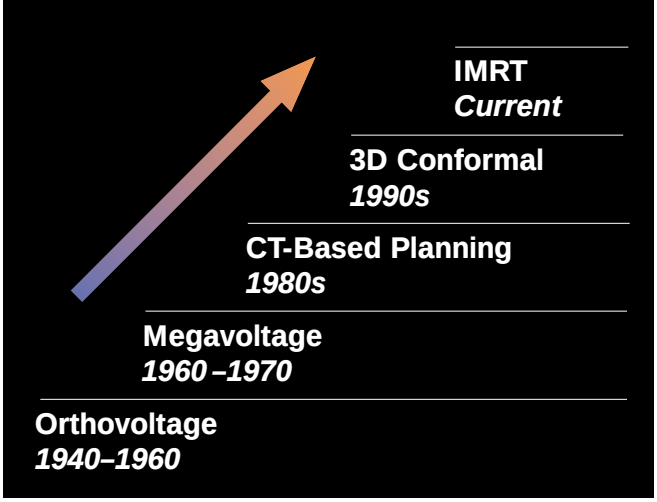
Clinical IMRT Applications for Non-Physicians

by Michael J. Zelefsky, M.D.

External beam radiation therapy has been around for the last 50 years. From the 1940s to the 1960s we had what is known as orthovoltage treatment. The X-ray beams were not very penetrating and could only reach the more superficial layers of targeted structures. In the 1960s, linear accelerators were developed. These machines produced megavoltage radiation, which allowed physicians to deliver high-energy X-rays deeper into targeted tissues. In the 1980s, CT scans facilitated the visualization of the tumor in situ. When practitioners could actually see the tumor's shape and where it was placed in relation to surrounding organs, treatment fields could be designed more accurately. Then came one of the most dramatic impacts technology has had on the delivery of radiotherapy in the last 50 years: the emergence of computer-designed, three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) (see Figure 1). These two approaches allow the radiation oncologist to deliver much more precise radiation doses to the tumor, and normal tissues are exposed to less radiation, resulting in fewer side effects.

When high-energy X-rays became available in the 1960s, tumors were conventionally treated with daily doses of radiation for about six to seven weeks. We had to rely on approximations of where the tumor was situated, and based on these approximations we designed our radiation fields. For instance, we knew that the prostate was located behind the pubic bone, so we would utilize broad margins and irradiate the area within them. Often, too much normal tissue was exposed to radiation using these methods, which led to severe side effects. In addition, not enough radiation reached the tumor. We wanted to deliver high doses of radiation because we knew that higher doses destroyed more cancer cells; but if we gave the dose we wanted, the level of damage to normal tissue was unacceptable.

Figure 1. Evolution of External Beam Radiotherapy Delivery



CT scans allowed us to target radiation more accurately, but the breakthrough came with the advent of computers in the late 1980s and the development of 3D-CRT. 3D-CRT uses sophisticated computer programs to generate the entire three-dimensional shape of the tumor and all the surrounding structures and organs. Images are taken sequentially, from the top to the bottom of the affected area, and then stacked to produce a three-dimensional image. This imaging process not only defines the tumor, but also defines the tumor's position in the body and its relationship to everything around it. 3D-CRT allows practitioners to shape the radiation beam to match the shape of the tissue they want to target, while reducing the volume of normal tissue exposed to higher radiation doses.

3D-CRT often takes advantage of beams that are shaped by a multileaf collimator to conform to the dimensions of the tumor (see Figure 2). For prostate cancer, treatment beams are often aimed from five to seven different angles. Since the beams are static, all the tissue touched by the beams receives the same intensity of radiation. The toxicity to surrounding tissues, although it is less than that produced by conventional techniques because the beam is shaped, has also limited the dose of radiation that can be used with this treatment method (see Figure 3, a six-portal 3D-CRT dose plan for a prostate cancer patient).

In recent years, studies from several hospitals, including M.D. Anderson Cancer Center, Fox Chase Cancer Center, and Memorial Sloan-Kettering Cancer Center, have demonstrated that the radiation dose makes a difference. In prostate cancer, for instance, significant subpopulations of tumor cells are resistant to radiation at 65 to 70 Gy, but succumb when dose levels rise to 75 Gy and above.[1] Several studies have indicated a direct relationship between local control and radiation dose in carcinoma of the prostate.[2,3,4] The problem with using

75 Gy doses or higher is the amount of tissue damage that results in the bladder and the rectum. The incidence of moderate to severe proctitis in patients with prostate cancer receiving conventional megavoltage radiation treatment is 20 percent if the dose is less than 75 Gy, but rises to 60 percent when the dose goes higher.[5] The lack of sophisticated treatment planning tools to precisely delineate the prostate from its surrounding pelvic organs and calculate the dose at each pixel within the irradiated tissue volume has prevented conventional radiotherapy from delivering more than 70 Gy to prostate tumors.[1]

3D-CRT techniques produce more precise radiation delivery; yet, although severe side effects have been significantly reduced, moderate side effects can still be seen.

Figure 2. A Multileaf Collimator

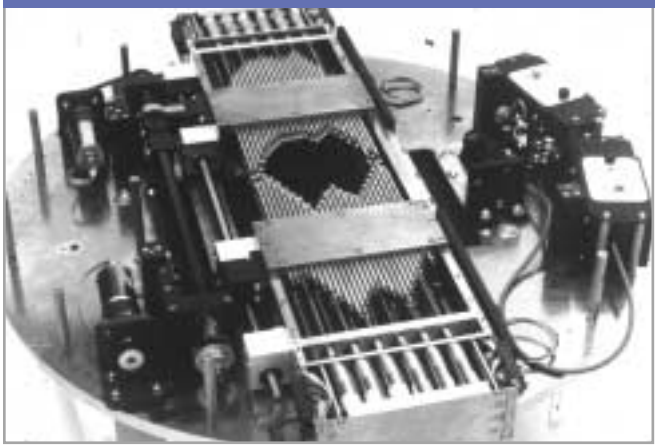
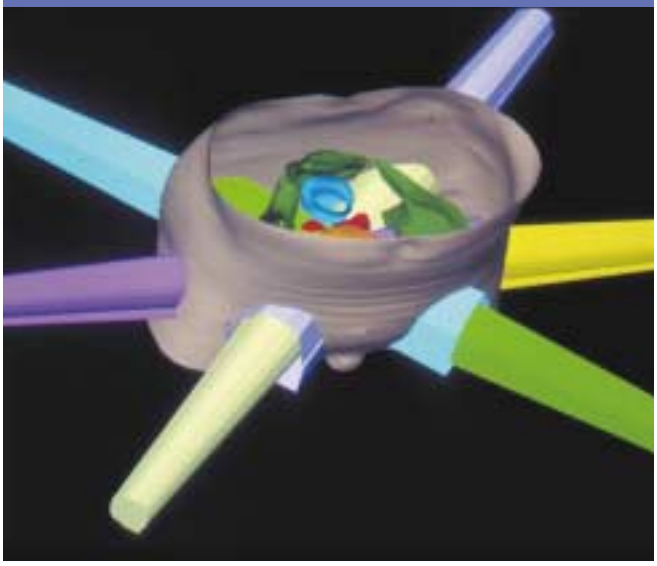


Figure 3. A Six Portal 3D-CRT Dose Plan for a Prostate Cancer Patient



The development of computer-automated treatment planning, which allowes the collimator leaves to slide back and forth across the treatment beam and modulate its intensity, led to the development of IMRT, which is an advanced form of 3D-CRT. IMRT dramatically enhances the ability of the accelerator to conform the radiation dose distribution to the needs of the tissue it touches, and facilitates the escalation of the radiation dose to previously unattainable levels.

IMRT TREATMENT OF PROSTATE CANCER

Beginning in April 1996, IMRT was introduced at the Memorial Sloan-Kettering Cancer Center to treat prostate cancer for the entire treatment course of 81 Gy, and was subsequently used for escalation to 86.4 Gy.[1,6,7] IMRT is now the standard mode of radiotherapy for clinically localized prostate cancer at Memorial Sloan-Kettering (see Figure 4 of a prostate cancer patient receiving IMRT). Examining the effect of IMRT on prostate cancer will illustrate how the technique works and how it differs from 3D-CRT and other radiotherapy modalities.

Conventional External-Beam Radiotherapy

Much of the current, long-term external-beam radiotherapy outcome data for prostate carcinoma are based on patients treated in the 1970s. During that era, the anatomical boundaries of the prostate and the treatment field size and shape were defined indirectly using plain films of the pubic bone, bladder, and rectum filled with contrast media. Foley catheter balloons and digital rectal examinations were the guidelines for portal design. Three-dimensional visualization was not possible. In general, conventional treatment volumes routinely included the prostate, seminal vesicles, and the regional lymph nodes. Treatment was delivered with a four-field, whole-pelvis approach followed by a boost that delivered a cumulative dose of 65 Gy to the prostate. Currently, the shape and location of the prostate are defined with CT scans and magnetic resonance imaging (MRI) scans, and even conventional treatment techniques utilize CT-assisted planning for the boost phases of therapy.[1]

Although the true rates of local relapse after conventional external-beam radiotherapy remain uncertain, data accrued over the past three decades indicate that these techniques yielded 10-year, clinically-assessed (no prostate-specific antigen [PSA] data) local control rates of 85 to 96 percent in patients with stage T1B to T2 disease, and 58 to 65 percent in T3 or T4 tumors.[1,8] These rates markedly overestimated the true degree of local control, since more recent PSA, relapse-free survival rates have been reported to be 65 percent in patients with stage T1 to T2 disease[9] and only 24 percent for more locally advanced T3 tumors.[2] Furthermore, biopsy-proven local recurrence rates have ranged from 23 to 65 percent in patients with T1 to T3 tumors treated only with dose levels of 65 to 70 Gy.[1,10,11]

Because dose computations are labor-intensive, conventional dose calculations provided only limited information about the way the radiation was distributed within the prostate. Data were mainly confined to the midaxial tissue plane in the center of the tumor. The dose to the remainder of the tumor was calculated based on reasonable, albeit imprecise, projections. This inability to ensure that the prescribed dose was delivered throughout the tumor target volume frequently resulted in regions of the tumor that were underdosed and

geographic misses, particularly at the tumor edges. Uncertainties about patient positioning for daily treatments and organ motion complicated these difficulties.[12] To decrease the risk of missing the tumor edges, extensive safety margins were frequently added to the presumed target volume. These margins extended into the adjacent rectum and bladder, which could not tolerate radiation doses larger than 70 Gy, and limited the radiation dose to the tumor to that amount.[1]

3D-CRT

Advances in computer engineering and software design brought about the development of 3D-CRT. The availability of high-performance workstations, sophisticated computer programs capable of rapid dose calculations, computer-controlled treatment delivery systems with multileaf collimation, and online portal imaging have made 3D-CRT a feasible option for the treatment of prostate cancer. These techniques allow the treatment beam to conform to the anatomical configuration of the tumor and reduce the volume of radiation delivered to critical surrounding organs.[1]

Early in our experience with 3D-CRT, patients were treated with a coplanar, six-field 3D-CRT technique (two lateral opposed fields and two pairs of oblique fields). We were able to vary the dose only from 4 to 7 percent to protect normal tissue, but we achieved improved biochemical (PSA) and biopsy-proven local control when dose levels greater than or equal to 75.6 Gy were administered.[1,13]

Since the early 3D-CRT techniques did not conform tightly to the prostate, rectal toxicity and bleeding occurred. A dose-escalation study of 871 patients with localized prostate cancer treated with first-generation 3D-CRT revealed a dose-related increase in late grade 2 rectal bleeding. This side effect occurred in 5 percent of patients receiving 64.8 to 70.2 Gy and 17 percent of those treated to 75.6 Gy. Research showed that doses above 75.6 Gy could not be safely administered without better protection of the rectum.[1,7,14]

To escalate the dose to 81 Gy, a two-phase approach was adopted. The first dose of 72 Gy was administered with the coplanar, six-field design and was followed by a 9 Gy boost in five treatment fractions. The boost phase ensured that the rectum was completely blocked in each field, but this technique only reduced the rate of rectal bleeding to 15 percent.[6] Until IMRT was introduced, rectal toxicity was considered an impediment to radiation doses higher than 75.6 and 81.0 Gy.

IMRT

The Memorial Sloan-Kettering Cancer Center system for IMRT delivery uses multileaf collimation in a dynamic mode. Each pair of opposing leaves creates an individual "sliding window" that travels across the target under computer control during radiation delivery. The width of the window and the speed of the leaves are continuously adjusted, according to a prescribed scheme, to produce the required intensity patterns. This, in turn, determines the dose absorbed at each point within the treated tissue segment exposed to the radiation beam (see Figure 5).[1] A comprehensive and rigorous quality assurance program to ensure the precision working of the machinery and software is critical to the success of any IMRT program.[1,15]

The Memorial Sloan-Kettering Cancer Center uses a

Figure 4. An Aquaplast Hip Fix for a Prostate Cancer Patient Receiving IMRT at the Memorial Sloan-Kettering Cancer Center

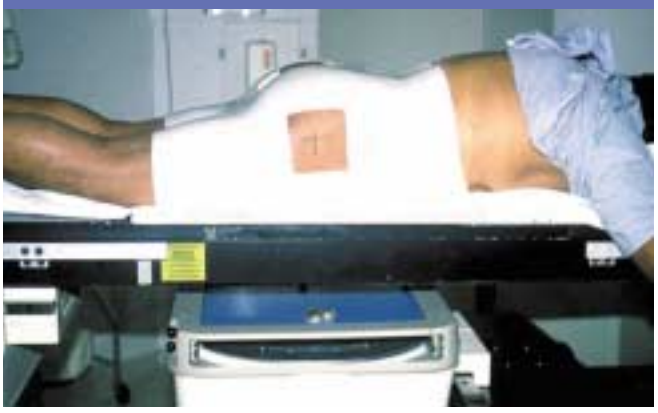


Figure 5. Beam Intensity Profiles for an IMRT Prostate Plan

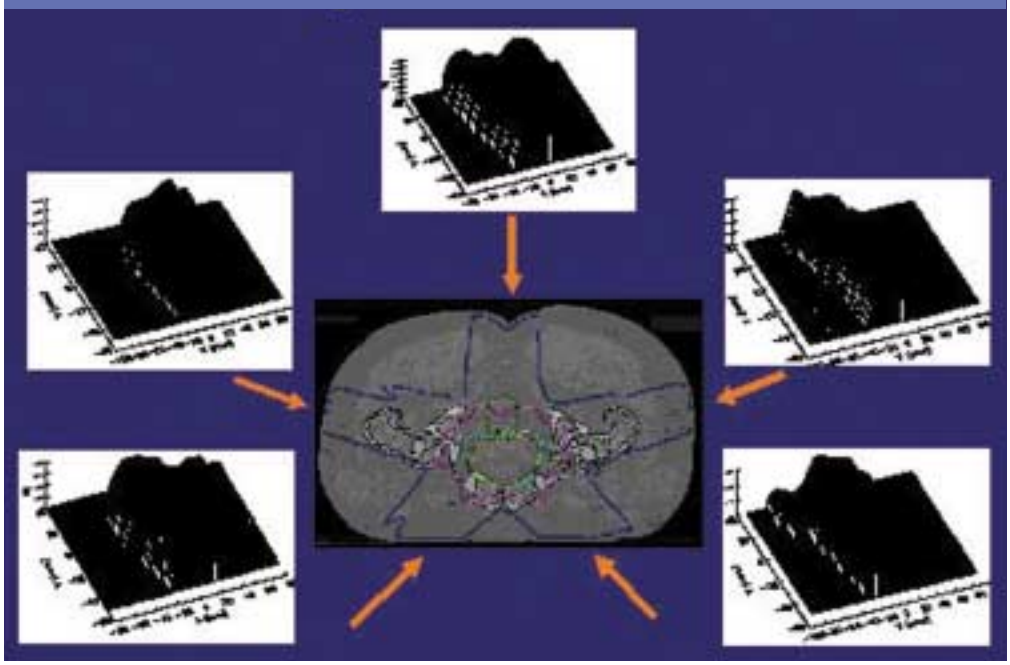


Figure 6. Dose Distributions of Conventional 3D-CRT and IMRT Plans

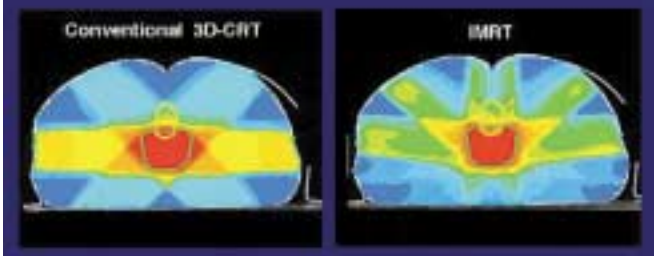


Figure 7. IMRT Applications at Memorial Sloan-Kettering Cancer Center

- Prostate
- Breast
- Head and neck
- Brain
- Liver and pancreas
- Pediatric tumors
- Paraspinous tumors
- Whole abdomen irradiation

five-field, isocentric, coplanar approach to the treatment of prostate cancer at gantry angles of 0º, 75º, 135º, 225º, and 285º. The patient set-up and delivery of this five-field dynamic multileaf collimation treatment requires no more time than treatment with six-field 3D-CRT, so the number of patients we can see has not changed with the advent of IMRT at our clinic.[1]

Comparison of 3D-CRT and IMRT

When we compared the dose distributions of the five-field IMRT plan and the six-field 3D-CRT plan (that involved initial treatment with 72 Gy followed by a 9 Gy boost), we found that IMRT delivered a better-conformed dose at 81 Gy and decreased the amount of radiation delivered to the surrounding normal tissues (see Figure 6).[1]

We performed several studies to validate our observations. The first was a dose escalation trial where the toxicity outcomes of 171 patients treated with IMRT to 81 Gy were compared with 61 patients treated with 3D-CRT at the same dose level. Acute and late urinary toxicities were not significantly different for the two methods, but the combined rates of acute grades 1 and 2 rectal toxicities and the risk of late grade 2 rectal bleeding were significantly lower in the IMRT patients ($p = 0.05$ and 0.0001, respectively).[6] The two-year actuarial rates of grade 2 rectal bleeding were 2 percent for IMRT and 10 percent for 3D-CRT ($p < 0.001$).[6] Only one case of grade 3 rectal bleeding was observed in each treatment group.

Since rectal toxicity was decreased with IMRT, we escalated the dose to 86.4 Gy. Forty-one patients were accrued to the 86.4 level of the study, which had a median follow-up time of 36 months (range 18 to 45 months). No grade 3 or higher toxicities were observed, and only two patients developed grade 2 rectal bleeding.[1]

In addition, we have recently analyzed the outcome of 772 patients treated with IMRT: 698 to 81.0 Gy and 74 to 86.4 Gy.[16] The median follow-up was 24 months (range 6 to 60 months), and during that time only 11 patients (1.5 percent) developed grade 2 rectal bleeding and 4 (0.5 percent) experienced grade 3 rectal toxicity. The three-year actuarial rate of grade 2 or higher rectal bleeding was 4 percent. IMRT patients treated to 81.0 Gy or higher continue to exhibit significantly lower rates of rectal bleeding compared to patients treated to 75.6 Gy or higher with 3D-CRT. Although the follow-up time is still short for patients treated to 86.4 Gy, so far there are no differences in rectal toxicity between the 81.0 and 86.4 Gy treatment groups.[13] Because both local control and long-term PSA relapse-free survival are dose-dependent, these data confirm that IMRT represents a noteworthy advance in the ability to deliver high-dose radiation in prostate cancer.[1,7,13,17-19]

Selective Dose Intensification: Dose Painting With Biologic-Based Imaging

Our dose escalation study suggested that IMRT was required to deliver 86.4 Gy safely, and that escalation to 91.8 Gy using IMRT would be limited by the inability of inverse planning to produce treatment regimens that would deliver high dose levels to the tumor but sufficiently spare the urethra and rectum (unpublished data). At the Memorial Sloan-Kettering Cancer Center, we are now considering increasing the dose only to selected, tumor-bearing regions within the prostate. Although the classic approach to radiotherapy calls for homogeneous dosing throughout the tumor volume, recent advances in imaging have identified clusters of tumor deposits within the prostate, and functional imaging may identify foci of highly resistant or hypoxic tumor clones that require locally enhanced doses.[1]

Biologic-based imaging techniques, such as positron emission tomography (PET) and magnetic resonance spectroscopic imaging (MRSI),[20] may be able to identify areas within the prostate that require selective dose intensification. Since IMRT can deliver different doses of radiation to multiple target sites, it will allow physicians to selectively paint increased doses of radiation onto specific, image-defined regions within the prostate. Researchers at the University of California at San Francisco have already conducted treatment-planning studies using IMRT guided by MRI/MRSI. They delivered 90.0 Gy to targeted lesions within the prostate while treating the remainder of the gland with 73.8 Gy and maintaining normal tissue dose constraints.[1,21,22]

CONCLUSIONS

IMRT is a new radiation therapy technique with enormous potential for multiple applications (see Figure 7). Preliminary results indicate that treatment with this enhanced conformal delivery system produces substan-

tial reductions in treatment-related toxicities[1,6,23,24] and achieves high rates of local control and long-term, relapse-free survival in patients with prostate cancer. IMRT is also useful in reducing the late gastrointestinal toxicities produced by whole-pelvic irradiation for prostate cancer lymph node metastases. The decreased risk of rectal bleeding observed after high-dose IMRT compared to conventional 3D-CRT shows promise and will positively impact patient quality of life.

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REFERENCES

[1]Zelefsky MJ, Fuks Z, Leibel SA. Intensity-modulated radiation therapy for prostate cancer. *Semin Radiat Oncol.* 2002;12(3):229-237.

[2]Zagars GK, Pollack A, Smith LG. Conventional external-beam radiation therapy alone or with androgen ablation for clinical stage III (T3, Nx/N0, M0) adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys.* 1999;44:809-819.

[3]Valicenti R, Lu J, Pilepich M, et al. Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated on the Radiation Therapy Oncology Group Trials. *J Clin Oncol.* 2000;18:2740-2746.

[4]Leibel SA, Hanks GE, Kramer S. Patterns of care outcomes studies: Results of the national practice in adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys.* 1984;10:401-409.

[5]Smit WGJM, Helle PA, Van Putte WLJ, et al. Late radiation damage in prostate cancer patients treated by high-dose external radiotherapy in relation to rectal dose. *Int J Radiat Oncol Biol Phys.* 1990;18:23-29.

[6]Zelefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiother Oncol.* 2000;55:241-249.

[7]Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol.* 2001;166:876-881.

[8]Hanks GE, Krall JM, Hanlon AL, et al. Patterns of care and RTOG studies in prostate cancer: Long-term survival, hazard rate observations, and possibilities of cure. *Int J Radiat Oncol Biol Phys.* 1994;28:39-45.

[9]Shipley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: A multi-institutional pooled analysis. *JAMA.* 1999;28:1598-1604.

[10]Crook JM, Bahadur YA, Bociek RG, et al. Radiotherapy for localized prostate carcinoma: The correlation of pre-treatment prostate specific antigen and nadir prostate specific antigen with outcome as assessed by systematic biopsy and serum prostate specific antigen. *Cancer.* 1997;79:328-336.

[11]Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 1997;37:247-252.

[12]Kutcher GJ, Mageras GS, Leibel SA. Control, correction, and modeling of setup errors and organ motion. *Semin Radiat Oncol.* 1995;5:134-145.

[13]Zelefsky MJ, Leibel SA, Gaudin PB, 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.

[14]Leibel SA, Fuks Z, Zelefsky MJ, et al. The treatment of localized prostate cancer with three-dimensional conformal and intensity modulated radiation therapy at the Memorial Sloan-Kettering Cancer Center. In: Purdy J, Grant W III, Palta J, eds. *3D Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in the Next Millennium.* Madison, Wisc: Advanced Medical Publishing; 2000.

[15]Burman CM, Chui CS, Kutcher GJ, et al. Planning, delivery, and quality assurance of intensity-modulated radiotherapy using dynamic multileaf collimator: A strategy for large-scale implementation for the treatment of carcinoma of the prostate. *Int J Radiat Oncol Biol Phys.* 1997;39:863-873.

[16]Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity-modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys.* 2002;53:1111-1116.

[17]Hanks GE, Hanlon AL, Pinover WH, et al. Dose selection for prostate cancer based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys.* 2000;46:823-832.

[18]Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose escalation study comparing 70 Gy to 78 Gy for prostate cancer. *J Clin Oncol.* 2000;18:3904-3911.

[19]Lyons JA, Kupelian PA, Mohans DS, et al. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. *Urology.* 2000;55:85-90.

[20]Kurhanewicz J, Vigneron DB, Hricak H, et al. Three-dimensional H-1 MR spectroscopic imaging of the in situ human prostate with high (0.24-0.7-cm^3) spatial resolution. *Radiology.* 1996:198:795-805.

[21]Pickett B, Vigneault E, Kurhanewicz J, et al. Static field intensity modulation to treat a dominant intra-prostatic lesion to 90 Gy compared to seven field 3-dimensional radiotherapy. *Int J Radiat Oncol Biol Phys.* 1999;43:921-929.

[22]Xia P, Pickett B, Vigneault E, et al. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intra-prostatics lesions of prostate cancer to 90 Gy. *Int J Radiat Oncol Biol Phys.* 2001;51:244-254.

[23]Nutting CM, Convery DJ, Cosgrove VP, et al. Reduction of small and large bowel irradiation using an optimized intensity-modulated pelvis radiotherapy technique in patients with prostate cancer. *Int J Radiat Oncol Biol Phys.* 2000;48:649-656.

[24]Teh BS, Mai WY, Uhly BM, et al. Intensity-modulated radiation therapy (IMRT) for prostate cancer with the use of rectal balloon for prostate immobilization: Acute toxicity and dose-volume analysis. *Int J Radiat Oncol Biol Phys.* 2001;49:6705-6712.