

Challenges and Choices in Prostate Cancer Irradiation: From the Three Dimensional Conformal Radiotherapy to the Era of Intensity Modulated, Image-Guided and Adaptive Radiation Treatment

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ABSTRACT

In the last decades the status of radiotherapy was tremendously increased in terms of conformity to the target as well as image-guided techniques in conjunction with intensity-modulated radiotherapy (IMRT). The technological improvement had a significant clinical outcome for better response and lower toxicity to the surrounding normal tissues. Nowadays the incidence of rectal toxicity has been significantly decreased, especially with image guided radiation therapy (IGRT), whereas the dose escalation to the prostate has driven the clinical practice to the fact that radical radiotherapy for low or intermediate risk prostate cancer is definitely equivalent to surgery. The treatment volume can be reduced by reducing the size of the necessary margins to count for inaccuracies in target position and patient setup. This can be achieved either by improving the daily localization of the target before treatment or by adapting the treatment in response to feedback. This is the goal of image-guided and adaptive radiotherapy, respectively. These techniques improve the accuracy of dose delivery with a significant impact on clinical outcome and toxicity.

Keywords: prostatic neoplasms; radiotherapy; humans; brachytherapy; treatment outcome.

INTRODUCTION

The prostate is the most common male malignancy and the second cause of death from solid tumors in males. Radiotherapy, in the form of either external beam radiotherapy (EBRT) or brachytherapy along with radical prostatectomy, endocrine therapy and new-age chemotherapy, constitutes the approved therapeutic approach to prostate cancer.⁽¹⁾

Traditional techniques of EBRT (i.e. conventional radiotherapy) have been well overpassed by novel techniques with the aim to increase tumor dose as a means of enhancing local control.

However, the maximum dose that can be delivered to the prostate tumor is restricted by the tolerance of normal tissues within the high dose volume and by the target motions as well. The treatment volume can be reduced by reducing the size of the necessary margins to account for inaccuracies in target position and patient setup. This can be achieved either by improving the daily localization of the target before treatment or by adapting the treatment in response to feedback. All those are goals of the newer techniques in order to enhance the delivered dose with a significant impact on clinical outcome while minimizing the probability of geographic miss and toxicity.

CHALLENGES AND CHOICES

Dose Escalation and Related Toxicity

Conventional radiotherapy using the “classical” four field technique (the so called “box- technique”) has been for long the standard radiotherapy approach and could safely deliver a total dose of 66.6-70 Gy.⁽²⁾ Currently this dose is considered insufficient to provide satisfactory local control.^(3,4) Several studies have shown that dose escalation for radiotherapy of prostate cancer leads to an improved clinical outcome and biochemical control.^(4,9) However, the higher dose to the prostate may lead to significant toxicity by increasing the dose to the organs at risk. This was the result of a multicenter, randomized trial comparing 68 Gy to 78 Gy for prostate cancer. The trial showed a considerably higher incidence of late rectal toxicity displayed with rectal bleeding in patients receiving 78 Gy with conventional technique.⁽¹⁰⁾ Overall, the meta-analysis carried out in randomized studies of dose-escalation showed that late side effects increase with increasing total radiation therapy (RT) dose.⁽¹¹⁾

Since there was a need to improve radiotherapy technique so that greater doses could be delivered without increasing normal tissue complications, conventional radiotherapy has largely been replaced by a more sophisticated form of EBRT, the so-called three-dimensional conformal radiotherapy (3D-CRT).⁽¹²⁾ The primary aim of 3D-CRT is to provide dose distributions accurately shaped to the target, following a treatment planning which defines the tumor and healthy organs with a volumetric image-based approach. The evidence-based American Society for Ra-

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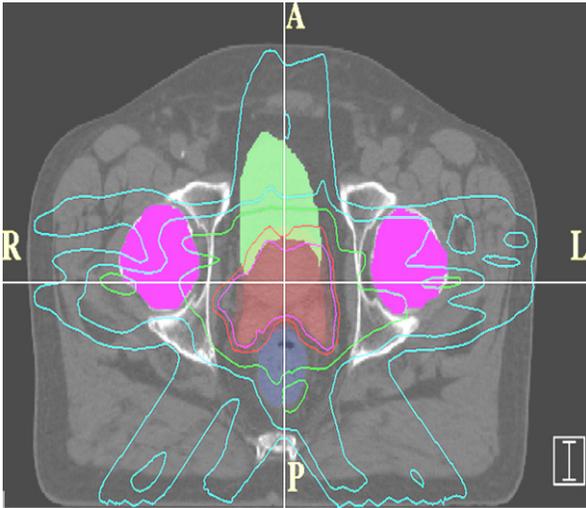


Figure 1. Typical intensity-modulated radiotherapy plan for prostate and seminal vesicles irradiation (personal archive).

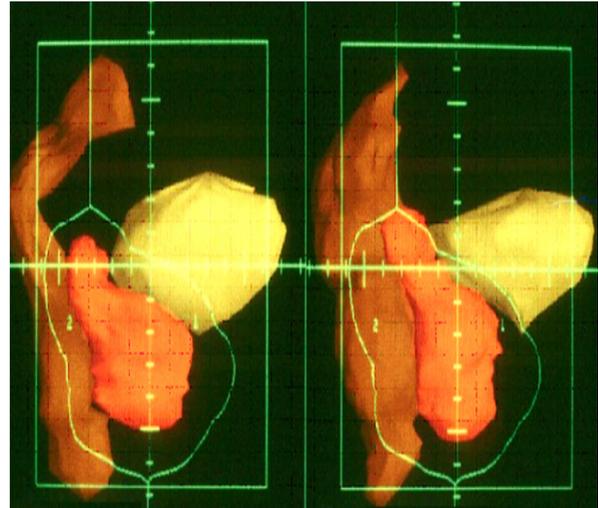


Figure 2. Uncertainties of target (prostate and seminal vesicles) due to movements of pelvic organs such as rectum and bladder in 1 stand 4th week of treatment.

radiation Oncology (ASTRO) systematic review showed a decrease in acute toxicity by virtue of 3D-CRT.⁽¹³⁾ A further step of conformal radiotherapy is IMRT which allows higher dose gradients^(14,15) that improve dose conformity relative to tumor coverage and exposure of normal tissues (**Figure 1**). Moreover, IMRT allows for “dose painting” by delivering different doses to different areas of the planning tumor volume (PTV). On the other hand, in the trials using IMRT to deliver increased RT dose, having however a shorter follow-up, the late gastrointestinal (GI) toxicity reported is lower to the one reported by trials using 3D-CRT technique.⁽¹¹⁾ With these advances in technology and more sophisticated treatment planning systems, more complex treatment plans with tightly conforming doses can be created. Thus, it is possible to deliver escalated doses to the treatment volume without increasing toxicity.

Moreover, the dose distribution delivered to the site of interest can be highly conformal with steep dose gradients.

Organ Motion, Set-Up Errors and Related Problems

A major concern in prostate cancer patients receiving radiotherapy is toxicity in relation to dose escalation. As mentioned above, the IMRT technique partially fulfilling this issue. However, any variation in organ volume or position during treatment may significantly alter the actual dose delivered to both the target volume (geographic miss of the target) and surrounding normal tissues (organ motion's related toxicity).

When treating the prostate the potential disadvantage of these novel techniques is the risk of geographic miss due to tight margins and organ motion.⁽¹⁶⁾ The position of the prostate within the pelvis from one treatment to another is affected by physiologic changes in the bladder filling and rectum volume.^(17,18) Moreover, during radiotherapy there is prostate deformation unrelated to differential rectum or bladder filling, but related to a prior transurethral resection of the prostate ($P = .003$).⁽¹⁹⁾ Even with the use of a variety of external immobilization devices, patient positioning by skin marks and lasers is not a precise way

to target the prostate since the gland itself moves within the pelvis, as shown in **Figure 2**. Although efforts have been made to reduce prostate motion with the placement of an endorectal balloon, this method cannot reduce the interfraction prostate motion.⁽²⁰⁾ These variations in position and shape can be left unchanged and compensated with wide margins, or reduced by image guidance resulting in smaller irradiated volumes of normal tissues. Since smaller margins are important to reduce the dose to the organs at risk, effort has been directed at reducing uncertainties with the use of image guidance that increases the precision of radiation dose delivery. As a result, although a safety margin of 8 mm laterally and 1 cm sagittally and coronally around the prostate is recommended without any image guidance^(21,22) comparable optimal target coverage can be achieved with a reduction of margins in combination to image guided techniques. The use of a newer technique, the so-called image-guided radiotherapy (IGRT) achieves the goal to reduce toxicity while maintaining dose escalation. IGRT implies the use of a variety of imaging techniques in the treatment room to determine the location of target areas within the patient in the treatment position.

There are many image guidance methods using ultrasound, X-ray systems, kilovoltage (kV)- or megavoltage computed tomography (MVCT) systems or even magnetic resonance imaging (MRI) technologies.⁽²³⁾ MRI-guided radiotherapy devices are not yet available for clinical use. However, their prototypes are being investigated as their routine use would allow image guidance without radiation exposure for image acquisition. The various image guidance devices may monitor soft tissue prostate anatomy or implanted markers.

Transabdominal ultrasound was the first widely used technique for daily prostate localization in the treatment room. Ultrasound imaging of the prostate provides a set-up tool for patients undergoing IMRT radiotherapy for localized prostate cancer that takes into account real-time prostate position and may make it possible to decrease tumor margins.⁽²⁴⁾ Morr and colleagues found that daily

computed assisted ultrasound positional verification of the prostate can be successfully performed through the acquisition of high-quality images in most patients with only a modest increase in setup time.⁽²⁵⁾ Nevertheless, in reports evaluating the acceptability of these images for target position verification in the setting of IMRT for prostate cancer the rates of usable images varies significantly. In the study of Morr and colleagues poor image quality was associated with patient inability to maintain a full bladder, large body habitus or other anatomic constraints.⁽²⁵⁾ Moreover ultrasound probe itself may displace the prostate.^(26,27)

Another widely studied imaging technique is the use of implanted markers in the prostate gland. Markers can be implanted using a transrectal ultrasound-guided procedure, similar to prostate biopsy. These markers can be detected using kV X-rays or an electronic portal image device (EPID) in the treatment room. Although there is interfractional motion for both the patient's prostate as well as bony anatomy, these move independently, so the pelvic bony anatomy should not be used as a surrogate for prostate position.⁽²⁸⁾ Implanted markers could be the golden standard for position verification if they are stable within the prostate. According to Poggi and colleagues, there is negligible seed migration within the prostate over the entire course of definite radiotherapy although there are small, detectable movements in individual seed locations perhaps resulting from topographic changes in the gland secondary to seed placement, anatomic changes in bladder or rectum and treatment itself.⁽²⁹⁾ Daily portal imaging with implanted fiducials has improved the ability to localize the prostate in patients receiving IMRT and is necessary for the reduction of the treatment margins.^(30,31) Nevertheless, these markers do not define the shape or volume of prostate during daily treatment, because of deformation or rotation of the gland. There is greater movement of the prostatic base and seminal vesicles than the apex and center of the gland with changes in rectal and bladder filling.⁽³²⁾ Fiducial markers are unable to count for this variability which may result in exclusion of portions of the prostate and seminal vesicles from treatment fields with reduced treatment margins of IMRT technique. Another disadvantage is that the implantation of markers is an invasive procedure requiring the service of an interventional radiologist, while there is the possibility of complications such as urinary frequency, hematuria, rectal bleeding, dysuria or hematospermia in up

to 13% of patients.⁽³³⁾ Most symptoms are grade 1 or 2 in severity, but can last more than two weeks in 9% of patients.⁽³²⁾ Despite these shortcomings, a recent study comparing prostate localization using three-dimensional ultrasound (3D-US) to a standard technique using implanted fiducial markers (FMs) for prostate image-guided radiation therapy indicated that US cannot replace FMs for prostate IGRT since the latter can offer greater sparing of the rectum and bladder.⁽³⁴⁾ The limitations of marker-based strategies argue for the development of another imaging modality. Linear accelerators equipped with kV cone-beam computed tomography (CBCT) have gained popularity. They enable direct visualization of soft-tissue targets such as prostate gland and organs at risk immediately before treatment using a kV-X ray tube with detectors on-board on the linear accelerator. CBCT permits the acquisition of 3D volumetric images of excellent quality while the patient is in the treatment position.⁽³⁵⁾ After acquiring a set of in-room CT images target alignment can be chosen to bone, soft tissues or implanted markers. IGRT with cone-beam computed tomography for IMRT prostate plans has the potential to improve target localization and to provide guidelines for margin definition.⁽³⁶⁻³⁸⁾

An issue that needs further study is the need for daily CBCT, since it increases the time between imaging and treatment, potentially increasing the impact of intrafraction motion. Moreover, each CBCT delivers an additional dose to the patient, ranging between 2 and 4 cGy centrally.⁽³⁹⁾

Wu and colleagues studied the combination of online and offline processes to increase the confidence in the delivery of image-guided radiation therapy.⁽⁴⁰⁾ For the online process, treatment and planning CTs were registered by matching the treatment CT image with the contours drawn on the reference CT. This was called image-based registration (IBR). For the offline process, treatment and reference CTs were registered using contours on these CTs. This was called contoured-based registration (CBR). This study indicated that offline compensation using IMRT can effectively repair the dose deficit incurred during early fractions and therefore complements the online image guidance procedure and offers the potential to further reduce margins. Compared with the single dose compensation at the end of the treatment course, dose compensation performed at weekly intervals is as effective and more biologically beneficial. In terms of quality assurance, the minimum requirements for the best treatment practice is

Table 1. Toxicity of high dose image-guided radiotherapy for prostate cancer.

Authors	Patients No. Dose (Gy)		Technique	Acute GI Toxicity (%)		Acute GU Toxicity (%)		Late GI Toxicity (%)		Late GU Toxicity (%)	
		(%)		Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3
Lips et al, ⁴⁴	331	76	IMRT	30	0	47	3	9	1	21	4
Martin et al, ⁴⁵	259	79.8	3D-CRT	10.1	33.3	0	3.1	1.2	7.4	1.2	
			IMRT								
Ghadjar et al, ⁴⁶	102	80	IMRT	2	0	43	5	5	0	21	1
Guckenberger et al, ⁴⁷	100	76.23	IMRT	≥ grade 2: 12		≥ grade 2: 42		≥ grade 2: 1.5		≥ grade 2: 7.7	
Nath et al, ⁴⁸	100	76	IMRT	11	0	90	0	2	0	17	0
Eade et al, ⁴⁹	101	78.3-84	IMRT	≥ grade 2: 6.9		≥ grade 2: 39		≥ grade 2: 2		≥ grade 2: 3	

Abbreviations: GI, gastrointestinal; GU, genitourinary; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

the weekly image-based registration and compensation of treatment planning.

In a study by Gill and colleagues,⁽⁴¹⁾ it was reported that \geq grade 3 urinary frequency and \geq grade 2 diarrhea were significantly more common in the non-IGRT group than the IGRT group (23% vs. 7%, $P = .0118$ and 15% vs. 3%, $P = .0174$, respectively). Overall, symptoms occurred later in the treatment course for IGRT patients compared to non-IGRT patients. The former group had also a shorter duration of toxicity.⁽⁴¹⁾ These results are in line with other studies reporting acceptable GI and genitourinary (GU) toxicity with daily image-guidance for the delivery of higher than conventional radiation doses (**Table 1**).⁽⁴²⁻⁴⁷⁾ There are also available systems based on the application of megavoltage (MV) for CT acquisition. Helical tomotherapy is the fusion of a linear accelerator with a helical MV fan beam CT that allows for daily CT-assisted positioning of the patient followed by a rotational IMRT. Helical tomotherapy has given encouraging results for prostate cancer radiation therapy.^(48,49) It is highly effective in a simultaneous integrated boost scenario⁽⁵⁰⁾ as well as in hypofractionated postprostatectomy radiotherapy.⁽⁵¹⁾

Patient-Specific Approach

The identification of treatment variations including setup errors, organ motion and deformation have increased the awareness of limitations in therapeutic gain using conventional radiation therapy (CRT) and IMRT.^(52,32) As mentioned before, while appreciable margins need to be added to the target volume to account for these inaccuracies these margins increase normal tissue toxicity and hinder dose escalation. A reduction of these margins can be achieved if they are not based on population averages but they become patient-specific. In fact, this is the goal of adaptive radiotherapy (ART) that introduces the use of patient-specific margins using image feedback of prostate location and patient setup position.

The ART process introduced in William Beaumont Hospital has been designed to improve accuracy of dose delivery, enhancing dose escalation.⁽⁵³⁾ There are two solutions for adaptive radiotherapy. An off-line solution to motion might include planning with somewhat larger margins initially, obtaining daily scans with the initiation of treatment for some number of treatment days, and then generating a margin that is specific to that patient and continues to be used from that point forward without much additional imaging. This strategy avoids systematic errors, primarily in patient positioning. An on-line solution might be to initiate therapy with small initial margins, image the patient daily and make daily positional adjustment for the patient. This is the best possibility avoiding both systematic and random errors, but the clinical workload will be dramatically greater.⁽⁵⁴⁾

Martinez and colleagues⁽⁵³⁾ reported that there was a potential for dose escalation for prostate patients enrolled in the ART process with an increase up to 10% (mean 5%) at the prescription dose level, in comparison to the conventional treatment process. This level could be further increased to 5-15% (mean 7.5%) when the IMRT delivery was combined with the ART process. Moreover, the ART process identified the group of patients for which the dose should not be escalated above conventional levels, due to the large variations in clinical target volume (CTV) position observed during treatment course. This

is paramount to keep complication rates low.⁽⁵³⁾ Brabins and colleagues studying 280 patients undergoing ART with CRT or IMRT technique for localized prostate cancer found that significant dose escalation can be achieved without increasing GU or GI toxicity.⁽⁵⁵⁾ Nuver and colleagues⁽⁵⁶⁾ reported that the adaptive off-line procedure allows for reduction of the PTV margin to 7 mm (from 10 mm) without decreasing target coverage during treatment. By decreasing the treatment volume one also treats less of normal dose-limiting tissue. The same study concluded that the dose received by the rectal wall will be reduced using ART and the number of patients who suffer from serious side effects, such as late rectal bleeding, is expected to be reduced.

When IMRT is applied for prostate cancer the irradiated treatment volume can be reduced by 29% leading to a significantly reduced probability by 19% and 16% for late rectal bleeding and fecal incontinence, respectively.⁽⁵⁷⁾

CONCLUSION

Nowadays in the PSA-screening era,⁽⁵⁸⁾ as recommended by National Comprehensive Cancer Network (NCCN),⁽⁵⁹⁾ to treat prostate cancer the use of a 3D-CRT technique is minimally required, while the IMRT technique should be preferred, as long as it is available. Either way IMRT/IGRT is required for doses \geq 78 Gy. Overall, IMRT/IGRT could become the standard of practice in dose-escalated radiotherapy since it can allow the delivery of higher doses while maintaining acceptable toxicity levels.⁽⁶⁰⁻⁶³⁾ However, there is still considerable scope for further improvement of IGRT systems. The ideal system would allow for precise daily imaging without significant extension of treatment time or patient exposure to additional radiation.

And, when all is said and done, we think there is no better conclusion than the one stated by G. Rodrigues in his recent commentary: "New innovations in radiotherapy technique need to be assessed for both treatment efficacy and for normal tissue toxicity to demonstrate improvements in the therapeutic ratio prior to widespread adoption".⁽⁶³⁾

CONFLICT OF INTEREST

None declared.

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