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Overview

The Emerging Role of High-dose-rate Brachytherapy for Prostate Cancer

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ABSTRACT:
By placing radioactive sources directly into the cancer, brachytherapy allows delivery of a highly conformal radiation dose to the prostate. Permanent seed brachytherapy is most commonly used for low-risk cancer, whereas high-dose-rate (HDR) brachytherapy is combined with external-beam radiotherapy to treat higher risk disease. The high rate of dose delivery and the large fraction size may be a radiobiological advantage for tumours with high sensitivity to radiation fraction size. The ability to optimise dose delivery allows for exquisite shaping of dose around the prostate and sparing of normal tissues. HDR brachytherapy is most commonly delivered in two or more fractions of 8–10 Gy combined with 40–50 Gy external beam. Published studies are almost entirely limited to single-institution case series. Most of the patients treated have relatively unfavourable localised disease, with a reported disease-free survival of 68–93%, and a local control rate of over 90%. Treatment is well tolerated, with urethral stricture the most common late effect (risk around 8%). Early results using HDR monotherapy in low-risk disease seem promising. Patients most likely to benefit from a combined HDR/external-beam approach have bulky local disease (stage T2b-T3) or intermediate to high-grade cancers. Prospective multicentre studies of HDR brachytherapy have begun in this patient group in Canada and the USA, which hopefully will allow future comparisons with high-dose conformal external-beam techniques. Morton, G. C. (2005). *Clinical Oncology* **17,** 219–227

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Introduction

Prostate cancer is the most common male malignancy in the Western world. Over the past decade, a significant shift has taken place in stage at diagnosis, with most patients now presenting with localised disease. Options for treatment include radical prostatectomy and radiotherapy. Radical prostatectomy offers the potential for complete removal of the tumour and surgical staging; however, modern radical radiotherapy seems to result in comparable disease control rates, at least in the short term, with less morbidity [1]. There is increasing evidence that radiotherapy needs to be delivered in higher than 'conventional' doses for many men with prostate cancer in order to optimise local control. For example, a sequential dose-escalating study from Zelefsky *et al.* [2] indicated a steady reduction in the post-treatment positive biopsy rate from 54% at 64.8 Gy, to 34% at 70.2 Gy, 23% at 75.6 Gy and 10% at 81 Gy. Similarly, a randomised study from the MD Anderson comparing 70 Gy to 78 Gy showed an improved disease-free survival with the higher radiation dose, with the 6-year freedom from failure rate increasing from 64% to 70% [3]. The improvement in failure rate was predominantly found in patients who had an initial prostate-specific antigen (PSA) level of over 10 ng/ml. There is general consensus that many patients with localised prostate cancer should receive at least 74 Gy [4].

High radiation dose delivery requires specialised radiation treatment techniques in order to avoid unacceptable toxicity. These techniques include three-dimensional conformal radiotherapy, intensity-modulated radiotherapy or brachytherapy. All external-beam techniques deliver a significant radiation dose to adjacent normal tissue unless sophisticated techniques are used to limit the volume of tissue irradiated. Interstitial brachytherapy consists of inserting radioactive sources directly into the target. Prostate brachytherapy can be performed using either low-dose-rate permanent seed implants (iodine-125 or palladium-103) or high-dose-rate temporary implants. Either form of brachytherapy delivers a high radiation dose within the prostate, with rapid dose fall-off beyond the gland and sparing of surrounding normal tissues. The rapid dose fall-off may also be a limitation, as there is inconsistent dose coverage of extracapsular disease extension. Because of this, brachytherapy monotherapy, usually using permanently implanted radioactive seeds, is generally reserved for low-risk localised disease (e.g. stage 1 or 2,

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with a serum PSA level <10 ng/ml and a Gleason score of 6 or less), but may also be combined with external-beam radiation for higher risk patients [5–7]. The latter approach uses brachytherapy to 'boost' gross disease within the prostate, and the external beam serves to cover extracapsular extension of disease, and also to 'fill in' potential cold areas within the prostate.

Rationale for High-dose-rate Brachytherapy

High-dose-rate (HDR) brachytherapy allows the delivery of a highly conformal radiation treatment to the target. Treatment is delivered using a stepping source, usually iridium-192, which is automatically advanced along catheters that have been placed into the target. By varying the length of time, the source stays at each dwell position, the resultant dose distribution can be optimised. Prostate HDR brachytherapy involves the delivery of two or more large radiation fractions over a short period of time. HDR brachytherapy differs from permanent seed implants radiobiologically and dosimetrically. The radiation dose from a permanent seed implant is delivered over months as the isotope decays. For iodine-125, with a half-life of 60 days, this results in a maximal dose-rate of about 10 cGy/h. In contrast, HDR dose-rate is a 1000-fold higher (about 100 Gy/h), which is similar to the dose-rate delivered by a linear accelerator. It would be expected that such treatment is selectively damaging to tissues sensitive to large radiation fraction sizes (e.g. late responding normal tissue). For most cancer sites, this would amount to a radiobiological disadvantage, as the same dose of radiation would, in theory, result in greater damage to late responding normal tissues than to the tumour. This disadvantage is offset by the ability to optimise dose delivery by a combination of optimised dosimetry and retraction or distancing of normal tissues away from the source. As a result, the toxicity of HDR brachytherapy seems to be no greater than that of traditional low-dose-rate brachytherapy in most clinical applications.

For prostate cancer, this apparent radiobiological disadvantage may actually be a therapeutic advantage. There is a growing belief that prostate cancer is particularly sensitive to radiation delivered at large dose per fraction, which is expressed as the cells having a low alpha–beta ratio. Tissues with a lower alpha–beta ratio will have greater cell killing by larger fraction size than tissues with a higher ratio. The alpha–beta ratio for prostate cancer is unknown, but most investigators believe it to be around 1.5 [8–10]. This is even lower than the typical alpha–beta ratio of late normal tissue (around 3), and much lower than the alpha–beta ratio of acutely reacting normal tissues and most cancers (around 10). The significance of this shown in Fig. 1. If the alpha–beta ratio of normal tissue is less than that of tumour, radiation delivered at high dose per fraction, or by high-dose-rate brachytherapy, will theoretically result in greater killing of normal tissue. If, however, the reverse were the case, and tumour had a lower alpha–beta ratio than that of normal tissue, high dose per fraction or HDR

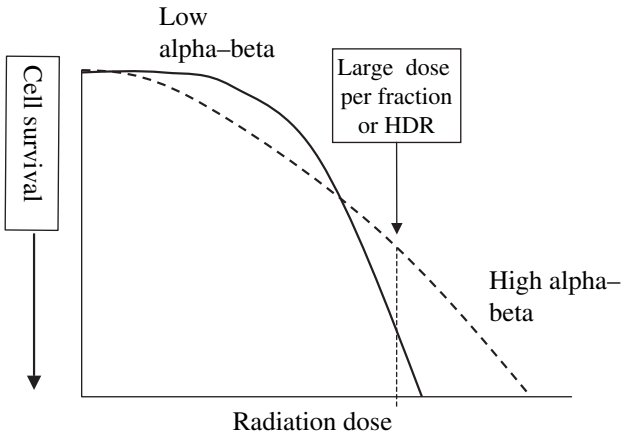

Fig. 1 – Idealised cell-survival curves of a tissue with a low alpha–beta ratio (solid line) and one with a high alpha–beta ratio (dashed). A high dose per fraction, or high-dose-rate brachytherapy, will result in lower cell survival for tissues with a lower alpha–beta ratio (e.g. prostate cancer). HDR, high-dose rate.

brachytherapy would result in relative sparing of normal tissues. This suggests that, for prostate cancer, HDR brachytherapy or hypofractionated external-beam regimens offer the potential for better tumour control rates than conventional treatments, with a reduction in late sequelae [11]. A low alpha–beta ratio for prostate cancer is not, however, universally accepted. Nahum *et al.* [12] have pointed out that the presence of hypoxia within the prostate may result in a significantly higher calculated value.

The greatest advantage of HDR brachytherapy is the ability to optimise dose distribution by varying source dwell times along the catheters. This allows for greater sparing of rectum and bladder than is achievable with conformal external-beam radiotherapy [13]. Optimisation enables coverage of the target without exceeding tolerance of urethra, bladder or rectum. Furthermore, it allows varying dose distributions across the target, with, for example, selective dosing of the peripheral zone, or boosting of a dominant intraprostatic lesion [14]. Such optimised dosimetry is not as readily achievable with permanent seed implants, where seed migration, difficulty implanting outside the gland and prostatic oedema often contribute to less than optimal seed placement and imperfect dose coverage. Although prostate swelling also occurs after HDR catheter insertion, the affect of this on ultimate dose distribution is probably minimal [15], perhaps related to the higher energy of photons emitted from iridium-192 compared with that from iodine-125 or palladium-103.

Prostate High-dose-rate Brachytherapy Technique

The technique of HDR brachytherapy has evolved over the past decade. Many varied techniques of prostate HDR brachytherapy have been described, all consisting of the following steps: (1) the placement of afterloading catheters