High-dose-rate Brachytherapy of Prostate Cancer

a report by

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Measurement of blood levels of prostate-specific antigen (PSA) and greater awareness have led to the detection of prostate cancer at an earlier and potentially more curable stage. As certain kinds of prostate cancer progress very slowly, some patients choose to undergo clinical observation (‘watchful waiting’) rather than active treatment. Alternatively, surgery and radiation therapy (RT) are the only curative treatment options. Hormone therapy (androgen deprivation) is another intervention used to enhance curative treatment or treat recurrent disease. RT can be administered in various ways, including external beam (EB), brachytherapy (the placement of a radiation source directly into a tumour) or a combination of both methods. Brachytherapy effectively targets the prostate and minimises the dose to adjacent organs such as the bladder and rectum, because the dose decreases very rapidly as the distance from the radiation source increases.

There are two types of prostate brachytherapy: high-dose-rate (HDR) and permanent-seed. HDR brachytherapy is a precision technology for the placement of a brachytherapy source that employs robotic technology to temporally deliver a high-intensity radiation source into the prostate and surrounding tissue. HDR is applicable to virtually all stages of localised prostate and many other types of cancer. It may be given as the only treatment (HDR monotherapy) for early disease or used in combination with external RT for locally advanced or higher-stage cancer. This article will describe HDR brachytherapy for prostate cancer.

High-dose-rate Brachytherapy

HDR describes more than the rate at which the radiation dose is given; it also offers a new dimension to brachytherapy. A single high-intensity radiation source located at the end of a wire is robotically inserted into thin brachytherapy catheters (close-ended straws) that have been temporarily inserted into the prostate. Instead of having a large number of uniform-strength permanent seeds, HDR applies a single radiation source that is time- and position-controlled during the treatment process. The longer the source stays in a particular location, the greater the effective radiation dose. Thus, HDR offers an infinite variety of source strengths at each of the hundreds of locations within the implant.

Along with the millimetre precision of source insertion, HDR provides the best opportunity to shape and control the distribution of the radiation. Delivery of treatment takes only about 20 minutes and occurs in a series of applications given over several hours or days. The radiobiology of prostate cancer favours large doses of radiation per session, thus HDR is well-suited for the control of prostate cancer. Due to the short duration of therapy, HDR has the benefit of a correspondingly short period of acute side effects.

The temporary HDR brachytherapy catheters act as stable scaffolding to permit precise and reproducible placement of the radiation source within and around the prostate gland. Consequently, there is a high degree of dose uniformity within the gland and excellent coverage of disease just beyond the edge of the prostate. Importantly, unlike with permanent-seed brachytherapy, the dose of radiation is known before treatment and can be adjusted and individually tailored. There is no radiation exposure to medical personnel or families and seed migration to other organs cannot occur. Organ motion, of great concern in EBRT, is not a problem with HDR as the applicator is fixed to the target. Rectal doses are predictably low with HDR brachytherapy compared with EBRT.

The four steps of HDR brachytherapy are:1 image-guided applicator insertion,2 image acquisition of the completed implant (simulation radiography),3 dose distribution calculation (computerised dosimetry)4 and treatment delivery.1,2 The initial placement of thin, hollow, closed-ended catheters is performed under image guidance (ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and cystoscopy. The radiation oncologist and the urologist usually perform the outpatient applicator insertion procedure together, combining their knowledge and skills to achieve optimal placement.
The radiation oncology team consists of a brachytherapy nurse, a dosimetrist, a medical physicist and radiation therapists. The images of the final implant position are acquired and downloaded into a treatment planning computer to create a virtual image of the implant and surrounding normal structures. The treatment planning computer is then used to calculate a unique patient-specific 3D dose distribution. The doses are viewed as isodose curves overlaid on an image such as a CT scan or ultrasound, compared as volume graphs (dose volume histograms) and represented as a 3D virtual image of the prostate tumour target and surrounding structures (see Figure 1). Once dosimetry calculations are completed, the instructions on where the source should be positioned within the implant catheters and for how long are sent to the robotic delivery device called the ‘remote afterloader’ (see Figure 2). Treatment is delivered under realtime source position monitoring. As the source is removed after treatment there is no residual radiation or radioactivity and the applicator is removed before the patient goes home.

HDR may be given in one or a series of implants (catheter placement procedures) with one or more treatments (radiation source delivery sessions called ‘fractions’) per implant. HDR prostate treatments are often given twice daily. The total number and sequence may vary between treatment centres depending in part on whether or not EBRT is also administered. Because there is no incision and no surgical wound to heal, recovery is rapid. Temporary urinary frequency and urgency are expected for one to two weeks after the implant. Urinary outflow problems occur more often in patients with symptomatic benign prostate hyperplasia (BPH). They are generally self-limited and best managed conservatively.

**California Endocurietherapy Cancer Center Protocols**
The treatment protocols described in this presentation were derived from ongoing long-term studies of patients in various risk groups treated at the California Endocurietherapy (CET) Cancer Center. The CET risk group classification is shown in Table 1. The protocols consist of two implant procedures performed approximately one week apart. Low-risk and ‘favourable’ intermediate-risk group patients are treated with HDR monotherapy (two brachytherapy procedures and a total of six HDR treatments without EBRT). Patients who are in the ‘less favourable’ intermediate- or high-risk groups are treated with a combination of HDR (two brachytherapy procedures and a total of four HDR treatments) and moderate-dose EBRT.

The intention of HDR monotherapy is to confine the curative dose of radiation to the prostate and immediate surrounding tissue and to keep normal tissue injury to a minimum. For more extensive disease, a larger area should be treated with EBRT, and HDR brachytherapy is used to safely deliver the high dose to the primary tumour. Dividing the implants into two separate sessions with multiple treatments allows for recovery of normal tissue and lessens the likelihood of normal tissue injury.

**California Endocurietherapy High-dose-rate Brachytherapy Results**
Approximately 1,700 patients with prostate cancer have been treated at the CET Cancer Center since 1991. Our outcome studies have confirmed that HDR brachytherapy is a safe and effective treatment for prostate cancer. Long-term outcome results from the first 209 patients treated with HDR and EBRT (no androgen deprivation) were published in 2005. General clinical control (no clinical or PSA evidence of disease) was achieved in 90% of cases and the cause-specific survival was 97%. The PSA control rates stratified by risk group were 90% for low-risk patients, 87% for intermediate-risk patients and 69% for high-risk patients. There were no statistically significant differences in outcome between the low- and intermediate-risk group patients. Complication rates were low (2% grade 1, 2% grade 2 rectal complications and 0% grade 3 or 4 rectal complications). The 7.7% grade 3–4 urinary effects were consistent with other forms of RT.

Table 1: California Endocurietherapy Risk Group Classification

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>T-stage</th>
<th>PSA ≤10</th>
<th>Grade Rules</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>T1–T2a</td>
<td>≤5</td>
<td>All required</td>
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<tr>
<td>Intermediate</td>
<td>12bc</td>
<td>&gt;5–10</td>
<td>7</td>
</tr>
<tr>
<td>High</td>
<td>T3</td>
<td>&gt;10</td>
<td>8–10</td>
</tr>
</tbody>
</table>

Figure 1: 3D Virtual Image of the Pelvic Anatomy

The prostate (dark red) is covered by the radiation isodose cloud (blue).

Figure 2: Afterloaders

C: The T凰ron afterloader Isodose Control BV (www.isodosecontrol.com).

The doses are viewed as isodose curves overlaid on an image such as a CT scan or ultrasound, compared as volume graphs (dose volume histograms) and represented as a 3D virtual image of the prostate tumour target and surrounding structures.
Table 2: High-dose-rate plus External-beam Radiation Therapy in Low-risk Patients

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Group</th>
<th>n</th>
<th>HDR</th>
<th>EBRT</th>
<th>F/U</th>
<th>PSA–PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eulau-Mate, 2000</td>
<td>40</td>
<td>3–4Gy x 4</td>
<td>50Gy</td>
<td>6</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Galalae, 2002</td>
<td>Low</td>
<td>46</td>
<td>5Gy x 2</td>
<td>40Gy/50Pelv</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>Vargas, 2005</td>
<td>High</td>
<td>55</td>
<td>4–5Gy x 4</td>
<td>45Gy</td>
<td>3.5</td>
<td>77</td>
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<tr>
<td>Neumann, 2005</td>
<td>Intermediate</td>
<td>n/a</td>
<td>5.5–6.75Gy x 4</td>
<td>45Gy</td>
<td>5</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 3: High-dose-rate plus External-beam Radiation Therapy in Intermediate- and High-risk Patients (<5-year Follow-up)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Group</th>
<th>n</th>
<th>HDR</th>
<th>EBRT</th>
<th>F/U</th>
<th>PSA–PFS (%)</th>
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</thead>
<tbody>
<tr>
<td>Demanes, 2005</td>
<td>Intermediate</td>
<td>110</td>
<td>5.5–6Gy x 4</td>
<td>36–40Gy</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>Phan, 2005</td>
<td>Intermediate</td>
<td>67</td>
<td>6Gy x 4</td>
<td>40–50Gy</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>Yamada, 2006</td>
<td>Intermediate</td>
<td>15</td>
<td>5.5–7Gy x 3</td>
<td>45–50Gy</td>
<td>3.5</td>
<td>100</td>
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Table 4: High-dose-rate plus External-beam Radiation Therapy in Intermediate- and High-risk (<5-year Follow-up)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Group</th>
<th>n</th>
<th>HDR</th>
<th>EBRT</th>
<th>F/U</th>
<th>PSA–PFS (%)</th>
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</thead>
<tbody>
<tr>
<td>Eulau-Mate, 2000</td>
<td>Intermediate</td>
<td>42</td>
<td>3–4Gy x 4</td>
<td>50Gy</td>
<td>6</td>
<td>72</td>
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<tr>
<td>Galalae, 2002</td>
<td>High</td>
<td>44</td>
<td>15Gy x 2</td>
<td>40Gy</td>
<td>3</td>
<td>73</td>
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<tr>
<td>Demanes, 2005</td>
<td>Intermediate</td>
<td>188</td>
<td>5.5–6Gy x 4</td>
<td>36</td>
<td>7</td>
<td>86</td>
</tr>
<tr>
<td>Neumann, 2005</td>
<td>Definition n/a</td>
<td>n/a</td>
<td>5.5–6.75Gy x 4</td>
<td>45</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>Phan, 2005</td>
<td>Intermediate</td>
<td>109</td>
<td>6Gy x 4</td>
<td>40–50Gy</td>
<td>5</td>
<td>9</td>
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Table 5: Results from Multi-institutional Studies

<table>
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<th>Author (year)</th>
<th>Group</th>
<th>n</th>
<th>HDR</th>
<th>EBRT</th>
<th>F/U</th>
<th>PSA–PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martínez, 2005</td>
<td>Gleason ≥7 or PSA ≥10 or Stage ≥12b</td>
<td>934</td>
<td>Variable</td>
<td>36–50</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Vargas, 2005</td>
<td>Roach &lt;15%</td>
<td>761</td>
<td>Variable</td>
<td>36–50</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>Swanson, 2006</td>
<td>Gleason 8–10</td>
<td>313</td>
<td>Variable</td>
<td>36–50</td>
<td>5</td>
<td>67</td>
</tr>
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Advantages and Comparisons of High-dose-rate Brachytherapy

High-dose-rate Brachytherapy is Intensity-modulated

HDR is ‘intensity-modulated’ (IM) because the longer the HDR radiation source resides in a particular location, the greater the intensity of radiation at that location. Modulating the intensity comes from adjusting the time the source stays at each position within the catheter matrix. It is the functional equivalent of having an infinite range of seed activity at every possible source position, so offers a new level of refinement in dose distribution control. IM HDR brachytherapy does not have the patient set-up and prostate motion problems associated with external-beam IMRT. HDR is delivered with great precision. The single high-intensity HDR source is robotically delivered into stable catheters with millimetre precision. The HDR source does not shift or migrate. Permanent seeds, in contrast, are manually inserted into deformable soft tissue and the final locations of the sources are usually, to some degree, different from those planned. Even if an ideal seed were 93% for the low-risk group, 87% for the intermediate-risk group and 70% for the high-risk group. Local tumour control was 96% across all risk groups. These findings bring into question the need for androgen deprivation therapy when high doses of radiation are given to the prostate and surrounding tissue.

Based on the favourable experiences with both HDR and permanent-seed brachytherapy without EBRT in early-stage disease, we started HDR monotherapy for low- and intermediate-risk group patients (T1 or T2, PSA ≤15 and Gleason ≤6). We accomplished control of disease in 96% of cases (PSA progression-free survival) and observed a very low complication rate. To confirm that the EBRT was not needed, we performed a matched-pair analysis that compared the results of patients who received HDR and EBRT with the results of those who received HDR monotherapy. HDR monotherapy was as effective as the combined treatment programme, so we concluded that for early cancer of the prostate HDR monotherapy is effective and ample treatment.

Published Literature

Table 2 shows the results from the literature of HDR in combination with EBRT in patients with low-risk disease. The mean PSA progression-free survival (survival with no clinical, radiological or PSA signs of disease progression) was over 90%, with most patients having five or more years of follow-up.

Tables 3 and 4 show HDR brachytherapy and EBRT outcomes in patients with intermediate- and high-risk disease based on the length of follow-up. The definition of intermediate- and high-risk patients varies in the prostate literature. This is significant as upgrading patients to high-risk can exaggerate the efficacy of therapy. Regardless of this, landmark prostate literature. This is significant as upgrading patients to high-risk...
High-dose-rate Brachytherapy of Prostate Cancer

High-dose-rate (HDR) is ‘intensity-modulated’ because the longer the HDR radiation source resides in a particular location, the greater the intensity of radiation at that location.

substantially from the planned dose because of anatomical changes during the time it takes a permanent-seed implant to emit the dose or through patient motion or organ deformation during the course of EBRT. In contrast, the precise sequence of HDR simulation, dosimetry and dose delivery, in conjunction with the short treatment duration, permits accurate pre-treatment dosimetry representations and reliable treatment delivery. Correct and reproducible geometric plan-to-target and source-to-target relationships are achieved with HDR brachytherapy.

The High-dose-rate Sequence of Events Allows Multiple Opportunities to Optimise Therapy

Inevitably, in some cases brachytherapy needle or catheter placement will be suboptimal. The sequencing of HDR permits the physician to discover and improve suboptimal positioning and dosimetry either by moving the catheters to better positions or by utilising computer software to optimise the dosimetry. In addition, relatively large prostates can be treated with HDR due to the flexibility of the catheter matrix system.

High-dose-rate Reliably Treats Cancer That Extends Beyond the Prostate

HDR brachytherapy’s ‘scaffolding matrix’ feature provides both general stability and the ability to place catheters at or beyond the prostate capsule and into the seminal vesicles without the possibility of source loss or migration to other organs.

Table 6: Results of High-dose-rate Monotherapy

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>HDR</th>
<th>EBRT</th>
<th>F/U</th>
<th>PSA–PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoshi, 2003</td>
<td>15</td>
<td>6Gy x 9</td>
<td>None</td>
<td>2</td>
<td>86*</td>
</tr>
<tr>
<td>Mark, 2003</td>
<td>193</td>
<td>7.25Gy x 6</td>
<td>None</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>Demanes, 2007</td>
<td>298</td>
<td>7.25Gy x 6 or 9.5Gy x 4</td>
<td>None</td>
<td>3.9</td>
<td>94</td>
</tr>
</tbody>
</table>

* Low- and intermediate-risk patients only.

Figure 3: Computed Tomography Cross-section of the Pelvis

With implant catheter positions in the prostate and the radiation isodose curves covering the target.

Control of Normal Tissue Doses Is Predictable with High-dose-rate Brachytherapy

The dose to the bladder and rectum is routinely kept within prescribed constraints (typically 75–80% at CET). It is a subtle but significant fact that at larger fraction sizes the biological differences are more pronounced than the simple percentages would imply. Thus, the biological doses to the bladder and rectum are actually lower than the nominal percentages. Dose limits are readily achieved by avoiding the urethra and rectum during catheter insertion and by making dwell time adjustments during the dosimetry calculations.

Radiobiological Advantages for High-dose Radiation in the Treatment of Prostate Cancer

It has been established that the repair of sub-lethal radiation damage for prostate cancer is comparatively lower than previously believed. It suggests that the large doses per session and the relatively short time course confer an important biological advantage to HDR brachytherapy.

Radiation Safety Is Excellent

Radiation exposure to people other than the patient does not occur with HDR brachytherapy. Complicated permanent-seed accounting measures are not relevant to HDR. There is no seed loss or environmental exposure.

High-dose-rate Causes a Comparatively Short Period of Acute Symptoms

All forms of RT cause transient acute inflammation of pelvic structures and temporary irritation of bowel or bladder function. The duration of these symptoms depends on the time taken to deliver the radiation, total dosage.
High-dose-rate brachytherapy is a safe and effective treatment of localised prostate cancer. It combines the best characteristics of permanent-seed brachytherapy and the intensity modulation that typifies external-beam IMRT. It has great precision and is a dynamic process that permits excellent control of radiation dosimetry and treatment delivery. The relationship of the implant and dose distribution to patient anatomy are known in advance of treatment so the dosimetry is prospective and hence modifiable. HDR reliably treats local extension of disease beyond the prostate. Normal tissue dose constraints are readily attainable, predictable and reliable. There is a radiobiological advantage to the HDR fractionation and the accelerated treatment course. Radiation safety is optimal. Acute radiation side effects are of short duration and chronic effects are relatively few. HDR may be safely and effectively applied to all risk groups either as monotherapy for early to intermediate disease or in combination with EBRT for intermediate to high disease. It can also be safely and effectively applied to patients with larger glands, often without the need for hormone therapy. As with all sophisticated technologies, the accuracy of the technique depends on when and how it is used.

Conclusions

HDR brachytherapy is appealing because the source both is reusable and can be applied to many patients and many different kinds of cancer other than prostate.

Follow-up Medical Care and Prostate-specific Antigen Testing After Therapy

Most patients are back to baseline status within one month of treatment. Subsequent PSA testing (every three months for two years and every six months thereafter) at the CET requires correct interpretation because transient risings (called PSA ‘spikes’ or ‘bounces’) may occur and should not be misinterpreted as treatment failures. Biopsies within two years of treatment are frequently unreliable indicators of persistent disease.

High-dose-rate Is a Reusable Resource


The Multinational Association of Supportive Care in Cancer (MASCC), a multinational, multidisciplinary organization, is dedicated to research and education in all aspects of supportive care for people with cancer worldwide regardless of the stage of their disease.

We invite you to visit our website, www.mascc.org, to find out about membership, learn about the organization, visit the Education and Research Centers, and to register for our annual international meeting in Houston, Texas, June 26-28, 2008.

To find out more about MASCC and the Journal of Supportive Care in Cancer please contact Cindy Rittenberg via e-mail at cindyrit@bellsouth.net or visit the website at www.mascc.org.