Conformal Radiation Therapy in Prostate Cancer - A Review.
A. Varghese, A. Juzer

Department of Radiation Oncology, Kuwait Cancer Control Centre.

Abstract

Purpose
Radiotherapy has progressed considerably over a century. It is mainly because of understanding of physical and biological principles. How to improve therapeutic ratio is major concern. Excellent dose conformity and homogeneity is possible due to recent advances in treatment techniques. But there are many areas of challenges in achieving increased tumor control and normal tissue effects. The aim of this review is to provide a brief update of the rapidly changing field of external radiotherapy and how it affects the clinical practice of treatment of prostate cancer.

Methods and Materials
A literature Search has been undertaken, only relevant articles in the management of prostatic cancer that had appeared in peer viewed journals were considered. We have tried to discuss the levels of evidence available for various treatment techniques with photons and particles. American Society for Therapeutic Radiology and Oncology web site (www.astro.org) provided a large menu for this article. New brochures of information materials provided by various International medical companies also forms immense source of information. Materials from review articles and abstracts from world literature were also included.

Results
The advances in imaging and computer visualization contribute greatly to radiotherapy planning by improving accuracy of treatment. It is possible to deposit a high conformal radiation dose within the tumor using highly targeted beam. Conformal radiation improved biochemical failures without an increased incidence of severe toxicity. Carefully conducted randomized studies are appropriate method for evaluating new treatment techniques and strategies. Proton therapy is an area of great therapeutic possibilities in the 21st century.

Conclusion
Great advancements are underway with IMRT and use of Particle therapies. We cannot have conservative approach to changing trends in treatment, no doubt, safety and efficacy of treatment is prime concern. Progress in technology is rapid and fundamental and this review will provide an update on what is happening in the changing field and how it affects our clinical practice.

Key words
Prostate Cancer, 3D-CRT, IMRT, IGRT, Protons.

Introduction
There is considerable increase in number of early cases of carcinoma of prostate worldwide with advent of Prostatic Specific Antigen (PSA). We have State-of-the-Art treatment options also in the management of prostatic cancers. Still management poses both dilemmas and challenges. With plenty of information’s in prognostic indicators, stage, grade and PSA, it is becoming more clear which patient will benefit from a particular treatment. We have century old treatment of surgery, hormone treatment for more than five decades and century of experience with radiotherapy. Most common form of therapy world wide is radical prostatectomy and external beam radiation and to a lesser extent brachytherapy. Each of these treatments has it associated benefits and risks. In this brief review, we will discuss external radiation, photons and particles and its conformal
Conformal Radiation Therapy in Prostate Cancer, A. Varghese, et al.

Radiation therapy in Prostatic Cancer

Prostatic cancer treatment started with isolation of radium by Pierre and Marie Curie in 1898. The first reported series of prostatic cancers with Co\textsuperscript{60} was by George and Colleagues in 1965. It was the pioneering work in 1950 by Kaplan, Del Regato and others in Stanford University, USA, which opened way for cure of prostatic cancer with radiation therapy. (Figure 1) Prostatic cancers are considered as having low radio sensitivity. High doses are necessary for control of the disease. It has low growth rate and effect of radiation is expected to be slow.

In the conventional treatment era, the majority of investigators considered 60 Gy to 70 Gy in 6-7 weeks or its biological equivalent as tumor lethal dose. The serum marker PSA (Prostatic Specific Antigen) is widely used for screening, diagnosis and determining prognosis and selecting the appropriate treatment for clinically localized cancer. Lack of standardization made it difficult to compare results in the early PSA era (early 1999). (1, 2)

Treatment planning for external beam

General considerations

Prostate and seminal vesicles are located between the rectum and the bladder. Position of the prostate is affected by physiological changes in bladder and rectum volume. How this variation can be left unchanged is a subject of debate. There are situations in which seminal vesicles and pelvic nodes needs to be included in the treatment field.

The benefit of pelvic radiation in particular remains controversial even though it was practiced 2-3 decades back. Now there is re-emergence of role of pelvic radiation at least in selected cases. Seminal vesicles elective radiation is done for high risk patients. Including seminal vesicles, lymph nodes or both, increase the field size and hence increase acute toxic effects and long term complications. The international commission on radiation unit and measurements has defined volume for treatment planning that take into account the extent of known gross tumor, the area of likely microscopic extension and daily variation in patient setup and tumor position. They are as follows: (3,4)

Fig. 1. Evolution of Prostate Radiation Therapy

Tumor Volumes

- **Gross tumor volume (GTV):** Palpable or visible extent of tumor.
- **Clinical target volume (CTV):** Gross tumor volume + a margin for suspected sub-clinical disease.
- **Planning target volume:** Clinical target volume + a margin to account for variation in size, shape and position relative to treatment beam.

There are three situations in external beam therapy delivery:

a. Prostate, seminal vesicles and pelvic nodes.

b. Prostate and seminal vesicles.

c. Prostate only (PORT).

The amount of margin to be added to gross tumor volume to get clinical and planning volumes has undergone extensive studies and discussions. (5,6) We need enough margin to encompass gross and microscopic disease, but there is strong reasons to keep margin as small
One of the major problems with treatment of prostatic cancer by external beam lies in fixation of prostatic or clinical target volume. The localization of exact position of prostate gland has two difficulties, external and internal. In external fixation, tattooing or similar skin marking system has been a traditional approach. Most prostatic patient are older, their skin tends to be looser. Thus, certain degree of uncertainty is present in daily alignment of the skin marks by the lasers in Linear Accelerator treatment room. If the patient is obese, further uncertainty can be expected. During past decades, the external fixation device have been used. Researchers from the University of Chicago compared four different immobilization techniques with no immobilization. They found no satisfactory significant difference in overall movement using any localization device compared with no localization device, other groups found immobilization helpful. Internal fixation of prostate target may be even more difficult. Image guidance techniques has been described to correct prostatic movements. This can be a major improvement as we know that multiple studies have indicated that the prostate is not stationary and can move as much as 2 cm. So, it is an area which needs considerable improvement for better treatment outcome.

Conventional external beam therapy for Localized prostatic cancer – 2D

During the conventional treatment, it was not possible to treat the organ in all dimensions. Standard radiation fields were based on bony pelvic landmarks. A common type of field was a four fields (box technique), with custom cerrobend blocking used for treatment of prostate, seminal vesicles and proximal lymphatic drainage. These fields were treated to a dose of 45-50 Gy. in 1.8 to 2.0 fractions. The prostate and sometimes seminal vesicles and a safety margin were boosted to 65-70 Gy. Fields were shaped to bisect the rectum when filled with contrast. Contrast injection was done with rectal tube just through internal sphincter to distort the rectum as little as possible and to outline the lower rectal segment. Retrograde urethrography was recommended to determine position of urogenital diaphragm. The narrow point or beak in the contrast column denoted the level where the urethra passed through urogenital diaphragm.

The most inferior aspect of the prostate gland is typically located 1 cm above the urethral apex and inferior field is placed > 1 cm below the apex as beak allowing 2 cm inferior margin for the prostate. This also covered the pelvic floor and proximal lymph nodes. It was found in later years that substantial inadequate coverage occurred with these techniques. (Figure 2).

In spite of the limitations during conventional era, radiation was effective. Although, overall survival numbers were generally higher for men treated with radical prostatectomy (often younger and healthier men), Cause-Specific
Conformal Radiation Therapy in Prostate Cancer, A. Varghese, et al.

survival rates were not significantly different. The prostate cancer specific survival was 86% which was similar to outcomes of most surgical series. (8,9) Zietman and associates reported 4-years PSA relapse-free survival of 65% for pre-treatment PSA less than 15 ng/ml and 6% for patients with more than 15 ng/ml. Widely used PSA level of failure was as per 1997 ASTRO Consensus statement for recurrence after radiation therapy as three consecutive increase in PSA levels (biochemical treatment failure).

Toxicity of conventional 2D external beam.

With conventional external beam dose escalation was limited. Acute toxicities like dysuria and diarrhea will subside within few weeks of completion of radiation. The RTOG trial (75-06 and 77-06) which reviewed 1020 patients, reported that the incidence of Grade 3 and 4 rectal and bladder complications were high. Surgical intervention was needed in 0.5% cases. Bowel obstruction and perforation was also found which needed surgical intervention in 0.6% cases. (10)

Risk of complications were significantly higher when doses higher than 70 Gys were administrated with non-conformal techniques. Risk of erectile dysfunction after external radiation was widely variable. Primary mechanism of radiation therapy associated impotence was found to be vascular rather than nerve damage. Second malignancy after external beam therapy is an infrequent occurrence. Using data from surveillance, epidemiology and end results (SEER) program cancer registry, Brenner and colleagues compared second malignancy risks in men (N=51584) who received radiation for prostatic cancer from 1973-1993 versus men (N=70539) who underwent radical prostatectomy during same period, showed a small, but significant increase in second malignancy with radiation therapy. For survival more than 10 years, the risk increased to 1 in 70. Common radiation induced tumors were of bladder, rectum and sarcoma. (11,12).

Three dimentional prostatic conformal radiotherapy.

This term is reserved for treatment with 3D anatomical information derived from modern cross section imaging devices and whose distribution is shaped, so that the regions of high dose confirm as closely as possible to target volume. Introduction of 3D imaging modalities in 1970’s and 1980’s opened the way for delivering 3D CRT. Like in any other sites, treatment by this method is complex: CT based simulator and treatment planning and introduction of multileaf collimators in modern linear accelerators have allowed increased precision and accuracy. 3D reconstruction of acquired CT images are generated and target volume (eg. Prostate and seminal vesicles) are delineated. Critical structures like rectum, bladder are also contoured. The processes are segmentation, display of the plan and dose distribution. An increase in processing speed of computers facilitates accurate and complex dose calculations. So, more plans can be evaluated per unit time. Target volumes and normal organ can be visualized in three dimensions (Figure 3). «Beams-eye-view» is a portrayal of target as if looking straight down the path of radiation beam. (Figures 3 & 4) Advanced graphic can give the planner an observer’s eye view of all the beams with respect to patient lying on the therapy couch. (Figures 4-7). These technologies were available by 1990 and this opened the way for dose escalation. The treatment planning system generates a dose volume histogram for selected treatment plan. This helps to limit the dose to the volume of organ receiving a given dose. (13). (Figures 4-6)
was evident. In the fox-chase case series, the 5-years incidence of grade 3 or 4 rectal toxicity at doses of 75 to 76 Gy was 8%. When the anterior rectal wall was shielded to keep the dose in the region under 72 Gy, grade 3 or 4 rectal toxicity dropped to 2%. From the M D Anderson, series, men who received 70 Gy to a defined rectal volume, had significant risk of rectal toxicity. Urinary toxicity with D-CRT in the form of urethral stricture have been noted in 1.5% of treated men with a 4% incidence of stricture in men with trans-urethral resection of prostate (TURP). Grade 2 haematuria, was noted in 1% of men treated to a dose of 75.6 Gy or higher and 4% of men treated with lower doses. Urinary incontinence is rare after treatment with 3D-CRT.

**Toxicity of 3D- Conformal Radiotherapy.**

3D-CRT has not solved the problem of toxicities, as increased normal tissue toxicity was evident. In the fox-chase case series, the 5-years incidence of grade 3 or 4 rectal toxicity at doses of 75 to 76 Gy was 8%. When the anterior rectal wall was shielded to keep the dose in the region under 72 Gy, grade 3 or 4 rectal toxicity dropped to 2%. From the M D Anderson, series, men who received 70 Gy to 30% or more of a defined rectal volume, had significant risk of rectal toxicity. Urinary toxicity with 3D-CRT in the form of urethral stricture have been noted in 1.5% of treated men with a 4% incidence of stricture in men with trans-urethral resection of prostate (TURP). Grade 2 haematuria, was noted in 13% of men treated to a dose of 75.6 Gy or higher and 4% of men treated with lower doses. Urinary incontinence is rare after treatment with 3D-CRT.

**Intensity modulated Radiotherapy – IMRT**

Intensity modulated radiotherapy is an advanced form of 3D-conformal therapy that not only conforms dose (high) to the...
target volume, but also conforms dose (low) to sensitive structures. It is based on a single concept, the intensity of beam is varied across the treatment field. IMRT delivers a spatially non-uniform radiation exposure to the patient to create a uniform dose distribution at the target site. Modulating collimators used in IMRT are two types, variable and binary. Modulated treatment can be delivered with few fields or many fields.\textsuperscript{(15,16)} (Figure 8)

High dose intra-prostatic IMRT boost is being developed on investigational basis. Use of biological target volume is gradually introduced to clinical practice. Here prostate magnetic resonance imaging (MRI) techniques can be fused with planning computed tomography (CT) and this has shown an improved target delineation. Functional MRI techniques have been developed. Dynamic contrast enhanced MRI (DCE-MRI) can visualize prostate cancer vascularity. H-spectroscopic (MRSI) has shown to provide high specificity for prostate cancer. These techniques leads to more accurate staging and localization of prostate.\textsuperscript{(18,19)} Combined DCE-MRI and MRSI functional image guided high dose intraprostatic DIL-IMRT planned as a boost to 90 Gy is theoretically feasible. Preliminary results are encouraging. Health related quality of life in patients with locally advanced prostatic cancer was published by Irene et al from Amsterdam. They compared 70 Gy conformal radiotherapy with 76 Gy IMRT dose escalation. IMRT group showed statistically significant and clinically improved quality of life changes over time, compared with the conformal 70 Gy treatment group. So, IMRT and accurate position verification provide the possibility of dose escalation with comparable and some even improved QoL results. The following constraints are important in IMRT planning.\textsuperscript{(20)}

**Dose constraints for Rectum**

Less than 50%, Vol should receive >50% dose. Less than 25%, Vol should receive >95% dose. Not more than 3%, rectum should receive 74 Gy.

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Grade 2 rectal</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years-DFS</td>
<td>complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D-CRT</td>
<td>70%</td>
<td>9%</td>
<td>Chism et al.\textsuperscript{(14)}</td>
</tr>
<tr>
<td>IMRT</td>
<td>86%</td>
<td>4%</td>
<td>Zelefsky et al.\textsuperscript{(4)}</td>
</tr>
</tbody>
</table>

Table 1: Biochemical Disease-Free Survival for 3D-CRT & IMRT.
Dose constraints for Bladder

Less than 50%, Vol. to receive 50 Gy.
Less than 25%, Vol. to receive 60 Gy.
Not more than 5%, Vol. should receive 74 Gy.

Femoral heads

Less than 50%, Vol. to receive 50 Gy

Image guided Radiotherapy – IGRT.

Organ motion has been a major concern in the clinical application of photon and particle therapy. Interfraction prostate motion is a major discussions since past few years. Large variation in daily prostate motion has been described. As mentioned earlier in discussion, there is poor correlation between location of the prostate and skin marks and bony marks. Ultrasound systems cannot reliably define the daily motion. As a result, large margin is necessary to ensure accurate delivery of prescribed dose to the prostate. Yan et al (21,22) used multiple computed tomography scan to define prostate motion and electronic daily images to qualify set-up inaccuracies. Another method known as on-line image guidance, relies on daily information to derive the daily prostate motion. Different approaches like cone beam CT, CT on rails, fiducial marker, rectal baloons and beacon transponders are under trials. Many studies have reported online image guidance strategies to correct for prostatic motion with daily off-line or on-line position verification. Fiducial marker based correction is a step forward, but has shortcomings. Implantation of marker is an invasive procedure. Marker based strategies correct for translations but tend to neglect rotation which are known to be a large component of prostate motion. Also, marker based correction do not take into account changes in position of seminal vesicles or the effect of a changed anatomy on planning especially relevant to IMRT. Linear accelerator equipped with kilovoltage (KV) cone-beam computed tomography (CBCT) allow soft tissue registration immediately before treatment, Samitma N et al developed an automatic, rigid three dimensional (3D), gray-value registration (3D-GR) method for fast prostate localization on CT scans.

Adoptive RT (ART) protocol for prostate cancer using kilovoltage cone-beam computed tomography (CBCT) in combination with a diet and mild laxative, safely reduced the irradiated treatment volume by 29% according to a study from the Netherlands cancer institute, Amsterdam. Bowel preparation is an important aspect. Prostate motion is larger for patients with full rectum. In the above mentioned protocol, dietary advice consisted of regulation of meals and avoid food known to cause bowel gas. The diet was prescribed in combination with a daily laxative (1000 mg. of Magnesium Oxide) to reduce intestinal gas and obtain a reproducible bowel volume during CT acquisition and treatment sessions. The treatment sessions also has to be modified with approximately regular treatment time.

A group of well known centres in USA adopted a real time monitoring of prostate gland during external therapy using the Calypso system with a target positioning device, that monitors three implanted electro magnetic transponder at a rate of 10Hz. They have reported that this device provide clinically efficient accurate and objective localization of prostate. Continuous, real time tracking of prostate position during delivery of treatment can potentially prevent inadvertent geographic miss of target areas. (23)

Tomotherapy

A CT guided IMRT treatment now available commercially, which is an advanced treatment solution. Tomotherapy Hi- Art system in cooperate unique design features that continue to precisely deliver image guided intensity modulated radio-therapy IG/IMRT. It is a completely integrated system, with verification CT (MVCT). Helical pattern delivery guided by a specialized multileaf collimator (MLC) machine can rotate 360 degree around the patient. Verification CT images are created using low intensity megavoltage x-rays from linear accelerator. Such systems are also under clinical evaluation. Rapid-Arc radiotherapy is another major advance in technology, it is claimed to be faster than the present dynamic treatments. This program delivers volumetric arc therapy with single rotation of treatment machine around the patient. It is able to deliver IMRT in less than two minutes that previously took an average of 10
Conformal Radiation Therapy in Prostate Cancer, A. Varghese, et al.

minutes with conventional IMRT. In Europe and some centres in USA, this approach is gaining momentum, as faster treatment will reduce the potential for involuntary movements, while treatment is being delivered. (24) (Figure 9)

Cyber-knife

It is an image guided stereotactic radiosurgery. The system consists of a light weight linear accelerator mounted on a robotic arm. Near-real time image allows for reduced patient movement tracing with 1mm spatial accuracy. It aims each beam independently without a fixed isocenter. Even though developed for brain tumors at Stanford University, its use in other sites including prostate is increasing. Synchrony software, is the latest advancement in Cyber-knife according to manufacturer accuray. Like any other innovations, Cyber-knife is also under clinical evaluation. (25) We know very well the controversies following the press release issued in Sept 07 on treatment of prostate cancer. More prospective and randomized studies are needed to assess rapidly developing technologies.

Particle Radiation Therapy in Prostatic cancer

Particle beam (Figure 10) therapy utilizes subatomic particles instead of x-rays or gamma rays to deliver radiation. Its physical property allows for precise dose localization and superior depth dose distribution. There is potential radiobiological advantage of high linear energy transfer neutron therapy. It was first begin in late 1930’s in an attempt to increase killing of hypoxic cells. There have been two randomized clinical trials comparing neutron therapy to photon therapy in patients with prostatic cancer. These studies has shown an advantage of neutrons in tumors for loco-regional control. High cost and limited availability of neutron treatment represent an area of controversy. Advocates claims, that it is a more efficacious treatment. IMRT neutron therapy has been developed which lead to lesser dosage to normal tissues. With reports of increased late toxicity and dose distribution far less optimal, interest in neutron is waning and role of proton is now on increase. (26,27)

Proton therapy

They are not generally considered as high linear energy transfer particles. Its advantage is because of its physical dose distribution. When a heavy charged particle like proton passes through tissues, the dose it deposits increases slowly with depth, then reaches sharp increase at its maximum depth of penetration. This is called as the Bragg peak (Figure 11). Using multiple beams or varying compensators, it is possible to design a 3D dose deposition that is precisely confirmed to the tumor volumes with normal dose to surrounding normal tissues. Prostate cancer is the only tumor in which dose escalation with protons has been tested against conventional radiation. In a randomized trial patients with
Proton therapy is one of the most promising modalities that have benefited from the recent technological developments in the field of radiation oncology. Use of double scattered proton technique completely changed the shape of the dose volume curves for both bladder and rectum. Target coverage is more homogenous with proton therapy. Double scattered proton therapy is under investigations. Studies in the University of Florida proton therapy institute reported that compared with IMRT, proton therapy reduced the dose to dose limiting normal structures like rectum and bladder, while maintaining excellent planning target volume coverage (PTV). (29)

Clinical trials of C-ion RT for prostate cancer was initiated at the Research Centre for charged particle therapy in Japan. Carbon-ion beams offer superior dose conformity than protons in the treatment of deep seated tumors. Hypofractionated carbon-ion therapy is also under phase I/II clinical studies. considering the low $\alpha/\beta$ value of prostatic tumor. (30)

**Hypofractionation**

The rational for hypofractionation is the difference in $\alpha/\beta$ ratio of prostate and rectum. Prostatic $\alpha/\beta$ being calculated about 1.5 Gy and rectum > 4.0 for late effects. So assuming a prostate $\alpha/B$ ratio of 1.5 Gy. The delivery of 70.2 Gy in 26 fractions would be biologically equivalent to 84.4 Gy in 2 Gy fractions. Using the same 26 fractions regimen and assuming an $\alpha/\beta$ for late effects of 4.0 for the rectum, the biologically equivalent dose in 2 Gy fractions would be < 78 Gy.

In a randomized trial of hypofractionation dose escalation using IMRT for intermediate to high risk prostate cancer, 76 Gy in 38 fractions at 2 Gy/fraction were delivered to one group while T3-T4 prostate cancer who received 50.4 Gy with photon to the pelvic field were randomized for either an additional dose via photon 16.8 Gy or 25.2 Gy via protons. There was no difference in the overall survival or local control between the two groups. Toxicity in the proton arm, was higher owing to the higher dose to rectum, but these studies were in 1970's which was prior to the recognition of importance of volume considerations to the toxicity of rectum. Newer studies have shown protons much more effective in prostate. Protons are currently being tested in randomized prospective way against 3D conformal radiation in early prostate cancer, using modern proton delivery techniques. (28)

The accuracy and precision of proton therapy for treatment delivery is approximately one millimeter. There are at least 5 functioning centres in the USA. It requires significant investment to build and equip a proton centre.

<table>
<thead>
<tr>
<th>Fraction level</th>
<th>Dose per Fx (Gy)</th>
<th># Fx</th>
<th>Total dose (Gy)</th>
<th>Tumor NTD (alpha/beta=1.5 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.94</td>
<td>22</td>
<td>64.68</td>
<td>82.6</td>
</tr>
<tr>
<td>II</td>
<td>3.63</td>
<td>16</td>
<td>58.08</td>
<td>85.1</td>
</tr>
<tr>
<td>III</td>
<td>4.3</td>
<td>12</td>
<td>51.6</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Table 2: UW Phase I/II Prostate Hypofractionation Trial. Predicted late toxicities equivalent to 75-77 Gy in 2 Gy fractions.
Conformal Radiation Therapy in Prostate Cancer, A. Varghese, et al.

the other group received 70.2 Gy in 26 fractions at 2.7 Gy/fraction. There was no difference in overall maximum acute gastro-intestinal or genitor-urinary toxicity. However, there was a small but significant increase in acute G.I reaction at week 2.3 and 4 in the hypofractionated group. (31,32)

Clinical results of phase I/II trials of hypofractionated stereotactic radiotherapy (SHARP) using 5 fractions of 6.7 Gy daily for a total dose of 33.50 Gy concluded that there are minimal acute and late toxicity and dose escalation should be possible. (33,34)

A shortened course of external beam therapy is a very attractive option for men who might not be candidate for brachytherapy or who find a 7 week or 8 week course of daily treatment prohibitive because of logistics and cost, additional clinical validation of hypofractionation is needed before this is adopted as an option for the treatment of prostatic cancer. (35) (Table 2)

Conclusion

Radiation oncologists continue to refine the application of radiotherapy for prostate cancer. Recent advances improved the potential of radiotherapy planning. Accurate imaging and 3-D visualization are the cornerstone in conformal radiotherapy. Combined with technical innovations in treatment delivery such as multileaf collimation and intensity modulation of therapy beams, image guided therapy, a scope for conformal radiation in the curative treatment of prostate cancer has increased considerably. Because radiation can be delivered with less toxicity, greater dose can be delivered to target volume, to achieve greater tumor control. Rapidly changing modalities needs to be evaluated for clinical outcomes and quality-of-life issues.

References


24. Results based on Varian medical systems survey of four clinical sites, Data on file VMS PALO ALTO 2008.


