

New Technologies for the Radiotherapy of Prostate Cancer

A Discussion of Clinical Treatment Programs

J.L. Meyer^a · S. Leibel^b · M. Roach^c · S. Vijayakumar^d

Departments of Radiation Oncology, ^aSaint Francis Memorial Hospital, San Francisco, Calif., ^bStanford University, Stanford, Calif., ^cUniversity of California, San Francisco, Calif., ^dUniversity of California, Davis, Calif., USA

New radiation therapy planning and delivery technologies have often been applied first to the treatment of localized prostate cancer. The development and optimization of these new applications for prostate cancer therapy can make this site a model for their use at other tumor sites. For prostate cancer or other tumors, the process of defining new roles for technology can lead to a reassessment of the basic goals of the treatments themselves. What clinical advances need to be made? What changes in the target volumes, their delineation and treatment doses are these technologies to be used for? These questions are central themes in the current investigations with intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) for prostate cancer treatment. In the following two sections, two of the authors give their insights into the use of advanced technologies for prostate cancer therapy. In the final section, provocative questions about the current directions of radiotherapy for prostate cancer are addressed in a roundtable discussion.

Target Definitions and Lessons in Clinical Treatment Planning (M. Roach)

The goals of this section are to discuss evidence for selecting targets and defining normal tissue constraints in the radiotherapy of prostate cancer. It must be recognized that there is a lack of evidence-based consensus on many of the issues involved. There are several problems that are faced in evaluating the literature on

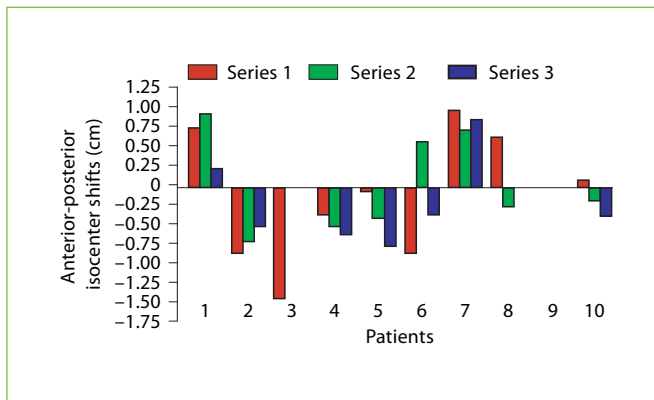


Fig. 1. Defining target volumes and the role of 3DCRT-IMRT for prostate cancer. Anterior-posterior isocenter shifts in patients receiving radiotherapy and rescanned every 2 weeks [1].

prostate radiotherapy. In assessing issues surrounding quality of life, there are large discrepancies between what physicians report and what patients report, and one must be careful in accepting complication rates that are reported without using validated quality of life instruments. Also, the ability to draw conclusions from studies is often limited by the duration and completeness of patient follow-up, since long follow-up periods are required but difficult to obtain. Finally, the radiation techniques are critical to the outcome results achieved, and yet the treatment methods for prostate radiotherapy have not been standardized. Despite these concerns, available data do support certain general recommendations, and clinical trials are continuing to develop additional conclusions.

Patient Setup and Target Localization

More than 10 years ago, the University of California, San Francisco (UCSF) group first performed studies evaluating prostate position during radiotherapy treatment courses [1]. Serial CT scans were obtained every 2 weeks during the radiotherapy, bony anatomy was used to register the scans, and the prostate position was compared between the scans. The results for individual patients are shown in figure 1. As an example, the results for the first patient show that his prostate was 0.75 cm more anterior on the second scan than the first, 2 weeks after treatment had started. Similar results were observed in other patients. Since this initial work, many other groups have obtained comparable findings. It is clear that the prostate does move during the therapy course, and its position is more variable than previously appreciated.

To address this issue and attempt to adjust for it, our group has used gold seed fiducial markers implanted into the prostate for the past 5 years. These are $1.1 \times$

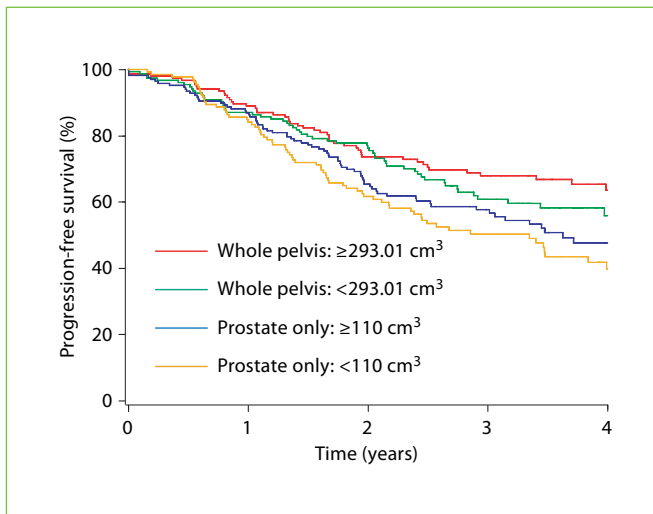


Fig. 2. RTOG 9413: progression-free survival in the 4-arm study [3].

3 mm in size; two are placed in the prostate base and one at the apex. Prior to each daily treatment, they are imaged, and adjustments are made to correct for setup error and organ movement, which can be significant problems. This is especially true in some patients. Our group has recently published a report on 3 patients with morbid obesity, indicating that if a patient is severely obese and internal markers are not used, therapy beams can miss the prostate when setup is based on skin marks alone [2]. Internal markers are especially recommended for these patients.

Planning Target Volume

The results of the Radiation Therapy Oncology Group (RTOG) protocol 9413 have been published and are relevant for patients at risk for lymph node involvement [3]. This double randomization study evaluated the effect of hormonal therapy timing (prior to or after radiotherapy), and the effect of radiotherapy field size (pelvis plus prostate or prostate alone). Pertinent outcome results are shown in figure 2. Superior progression-free survivals were achieved in patients receiving whole pelvic radiotherapy and neoadjuvant hormonal therapy. One must conclude that it is important to irradiate the regional pelvic lymph nodes when they are at risk for involvement.

Since this protocol permitted some differences in the actual size of the fields used, the RTOG 9413 results have been further analyzed by evaluating the results according to the actual fields [4]. These have been divided into groups: prostate-only, prostate-plus-mini-pelvis, and prostate-plus-whole-pelvis fields. Reanalysis shows two findings. First, the complication rates with the prostate-plus-mini-

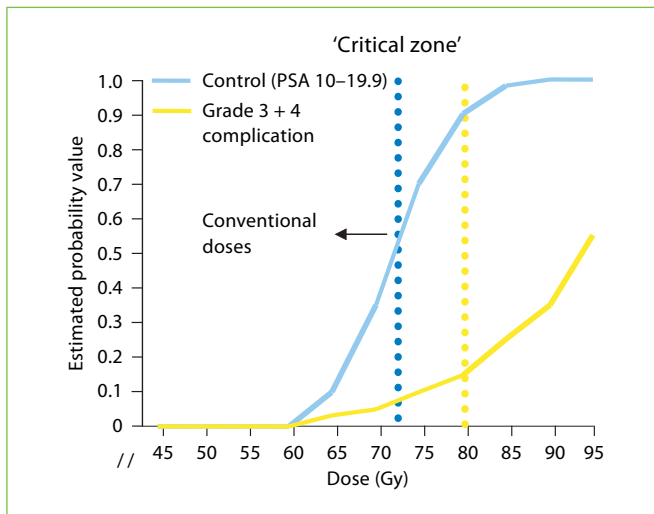


Fig. 3. 3DCRT dose-response functions: actuarial biochemical 5-year disease control and grade 3 and 4 complication rates with increasing radiation dose. Modified from Hanks et al. [5].

pelvis fields were nearly the same as with the larger prostate-plus-whole-pelvis fields. Second, the control rates did correlate with the size of the fields: 4-year progression-free survival rates were 60% for the prostate-plus-whole-pelvis, 48% for the prostate-plus-mini-pelvis and 40% for the prostate-only groups. Thus, the larger the field (and logically the more nodes treated), the greater the control rate.

Normal Tissue Effects of Treatment and Radiation Planning

In figure 3, Dr. Hanks et al. [5] show useful information about the risk of grade 3 and 4 complications after increasing radiation doses, as well as the relationship between dose and tumor control in patients with intermediate-risk disease. For high rates of tumor control, it is apparent that radiation doses need to exceed 70 Gy and perhaps approach 80 Gy or possibly higher. It is also known that the shape of the complication curve is such that the rates of complication climb steeply when these dose levels are approached. In order to spare normal tissues, it is critical to evaluate and understand the technique of treatment used to deliver the doses that are required.

In this volume, Dr. Vijayakumar et al. [pp. 180–192] report on the use of benchmarking with dose-volume histogram (DVH) analysis for assessing and guiding the use of new technologies in the clinic. This type of approach has been used at UCSF for introducing treatment programs for prostate cancer therapy, first with conformal therapy dose escalation. Prior to dose escalating any patient, a treat-

Table 1. Dose to the bulb of the penis and risk of impotence: change in potency based on a survey of men treated with 3DCRT at UCSF for localized prostate cancer [6]

Impact of 3DCRT on potency	Dose to 5% of bulb Gy		Dose to 70% of bulb Gy		Dose to 95% of bulb Gy	
	median	range	median	range	median	range
No change	48.5	40–70	29.0	22–69	14.0	7–47
Decline = 1	69.8	56–75	56.1	45–75	33.2	0–74
Decline >1	67.3	62–90	66.8	42–88	51.1	16–84
Kruskal-Wallis test	p = 0.08		p = 0.17		p = 0.05	

ment plan using a standard therapy technique was constructed. A three-dimensional conformal radiation therapy (3DCRT) plan was also generated, and the normal tissue DVHs compared. Dose escalation was allowed to proceed when the dose to normal tissues did not significantly increase. This approach has proved reliable, and over the past 15 years the complication rates for prostate radiotherapy at UCSF have remained low with ever more advancing external beam radiation techniques and treatment doses. One is using what one already knows to prevent higher complication rates.

Impotence

Urologists often refer to sexual function after radical prostatectomy as an improving outcome; patients are initially impotent, but this gradually resolves. The opposite is true with radiation therapy. Rates of impotence increase after treatment, and are even worse when combined with hormone therapy. Ultimately, there may be little outcome difference in sexual function between these approaches. However, one must evaluate this literature carefully, because the baseline characteristics of the patients may be different. The age of the patient and his degree of infirmity can be major considerations in the initial treatment selection.

Recent data show that it is probably important to avoid irradiating the base of the penis. Dr. Fisch et al. [6] published our data that indicated that the risk of impotence increased as the dose to the penis increased, whether measured as dose to 5% of the bulb, or 70%, or 95% (table 1). If the dose was over about 50–52 Gy, there was a higher risk of impotence. To substantiate these results, data from the RTOG 9406 dose escalation study were analyzed [7]. Without knowing the outcomes of patients in terms of sexual functioning, the planning scans of approximately 150 cases were evaluated and the bulb of the penis was delineated. A statistician then used a threshold dose to that area of 52.5 Gy, based on other studies at our institution, and found that the risk of becoming impotent after radio-

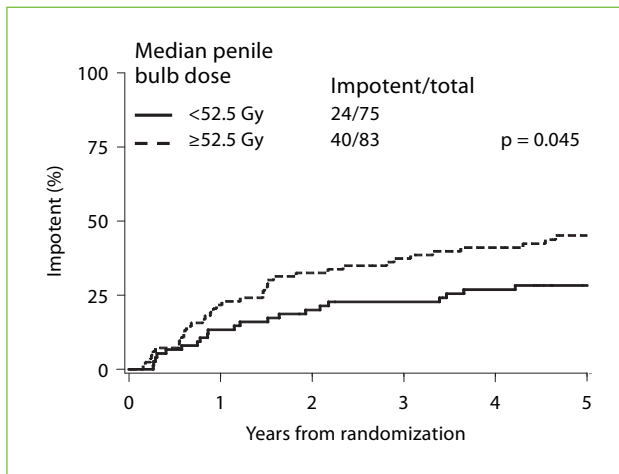


Fig. 4. RTOG 9406 dose levels: time to impotence.

therapy was significantly higher above that dose (fig. 4). Avoiding high radiotherapy doses to the penile bulb is an easy yet important aspect of defining the target volumes. IMRT can achieve this sparing somewhat more efficiently, although acceptable results can be obtained with 3DCRT.

Rectal Toxicity

The RTOG and other groups have reported their toxicity results in treating patients to 78–80 Gy for prostate cancer [8]. In general, a modest risk of greater than grade 2 rectal complications has been reported, about 2% or less at a median of 3.0 years after therapy. Often these were physician-reported rates, and measures using validated quality of life instruments could report more accurate results. As reviewed below, investigators at the Memorial Sloan-Kettering Cancer Center (MSKCC) have done perhaps the most work with IMRT for prostate cancer, and have made important observations about the value of IMRT compared with conventional 3DCRT in terms of reducing the risk of complications, especially of rectal toxicity. It is important to have longer-term follow-up in assessing these late risks of complication. Nevertheless, there is little question that improvements derived from IMRT are valid, based upon our own experience at UCSF and elsewhere.

Several groups have investigated the risks of rectal toxicity based on dose/volume assessments. For example, work published by Kuban et al. [9] is shown in figure 5, and demonstrates that 70 Gy to $\geq 26\%$ of the rectal volume correlated with a higher risk of grade 2 or higher complications to the rectum. An interesting observation made by the William Beaumont group is that patients who had more

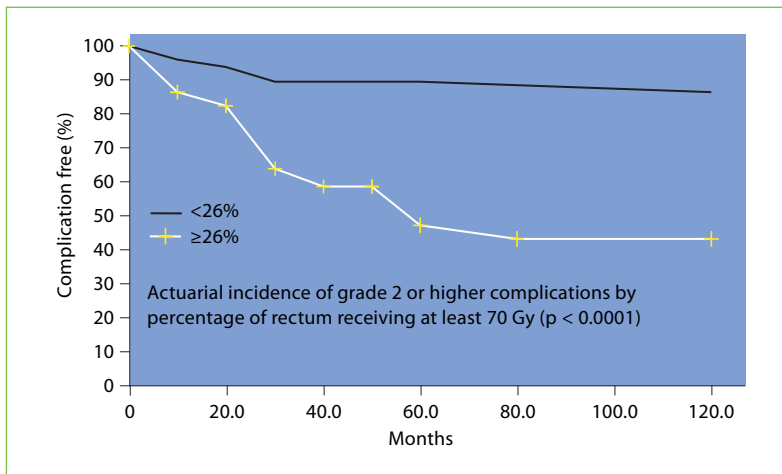


Fig. 5. Hazards of dose escalation in prostate cancer radiotherapy [9].

acute toxicity also tended to have more late toxicity. This has not been well described before, and not all series observe this phenomenon. However, if a patient is having significant acute toxicity, a reevaluation of the treatment approach may be worth considering.

If one cumulates several late rectal toxicity studies together, one can derive a threshold curve as shown in figure 6. At UCSF, the dose constraints for IMRT have been based on this curve, and the goal is set to be about 30% below what the literature suggests will be the threshold for complication. It is possible to achieve this goal with IMRT. Based upon the data of several groups [9–12], reasonable goals include keeping the radiation dose to 25% of the rectum at <70 Gy and the mean dose at <50 Gy.

Bladder Toxicity

Bladder toxicity is not as common as rectal toxicity, but can be a very late phenomenon, several years after therapy. The determination of bladder dose constraints is complicated by the changing volume of the bladder during treatment. A patient's bladder may be full during planning but will rarely be full to the same degree during therapy, and the bladder DVH that was initially planned will often not reflect the actual treatment experience. This is especially true toward the end of therapy; because of developing inflammation, patients may think that their bladder is full when it is not, resulting in an even larger dose to the bladder than planned. While these are identified problems, treatment planning investigations do show that IMRT can achieve significantly better sparing of bladder tissues than 3DCRT.

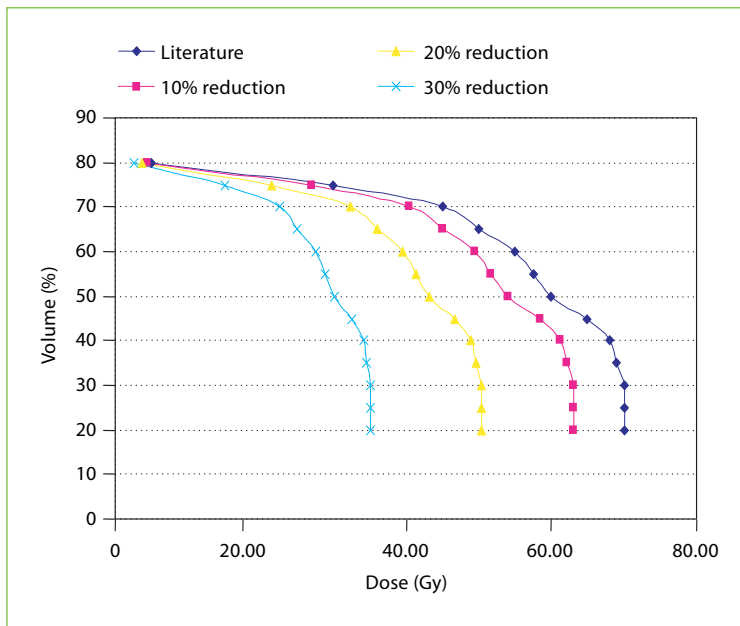


Fig. 6. Rectum dose constraints. Evidence-based constraints for rectal complications at UCSF.

Comments

In summary, accuracy is important in prostate radiotherapy to achieve the doses required for cure without increasing normal tissue damage. Validated instruments that address quality of life issues are needed. To reduce the risk of impotence, it is important to limit the radiation doses to the penile bulb. It is equally important to limit the rectal doses, and studies suggest that no more than 25% of the rectum should receive 70 Gy or more, and the mean rectal dose should be less than 50 Gy. Bladder toxicity can also occur, though not as frequently and often later than rectal effects. Finally, the future of our new technology depends on improving the quality assurance of the treatment procedures, to guarantee that everyone is treated appropriately.

The Development of Dose Objectives for Prostate Radiotherapy (S. Leibel)

What is necessary to improve local tumor control with radiotherapy in prostate cancer? First, dose levels must be sufficiently high to eliminate the most resistant tumor clonogens. Conformal treatment techniques are required if high doses are to be administered without increasing normal tissue toxicity. Another approach to improving local tumor control is to use agents that enhance the sensitivity of

Table 2. MSKCC dose escalation study in prostate cancer: patient characteristics (n = 1,684)

	Number	Percent
Stage		
T1c	573	34
T2a	309	18
T2b	271	16
T2c	217	13
T3	314	19
Dose		
64.8 Gy	96	
70.2 Gy	274	
75.6 Gy	476	
81 Gy	764	
86.4 Gy	74	

Age: median = 68 years, range = 46–86 years; follow-up: median = 68 months; range = 36–168 months; neoadjuvant androgen deprivation = 746 patients (44%).

tumor clonogens to the biological effects of irradiation. Some of these agents may cause a general increase in the level of radiosensitivity of tissues. Thus, the ability to deliver combined-modality therapy without overlapping toxicities represents another rationale for conformal therapy. Based on these two ideas, the hypothesis of dose escalation with conformal radiotherapy was formed: that conforming the high-dose region to the shape of the tumor will enable an increase in the tumor dose without an increase in toxicity, and an increase in the tumor dose will improve local tumor control and ultimately patient survival.

Dose Escalation for the Radiotherapy of Prostate Cancer

To test this hypothesis in the treatment of prostate cancer, a dose escalation study, designed to assess the morbidity of 3DCRT and to establish the maximum feasible dose, was initiated at MSKCC in 1988 [13, 14]. Patients with stage T2c–T3 disease were eligible for the study and evaluated for late complications at incremental dose levels of 75.6, 81 and 86.4 Gy (table 2). Forty patients were treated at each dose level and escalation to the next level was permitted if the rate of grade 3 toxicity remained less than 10%. Between 1988 and 1992, patients were treated at conventional dose levels of 64.8–70.2 Gy to establish baselines for acute tolerance and late toxicity. The 75.6-Gy arm was opened in April 1991. The dose for all other patients treated during this period was 70.2 Gy. Once it was determined that there was no excess in toxicity, the investigational dose in October 1992 was escalated to 81 Gy, and all other patients received 75.6 Gy. In October 1995, the first patient was

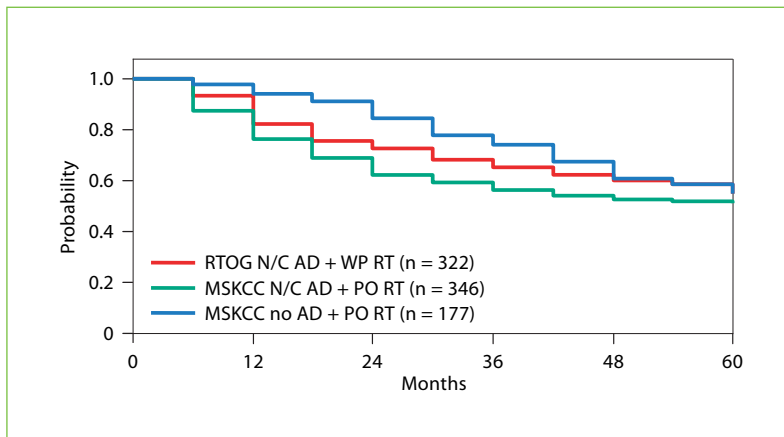


Fig. 7. Progression-free survival in prostate cancer patients with >15% risk of pelvic lymph node metastases. RTOG 9413 patients [3] treated with whole-pelvis (WP) radiotherapy (RT). MSKCC patients treated with prostate-only (PO) radiotherapy, with or without neoadjuvant (N/C) androgen deprivation (AD) (reported by Zelefsky et al. at the ASTRO-ASCO Prostate Conference, 2005).

treated with IMRT, first as a boost approach. Six months later, all patients with prostate cancer were treated to 81 Gy with IMRT. Finally, the 86.4-Gy arm was opened in May 1996. A total of 1,684 patients were treated in this fashion through July 2001.

Field Size and Dose Constraints

The planning target volume (PTV) encompassed the prostate and seminal vesicles but did not include the regional pelvic lymph nodes. Pelvic nodal irradiation was omitted because of the absence at that time of any proven benefit to prophylactic pelvic lymph node irradiation. Also, data already existed indicating that outcome was not affected by local control in patients with biopsy-proven pelvic lymph node metastases [15]. Further, there was concern that the larger volume of irradiated tissue might restrict the ability to safely escalate the dose to the prostate. The results of our study continue to support this approach, as reported by Zelefsky et al. at the ASTRO-ASCO Prostate Conference in 2005 and shown in figure 7. This compares data from the RTOG 9413 study (shown in red) with patients at MSKCC who had greater than a 50% risk of pelvic lymph node metastases and were treated to 81 Gy without neoadjuvant androgen deprivation (shown in green). There does not appear to be a significant decrement in outcome by omitting the pelvic lymph nodes from treatment.

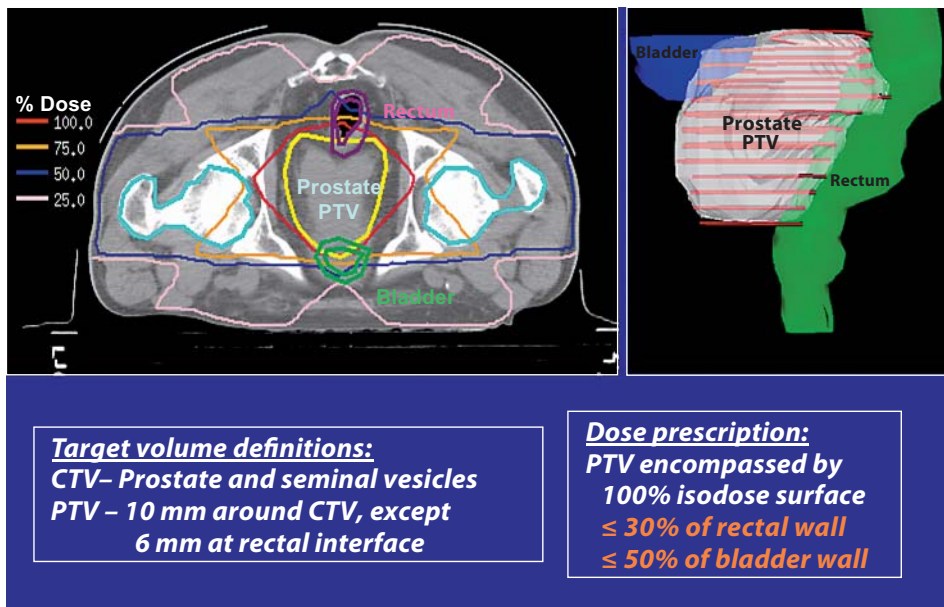


Fig. 8. Six-field 3DCRT plan for prostate cancer at MSKCC.

IMRT for Additional Dose Escalation

Early in our dose escalation study, it was recognized that the volume of rectal wall irradiated to high dose impacted the risk of treatment-related complications. After careful analysis of the dose profiles, a constraint was introduced that no more than 30% of the rectum and no more than 50% of the bladder could receive the prescription dose (fig. 8). If the DVHs indicated that this would occur, patients received a 3-month course of neoadjuvant androgen deprivation therapy before beginning radiotherapy.

Evaluating patients at 30 months following radiotherapy using 3DCRT in the MSKCC and other series, the rectal toxicity rates increased steeply after 75.6 Gy (fig. 9) [16]. Thus, dose escalation using conventional conformal techniques appears to be limited by rectal toxicity indicating that if the dose was to be escalated to a higher level, an improvement in the conformality of the dose distribution would be necessary. The new IMRT methodologies provided a solution. The physics group at MSKCC developed algorithms to calculate the dose distribution from dynamic multileaf collimation, allowing intensity-modulated fields to be implemented. After evaluating a series of different IMRT treatment plans, a 5-field plan was selected and implemented as a standard radiotherapeutic approach for prostate cancer (fig. 10).

For patients treated with the 3DCRT approach, it was shown that the mean rectal wall DVH was significantly different in those who did or did not develop rectal