Study of associations of radionuclides in order to be used in curative medicine: influence of physical parameters of the source configuration and its radiation emission

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PhD Thesis

Introduction

Interstitial brachytherapy using permanent implants is one of the most common methods of treatment of low-risk prostate cancer. In this procedure, dose delivery to healthy surrounding organs and dose homogeneity delivered to the prostate are of prime concern. Surrounding organs at risk (OAR) may be more radiosensitive, giving rise to complications such as incontinence, erectile dysfunction, proctitis, ulceration, and bleeding.\textsuperscript{1-4} Irregularities within the prostate, swelling of the traumatized prostate, movement of the gland during implantation, and seed migration can lead to errors in the final position of the source, and consequently to deviation from the prescribed dose within the target volume.\textsuperscript{5, 6}

In order to circumvent these problems, brachytherapy design of sources and associated equipment has evolved during the past 10 years. Improved delivery apparatus and seed designs have been proposed to minimize placement errors and seed migration that may result in unacceptable area underdosage or overdosage.

Moreover, few innovations have been proposed for radionuclide selection. At present, iodine-125 (\textsuperscript{125}I) and palladium-103 (\textsuperscript{103}Pd) are the main radionuclides used for this purpose. Cesium-131 (\textsuperscript{131}Cs) has been recently introduced in the market of permanent seed for brachytherapy. Long term morbidity is the main drawback of \textsuperscript{125}I and is related to its long half-life (59.40 days) and its emitted energy (28.37 keV). On the other side, \textsuperscript{103}Pd is preferred for its high dose rate thanks to its shorter half-life (16.991 days) that allows the treatment of more aggressive tumor. Its dose distribution falls off more rapidly than \textsuperscript{125}I thanks to its low-energy emission (20.74 keV) reducing the dose to OAR. However, this short penetration depth can lead to cold spot (underdosage) where a reemergence of the cancer could appear. The newly used \textsuperscript{131}Cs has similar depth penetration than \textsuperscript{125}I, the spectrum being analogous (30.38 keV). Its short half-life (9.689 days) permits the treatment of even more aggressive tumor than \textsuperscript{103}Pd. Long term morbidity is therefore small but short term morbidity exists. Indeed, Prestidge et al. observed urethral and rectal complications at a similar frequency than \textsuperscript{125}I. However, resolution occurs more rapidly than \textsuperscript{125}I.\textsuperscript{7} These complications can be linked to a too high dose and dose rate to these organs.

A compromise had to be found between good implant uniformity and low dose to OAR. This could be reached by combining two radionuclides inside the same source. The goal of this work is to evaluate the potentiality of bi-radionuclide brachytherapy. For that purpose, we first adapt the AAPM TG-43U1 dosimetry formalism to make multiple-radionuclides sources compatible with current Treatment Planning Systems (TPS).\textsuperscript{8} This adaptation allows the definition of bi-radionuclide sources in the TPS. Second, the prescription dose for a source based on a mixture of \textsuperscript{103}Pd and \textsuperscript{125}I and \textsuperscript{103}Pd mixed with \textsuperscript{131}Cs is derived using the linear quadratic model of tumor cell surviving fraction (SF). Finally, treatment plans and Dose-Volume Histograms (DVH) have been computed on the same virtual patient for an implant with monoradionuclide \textsuperscript{103}Pd, \textsuperscript{125}I or \textsuperscript{131}Cs seeds and for an implant with bi-radionuclide seeds.

AAPM TG-43U1 adaptation for current TPS

The goal of this adaptation is to avoid any modification in current TPS. This adaptation uses the same form of equations as the current AAPM TG43U1 dosimetry formalism\textsuperscript{9} but the dosimetry parameters include the contribution of all radionuclides.\textsuperscript{8} The dose is therefore expressed in terms of a total “dose constant” (Λ\textsuperscript{T}), a total radial dose function (\(g^r_L (r)\)), a total 1D anisotropy function (\(\phi^r_L (r)\)), and a total 2D anisotropy function (\(F^T (r, \theta)\)). Their definitions change in the fact that they represent a dose ratio instead of a dose rate ratio. This is necessary in order to avoid the temporal dependence that the different half-lives would introduce in the dosimetry parameters. Consequently, the expression of the dose in this adapted general 2D formalism is:

\[
D(r, \theta) = I_k \cdot \Lambda^T \cdot \frac{G_L (r, \theta)}{G_L (r_0, \theta_0)} \cdot g^r_L (r) \cdot F^T (r, \theta),
\]

where \(I_k\) is the integrated air-kerma strength of the source, i.e. the air-kerma strength integrated over the same period as if it were implanted in the human body; \(\Lambda^T\) is the ratio of the dose at the reference point and the integrated air-kerma strength; \(G_L (r, \theta)\) is the geometrical function at the considered point. For more details, see Nuttens \textit{et al.}\textsuperscript{8}

It is important to note that in the case of mono-radionuclide brachytherapy, the adapted definitions of the dosimetry parameters coincide with the AAPM TG43U1 definitions.
As geometry of the source, we choose the InterSource seed. This device is well adapted for this work because it can be loaded with $^{103}$Pd or $^{125}$I. $^{10}$, $^{11}$ Monte-Carlo simulations have been performed to derive the dosimetry characteristics of this seed loaded with either $^{103}$Pd, $^{125}$I, or $^{131}$Cs. As shown in reference, the dosimetry characteristics of the bi-radionuclide source can be generated from the mono-radionuclide one, provided that the relative activity of each radionuclide is known.

**Determination of the prescription dose**

The determination of the prescription dose is based on tumor cell SF calculation. The linear quadratic model is used to derive the SF corresponding to a $^{103}$Pd, $^{125}$I, or $^{131}$Cs implant ($i=1,2$):

$$\ln S(T_{ef}) = -\alpha \int_0^{T_{ef}} RBE_i \cdot \tilde{D}_i(t) dt - \beta \int_0^{T_{ef}} \tilde{D}_i(t) dt + \mu \int_0^{T_{ef}} \tilde{D}_i(t) e^{-\beta(t-T_{ef})} dt + \gamma \cdot T_{ef}$$

where $T_{ef}$ is the effective treatment time; $\alpha$ and $\beta$ are respectively the linear and quadratic coefficient; $RBE_i$ is the relative biological effectiveness of the $i$th radionuclide; $\mu = \ln 2/T_r$ is the sublethal cell damage repair rate; $T_r$ corresponding to the sublethal repair half-life; $\gamma = \ln 2/T_p$ is the effective tumor-cell repopulation. $T_p$ being the tumor-cell potential doubling time. $\tilde{D}_i(t)$ is the dose rate delivered by the $i$th radionuclide in the seed at time $t$ at the point where the survival fraction is evaluated. Its expression takes the effect of an edematous prostate into account and is directly related to the radionuclide contribution to the prescription dose $D_{i,ij}$.

This survival fraction is then evaluated for the bi-radionuclide implant ($i=j=1,2$) for different dose couples ($D_1, D_2$). The iso-SF corresponding to the SF obtained with the chosen reference radionuclide ($^{103}$Pd, $^{125}$I, or $^{131}$Cs) is extracted.

A second relationship between the contributions to the prescription dose is necessary to select one couple of dose. Depending on the relative activity of each radionuclide in the seed, the relative contribution of each radionuclide to the prescription dose will be more or less important. A linear relationship between these two physical quantities exists and intersects the iso-SF corresponding to the reference radionuclide at a specific couple of dose. In conclusion, the dose prescription corresponding to these specific relative activities is the sum of the $D_i$’s.

The prescription dose has been determined for different value of biological parameters ($\alpha$, $\beta$, $T_r$, and $T_p$) and edema characteristics (resolving rate and magnitude). The derived prescription dose is similar if $^{103}$Pd or $^{125}$I are used as benchmarks but differs by about 30 Gy if $^{131}$Cs brachytherapy is used as a reference.

**Dose-volume histogram study**

Using the dosimetry characteristics of the bi-radionuclide and the determined prescription dose, treatment plans and DVH can be computed on virtual patients. Treatment plans have been performed on the same virtual patient for the different seeds: InterSource loaded with $^{103}$Pd, $^{125}$I, $^{131}$Cs, $^{103}$Pd$^{75\%}$-$^{125}$I$^{25\%}$, and $^{103}$Pd$^{25\%}$-$^{131}$Cs$^{75\%}$. The DVH show that these bi-radionuclide sources decrease the dose and dose rate to the surrounding organs at risk and reduce also the number of cold spots caused by dose inhomogeneities.

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