Cancer/Radiothérapie 18 (2014) 437–440

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Elsevier Masson France EM|consulte www.em-consulte.com

Review

Dose rate in brachytherapy using after-loading machine: Pulsed or high-dose rate?

Débit de dose en curiethérapie avec projecteur de source : débit pulsé ou haut débit ?

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ARTICLE INFO

Keywords:
Brachytherapy
High-dose rate
Pulsed-dose rate
After-loading machine

ABSTRACT

Since February 2014, it is no longer possible to use low-dose rate 192 iridium wires due to the end of industrial production of IRF1 and IRF2 sources. The Brachytherapy Group of the French society of radiation oncology (GC-SFRO) has recommended switching from iridium wires to after-loading machines. Two types of after-loading machines are currently available, based on the dose rate used: pulsed-dose rate or high-dose rate. In this article, we propose a comparative analysis between pulsed-dose rate and high-dose rate brachytherapy, based on biological, technological, organizational and financial considerations.

Mots clés :
Curiethérapie
Haut débit de dose
Débit de dose pulsé
Projecteur de source

RÉSUMÉ

Depuis février 2014, il n'est plus possible d'utiliser des sources radioactives d'iridium 192 de bas débit de dose du fait de l'arrêt de la production industrielle des sources d'IRF1 et d'IRF2. Le groupe de curiethérapie de la Société française de radiothérapie oncologique a recommandé de passer des fils d'iridium aux projecteurs de sources. Actuellement, deux types de projecteurs de source sont disponibles selon le débit de dose utilisé : pulsé ou haut débit. Dans cet article, nous proposons une analyse comparative entre la curiethérapie de débit pulsé et celle de haut débit de dose, selon des critères biologiques, technologiques, organisationnels et financiers.

1. Introduction

Brachytherapy is a very efficient weapon against cancer and can be described by the "3S system". Indeed, brachytherapy is an irradiation technique, which allows delivering a smart dose, in a small volume, during a short time. The smart dose is due to the intrinsic dose escalation linked to the hyperdose volumes within the clinical target volume, leading to increase the chance of local control. A small volume is due to the important dose fall-off outside of the clinical target volume, which protects organs at risk from radiation injuries and consequently, decreases the risk of side effects. A short time is due to the possibility to deliver a higher dose per fraction decreasing the overall treatment time and consequently, allowing a more comfortable/convenient/cost-effective treatment.

Since February 2014, it is no longer possible to use low-dose rate 192 iridium wires due to the end of industrial production of IRF1 and IRF2 sources. The Brachytherapy Group of the French society of radiation oncology (GC-SFRO) has recommended switching from iridium wires to after-loading machines [1]. Currently, two types of after-loading machines are available, based on the dose rate used: pulsed-dose rate and high-dose rate. In this article, we propose a comparative analysis between pulsed-dose rate and high-dose rate

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http://dx.doi.org/10.1016/j.canrad.2014.07.156
1278-3218/

brachytherapy, based on biological, technological, organizational and financial considerations.

2. Biological approach

Even if the biological effects of pulsed-dose rate brachytherapy are not strictly stackable to those observed after low-dose rate brachytherapy, the former gets closer to latter than to high-dose rate brachytherapy. The results of the comparative studies mainly performed for cervical cancer confirm that there is no significant difference (with even a small advantage for high-dose rate) between low- and high-dose rate brachytherapy [2–5]. Currently high-dose rate brachytherapy for cervical cancer is considered by the American Brachytherapy Society as the gold standard technique [6]. However, trying to compare low- and high-dose rate brachytherapy is confronted to an important bias because the dose rate is not the only difference between the two techniques. Indeed, dose distribution optimization is possible with high-dose rate brachytherapy by playing with the dual time positions of the source, while this type of optimization is not possible with the low-dose rate technique. This optimization can deeply impact the clinical outcome independently of the dose rate used. A French multicentric study confirmed that pulsed-dose rate brachytherapy improved local control with half the toxicity observed with low-dose rate brachytherapy [7]. Currently, there is no comparison (randomized or not) between pulsed- and high-dose rate brachytherapy performed for cervical cancer, so it remains difficult to precisely analyse the hypothetical difference between the two techniques only based on the difference of the dose rate (both techniques allowing the dose optimization by modifying the time of stepping source).

The definition of the optimal dose prescription scheme for high-dose rate brachytherapy represents another important issue: which dose per fraction? Which fractionation? Which total dose? The biological models currently available to calculate the biological equivalent dose at 2 Gy (BED) between low- and high-dose rate are not validated for doses per fraction higher than 8 Gy [8]. But, is the biological equivalent dose, derived from a mathematical model, the only one parameter to consider? What about more pragmatic parameters such as the “clinical equivalent dose” or the “pathological equivalent dose”? Could the clinical equivalent dose and/or the pathological equivalent dose contribute with the biological equivalent dose calculation to establish new protocols routinely applicable? Indeed, a total dose of 39 Gy delivered in 9 fractions over 5 consecutive days leads to a rate of 92% of complete pathological response observed on the hysterectomy specimen after preoperative high-dose rate brachytherapy for high-risk T1B1 squamous cell cervical cancers (size larger than 20 mm, vascular emboli) without urinary or digestive grade 2 or above toxicities [9]. The calculated biological equivalent dose of this protocol is 59 Gy for normal tissues ($\alpha/\beta = 3$) and 47 Gy for the tumour ($\alpha/\beta = 10$), therefore, significantly lower compared to the classical dose of 60 Gy delivered by low-dose rate brachytherapy but giving (at least) equivalent pathological results. Based on the clinical equivalent dose approach applied for lips cancers, Guinot et al., retrospectively compared 99 patients treated with interstitial low-dose rate brachytherapy to 104 patients treated with high-dose rate brachytherapy (no significant difference in terms of tumour stage between the two groups) [10]. The high-dose rate protocol was 40.5 Gy in 9 fractions over 5 consecutive days. With a median follow-up of 51 months for the high-dose rate group, the authors reported a local control rate higher than 90% in the low- and high-dose rate treatment groups. In this study, the calculated biological equivalent dose of the delivered dose was 61 Gy for normal tissue ($\alpha/\beta = 3$) and 49 Gy for the tumour ($\alpha/\beta = 10$). Then, it could be not necessary to absolutely reach the 60 Gy biological equivalent dose delivered by low-dose rate brachytherapy for achieving an equivalent clinical or pathological result by high-dose rate brachytherapy.

Equivalence of the dose between low- and high-dose rate was also investigated for prostate cancer with comparable clinical outcome observed between the two dose rates in terms of efficacy and toxicity (an advantage for high-dose rate is even suggested) [11,12]. American Brachytherapy Society (ABS) as well as *Groupe Européen de Curiethérapie* of the European Society of Therapeutic Radiation Oncology (GEC-ESTRO) reported numerous high-dose rate protocols used for prostate boost after a first course of external beam radiation therapy [13,14]. However, regarding patient comfort and organizational considerations, a single fraction of 14 to 15 Gy is now generally accepted. A prostate boost of 14 Gy in one fraction is used in the French phase III protocol GETUG-P05 randomizing for intermediate risk prostate cancer, an external beam radiation therapy boost versus a brachytherapy boost based on low-dose rate (iodine seed implant) or high-dose rate. While high-dose rate brachytherapy is now a well-established technique for the boost, it remains under evaluation in case of sole therapy with various dose protocols using hypofractionated approach or single dose (around 20 Gy) [8,11].

For breast cancer, no comparative analysis between low- and high-dose rate brachytherapy has been performed; however, the protocol which delivers a total dose of 34 Gy in ten fractions (twice daily) over five consecutive days (biological equivalent dose of 42 Gy for $\alpha/\beta = 4$) is used in the two phase III randomized trials of partial breast irradiation conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the GEC-ESTRO [15,16].

3. Technological approach

Currently, there is no difference in terms of technical considerations for the implant between pulsed- and high-dose rate brachytherapy, whatever the indication. Vectors (applicators, tubes, needles) are the same and after-loading machine are quite similar. Treatment planning systems can be used equally for protocols, allowing the same optimization of the dose distribution. However, for prostate cancer, high-dose rate brachytherapy enables intraoperative irradiation using a dedicated treatment planning system based on ultrasound imaging (such treatment is not compatible with a pulsed-dose rate approach). For pulsed- and high-dose rate brachytherapy, postimplant imaging can be equally used based on CT-scan or MRI.

Guedea et al. reported the results of a survey, which evaluated brachytherapy practices and resources in Europe [17]. A total of 1121 radiotherapy centres from 41 countries were investigated. High-dose rate brachytherapy was the most commonly reported technique (65% of centres), while most brachytherapy interventions were for gynaecological tumours (59% of all cases), prostate (17%), breast (9%), lung/bronchus (3%), and oesophagus tumours (2%). In France, 37 pulsed-dose rate after-loaders are implanted, representing almost 50% of the total number of pulsed-dose rate machines in the world, while 50 high-dose rate after-loaders are regularly used (data provided by the French brachytherapy providers). Unlike pulsed-dose rate, different radioactive sources can be used with high-dose rate, such iridium 192 or cobalt 60, giving comparable dose distribution [18].

4. Organizational approach

While the organizational management of pulsed-dose rate brachytherapy is very close to low-dose rate brachytherapy in terms of treatment delivery and nursing care, high-dose rate brachytherapy is comparable to linear accelerator treatments, with one or two teams of dedicated technicians, a devoted bunker and