

A New Zealand  
Guidelines Group  
Rapid Review  
May 2005

# The Addition of High-dose-rate Brachytherapy to External Beam Radiotherapy in the Treatment of Locally Advanced Prostate Cancer

Report to the Ministry of Health and CEOs of DHBs

Principal authors:

Robert Cook

Stephen Schaapveld



## **Copyright**

The New Zealand Guidelines Group (NZGG) encourages the free exchange and sharing of evidence, and the adaptation of their publications for local conditions. However, please note that NZGG publications are subject to copyright. If you wish to replicate or reproduce this review, in part or in full, please obtain agreement with NZGG. Access will not be unreasonably withheld.

Please cite this report as:

New Zealand Guidelines Group. *The Addition of High-dose-rate to External Beam Radiotherapy in the Treatment of Locally Advanced Prostate Cancer. Rapid Review.* Wellington; 2005.

# Contents

|  |           |
|--|-----------|
| <b>1. Executive Summary .....</b>  | <b>5</b>  |
| <b>2. Introduction .....</b>   | <b>9</b>  |
| Background .....   | 10        |
| Treatment descriptions.....  | 13        |
| <b>3. Methods.....</b>   | <b>21</b> |
| Searching .....  | 21        |
| Selection of studies .....   | 22        |
| Appraisal methodology (validity assessment) .....  | 24        |
| Presentation of results.....   | 24        |
| Study Characteristics .....  | 24        |
| Quantitative data synthesis .....  | 24        |
| <b>4. Results .....</b>  | <b>25</b> |
| Topic 1: The evidence for a ‘dose-response’ relationship between total dose and outcomes for radiotherapy..... | 25        |
| Topic 2: The evidence for HDR BT used as a radiotherapy boost with EBRT compared to EBRT alone .....           | 33        |
| <b>5. Discussion .....</b>   | <b>39</b> |
| Dose escalation.....   | 39        |
| HDR BT .....   | 40        |
| dose escalation using HDR BT compared to other forms of dose escalation .....                                  | 41        |
| <b>References.....</b>   | <b>45</b> |
| <b>Appendices (separate document)</b>  |           |
| Evidence tables  |           |
| • Benefits of dose escalation  |           |
| • Harms of dose escalation   |           |
| • Benefits of HDR BT compared to EBRT  |           |
| • Harms of HDR BT compared to EBRT   |           |
| • Quality of life studies  |           |



# 1. Executive Summary

## OBJECTIVES (CLINICAL QUESTIONS)

This report aims to answer key questions in two topic areas:

### **In the treatment of localised prostate cancer...**

- **what is the evidence for a 'dose-response' relationship between total radiotherapy dose and outcomes?**
- **what are the quantifiable benefits and harms of high-dose rate brachytherapy (HDR BT) used as a boost with external beam radiotherapy (EBRT) compared to EBRT alone?**

These topics have been re-framed as clinical questions for searching the published literature and the results are presented as evidence tables and summarised.

This evidence has been requested by the National Service and Technology Review (NSTR) Sub-Committee, as support (or challenge) to the clinical business case development for a national HDR BT service.

## REVIEW METHODS

A literature search was undertaken in May 2005 using six databases and was supplemented with a data extraction from other key references/reviews, including the studies referred to in a recent discussion document.<sup>1</sup>

Studies of patients with (low, intermediate and high-risk) disease were identified; all grades (T1 to T3) of localised prostate cancer without metastasis were eligible. Papers were only included if the risk groups and T stage were reported or could be identified. For measures of effectiveness the intervention of interest is HDR BT with Iridium-195 delivered by an after loading technique. Papers that reported one of the following outcomes were included: overall survival (OS), disease free survival (DFS), freedom from metastasis (FDM), freedom from failure (FFF) or biochemical no evidence of disease (bNED) as defined by Radiation Therapy Oncology Group (RTOG), quality of life measures, or toxicity (acute and late) graded using a scale such as the RTOG scale.

This rapid review has been conducted to provide timely, summarised knowledge for decision making, there has been limited peer-review and restricted time for formatting of evidence tables, proof reading and full appraisal of study quality.

## RESULTS

- There is RCT evidence that patients with localised, intermediate risk and high risk (Pre-treatment PSA  $\geq 10$  and/or GS  $\geq 7$  and/or  $>T2$ ) disease i.e. patients not suited to surgery, benefit from dose escalation (doses higher than conventional doses of radiotherapy). Biochemical evidence of cure is improved by about 10 to 12% over 5 years but no overall survival benefit has

yet been shown in randomised studies. In prospective studies 5-year biochemical control rates in the intermediate risk groups have been less than 80% with external beam dose escalation.

- Dose escalation can be performed with 3D conformal radiotherapy (photon or proton) boost, with Ir-192 high-dose rate brachytherapy boost, or brachytherapy boost with permanent seed implantation.
- The minimum total dose delivered by HDR BT to the prostate gland generally exceeds the maximum doses yet delivered with modern 3DCRT dose escalation and exceeds the doses achievable with conventional EBRT and Pd-103 or I-125 permanent seed implantation BT. These higher doses delivered by HDR BT boost to intermediate risk patients can achieve up to 87% 5-year biochemical control rates.
- For men with unfavourable high-risk disease recent prospective and retrospective studies have shown a relatively favourable outcome (69% 5 year biochemical control rate) with HDR BT combined with EBRT, better than any study of alternative dose escalating treatments for this sub-group so far.
- There is an increased risk of late urinary tract and/or rectal side effects with higher doses of radiotherapy, but HDR BT has comparable safety to the other techniques and the dose delivered to the prostate can be accurately planned, sparing the adjacent normal rectal and bladder tissue.
- Serious long term toxicity is rare. Late grade 3 GU complications such as urinary stricture and incontinence are more common in men who have also had prostate resection (TURP). Most series report rates of stricture requiring surgery of less than 7%.
- There are several advantages reported to delivering the boost with Ir-192 HDR BT:
  - improvement in quality of life
  - patient convenience
  - staff safety.

There is a lack of high quality data quantifying these benefits.

## CONCLUSIONS

The use of HDR BT as a method of dose escalation in the treatment of locally advanced prostate cancer is a promising approach. There is good evidence that for intermediate risk localised prostate cancer dose escalation improves biochemical cure rates. There is also fair evidence, from prospective studies, that for high risk localised prostate cancer HDR BT (22–24 Gy) combined with EBRT (36 Gy) can result in biochemical control rates of around 69% over 7 years. Of the techniques that allow biologically equivalent doses in excess of 75 Gy delivered to the prostate, there is fair evidence from uncontrolled studies, that the biochemical control rates are at least as good with EBRT combined with HDR BT, compared to existing treatments.

There is a balance between the need to reduce the toxicity of radiotherapy with treatments that which better target the prostate and the need to also achieve higher

cure rates with increased radiotherapy doses. It is likely that this balance will be only achievable with combination treatments, EBRT with either conformal boost (3DCRT), HDR BT boost or IMRT. HDR BT provides at least as good cure rates as these other forms of combined treatment, with comparable long term toxicity. There is a lack of consistency in reporting side effects, risk groups and biochemical outcomes that makes direct comparisons across studies unreliable and this report is unable to confirm the superiority of any single technology for dose escalation in terms of toxicity. Long term toxicity particularly grade 3 complications (such as severe rectal bleeding, urinary stricture or fistulae) is rare with all forms of treatment. Any erectile dysfunction resulting from the various procedures can in most cases (80%) be successfully managed with medication (selective inhibitors of cyclic-GMP).

Patient acceptability, convenience and staff safety are important considerations, and there is some descriptive evidence that HDR BT has an advantage over other methods of dose escalation for these outcomes.

Targeting of this new technology towards those men who have intermediate and high-risk localised prostate cancer will be a strategy that maximises the effectiveness and value of this new technology.

The resource consequences of any increasing use of this technology should also be considered along with the evidence of effectiveness. The workforce development and training implications, increased capital expense of equipment and shielded rooms, the potential saving in reduced need for EBRT and the expanding indications for HDR BT use are all relevant to this discussion.

## ACKNOWLEDGEMENTS

NZGG acknowledges and thanks Associate Professor Graham Stevens, Radiation Oncologist at Auckland Hospital for his assistance with the providing clinical and research background to this report.



## 2. Introduction

The purpose of this report is to provide a review of evidence for the National Cancer Treatment Working Party (NCTWP) and a subcommittee, the Radiation Oncology Working Group (ROWG) regarding the use of high dose rate brachytherapy (HDR BT) as a boost to external beam radiation (EBRT) in the treatment of prostate cancer.

### EPIDEMIOLOGY

---

Prostate cancer is the most commonly diagnosed cancer in men. In New Zealand, in 2000, there were 3045 prostate cancer registrations (an age-standardised rate of 117.1/100,000 men).

There were 594 deaths from prostate cancer in 2000, making this the second most common cause of male cancer death after lung cancer. Prostate cancer has a low fatality/case ratio of 0.20, with five times more registrations than deaths.

Prostate cancer accounts for about 4 percent of all male deaths in New Zealand, with two-thirds of these occurring in men aged 75 years and older. Maori registration rates for cancer of the prostate were lower than non-Maori rates.

Approximately two-thirds of deaths occur in men aged 75 years or older, 17% in men aged 70–74 years, 15% in men aged 60–69 years, 2% in men aged 50–59 years, and 0.2% in men aged 40–49 years.<sup>2</sup>

### RISING PROSTATE CANCER RATES

Between 1993 and 1994 the number of primary prostate cancer registrations rose from 1237 to 2013 (an increase of 62.7 percent). This was followed by a further increase of 23.2 percent between 1994 and 1995 (from 2013 to 2481 registrations).

This rise is partly attributed to the availability of prostate-specific antigen (PSA) testing, which allows symptom-free detection of the disease.<sup>2</sup>

### NEW ZEALAND PREVALENCE

The best estimates of the prevalence of localised prostate cancer from New Zealand data are 4.4% in men aged 50–59, 6.4% in men aged 60–69 years and approximately 12% in men aged 70 years or older.<sup>2</sup> Even these estimates are much higher than the age-standardised mortality rates for prostate cancer reflecting the overall good prognosis for this disease compared to other cancers.

## BACKGROUND

---

A comprehensive discussion document was circulated in Jan 2005 and has identified several drivers that are increasing the demand for HDR BT in New Zealand. One of these major drivers is the developing clinical indication for the treatment of intermediate and high-risk localised prostate cancer with HDR BT. Manual loading of permanent seed BT and low dose BT have been used for gynaecological cancers for several years but brachytherapy for prostate cancer is currently not a common treatment in New Zealand. If HDR BT were available, it has been estimated that 150 patients per annum could be suitable for this treatment in New Zealand (of 2400 diagnosed p.a. with prostate cancer) and that the use of HDR BT would also result in other time and cost savings. For example, depending on the regimen used it is possible that approximately 13 EBRT fractions per patient, could also be saved.<sup>1</sup>

NZGG has been asked to evaluate the clinical effectiveness of HDR BT and to provide a critique of the evidence for consideration by the NSTR sub-committee as part of a developing process for assessing new technologies.

This report has been commissioned by the National Service and Technology Review (NSTR) Sub-Committee and the CEOs of District Health Boards within New Zealand. A further report has been requested comparing the cost and cost effectiveness of setting up and running HDR BT units in New Zealand versus alternative options. These two reports should be considered together.

## STAGES OF PROSTATE CANCER

Prostate cancer is staged clinically after diagnosis according to an international standard. This tumour stage is one of the major determinants of outcome. Staging systems have always acknowledged the significance of extraglandular disease. In both the Jewett-Marshall classification schema and, more recently, the Tumour Node Metastasis (TNM) system (see Table 1), the presence of disease beyond the prostate (ie, stage C and stage T3, respectively) has been recognised as indicating a poor prognosis. This observation predates the use of modern prognostic variables associated with increased risk of extracapsular disease (ie, elevated PSA and high Gleason score).

**Table 1: TNM classification system**

|    |     |  |
|----|-----|--|
|    | TX  | Primary tumour cannot be assessed                                  |
|    | T0  | No evidence of primary tumour                                      |
| T1 |     | Clinically unapparent tumour, not palpable, nor visible by imaging |
|    | T1a | Incidental histological finding in 5% or less of tissue resected   |
|    | T1b | Incidental histological finding in more than 5% of tissue resected |

|    |     |   |
|----|-----|---|
|    | T1c | Tumour identified by needle biopsy (e.g. because of elevated PSA) screen detected prostate cancer |
| T2 |     | Tumour confined within prostate   |
|    | T2a | Involves half of a lobe or less   |
|    | T2b | Involves more than half of a lobe but not both lobes  |
|    | T2c | Involves both lobes   |
| T3 |     | Tumour extends through prostate capsule   |
|    | T3a | Unilateral extracapsular extension  |
|    | T3b | Bilateral extracapsular extension   |
|    | T3c | Invades seminal vesicle(s)  |
| T4 |     | Tumour is fixed or invades adjacent structures other than seminal vesicles                        |
|    | T4a | Invades bladder neck and/or external sphincter and/or rectum                                      |
|    | T4b | Invades levator muscles and/or is fixed to pelvic wall  |

N+ refers to lymph node involvement and M+ refers to the presence of distant metastases

## GLEASON SCORE

The Gleason score is a histological grading system for prostate cancer cells obtained by biopsy. The degree of differentiation is given a score of 1 to 5 in two areas of the specimen. A primary score is assigned to the pattern occupying the greatest area of the specimen and a secondary score to the pattern occupying the second greatest area. These are added together to give a range from 2 to 10. Low grade cancers (Gleason score 2, 3, 4) are slower growing and less aggressive than high grade (Gleason score 8, 9, 10) cancers.

## ESTIMATING THE RISK OF DEVELOPING CANCER OUTSIDE THE PROSTATE

Low, intermediate and high risk prostate cancers have been defined by several groups including the American Society for Therapeutic Radiology and Oncology (ASTRO). Prognosis is increasingly calculated using the Partin tables.<sup>4</sup> These tables have been validated in several cohorts and give a probability of organ confined disease, extra-prostatic extension, seminal vesicle invasion and lymph node invasion. They are used to guide decisions on the best course of treatment.  
<http://urology.jhu.edu/prostate/partintables.php>

Various definition of risk groups exist in the literature (see Table 2). A commonly accepted classification is based on the work of Galalae<sup>5</sup> and has since been further modified by Demanes.<sup>6</sup> These varying definitions make detailed interpretation across studies complex, but in practice all schemes use a three tier approach which allows a 'broad brush' categorisation allowing comparisons sufficient for this report.

**Table 2: Comparison of risk group definitions**

| Author                       | Risk group     | T stage | PSA (ng/mL) | Gleason score | Indicator rules            |
|------------------------------|----------------|---------|-------------|---------------|----------------------------|
| D'Amico (1998) <sup>7</sup>  | Low            | T1c-T2a | ≤10         | ≤6            | All required               |
|                              | Intermediate   | T2b     | >10, ≤20    | 7             | One or more                |
|                              | High           | T2c     | >20         | 8–10          | One or more                |
| Blasko (2000) <sup>8</sup>   | Low            | T1-T2   | ≤10         | ≤6            | All required               |
|                              | Intermediate   | T1-T2   | >10         | 7–10          | PSA or Gleason score       |
|                              | High           | T1-T2   | >10         | 7–10          | Both PSA and Gleason score |
| Zelevsky (1998) <sup>9</sup> | Low            | T1-T2   | ≤10         | ≤6            | All required               |
|                              | Intermediate   | T3      | ≥10         | 7–10          | One                        |
|                              | High           | T3      | ≥10         | 7–10          | Two or more                |
| Kuban (2003) <sup>10</sup>   | Low            | T1-T2a  | ≤10         | ≤6            | All required               |
|                              | Intermediate#1 | T1-T2a  | >10, ≤20    | ≤7            | All criteria               |
|                              | Intermediate#2 | T2bc    | ≤20         | ≤7            | All criteria               |
|                              | High           | —       | >20         | 8–10          | One                        |
| Galalae (2004) <sup>5</sup>  | Low            | T1-T2a  | ≤10         | ≤6            | All required               |
|                              | Intermediate   | ≥T2b    | ≥10         | ≥7            | Any one                    |
|                              | High           | ≥T2b    | ≥10         | ≥7            | Two or more                |
| Demanes (2005) <sup>6</sup>  | Low            | T1-T2a  | ≤10         | ≤6            | All required               |
|                              | Intermediate   | T2b/c   | >10, ≤20    | 7             | One or more                |
|                              | High           | T3      | >20         | 8–10          | One or more                |

For example using the features as defined in Galalae's<sup>5</sup> report.

T1c / GS 5 / PSA 20 would describe an intermediate-risk patient.

T2a / GS 8 / PSA 20 would describe a high-risk patient.

Current management of early prostate cancer includes watchful waiting, radical prostatectomy or radiotherapy. The main active local treatment modalities for localised prostate cancer are radical prostatectomy and radiotherapy. These local therapies might also be combined with systemic hormonal therapy.

## TREATMENT DESCRIPTIONS

---

The two groups of radiotherapy available to treat localised prostate cancer are external beam radiation therapy (EBRT) and Brachytherapy (BT).

### External beam radiation therapy

EBRT uses high-energy linear accelerators and remains the most common approach in most centres. EBRT is an outpatient procedure and in New Zealand is usually given as 5 daily outpatient sessions for 7 weeks, delivering 70 Gy. Thus patients living far from the hospital must either have extensive daily travelling or stay at or near the hospital during the treatment period.

Conventional external beam radiotherapy typically is delivered using a 4-field technique. The 4 fields (anteroposterior/posteroanterior, left/right lateral) are designed to include the prostate, seminal vesicles, and regional lymphatics. This technique is employed for cumulative doses of 4500–5000 cGy, delivered over 5–5.5 weeks. An additional dose of approximately 20 Gy to a smaller field (ie, a boost) is offered to the prostate and periprostatic tissues. Total doses of 65–70 Gy typically are employed, these central axis doses must be limited to prevent significant damage to nearby normal tissues. The boost field is designed to limit treatment to the target volume (prostate, seminal vesicles, and a 1–2 cm margin) and offer additional shielding to the posterior wall of the rectum, the urethra, and the small bowel. The reduced volume of normal tissue included within the radiation field is associated with a reduction in morbidity.

**Three-dimensional conformal radiation therapy (3DCRT)**, defining the target organ(s) accurately in three dimensions, allows higher doses to the target without a significant increase in normal tissue complications. Meticulous attention to treatment technique and dose volume histogram analysis are critical for the safe implementation of the higher doses delivered by 3DCRT. These doses do not usually exceed 78 Gy.

**Intensity modulated radiotherapy (IMRT)** methods allows for greater sparing of the surrounding normal tissues and also the potential to further escalate doses.

New imaging methods are often combined with IMRT to more accurately target the prostate, and avoid high doses to the rectum and bladder.

The emergence of intensity-modulated treatment and other advances in planning have provided the opportunity to further escalate the radiation dose to 86.4 Gy while still respecting the surrounding normal tissue tolerance. However Phase I studies are still needed to define more clearly the maximal dose of radiation that can be delivered safely with this new modality.<sup>11</sup>

*Dose escalation for EBRT:* Investigators are actively searching for the optimal dose for prostate cancer RT. An important component of this research is the characterisation of the 'dose–response' relationship to guide dose escalation. This

dose–response relationship (the extent to which increasing doses of radiotherapy result in increased destruction of prostate cancer) has been found to be risk group dependent.

Dose escalation studies have been done to enhance the biochemical control rate of prostate cancer. Long-term follow-up is necessary both for assessment of biochemical control and normal tissue toxicity.

## Brachytherapy

*Interstitial brachytherapy* places radioactive sources in direct contact with the tumour in the prostate gland as a temporary or permanent implant. The permanent implants deliver a lower dose rate and are usually inserted manually. This contrasts with temporary implants, such as those used by HDR BT, which are inserted using remote afterloading techniques.

*HDR brachytherapy* delivers higher dose rates (10–100 cGy per minute) and involves the use of high-intensity radioelements with source radioactivity and energy too great to allow manual handling. The tiny (1mm by 3mm) sources contain a highly radioactive source of Iridium-192 that is laser welded to the end of a thin, flexible stainless steel cable. The device, called a remote afterloader, safely stores the radiation source between treatments and delivers the source directly into the patient during therapy. The first step in the HDR BT process is the placement into the patient of the brachytherapy catheters, needles or other applicators. Then, following localisation radiographs or scans and related computer based treatment planning calculations, HDR treatment is administered to the patient in a shielded vault. The computer-guided remote afterloader is used to direct the source with millimetre precision into the source with millimetre precision into the applicator system. The source moves in 5mm steps to specific locations within the hollow conduits implanted in the target volume. It stops at designated positions called ‘dwell’ positions. The distribution of radiation dose is determined by the dwell position location and how long the source remains at each of the many potential sites. HDR brachytherapy treatment courses may vary from one to 12 or more treatments (also known as fractions), depending on the type of cancer being treated, the prescribed dose, whether external radiation is also being administered and many other factors. HDR BT requires a shielded room for the procedure and hospitalisation of the patient.

Several types of brachytherapy boost techniques are reported in the literature. Techniques based on transrectal ultrasound (TRUS) guidance clearly provide the most accurate method of radioactive source placement with reduced toxicity. The Boost with HDR BT can be given before, after or during a course of treatment with EBRT. The dose delivered to the prostate is calculated and controlled by the dwell time of the radiation source at specified locations within each needle. The advantages of HDR brachytherapy include improved implant dosimetry, shorter treatment time, no requirement for permanent seed implantation, and no risk of seed migration or radiation exposure to personnel. The proposed scheme for New Zealand would deliver EBRT at 40-46 Gy in 20 to 25 daily fractions followed by 3 to 4 HDR BT treatments.

HDR BT is one of a number of relatively new treatments studied in an attempt to develop therapies for early localised cancer that are effective, minimally invasive and result in fewer side-effects. These new and emerging treatments include developments in brachytherapy (permanent, low dose rate and high dose rate) three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated conformal radiotherapy (IMRT), there are also new techniques in cryotherapy, high-intensity focused ultrasonography and hormonal therapies.

*Low dose rate brachytherapy* does not require special facilities other than dosimetric planning equipment, transrectal ultrasound and computer tomography.

## WHAT IS KNOWN SO FAR

Previous studies have suggested that for patients with low-risk prostate cancer (Stage T1c-T2a, Gleason score less than 7, prostate-specific antigen of 10.0 ng/mL), monotherapy with radical prostatectomy, three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated RT, or prostate brachytherapy results in similar biochemical relapse-free survival.<sup>7, 12, 13</sup> Treatments give a reported 5-yr biochemical control rate of about 93%. Patient and physician preferences usually influence the treatment selection, based on a critical assessment of the relative side-effect profiles and quality-of-life evaluations.

In patients with intermediate or high-risk disease (Gleason score greater than 6 and/or PSA level greater than 10 ng/mL) brachytherapy as monotherapy is less than optimal.<sup>13</sup> Even with modern brachytherapy techniques, intermediate-risk and high-risk patients fair poorly with brachytherapy alone and the 5-year biochemical control rate with iodine-125 prostate was a disappointing 63% and 24% for intermediate-risk and high-risk patients, respectively.<sup>14</sup>

In centres that are performing brachytherapy, EBRT has been added to therapy and in centres where ERBT therapy is the standard treatment HDR BT is being considered to boost the dose. The combination of EBRT in conjunction with a prostate brachytherapy boost is seen as a key therapy to improve outcomes in intermediate-risk and high-risk patients. The benefits of combining EBRT with prostate brachytherapy include delivery of a greater radiation dose to the prostate, inclusion of disease that has extended beyond the prostatic capsule, and coverage of pelvic lymph node metastasis, when indicated.

Improved disease free survival (DFS), freedom from distant metastasis (FDM), and overall survival (OS) has been shown with delivery of greater radiation doses to the prostate.<sup>15, 16</sup> Multiple approaches have been used to deliver this dose escalation, including intensity-modulated RT, high-energy neutrons, hyper-fractionated RT, and permanent prostate brachytherapy in conjunction with EBRT. The maximum dose and risk/benefit balance for the different approaches is not yet agreed.

Both 3D-CRT and prostate brachytherapy data have supported a dose-response relationship in intermediate-risk and high-risk patients. The Radiation Therapy Oncology Group (RTOG) reported improved disease-specific and overall survival in patients with high Gleason scores who received higher doses of EBRT.<sup>17</sup> Dose was

the most statistically significant predictor of biochemical control for permanent iodine-125 implants BT.<sup>18</sup> The benefit was greater for those patients presenting with PSA levels greater than 10 ng/mL. The 4-year freedom from biochemical failure (PSA level less than 1.0 ng/mL) rate was 51% and 100% in patients with a dose covering 90% of the prostate of less than 140 Gy versus one greater than 140 Gy, respectively (P = 0.009).

The response of prostate cancer to radiation was well-documented in the pre-PSA era. Large palpable tumours resolved within months of treatment with relatively modest radiation doses of 64–70 Gy. The use of PSA-based failure as an endpoint, however, has made it clear that cure rates were much lower than appreciated. While doses in this range are still widely used today, data from retrospective, sequential prospective and now randomised studies indicate that for patients with intermediate-to-high risk disease, doses above 70 Gy are associated with a significant reduction in biochemical failure.

Higher doses run the risk of increased toxicity and in an attempt to reduce this toxicity, several techniques and treatment modalities have been used to provide dose-escalation while minimising long-term toxicity. This report attempts to clarify the dose response data that exists for EBRT and HDR BT and to investigate the data that can quantify the benefits and risks associated with dose escalation using HDR BT.

## TOXICITY

Morbidity of radiation treatment is intimately linked to the volume of normal tissue treated. Conventional radiotherapy, EBRT, includes the irradiation of large volumes of tissue, including the skin, small bowel, bladder, large bowel, bones of the pelvis, and additional areas of soft tissue (including nerves). Each organ can experience irritation during a course and, potentially, following a course of radiotherapy.

The acute and long term toxicities of doses above 70 Gy have been reduced by using conformal radiotherapy techniques and imaging techniques that improve the accuracy of radiotherapy planning (see Table 5).

## UNRESOLVED ISSUES

Vicini<sup>19</sup> has acknowledged that there is currently little RCT evidence on how to best deliver these higher tumouricidal doses of RT. However, there are pathophysiological reasons why HDR BT may be a useful technique. By placing HDR afterloading needles directly into the prostate gland under real-time ultrasound guidance, a steep dose gradient between the prostate and adjacent normal tissues can be generated that is unaffected by organ motion, oedema or treatment setup uncertainties. The ability to control the amount of time the single radioactive source dwells at each position along the length of each brachytherapy catheter further enhances the conformity of the dose. In addition, recent radiobiologic data on prostate cancer treatment suggest that the alpha/beta ratio for tumour control is similar to (or possibly even smaller) than that for surrounding late-responding normal tissues. If true,

hypofractionation (as practiced with HDR BT combined with EBRT) would be expected to produce tumour control and late sequelae that are at least as good as achieved with conventional fractionation, with the additional possibility that early sequelae might be reduced. Recent data from several groups (see table x) performing HDR BT in patients with locally advanced disease is included in this report and helps to confirm these assumptions. Combined with the physical advantages discussed earlier, HDR BT as a means of dose escalation should provide similar tumour control as 3D conformal EBRT with the added advantages of reduced treatment times, less acute toxicity, and no additional technological requirements to account and correct for treatment setup uncertainties and organ motion. Other issues that remain unresolved with this technique (as with other methods of dose escalation) revolve around the amount of additional dose required to provide optimal tumour control, the role of androgen deprivation in the management of patients with locally advanced disease, and whether the regional lymphatics should be irradiated.<sup>20</sup>

## OUTCOME DEFINITIONS

There is debate about how best to define biochemical failure after external beam radiotherapy, this is compounded by the fact that alternative definitions are often used in studies of surgery or other treatment modalities making comparisons across studies difficult. The commonest definition of biochemical failure used in the literature has been defined by ASTRO consensus.<sup>21</sup>

- Three rises backdated to the midpoint between PSA nadir and first rise

Other definitions are used and include:

- Two rises  $\geq 0.5$ ng/mL
- Nadir + 2ng/mL
- PSA > 0.2 ng/mL

In practice there can be a variation of about 4% when using different definitions with varying sensitivities in terms of their ability to predict true clinical control.<sup>6</sup>

The commonest morbidity grading system in use for defining toxicity is also promoted by the Radiation Therapy Oncology Group<sup>22</sup> and in summary gives definitions for four stages of GI or GU toxicities as below.

- grade 1:** minimal side effects not requiring medication for symptom control
- grade 2:** symptoms requiring medication
- grade 3:** complications requiring minor surgical intervention, such as transurethral resection, laser coagulation or blood transfusion
- grade 4:** hospitalisation and major intervention.

These definitions have been used to a varying extent in the literature and outcomes are further complicated by definitions of acute versus chronic (usually taken to mean a complication persisting for more than 3 months after radiotherapy).

## THE NEW ZEALAND CONTEXT

---

This rapid review is to be interpreted in the New Zealand context:

- A review of HDR brachytherapy was requested by Capital and Coast DHB, the stimulus for this was a need to relocate the oncology unit
- Waikato DHB, the only current supplier of HDR BT in New Zealand has signalled an intention to expand its HDR BT facility
- The New Zealand Ministry of Health and DHBs have acknowledged the need for a national approach to service planning
- There may be a longer term need to replace manual BT systems and obsolete low dose rate brachytherapy (LDR BT) units with units capable of delivering HDR BT over time.

## THE RATIONALE

In the treatment of prostate cancer combining EBRT with after-loading of Ir-192 as a HDR BT boost to the prostate has attracted increasing attention for several reasons:

- With this technique it is possible to use high dose rate techniques and protect staff from irradiation
- Ir-192 has a greater range than radionuclides such as I-125 and Pd-103 which are used as permanent seed BT, and is therefore suited for patients with bulkier tumours
- Hypofractionated treatment with Ir-192 can be given and by protecting the rectum  $\geq 100\text{Gy}$  is obtained when the combination regimen is used i.e well above levels so far achieved by escalation with 3DCRT using EBRT only or with brachytherapy using permanent I-125 or Pd 103 seed implantation.

So far the use of HDR BT in prostate cancer treatment has almost exclusively been used to deliver a boost to the prostate for men who also receive EBRT. The use of Ir-192 as monotherapy is under development and is not the subject of this report.

## RESEARCH OBJECTIVES

---

This report aims to answer key questions in two topic areas:

In the treatment of localised prostate cancer...

- what is the evidence for a 'dose-response' relationship between total radiotherapy dose and outcomes?
- what are the quantifiable benefits and harms of high-dose rate brachytherapy (HDR BT) used as a boost with external beam radiotherapy (EBRT) compared to EBRT alone?

The research reported in this monograph was commissioned by the National Service and technology Review Sub-committee and has been completed in one month.

Rapid reviews are completed in a limited time to inform critical decisions about implementing new technologies in a timely manner.

There are limitations to the process of a rapid health technology assessment and review. The overall aim has been to bring together evidence on the use of the technology from several different sources in a timely manner. Because of this time constraint the methodology and documentation of the methodology does not adhere to accepted Cochrane systematic review methodology. Secondly, the integration of evidence requires a balance between all the sources of evidence from different information sources (cost, cost effectiveness, pathological including the information sourced from expert opinion) the collation of this information may not be possible in the time. Some relevant non-published studies, or papers not available online may can not be retrieved in full in the time allocated. Finally, as there is a short and limited peer review process there is a risk that a further phase of appraisal in areas outside the original scope of the review and/or more extensive peer review may be advised if the review identifies new issues that are also critical to the decision making process.



## 3. Methods

### SEARCHING

---

A literature search was undertaken in May 2005 using the following databases:

- Ovid MEDLINE ® - (1966 – May Week 2 2005)
- Ovid MEDLINE ® In-Process & Other Non-Indexed Citations – May 19, 2005
- EMBASE ®1980 to 2005 – Week 20
- Cochrane Database of Systematic Reviews – 2nd Quarter 2005
- Cochrane Central Register of Controlled Trials – 2nd Quarter 2005
- Database of Abstracts of Reviews of Effectiveness – 2nd Quarter 2005
- HTA database of the Centre for Reviews and Dissemination, University of York

The abstracts of papers contained in the reference lists of articles returned were also retrieved.

Hand searching of journals was not performed.

The search was restricted to studies published after 1990 in English.

### MAIN SEARCH TERMS

Prostatic Neoplasms/ Brachytherapy/ Dose-Response Relationship, Radiation/ Neoplasm Recurrence, local/ Radiotherapy Dosage/ Prostate-Specific Antigen/ Tumour Markers, Biological/ Radiation Injuries/ morbidity/ proctitis/ Urethral Stricture/ Urinary Incontinence/ Impotence/ Survival analysis/ survival rate/treatment outcome

### MEDLINE SEARCH STRATEGY

Database: Ovid MEDLINE(R) <1966 to March Week 4 2005>

Search Strategy: for key question 1

-----

1. Prostatic Neoplasms/
2. BRACHYTHERAPY/
3. Dose-Response Relationship, Radiation/
4. Neoplasm Recurrence, Local/
5. Radiotherapy Dosage/
6. Prostate-Specific Antigen/
7. Tumour Markers, Biological/
8. Radiation Injuries/
9. morbidity/

10. proctitis/
11. Urethral Stricture/
12. Urinary Incontinence/
13. Impotence/
14. SURVIVAL ANALYSIS/ or SURVIVAL RATE/
15. Treatment Outcome/
16. 1 and 2
17. 3-15/or
18. 16 and 17
19. limit 18 to (humans and english language and yr  $\geq$  1990)

Search Strategy: for key question 2

-----

20. 1 and 3

21. limit 20 to (humans and English language and yr  $\geq$  1990)

Results from these two searches were filtered by a two stage process. First the Cochrane filters for systematic reviews and RCTs (Phase 1 filter) was applied and secondly the Cochrane filter for non-randomised studies (Phase 2 filter) was applied to the search results. The reference lists of systematic reviews and review articles were searched to retrieve other suitable studies for inclusion, additional papers were also suggested by expert peer review.

## SELECTION OF STUDIES

---

### PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Studies of patients with low, intermediate and high-risk disease were included, all grades of localised (T1 to T3) prostate cancer without metastasis were eligible. For measures of effectiveness the intervention of interest is HDR BT with Iridium-195 delivered by an after loading technique.

Participants: Papers were only included if the risk groups low, intermediate or high and T stage were reported or could be extracted. Where possible those with localised intermediate (one of pre-treatment PSA  $\geq$  10 and/or Gleason score  $\geq$ 7 and/or > stage T2) or high risk (two of pre-treatment PSA  $\geq$  10 and/or Gleason score  $\geq$ 7 and/or > stage T2) prostate cancer were analysed separately.

Primary interventions to be compared for question 1: conformal high dose rate brachtherapy (HDR BT) as boost therapy before or after external beam radiotherapy (EBRT).

Secondary interventions compared for question 2: comparative interventions for the primary treatment of localised prostate cancer are included where these are part of a study looking at dose escalation or the dose responsiveness of prostate cancer to radiotherapy. Interventions included were conformal external beam radiotherapy

(3DCRT), conformal external beam radiotherapy with intensity modulation (IMRT) and different fractionation schedules.

Papers that reported at least one of these outcomes were considered:

- Biochemical control for example PSA failure (defined by American Society for Therapeutic Radiology and oncology) biochemical evidence of freedom from recurrence (bEFR). Biochemical no evidence of disease (bNED) freedom from failure (FFF)
- Overall survival (OS)
- Clinical recurrence-free survival
- Disease-specific survival
- Quality of life (including complications and adverse consequences of therapy)
- Acute or late toxicity (defined by recognised scale where possible)
- GU toxicity (frequency, dysuria or stricture),
- GI toxicity (urgency, proctitis, rectal bleeding or fistula)
- Erectile dysfunction (ED).

Studies published in 1990 or later in English

## STUDY DESIGN

### Inclusion criteria

The following criteria were used to **include** studies for appraisal:

- Peer reviewed studies will be considered for this review if they used one of the following study designs:
- Systematic review or meta-analysis
- Randomised Controlled Trials
- Cohort studies (measuring harm/benefit)
- Randomised or quasi-randomised controlled trials,
- Prospective and retrospective observational studies
- Phase 2 clinical trials

### Exclusion criteria

The following criteria were used to **exclude** studies from appraisal:

- Outcomes reported from studies primarily of surgery for prostate cancer.
- Studies evaluating the methods of delivery alone
- Studies with fewer than 20 persons included in reported outcomes for RCT's
- Citations that are narrative reviews, expert opinion, letters to the editor, comments, editorials, conference proceedings, abstract only, books and book chapters.
- Studies of androgen deprivation alone

## APPRAISAL METHODOLOGY (VALIDITY ASSESSMENT)

---

Articles were formally appraised using the Generic appraisal tool for epidemiology (GATE) process for systematic reviews, randomised controlled trials, and Cohort studies (intervention benefit/harm). [www.auckland.ac.nz](http://www.auckland.ac.nz) The validity of an individual studies was scored as either good, fair or poor using a modified NHMRC check list. [www.health.gov.au/nhmrc](http://www.health.gov.au/nhmrc)

## PRESENTATION OF RESULTS

---

Results are presented in evidence tables and summarised in text and tabular form where appropriate.

## STUDY CHARACTERISTICS

---

The search returned 880 studies of these 140 abstracts were retrieved. 62 were included in tables. The reasons for exclusion were various, but mainly because they were not primary investigational studies (letters, comments and reviews). See Appendices for a full list of included studies within evidence tables.

## STUDIES

The inclusion and exclusion criteria were applied in two stages. At the first stage, the criteria for participants, intervention and outcomes were applied. At the second stage, depending upon the quantity and level of evidence, the inclusion criteria for study design were decided upon by intervention and applied. Two reviewers selected the studies, and applied the exclusion criteria based on the abstract retrieved in the first instance and on the full text of the paper when this was retrieved. Disagreements were resolved by consensus.

## QUANTITATIVE DATA SYNTHESIS

---

It was not possible to perform a quantitative synthesis of the data retrieved because of the degree of heterogeneity of the populations studied and the lack of high quality RCTs in the topic area.

## 4. Results

### TOPIC 1: THE EVIDENCE FOR A 'DOSE-RESPONSE' RELATIONSHIP BETWEEN TOTAL DOSE AND OUTCOMES FOR RADIOTHERAPY

---

#### BIOCHEMICAL CURE AND SURVIVAL

We found one systematic review,<sup>23</sup> two evidence based reviews,<sup>19,24</sup> three RCTs<sup>16, 25-27</sup> (one study was reported after two different follow up periods) and 17 prospective or retrospective studies<sup>9, 15, 17, 28-41</sup> that provided data to answer this question and met the inclusion criteria. These were all of fair quality and had on average 4 to 8 years of follow up. These studies are listed in evidence table 1 (available separately) and the key outcomes from relevant studies summarised in Table 3 and 4.

In one major RCT<sup>16</sup> the disease-free rate (bNED) was significantly higher for patients with intermediate risk disease treated with 78 Gy (62%) compared to those treated with 70 Gy (43%) at 6 years,  $p=0.012$ . One sequential dose escalation study<sup>9</sup> showed a significant improvement in biochemical control for patients with intermediate risk receiving  $\geq 75.6$  Gy (79%) compared to those receiving  $<75$  Gy (~55%)  $p=0.04$ . This same study also stratified results by risk group showing a 5-year actuarial relapse-free survival for patients at low risk was 85%, compared to 65% for those with intermediate prognosis and 35% for the high-risk group with unfavourable prognosis ( $p < 0.001$ ). Dose escalation for treatment of prostate cancer therefore shows an incremental beneficial effect on biochemical control with higher radiotherapy doses to about 78 Gy. Doses above 81 Gy were not investigated in the studies of EBRT vs. 3DCRT. Across all these studies five year biochemical control (bNED) rates of about 80% were achieved with the higher doses of radiotherapy (~78 Gy) in intermediate risk groups compared to rates of about 50–60% for lower doses (~70 Gy) for the same patient risk groups.

One retrospective sequential dose escalation study<sup>33</sup> using HDR BT was identified. When doses of  $<93$  Gy were compared with doses of  $\geq 93$  Gy a significant difference in 5-year bNED rate between low and high dose groups, 52% vs. 87% was observed ( $p<0.001$ ).

A recent Phase 3 randomised pilot study<sup>26</sup> of dose escalation (after initial androgen suppression) using 3DCRT has confirmed the findings of the earlier RCTs. This showed a 5-year actuarial bNED rate of 59% (95%CI: 45–70%) in the group treated with 64 Gy compared to 71% (95% CI: 58–81%) in the 74 Gy treatment group.

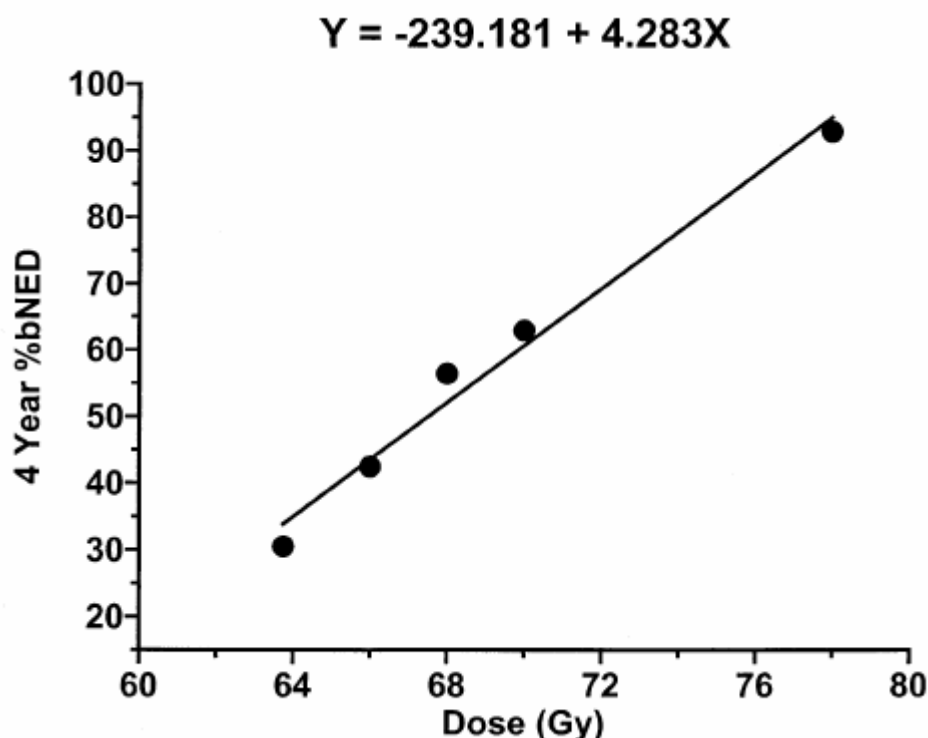
In this study<sup>26</sup> therefore about 12 men per 100 from all risk groups are saved from biochemical failure over five years by the dose escalation. This compares to about 10 in 100 men after 5 years when the dose was escalated from 70 to 78 Gy in the MD Anderson Cancer Centre RCT 69% to 79% ( $p=0.06$ ).<sup>16</sup>

A critical issue is how PSA control will relate to disease recurrence or to overall survival. A retrospective analysis<sup>17</sup> suggests that dose escalation may indeed be related to improved survival. This study was of 1465 men with high-grade cancers treated in four protocols. The men who received higher radiation doses ( $\geq 66$  vs.  $< 66$  Gy) had a 20% lower risk of death from prostate cancer and a 27% reduction in overall mortality. This benefit was not seen in men with well- or moderately-differentiated cancers.

It is important to recognise that all these retrospective studies of sequentially treated cohorts may be subject to bias from 'stage migration', which has occurred during the 1990s, resulting in an apparent overall improvement in treatment outcome.<sup>42</sup> Stage migration is the result of earlier detection of disease partly due to increased PSA testing (and screening for prostate cancer in the USA). There is evidence that the stage of disease treated in the 2000s is less than the average stage treated in the 1990s. Prospective randomised trials are therefore needed to fully address the question of optimal dosing for the different stages and risk groups. Phase 3 randomised trials are in progress.

One study<sup>34</sup> illustrated the dose response relationship graphically (figure 1).

**Figure 1: Actuarial 4-year bNED rates for the mean doses of 5 dose levels plotted using linear regression ( $p < 0.001$ ): (source Pollack 2000)<sup>34</sup>**



**Table 3: Summary of studies relating to dose escalation benefits (SR and RCT)**

| Author (Date)<br>Country<br>Study type   | Radiotherapy<br>Type   | Patients (n)   | Dose (Gy)                | Risk group                                    | Follow<br>up<br>(years) | % FFBF                                       | Comments   |
|--|--|--|--------------------------|---|-------------------------|--|--|
| <b>Brundage (2002)</b> <sup>23</sup><br>Canada:<br>Systematic review                 | 3DCRT versus<br>EBRT   | 1 RCT and 11<br>non-randomised<br>comparative<br>studies | 65-81                    | All   | 4-8                     | No pooling of<br>data was<br>appropriate     | Intermediate risk<br>(PSA 10-20) should<br>be offered 75-78 Gy |
| <b>Pollack (2000)</b> <sup>25</sup><br>USA:Texas<br>dose escalation RCT              | EBRT<br>EBRT +<br>(conformal<br>boost)<br><br>subgroup<br>analysis | 150<br>151<br><br>(PSA > 10)                             | 70<br>78<br><br>70<br>78 | All<br><br>Unfavourable<br>(T1/2:PSA ><br>10) | 5<br><br>5              | 69<br>79<br><br>60<br>90<br>(p<0.0011)       | 'Fraction failing' =<br>PSA rise or clinical<br>progression    |
| <b>Pollack (2002)</b> <sup>16</sup><br>USA:Texas<br>dose escalation RCT              | EBRT<br>EBRT +<br>(conformal<br>boost)<br><br>subgroup<br>analysis | 150<br>151<br><br>(PSA > 10)                             | 70<br>78<br><br>70<br>78 | All<br><br>Unfavourable<br>(PSA > 10)         | 6<br><br>6              | 64<br>70<br><br>43<br>62<br>(p=0.012)        | Same study sample<br>as above with 6 year<br>results reported  |
| <b>Dearnaley (2005)</b> <sup>26</sup><br><br>UK<br>Phase 3 2x2 factorial RCT         | EBRT<br><br>EBRT + 10 Gy<br>boost (1.0 or<br>1.5 cm margin)        | 127<br><br>127   | 64<br><br>74             | All   | 6.2                     | 59 (95%CI;44-<br>70)<br>71 (95%CI;58-<br>81) | not significant  |
| <b>Shipley (1995)</b> <sup>27</sup><br><br>USA; Massachusetts<br>dose escalation RCT | EBRT<br><br>Proton Boost<br>EBRT                                   | 99<br><br>103  | 67.2<br><br>75.6         | Poorly<br>differentiated                      | 8                       | 19<br><br>84<br><br>(p=0.0014)               |  |

**Table 3 (cont): Summary of studies relating to dose escalation benefits (OBSERVATIONAL STUDIES)**

| Author  | RT Type | n                 | Dose                         | Risk                  | F/U | % FFBF                                      | Comments   |
|---|---------|-------------------|------------------------------|-----------------------|-----|---|--|
| <b>Zelevsky (1998)<sup>9</sup></b><br>USA;<br>Retrospective<br>Sequential dose<br>escalation            | EBRT    | 116<br>94         | 64.8-70.2<br>75.6-81.0       | Intermediate<br>risk  | 4   | ~55<br>79<br>(p=0.04)                       |  |
| <b>Pollack (2000b)<sup>34</sup></b><br>USA: Texas<br>Retrospective<br>Sequential dose<br>escalation     | EBRT    | 500<br>495<br>132 | ≤ 67<br>67-77<br>>77         | All                   | 4   | 54<br>71<br>77<br>(p<0.0001)                |  |
| <b>Lyons (2000)<sup>38</sup></b><br>Retrospective<br>Sequential dose<br>escalation                      | EBRT    | 546<br>192        | < 72<br>≥72                  | All                   | 5   | 54<br>85<br>(p<0.001)                       |  |
| <b>Hanks (2002)<sup>31</sup></b><br>USA; Fox Chase CC<br>Retrospective<br>Sequential dose<br>escalation | EBRT    | 21<br>21<br>28    | <71.5<br>71.5-75.5<br>>75.75 | PSA 10-20<br>Int risk | 8   | 19<br>31<br>84<br>(p=0.0003)                | Dose response most<br>apparent in this<br>intermediate risk group<br>(PSA 10-20) |
| <b>Fukunaga-Johnson<br/>(1997)<sup>37</sup></b><br>USA; Michigan<br>Single cohort descriptive           | 3DCRT   | 685               | Median 69<br>(range 49-80)   | T1/2 86%              | 5   | No association                              | Includes a multivariate<br>model   |
| <b>Kupelian (2000)<sup>39</sup></b><br>USA<br>Retrospective cohort                                      | EBRT    | 1041              | < 72<br>≥72                  | T1-3                  | 5   | 55 (95%CI;49-<br>60)<br>87(95%CI;82-<br>92) |  |

**Table 4: Studies of dose escalation with HDR BT**

| Author                                   | RT            | Patients (n) | Dose | Risk group | f/u (yrs) | % FFBF          |
|--|---------------|--------------|------|------------|-----------|-----------------|
| <b>Martinez (2002)<sup>33</sup></b>      |               | 58           | <93  |            |           | 52              |
| Retrospective Sequential dose escalation | <b>HDR BT</b> | 149          | ≥ 93 | All        | 5         | 87<br>(p<0.001) |

## TREATMENT-RELATED COMPLICATIONS

### Rectal and urinary toxicity

We found one systematic review,<sup>23</sup> three RCTs,<sup>16,43,44</sup> one questionnaire of RCT participants<sup>45</sup> and 14 non-randomised observational studies<sup>29-31,36-38,46-53</sup> that reported on a variety of the treatment related complications occurring in dose escalation studies. These studies are listed in Evidence Table 2 (available separately) and the key outcomes from relevant studies are summarised in Table 5.

One RCT<sup>16</sup> which reported significant benefits from dose escalation also reported an increase in rectal toxicity in the 78 Gy arm (26%) compared to the 70 Gy arm (12%) and recommended that dose escalation techniques should limit the rectal volume that receives ≥70 Gy to <25%. Another RCT<sup>44</sup> reported chronic adverse effects (symptoms >1 year after treatment), participants received the same dose of radiation in both the conventional and conformal arms, there were significantly more grade 2 or greater bowel toxicity in the conventional arm (15 vs. 5%;P = 0:01).

Various grading systems were used to score the outcomes which were reported at various time intervals and with various data collection techniques (one RCT study<sup>45</sup> sourced data on complications by retrospective questionnaire). Importantly most investigators used their own protocols and regimes which were seldom standardised across difference centres. It was difficult, and of minor utility, to compare the rates directly across studies but several authors concluded that radiotherapy delivered by 3DCRT compared to EBRT at a similar dose resulted in fewer grade 2 and above GI complications. Higher doses of 3DCRT compared to lower doses of EBRT resulted in a similar proportion of grade 2 and above complications. The absolute rates of grade 2 late GI complications such as rectal bleeding etc was about 10 to 20%, with one study reporting a rate as low as 5%.

We found one recent randomised trial that also addressed the issue of a radiation ‘safety margin’ after initial hormone therapy.<sup>26</sup> The late side effects following radiotherapy were in line with other studies, and 2 years after therapy, 17% of men had experienced Grade 2 or more bowel toxicity and 15% Grade 2 or more bladder side effects. At 2 years after radiotherapy, there was a statistically significant increase in bowel toxicity for both the 74 Gy and 1.5 cm margin groups, compared to the 64Gy and 1.0 cm group. Although an excess of bladder side effects was seen at this time point, they did not reach statistical significance.

## Erectile dysfunction

The assessment of erectile dysfunction was again complicated by non-standard reporting. There is an incidence of erectile dysfunction prior to therapy and a risk of recall bias in those studies that report result retrospectively. However, one recent randomised dose escalation study<sup>26</sup> looked at erectile dysfunction separately and reported that in 128 men, 38% reported erectile dysfunction at baseline increasing to 66% at 6 months after treatment and 81% by 5 years. However there were no significant differences between the two dose groups (64 Gy and 74 Gy) studied.

**Table 5: Acute toxicities from dose escalation**

| <b>Reference<br/>(author, date<br/>and country)<br/>Study type</b> | <b>RT Type</b> | <b>Patients (n)</b> | <b>Dose (Gy)</b> | <b>Group</b>           | <b>Outcomes %</b>  | <b>Comments</b>  |
|--|----------------|---------------------|------------------|------------------------|--|--|
| <b>Acute toxicity</b>  |                |                     |                  |                        |  | <b>RTOG criteria except<br/>where indicated</b>                                  |
| <b>Koper et al (1999)<sup>54</sup></b><br>Rotterdam<br>RCT         | 3DCRT vs. EBRT | 134                 | 66 EBRT          | T1-4<br>(59% T1 and 2) | GI grade 2 = 32%<br>Anal Grade 2 =16%<br>GU grade ≥2 = 17% |  |
|  |                | 129                 | 66 3DCRT         |                        | GI grade 2 = 19%<br>Anal Grade 2 =8%<br>GU grade ≥ 2 = 18% | For comparison (p=0.02)<br>For comparison<br>(p<0.0001)<br>For comparison (p=NS) |
| <b>Pollack et al (1996)<sup>55</sup></b><br>MD Anderson CC<br>RCT  | 3DCRT vs. EBRT | 31                  | 70 EBRT          | T2 65%                 | No significant<br>difference                               |  |
|  |                | 29                  | 78 3DCRT         |                        |  |  |

**Table 5 (cont): Late toxicities from dose escalation**

| <b>Reference (author, date and country)<br/>Study type</b>                   | <b>RT Type</b>          | <b>Patients (n)</b> | <b>Dose (Gy)</b> | <b>Group</b>      | <b>Outcomes %</b>                                  | <b>Comments</b>   |
|--|-------------------------|---------------------|------------------|-------------------|--|---|
| <b>Dearnaley (2005)<sup>26</sup></b><br>Royal Marsden UK<br>2x2 RCT          | 3DCRT                   | 64                  | 64 3DCRT         | all               | GI grade ≥ 2 = 11%<br>GU grade ≥2 = 11%            | For comparison (P= 0.02)  |
|  |                         | 63                  | 74 3DCRT         | all               | GI grade ≥ 2 = 23%<br>GU grade ≥2 = 18%            | For comparison (P= 0.17)  |
| <b>Dearnaley (1999)<sup>44</sup></b><br>Royal Marsden UK<br>RCT              | 3DCRT vs. EBRT          | 111                 | 64 EBRT          |                   | GI grade ≥ 2 = 15%<br>GU grade ≥2 = 23%            |   |
|  |                         | 114                 | 64 3DCRT         |                   | GI grade ≥ 2 = 5%<br>GU grade ≥2 = 20%             | For comparison (p=0.01)<br>For comparison (p=NS)  |
| <b>Storey (2000)<sup>43</sup></b><br>MD Anderson CC<br>RCT                   | 3DCRT vs. EBRT          | 98                  | 70 EBRT          |                   | GI grade ≥ 2 = 14%<br>GU grade ≥ 2 = 20%           | LENT criteria   |
|  |                         | 91                  | 78 EBRT          | T1c and T2<br>74% | GI grade ≥ 2 = 21%<br>GU grade ≥ 2 = 9%            | For comparison (p = 0.8)<br>For comparison (p = 0.4)                                    |
| <b>Bergstrom (1998)<sup>56</sup></b><br>Sweeden<br>retrospective             | 3DCRT high<br>precision | 23                  | 70-76            | T1-3              | GI grade 2 = 13%<br>GU grade 2 = 25%               | No increase with dose<br>escalation   |
| <b>Kupelian et al (2000)<sup>39</sup></b><br>Cleveland<br>retrospective      | SCIM-RT vs.<br>3DCRT    | 101                 |                  |                   | GI grade 2 = 12%<br>GI grade 3 = 3%                |   |
| <b>Magrini et al (1998)<sup>53</sup></b><br>Florence: Italy<br>retrospective |                         | 208                 |                  | T2 60%            | All grades 13%<br>Grade ≥ 2 = 6%<br>Grade 4 = 1.5% | Any grade more frequent<br>amongst patients treated<br>with larger volumes<br>(p= 0.02) |

## TOPIC 2: THE EVIDENCE FOR HDR BT USED AS A RADIOTHERAPY BOOST WITH EBRT COMPARED TO EBRT ALONE.

---

### BIOCHEMICAL CONTROL AND SURVIVAL

We found 1 RCT<sup>57</sup> and 22 non-randomised studies<sup>33, 58-73, 5, 6, 29, 74</sup> that reported biochemical control rates or survival after treatment with HDR BT combined with EBRT. These studies are listed in Evidence Table 3 (available separately) and key outcomes from relevant studies are summarised in Table 6.

One recent RCT was of a manual loading system in men with T2 and T3 cancers. A lower dose-rate implant (Iridium) was used and compared to lower doses of EBRT than would currently be used in New Zealand. However, a large significant improvement in 5 year biochemical control rates was observed in the group treated with HDR BT combined with EBRT compared to the group who received EBRT only 71% vs. 39% (p=0.0024) respectively.<sup>57</sup> Another recent study was designed to compare hormone ablation therapy in two arms who both received EBRT and HDR boost. This study reported equivalent control rates of about 90% in both arms.<sup>58</sup> There are also biochemical control rates reported in lower level studies (see Table 6) One prospective study was of 104 men with T1b-T3 clinically node-negative prostate cancer treated with whole pelvis EBRT combined with two fractions of HDR brachytherapy consisting of 15 Gy/Fx to the peripheral prostate and 9 Gy to the entire prostate. Approximately 85% of patients whose initial PSA was less than 20 ng/ml were free of progression at 5 years by actuarial analysis.<sup>66</sup> These biochemical control rates are dependent on risk group and sufficient numbers are now appearing in the prospective studies from the major centres internationally to allow analysis by risk group. These show that 5 year biochemical control rates of around 85% can be expected in intermediate risk groups<sup>6</sup> and around 70% in high risk groups.<sup>5, 6</sup>

Overall survival of more than 90% can be expected with all treatments.

**Table 6: 5-year biochemical control rates and overall survival reported in studies of HDR BT (ordered by pre-treatment PSA)**

| Reference<br>(author, date and<br>country)<br>Study type | Patients<br>(n) | Clinical Tumour<br>stage               | PSA failure<br>definition | Pre-Rx PSA     | Median follow-up<br>(months) | Biochemical<br>control (%) | Overall survival<br>(%)     |
|--|-----------------|--|---------------------------|----------------|------------------------------|----------------------------|-----------------------------|
| <b>RCT</b>   |                 |  |                           |                |                              |                            |                             |
| Sathya (2005) <sup>57</sup>                              | 104             | T2 60%<br>T3 40%                       | ASTRO CP                  | 19.5 (mean)    | 98.4                         | 71 (IM +EBRT)<br>39 (EBRT) | 94 (IM + EBRT)<br>92 (EBRT) |
| <b>Observational</b>                                     |                 |  |                           |                |                              |                            |                             |
| Demanes (2000) <sup>72</sup>                             | 110             | T2b-T3 80%<br>T1b-T3c                  | >1.5 ng/ml                | NS             | 36                           | 85                         | NS                          |
| Borghede (1997) <sup>75</sup>                            | 50              | T1-T2 74%                              | >1.0 ng/ml                | NS             | 45                           | 78                         | 96                          |
| Kestin (2000) <sup>62</sup>                              | 161             | T2 (median)                            | ASTRO CP                  | 9.9 ng/ml      | 30                           | 67                         | 95                          |
| Syed (2001) <sup>73</sup>                                | 200             | T2a 32.5%                              | ASTRO CP                  | 10             | 24                           | 97                         | 97                          |
| Martinez (2000) <sup>64</sup>                            | 142             | >=T2 75%                               | ASTRO CP                  | 10.2 ng/ml     | 25.2                         | 89@ 2yrs<br>63@ 5yrs       | 95                          |
| Curran (2000) <sup>70</sup>                              | 61              | T3 42.5%<br>T1-T2                      | 3 rises                   | 10.4 (mean)    | 11.8                         | 92.2                       | 98                          |
| Martinez (2002 and<br>2003) <sup>33, 74</sup>            | 207             | T1c-T3c                                | ASTRO CP                  | 11.5 (mean)    | 52.8                         | 74                         | 91.6                        |
| Jo (2004) <sup>61</sup>                                  | 98              | T1 19.4%<br>T2a-b 55.1%<br>T3a-b 25.5% | ASTRO CP                  | 11.7 (median)  | 43                           | 95                         | NS                          |
| Kovacs (2003) <sup>63</sup>                              | 144             | T1b-T2a 20.1%<br>T2b-T3 79.1%          | ASTRO CP                  | 12.15 (median) | 96 (mean)                    | 72.9                       | 71.5                        |

**Table 6 (cont): 5-year biochemical control rates and overall survival reported in studies of HDR BT (ordered by pre-treatment PSA)**

| Reference<br>(author, date<br>and country)<br>Study type | Patients<br>(n) | Clinical Tumour<br>stage              | PSA failure<br>definition | Pre-Rx PSA                                     | Median follow-<br>up (months) | Biochemical control<br>(%)                 | Overall survival (%) |
|--|-----------------|---------------------------------------|---------------------------|--|-------------------------------|--|----------------------|
| <b>Observational</b>                                     |                 |                                       |                           |  |                               |  |                      |
| Deger (2002) <sup>68</sup>                               | 230             | T3 26%<br>T2 34.8%                    | ASTRO CP                  | 12.8 (median)                                  | 40                            | T2= 75                                     | 93                   |
| Mate (1998) <sup>66</sup>                                | 104             | T1b-T3c                               | 3 rises                   | 12.9 (mean)                                    | 45                            | 85   | NS                   |
| Dinges<br>(1998) <sup>59</sup>                           | 82              | T2 25.6%<br>T3 74.4%                  | >1.0 ng/ml                | 14 (median)                                    | 24                            | 52.9                                       | NS                   |
| Stromberg<br>(1997) <sup>65</sup>                        | 58              | T2B-T3c                               |                           | 14.3 (median)                                  | 26                            | 85   |                      |
| Pellizzon<br>(2003) <sup>71</sup>                        | 108             | T1c 51.8%<br>T2a-b 35.1%<br>T3a 13.1% | ASTRO CP                  | 15.3 ng/ml                                     | 41                            | 75.3                                       | NS                   |
| Chiang<br>(2004) <sup>58</sup>                           | 42              | T1 14.3%<br>T2a-b 50%<br>T3a-b 35.7%  | >1.0 ng/ml                | 23.48 (HDR +EBRT)<br>25.01 (HDR +EBRT +<br>HT) | 16.5 (median)                 | 90% (HDR +EBRT)<br>91% (HDR +EBRT +<br>HT) | NR                   |
| Galalae<br>(2002) <sup>29</sup>                          | 144             | T2b 32%<br>T3a-b 21.5%<br>T1b-T2a 20% | 3 rises all> 1ng/ml       | 25.6 (mean)                                    | 96                            | 74   | 80.4                 |
| Paul (1997) <sup>67</sup>                                | 40              | T3 58.3%<br>T2 45%                    | Local control             | 40.7   | 74                            | T2 = 79.5                                  | 87.5 at 5 yrs        |

## TREATMENT-RELATED SIDE EFFECTS

The main serious complications of HDR BT are rectal injury, fistula formation, urinary incontinence, urethral stricture and impotence. However the severe complications requiring surgery or hospitalisation are rare and comparable to be the complication rates from the alternative options for radiotherapy. We found 10 observational studies that reported these outcomes. These studies are listed in Evidence Table 4 (available separately) and key outcomes summarised in Table 7.

### Gastrointestinal (rectal) and urinary toxicity

The morbidity from combined EBRT and HDR BT treatment appears to be comparable to high-dose 3D-CRT or surgery for similar-risk patients. The most commonly observed toxicity with combined 3D-CRT and brachytherapy boost is acute RTOG grade 1 and 2 rectal and urinary toxicity. The most commonly reported acute side effects of treatment were mild urinary frequency, urgency, nocturia and haematuria. Rates varied from 10 to 80% with the higher range in one study probably being due to varied reporting definitions. Late GU complications were usually reported in less than 5% of cases though one study<sup>68</sup> reported a 7.4% urinary stricture rate and another<sup>66</sup> had a 6.7% rate of stricture. Observed rates of incontinence have ranged from 0.5% to 3%. One patient in a study from Germany<sup>29</sup> was reported with osteoradionecrosis.

Similar to the urinary toxicity profile, rectal toxicity with combined-modality therapy is most likely to be RTOG grade 1 or 2. About 10 -15% of patients experienced rectal bleeding and 8% experienced increased frequency of bowel movements. The more severe grade 3 GI complications were reported in less than 5% of cases with some studies reporting no grade 3 or 4 rectal toxicities

### Erectile dysfunction

The rates of erectile dysfunction (ED) are less consistently reported and may be difficult to assess reliably as there is a wide variation in reported rates of dysfunction prior to treatment. From the limited data describing the effects of combined prostate brachytherapy and EBRT on sexual function, it appears that post treatment ED rates fall between those reported for either modality alone. The rates vary from 12 to 30% of sexually potent men developing erectile dysfunction after combined-modality treatment. If we assume a probability of maintaining potency of around 70-80%, this can be compared to the reported rate in a recent Cochrane review of other treatments for prostate cancer. In this logistic regression analysis the probability of maintaining normal erectile function was 0.69 (95%CI:0.661 to 0.709) after radiotherapy and 0.42 (95%CI; 0.400 to 0.433) after prostatectomy. One study<sup>76</sup> was found that reported on erectile dysfunction after HDR BT combined with EBRT. This also examined the efficacy of sildenafil. Out of 42 men in this trial, 40.4% were potent before treatment. 10 of these men (58.8%) maintained their potency 12 months after treatment and a further 10 requested sildenafil. Eight of these 10 men (80%) responded to the drug within 12 months of HDR BT treatment.

**Table 7: Acute and late toxicity from HDR BT**

| <b>Reference author,<br/>(date) country<br/>All observational</b> | <b>n</b> | <b>Acute GU toxicity</b>     | <b>Late GU toxicity</b>   | <b>Acute GI toxicity</b> | <b>Late GI toxicity</b>                           | <b>Erectile<br/>dysfunction</b> |
|---|----------|------------------------------|---|--------------------------|---|---------------------------------|
| <b>Pellizzon (2003)</b><br>Brazil <sup>71</sup>                   | 119      | 18.5% acute Grade 1-2        | 4.6% Chronic Grade 1-2  | 10% Grade 1-2            | 12% Grade 1-2                                     | -                               |
| <b>Martinez (2000,2001)</b><br>USA <sup>64, 77</sup>              | 207      | 5% mild<br>frequency/urgency | 4.5% Grade 1-2<br>4% Urethral stricture or<br>incontinence                                      |                          | 12% Grade 1-2<br>nil Grade 3                      | 27%                             |
| <b>Galalae (2002)</b><br>Germany <sup>29</sup>                    | 144      |                              | 7% mod<br>frequency/urgency<br>2% severe<br>frequency/urgency<br>1 case osteo-<br>radionecrosis |                          | 6% mod<br>frequency/urgency<br>3% rectal bleeding | -                               |
| <b>Demanes (2000)</b><br>USA <sup>72</sup>                        | 110      |                              | 4% incontinence   |                          | 0.5% rectal bleeding                              | 25%                             |
| <b>Borghede (1997)</b><br>Sweden <sup>60</sup>                    | 50       | 8% acute dysuria             | 4% chronic dysuria<br>2% chronic haematuria   |                          | 2% rectal bleeding                                | 12%                             |

Table 7 (cont): Acute and late toxicity from HDR BT

| Reference author,<br>(date) country          | n   | Acute GU toxicity            | Late GU toxicity  | Acute GI toxicity             | Late GI toxicity                                     | Erectile<br>dysfunction |
|--|-----|------------------------------|---|-------------------------------|--|-------------------------|
| <b>Deger (2002)</b><br>Germany <sup>68</sup> | 230 |                              | 10% frequency/dysuria<br>7.4% urethral stricture<br>3% incontinence |                               | 1.7% G3-4 recto-<br>urethral fistula                 | -                       |
| <b>Mate (1998)</b><br>Germany <sup>66</sup>  | 104 |                              | 6.7% stricture<br>1.9% mod<br>frequency/dysuria                     |                               | 2% rectal bleeding                                   | -                       |
| <b>Curran (2000)</b><br>USA <sup>70</sup>    | 61  | 57% mild frequency           |   | 74% mild<br>frequency/urgency | 1.6% rectal wall<br>necrosis<br>1.6% rectal bleeding | -                       |
| <b>Syed (2001)</b><br>USA <sup>73</sup>      | 200 | 10% acute grade 3-4          | 1.5% urethral stricture<br>0.5% incontinence                        | 20% grade 3-4                 | 1.5% grade 3   | 30%                     |
| <b>Paul (1997)</b><br>USA <sup>67</sup>      | 40  | 80% acute mild<br>haematuria | 5% prostate necrosis<br>10% urethritis                              | 10% proctitis                 | 2.5% recto-vesical<br>fistula                        | 23%                     |

## 5. Discussion

### DOSE ESCALATION

---

In most cases prostate cancer progresses slowly. Average 5-year survival for localised prostate cancer is around 80%, but the absolute rates vary depending on stage of disease. None of the included studies had sufficient follow up for overall or disease free survival to allow for a valid comparison of survival measures for different doses. All observational studies had a risk of bias due to the study design itself. The baseline characteristics of comparison groups often differed significantly in terms of tumour stage, initial PSA and other characteristics, further, many centres have increased the dose prescribed over time so that those men treated with higher doses have also had the benefit of other newer treatment techniques and often less time for follow up. These factors may have introduced a bias that improved the prognosis in groups prescribed higher doses.

Five-year and 10-year follow-up results indicate increased rates of biochemical control, especially for patients with intermediate prognostic factors (ie, Gleason score of 7 and PSA of 10–20 ng/mL). Patients with pre-treatment PSA levels of 10–20 ng/mL treated with higher doses have an approximate 30% improvement in bNED when compared to patients treated with conventional radiotherapy (5-y results). Patients with more favourable prognostic factors (ie, Gleason score of <6 and PSA of <10 ng/mL) may not benefit from dose escalation. Similarly, patients at high risk for locally or regionally advanced disease (ie, Gleason scores 8–10 and PSA >20 ng/mL) may not experience marked improvement in bNED from dose escalation. This group of patients is ultimately at higher risk for distant spread of disease. Therefore the group who would seem to benefit most from dose escalation are those with intermediate risk disease. Dose escalation studies that were found predominantly used conventional EBRT techniques with 3DCRT boosts. However, one study of dose escalation using I-125 permanent implants was found<sup>18</sup> and this showed that a dose response occurred at a D90 of 140 Gy (the dose delivered to 90% of the prostate as defined by CT), this dose is not directly comparable to the other dose ranges quoted in this report but the 4-year FFBF rates were an impressive 51% and 100% in the low (<140 Gy) and high-dose (>140 Gy) groups respectively (p=0.009).<sup>18</sup>

One study of dose escalation using HDR BT was found<sup>33</sup> and this showed an improvement in biochemical control with dose escalation in unfavourable groups. For men in the higher dose group receiving 83.2 Gy, BC at 5 years was 87% compared 52% in the lower dose group receiving 75.6 Gy (p<0.001).<sup>33</sup> This result also translated into a significant statistical benefit in cause-specific survival (p=0.014). This observational study had imbalance of the 2 dose groups in terms of stage and pre-treatment PSA and a shorter follow-up time for the high-dose group. Despite these validity doubts, in the multivariate Cox proportional hazards analysis of factors associated with biochemical failure none of these variables (stage, pre-treatment PSA, number of prognostic factors, and follow-up time) were predictors of failure.

This suggests that the brachytherapy dose level was the strongest predictor of failure or success and that a dose response effect is also observed with HDR BT therapy. A discussion of Biological Equivalent Doses, hypo-fractionation and the impact of various  $\alpha/\beta$  ratios is beyond the scope of this report. These factors can impact on determining the appropriate dose of HDR BT and calculations of the equivalent EBRT dose in Gy to compare with radiation dose delivered by HDR BT fractions.

These studies together show that a dose response exists and suggest that further increases in disease free survival can be expected with the increasing the dose above 78 Gy, for example to more than 83 Gy. These doses are only possible using newer technologies.

The toxicity rates after EBRT shows a range from about 3.3% to 5% for moderate to severe gastrointestinal complications and 6.0 to 7.7% for late urinary side effects.

The gastrointestinal (GI) and genitourinary (GU) complications requiring treatment with medications (grade 2) or minor surgery (grade 3) have been somewhat higher in the higher dose groups of dose escalation studies (3DCRT versus EBRT).

## HDR BT

---

Published results with HDR BT when used as a boost to EBRT in patients with locally advanced disease have shown consistently impressive biochemical control (BC) rates. Overall survival (OS) rates are also similar to other methods of treatment (see Table 6). If the studies with low risk cancers or pre treatment PSA medians around 10 are excluded<sup>70, 73</sup> one of which also used a retro-pubic approach to insertion<sup>73</sup> then the overall biochemical control rates range from 74 to 85% and overall survival is about 80 to 96%. The lower rates occur in high-risk groups and the higher rates in low-risk groups.

When assessing morbidity data from the studies of HDR BT added to EBRT the distinction needs to be made between the complications which are easily managed with medication and those that require surgery. This division occurs between grade 2 and 3. For example in a large 119 patient study<sup>71</sup> chronic grade 1 or 2 gastrointestinal complications were reported to be 12% however grade 3 GI complications were around 1%. Only one study<sup>75</sup> reported grade 3 GI complications of more about 3.5%. Mild early (GU) toxicity is also relatively common with acute haematuria reported in up to 80% of cases in one study,<sup>67</sup> longer term (chronic) grade 1 to 2 GU morbidity is reported less commonly with on average about a 2 to 7% rate of moderate or severe frequency/dysuria (see Table 4). Strictures appear to be a particular problem with about 7% of men needing treatment for these in two series.<sup>66, 68</sup> Strictures account for most of the late grade 3 GU complications in many studies. It is possible that improved techniques, and avoidance of TURP, may reduce this rate further as one study of 200 men<sup>73</sup> has reduced grade 3 GU complication to close to 2% (only 1.5% strictures and 0.5% incontinence)

In the most recent study<sup>6</sup> the late urinary morbidity incidence associated with HDR-BT and EBRT was:

- 4–7% for Grade 2
- 2–8% for Grade 3
- 0% for Grade 4.

This is quantitatively similar to other radiation modalities.<sup>5, 33, 66</sup> The urinary morbidity score is the result of a complex mixture of the effects of radiation, the underlying benign pathologic features, and post-treatment management decisions. Because of the high incidence of urethral strictures after all forms of BT some authors believe that TURP should be avoided after BT and that any obstructive symptoms should be given time to resolve with conservative management.

The overall GI morbidity rates in the literature<sup>29, 33, 66</sup> after HDR-BT and EBRT were:

- 2–10% for Grade 1
- 2–7% for Grade 2
- 0–4% for Grade 3
- 0–0.5% for Grade 4

## DOSE ESCALATION USING HDR BT COMPARED TO OTHER FORMS OF DOSE ESCALATION

---

It can be misleading to evaluate directly the results of the various radiation modalities because of the diversity of disease, the varying definitions of biochemical control, differing radiation techniques and doses, the variable use of androgen suppression, and the different lengths of follow-up. With these limitations in mind, Table 8 shows some of the survival rates across studies and is useful in that it highlights the higher rates of control, up to about 70%, that are now being achieved in some centres using HDR BT in high risk groups. These men could have expected biochemical cure rates of around 50% with lower doses radiotherapy using other modalities.

In conclusion, this report demonstrates that HDR BT combined with EBRT is an effective treatment modality for localised prostate cancer, with few serious long term complications. The prognosis for low risk groups treated with a combination of HDR BR and EBRT is similar to that achieved with other technologies. The relatively favourable outcomes achieved in intermediate and high risk groups by using this combination technology suggest that it is men in these risk groups who would benefit most from an increase in HDR BT availability in New Zealand.

Up to 2 in 10 high risk men treated with high dose combined HDR BT and EBRT could benefit from improved 5 year biochemical control compared to lower dose EBRT treatments.

**Table 6: Comparison of HDR BT biochemical control to other radiotherapy modalities from (Demanis 2005)<sup>6</sup>**

| <b>Author</b>                         | <b>Group definitions</b>  | <b>Dose (Gy)</b>                                | <b>Median follow-up (y)</b> | <b>ASTRO PSA-PFS (%)</b> |
|---------------------------------------|---|---|-----------------------------|--------------------------|
| <b>3D EBRT</b>                        |   |   |                             |                          |
| Hanks et al. (2002) <sup>78</sup>     | T2b-T3, Gleason score 7–10<br>PSA <10 ng/mL (unfavourable)<br>PSA 10–20 ng/mL (favourable/unfavourable)<br>PSA >20 ng/mL        | 74  | 9                           | 62<br>44/56<br>14        |
| Kupelian et al. (2004) <sup>79</sup>  | T2b,* Gleason score ≥7, PSA >10 ng/mL   | >72   | 4                           | 76                       |
| Pollack et al. (2002) <sup>16</sup>   | PSA >10 ng/mL   | 78  | 5                           | 62                       |
| Zelevsky et al. (1998) <sup>9</sup>   | T3, Gleason score ≥7, PSA ≥10 ng/mL<br>Intermediate: one factor<br>High: two or more factors                                    | >75–81  | 3                           | 79<br>≈55                |
| <b>IMRT</b>                           |   |   |                             |                          |
| Zelevsky et al. (2001) <sup>80</sup>  | T3, Gleason score ≥7, PSA ≥10 ng/mL<br>Intermediate: one factor<br>High: two or more factors                                    | 81–86   | 2                           | 86<br>81                 |
| <b>Seed monotherapy</b>               |   |   |                             |                          |
| Blasko et al. (2000) <sup>81</sup>    | T3, Gleason score 7–10, PSA >10 ng/mL<br>Intermediate: two factors<br>High: three factors                                       | <sup>125</sup> I 145<br><sup>103</sup> Pd 115   | 5                           | 84<br>54                 |
| Kupelian et al. (2004) <sup>79</sup>  | T2b,* Gleason score ≥7, PSA >10 ng/mL   | <sup>125</sup> I 144<br><sup>103</sup> Pd 136   | 4                           | 64                       |
| Beyer et al. (2003) <sup>82</sup>     | ≥T2b, Gleason score ≥7, PSA >10 ng/mL<br>Intermediate: one factor<br>High: two or more factors                                  | <sup>125</sup> I 145 or <sup>103</sup> Pd 120   | 4                           | 77<br>55                 |
| Kollmeier et al. (2003) <sup>83</sup> | Intermediate*: T2bc, Gleason score 7, PSA >10–20 ng/mL<br>High: 2 or more intermediate risk factors or GS 8–10 or PSA >20 ng/mL | <sup>125</sup> I >140<br><sup>103</sup> Pd >100 | 6                           | 81<br>65                 |

**Table 6 (cont): Comparison of HDR BT biochemical control to other radiotherapy modalities from (Demanes 2005)<sup>6</sup>**

| Author                                | Group definitions   | Dose (Gy)   | Median follow-up (y) | ASTRO PSA-PFS (%) |
|---------------------------------------|---|---|----------------------|-------------------|
| <b>EBRT + seeds</b>                   |   |   |                      |                   |
| Kupelian et al. (2004) <sup>79</sup>  | T2b,* Gleason score $\geq 7$ , PSA >10 ng/mL                        | EBRT 41–45 + <sup>125</sup> I<br>108 or <sup>103</sup> Pd 102 | 4                    | 75                |
| Blasko et al. (2000) <sup>84</sup>    | T3, Gleason score 7–10, PSA >10 ng/mL                               | EBRT 45   | 5                    |                   |
|                                       | Intermediate: one factor  | <sup>125</sup> I 110  |                      | 85                |
|                                       | High: two or more factors   | <sup>103</sup> Pd 90  |                      | 62                |
| Ragde et al. (2000) <sup>85</sup>     | >T2b and/or Gleason score $\geq 7$                                  | EBRT 45 or <sup>125</sup> I 120                               | 10                   | 79                |
| Sylvester et al. (2003) <sup>86</sup> | $\geq$ T2c, Gleason score $\geq 7$ , PSA >10 ng/mL                  | EBRT 45   | 5                    |                   |
|                                       | Intermediate: one factor  | <sup>125</sup> I 108  |                      | 77                |
|                                       | High: two or more factors   | <sup>103</sup> Pd 100   |                      | 47                |
| Dattoli et al. (1999) <sup>87</sup>   | >T2b, Gleason score $\geq 7$ , PSA >15 ng/mL<br>One or more factors | EBRT 41<br><sup>103</sup> Pd 80                               | 4                    | 79 <sup>†</sup>   |
| <b>EBRT + HDR-BT</b>                  |   |   |                      |                   |
| Mate et al. (1998) <sup>66</sup>      | T2c-T3, Gleason score 7–10, PSA >15 ng/mL                           | EBRT 50   | 6                    |                   |
|                                       | Intermediate: one or two factors                                    | HDR-BT 12–16  |                      | 72                |
|                                       | High: three factors   |   |                      | 49                |
| Martinez et al. (2002) <sup>33</sup>  | T2b-T3, Gleason score 7–10, PSA $\geq 10$ ng/mL                     | EBRT 46   | 4                    | 87                |
|                                       | High-dose group   | HDR-BT 23   |                      |                   |
| Galalae et al. (2004) <sup>5</sup>    | $\geq$ T2b, Gleason score $\geq 7$ , PSA $\geq 10$ ng/mL            | EBRT 46–50  |                      |                   |
|                                       | Intermediate: any one factor  | HDR-BT 16–30  | 5                    | 88                |
|                                       | High: any two factors   |   |                      | 69                |
| Demanes et al. (2005) <sup>6</sup>    | Intermediate: T2bc, PSA >10, $\leq 20$ ng/mL, GS 7                  | EBRT 36   | 7.25                 | 87                |
|                                       | High: T3, PSA >20 ng/mL, Gleason score 8–10                         | HDR-BT 22–24  |                      | 69                |
|                                       | 1 or more factors   |   |                      |                   |

*Abbreviations:* IMRT = intensity-modulated radiotherapy. \* No T3 included. † PSA >1.0 ng/mL.



# References

1. Radiation Oncology Working Group *Utility of High Dose Rate Brachytherapy (HDR BT) in New Zealand*. 2005: Wellington, New Zealand.
2. *Cancer: New registrations and deaths 2000, revised edition*. 2004, New Zealand Health Information Service: Wellington, New Zealand.
3. Durham J. *Population screening for prostate cancer. A systematic review*:. 2002, New Zealand Guidelines Group: Wellington, New Zealand.
4. Partin AW, Kattan MW, Subong EN, *et al*. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *Jama* 1997.277(18):1445-1451.
5. Galalae RM, Martinez A, Mate T, *et al*. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004.58(4):1048-55.
6. Demanes DJ, Rodriguez RR, Schour L, *et al*. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005.61(5):1306-1316.
7. D'Amico AV, Whittington R, Malkowicz SB, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer.[see comment]. *Jama* 1998.280(11):969-74.
8. Blasko JC, Grimm PD, Sylvester JE, *et al*. Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000.46(4):839-50.
9. Zelefsky MJ, Leibel SA, Gaudin PB, *et al*. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998.41(3):491-500.
10. Kuban DA, Thames HD, Levy LB, *et al*. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era.[see comment]. *Int J Radiat Oncol Biol Phys* 2003.57(4):915-28.
11. Zelefsky MJ, Leibel SA, Kutcher GJ, *et al*. Three-dimensional conformal radiotherapy and dose escalation: where do we stand? *Semin Radiat Oncol* 1998.8(2):107-14.
12. Zelefsky MJ, Wallner KE, Ling CC, *et al*. Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. *J Clin Oncol* 1999.17(2):517-22.
13. Blasko JC, Wallner K, Grimm PD, *et al*. Prostate specific antigen based disease control following ultrasound guided 125iodine implantation for stage T1/T2 prostatic carcinoma. *J Urol* 1995.154(3):1096-9.

14. Kwok Y, DiBiase SJ, Amin PP, *et al.* Risk group stratification in patients undergoing permanent (125)I prostate brachytherapy as monotherapy. *Int J Radiat Oncol Biol Phys* 2002.53(3):588-94.
15. Hanks GE, Hanlon AL, Pinover WH, *et al.* Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. *Cancer J Sci Am* 1999.5(3):152-8.
16. Pollack A, Zagars GK, Starkschall G, *et al.* Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002.53(5):1097-105.
17. Valicenti R, Lu J, Pilepich M, *et al.* Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated on the Radiation Therapy Oncology Group trials. *J Clin Oncol* 2000.18(14):2740-6.
18. Stock RG, Stone NN, Tabert A, *et al.* A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998.41(1):101-8.
19. Vicini FA, Abner A, Baglan KL, *et al.* Defining a dose-response relationship with radiotherapy for prostate cancer: is more really better? *Int J Radiat Oncol Biol Phys* 2001.51(5):1200-8.
20. Vicini FA, Vargas C, Edmundson G, *et al.* The role of high-dose rate brachytherapy in locally advanced prostate cancer. *Semin Radiat Oncol* 2003.13(2):98-108.
21. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997.37(5):1035-41.
22. Leibel SA, Ling CC, Kutcher GJ, *et al.* The biological basis for conformal three-dimensional radiation therapy. *Int J Radiat Oncol Biol Phys* 1991.21(3):805-11.
23. Brundage M, Lukka H, Crook J, *et al.* The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 low or intermediate risk prostate cancer - a systematic review. *Radiotherapy and Oncology* 2002.64(3):239-250.
24. Morris DE, Emami B, Mauch PM, *et al.* Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: An ASTRO outcomes initiative. *Int J Radiat Oncol Biol Phys* 2005.62(1):3-19.
25. Pollack A, Zagars GK, Smith LG, *et al.* Preliminary Results of a Randomized Radiotherapy Dose-Escalation Study Comparing 70 Gy With 78 Gy for Prostate Cancer. *J Clin Oncol* 2000.18(23):3904-3911.
26. Dearnaley DP, Hall E, Lawrence D, *et al.* Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005.92(3):488-98.
27. Shipley WU, Verhey LJ, Munzenrider JE, *et al.* Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys* 1995.32(1):3-12.

28. Fiveash JB, Hanks G, Roach M, *et al.* 3D conformal radiation therapy (3DCRT) for high grade prostate cancer: a multi-institutional review. *Int J Radiat Oncol Biol Phys* 2000.47(2):335-42.
29. Galalae RM, Kovacs G, Schultze J, *et al.* Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 2002.52(1):81-90.
30. Hanks GE, Hanlon AL, Schultheiss TE, *et al.* Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys* 1998.41(3):501-10.
31. Hanks GE, Hanlon AL, Epstein B, *et al.* Dose response in prostate cancer with 8-12 years' follow-up. *Int J Radiat Oncol Biol Phys* 2002.54(2):427-35.
32. Jacob R, Hanlon AL, Horwitz EM, *et al.* Role of prostate dose escalation in patients with greater than 15% risk of pelvic lymph node involvement. *Int J Radiat Oncol Biol Phys* 2005.61(3):695-701.
33. Martinez AA, Gustafson G, Gonzalez J, *et al.* Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. *Int J Radiat Oncol Biol Phys* 2002.53(2):316-27.
34. Pollack A, Smith LG and von Eschenbach AC External beam radiotherapy dose response characteristics of 1127 men with prostate cancer treated in the PSA era. *Int J Radiat Oncol Biol Phys* 2000.48(2):507-12.
35. Vicini FA, Kestin LL and Martinez AA Use of conformal high-dose rate brachytherapy for management of patients with prostate cancer: optimizing dose escalation. *Tech Urol* 2000.6(2):135-45.
36. Bey P, Carrie C, Beckendorf V, *et al.* Dose escalation with 3D-CRT in prostate cancer: French study of dose escalation with conformal 3D radiotherapy in prostate cancer-preliminary results. *Int J Radiat Oncol Biol Phys* 2000.48(2):513-7.
37. Fukunaga-Johnson N, Sandler HM, McLaughlin PW, *et al.* Results of 3D conformal radiotherapy in the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997.38(2):311-7.
38. Lyons JA, Kupelian PA, Mohan DS, *et al.* Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. *Urology* 2000.55(1):85-90.
39. Kupelian PA, Mohan DS, Lyons J, *et al.* Higher than standard radiation doses (> or =72 Gy) with or without androgen deprivation in the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000.46(3):567-74.
40. Shipley WU, Thames HD, Sandler HM, *et al.* Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *Jama* 1999.281(17):1598-604.
41. Kestin LL, Goldstein NS, Vicini FA, *et al.* Pathologic evidence of dose-response and dose-volume relationships for prostate cancer treated with combined

- external beam radiotherapy and high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002.54(1):107-118.
42. D'Amico AV How to compare results after surgery or radiation for localized prostate carcinoma. *Cancer* 2002.95(10):2041-3.
  43. Storey MR, Pollack A, Zagars G, *et al.* Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2000.48(3):635-42.
  44. Dearnaley DP, Khoo VS, Norman AR, *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *The Lancet* 1999.353(9149):267-272.
  45. Nguyen LN, Pollack A and Zagars GK Late effects after radiotherapy for prostate cancer in a randomized dose-response study: results of a self-assessment questionnaire. *Urology* 1998.51(6):991-7.
  46. Cheung R, Tucker SL, Ye J-S, *et al.* Characterization of rectal normal tissue complication probability after high-dose external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004.58(5):1513-9.
  47. Huang EH, Pollack A, Levy L, *et al.* Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002.54(5):1314-21.
  48. Kuban D, Pollack A, Huang E, *et al.* Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2003.57(5):1260-8.
  49. Zelefsky MJ, Cowen D, Fuks Z, *et al.* Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. *Cancer* 1999.85(11):2460-8.
  50. Lee WR, Hanks GE, Hanlon AL, *et al.* Lateral rectal shielding reduces late rectal morbidity following high dose three-dimensional conformal radiation therapy for clinically localized prostate cancer: further evidence for a significant dose effect. *Int J Radiat Oncol Biol Phys* 1996.35(2):251-7.
  51. Leibel SA, Zelefsky MJ, Kutcher GJ, *et al.* Three-dimensional conformal radiation therapy in localized carcinoma of the prostate: interim report of a phase 1 dose-escalation study. *J Urol* 1994.152(5 Pt 2):1792-8.
  52. Michalski JM, Purdy JA, Winter K, *et al.* Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000.46(2):391-402.
  53. Magrini SM, Cellai E, Pertici M, *et al.* Radical radiotherapy of localised prostate cancer: the relationship between radiation dose and survival. *Cancer Radiother* 1998.2(4):351-8.
  54. Koper PC, Stroom JC, van Putten WL, *et al.* Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *Int J Radiat Oncol Biol Phys* 1999.43(4):727-34.
  55. Pollack A, Zagars GK, Starkschall G, *et al.* Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996.34(3):555-64.

56. Bergstrom P, Lofroth PO and Widmark A High-precision conformal radiotherapy (HPCRT) of prostate cancer--a new technique for exact positioning of the prostate at the time of treatment. *Int J Radiat Oncol Biol Phys* 1998.42(2):305-11.
57. Sathya JR, Davis IR, Julian JA, *et al.* Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005.23(6):1192-9.
58. Chiang PH, Fang FM, Jong WC, *et al.* High-dose rate iridium-192 brachytherapy and external beam radiation therapy for prostate cancer with or without androgen ablation. *Int J Urol* 2004.11(3):152-8.
59. Dinges S, Deger S, Koswig S, *et al.* High-dose rate interstitial with external beam irradiation for localized prostate cancer--results of a prospective trial. *Radiother Oncol* 1998.48(2):197-202.
60. Borghede G, Hedelin H, Holmang S, *et al.* Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. *Radiother Oncol* 1997.44(3):237-44.
61. Jo Y, Hiratsuka J, Fujii T, *et al.* High-dose-rate iridium-192 afterloading therapy combined with external beam radiotherapy for T1c-T3bN0M0 prostate cancer. *Urology* 2004.64(3):556-60.
62. Kestin LL, Martinez AA, Stromberg JS, *et al.* Matched-pair analysis of conformal high-dose-rate brachytherapy boost versus external-beam radiation therapy alone for locally advanced prostate cancer. *J Clin Oncol* 2000.18(15):2869-80.
63. Kovacs G and Galalae R Fractionated perineal high-dose-rate temporary brachytherapy combined with external beam radiation in the treatment of localized prostate cancer: is lymph node sampling necessary? *Cancer Radiother* 2003.7(2):100-6.
64. Martinez AA, Kestin LL, Stromberg JS, *et al.* Interim report of image-guided conformal high-dose-rate brachytherapy for patients with unfavorable prostate cancer: the William Beaumont phase II dose-escalating trial. *Int J Radiat Oncol Biol Phys* 2000.47(2):343-52.
65. Stromberg JS, Martinez AA, Horwitz EM, *et al.* Conformal high dose rate iridium-192 boost brachytherapy in locally advanced prostate cancer: superior prostate-specific antigen response compared with external beam treatment. *Cancer J Sci Am* 1997.3(6):346-52.
66. Mate TP, Gottesman JE, Hatton J, *et al.* High dose-rate afterloading 192Iridium prostate brachytherapy: feasibility report. *Int J Radiat Oncol Biol Phys* 1998.41(3):525-33.
67. Paul R, Hofmann R, Schwarzer JU, *et al.* Iridium 192 high-dose-rate brachytherapy--a useful alternative therapy for localized prostate cancer? *World J Urol* 1997.15(4):252-6.

68. Deger S, Boehmer D, Turk I, *et al.* High dose rate brachytherapy of localized prostate cancer. *Eur Urol* 2002.41(4):420-6.
69. Lennernas B, Holmang S and Hedelin H High-dose rate brachytherapy of prostatic adenocarcinoma in combination with external beam radiotherapy a long-term follow-up of the first 50 patients at one center. *Strahlenther Onkol* 2002.178(10):537-41.
70. Curran MJ, Healey GA, Bihrlle W, 3rd, *et al.* Treatment of high-grade low-stage prostate cancer by high-dose-rate brachytherapy. *J Endourol* 2000.14(4):351-6.
71. Pellizzon ACA, Nadalin W, Salvajoli JV, *et al.* Results of high dose rate afterloading brachytherapy boost to conventional external beam radiation therapy for initial and locally advanced prostate cancer. *Radiother Oncol* 2003.66(2):167-72.
72. Demanes DJ, Rodriguez RR and Altieri GA High dose rate prostate brachytherapy: the California Endocurietherapy (CET) method. *Radiother Oncol* 2000.57(3):289-96.
73. Syed AM, Puthawala A, Sharma A, *et al.* High-dose-rate brachytherapy in the treatment of carcinoma of the prostate. *Cancer Control* 2001.8(6):511-21.
74. Martinez A, Galalae R, Gonzalez J, *et al.* No apparent benefit at 5 years from a course of neoadjuvant/concurrent androgen deprivation for patients with prostate cancer treated with a high total radiation dose. *J Urol* 2003.170(6 Pt 1):2296-301.
75. Borghede G, Hedelin H, Holmang S, *et al.* Irradiation of localized prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with three target definitions and dose levels inside the prostate gland. *Radiother Oncol* 1997.44(3):245-50.
76. Fujioka H, Ishimura T, Sakai Y, *et al.* Erectile function after brachytherapy with external beam radiation for prostate cancer. *Arch Androl* 2004.50(4):295-301.
77. Martinez AA, Pataki I, Edmundson G, *et al.* Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. *Int J Radiat Oncol Biol Phys* 2001.49(1):61-9.
78. Hanks GE Conformal radiotherapy for prostate cancer. *Ann Med* 2000.32(1):57-63.
79. Kupelian PA, Potters L, Khuntia D, *et al.* Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer.[see comment]. *Int J Radiat Oncol Biol Phys* 2004.58(1):25-33.
80. Zelefsky MJ, Fuks Z, Hunt M, *et al.* High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001.166(3):876-81.
81. Blank LE, Gonzalez Gonzalez D, de Reijke TM, *et al.* Brachytherapy with transperineal (125)Iodine seeds for localized prostate cancer. *Radiother Oncol* 2000.57(3):307-13.

82. Beyer DC Brachytherapy for recurrent prostate cancer after radiation therapy. *Semin Radiat Oncol* 2003.13(2):158-65.
83. Kollmeier MA, Stock RG and Stone N Biochemical outcomes after prostate brachytherapy with 5-year minimal follow-up: importance of patient selection and implant quality. *Int J Radiat Oncol Biol Phys* 2003.57(3):645-53.
84. Blasko JC, Grimm PD, Sylvester JE, *et al.* The role of external beam radiotherapy with I-125/Pd-103 brachytherapy for prostate carcinoma. *Radiother Oncol* 2000.57(3):273-8.
85. Ragde H, Korb LJ, Elgamal AA, *et al.* Modern prostate brachytherapy. Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000.89(1):135-41.
86. Sylvester JE, Blasko JC, Grimm PD, *et al.* Ten-year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: the Seattle experience. *Int J Radiat Oncol Biol Phys* 2003.57(4):944-52.
87. Dattoli M, Wallner K, True L, *et al.* Prognostic role of serum prostatic acid phosphatase for 103Pd-based radiation for prostatic carcinoma. *Int J Radiat Oncol Biol Phys* 1999.45(4):853-6.