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Review article

Radiobiology of brachytherapy: The historical view based on linear quadratic model and perspectives for optimization

Radiobiologie de la curiethérapie : de l'approche historique basée sur le modèle linéaire-quadratique aux perspectives d'optimisation

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ABSTRACT

Most preclinical studies examining the radiobiology of brachytherapy have focused on dose rate effects. Scarcer data are available on other major parameters of therapeutic index, such as cell cycle distribution, repopulation or reoxygenation. The linear quadratic model describes the effect of radiotherapy in terms of normal tissue or tumour response. It allows some comparisons between various irradiation schemes. This model should be applied cautiously for brachytherapy, because it relies on cell death analysis only, and therefore partially reflects the biological effects of an irradiation. Moreover, the linear quadratic model validity has not been demonstrated for very high doses per fraction. A more thorough analysis of mechanisms involved in radiation response is required to better understand the true effect of brachytherapy on normal tissue. The modulation of immune response is one promising strategy to be tested with brachytherapy. A translational approach applied to brachytherapy should lead to design trials testing pharmacological agents modulating radiation response, in order to improve not only local control, but also decrease the risk of distant failure. Here we review the radiobiology of brachytherapy, from the historical view based on linear quadratic model to recent perspectives for biological optimization.

Mots clés :
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Système immunitaire
Modèle linéaire-quadratique

RÉSUMÉ

La plupart des études ayant porté sur les mécanismes radiobiologiques impliqués dans la réponse à la curiethérapie se sont intéressées uniquement à l'effet du débit de dose. Les données sont plus rares en ce qui concerne d'autres paramètres majeurs de l'effet différentiel, tels que la redistribution dans le cycle, la repopulation, ou la réoxygénation. Le modèle linéaire-quadratique décrit l'effet d'une irradiation en termes de réponse des tissus sains ou des tissus tumoraux. Il permet des comparaisons entre différents schémas d'irradiation. Cependant, ce modèle doit être appliqué avec prudence en curiethérapie, puisqu'il ne repose que sur l'étude de la létalité cellulaire, ne reflétant donc que partiellement les effets biologiques d'une irradiation. Par ailleurs, le modèle linéaire-quadratique n'a pas été validé pour des fortes doses par fraction. Une analyse exhaustive des mécanismes impliqués dans la réponse à l'irradiation est nécessaire pour appréhender l'effet réel de la curiethérapie sur les tissus sains. La modulation de la réponse immunitaire est une stratégie prometteuse à tester en association à la curiethérapie. Une approche translationnelle appliquée à la curiethérapie devrait conduire à des essais testant des agents pharmacologiques modulant la réponse à l'irradiation, afin d'améliorer non seulement le taux de contrôle local mais également de diminuer le risque de rechute à distance. Nous effectuons une revue des données concernant la

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radiobiologie de la curiethérapie, de l'approche historique basée sur le modèle linéaire-quadratique, aux perspectives d'optimisation biologique.

1. Introduction

Contrary to external beam radiotherapy, which involves irradiation of large volumes at intermediate doses with an objective of homogeneity of dose distribution within treated volume, brachytherapy is characterized by a very heterogeneous dose distribution, with sharp dose gradients. The ballistic properties of brachytherapy are unequalled, even by high tech external beam radiotherapy techniques, including stereotactic devices or proton therapy. Furthermore, the quality of brachytherapy treatments has improved with the implementation of 3D imaging and the increasing possibility to perform optimization to escalate the dose without additional morbidity [1]. However, the radiobiological mechanisms of brachytherapy have been poorly understood, and most available data have been obtained in the 1980s from studies focusing on dose rate effect. The paucity of radiobiological data can be seen as the consequence of ballistic properties of the technique, which allows to deliver high doses, while keeping doses to organs at risk an acceptable level. Therefore, high local control rates are achievable with usually low to moderate side effects. However, dose escalation strategy has some limitations. First, there remains a significant rate of relapses after brachytherapy, more particularly for locally advanced disease. Second, long-term side effects may still compromise quality of life, even when a particular attention is paid to critical organs dose/volume parameters. Lastly, there are some biological mechanisms involved in tumour radioresistance that are also implicated in the metastatic phenotype acquired by tumours during oncogenesis.

Tissue response after brachytherapy involves the same biological mechanisms than external beam radiotherapy, and the '4R' concept (DNA repair, reoxygenation, repopulation, cell cycle redistribution) does apply, though with some specificities which have been poorly studied [2]. In this article, we review available radiobiological data in the context of brachytherapy, and some promising biological strategies are highlighted.

2. DNA repair and dose rate

2.1. Dose rate effect

Most data on brachytherapy radiobiology and dose prescription rules (e.g. Paris system) have been obtained with low dose rate irradiation (dose rates ranging from 40 to 100 cGy/h). Radiation-induced cell damages leading to cell death include: 1/potentially lethal damages that are lethal if not repaired (mainly double strand DNA break) and sublethal damages that become lethal when accumulating during a fractionated irradiation. For dose rates that are being used in brachytherapy (ranging from 0.3 Gy/h to 1 Gy/min), DNA repair is the preeminent parameter of cell lethality. More than four decades ago, it was demonstrated that the ability to repair sublethal damages was a major factor of the radiobiological effect [3]. For fractionated irradiation, the capacity of repairing sublethal damages depends on the time interval between two fractions, and at least 6 to 8 hours are required to allow their repair in normal tissues. For continuous irradiation, DNA damages can be repaired during irradiation when dose rate decreases, and consequently sublethal damages less accumulate and cell survival probability increases [4]. The radiobiological superiority of low dose rate brachytherapy on other irradiation modalities relies on the ability of normal tissues to repair sublethal damages. Despite a lower biological activity (as compared with high dose rate irradiation), low dose rate remains the best irradiation modality in terms of therapeutic index because when tumour has low repair capacity organs at risk a high capacity. In fact, it specifically spares slowly proliferating tissues that are implicated in the onset of late toxicity. If the tumour has a high repair capacity as in prostate cancer, high dose rate irradiation is more beneficial. Isoeffect dose responses curves published in the 1980s illustrate dose rate effect: a physical dose of 60 Gy delivered at 1 cGy/min (0.6 Gy/h) was radiobiologically equivalent to a total dose of 30 Gy delivered at 10 cGy/min (6 Gy/h) [5]. Measurements of sublethal damages have shown that for a same total dose, dose rate and residual double strand DNA break increased concomitantly, and this effect was associated with a decrease of surviving fraction in clonogenic assays [6]. These preclinical findings were confirmed by large retrospective studies, showing that dose rate correlated with the probability of normal tissue complication. For cervical cancer treated by brachytherapy followed by surgery, a randomized trial has shown that the probability of grade 2+ toxicity increased when dose rate increased from 0.4 to 0.8 Gy/h [7]. Patients treated for a penile carcinoma have a higher risk of necrosis if dose rate is superior to 0.43 Gy/h (6.5% versus 30.7%, $P = 0.021$) [8]. For interstitial brachytherapy according to Paris System of mobile tongue and mouth floor tumours, it has been shown that necrosis probability was 44% at five years for a total dose at least 62.5 Gy and a dose rate at least 0.5 Gy/h, versus 5% for a total dose less than 62.5 Gy and a dose rate less than 0.5 Gy/h. However, local control probability was also decreased by decreasing total dose and dose rate, from 93 to 52% [9]. The negative impact of a dose rate decrease in terms of local control has also been shown in a cohort of 340 patients with breast cancer receiving a brachytherapy boost, with 31% of local relapses for a dose rate of 0.3 to 0.4 Gy/h, versus 0% for a dose rate of 0.8 to 0.9 Gy/h [10]. The superiority of low dose rate irradiation has therefore some limitations in terms of therapeutic index, and an excessive decrease of dose rate without adaptation of total dose is a hazardous strategy for tumours having the capacity to proliferate and repopulate during treatment.

Low dose rate brachytherapy has now been replaced by either high dose rate or pulsed dose rate technique, although a low level of evidence suggests the equivalence of these irradiation modalities in terms of locoregional control or late normal tissue complication probability. High dose rate brachytherapy delivers treatments with dose rate above 12 Gy/h, through a remote afterloader using iridium-192 or cobalt-60 sources. Stepping source technology allows more optimization as compared to Iridium wires, and this is also a major improvement in terms of radioprotection of the medical/paramedical staff. The treatment is delivered within few minutes, through fractions that are distant from 8 hours to one week, according to protocols. For high dose rate brachytherapy, the dose per fraction is an important parameter in the radiobiological model. Slowly proliferating tissues are the most sensitive to fractionation, and the increase of dose per fraction should be taken into account when deciding total dose [11]. However, most preclinical data have focused on clonogenic survival and few authors have investigated the histological effects of dose per fraction. In rabbit

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