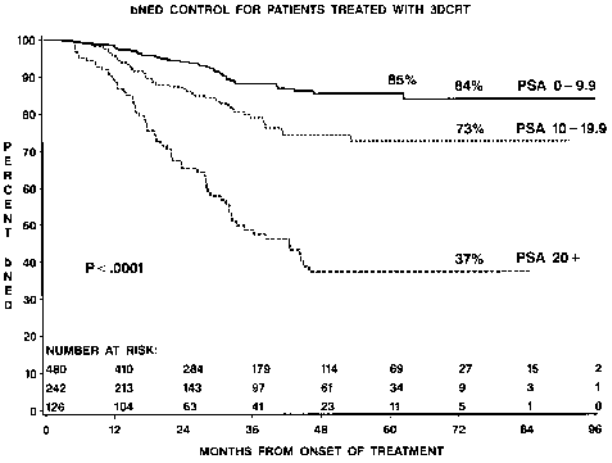

Fig. 2. Actuarial plot of bNED status by pretreatment PSA group.

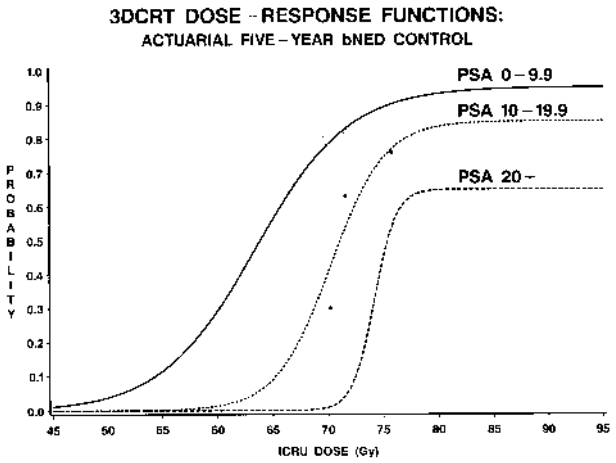

Fig. 3. Dose-response functions for 3D CRT-treated patients by pretreatment PSA groupings.

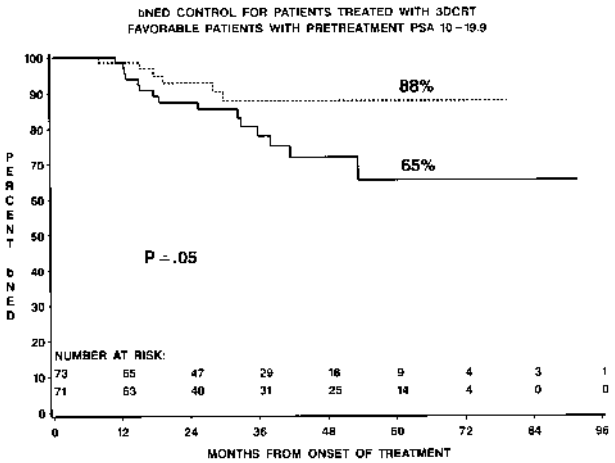

Fig. 5. Dose comparison for pretreatment PSA group 10–19.9 ng/ml with all of: T12A, Gleason 2-6, no perineural invasion. Broken line represents dose of ≥ 74 Gy median 76; solid line represents dose of < 74 Gy median 72.

Gleason 2 to 6 disease and no perineural invasion. The unfavorable subgroup includes patients that have any one or more of the following: T2B,3 and/or Gleason 7 to 10 and/or PNI +. We believe these subgroups represent different cancer volumes and/or different levels of cellular aggressiveness.

We examined dose comparisons for the favorable and unfavorable subgroups of each pretreatment PSA grouping ($<$ 10 ng/ml, 10–19.9 ng/ml and 20 + ng/ml) and found no difference in outcome for the favorable PSA $<$ 10 ng/ml group comparing < 73.1 Gy to ≥ 73.1 Gy. There is also no difference in outcome for the unfavorable subgroup of the PSA 20 + ng/ml comparing < 75.6 Gy with ≥ 75.6 Gy. There are significant dose comparison differences for the other subgroups, as shown in Figs. 4–7. With high dose, the unfavorable < 10 ng/ml subgroup increases 5 year bNED from 77% to 95%. With high dose, the favorable 10–19.9 ng/ml subgroup increases 5-year bNED from 65% to 88% and for the unfavorable 10–19.9 ng/ml subgroup 5-year bNED increases from 48% to 81%. The favorable subgroups of the > 20 ng/ml subgroup increase from 22% to 68% with high dose.

Local control and metastasis and survival

The improvement observed in local control with 3D CRT and high doses predicts an ultimate improvement in survival due to dose (36). We examined two groups of matched patients to evaluate this prediction. The first group included 296 patients treated with > 74 Gy and matched on pretreatment PSA level, Gleason score and palpation T stage with 296 patients treated with < 74 Gy. The second group comprised 357 patients treated with

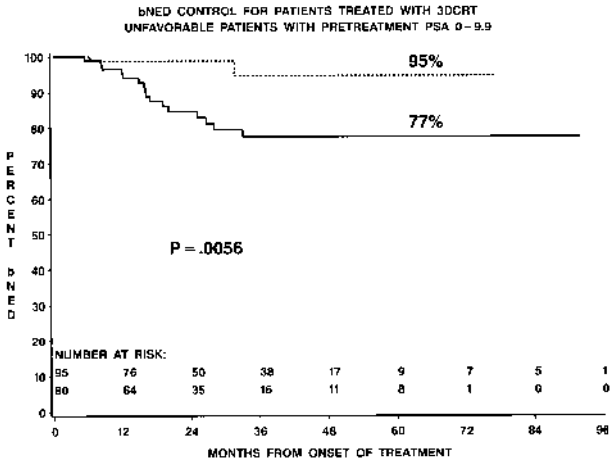

Fig. 4. Dose comparison for pretreatment PSA group 0–9.9 ng/ml, with one or more of: Gleason 7–10, T2B or T3, perineural invasion. Broken line represents dose of ≥ 74 Gy median 76; solid line represents dose of < 74 Gy median 72.

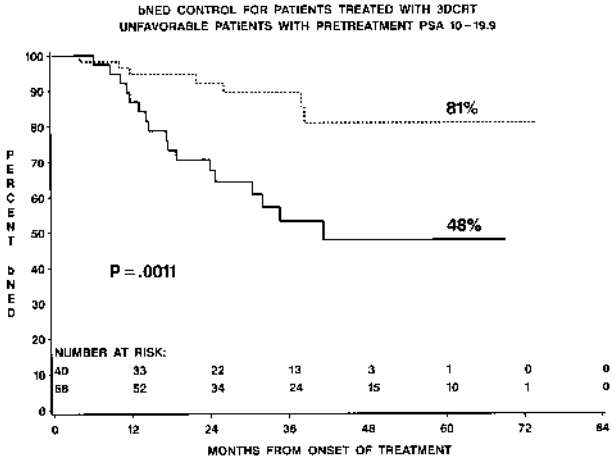

Fig. 6. Dose comparison for pretreatment PSA group 10–19.9 ng/ml with one or more of: Gleason 7-10, T2B, T3, perineural invasion. Broken line represents dose of ≥ 74 Gy median 76; solid line represents dose of < 74 Gy median 72.

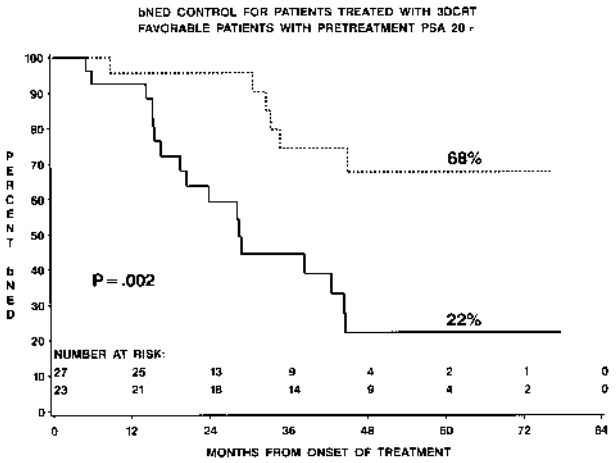

Fig. 7. Dose comparison for pretreatment PSA group 20+ ng/ml with one or more of: Gleason 7–10, T2B, T3, perineural invasion. Broken line represents dose of ≥ 74 Gy median 76; solid line represents dose of < 74 Gy median 72.

> 74 Gy matched on palpation stage and grade with 357 patients treated with < 74 Gy. (PSA was known in only 90% of these patients.) The low-dose group had a lower median PSA than the high-dose group (8.4 ng/ml vs. 11.1 ng/ml), predicting a better outcome but included patients treated with conventional technique to dose between 64 and 70 Gy.

Table 1 shows the univariate comparison of the high- and low-dose groups in each of the two study groups for bNED, FDM, CSS, and OS and the multivariate analysis of dose as an independent predictor of the same endpoints.

In group I, univariate analysis shows that bNED, FDM and CSS are significantly improved with high dose while multivariate analysis shows that there is a difference in bNED and distant metastasis due to treatment dose. With a longer follow-up, we expect that CSS and OS will become significantly different.

Table 2

Daily prostate localization with BAT (U/S) compared to CT: 75 studies in 35 patients

	Correlation	Average (mm)	SD (mm)
AP	0.88	0.00	2.9
LAT	0.91	0.20	2.5
S/I	0.82	0.20	2.7

In group II, where conventional technique low-dose patients are added to the low-dose 3D CRT patients, there is a significant advantage of high dose for all endpoints on univariate and multivariate analysis. The low-dose group II has patients with a longer follow-up than the high-dose group, which may add uncertainty to the observation. We believe, however, that the results in 3D CRT patients alone, supported by the results in group II, provide strong support for continuing high-dose treatment of prostate cancer and further encouragement for a large randomized trial of high dose (75–80 Gy) versus conventional dose (65–70 Gy).

THE FUTURE

The last 10 years have seen a continuing effort to ensure that the radiation beam hits the entire target on a daily basis. We have recently introduced a new technology that uses ultrasound to measure the location of the prostate on a daily basis (BAT—NOMOS Corp.) (37). When prostate ultrasound is done in two dimensions on the treatment table, the computer can calculate the couch movement necessary to obtain ideal localization on a daily basis. Results in the first 35 patients studied with CT and ultrasound performed at the same time are presented in Table 2. This technology was first studied by us in January 1998, and was introduced for common use in our department in the Fall of 1998 and will be routine in all prostate cancer patients beginning in January of 1999. We use the technol-

Table 1

Comparison of matched high- and low-dose groups

	Group I (3D CRT only)			
	Five-year rates (%) High Dose	Univariate (%) Low Dose	p-value	Multivariate* analysis dose p-value
bNED	73	55	0.016	0.05
FDM	97	91%	0.003	0.008
CSS	100	97	0.017	N.S.
O.S.	90	85	0.211	N.S.
	Group II (3D CRT and conventional)			
bNED	71	56	0.003	0.019
FDM	97	88	0.0004	0.004
CSS	99	94	0.007	0.048
OS	88	79	0.011	0.030

*In multivariate analysis, dose is evaluated against PSA level, grade and stage.

ogy to assure positioning on the final six treatment days where the CTV = PTV.

We believe that for the next decade important progress will continue to be made by means of 3D CRT, but rather than being based almost exclusively on technological advances, the future improvements will in part be related to the use of biological, molecular and isotope-imaging demonstrations of the location of bulk cancer within the gland and where relatively resistant portions of the cancer are located within the gland. This will enable the dose to be increased to these identified volumes. Irregular dose distributions within the gland can then be prospectively planned, based on the biology of the individual patient's cancer.

A recent example in our department comes from the work of Movsas et al., who carried out the first direct measurements of hypoxia in prostate cancer patients by direct measurement with the Eppendorf Oximeter (38).

Using custom-constructed Eppendorf pO_2 microelectrodes, pO_2 measurements have been obtained from the pathologically involved side of the prostate as well as from normal muscle and from either side of normal glands. The tumor-side measurements have consistently shown significantly lower pO_2 values compared to normal prostate or normal muscle. This work provides an important insight into the biology of prostate cancers and may lead to more effective treatment strategies (38).

DISCUSSION

The decade of the 1990s has seen remarkable progress in technical delivery of radiation treatment with the development of 3D CRT. Prostate cancer has proven to be the ideal site for developing this technology and we have the first dose responses for cure and complications to allow treatment optimization. In Table 3 we include our estimate of what will be the optimal dose for prostate cancer in the new millennium and Table 4 details our current treatment program. A major task of the next 5 years is to expand the technology of 3D CRT and higher doses to many more facilities world-wide. An improved cure rate with high dose will fuel that development.

We have already seen some applications of MRI spectroscopy and imaging, PET scanning and measurements of hypoxia that indicate that our treatment in the future will be biology based rather than technology based. We look forward to these developments.

Table 3

Fox Chase Cancer Center: 3D CRT prostate cancer—estimate of optimal dose

	ICRU Point dose	Projected 5-year bNED (%)
PSA < 10 ng/ml		
Favorable	≥ 71.5 Gy	95
Unfavorable	≥ 75–80 Gy	95
PSA 10-19.9 ng/ml		
Favorable	≥ 75–80 Gy	85
Unfavorable	80–85 Gy	65–75
PSA 20+ ng/ml		
Favorable	80–85 Gy	65–75
Unfavorable	80–85 Gy	35–45

Table 4

*Fox Chase Cancer Center: 1/1/99 treatment program**

PSA < 10 ng/ml All T1, 2A 9/2-6 PNI0	Prostate only	75.6 Gy
PSA < 10 ng/ml		
Any T2B/3 gl 7–10 PNI(+)	Small pelvis	48.3 Gy
PSA 10–19.9 ng/ml	Prostate + S.V.	10.6 Gy
All	Prostate + 1.5 cm	12.6 Gy
	Prostate + 0.5 cm	10.5 Gy
PSA 20+ ng/ml		
All		82.0 Gy

*Dose is at ICRU point.

ACKNOWLEDGEMENTS

This publication was supported in part by grant number CA-60264-02 from the National Cancer Institute, Division of Cancer Treatment. Its contents are solely the responsibility of the author and do not necessarily represent the official views of the National Cancer Institute. I am grateful for the help of many colleagues who have made major contributions to the Fox Chase program. These include Tim Schultheiss, PhD, Alex Hanlon, PhD, Margie Hunt, MS, Barry Epstein, MD (deceased), Robert Lee, MD, Wayne Pinover, DO, Ed Soffen, M D, Eric Horwitz, MD, Shawn McNeeley, MS, Ruth Peter, MS, Ann Slivjak, MS, and a host of residents and other staff. I also acknowledge Lorraine Medoro for manuscript preparation.

REFERENCES

1. ICRU Report No. 50. International Commission on Radiation Units and Measurements: prescribing, recording, and reporting photon beam therapy. Washington, DC: International Commission on Radiation Units and Measurements, 1993.
2. Nishidai T, Nagata Y, Takahashi M, et al. CT simulator: a new 3-D planning and simulating system for radiotherapy. Part 1: Description of system. Int J Radiat Oncol Biol Phys 1990; 18: 499–504.
3. Takahashi S. Conformation radiotherapy. Acta Radiol; (Suppl 1) 1965; 142.
4. Umegaki Y. Dose distribution in the moving field radiotherapy. Nippon Acta Radiol 1960; 20: 2191–209.
5. Sandler HM. 3-D conformal radiotherapy for prostate cancer: the University of Michigan experience. Basel: S. Karger 1996: 238–43.
6. Lichter AS. Three-dimensional conformal radiation therapy: a testable hypothesis. Int J Radiat Oncol Biol Phys 1991; 21: 853–5.
7. McShan DL, Fraass BA, Lichter AS. Full integration of the beams eye view concept in computerized treatment planning. Int J Radiat Oncol Biol Phys 1990; 18: 1489–94.

8. Sandler HM, Perez-Tamayo C, Ten Haken RK, Lichter AS. Dose escalation for stage C (T3) prostate cancer: minimal rectal toxicity observed using conformal therapy. Radiother Oncol 1992; 23: 53–4.
9. Ten Haken RK, Perez-Tamayo C, Tesser RJ, McShan DL, Fraass BA, Lichter AS. Boost treatment of the prostate using shaped, fixed fields. Int J Radiat Oncol Biol Phys 1989; 16: 193–200.
10. Leibel SA, Heimann R, Kutcher GJ, et al. Three-dimensional conformal radiation therapy in locally advanced carcinoma of the prostate: preliminary results of a Phase I dose-escalation study. Int J Radiat Oncol Biol Phys 1993; 28: 55–65.
11. Leibel SA, Ling CC, Kutcher GJ, Mohan R, Cordon-Cordo C, Fuks Z. The biological basis for conformal three-dimensional radiation therapy. Int J Radiat Oncol Biol Phys 1991; 21: 805–11.
12. Ling C, Burman C, Chui CS, et al. Perspectives of multidimensional conformal radiation treatment. Radiother Oncol 1993; 29: 129–39.
13. Ling CC, Burman C, Chui C, et al. Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. Int J Radiat Oncol Biol Phys 1996; 35: 721–30.
14. LoSasso T, Chui C, Kutcher G, Leibel S, Fuks Z, Ling C. The use of a multi-leaf collimator for conformal radiotherapy of carcinomas of the prostate and nasopharynx. Int J Radiat Oncol Biol Phys 1993; 25: 161–70.
15. Mohan R, Mageras G, Baldwin B, et al. Clinically relevant optimization of 3D conformal treatments. Med Phys 1992; 19: 933–44.
16. Zelefsky MJ, Leibel SA, Kutcher GJ, Kelson S, Ling C, Fuks Z. The feasibility of dose escalation with three-dimensional conformal radiotherapy in patients with prostatic carcinoma. Cancer J Sci Am 1995; 1: 142–50.
17. Bonin S, Hanlon A, Lee W, Movsas B, Al-Saleem T, Hanks G. Evidence of increased failure in the treatment of prostate carcinoma patients who have perineural invasion treated with three-dimensional conformal radiation therapy. Cancer 1997; 79: 75–80.
18. Hanks GE, Hanlon AL, Schultheiss TE, et al. Conformal external beam treatment of prostate cancer. Urol 1997; 50: 87–92.
19. Hanks GE, Lee WR, Hanlon AL, et al. Conformal technique dose escalation for prostate cancer: improved cancer control with higher doses in patients with pretreatment PSA $\geq$ 10 ngm/ml. Int J Radiat Oncol Biol Phys 1996; 35: 861–8.
20. Lee WR, Hanks GE, Hanlon A, Schultheiss TE, Hunt MA. Lateral rectal shielding reduces late rectal morbidity following high dose three-dimensional conformal radiation therapy for clinically localized prostate cancer: further evidence for a significant dose effect. Int J Radiat Oncol Biol Phys 1996; 35: 251–7.
21. Nicolaou N, Watkins-Bruner D, Hanks GE, Hanlon A. Preservation of sexual function in young prostate cancer patients after radiation therapy: a positive factor in choice of a treatment modality. Int J Radiat Oncol Biol Phys 1996; 36: 270.
22. Pinover WH, Hanlon AL, Hanks GE. The correlation of PSA nadir and biochemical freedom from cancer after external bBeam radiation therapy. Cancer. (Submitted 1997.)
23. Schultheiss TE, Hanks GE, Hunt MA, Lee WR. Incidence of and factors related to late complications in conformal and conventional radiation treatment of cancer of the prostate. Int J Radiat Oncol Biol Phys 1995; 32: 643–50.
24. Schultheiss TE, Lee WR, Hunt MA, Hanlon AL, Peter RS, Hanks GE. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37: 3–12.
25. Soffen EM, Hanks GE, Hwang CC, Chu JCH. Conformal static field therapy for low volume low grade prostate cancer with rigid immobilization. Int J Radiat Oncol Biol Phys 1991; 20: 141–6.
26. Hanks GE. Strategies for improving the outcome of patients with poor prognosis prostate cancer. Acta Oncol 1998; 37: 5–10.
27. Hanks GE, Hanlon AL, Schultheiss TE, et al. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization and future directions. Int J Radiat Oncol Biol Phys 1998; 41: 501–10.
28. Rajapakshe R, Shalev S. Noise analysis in real-time portal imaging. I. Quantization noise. Med Phys 1994; 21: 1263–8.
29. Stafford PM, Martin EE, Chu JCH, Davidson BA, Hanks GE. Digital imaging in the radiation oncology environment: a personal computer local area network solution. J Digit Imaging 1991; 4: 177–84.
30. Corn BW, Hanks GE, Schultheiss TE, Hunt MA, Lee WR, Coia LR. Conformal treatment of prostate cancer with improved targeting: superior prostate-specific antigen response compared to standard treatment. Int J Radiat Oncol Biol Phys 1995; 32: 325–30.
31. Hanks GE, Schultheiss TE, Hunt MA, Epstein B. Factors influencing incidence of acute grade 2 morbidity in conformal and standard radiation treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1995; 31: 25–29.
32. Hanks GE. External beam radiation therapy for clinically localized prostate cancer: patterns of care studies in the United States. NCI Monographs 1988; 7: 75–84.
33. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991; 21: 935–9.
34. Zelefsky M, Leibel S, Gaudin P, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998; 41: 491–500.
35. Pollack A, Zagars G. External beam radiotherapy dose response of prostate cancer. Int J Radiat Oncol Biol Phys 1997; 39: 1011–8.
36. Hanks G, Hanlon A, Pinover W, Horwitz E, Schultheiss T. Survival advantage for prostate cancer patients treated with high dose 3D conformal radiation. Cancer J Sci Am. (Submitted 1998.)
37. Lattanzi J, McNeely S, Barnes S, Das I, Schultheiss TE, Hanks GE. Initial results of using daily CT localization to correct portal error in prostate cancer. Int J Radiat Oncol Biol Phys 1997; 39: 193.
38. Movsas B, Chapman J, Horwitz E, et al. Hypoxic regions exist in human prostate carcinoma. Urol 1998.