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On the need to compensate edema-induced dose reductions in pre-planned ^{131}Cs prostate brachytherapy

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Abstract

Purpose—Surgical-trauma-induced edema and its protracted resolution can lead to significant dose reduction in pre-planned ^{131}Cs prostate brachytherapy. The purpose of this work was to examine whether these dose reductions should be actively compensated and to estimate the magnitude of additional irradiations needed for dose compensation.

Methods and Materials—Quantitative edema resolution characteristics observed by Waterman et. al. were used to examine the physical and radiobiological effects of prostate edema in pre-planned ^{131}Cs implants. The need for dose compensation was assessed based on the dose-responses observed in ^{125}I and ^{103}Pd prostate implants. Biologically effective dose calculated with full consideration of edema evolution was used to estimate the additional irradiations needed for dose compensation.

Results—Edema-induced dose reduction in pre-planned ^{131}Cs implants could easily exceed 10% prescription dose for implants with moderate or large edemas. These dose reductions could lead to more than 10% reduction in biochemical recurrence-free survival for individual patients if the effect of edema was ignored. For a prescribed dose of 120 Gy, the number of 2-Gy external-beam fractions needed to compensate a 5%, 10%, 15%, 20%, or 25% edema-induced dose reduction could be 1, 4, 6, 7, or 9, respectively, for prostate cancers with a median potential doubling time of 42 days. The required additional irradiation increases for tumors that are fast growing and/or are less efficient in sub-lethal damage repair.

Conclusions—Compensation of edema-induced dose reductions in pre-planned ^{131}Cs prostate brachytherapy should be actively considered for those implants with moderate or large edemas.

Keywords

Prostate Edema; Prostate Brachytherapy; Edema; induced Dose Reduction; Cesium; ^{131}I ; Iodine; ^{125}I

I. Introduction

Interstitial brachytherapy using low-energy photon-emitting radioactive sources has been applied to the treatment of early stage prostate cancer since early 1970s and has become a popular treatment modality in the last decade due to the advent of image-guided source

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Conflicts of Interest Notification

None

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implantation techniques^{1–3}. By implanting the radioactive sources directly into the prostate gland interstitial brachytherapy is capable of delivering highly conformal radiation dose to the three-dimensional tumor volume while minimizing radiation exposure to the normal tissues outside prostate. The surgical procedure used to implant the radioactive sources, however, is known to induce prostate edema: causing the prostate gland to swell initially in response to the surgical trauma and followed by gradual resolution of edema that can last more than one month^{4–6}. Previous studies have shown that the quantitative characteristics of prostate edema vary widely from patient to patient^{4–6}. The edema magnitude (net initial increase in prostate volume) measured in the Waterman study varied from approximately 30% to 100% of the pre-implant prostate volume⁴. Similarly, the time needed to resolve the initial swelling by a factor of one-half (often referred to as the edema resolution half-life) varied in the same study from approximately 4 days in some patients up to 25 days in others⁴. A recent work by Leclerc et. al. reported even greater variations in edema magnitude (15% to 140%) and half-life (3 to 170 days)⁷. Since the presence of prostate edema forces the treatment volume and the location of the implanted sources to vary with time, the dose delivered by a permanent implant becomes dependent on the size and the resolution dynamics of edema.

Many studies have been performed to quantify the edema characteristics and its impact on implant dosimetry^{4–15}. In general, it has been shown that the dosimetric impact of prostate edema is dependent on the dynamics of dose delivery (characterized by the decay half-life of the radionuclide) and the spatial dose fall-off characteristics of individual sources (determined primarily by the energy of its emitted photons)¹⁴. Implants using sources with shorter decay half-life and lower effective photon energy were found to be more susceptible to the influence of prostate edema¹⁴. Of the radioactive sources currently used in prostate brachytherapy, the ¹³¹Cs and ¹²⁵I sources emit similar mean photon energies (~30.4 keV and 28.5 keV, respectively); both are greater than that of the ¹⁰³Pd source (~21 keV). On the other hand, the ¹³¹Cs source has the shortest decay half-life (~9.7days) compared to ¹⁰³Pd (~17 days) and ¹²⁵I (~60 days) sources. As a result, the magnitude of edema-induced dosimetry change is much greater in ¹³¹Cs and ¹⁰³Pd implants compared to ¹²⁵I implants¹⁴.

The clinical impact of prostate edema depends on how an implant dosimetry is performed and used in dose prescription. The conventional approach based on a pre-implant dose-plan does not consider the temporary increase of inter-source distance caused by edema and the dose received by the tumor is expected to be lower than what was planned^{11, 13, 14}. Ignoring effects of edema in this approach may lead to unexpected reduction in local control of the cancer. On the other hand, more clinics are moving towards performing real-time or near real-time dosimetry in the operating room (OR)^{16–20}. The dosimetry for these implants is based on a prostate volume determined in OR using either OR-planned or the actual implanted source locations. Since the swelling of prostate gland begins shortly after the first guiding-needle insertion²¹, the OR-dosimetry is hence based on an partially enlarged prostate volume. The amount of edema that was included in an OR-dosimetry vary from patient-to-patient depending on the patient's prostate swelling rate and on the timing of OR-dosimetry. Since the current OR-dosimetry does not explicitly consider the post-implant expansion (if the maximum edema was not reached at the time of OR-dosimetry) and subsequent contraction of inter-source distances the impact of edema would be dependent on the timing of OR-dosimetry. When an OR-dosimetry is performed and prescribed at maximum edema the delivered dose could exceed the prescription and lead to unwanted high doses to the adjacent critical structures¹⁵. In this work, we focused our attention on the impact of edema-induced dose reduction in pre-planned prostate implants. The specific aims were to 1) examine whether the edema-induced dose reduction in pre-planned ¹³¹Cs prostate brachytherapy should be actively compensated and 2) to investigate if the magnitude of additional irradiations needed for dose compensation can be estimated for individual patients.

II. Method and Materials

A. The need to compensate edema-induced dose reductions for ^{131}Cs implants

Whether an edema-induced dose reduction in pre-planned ^{131}Cs prostate brachytherapy should be actively compensated depends on whether the edema-induced dose reduction will lead to significant reduction in the expected clinical efficacy for the implant. The answer to this question depends on the level of dose prescription for ^{131}Cs prostate implants and the dose-response properties of prostate cancer. Because the ^{131}Cs source is relatively new in clinical applications, the dose-response data observed from ^{125}I and ^{103}Pd prostate implants^{21–24} were used to assess the potential clinical impact of edema-induced dose reductions calculated in section II.B.

B. Edema-induced dose reduction

The dose rate delivered to a tumor sub-volume (labeled by P) by a permanent implant of M radioactive sources was calculated using the formalism of American Association of Physicists in Medicine (AAPM) TG-43 report²⁵ (in point source approximation) as

$$\dot{D}_p(t) = \sum_{i=1}^M S_{ki} \Lambda \frac{r_0^2}{r_{pi}^2(t)} g(r_{pi}(t)) \bar{\phi}_{an} e^{-\lambda_I t}, \quad (1)$$

where $r_{pi}(t)$ is the distance between source i and point P at time t , S_{ki} is the initial air-kerma strength of source i , Λ is the dose-rate constant, r_0 is the reference distance (1 cm) for Λ , $g(r)$ is the radial dose function, $\bar{\phi}_{an}$ is the average anisotropy constant, and λ_I is the decay time constant of the radionuclide.

In conventional implant dosimetry, the distance between the source and point P is assumed independent of time and Eq.(1) becomes a simple exponential function of time,

$$\dot{D}_p(t) = \dot{D}_p(0) e^{-\lambda_I t} \quad (2)$$

where $\dot{D}_p(0)$ is the total initial dose-rate at P produced by the implant. In presence of edema, both prostate volume and source locations vary with time. To evaluate Eq.(1), the post-implant edema resolution characteristics observed by Waterman et al. al⁴ was used to determine the time dependence of $r_{pi}(t)$. According to Waterman et al. al⁴, the prostate volume $V(t)$ during edema resolution was described by

$$V(t) = V_p \times (1 + \Delta e^{-\lambda_E t}), \quad (3)$$

where V_p denotes the pre-implant prostate volume, $\Delta = (V_{\max} - V_p)/V_p$ is the edema magnitude (with $V_{\max}$ denoting the prostate volume at maximum edema), and $\lambda_E = \ln 2/\text{edema-resolution-half-life}$. Note that the edema magnitude used in this work is defined relative to the pre-implant prostate volume as compared to the implant-day volume used in Reference 4. In addition, Eq. (3) does not take into account the post-implant prostate volume evolution before it reaches the maximum swelling. When the implanted sources are assumed to follow the movement of its surrounding tissue without relative migration and the edema is spatially isotropic, Eq.(3) implies that

$$r_{pi}(t) = r_{pi}(0) \times (1 + \Delta e^{-\lambda_E t})^{1/3}. \quad (4)$$

where $r_{pi}(0)$ the distance before the onset of edema. To make the time integration in Eq.(1) expressible in a closed analytic form for easy analysis, we have parameterized the overall dose

fall-off around the radioactive source, $g(r)/r^2$, by a single inverse power function of distance, $\propto r^{-\tau}$, such that the instantaneous dose rate at P in presence of edema became,

$$\dot{D}_p(t) = \dot{D}_p(0) \frac{e^{-\lambda_t t}}{(1 + \Delta e^{-\lambda_E t})^{\tau/3}}, \quad (5)$$

where $\dot{D}_p(0)$, identical to the same quantity in Eq.(2), is thus related to the conventional dose prescription in absence of edema. The edema-induced dose reduction measured in percentage of the nominal prescription dose was obtained by time integration of Eq.(5) and Eq. (2),

$$R_D \equiv 100 \times \left(1 - \frac{D_p(\text{with edema})}{D_p(\text{without edema})} \right) = 100 \times \left(1 - \lambda_t \int_0^\infty \frac{e^{-\lambda_t t}}{(1 + \Delta e^{-\lambda_E t})^{\tau/3}} dt \right). \quad (6)$$

The exponent τ was found to be 2.20 for the Model CS-1 ^{131}Cs sources in our earlier study¹⁴.

C. Biologically effective dose for prostate implants with edema

In permanent prostate brachytherapy, the tumor cells are subjected to perpetual irradiation of low-energy photons with continuously decreasing dose rates. Because tumor cell repopulation and sub-lethal damage repair occur simultaneously during this protracted dose delivery, the net cell kill produced by a permanent implant is dependent on both the delivered dose and the interplay between the temporal patterns of dose delivery and cell kinetics. To estimate the additional irradiations (e.g. in the form external-beam radiotherapy (EBRT)) needed to compensate edema-induced dose reductions, we used the concept of biologically effective dose (BED)²⁶ to quantify this temporal interplay. By definition, the BED provides a measure of cell survival from a radiation treatment as

$$S = \exp[-\alpha \cdot \text{BED}], \quad (7)$$

where the symbols S and α denote the surviving fraction and radio-sensitivity of the irradiated cells, respectively.

For a course of EBRT given in N acute fractions with dose d per fraction, the surviving fraction according the linear-quadratic (LQ) cell survival model²⁶ is

$$S = \exp[-\alpha N d - \beta N d^2 + \ln 2 \frac{(N-1)\gamma}{T_p}]. \quad (8)$$

where β is the coefficient for cell kills resulted from sub-lethal damage, T_p is the average doubling time of tumor cells, and γ is the unit for time (equals to 1 day for consecutive daily delivery). Hence, the BED for the EBRT is

$$\text{BED}_{\text{EB}} = N d [1 + (\beta/\alpha) d] - \ln 2 \frac{(N-1)\gamma}{\alpha T_p}. \quad (9)$$

In absence of prostate edema, Dale²⁷ has derived an analytic expression of BED for permanent implants with dose rate characterized by an single exponential function of time. In presence of edema, the dose rate (Eq.(5)) is governed by a non-exponential function. To calculate the BED, a Taylor expansion of Eq.(5) was performed such that

$$\dot{D}_p(t) = \sum_{n=0}^{\infty} \dot{D}_p^{(n)}(0) e^{-\lambda_n t}, \quad (10a)$$

with

$$\dot{D}_p^{(n)}(0) = (-1)^n \prod_{j=0}^{n-1} (j + \tau/3) \frac{\Delta^n}{n!} \dot{D}_p(0), \quad (10b)$$

and

$$\lambda_n = \lambda_I + n\lambda_E. \quad (10c)$$

Equation (10) implies that the dose rate at P in presence of edema is mathematically equivalent to an implant containing multiple exponentially decaying “sources” whose initial dose rates and decay time constants are functions of edema magnitude and half-life. Indeed, the $n = 0$ source represents the dose contribution by the implant in absence of edema and the rest of the “sources” ($n \geq 1$) collectively give the correction due to edema. The Taylor expansion (well behaved mathematically for edemas with magnitude $< 100\%$) enabled us to calculate the BED by a generalized Dale-formula previously derived by Chen and Nath for implants containing a mixture of sources with different half-lives²⁸. Explicitly, we have

$$BED_{IMP} = D(T_{eff}) \times RE(T_{eff}) - \ln 2 \frac{T_{eff}}{\alpha T_p}, \quad (11a)$$

where

$$D(T_{eff}) = \sum_{n=0}^{\infty} \frac{\dot{D}_n(0)}{\lambda_n} (1 - e^{-\lambda_n T_{eff}}) \quad (11b)$$

and

$$RE(T) = 1 + \left(\frac{\beta}{\alpha} \right) \frac{2}{D(T)} \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \frac{\dot{D}_i(0) \dot{D}_j(0)}{\mu - \lambda_i} \left\{ \frac{1}{\lambda_i + \lambda_j} (1 - e^{-(\lambda_i + \lambda_j)T}) - \frac{1}{\lambda_j + \mu} (1 - e^{-(\mu + \lambda_j)T}) \right\}, \quad (11c)$$

In the above equations, T_{eff} denotes the effective treatment time at which the instantaneous tumor cell-proliferation rate exceeds the cell-kill rate, $D(T_{eff})$ the cumulative dose delivered up to T_{eff} , and $\mu = \ln 2 / \text{repair-half-life}$. It should be noted that Dale et al²⁹ and Antipas et al³⁰ had obtained a simpler formulation of BED when investigating the effects of tumor shrinkage in permanent implants using a simpler isotropic and exponential volume shrinkage model, in which the tumor volume shrinks from an initial volume continuously until zero as opposed to a finite limiting volume in the case of edema resolution. To calculate the quantitative radiobiological effects of prostate edema, equation (11) has to be used.

The radiobiological parameters for prostate cancer have been discussed intensively in recent literature^{31–37} following an analysis by Brenner et. al. that indicated an unusually low α/β ratio for prostate cancer ($< 3 \text{ Gy}$)³¹ as compared to typical tumors ($> \sim 8 \text{ Gy}$)^{36, 38}. While the debate on the α/β ratio is still ongoing, the emerging consensus is that the α/β may indeed be low for prostate cancer³⁶. In this work, we have chosen a self-consistent set of parameters based on the report by Wang et al^{33, 34} as the nominal values for numerical calculations. In this set, $\alpha = 0.15 \text{ Gy}^{-1}$, $\beta = 0.05 \text{ Gy}^{-2}$, $\alpha/\beta = 3.0 \text{ Gy}$, $T_p = 42 \text{ days}$, and repair half-life equals to 0.27 hour. The uncertainty associated with the model parameter was assessed by comparing

results calculated with different parameter values sampled over the expected variance of each parameter.

D. Additional irradiations needed for compensation of edema-induced dose reductions

The additional irradiations needed to compensate an edema-induced dose reduction was determined from the edema-induced BED reduction calculated from Eq.(11) as

$$\Delta BED_{IMP} = BED_{IMP}(\text{no edema}) - BED_{IMP}(\text{with edema}) \quad (13)$$

Many different treatment options, ranging from a second implant to EBRT, can theoretically be used to compensate a calculated BED reduction. Because a second implant could pose many technical challenges, such as the need to avoid overlapping of newly implanted seeds with the old ones and the need to consider the prostate edema induced by the second implant, we chose the intensity-modulated external beam radiotherapy (IMRT) delivered consecutively on a daily basis to illustrate the magnitude of required additional irradiations. Other fractionation schemes, e.g. 5 consecutive daily fractions followed by a 2-day break, can also be handled within the framework of LQ model by modifying the second term on the right-hand-side of Eq.(9).

The number of required IMRT fractions depends on the timing of IMRT delivery relative to the effective treatment time of the implant (see II.C). When the IMRT delivery starts with a time gap of T_{gap} after T_{eff} , the required IMRT fractions was determined by the following equation,

$$BED_{EB} - \frac{T_{gap}}{\alpha T_p} \cdot \ln 2 = \Delta BED_{IMP}. \quad (14)$$

By substituting Eq.(9) to Eq.(14), one has

$$N = \frac{\Delta BED_{IMP} + \frac{T_{gap} - \gamma}{\alpha T_p} \cdot \ln 2}{d + (\beta/\alpha)d^2 - \frac{\gamma}{\alpha T_p} \cdot \ln 2} \quad (15)$$

When the IMRT starts and finishes before T_{eff} , only the first term of Eq.(9) is needed for the BED of IMRT since the effect of cell re-population has already taken into account in the BED for the implant. In this case, the required IMRT fractions was calculated by

$$N = \frac{\Delta BED_{IMP}}{d + (\beta/\alpha)d^2} \quad (16)$$

Because the T_{eff} for an ^{131}Cs implant prescribed to 120 Gy is approximately 61 and 31 days for T_p of 42 and 5 days, respectively, one could always use Eq.(16) by delivering the needed IMRT before T_{eff} .

As expected, less IMRT fractions are needed when it is delivered before T_{eff} . For slow-growing prostate cancers with a median T_p of 42 days, the reduction in N is very small (about 3%). However, for fast-growing tumors with a T_p of 5 days, the required IMRT fractions can be reduced by more than 25% compared to the delivery after T_{eff} .

III. Results

A. Edema-induced dose reductions in pre-planned ^{131}Cs implants

Figure 1 illustrates the edema-induced dose reduction, R_D , for pre-planned ^{131}Cs prostate implants as a function of edema characteristics. The magnitude of R_D was highly dependent on edema characteristics. When the edema magnitude was less than 10%, R_D was less than 5% for all observed edema half-lives. As the edema magnitude increases, R_D increased with both the edema magnitude and half-life. In the extreme with edema magnitude of 90% and half-life of 25 days, R_D exceeded 30%. Even for an “average” edema (with magnitude of 50% and half-life of 10 days) the dose reduction was approximately 15%. As will be discussed in section IV.A, dose reductions of this magnitude, at current level of dose prescription for ^{131}Cs implants, could lead to significant reduction in biochemical recurrence-free survival rates based on the dose responses observed in ^{125}I and ^{103}Pd implants.

B. Additional IMRT irradiations needed to compensate edema-induced dose reductions

The number of 2-Gy IMRT fractions, N , needed to compensate an edema-induced dose reduction in pre-planned ^{131}Cs implants was calculated as a function of edema magnitude and half-life. Figure 2 shows one of the calculations for a pre-planned dose of 120 Gy using the nominal radiobiological parameters for the IMRT delivered before T_{eff} . In general, N increased with edema half-life and magnitude, similar to that shown in Fig. 1 for edema-induced dose reductions. For examples, N increased from 1 for a “small” edema (with magnitude of 20% and half-life of 4 days) to 5 for an “average” edema (with magnitude of 50% and edema half-life of 10 days) and to 9 for a “large” edema (having magnitude of 70% and half-life of 18 days). Figure 3 summarizes the information contained in Figs. 1 and 2 by plotting N (in solid circles) as a function of percent dose reductions. Because N has to be an integer, the numerical rounding of Eq.(16) forced the N vs R_D curve to appear step-wise and non-smooth. The N needed to compensate a 5%, 10%, 15%, 20%, and 25% dose reduction was about 1, 4, 6, 7, and 9, respectively. The open circles connected by the dashed line represent the number of 2-Gy fractions calculated directly from the dose reductions without considering tumor radiobiology. In this case, the simple dose-only calculation overestimated N by 2, 2, 3, 5, and 6 fractions for dose reductions of 5%, 10%, 15%, 20%, and 25%, respectively.

A general computer program has been written to calculate the needed irradiations for any combinations of edema magnitude, edema half-life, average tumor doubling time, sub-lethal repair half-life, α , and α/β ratio. The N needed to compensate a given dose reduction was found to vary with the radiobiological characteristics of tumor. Our calculations had shown that more fractions were generally needed for fast-growing tumors. For examples, an extra 1, 3, and 5 fractions were needed, respectively, to compensate a dose reduction of 10%, 15%, and 25% for tumors with T_p of 5 days as compared to that with T_p of 42 days if the compensatory IMRT delivery starts one day after T_{eff} . The needed fractions also increased slightly for tumors with less efficient sub-lethal damage repair (i.e. longer repair half-lives). The simple dose-only estimation cannot take into account these variations in tumor characteristics.

IV. Discussions

A. The need to compensate edema-induced dose reductions in pre-planned ^{131}Cs implants

The long-term dose response data for permanent prostate implants come mostly from implants using ^{125}I and ^{103}Pd sources. For these implants, proper dosimetric coverage was found of critical importance in determining the local recurrence free survival, regardless of tumor grade²¹. Dose variations on the order of 10% prescription dose were found to have significant effects on biochemical recurrence-free survival rates (PSA-RFS)^{23, 24} and on long-term recurrence-free survival rates (RFS) at 5, 10, and 15 years ($p=0.001$)²². Using the dose

delivered to 90% prostate volume, D_{90} , as a dosimetry index, Stock et al found that the PSA-RFS at 4 years had a dramatic 20% reduction between implants with $D_{90} \geq 90\%$ prescription dose (PSA-RFS of 92%) and those with $D_{90} < 90\%$ prescription dose (PSA-RFS of 68%)²³. Similar reduction in PSA-RFS (about 12%) was also seen by Potters et al when D_{90} changed from greater than 90% to less than 90% prescription dose²⁴. These results strongly suggest that adequate dose coverage is very important to the success of permanent prostate brachytherapy.

Since the current prescription for clinical ^{131}Cs implants was established primarily to match the clinical experience of ^{125}I implants without explicit consideration of prostate edema, a dose response similar to that observed in the ^{125}I implants is expected to occur in the ^{131}Cs implants. As such, a dose reduction of greater than 10% prescription could lead to significant reduction in PSA-RFS for pre-planned ^{131}Cs implants. Furthermore, because the magnitude of dose-reduction caused by an equal-sized edema has been shown to be much greater in the ^{131}Cs implants compared to that in ^{125}I implants¹⁴, more patients in the ^{131}Cs implant group could fail to achieve the expected clinical response if the effect of edema is ignored. As shown in III.A, the edema-induced dose reduction for “average” and large edemas is greater than 15% prescription dose; there is a strong theoretical need to compensate these dose reductions in pre-planned ^{131}Cs prostate implants.

B. Technical issues and precautions

Because of the protracted dose delivery, it is important to take into account the cell kinetics in the determination of clinical impacts of procedure-induced edema in prostate brachytherapy. In this work, we have developed a formalism based on the linear-quadratic model for studying the impact of edema and for estimating the additional irradiations needed to compensate edema-induced dose reductions. The preliminary results calculated from this formalism were consistent with the general clinical expectations for different tumor characteristics. Whether this formalism can be used confidently in clinical practice to quantitatively predict the IMRT fractions needed for individual implants remains to be further validated. In the following, we discuss some of the factors that could affect the outcomes of such validations.

The linear-quadratic model has been used widely for analyzing *in vitro* cell survival and for comparing different radiotherapy regimens because of its simple analytic form with relatively few model parameters^{26, 39}. The mechanistic underpinning and its applicability in modeling radiotherapy dose response have been discussed extensively in literature^{39, 40}. Sachs and Brenner³⁹ have argued that LQ model do have a mechanistic base even though it is mathematically less sophisticated compared to other models described by differential equations⁴¹. The LQ model used in this work is characterized by four parameters which takes into account the two primary causes of cell death arising from lethal (α) and sub-lethal (β) radiation damages, the first order repair of sub-lethal damages (μ), and the cell proliferation (T_p) during the therapy. Nonetheless, many other biological factors, such as the cell cycle effects, radiation induced apoptosis, cell loss and tissue architecture were not modeled explicitly. In addition, potential cell heterogeneity across the target volume was also not considered. Consequently, the current model would not be able to quantify or predict the individual contributions from these biological factors to the dose response. Indeed, the model could become invalid for those biological systems in which some of these factors become the dominant cause of radiation-induced cell inactivation and their functional dependence on dose are mathematically different from the LQ model. For these situations, a better model is required.

On the other hand, when the LQ model is used as a phenomenological model to fit an observed dose response, the biological underpinning of its model parameters may not be interpreted too literally. In fitting the model to the observed dose response, the effects of those biological factors not described explicitly by the model are incorporated to a certain extent mathematically

in the fitted values of the model parameters (when their contributions are relatively small). If a set of fitted parameters describes the dose response well over a known range of clinical practice, the model provides a quantitative tool for summarizing the dose response within the established practice range. It is under these considerations, we chose the set of LQ model parameters reported by Wang et al^{33, 34} as the nominal values in our numerical calculations for self-consistency. This particular set of parameters, as well as those from many other recent analyses, was derived from the clinical dose responses of prostate cancer treated by both EBRT and permanent brachytherapy, which is particularly relevant to this work as we were determining the number of EBRT fractions needed to compensate an edema-induced dose reduction in permanent implants. Indeed, the number of needed fractions calculated by using these parameters was not unreasonably different from the estimations by the dose-only method.

However, this does not diminish the need for radiobiological parameters of individual patients. The dose responses reported in literature usually represent an average dose response from a population of patients treated in one or several institutions. Hence, the nominal values deduced by Wang et al and by others represent at best a population-averaged “patient” (associated with the clinical practice of particular institutions). Indeed, the nominal value estimated by different research groups for prostate cancer were quite different⁴². Since no patient is an “average” patient, the parameters of a given patient can be significantly different from the nominal values. While the implications of different parameter values can be assessed quantitatively by comparing calculations that use values sampled over the entire observed or expected uncertainty range, a reliable and accurate tool for the determination of patient-specific radiobiological parameters is needed to confidently compensate patient-specific edema-induced dose reductions.

Although the exponential edema resolution reported by Waterman et al⁴ was based on measurements of mean inter-source distances from serial post-implant CT images, the isotropic edema resolution assumed in this work is rather simplistic. It does not include anisotropic tissue deformations that might be existed due to the spatial constraints posed by nearby anatomy or the nonlinearity of soft tissue mechanics within the prostate. Therefore its predictions remain qualitative until the model is fully validated or the effect of local anisotropic variations is proven to be small. Besides prostate edema, several other factors such as source migration and radiation-induced tumor shrinkage were not considered in this work. Because the occurrence and magnitude of source migration, irradiation-induced tumor shrinkage, and anisotropic tissue deformation are difficult to predict, one must conduct serial post-implant imaging studies in order to fully quantify their effects on dosimetry. The serial post-implant imaging approach can also be used to systematically validate our calculations on the edema-induced dose reduction and the required additional IMRT irradiations. In particular, the dose contribution to critical structures from the IMRT irradiations can be accurately quantified. Although IMRT provides an unprecedented ability for dose shaping, the combined dose to critical structures should be carefully evaluated because the dose fall-off across the prostate-rectum interface can be different between IMRT and the implant and the tissue response to edema can be different between the critical structures and prostate gland.

Intuitively, a better approach to minimize the impact of edema is to reduce the size of procedure-induced prostate edema. The presence of edema is inevitable in prostate brachytherapy because of the required surgical source implantation. However, the magnitude of procedure-induced edema could be reduced by optimizing the design of implant needles to lessen its invasive impact and, especially, by improving the accuracy of needle insertion (thereby minimizing the number of trial insertions needed to reach a pre-determined needle position) to reduce the overall trauma to the gland. Alternatively, replacing the permanent prostate implant by multi-fraction high dose rate (HDR) temporary implants would largely eliminate the effect of prostate edema. Under image-guidance, the HDR implant for each fraction can be planned in real time

for accurate dose coverage and the impact of edema as well as the kinetics of sub-lethal damage on dosimetry would be significantly reduced because of the short duration of dose delivery for each fraction. Such a treatment scheme is indeed favored radiobiologically by the low α/β ratio recently suggested for prostate cancer. Along this line of thinking, image-guided IMRT with hypo-fractionation would avoid completely the issue of procedure-induced edema in treating prostate cancer.

V. Conclusions

Because of the short radioactive decay half-life of ^{131}Cs , edema-induced dose reduction in pre-planned ^{131}Cs prostate implants could easily exceed 10% nominal dose prescription for patients having moderate or large procedure-induced prostate edema. If not compensated, it may lead to significant reduction in local control for these patients. When the edema characteristics of an implant is known, the number of external beam irradiations needed to theoretically compensate an edema-induced dose reduction can be determined with explicit account of the interplay between the cell kinetics of prostate cancer and the dynamics of edema resolution and brachytherapy dose delivery. While the readers are reminded of the intensive discussions and continued debates on the quantitative radiobiological characteristics of prostate cancer, we are hopeful that this work would stimulate further interest in quantitative radiobiology that may eventually lead to effective compensation of edema-induced dose reductions based on individual patient's edema and radiobiological characteristics.

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Figure 1. Edema-induced dose reduction (expressed in percentage of conventional prescription dose) in pre-planned ^{131}Cs prostate implants plotted as a function of edema half-life and magnitude.

Figure 2. Number of IMRT fractions needed to compensate an edema-induced dose reduction plotted as a function of edema half-life and magnitude. A prescription dose of 120 Gy and the nominal values of radiobiological parameters were used in the calculation.

Figure 3.

Number of IMRT fractions needed to compensate an edema-induced dose reduction in pre-planned ^{131}Cs prostate implants plotted as a function of edema-induced percent dose reduction. The calculation was based on the same parameters used in Fig. 2.