Physica Medica xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

Time resolved dose rate distributions in brachytherapy

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ARTICLE INFO

Article history:
Received 30 December 2016
Received in Revised form 18 March 2017
Accepted 9 April 2017
Available online xxxx

Keywords:
Dose rate
Brachytherapy
Radiobiology

ABSTRACT

Purpose: To investigate the biological significance of introducing time-resolved dose rate distributions (TR-DRD) in brachytherapy.

Materials and methods: The treatment plan of a head and neck patient treated with pulsed-dose-rate (PDR) brachytherapy was considered. The TR-DRD was calculated on the basis of a Monte Carlo generated single source dose rate matrix taking into account the dose rate per source dwell position. Biologically Effective Dose (BED) was obtained considering either the mean dose rate per pulse (analytical method) or the TR-DRD (numerical method). Corresponding Tumor Control Probabilities (TCP) were calculated and compared for various PDR schemes and repair half-times from the literature. The dose of the biologically equivalent high-dose-rate (HDR) treatment schedule was also evaluated.

Results: The analytical method presents an overall BED underestimation (up to 2%) relative to TR-DRD results. This is associated with an analytical-based TCP underestimation which increases with dose/pulse, pulse duration and period time and decreases with total dose. The half-time of repair seems to have the largest impact on the TCP calculations, with significant differences (up to 39.1%) corresponding to the shorter repair half-times. Regarding the equivalent HDR treatment schedule, the analytical method resulted to a HDR isoeffective dose underestimation lower than 2.2% and thus does not warrant any change in the derivation of the equivalent HDR scheme.

Conclusion: TR-DRD data should be taken into account for PDR biological effectiveness estimations, especially for short tissue repair half-times. This does not appear however to influence dose prescription of the equivalent HDR treatment schedule for mobile tongue carcinoma.

1. Introduction

Base-of-tongue cancer can be effectively treated using External Beam Radiotherapy (EBRT) combined with ^{192}Ir brachytherapy boost [1]. Pulsed-dose-rate (PDR) interstitial brachytherapy constitutes an effective treatment for patients with head and neck squamous cell carcinoma, with excellent long-term results [2–4]. Recently, published data have demonstrated that high-dose-rate (HDR) brachytherapy could also be a safe alternative for the treatment of oral cancer with excellent local control and a low incidence of side effects [5–7].

The Biologically Effective Dose (BED) is a clinical tool frequently used to assess and compare the biological effects in malignant and normal tissues, as well as to convert between different fractionation schedules [8,9]. Although local control and complications are strongly dependent on dose rate [10,11], studies published on the biological effectiveness of PDR and HDR brachytherapy [12–14], as well as on the derivation of the biologically equivalent HDR scheme [12,15] rely on time-integrated dose rate calculations ignoring the intra-fraction dose rate from each individual source dwell position. While the dose rate response of tissues to radiation is considered to be stable in HDR brachytherapy [16], the effect of varying dose rate on the treatment outcome of PDR brachytherapy should be evaluated since dose rates lower than 1 Gy/min, where the response begins to change [11,17], can be observed.

Lately, the radiation therapy community has shown an interest in the assessment of the time-resolved distribution of dose rates across the patient geometry [18–22]. Podesta et al. [18] and Mackeprang et al. [19] have recently developed methods to calculate the dose rate distributions in volumetric modulated arc therapy (VMAT) plans, which could serve as input for future radiobiological studies. Andersen et al. [22] performed *in vivo* dosimetry in five patients undergoing PDR brachytherapy and demonstrated that time-resolved dose rate measurements revealed an increased sensitivity in detecting dose-delivery errors. This work presents a method to calculate the intra-fraction dose rate distribution in PDR brachytherapy using Monte Carlo (MC)

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http://dx.doi.org/10.1016/j.ejmp.2017.04.013
1120-1797/

simulation. Furthermore, a formalism including tools that are frequently used in clinical practice was developed in order to assess the effect of accounting for time-resolved dose rate distributions (TR-DRD) on biological effectiveness of PDR brachytherapy as well as on the choice of the biologically equivalent HDR treatment schedule.

2. Materials and methods

2.1. Treatment planning details and dose rate calculation

The treatment plan of a clinical case of mobile tongue carcinoma was selected in this study. PDR brachytherapy was performed using 4 flexible plastic catheters and 27 dwell positions of the ^{192}Ir microSelectron PDR source (Fig. 1) [23], with source step size of 5 mm. The planning aim dose was 15 Gy delivered with a dose rate/pulse dose of 0.5 Gy/h/24 h, following surgery as well as external beam radiotherapy delivery of 45 Gy.

Two methods were developed in this work for the calculation of the dose rate. The analytical method, where the mean dose rate per pulse was considered, and the numerical method (TR-DRD), where the dose rate of each dwell position was taken into account. A reference dose rate distribution was first generated using version 6.1 of the MCNP Monte Carlo code [24]. In short, the radioactive core of the ^{192}Ir microSelectron PDR source was centered in a 15 cm radius water sphere, mimicking TG43 conditions [25]. The ^{192}Ir spectrum presented in the work of Glasgow and Dillman [26] was considered in this study, since this spectrum was used for the generation of the TG43 data for the microSelectron PDR source included in Treatment Planning Systems (TPSs) [23]. Dose was approximated by collision Kerma and $D_{w,w}$ was calculated using the *FMESH4 tally over the whole geometry ($1 \times 1 \times 1$ mm^3 resolution), along with the corresponding mass energy absorption coefficients to convert MC output data from MeV/cm^2 per starting particle to MeV/g. 8×10^8 initial photon histories were used yielding a MC Type A uncertainty of 2.5% at points most distal to the source. A separate simulation was also performed for the calculation of the source air-kerma strength to convert MC results from MeV/g per starting particle to Gy/hU.

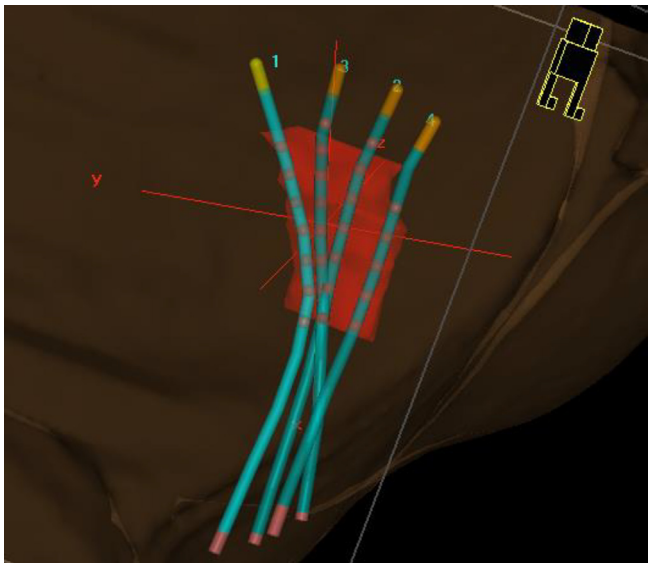

Fig. 1. A 3D reconstruction of the external patient contour (brown) and the Planning Target Volume (red) along with the 4 plastic catheters and the 27 source dwell positions.

The source dwell positions, directions and corresponding dwell times were parsed from the treatment's RT plan file using BrachyGuide, an in-house developed software for the preparation of MCNP input files from treatment plans exported in DICOM RT format [27]. The TR-DRD was calculated within the Planning Target Volume (PTV) using the MC-based reference dose rate distribution applying the appropriate translations and rotations according to each dwell position and direction of the source, respectively, using a custom routine developed in MATLAB (MathWorks, Natick, MA). This resulted to a total number of 27 dose rate distributions (equal to the number of the dwell positions used in the treatment plan) which were multiplied by the air-kerma strength included in the RT plan to convert results from Gy/hU to Gy/h. The mean dose rate was considered as the fraction of the dose distribution delivered within a pulse, per pulse duration. The dose distribution was calculated by the sum of the MC-based dose distributions of all dwell positions weighted by the corresponding source dwell times. The volume of the PTV receiving dose levels higher than 800% of the prescribed dose was excluded from the analysis of this study, since this region lies within the catheters and presents no clinical interest. The same upper dose limit is applied in TPSs employed for clinical treatment planning.

In order to evaluate the impact of TR-DRD on biological effectiveness of PDR brachytherapy in head and neck patients as well as on the prediction of the isoeffective dose of a different HDR brachytherapy treatment schedule, a formalism including frequently used clinical tools that account for the effect of dose rate was developed in this work.

2.2. Formalism

2.2.1. Cell Surviving fraction, S

The Linear-Quadratic (LQ) model [9] was considered to define the cell surviving fraction. According to this model, the surviving fraction S is given by:

$$S(D) = \exp[-\alpha D - \beta q(t) D^2 + \gamma T_{tot}] \quad (1)$$

where a and β characterize intrinsic radiosensitivity, D is the total dose, T_{tot} is the treatment duration, γ is the effective tumor-cell repopulation rate ($\gamma = \ln(2)/T_d$, for tumor-cell doubling time T_d). The effect of dose rate is represented in Eq. (1) by the dose rate function $q(t)$ [16]:

$$q(t) = \frac{\int_0^t \tau(t) h(u) du}{\int_0^t h(u) du} \quad (2)$$

In this expression,

$$\tau(t) = e^{-\mu t} \quad (3)$$

stands for the probability that a sublesion remains unrepaired t units of time after being formed, $h(t)dt$ is the pairwise probability distribution of time intervals between pairs of sublesions and $\mu = \ln 2/T_{1/2}$, where $T_{1/2}$ is the half-time of sublethal damage repair. If $I(t)$ is the dose rate at time t, it follows that:

$$h(t) \propto \int_0^\infty I(u) I(u+t) du \quad (4)$$

Taking into account the dose rate of each dwell position, Eq. (2) leads to:

$$q(t) = \frac{\sum_0^T e^{-\mu dt_i} R_i t_i R_{i+1} t_{i+1} dt_i}{\sum_0^T R_i t_i R_{i+1} t_{i+1} dt_i}, \quad (5)$$

Please cite this article in press as: Peppa V et al. Time resolved dose rate distributions in brachytherapy. Phys. Med. (2017), http://dx.doi.org/10.1016/j.ejmp.2017.04.013