Original Article

Changes in radiobiological parameters in ^{131}Cs permanent prostate implants

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Abstract

In prostate permanent implants using ^{131}Cs seeds, the prostatic edema developed during the implantation procedure, increases the separation between the seeds. This leads to a decrease in the prostate coverage and thus causes an edema induced dose reduction, which results in an increase in tumour cell surviving fraction (SF) with a corresponding decrease in tumour control probability (TCP). To investigate the impact of edema on the SF and the TCP, the expression of the SF of the linear quadratic (LQ) model was extended to account for the effects of edema using the exponential nature of edema resolution and the dose delivered to the edematous prostate. The SF and the TCP for edematous prostate implants were calculated for 31 patients who underwent real time ^{131}Cs permanent seed implantation. The dose delivered to the edematous prostate was calculated to compute the SF and the TCP for these patients for edema half lives (EHL) ranging from 4 days to 34 days and for edema of magnitudes (M_0) varying from 5 to 60% of the actual prostate volume.

A reduction in the dose delivered to the edematous prostate was found with the increase of EHL and edema magnitude which results in an increase of the SF, and corresponding decrease in the TCP. The dose reductions in ^{131}Cs implants varied from 1.1% (for EHL = 4 days and M_0 = 5%) to 32.3% (for EHL = 34 days and M_0 = 60%). These are higher than the dose reduction in ^{125}I implants, which vary from 0.3% (for EHL = 4 days and M_0 = 5%) to 17.5% (for EHL = 34 days and M_0 = 60%). As edema half life increased from 4 days to 34 days and edema magnitude increased from 5 to 60% the SF increased by 4.57 log, and the TCP decreased by 0.80. Compensation of edema induced increase in the SF and decrease in the TCP in ^{131}Cs seed implants should be carefully done by redefining seed positions with the guidance of post-needle plans. The presented model in this study can be used to estimate the SF or the TCP for pre plan or real time permanent prostate implants using day 0 post-implant CT images.

Keywords

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INTRODUCTION

Permanent brachytherapy seed implantation to treat prostate cancer is an old technique in which historically radium (^{226}Ra) and gold (^{198}Au) sources were used.[1−3] In the present era of prostate permanent seed brachytherapy, ^{125}I and ^{103}Pd seeds have been used with the help of ultrasound (US) guided transperineal technique. Recently, ^{131}Cs seeds have been implemented in many centres across USA, including UPMC Cancer Centres.[4−6] The design of ^{131}Cs seed is similar to that of ^{125}I and ^{103}Pd, but has a shorter half life of 9.7 days, and slightly higher average photon energy than ^{125}I and ^{103}Pd.[7−9] The shorter half life of ^{131}Cs can induce differences between planned and delivered doses due to prostatic edema, thus potentially impacting values of dosimetric and radiobiological quantities of interest. The present study investigates the effect of edema on radiobiological quantities, such as tumour cell surviving fraction (SF) and tumour control probability (TCP), for ^{131}Cs seed permanent prostate implants. In prostate implantation, the radioactive seeds are implanted via surgical procedure and edema develops in the prostate immediately after implantation. The edema increases the size of the prostate and consequently changes the relative distances between the radioactive seeds which alters the dosimetric and radiobiological quantities. The effects of edema on dosimetric and radiobiological quantities in ^{125}I and ^{103}Pd implants have been studied by many investigators.[10−20] Since ^{131}Cs is a relatively new radioactive source used for prostate permanent seed implants, limited number of studies have been done to investigate the effect of edema for ^{131}Cs permanent seed implants.[5,6,21−24]

In a recent study, we derived prostate volume changes after prostate brachytherapy from its original volume using US and CT images acquired at day 0, day 14 and day 28 after implant, and found that the prostate edema resolves exponentially with post-implant time.[5] Willins and Wallner,[25] and Waterman et al.[11] also observed that in ^{125}I seed permanent implants the prostatic edema decayed exponentially with post-implant time. The exponential decay of prostatic edema induces a significant amount of change in dosimetric and radiobiological quantities in ^{131}Cs implants due to its short half life of 9.7 days.[5,6] Chen et al.[22] have derived an equation to compute the edema induced dose reduction in ^{131}Cs implants with post-implant time as a function of the magnitude and half-life of the prostatic edema. In this article, the equation of the SF (and the TCP) is extended to account for the edema induced changes for non-uniform dose distribution within the prostate as a function of the magnitude and edema half life (EHL). In the calculations of the SF (and the TCP), the equation derived by Chen et al.[22] to compute edema induced dose reduction was used. The calculations of the SF are based on the volumes obtained from the CT images taken at day 0, day 14 and day 28 after the implantation. The purpose of this study was to examine the influence of edema on the surviving fraction and on the tumour control probability in the prostate tumours implanted using ^{131}Cs seeds.

METHODS AND MATERIALS

Derivation of survival fraction to account for edema effect

Nahum and Tait[26] have derived a double exponential model of the tumour control probability (TCP) for homogeneous dose distributions. This is given by

$$TCP = \exp[-NS(D)] \qquad (1)$$

where N is the initial number of clonogenic cells in tumour volume (V) and $S(D)$ is the clonogen surviving fraction at dose (D). The number N can be related to the tumour volume (V) using the relationship $N = \rho V$, where ρ is the clonogenic cell density. Equation (1) can then be written as

$$TCP = \exp[-\rho V S(D)] \qquad (2)$$

The $S(D)$ can be written as

$$S(D) = \exp[-\alpha D(t) - \beta q(t)D(t)^2 + \gamma(t - T_k)] \quad (3)$$

where α and β represent the single-track and inter-track cellular radiosensitivities. The α is associated with indirect chemical damage, which is independent of dose rate, fraction size and inter-fraction interval, although has partial reparability over a period of time. The β represents cell kill due to interactions between individual particle tracks and is therefore sensitive to fraction size, dose-rate (if small enough), and inter-fraction interval. The γ is the proliferation constant and is given by $\gamma = 0.693/\alpha T_p$, where T_p is the potential doubling time of tumour cells, and t is the irradiation time of the implant in days, with an account of proliferation kickoff time (T_k). The $q(t)$ is a dose protraction factor to account for the sublethal damage repair[27] given by

$$q(t) = [2(\lambda t)^2 / \{(\mu t)^2(1 - \lambda^2/\mu^2)(1 - e^{-\lambda t})^2\}][\{e^{-(\lambda+\mu)t}\} \\ + \mu t(1 - e^{-2\lambda t})/(2\lambda t) - (1 + e^{-2\lambda t})/2] \quad (4)$$

where λ and μ are the decay constant of radioactive source and repair constant of sublethal damage, respectively. These can be defined by $\lambda = \ln(2)/t_{1/2}$ and $\mu = \ln(2)/t_{rep}$, where $t_{1/2}$ and t_{rep} are the half-life of radionuclide used in the implant and half-repair time of sublethal damage, respectively.

In permanent implants, the dose rate at a point 'P' by decaying radioactive sources is a simple exponential function of time

$$R_p(t) = R_p(0)\exp(-\lambda t) \quad (5)$$

and the total dose delivered to point 'P' is given by

$$D_p = R_p(0) \int_0^\infty \exp(-\lambda t)dt \quad (6)$$

where $R_p(0)$ is the initial dose rate at point 'P' in the tumour.

Effective treatment time t_{eff}

Theoretically, the radiation dose is delivered throughout the life time of the patient, i.e., the treatment time 't' approaches to infinity. Hence, the term $\gamma(t - T_k)$ in equation (3) becomes unrealistic. Antipas et al.[28] had shown that in permanent implants the biologically effective dose rate delivered to the tumour cells falls with time due to radionuclide decay and extends to the point at which the biological dose rate falls to the critical dose rate, where it is equal to or less than the tumour cell repopulation. Below this critical dose rate the delivered dose is a waste, because instantaneous tumour cell proliferation rate exceeds the rate of cell killing. The biological dose rate in ^{131}Cs implants approaches the critical dose rate in a shorter period of time due to the short half life of the source. The time interval between the implantation time (day 0) and the time at which the dose rate reaches this critical value is called the effective treatment time (t_{eff}).[28] The t_{eff} provides a measure of the time over which tumour cell kill is ensured and is given by

$$t_{eff} = -(1/\lambda)\ln[0.693/(\alpha R_p(0)T_p)] \quad (7)$$

where T_p, is the tumour cell potential doubling time.

By truncating equation (6), the dose delivered at point 'P' in time 't_{eff}' can be given by

$$D_p = R_p(0) \int_0^{t_{eff}} \exp(-\lambda t)dt \quad (8)$$

It is clear from the literature that the potential doubling times (T_p) of the prostatic tumour cells are very long.[39–32] Different investigators have different views about the use of kick-off time (T_k) in the time factor of the linear quadratic (LQ) model for radiobiological interpretations of the treatment of prostate cancer.[18,33–35] One group of the investigators[33] suggests that the proliferation of the prostate tumour cells speeds up as soon as the tumour shrinks, which can be as early as two or three delivered fractions. Cells in regions of poor nutrition would then become closer to the capillary supplies, so that the growth fraction could increase. Many other researchers have discussed the impact of tumour repopulation on the treatment effectiveness for prostate cancer[36–39] and have ignored the "kick-off" time T_k i.e., take $T_k = 0$ as a common assumption. On the other hand, a second group of investigators[34–35] argued that the values of T_k estimated from clinical data for head-and-neck tumours varied from 21 to 35 days,[40,41] which is six to seven times longer than with short pretreatment median values of T_p of 3.5 days[42] or 4.7 days.[43] In another publication, an author of this group,[44] iterated that the value of T_k depends on the pretreatment cell kinetics that determine how rapidly cells are lost from the tumour or tissue, so that spontaneous cell loss can fall close to zero during the later period of treatment. The median T_p of prostate tumours is 42 days[32] which is 10 times the value of head-and-neck tumours. Therefore, it is likely that the value of T_k for prostate be 10 times that of T_k for head-and-neck tumours ranging from 210−350 days.[34] The scope of this debate is beyond the limits of this article. However, for calculation purposes, we had adopted the arguments of the second group and ignored the time correction factor while calculating the SF and the TCP, considering the fact that even if the T_p of the prostate is as short as 15 days,[32] the T_k would be 90−105 days (6 to 7 times of T_p), which is well in excess of the effective treatment time of $_{131}$Cs implants of 61 days. Hence, the factor accounting for proliferation correction in equation (3) can be neglected yielding

$$S(D) = \exp[-\alpha D(t) - \beta q(t)D(t)^2] \quad (9)$$

Using equation (8) into equation (9), $S(D)$ at 'P' can be written as

$$S_p(D) = \exp[-\alpha R_p(0) \int_0^{t_{eff}} \exp(-\lambda t)dt$$

$$-\beta q(t_{eff})\{R_p(0) \int_0^{t_{eff}} \exp(-\lambda t)dt\}^2] \quad (10)$$

Edema-induced dose reduction

In a permanent prostate implant, if there is no implant induced edema observed, the instantaneous dose rate at point 'P' and at time 't' can be given by equation (5), which is a simple exponential function of time. With implant induced prostatic edema, the prostate volume and source locations become function of time and thus instantaneous dose rate at point 'P' will not be a simple exponential function of time but is given by the following relation[45] which accounts for an edema - induced dose reduction at time 't'

$$R_p(t) = R_p(0)[\exp(-\lambda t)/[1 + M_0\exp(-\lambda_e t)]^{\tau/3}] \quad (11)$$

and the instantaneous dose at point 'P' is given by

$$D_{p,int}(t) = D_p(0)[\exp(-\lambda t)/[1 + M_0\exp(-\lambda_e t)]^{\tau/3}] \quad (12)$$

where $D_{p,int}(t) = R_p(t)/\lambda$ and $D_p(0) = R_p(0)/\lambda$ are doses at times 0 and t, respectively. M_0 is the initial magnitude of the edema (is defined by $M_0 = (V_0 − V_p)/V_p$, where V_p and V_0 are the pre-implant volume and post-implant volume at day 0, respectively), λ_e is the edema decay constant (defined by $\lambda_e = \ln(2)/t_e$, where t_e is the edema half life (EHL)), and the exponent τ was determined to have a value of

2.20 by Chen et al.[46] for the Model CS-1 $_{131}$Cs sources.

By integrating equation (11), the dose delivered at point 'P' in time 't'is given by

$$D_p(t) = R_p(0) \int_0^t [\exp(-\lambda t)/\{1 + M_0\exp(-\lambda_e t)\}^{\tau/3}] \, dt \qquad (13)$$

Equation (1) or equation (2) gives the TCP when the dose is spatially uniform throughout the target volume. However, uniform dose distributions are not achievable in permanent implants. Therefore, it is difficult to deduce

$$TCP_i = \exp[-\rho_i V_i S_i(D)] \qquad (15)$$

where ρ_i, V_i and $S_i(D)$ are the initial clonogenic cell density, voxel volume and surviving fraction of tumour cells in the ith voxel. In the calculations of $S_i(D)$, it was assumed that the ith voxel received an average dose rate of $R_i(0)$ at day 0. With help of equation (13), the $S_i(D)$ for i^{th} voxel can be written as

$$S_i(D) = \exp[-\alpha R_i(0) \int_0^t [\exp(-\lambda_e t)/\{1 + M_0\exp(-\lambda_e t\}^{\tau/3}] dt$$
$$- \beta q(t)\{R_i(0) \int_0^t \exp[(-\lambda t)/\{1 + M_0\exp(-\lambda_e t)\}^{\tau/3}] dt^2] \qquad (16)$$

the TCP directly from non-uniform dose distributions using above said equations. Niemierko[47] and Sanchez-Nieto and Nahum[48] and looked into the problem and suggested possible solutions to deduce the outcome in terms of delta-TCP and equivalent uniform dose (EUD), respectively. Webb and Nahum[49] modified the TCP model for non-uniform clonogenic cell density and non-uniform dose distributions. In their derivation the tumour volume was divided into n number of infinitesimally small voxels and the TCP for such a system can be written as

$$TCP = TCP_1 \times TCP_2 \times TCP_3$$
$$\times \cdots \times TCP_n, = \sum_{i-1}^n TCP_i \qquad (14)$$

where n is the number of voxels, TCP_1, TCP_2, ...,TCP_n are the TCPs corresponding to the voxels 1, 2, ...,n. TCP_i is the tumour control probability of cells in the ith voxel and can be written as

Equation (14), may now be written as

$$TCP = \Pi_{i-1}^n \exp[-\rho_i V_i S_i(D)]$$
$$= \exp[-\sum_{i-1}^n \rho_i V_i S_i(D)] \qquad (17)$$

If it is assumed that the clonogenic cell density ρ is uniform throughout the tumour volume then equation (17) may have the form given by

$$TCP = \exp[-\sum_{i-1}^n \rho V_i S_i(D)] \qquad (18)$$

By comparing equation (2) and equation (18), $S(D)$ can be written as

$$S(D) = (1/V) \sum_{i-1}^n V_i S_i(D)] \qquad (19)$$

This is the same equation as discussed in earlier articles.[18,19]

Many investigators have modeled resolution of post-implant edema.[5,11,45,50] Mathematically, the volume of prostate at time 't' with edema resolution can be expressed by

$$V_i(t) = V_{pi}[1 + M_0\exp(-\lambda_e t)] \qquad (20)$$

where $V_i(t)$ and V_{pi} are the volumes of the ith voxel at time 't' with edema and at the time before implant (pre-implant volume).

By replacing V_i of equation (19) with $V_i(t)$ of equation (20), the S(D) can be written as

$$SD = (1/V) \sum_{i-1}^{n} [V_{pi}\{1 + M_0\exp(-\lambda_e t)\}S_i(D)] \qquad (21)$$

where V is the prostate volume with edema at day 0. In above equations of TCP the prostate volume was used with edema at day 0. It is clear that the total number of clonogenic cells in the prostate remain constant irrespective of the increase of the volume due to increase in the amount of edema. Hence, the TCP for pre-implant prostate volume can be written as

$$TCP = \exp[-\rho V_p S(D)] \qquad (22)$$

where V_p and ρ are the prostate volume and clonogenic cell density before implant procedure, respectively.

Radiobiological parameters

A set of radiobiological parameters is required for the S(D), TCP and t_{eff} calculations. The values of these parameters were taken from previously published reports and are as follow: $\alpha = 0.15$ Gy^{-1}, $\beta = 0.05$ Gy^{-2}, $\alpha/\beta = 3.0$ Gy, $T_p = 42$ days, $\mu = 61.6$ d^{-1} (i.e., $\mu = \ln(2)/t_{rep}$, here repair half life $t_{rep} = 0.27$ h , $\rho = 1 \times 10^6$ (Nath et al. 2009),[51] and edema decay constant

$\lambda_e = 0.0713$ d^{-1} (i.e., $\lambda_e = \ln(2)/t_{1/2\_edema}$, where $t_{1/2\_edema}$ is the half life of edema decay with a value of 9.72 days).[5]

Patients

Thirty-one patients of prostate cancer, who received a prescribed dose of 115 Gy to the prostate by permanent ^{131}Cs seed implants, were analysed in this study. Details of the implant procedure, technique and seed loading were discussed in previous studies.[4,5] Briefly, for each patient the transrectal ultrasound (US) was used to obtain images of the prostate prior to the implantation, as well as pre- and post-needle prior to ^{131}Cs seed implantation. The positioning of the needles and seeds in the needles were defined with the guidance of pre- and post-needle US images. The post-implant CT images were also obtained on the day of the implant (day 0) and at day 14 and day 28. Contouring of the prostate on US and CT images, and seed localisation and analysis of the data were performed by the same individual for each patient. The seed locations were generated for US images of pre-needle and pre-seed (but post needle) prostate volumes, and for the CT images of post-implant prostate volumes at days 0, 14 and 28.

RESULTS AND DISCUSSIONS

It was reported in our previous study[5] that for all 31 patients, the initial magnitude of edema (M_0) developed immediately after the implantation on day 0 and was determined by comparing the volumes obtained for pre-needle US and post-needle US images, and pre-needle US images and post-seed implant CT images at day 0. The initial M_0 was found to be 22.76 ± 5.99 % (ranged from 5.15 to 84.47 %) for pre-needle US and post-needle US images, and 19.81 ± 4.94 % (ranged from 5.36 to 63.23 %) for pre-needle US images and post-seed implant CT images at day 0. The Student's t-test indicates that there were no statistically significant differences between the magnitude of the edema or between the volumes obtained from post-needle US versus post-seed implant CT images at day 0 ($p > 0.05$, Student's

t-test). The magnitude of post-implant edema was also determined by comparing the volumes obtained for pre-needle US and post-seed implant CT images at day 14 and 28. These values of M_0 were fitted to equation (20) using the method of least square fit to get EHL for these patients, and was found to range from 3.64 days to 34.48 days with a mean of 9.72 $\pm$ 8.31 days (mean $\pm$ 1SD). In another study, the EHL was reported to vary from 4 days to 30 days.[11]

The increased use of ^{125}I, ^{103}Pd and more recently ^{131}Cs for permanent prostate seed the implants poses interesting radiobiological challenges, because during the long period of dose delivery, significant tumour cell repopulation may occur even in slow growing tumours. So, to account for this the t_{eff} for ^{131}Cs prostate implants was calculated using equation (7) with an assumption that the prescribed dose of 115 Gy is delivered uniformly to the prostate. The value of t_{eff} for the prescribed dose was found to be 60.36 days, which is very close to the 61 days recommended in AAPM TG -137 report[51] for ^{131}Cs prostate implants. Kehwar et al.[6] have discussed that in reality the dose distribution within the prostate in permanent implants will never be uniform, hence each of its voxels will have its own effective treatment time. However, it is not clear which value of t_{eff} should be used in the calculations of SF or TCP. Should it be the t_{eff} of each voxel, or an average value of t_{eff} of all voxels within the prostate based on the doses to these voxels, or the value calculated for the prescribed dose? We suggest that the use of t_{eff} calculated for the prescribed dose is appropriate due to the fact that most of the tumour cells will receive adequate dose during this period of time. An average value of t_{eff} of all voxels within the prostate would also be an appropriate option but will increase the complexity in calculation process to find out a separate t_{eff} for each voxel to get an average. The total dose, in absence of edema, delivered during t_{eff} is 113.46 Gy, which is 1.33 % lower than the prescribed dose.

Figure 1 shows the relationship between mean surviving fractions and post-implant time. In the figure, the line 'a' represents the

SF for the prescribed dose calculated using equation (9), where it was assumed that the prescribed dose is uniformly distributed throughout the prostate volume and the effects of edema and cell proliferation were negligible. The line 'b' represents for the SF calculated using equation (21) taking into account the initial CT volumes obtained at day 0 and magnitude of the edema with half life of 9.72 days, and the line 'c' represents the SF calculated, using equation (9) and (19), for the seed locations generated for individual post-implant CT volumes obtained at days 0, 14 and 28. The values of SF for delivered prescribed dose have single point data, while the SF calculated using either equation (21) or for individual post-implant CT volumes have a range of data for all 31 patients at 14 and 28 days. Hence, to compare the SFs calculated for prescribed dose and for edema decay using equation (21), and for prescribed dose and for individual CT volumes, the Z − test was applied. On the other hand, when comparisons were made for the SFs calculated using equation (21) and for individual post-implant CT volumes, the Student *t*-test was used. These tests indicate that there were statistically significant differences in the SFs at days 14 and 28 for (i) delivered prescribed dose and that calculated using equation (21) ($p = 0.02$ and 0.01, respectively, Z-test), and (ii) prescribed dose and that calculated using
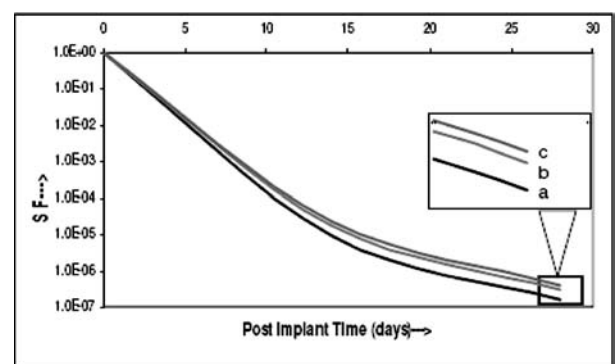

Figure 1. Changes in SF with post-implant time. The line 'a' represents SF for prescription dose without edema correction, line 'b' represents for calculated SF using equation (21) for day 0 CT images and line 'c' for individual CT images obtained at day 0, day 14 and day 28.
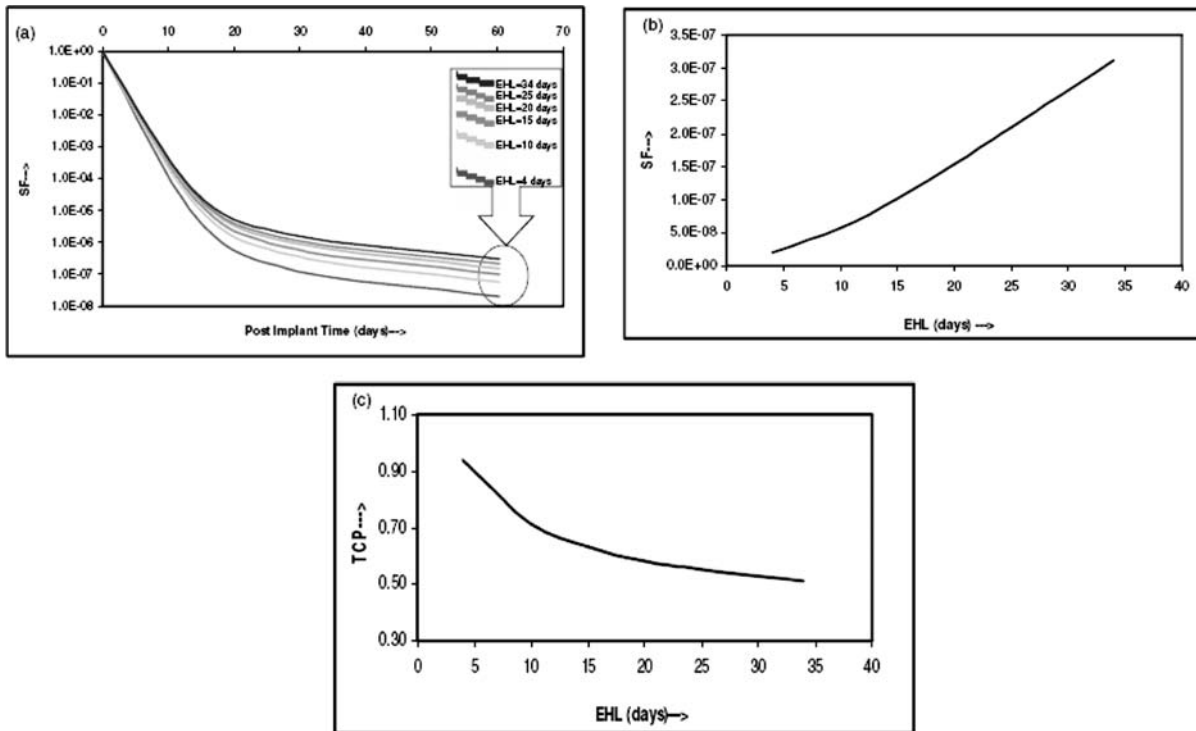
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Figure 2. Change in the SF with post-implant time: (a) plot of SF versus post-implant time for different EHL, (b) plot of SF calculated at t_{eff} versus EHL ranging from 4 days to 34 days, and (c) plot of TCP with EHL ranging from 4 days to 34 days corresponding to the SF of (b).

individual post-implant CT volumes ($p = 0.02$ and 0.03, respectively, Z-test). However, no statistically significant differences were found between the SFs calculated using equation (21) and individual post-implant CT volumes ($p = 0.11$ and 0.16, respectively, Student's t-test), hence it is clear that equation (21) calculates the SF fairly accurate. The plots in Figure 1 revealed that the SF calculated using prescribed dose without edema resolution correction overestimates the results than that of actual implants.

The TCP values calculated using equation (22) and individual post-implant CT volumes obtained at day 28 have no statistically significant differences ($P > 0.05$). The calculated values of TCP using equation (22) for the dose delivered in t_{eff}, were found to range from 0.55 to 0.99 with a mean and SD of 0.76 ± 0.14. The TCP model described in equation (22) is unique, in that it accounts for the resolution of edema and its magnitude, and a heterogeneous dose distribution throughout the prostate.

The patients with low values of TCP represent the poor quality of the implant. Although extremely low TCP values may not be clinically relevant, TCP calculations could be used to identify patients with suboptimal implants who require careful monitoring.

It was mentioned earlier that EHLs calculated for these patients were found to vary from 3.64 days to 34.48 days.[5] Hence, to estimate the effect of different EHL on the SF and the TCP, calculations were performed using equations (21) and (22) for EHLs of 4, 10, 15, 20, 25, and 34 days for all patients.

Figure 2(a) shows the plots of the mean values of the SF versus post-implant time for edema half lives of 4, 10, 15, 20, 25, and 34 days. The curves shown in Figure 2(a) were calculated using equation (21) for above mentioned values of EHLs for each patient, and show that the mean SF increased steadily with increasing EHL. Figure 2(b) shows a plot of
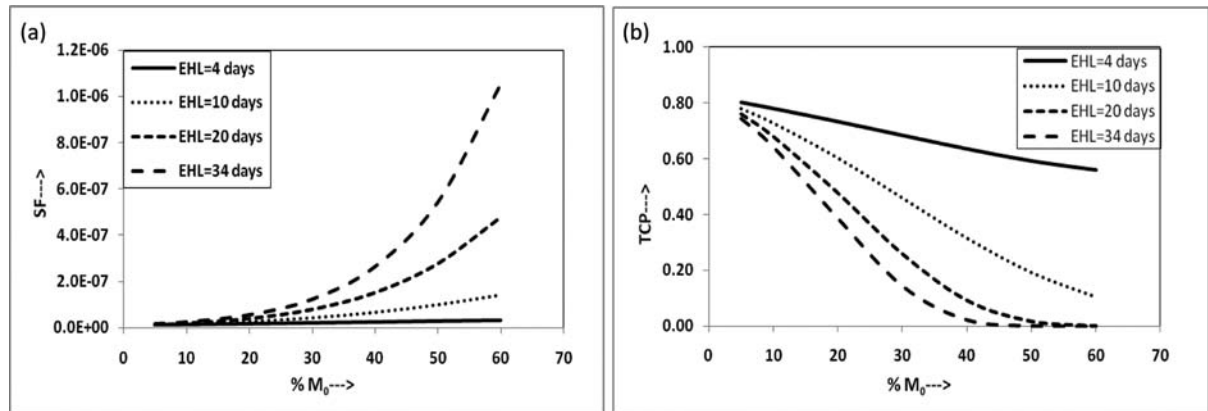
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Figure 3. Schematic demonstration of role of EHL on SF and TCP calculated post-implant time at T_{eff}. (a) plots of SF as a function of magnitude of edema at different EHL, and (b) plots of TCP as a function of magnitude of edema at different EHL.

the dependence of SF on EHL, calculated at T_{eff}. It can be seen from the figure that as EHL is increased from 4 days to 34 days, the mean SF increased by 2.71 log. The changes in TCP resulting from the changes in the SF (shown in Figure 2(b)) are shown in Figure 2(c), which shows that as the EHL is increased from 4 days to 34 days, the mean TCP decreases from 0.94 to 0.51.

As mentioned earlier, the values of M_0 obtained from pre-needle US images and post-seed implant CT images at day 0 were found to range from 5.36 to 63.23 %. Hence, to predict the effect for different amount of edema, calculations of the SF and the TCP were done for edema magnitudes of 5%, 10%, 20%, 40% and 60%. The pre-implant volumes were calculated by reducing the day 0 CT volumes for corresponding edema size. In the calculations of the TCP, the same number of clonogenic cells were used as those calculated for real pre-implant volumes. The plots of the SF versus M_0, and the TCP versus M_0 are shown in Figures 3(a) and (b) for EHL ranging from 4 days to 34 days. Figures 3(a) and (b) illustrate that the SF increases and the TCP decreases steadily with increasing the values of EHL and M_0. At EHLs of 4 days, 10 days, 20 days and 34 days, as M_0 increases from 5 to 60% the SF increases by 1.04 log, 2.44 log, 3.54 log and 4.26 log, respectively, and the TCP decreases by 0.24, 0.67, 0.76

and 0.74, respectively. Similarly, at M_0 of 5%, 10%, 20%, 40% and 60%, as EHL increased from 4 days to 34 days, the SF increased from −18.34 log to −18.02 log, −18.21 log to −17.59 log, −17.97 log to −16.74 log, −17.56 log to −15.15 log, and −17.29 log to −13.77 log, respectively, and the TCP decreased from 0.80 to 0.74, 0.78 to 0.64, 0.73 to 0.39, 0.64 to 0.02, and 0.56 to 0.00, respectively. The change in the SF and TCP is more dramatic when the values of EHL and M_0 are greater than 10 days and 30%, respectively, and is more pronounced for extreme values of EHL and M_0, such as 34 days and 60%, respectively.

Similar results were reported in a study used by Yue et al.[15] for [103]Pd seed implant, as the SF increased from 1.68 log to 4.73 log when values of EHL were increased from 4 days to 30 days for a fixed edema magnitude of 50%, and by 4.75 log when the edema magnitude was increased from 0 to 95% for a fixed EHL of 10 days. In the same study, it was reported that in an ^{125}I permanent seed implant, the SF increased from 0.46 log to 2.29 log when the values of EHL were increased from 4 days to 30 days for a fixed edema magnitude of 50%, and by 1.68 log when the edema magnitude was increased from 0 to 95% for a fixed EHL of 10 days. In the study by Yue et al.,[15] the SF was calculated using $\alpha/\beta = 10$ Gy. The authors mentioned that the general pattern of
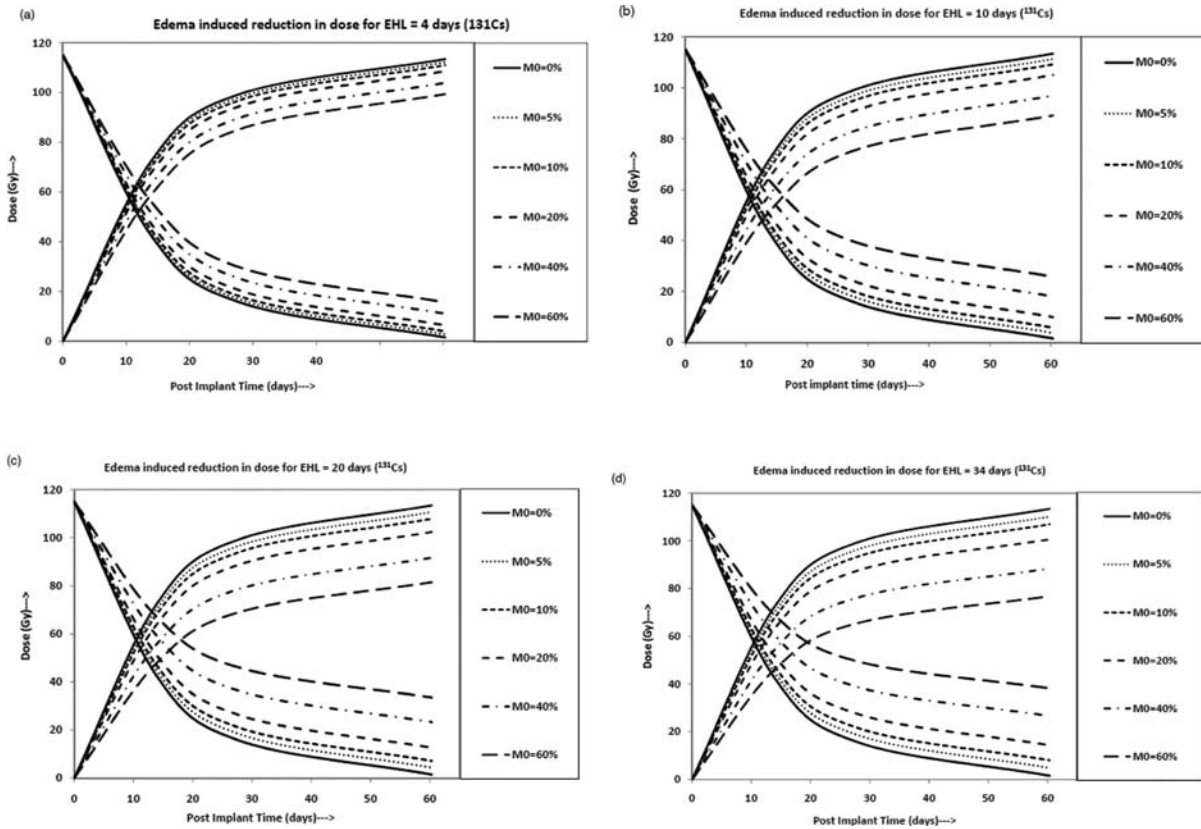
Figure 4. Edema induced dose reduction in ^{131}Cs implants as a function of post-implant time at different edema magnitude. (a) EHL of 4 days, (b) EHL of 10 days, (c) EHL of 20 days, and (d) EHL of 34 days.

effects caused by edema are very similar for α/β = 10 Gy and α/β = 2 Gy, and found that the SF decreases with the decrease of the α/β ratio. It was also reported in this study that the edema-induced increase in the SF is independent of tumour cell proliferation rates; it was found to be a function of EHL, amount of edema magnitude, and characteristics of the radioactive source used in the implants.

Figures 4(a)−(d) and Figures 5(a)−(d) illustrate the edema-induced reduction in dose for ^{131}Cs and ^{125}I prostate permanent implants as a function of the edema magnitude and edema half lives, respectively. In these figures, two sets of curves are shown. One is for delivered dose and the other for instantaneous dose with time. The curves which show increasing trend with time represent the delivered dose and the curves with decreasing trend represent the

instantaneous dose with implant time. The edema-induced dose reduction calculations were done using the values of τ of 2.20 for the Model CS-1 ^{131}Cs sources and 2.35 for the Model 6711 ^{125}I sources[51] for prescription doses of 115 Gy and 145 Gy, respectively. The values of T_{eff} used for these calculations are 60.36 days and 236 days, respectively, for ^{131}Cs and ^{125}I permanent implants.

Figures 4(a)−(d) and Figures 5(a)−(d) show that the dose reductions in ^{131}Cs implants varied from 1.1% (for EHL = 4 days and M_0 = 5%) to 32.3% (for EHL = 34 days and M_0 = 60%). These values are higher than the corresponding dose reduction for ^{125}I implants, shown in Figures 5(a)−(d), which are found to vary from 0.3% (for EHL = 4 days and M_0 = 5%) to 17.5% (for EHL = 34 days and M_0 = 60%). The dose reductions in ^{131}Cs and
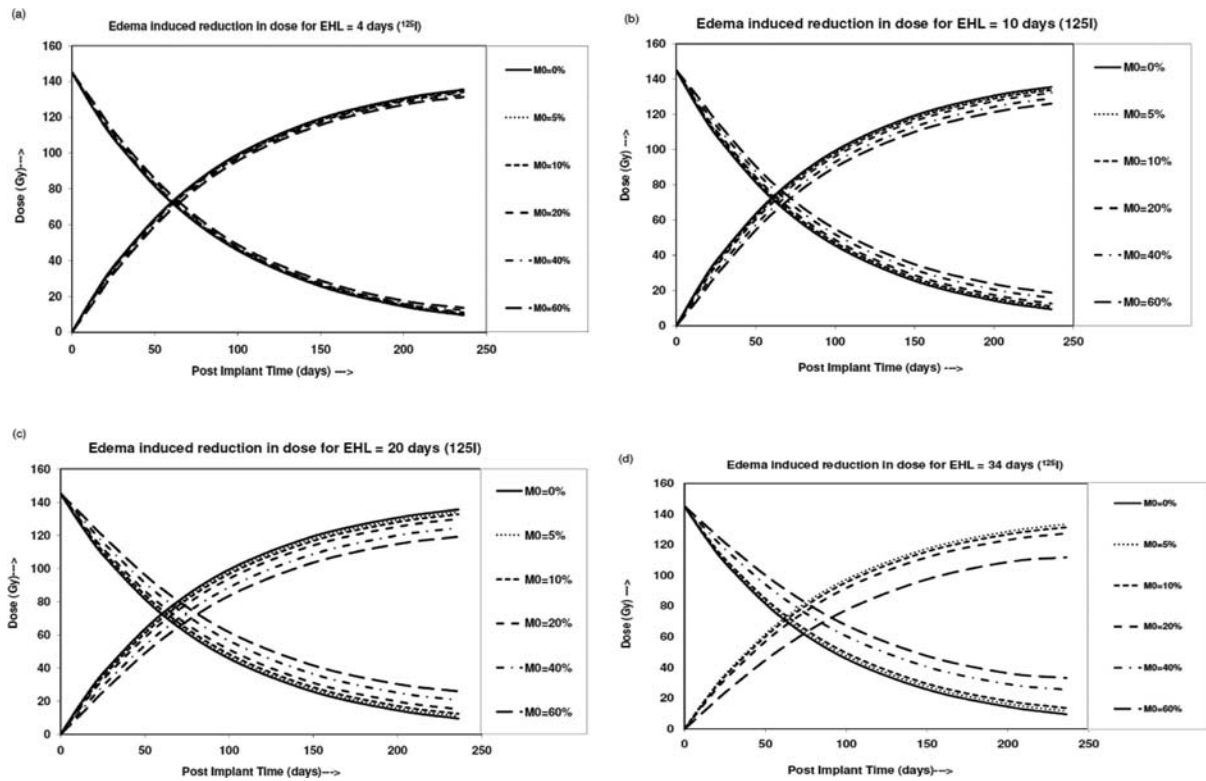
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Figure 5. Edema induced dose reduction in ^{125}I implants as a function of post-implant time at different edema magnitude. (a) EHL of 4 days, (b) EHL of 10 days, (c) EHL of 20 days, and (d) EHL of 34 days.

Table 1. *Percentage dose reduction for different edema magnitude with edema half lives.*

EHL (days)	Mo 5%		10%		20%		40%		60%	
	^{131}Cs	^{125}I	^{131}Cs	^{125}I	^{131}Cs	^{125}I	^{131}Cs	^{125}I	^{131}Cs	^{125}I
4	1.08%	0.26%	2.15%	0.52%	4.27%	1.03%	8.41%	2.04%	12.41%	3.03%
10	1.88%	0.59%	3.74%	1.19%	7.41%	2.36%	14.55%	4.67%	21.42%	6.93%
20	2.48%	1.04%	4.95%	2.08%	9.79%	4.13%	19.18%	8.17%	28.17%	12.10%
34	2.86%	1.51%	5.70%	3.01%	11.27%	5.98%	22.03%	11.79%	32.29%	17.45%

^{125}I implants as a function of EHL and M_0 are listed in Table 1.

It is seen from both sets of curves and Table 1 that the window of dose reduction increases with increasing M_0, and found to be more pronounced in ^{131}Cs permanent implants compared to the ^{125}I implants and becomes worse for the extreme combination of EHL of 34 days and M_0 of 60%.

Chen et al.[22] reported that the edema-induced dose reduction in preplanned ^{131}Cs implants could exceed 10% of prescription dose with moderate or large edemas. In our study, we did not compute edema-induced dose reduction in pre-planned implants, but calculated the dose reduction in real time implants with the resolution of the edema with post-implant time and found that for an average edema magnitude of 20%, as the EHL is

increased from 4 days to 34 days, the dose reduction increased from 4.27 to 11.27% in ^{131}Cs, and 1.03 to 5.98% in ^{125}I implants. In both studies it can be seen that the edema-induced dose reduction is a critical issue and must be addressed to compensate for this effect. In pre-planned ^{131}Cs implants, Chen et al.[22] suggested that to compensate 5%, 10%, 15%, 20%, or 25% edema-induced dose reduction an external beam radiotherapy dose of 2 Gy, 8 Gy, 12 Gy, 14 Gy, or 18 Gy in 1, 4, 6, 7, or 9 fractions, respectively, with 2 Gy per fraction could be delivered. In real time implants, this compensation should be done by redefining the seed positions.

Results of the present study show that the prostatic edema causes significant changes in the SF and the TCP due to drastic edema induced dose reduction in ^{131}Cs implants because of the shorter half life of the source. However, it would not be appropriate to conclude that ^{131}Cs prostate seed implants are inferior to ^{125}I prostate seed implants. The effect of edema on the SF and the TCP can be minimised by redefining seed positions in real time implantation with the guidance of post-needle plans.

CONCLUSIONS

In this study, the impact of edema and dose non-uniformity on SF and TCP has been discussed. The exponential decaying nature of the edema in prostate implants has been incorporated into the SF equation of the linear quadratic model. The model calculates reasonably accurate values of the SF and the TCP with no statistically significant differences ($p > 0.05$) compared to that calculated for individual post-implant CT images obtained at day 0, day 14 and day 28.

Prostatic edema in ^{131}Cs implants may cause significant increase in the SF and consequently decrease in the TCP due to the short half life of radioactive source. The short half life of ^{131}Cs seeds causes drastic edema-induced dose reduction, in the implants, because approximately 80% of the prescribed dose is delivered during first 3 weeks of the implant. As edema magnitude becomes larger and decays more

slowly, the dose reduction is more pronounced and consequently more tumour cells survive the treatment of ^{131}Cs seed implants. If this increase in the SF is not compensated for, it may lead to poor local control of these patients. Since the magnitude and resolution time of edema are two major unpredictable factors in the implants, it is difficult to compensate these factors in the implants using pre-plans. The only way to compensate is using real time implants by properly defining the seed positions with the guidance of post-needle plans, because the edema magnitude of an implant is known by that time.

References

1. Pasteau O, Degrais P. The radium treatment of cancer of the prostate. Arch Roentgen Ray 1914; 18:396−410.

2. Barringer BS. Radium in the treatment of carcinoma of the bladder and prostate. JAMA 1917; 68:1227−1230.

3. Flocks RH, Kerr HD, Elkins HB, Culp D. Treatment of carcinoma of the prostate by interstitial radiation with radio-active gold (Au 198): a preliminary report. J Urol 1952; 68:510−522.

4. Smith RP, Beriwal S, Komanduri K, Gibbons E, Benoit R. Planning based on postneedle volume with early dosimetric assessment is beneficial for Cesium-131 permanent prostate seed implantation. Brachytherapy 2008; 7:237−241.

5. Kehwar TS, Jones HA, Huq MS, Beriwal S, Benoit RM, Smith RP. Effect of edema associated with 131Cs prostate permanent seed implants on dosimetric quality indices. Med Phys 2009; 36:3536−3542.

6. Kehwar TS, Jones HA, Huq MS, Smith RP. Influence of prostatic edema on 131Cs permanent prostate seed implants: a dosimetric and radiobiological study. Int J Radiat Oncol Biol Phys 2011; 80:621−627.

7. Henschke UK, Lawrence DC. Cesium-131 seeds for permanent implants. Radiology 1965; 85:1117−1119.

8. Murphy MK, Piper RK, Greenwood LR, Mitch MG, Lamperti PJ, Seltzer SM, Bales MJ, Phillips MH. Evaluation of the new cesium-131 seed for use in low-energy x-ray brachytherapy. Med Phys 2004; 31:1529−1538.

9. Rivard MJ. Brachytherapy dosimetry parameters calculated for 131Cs source. Med Phys 2007; 34(2): 75−762.

10. Waterman FM, Yue N, Reisinger S, Dicker A, Corn BW. Effect of edema on the post-implant dosimetry of an I-125 prostate implant: a case study. Int J Radiat Oncol Biol Phys 1997; 38:335−339.

11. Waterman FM, Yue N, Corn BW, Dicker AP. Edema associated with I-125 or Pd-103 prostate brachytherapy

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and its impact on post-implant dosimetry: an analysis based on serial CT acquisition. Int J Radiat Oncol Biol Phys 1998; 41:1069−1077.

12. Narayana V, Roberson PL, Pu AT, Sandler H, Winfield RH, McLaughlin PW. Impact of differences in ultrasound and computed tomography volumes on treatment planning of permanent prostate implants. Int J Radiat Oncol Biol Phys 1997; 37:1181−1185.

13. Merrick GS, Butler WM, Dorsey AT, Walbert HL. Influence of timing on the dosimetric analysis of transperineal ultrasound-guided, prostatic conformal brachytherapy. Radiat Oncol Investig 1998; 6:182−190.

14. Yue N, Dicker AP, Nath R, Waterman FM. The impact of edema on planning 125I and 103Pd prostate implants. Med Phys 1999; 26:763−767.

15. Yue N, Chen Z, Nath R. Edema-induced increase in tumour cell survival for 125I and 103Pd prostate permanent seed implants−a bio-mathematical model. Phys Med Biol 2002; 47:1185−1204.

16. Yue N, Mori J, Nath R, Heron DE, Huq MS. External beam radiotherapy boosts to reduce the impact caused by edema in prostate permanent seed implants. Phys Med Biol 2006; 51:2267−2277.

17. Dogan N, Mohideen N, Glasgow GP, Keys K, Flanigan RC. Effect of prostatic edema on CT-based postimplant dosimetry. Int J Radiat Oncol Biol Phys 2002; 53:483−489.

18. Li XA, Wang JZ, Stewart RD, DiBiase SJ. Dose escalation in permanent brachytherapy for prostate cancer: dosimetric and biological considerations. Phys Med Biol 2003; 48:2753−2765.

19. Wang JZ, Mayr NA, Nag S, Montebello J, Gupta N, Samsami N, Kanellitsas C. Effect of edema, relative biological effectiveness, and dose heterogeneity on prostate brachytherapy. Med Phys 2006; 33:1025−1032.

20. Butler WM, Stewart RR, Merrick GS. A detailed radiobiological and dosimetric analysis of biochemical outcomes in a case-control study of permanent prostate brachytherapy patients. Med Phys 2009; 36:776−787.

21. Bice WS, Prestidge BR, Kurtzman SM, Beriwal S, Moran BJ, Patel RR, Rivard MJ; Cesium Advisory Group. Recommendations for permanent prostate brachytherapy with (131)Cs: a consensus report from the Cesium Advisory Group. Brachytherapy 2008; 7:290−296.

22. Chen ZJ, Deng J, Roberts K, Nath R. On the need to compensate for edema-induced dose reductions in preplanned (131)Cs prostate brachytherapy. Int J Radiat Oncol Biol Phys 2008; 70:303−310.

23. Sahgal A, Jabbari S, Chen J, Pickett B, Roach M 3rd, Weinberg V, Hsu IC, Pouliot J. Comparison of dosimetric and biologic effective dose parameters for prostate and urethra using 131 Cs and 125 I for prostate permanent implant brachytherapy. Int J Radiat Oncol Biol Phys 2008; 72:247−254.

24. Kehwar TS. Use of Cesium-131 radioactive seeds in prostate permanent implants. J Med Phys 2009; 34:191−193.

25. Willins J, Wallner K. CT-based dosimetry for transperineal I-125 prostate brachytherapy. Int J Radiat Oncol Biol Phys 1997; 39:347−353.

26. Nahum AE, Tait DM. Maximising control by customized dose prescription for melvic tumours. Advanced Radiation Therapy: Tumour Response Monitoring and Treatment Planning ed A Breit (Heidelberg: Springer) 1992; 425−431.

27. Zaider M, Minerbo GN. Tumour control probability: a formulation applicable to any temporal protocol of dose delivery. Phys Med Biol 2000; 45:279−293.

28. Antipas V, Dale RG, Coles IP. A theoretical investigation into the role of tumour radiosensitivity, clonogen repopulation, tumour shrinkage and radionuclide RBE in permanent brachytherapy implants of 125I and 103Pd. Phys Med Biol 2001; 46:2557−2569.

29. Schmid HP, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer 1993; 71:2031−2040.

30. Hanks GE, Lee WR, Corn B, Schultheiss TE. Response to ''only 20% of irradiated prostate cancer patients are cured and the remainder may be made worse. Int J Radiat Oncol Biol Phys 1994; 30:217−218.

31. Haustermans KM, Hofland I, Van Poppel H, Oyen R, Van de Voorde W, Begg AC, Fowler JF. Cell kinetic measurements in prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37:1067−1070.

32. Hausterman K, Fowler JF. A comment on proliferation rates in human prostate cancer. Int J Radiat Oncol Biol Phys 2000; 48:303.

33. Wang JZ, Li XA, Yu CX, DiBiase SJ. The low alpha/beta ratio for prostate cancer: what does the clinical outcome of HDR brachytherapy tell us? Int J Radiat Oncol Biol Phys 2003; 57:1101−1108.

34. Fowler JF, Ritter MA, Fenwick JD, Chappell RJ. How low is the alpha/beta ratio for prostate cancer? In regard to Wang et al., IJROBP 2003;55:194−203. Int J Radiat Oncol Biol Phys 2003; 57:593−5; author reply 595.

35. Ritter M. Rationale, conduct, and outcome using hypofractionated radiotherapy in prostate cancer. Semin Radiat Oncol 2008; 18:249−256.

36. Ling CC, Roy J, Sahoo N, Wallner K, Anderson L. Quantifying the effect of dose inhomogeneity in brachytherapy: application to permanent prostatic implant with 125I seeds. Int J Radiat Oncol Biol Phys 1994; 28:971−978.

37. Fowler JF, Ritter MA. A rationale for fractionation for slowly proliferating tumors such as prostatic adenocarcinoma. Int J Radiat Oncol Biol Phys 1995; 32:521−529.

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38. King CR. What is the T(pot) for prostate cancer? Radiobiological implications of the equivalent outcome with (125)I or (103)Pd. Int J Radiat Oncol Biol Phys 2000; 47:1165−1167.

39. King CR, DiPetrillo TA, Wazer DE. Optimal radiotherapy for prostate cancer: predictions for conventional external beam, IMRT, and brachytherapy from radiobiologic models. Int J Radiat Oncol Biol Phys 2000; 46:165−172.

40. Roberts SA, Hendry JH. The delay before onset of accelerated tumour cell repopulation during radiotherapy: a direct maximum-likelihood analysis of a collection of worldwide tumour-control data. Radiother Oncol 1993; 29:69−74.

41. Brenner DJ. Accelerated repopulation during radiotherapy; quantitative evidence for delayed onset. Radiat Oncol Invest 1993; 1:167−172.

42. Begg AC, Hofland I, Van Glabekke M, Bartelink H, Horiot JC. Predictive value of potential doubling time for radiotherapy of head and neck tumor patients. Semin. Radiat. Oncol. 1992; 1:22−25.

43. Zackrisson B, Gustafsson H, Stenling R, Flygare P, Wilson GD. Predictive value of potential doubling time in head and neck cancer patients treated by conventional radiotherapy. Int J Radiat Oncol Biol Phys 1997; 38:677−683.

44. Fowler JF. Rapid repopulation in radiotherapy: a debate on mechanism. The phantom of tumor treatment−continually rapid proliferation unmasked. Radiother Oncol 1991; 22:156−158.

45. Chen Z, Yue N, Wang X, Roberts KB, Peschel R, Nath R. Dosimetric effects of edema in permanent prostate seed implants: a rigorous solution. Int J Radiat Oncol Biol Phys 2000; 47:1405−1419.

46. Chen Z, Deng J, Roberts K, Nath R. Potential impact of prostate edema on the dosimetry of permanent seed implants using the new 131Cs (model CS-1) seeds. Med Phys 2006; 33:968−975.

47. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys 1997; 24:103−110.

48. Sanchez-Nieto B, Nahum AE. The delta-TCP concept: a clinically useful measure of tumor control probability. Int J Radiat Oncol Biol Phys 1999; 44:369−380.

49. Webb S, Nahum AE. A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. Phys Med Biol 1993; 38:653−666.

50. Van Gellekom MP, Moerland MA, Kal HB, Battermann JJ. Biologically effective dose for permanent prostate brachytherapy taking into account postimplant edema. Int J Radiat Oncol Biol Phys 2002; 53:422−433.

51. Nath R, Bice WS, Butler WM, Chen Z, Meigooni AS, Narayana V, Rivard MJ, Yu Y; American Association of Physicists in Medicine. AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: report of Task Group 137. Med Phys 2009; 36:5310−5322.