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Review article

High dose rate brachytherapy for prostate cancer: Standard of care and future direction

Curiethérapie de haut débit de dose dans les cancers de la prostate : standard de soin et perspectives

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ABSTRACT

High dose rate brachytherapy is a highly conformal method of radiation dose escalation for prostate cancer and one of several treatment options for men with localised disease. The large doses per fraction exploit the low alpha/beta ratio of prostate cancer cells so that biological radiation dose delivered is substantially greater than that achieved with conventional external beam delivery. This review article presents contemporary data on the rationale for high dose rate brachytherapy including treatment technique and future directions.

Mots clés :
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RÉSUMÉ

La curiethérapie de haut débit de dose est une technique d'irradiation de haute précision autorisant, grâce à une grande conformité des volumes traités, une escalade de dose. Elle constitue désormais un standard de la prise en charge des patients atteints de cancer localisé de la prostate. Les hautes doses délivrées par fraction permettent d'exploiter le rapport alpha/bêta bas de l'adénocarcinome prostatique et d'obtenir des doses biologiques significativement supérieures à ce qui est réalisable avec des techniques d'irradiation externe. Cette mise au point a pour but de faire le point sur les connaissances actuelles du rationnel de la curiethérapie de haut débit de dose dans les cancers de prostate, les techniques disponibles, et perspectives de développement.

1. The evolution of high dose rate prostate brachytherapy

Brachytherapy is the placement of radioactive sources close to or within a tumour and takes advantage of one of the most fundamental principles of radiation physics. Its roots can be traced back to as early as the 1900s following the discovery of radium where clinicians introduced radioactive sources interstitially into tumours of the breast, prostate and skin [1].

The first reported cases of prostate brachytherapy resulted from the separate works of three urologists, Ernst-Louis Desnos, Henri Minet and Octave Pasteau with similar methods of introducing radium via a urinary catheter [2]. It was Benjamin Berringer who subsequently reported the technique of transperineal interstitial radium guided into the prostate gland by a finger in the rectum [3,4]. By this time given that surgical methods of treating prostate cancer had fallen out of favour, prostate brachytherapy was the preferred option for treatment by leading clinicians.

This was short lived however and its use began to drastically decline by the mid-1950s with the reports of detrimental effects to staff [5]. At this time we see the resurgence of radical surgical prostatectomy and megavoltage external beam radiotherapy.

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Table 1
Patient selection criteria for high dose rate brachytherapy boost for prostate cancer.

Inclusion criteria	Exclusion criteria
Stage: T1–T3b Gleason Score: 6–10 Prostate-specific antigen: no limit	Regional or distant metastases Transurethral resection of the prostate less than 3 months ago International Prostate Symptom score > 20 Significant urinary obstruction Rectal fistula Pubic arch interference Contraindication to anaesthesia Absent rectum (post surgery)

The technique of brachytherapy only resurfaces as a major player in this dynamic landscape following the discovery of manual and then remote afterloading systems pioneered by Henschke [6]. This coupled with simultaneous advances in medical imaging enabled the evolution of highly conformal planning that we have today.

One of the earliest phase I/II trials in modern high dose rate brachytherapy was reported by Martinez et al. in 1995 [7]. A total of 59 patients had high dose rate brachytherapy boost ranging from 5.5 to 6.5 Gy per fraction for three fractions. Their toxicity profile was comparable to that of treatment with external beam radiotherapy alone. Multiple investigations have since followed into high dose rate brachytherapy boost and more recently the role of high dose rate brachytherapy alone for organ confined prostate cancer.

2. What are the advantages of high dose rate brachytherapy?

It has been hypothesized that the alpha/beta ratio for prostate cancer is significantly lower than other carcinomas with values ranging from 1.5 to 3 [8–10]. Given that the ratio describes the effect of radiation on tissue, a lower value implies cells are more responsive to large dose per fractionation which is the advantage that brachytherapy provides over conventional fractionated external beam radiotherapy in treating prostate cancer. The biological equivalent dose (BED) for high dose rate brachytherapy ranges from 120 to 280 with an alpha/beta ratio of 1.5 to 3, which equates to an equivalent dose in 2 Gy per fraction ($EQD_{2\,Gy}$) of 72 to 120 Gy.

Practical advantages of high dose rate brachytherapy include a short duration of radiation exposure and delivery as either a day case procedure or short in-patient hospital stay. Unlike low-dose rate brachytherapy, high dose rate planning is prospective and target coverage is known prior to treatment which allows for plan optimisation.

There is some data to support the cost effectiveness of high dose rate brachytherapy which is comparable to external beam radiotherapy. External beam radiotherapy combined with high dose rate brachytherapy boost is comparable to external beam radiotherapy alone and dependent on total number of fractions and technique with increased costs associated with intensity-modulated radiotherapy and long fractionation schedules [11].

3. Patient evaluation and selection

Patient selection for high dose rate brachytherapy should be based on tumour factors or clinical risk category and patient factors that may compromise treatment delivery and toxicity (Table 1). Temporary high dose rate brachytherapy is an appropriate treatment option for intermediate and high-risk prostate cancer with disease confined to the organ or immediate surrounding tissue. Low-risk patients can also be treated with this approach.

Diagnostic work up should include recent serum prostate-specific antigen (PSA) level, digital rectal exam and transrectal ultrasound-guided biopsy to confirm histology. Staging with a whole body bone scan is recommended for selected intermediate-risk and all high-risk disease or if PSA concentration is higher than 20 ng/ml [12]. Multiparametric magnetic resonance imaging (mpMRI) using diffusion weighted imaging, dynamic contract enhanced and spectroscopy (MRS) may have a role to play in detecting clinically significant disease and performing targeted biopsies in intermediate and high-risk patients [13].

Additional functional assessment should be performed to determine any underlying significant obstructive symptoms that would preclude brachytherapy as a viable option [14,15]. Absolute contraindications for high dose rate brachytherapy include the presence of rectal fistula and comorbidities which would exclude anaesthesia [15]. Relative contraindications include recent transurethral resection of the prostate and large prostatic volume. Traditionally there was a reluctance to offer high dose rate brachytherapy to such patients but contemporary data suggest that prostate volume should not be a limiting factor in case selection [16,17]. With respect to transurethral resection of the prostate the data is conflicting, with some suggestion of increased genitourinary toxicity, albeit still less than reported with external beam radiotherapy in this setting [18–21]. Keeping this in mind optimal imaging of the urethra and careful attention to urethral dose constraints is essential. A minimum of three months from the time of transurethral resection of the prostate to implantation is required to allow for adequate healing [22].

There are a few special circumstances where high dose rate brachytherapy may have particular advantages. These include prior pelvic radiotherapy and pre-existing rectal pathology [23]. Prior pelvic radiotherapy is most commonly seen with a previous history of rectal cancer and in general if prior pelvic dose is equivalent to an $EQD_{2\,Gy}$ of 50 Gy or less, then high dose rate monotherapy can be a curative treatment option. In the setting of previous prostate radiotherapy where locally recurrent disease within the gland has been confirmed on histology, then the option of salvage high dose rate brachytherapy is a possibility [24,25]. Prior rectal surgery or inflammatory bowel disease requirse special attention [26]. In the setting of inflammatory bowel disease, surgery if suitable is the best choice. However, if the patient is not a surgical candidate then high dose rate brachytherapy as a boost or as monotherapy will reduce bowel radiation doses compared to radical external beam radiotherapy alone.

Strict adherence to rectal dose constraints at the level of any anastomosis or surgical clips is important erring on the more conservative side.

4. Is there a role for androgen-deprivation therapy in the setting of high dose rate brachytherapy?

The role of androgen-deprivation therapy in the setting of high dose rate brachytherapy remains poorly defined, with conflicting data from various case series, some reporting a benefit with the addition of androgen-deprivation therapy in dose escalation but majority of the body of evidence appears to suggest that the benefit of androgen-deprivation therapy in dose escalation is likely to be less than originally predicted [27–30]. Krauss et al. published their series on androgen-deprivation therapy in the setting of dose escalated radiotherapy in 1044 patients with intermediate and high-risk prostate cancer [27]. In the patients that were treated with brachytherapy alone (high- or low-dose rate; $n = 150$) with the vast majority being intermediate risk, the 8-year biochemical control favoured the androgen-deprivation therapy arm but this did not translate to overall survival. In the patients that received a high dose rate boost ($n = 425$) no statistically significant effect was found for biochemical control, freedom from distant metastasis or overall survival. The overall conclusion is that there is a lack of benefit for