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Is high dose rate brachytherapy reliable and effective treatment for prostate cancer patients? A review of the literature

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Abstract

The intrinsic physical and radiobiological characteristics of High Dose Rate Brachytherapy (HDR-BT) are well suited to the treatment of prostate cancer. HDR-BT was initially used as a boost to external beam brachytherapy, but has subsequently been employed as the sole treatment, which is termed HDR monotherapy. This review summarizes the clinical outcomes and toxicity results of the principal studies and discusses the radiobiological basis supporting its use.

Keywords: Prostate cancer; High-dose rate brachytherapy; Salvage brachytherapy; HDR-BT; Brachytherapy boost, Radiobiology.

1. General concepts

Prostate cancer (PC) is an increasing health issue in Europe [1]. In the last two decades public awareness and effective screening decreased the age at diagnosis by over a decade [2]. Brachytherapy (BT) is a widely used modality in the management of prostate cancer [3]. Initial outcomes of the Low Dose Rate BT (LDR-BT) performed with a trans-abdominal access were unsatisfactory, because of suboptimal technique and inadequate dose distributions, which resulted in high morbidity and poor local control rates [4]. Contemporary image guided transperineal template implant techniques have lead to improved implant quality [5]. Usually, a LDR technique (average dose rate : 0,1 Gy/h) has been preferred in most of the published experiences. The rapid fall-off of the

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dose over a distance of a few millimeters spares the surrounding structures, but may potentially result in underdosage of the immediate periprostatic tissue. For these reasons, several guidelines have been produced in order to improve the quality of the implant [6–8]. The validity of these guidelines has been indirectly confirmed by the very good clinical results in terms of biochemical control obtained by LDR-BT [3]. High Dose Rate brachytherapy (HDR-BT) was firstly introduced as a boost after EBRT and it has been proven to be a safe and effective treatment method [9]. More recently, HDR-BT has been used also in prostate cancer recurrence after radiotherapy, and the preliminary results show good local control rates, but they should be further confirmed on populations with longer follow-up times [10].

Major issues in evaluating the results of prostate HDR-BT are the heterogeneity of the prescribed doses, both in terms of total dose and dose/fraction, and of the dose reporting in the available studies. They are a limiting factor in comparing the clinical results, particularly concerning the side effects of the treatment [11,12]. For these reasons, clinical and technical guidelines have been published (and recently updated) by the American and European societies of Radiation Oncology [6–8]. Another important limitation in comparing available studies are the differences in the toxicity scores used to report acute and late toxicity rates. The current clinical evidence supports the equivalent outcomes for localized cancer with either LDR or HDR-BT, using current dose regimens and when the implant is correctly performed. A stage by stage comparison of the clinical outcomes of the two techniques suggests that they are equally safe and effective in terms of control of the disease and toxicity rates [13,14].

In this review, we summarize published results in terms of clinical outcomes and toxicity of HDR-BT in the treatment of prostate cancer. Radiobiological basis supporting its use in this clinical setting are also discussed.

2. Radiobiology: the alpha/beta (α/β) value of the prostate cancer and the role of high doses/fraction

The interest of HDR-BRT in the treatment of prostate cancer could not be fully understood if adequate information is not given about radiobiology of prostate cancer and of hypofractionation. HDR-BRT is based upon the radiobiology of hypofractionation and it is for this reason that radiation oncologists believe that it is well suited to prostate cancer. Total duration of a conventional curative course of radical external beam radiotherapy (EBRT) represents a significant issue for patients, as it usually lasts 7–9 weeks. Current conventional fractionation emerged from the evidence that late complications due to radiation injuries on healthy tissues, especially for rectal mucosa, can be reduced by reducing the dose/fraction while increasing the number of fractions, without a detrimental impact on local control [15]. In order to describe the response of normal tissues and of tumors to radiation, the concept of α/β value has been introduced. This ratio represents a radiobiological parameter explaining how normal and cancer tissues will respond to different radiation schedules. In particular, a low α/β value is characteristic of some slowly proliferating tumors and of some normal tissues preferentially showing late responses to radiation: it has been demonstrated that both these tissues are mainly sensitive to high doses per fraction [16]. Several clinical experiences in the treatment of prostate cancer showed that it probably has a low α/β value, ranging between 1.5–2 Gy (vs. 3 Gy for the rectal wall) and that prostate cancer could be more sensitive to high doses par fraction, typically delivered with hypofractionated schedules [17]. A recent retrospective analysis on 5969 prostate cancer patients previously treated with EBRT was published by Miralbell et al. [18]. Linear-quadratic model (LQM) is a radiological model which describes cell killing, both for tumor control and for normal tissue complications. This model was used by Miralbell et al. to analyze 5-year biochemical relapse – free survival rates (BRFS) and to estimate the sensitivity to dose fractionation. The authors reported a value of prostate cancer α/β for the pooled data of 1.4 Gy (range: 0.9–2.2 Gy), confirming an overall α/β value consistently lower than the expected values for late normal-tissue morbidity, irrespective from the stage of prostate disease. Proust-Lima et al. used a biphasic linear model to estimate the α/β value by the long term dynamics of PSA in a population of 5093 hormone-naïve prostate cancer patients treated with EBRT [19]. The robustness of the estimation of α/β value by this model was based not only on the post-treatment PSA but also on: (a) various prognostic factors, including T stage, initial PSA, Gleason score sum; (b) the prescribed radiation dose. The α/β value estimated by means of this model was 1.55 Gy (range: 0.46–4.52 Gy).

Despite these studies, some questions remain about the α/β values. LQM which is usually adopted and which is currently considered reliable, is based on PSA kinetics after treatment, but it is noteworthy that PSA is only a surrogate of a clinical outcome and it is not a direct measure of radiation induced tumour cell killing. As showed by Kal et al., when other parameters are taken into account, α/β values could change. These authors re-analysed reports on low α/β values of prostate cancer, derived from clinical results of external beam radiotherapy and of permanent BRT implants, and they found values ranging between 1.2 and 1.5 Gy [20]. With their model the authors considered other factors, including data about tumor re-population and oedema (due to the implantation and to the radioactive seeds in the case of BRT), they found higher α/β values, ranging between 3.1–3.9 Gy.

These data derived from LQM indicating that the slow proliferating prostate cancer cells have high sensitivity to dose per fraction, support the use of hypofractionated radiotherapy schedules, as those delivered with HDR-BT [20,21]. These radiobiological conclusions have been confirmed by the results of published randomized trials on hypofractionation [22]. These studies showed that hypofractionation potentially improves the therapeutic value of prostate cancer