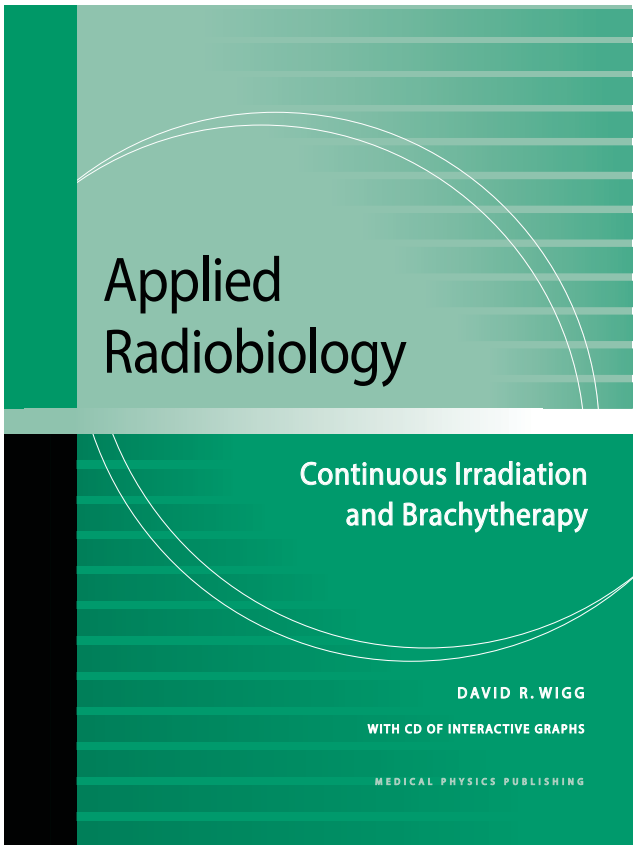

Here is a sample chapter from this book.

3

PERMANENT SEED IMPLANTS

With the development of improved implanting equipment, interest in the use of permanently implanted radioactive seeds has been rekindled. Currently, the main radionuclides of interest are ^{125}I and ^{103}Pd, but ^{131}Cs sources have recently been manufactured.

The radiobiological and physical bases of seed implants are examined in this chapter and permanent seed implant models have been derived. These models include radiobiological effects (RBE) because the very low dose rate delivered by decaying seeds causes a substantial RBE, which is frequently ignored.

To simplify calculations, the models are available on the accompanying CD. These models calculate BED values in tumor and stroma following treatment using monoexponential repair, reciprocal repair, and LDR continuous repair equations. Using these models, comparisons can be made between the use of ^{103}Pd, ^{125}I, and ^{131}Cs seeds and implants and fractionated radiotherapy.

It is apparent that resistant and rapidly growing tumors are best treated with ^{103}Pd, which delivers an effective dose faster than ^{125}I. The disadvantage of ^{125}I for fast-growing tumors decreases as tumor-doubling times increase, but ^{103}Pd remains superior for all tumor-doubling times.

3.1 Introduction

Permanent seed implants have been used for several decades, but the development of modern remote-controlled implanting equipment has facilitated the flexibility and accuracy of dose delivery, and the use of this technique is increasing. Seeds have been used for treating many types of tumors such as head and neck cancer, breast, and, especially recently, prostate cancer. A better understanding of the radiobiological basis of seed implants is becoming more and more important.

Nowadays the two most commonly used seed implants are ^{125}I and ^{103}Pd. ^{125}I decays more slowly than ^{103}Pd. ^{125}I has a transformation constant (λ) of 0.012 per day and a decay half-time of 59.4 days and produces gamma- and x-rays below 35.5 keV. The transformation constant of ^{103}Pd is 0.041 per day and the decay half-time is 16.97 days; it produces x-rays of 20.0 to 23.0 keV. While the gamma rays produced by both isotopes are

similar, an important difference when commonly prescribed doses are used is that ^{103}Pd initially delivers a dose more rapidly and over a shorter time than ^{125}I. This important difference has considerable clinical implications, as will be shown below.

^{131}Cs seeds have been developed very recently; but due to a paucity of clinical data and the absence of RBE values, this source is discussed separately in section 3.4.

To demonstrate the biological effects of treating with ^{125}I and ^{103}Pd, a model is described in this chapter to calculate the BED values in tumors and dose-limiting stroma. This model KI2RECIPIOD (see figure 3.1) has been used to calculate BED values for seed implants, as shown in figure 3.2 (PDT2A). Because repopulation of tumors during the effective treatment time would affect the final BED in figure 3.2 (PDT2A), the BED values have been plotted against the clonogen-doubling time. The full equation (A24) for BED values for permanent seed implants is described in appendix A.

The calculations may conveniently be made using the CD model KI2RECIPIOD. An example of calculations using the CD equation KI2RECIPIOD is shown in figure 3.1.

3.2 Derivation of the Permanent Seed Implant Model

The biologically effective dose is conceptually the same as the extrapolated response dose of Barendsen (1982) where

$$\text{BED} = \text{Total dose} \cdot \text{Relative effectiveness.} \tag{3.1}$$

BED is a number (Gy) by which differing treatments of both continuous and fractionated irradiation can be compared. BED may be considered as being equal to the total dose when treatment is given with an infinite number of very small doses. The total dose for seed implants may be considered as the total dose delivered during the effective treatment time equation as shown in appendix A equation (A22B).

The basic form of equation KI2RECIPIOD for the BED seed implant model [equation (A24) in appendix A] is

$$\text{BED} = \text{Total dose delivered during the effective treatment time} \cdot \text{Relative effect} - \text{Repopulation factor.} \tag{3.2}$$

3.2.1 The Effective Treatment Time (T_{eff})

Because the dose rate from implanted seeds is very low, surviving clonogens can continue to repopulate until sterilization occurs. Extra dose is required to compensate for repopulation with an effect as if this extra

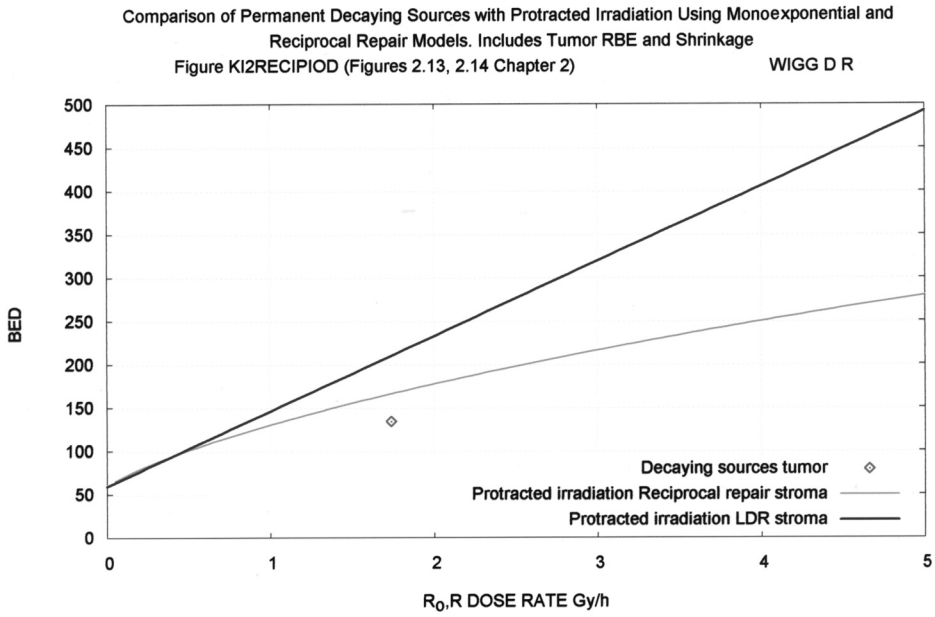

Figure 3.1 Comparison of BED values using the model KI2RECIPIOD when treating a typical SCC with decaying sources of ^{125}I. Protracted irradiation using reciprocal repair and LDR models are compared. See text in chapter 2 (section 2.9) for details.

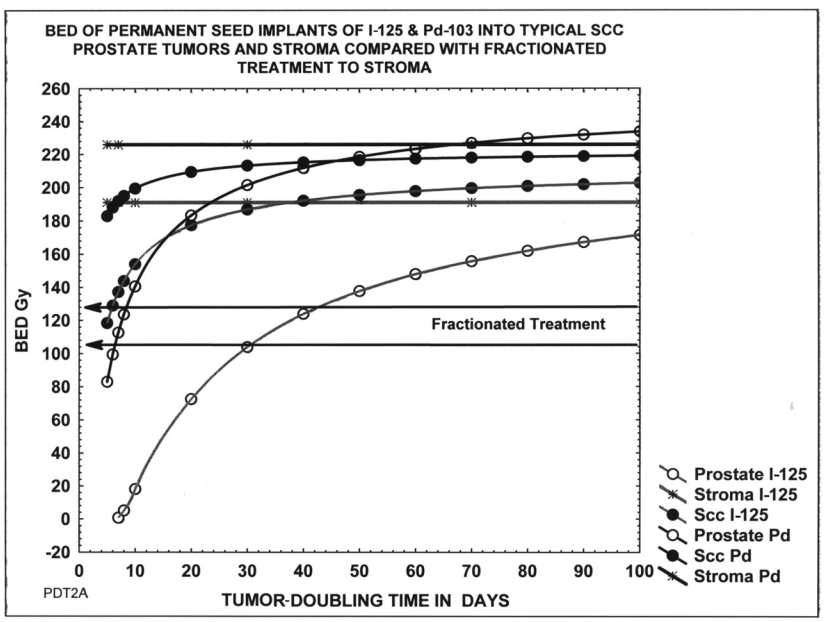

Figure 3.2 BED values for permanent seed implants into a typical SCC and prostate tumor calculated using equation (A24). Isoeffective stromal tolerance doses of 145 Gy for ^{125}I and 124 Gy for ^{103}Pd have been used. BED values for both the seed implants and BED Gy_3 values for stroma for both radionuclides are shown. BED Gy_3 for fractionated treatment of stroma with 32 to 38 fractions or 2.0 Gy per fraction are clearly less than the seed implants. See text for details.

dose is "wasted." The "wasted" dose (K) may be described by $K = \ln(2)/(\alpha \cdot T_{pot})$ Gy per day. From this equation it is clear that the "wasted" dose is higher for fast-growing and resistant tumors.

The dose from the seeds is effective in treating the existing and repopulating clonogens until the dose rate is too low to sterilize any residual cells. The time from the start of treatment up to the time effective treatment ceases is called the *effective treatment time* described by Dale (1989) and modified by Antipas, Dale, and Coles (2001), who included a shrinkage factor and a factor for relative biological effectiveness (RBE_{max}). The equation for the effective treatment time is shown here and in the appendix A equation (A22A).

$$\text{Effective treatment time} = -\left(\frac{1}{\lambda - 2 \cdot Z}\right) \cdot \ln\left[\frac{0.693}{\left(\alpha \cdot R_0 \cdot T_{pot} \cdot RBE_{max}\right)}\right], \qquad (3.3/A22A)$$

where α (Gy^{-1}) is the linear coefficient of the linear-quadratic equation. The potential tumor-doubling time (T_{pot} days) has been used for the clonogen doubling time as proposed by Dale (1989). Z is the average linear rate of shrinkage that was introduced by Antipas, Dale, and Coles (2001) to allow for the increase in dose rate as the tumor cells move closer to the seeds as shrinkage occurs, or for the reverse effect with swelling. Antipas et al. proposed making allowances for weekly linear shrinkage of 0.014 (14%) and 0.028 (28%), corresponding to 90-day volume shrinkage of 58% and 34% of the initial tumor volume. If shrinkage per day is required, for example in the appendix A equation (A24), then the weekly shrinkage value should be divided by 7, e.g., 0.014/7 and 0.028/7. R_0 is the initial dose rate per day where $R_0 = \textit{Total dose} \cdot \lambda$. λ is the transformation (decay) constant per day of the radionuclide used, and $\lambda = \ln(2)/\textit{Radioactive decay half-time}$. Because the radioactive decay half-time of ^{103}Pd is approximately 17 days and is shorter than ^{125}I (which is approximately 60 days), the initial dose rate for ^{103}Pd is higher than ^{125}I.

The dose rates decline during the effective treatment time and are very low compared with, for example, the dose rates used with conventional fractionated therapies. As discussed previously, and as shown in figure 1.13, α cell kill dominates at these low dose rates. Consequently, the biologically effective dose of treatment with ^{103}Pd and ^{125}I seeds is more sensitive to absolute values of α than to α/β ratios; this is expressed in equations (3.3) and (A22A).

At low dose rates the RBEs of ^{103}Pd and ^{125}I relative to $_{60}$Co are significant and will affect the predicted BED values. Ling, Li, and Anderson (1995) proposed an RBE of 1.4 for ^{125}I; Wuu and Zaider (1998) proposed

a value of 1.5 (mean 1.45). For ^{103}Pd, Ling et al. proposed an RBE of 1.9 and Wuu and Zaider obtained a value of 1.6 (mean 1.75). The mean values of 1.45 and 1.75 have been used in this book and are the same values used by Antipas, Dale, and Coles (2001).

Worked examples of equation (3.3/A22A) show that, when isoeffective tolerance doses are used, ^{103}Pd delivers a higher initial dose rate with a higher RBE over a shorter effective treatment time compared with ^{125}I (92 vs. 178 days), although the total doses delivered during the effective treatment time when tolerance doses are prescribed are similar for both radionuclides.

3.2.2 Total Dose Delivered during the Effective Treatment Time (T_{eff})

As described above, *Total dose* = R_0/λ. Allowing for linear shrinkage (Z), the total dose is $R_0/(\lambda - 2 \cdot Z)$ and, as described by Dale (1989, his equation [5]), the total dose delivered during the effective treatment time is shown in appendix A equation (A22B). In this equation the effect of tumor shrinkage (Z) has been added to Dale's equations.

$$\text{Total dose delivered in time} = \left(\frac{\mathrm{R_0}}{\lambda - 2\cdot \mathrm{Z}}\right)\cdot\left[1 - \exp\left[-\mathrm{t_{eff}}\cdot\left(\lambda - 2\cdot \mathrm{Z}\right)\right]\right] \quad (3.4/\mathrm{A22B})$$

For further discussion on the derivation of equations for protracted irradiation and equations (3.3/A22A) and (3.4/A22B) see Dale (1985). Sample calculations for this monograph show that when isoeffective tolerance doses are used, the total dose delivered with ^{103}Pd and with ^{125}I are similar.

3.2.3 Relative Effect

Calculation of BED values of permanent seed implants requires a description of the relative effectiveness (RE) of the dose delivered. The RE may be described using equation (3.5).

$$\text{Relative effectiveness} = \mathrm{RBE_{max}} + \left[\frac{\left[2\cdot \mathrm{R_0}\left(\lambda - 2\cdot \mathrm{Z}\right)\right]}{\left(\mu - \lambda + 2\cdot \mathrm{Z}\left(\frac{\alpha}{\beta}\right)\right)}\right]\cdot \mathrm{A}\left(\mathrm{B} - \mathrm{C}\right). \qquad (3.5)$$

The derivation of the equation for RE for decaying seeds was described by Dale (1985, app. 2, pp. 526–527). To Dale's original equation an RBE factor ($\mathrm{RBE_{max}}$) and a shrinkage factor (Z) have been added, as shown in

equation (3.5). A, B, and C are expressions derived by Dale to describe α cell kill (type A damage), B and C describe β cell kill (type B damage), and are described in appendix A as equations (A, B, C), immediately following equation (A23). Calculation of BED (*Total dose · Relative effectiveness*), excluding the repopulation factor is as follows

$$\text{BED} = \text{Total dose delivered in } T_{\text{eff}} \cdot \left[\text{RBE}_{\max} + \left[\frac{\left[2 \cdot R_0 \left(\lambda - 2 \cdot Z \right) \right]}{\left(\mu - \lambda + 2 \cdot Z \left(\frac{\alpha}{\beta} \right) \right)} \right] \cdot A \left(B - C \right) \right]. \qquad (3.6/A23)$$

3.2.4 The Repopulation Factor

As shown in equation (3.2), when calculating BED for decaying sources, a *repopulation factor* needs to be deducted to allow for the extra dose required as a consequence of repopulation occurring during the effective treatment time, T_{eff}. The "wasted" dose (K) Gy per day due to repopulation may be derived from $K = \ln (2/\alpha \cdot T_{\text{pot}})$. The "wasted" dose during the effective treatment time is $K \cdot T_{\text{eff}}$. The equation for effective treatment time (3.3/A22A) has been written to include RBE and tumor shrinkage. The repopulation factor is therefore

$$\text{Re population factor} = \left[\frac{0.693}{\left(\alpha \cdot T_{\text{pot}} \right)} \cdot \left[- \left[\frac{1}{\left(\lambda - 2 \cdot Z \right)} \right] \cdot \ln \left[\frac{0.693}{\left(\alpha \cdot R_0 \cdot T_{\text{pot}} \cdot \text{RBE}_{\max} \right)} \right] \right] \right]. \qquad (3.7)$$

3.2.5 The BED Equation for Permanent Seed Implants

The full BED equation for permanent seed implants is shown in appendix A equation (A24). In summary, the BED equation is as follows

$$\begin{aligned} \text{BED} = &(\text{Total dose in time } T_{\text{eff}} \cdot \text{Relative Effectiveness}) \\ &- (\text{"Wasted" dose per day} \cdot \text{Effective Treatment Time}). \end{aligned} \qquad (3.8)$$

This equation has been used to prepare figure 3.2 in which BED is plotted against the tumor-doubling times (T_{pot}).

Although equation (A24) has been written using Mathcad software, it is also available on the accompanying CD. In the CD version there are two models: model KI2FIG35, which calculates tumor and stromal BED and their ratios and model KI2RECIPIOD. The BED ratio tumor/stroma percent is a guideline to therapeutic gain. A higher ratio of BED tumor/stroma indicates relatively more tumor effect per tolerable effect stromal dose.

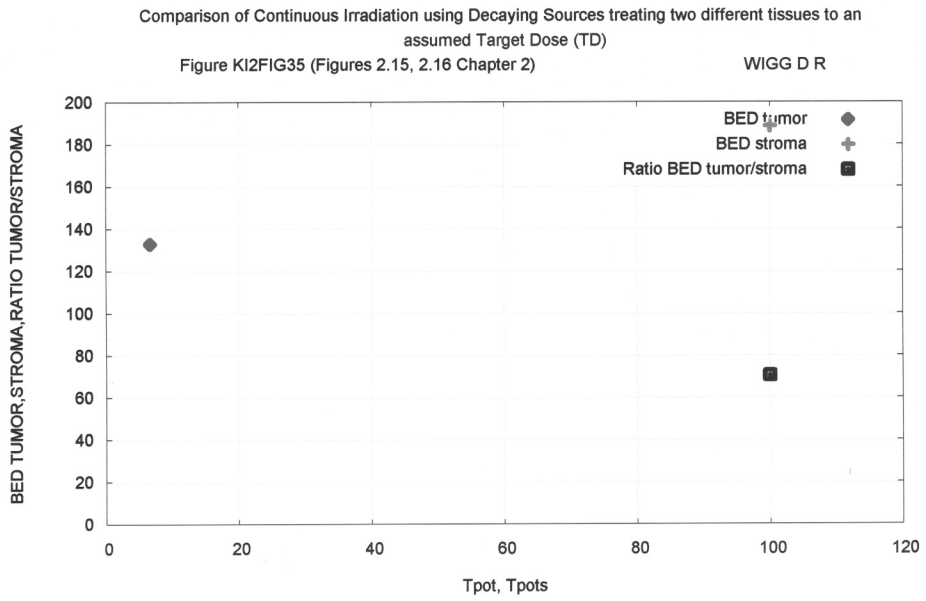

Figure 3.3 The use of the CD model KI2FIG35. The BED values in tumor, stroma and the ratio BED tumor/stroma are calculated. The tumor parameters were appropriate for a typical SCC: α = 0.35 Gy^{-1}, β = 0.035 Gy^{-2}, T_{pot} = 6.7 days. See text in chapter 2 (section 2.9) for details.

Model KI2RECIPIOD, used for figure 3.1, compares BED values for decaying sources implanted into the target volume of the tumors and also predicts BED in the stroma using either a Reciprocal Repair model or an LDR Monoexponential Repair model proposed by Dale (1985); this is shown in appendix A equation (A25). These two models have been used to generate figures 3.1 and 3.3. As tumor, stromal, and treatment parameters are varied, the predicted BED values may be read using the cursor in the CD model.

3.3 Comparison of ^{103}Pd and ^{125}I Implants for a Typical Squamous Cell Carcinoma, Prostate Cancer, and Cancers of Varying Radiosensitivity

BED values of tumors treated with permanent seed implants are very dependent on tumor repopulation that may occur during the effective treatment time. It is therefore useful to plot BED values derived using equation (A24) against tumor-doubling times, as for example in figure 3.2.

Equation (A24) may be applied to any radionuclide but only two, ^{103}Pd and ^{125}I, have been used in figure 3.2. The parameters chosen for ^{125}I were: decay half-time = 60 days, transformation constant λ = 0.012 per day, RBE = 1.45; and for ^{103}Pd: decay half-time = 17 days, λ = 0.041 per day, RBE = 1.75.

So that treatments with two different radionuclides can be compared, isoeffective total doses with respect to stromal tolerance for late effects have been used. The tolerance doses chosen were 145 Gy for ^{125}I and 124 Gy ^{103}Pd. Both these doses have been derived from extensive clinical data from seed and external beam treatments. Fowler, Chappell, and Ritter (2001) derived these guidelines following a review of the available literature of treatment of prostate cancer with external beam treatments and with ^{125}I and ^{103}Pd seed implants. Wang, Guererro, and Li (2003) adopted the same values.

For many years a commonly prescribed dose for ^{103}Pd was 115 Gy. In 2000, the American Association of Physicists in Medicine (AAPM) (Williamson et al. 2000) determined that this prescription resulted in an administered dose of 124 Gy and suggested that this dose was supported by long-term follow-up.

Peschel et al. (1999) reviewed the long-term complication rates following ^{125}I and ^{103}Pd seed implants and concluded that tolerable isoeffective doses were 145 Gy for ^{125}I and 130 Gy for ^{103}Pd.

Grimm (2006) now recommends 145 Gy for ^{125}I, and ^{103}Pd doses have been increased from 115 to 125 Gy, which is consistent with AAPM guidelines. Recent reviews of trials in Australia (Miller et al. 2006) reported that the acute and late morbidity using 145 Gy with ^{125}I were acceptable.

Figure 3.2 shows the BED Gy_3 values for stroma with tolerance doses of 145 Gy for ^{125}I and 124 Gy for ^{103}Pd are 191 and 226 Gy_3, respectively. Parameter values used were $\lambda = 0.46 \cdot 24$ per day; RBE for ^{125}I = 1.45 and for ^{103}Pd, RBE = 1.75. Shrinkage was not included. Equation (A24) requires α and β values. For late-reacting stroma, Brenner and Hall (1991) proposed values of $\alpha = 0.1$ Gy^{-1}, $\beta = 0.024$ Gy^{-2}. A widely accepted α/β value for late-reacting tissues is 3.0 Gy; this is used in figure 3.2 by retaining $\alpha = 0.1$ Gy^{-1} and using $\beta = 0.033$ Gy^{-2}.

Figure 3.2 shows BED Gy_3 values for fractionated external beam data for a range of 32 to 38 fractions of 2.0 Gy per fraction (64 to 76 Gy total dose). This range of fractions is appropriate for prostate cancer treatment (Fowler, Chappell, and Ritter 2001) and are commonly used elsewhere; for example, with head and neck cancer. The BED Gy_3 values for this treatment were between 118 and 127 Gy_3. As would be expected when the same total doses of 64 and 76 Gy are used with continuous LDR irradiation at 0.5 Gy h^{-1} and fractionated treatment with 2.0 Gy fractions, the BED values were similar: 107 and 127 Gy_3 for fractionated treatment and 110 and 130 Gy_3 for continuous irradiation.

Two different tumors have been used in figure 3.2: a typical squamous cell carcinoma (SCC) and a prostate carcinoma, which commonly have

α/β values much lower than most tumors. The parameter values used for the SCC were $\alpha = 0.35\ Gy^{-1}$, $\beta = 0.035\ Gy^{-2}$, $\alpha/\beta = 10$ Gy. For prostate carcinoma (Fowler, Chappell, and Ritter 2001), $\alpha = 0.0391\ Gy^{-1}$, $\beta = 0.0263\ Gy^{-2}$, $\alpha/\beta = 1.486$ Gy. No standard deviations of α or β for either tumor were included. The monoexponential repair constant was assumed to be $\mu = 0.46 \cdot 24$ per day for both tumors and no shrinkage factor was included.

Despite uncertainties of parameter values, especially α and RBE, it is apparent that ^{103}Pd shows an advantage when treating the more radiosensitive but typically rapidly growing SCCs, which usually have mean doubling times of less than 10 days. The advantage diminishes as the doubling rates decreases. ^{103}Pd is also superior to ^{125}I for the relatively resistant prostate carcinoma, which are usually slow growing with mean doubling times of about 40 days. With a 40-day doubling time the predicted effects for ^{125}I are similar to external beam fractionated treatment, as clinical results indicate (D'Amico et al. 1998). Increasing the ^{125}I dose to increase the tumor BED values for both tumors is limited by tolerance constraints.

A series of calculations have been done, as in figure 3.2, for prostate carcinoma of different sensitivities: $\alpha = 0.391\ Gy^{-1}$ and $\beta = 0.0263\ Gy^{-2}$ as described by Fowler, Chappell, and Ritter (2001); $\alpha = 0.26\ Gy^{-1}$, $\beta = 0.0312\ Gy^{-2}$ and $\alpha = 0.149\ Gy^{-1}$, $\beta = 0.0009\ Gy^{-2}$ as described by Nahum et al. (2003) for oxic and hypoxic prostate cancer cells, respectively. As the position on the *y*-axis of the curves in this graph are very dependent on α values, the oxic prostate curve is very similar to SCC cells: $\alpha = 0.35\ Gy^{-1}$ and $\beta = 0.0351\ Gy^{-2}$, and the hypoxic cell curve is closer to the curve for prostate carcinoma in Fowler, Chappell, and Ritter (2001).

Figures 3.4 and 3.5, prepared to further explore the dependence of tumor BED on cell type, demonstrate the use of ^{125}I and ^{103}Pd treating to tolerance doses of 145 and 124 Gy, respectively. Three tumors of differing radiosensitivity are examined: group 1 tumors $\alpha = 0.54$ Gy−1, $\beta = 0.076\ Gy^{-2}$; group 2 tumors $\alpha = 0.38\ Gy^{-1}$, $\beta = 0.042$ Gy−2; and group 3 tumors $\alpha = 0.28\ Gy^{-1}$, $\beta = 0.046\ Gy^{-2}$ (Wigg 2001, p. 245). The tumor, treatment, and isotope parameters are otherwise the same as in figure 3.2.

From these figures it is apparent that resistant and rapidly growing tumors are best treated with ^{103}Pd, which delivers its effective dose faster than ^{125}I. Because of the rapid dose delivery over a shorter effective treatment time, the final cell kill will be less dependent on the tumor-doubling time. Consequently, the tumor BED curves for ^{103}Pd are flatter and there is a marked plateau effect. The disadvantage of ^{125}I for fast-growing tumor decreases as the tumor-doubling time increases, but ^{103}Pd remains superior for all tumor-doubling times, as was predicted by

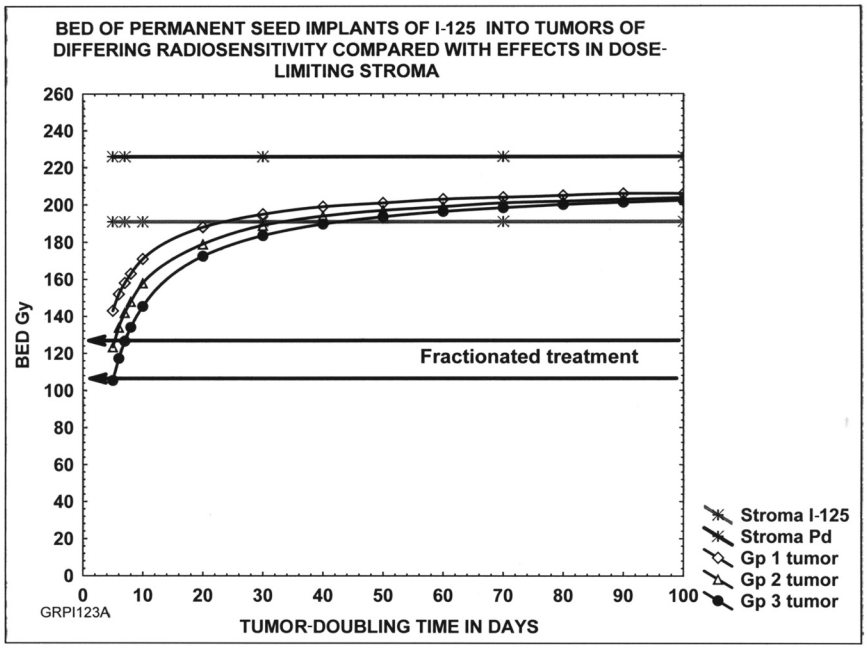

Figure 3.4 BED values derived in the same way as used in figure 3.2. Treatment with ^{125}I has been given to three tumor types of increasing resistance from group 1 to group 3. The disadvantage of ^{125}I for rapidly growing tumors diminishes as the tumor-doubling time increases.

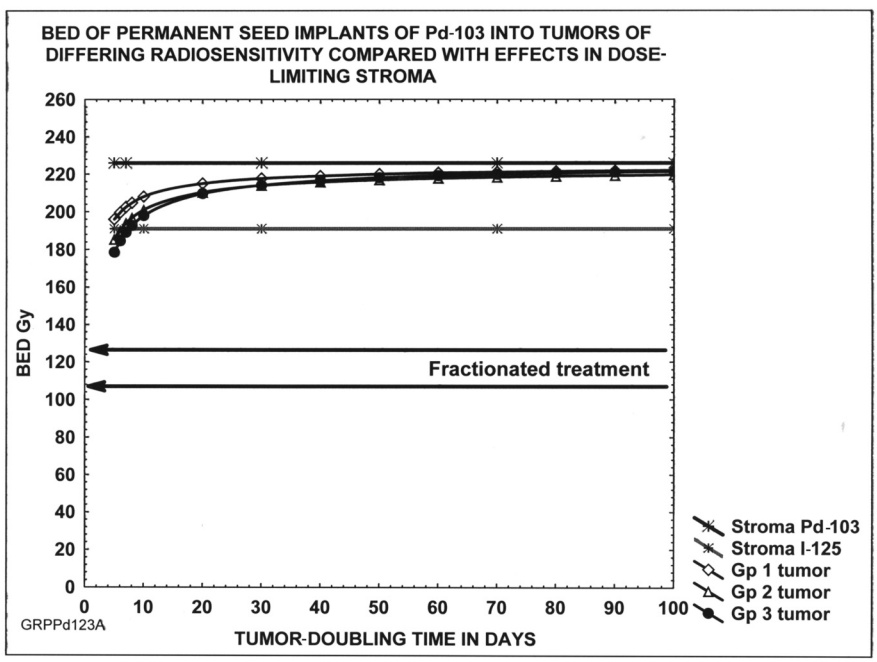

Figure 3.5 As for figure 3.4 except that ^{103}Pd is used. ^{103}Pd remains superior to ^{125}I for all tumor-doubling times and is particularly advantageous for resistant tumors.

Peschel et al. (1999). Figures 3.4 and 3.5 show that ^{103}Pd is particularly advantageous for resistant tumors.

The generally flatter tumor BED curves with ^{103}Pd mean that predictions are less sensitive to the uncertainties of tumor variables. The generally higher tumor BED values with ^{103}Pd suggest the possibility of reducing the prescribed dose for suitable low-risk tumors. Because the α value of stroma is low, predicted stromal tolerance BED values are relatively insensitive to the uncertainties of the value of α.

Peschel et al. (1999) used isoeffective tolerance doses using BED calculations but did not include RBE values in these calculations. They similarly concluded that log kill will be greater using ^{103}Pd for all tumor-doubling times and for high- and low-grade tumors.

BED predictions are sensitive to RBE values. Values for ^{125}I have been studied extensively and values of between 1.4 and 1.5 have been proposed. RBE values for ^{103}Pd are less certain and have been estimated to be between 1.6 (Wuu and Zaider 1998) and 1.9 (Ling, Li, and Anderson 1995). Antipas, Dale, and Coles (2001) proposed using 1.45 ^{125}I and 1.75 for ^{103}Pd.

A series of calculations have been done to test the sensitivity of BED to changes in RBE by using the same squamous cell and prostatic carcinomas and the same treatment as in figure 3.2 but with a fixed RBE value of 1.45 for both tumors. Although the differences between the BED values for the two radionuclides diminished as the RBE for ^{103}Pd was reduced from 1.75 to 1.45, the conclusions were unchanged. For the prostate tumor ^{103}Pd remains superior up to doubling times of 15 days and was clearly better for the rapidly growing resistant tumors.

Equation (A24) makes it possible to explore, in a qualitative manner, other effects of changing the tumor, normal tissue, and treatment variables. For example, prostate-specific antigen (PSA) screening has substantially improved the detection rates of low-risk prostate cancer for which ^{125}I and ^{103}Pd seed implants have both proved to produce very high and comparable tumor control probabilities. Higher risk cases are often treated with combined external beam and seed implants. Under these conditions when tumor control probabilities are likely to be relatively low, using ^{103}Pd seeds is likely to be more effective than using ^{125}I.

A series of calculations using equation (A24) demonstrate the following:

- RBE substantially affects the predicted BED values yet is usually not considered. The relationship between RBE and BED values are complicated but may be quantified by equation (A24).
- Dose rates with seed implants are very low. Consequently, cell kill is almost entirely α cell kill. Radiosensitivity predictions are therefore very sensitive to absolute α values, especially with ^{125}I.

- The importance of tumor-doubling time is clearly seen in figures 3.2, 3.4, and 3.5. Because of the initial high dose rate delivered over a shorter effective treatment time when ^{103}Pd is used compared with ^{125}I, sensitivity to changes in tumor-doubling time is greater with ^{125}I.
- The magnitude of the effect of tumor shrinkage depends on the radionuclide used. With the higher dose rate and relatively short effective treatment time of ^{103}Pd, the effect of shrinkage is substantially less than that of ^{125}I, with which a longer duration of change in dose rate occurs.
- Increasing the total dose increases the BED predictions, but there is no difference in sensitivity to changes in the total dose between ^{125}I and ^{103}Pd.

The BED values for fractionated treatment and LDR continuous irradiation are substantially less than the seed implants. There are probably several reasons for this. First, there is a large additional RBE for both ^{103}Pd and ^{125}I due to the very low dose rates from these sources. Second, the treated volume with external beam treatments would be larger and include more normal tissues than the seed implants, thereby limiting the tolerance and dose for fractionated treatment.

An additional benefit using seeds, not demonstrated by equation (A24)—which assumes uniform dose distributions—is the dose inhomogeneity with seeds that have an increase in dose close to the seeds. This provides a partial volume boost effect, discussed in chapter 4. These three factors contribute to the generally recognized good results using seed implants.

While dose inhomogeneities may be a bonus, inhomogeneities may work in the opposite direction as a consequence of cold spots that may occur due to imperfections of the implant. This is more likely with larger tumors. Such cold spots can lead to inadequately treated "crumbs" and may increase the risk of failure of treatment. The biological consequences of dose inhomogeneities are examined in chapter 4.

3.4 ^{131}Cs Seeds

^{131}Cs seeds for permanent implants have recently been developed (Murphy et al. 2004). This isotope produces low-energy x-rays, the energy spectrum of which has the most prominent peaks in the 29 to 34 keV range, which is similar to ^{125}I. The photon energies of ^{103}Pd are slightly lower than ^{125}I (Wuu and Zaider 1998) and therefore have a slightly more rapid fall-off of dose with distance, whereas the dose pene-

tration of ^{125}I and ^{131}Cs is similar to one another. The half-life of ^{131}Cs is 9.65 days, which is shorter than the 17 days for ^{103}Pd and the 60 days for ^{125}I.

Currently, the RBE of ^{131}Cs is not known, so some assumptions have to be made. Because of the similarity of the x-ray spectra of ^{125}I and ^{131}Cs, preliminary calculations have been made assuming an RBE of 1.45 for both. This has been used in the calculation of the BED values shown in figure 3.6. Although the x-ray spectra are similar, the initial dose rate of ^{131}Cs is higher (0.39 Gy h^{-1} vs. 0.07 Gy h^{-1}) and consequently the RBE of ^{131}Cs may be a little lower than ^{125}I. It is not likely that the RBE is significantly altered by small differences of the energy spectra of ^{131}Cs and ^{125}I. Uncertainties of the RBE for ^{131}Cs will remain until more data become available.

So that comparisons can be made between ^{125}I, ^{103}Pd, and ^{131}Cs, BED calculations have been made using equation (A24) for typical SCCs of the head and neck (α = 0.35 Gy^{-1}, β = 0.035 Gy^{-2}, α/β = 10 Gy) and prostate cancer (α = 0.0391 Gy–1, β = 0.0263 Gy^{-2}, α/β = 1.48 Gy). Doses near stromal tolerance have been used assuming an α/β ratio of stroma to be 3.0 Gy (α = 0.1 Gy^{-1}, β = 0.033 Gy^{-2}). The total doses used were 145 Gy for ^{125}I and 124 Gy for ^{103}Pd, as described previously. A monoexponential repair half-time of 1.5 hours was assumed for tumors and stroma.

To derive a total dose for ^{131}Cs seeds that results in a tolerable BED for stroma, a series of calculations with a range of total doses and RBE values have been made. Using a total dose of 130 Gy and RBE of 1.45 results in a stromal BED Gy_3 of 218 Gy, which is just below the guidelines for ^{103}Pd. This tolerance dose is shown in figure 3.6. Other examples of calculated stromal BED values include using a total dose of 100 Gy and an RBE of 1.45, giving a BED value of 161 Gy_3. Using a total dose of 120 Gy with an RBE of 1.45 gives a BED value of 199 Gy_3. A total dose of 120 Gy with an RBE of 1.6 gives a BED value of 216 Gy_3.

Figure 3.6 shows that when prostate cancer (α/β = 1.48 Gy) is treated to tolerance doses, ^{125}I is clearly inferior to ^{103}Pd, and ^{131}Cs produces the highest tumor BED values. This occurs at all values of tumor-doubling times. Prostate cancers are usually slow growing with median doubling times of approximately 42 days (range 15 to 170 [Haustermans et al. 1997b]). The differences between ^{131}Cs and ^{103}Pd are small compared with ^{125}I and are largely a function of the differing dose rates.

For the typical SCCs of the head and neck, which usually have doubling times of less than 10 days (typical mean values 4.2 to 5.6 days as shown in table B11), ^{125}I is again consistently inferior to ^{103}Pd, especially for the rapidly growing tumors, as would be expected with the more rapid initial dose rate of ^{103}Pd. These differences diminish as the repopulation

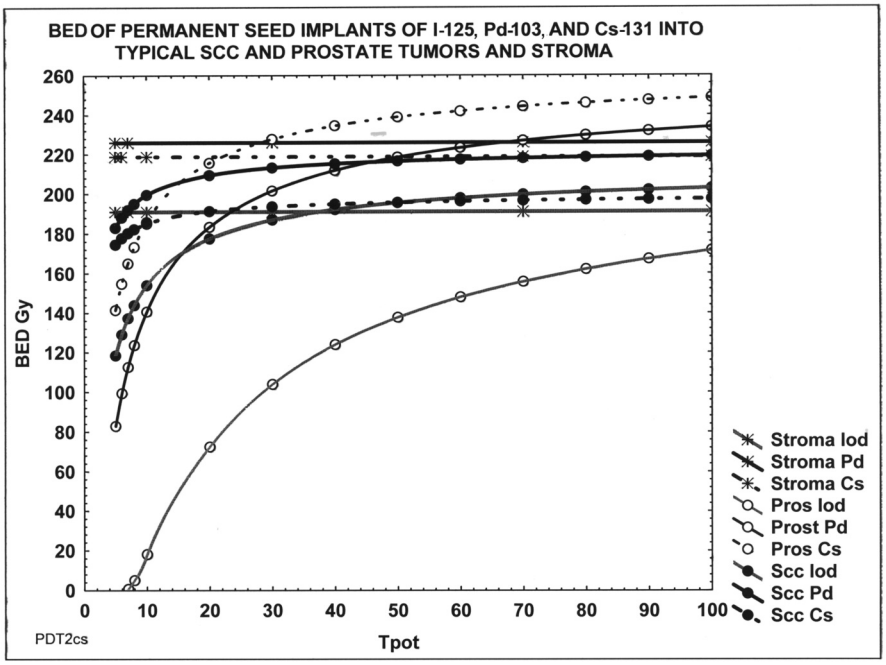

Figure 3.6 BED curves for treatment of prostate cancer (Pros) and typical head and neck cancer (Scc) using tolerance doses to stroma (Stroma). ^{125}I (Iod), ^{103}Pd (Pd), and ^{131}Cs (Cs) sources have been used.

rate slows. The ^{131}Cs source, with its short half-life and rapid initial dose rate, has similar BED Gy_{10} values to ^{103}Pd for the tumors with rapid repopulation rates, but the relative advantage of ^{103}Pd increases as the repopulation rate decreases. As figure 3.6 shows, the biggest advantage of ^{131}Cs occurs when treating rapidly repopulating tumors. As the repopulation rate decreases, the BED Gy_{10} curve for ^{131}Cs becomes flatter compared to ^{103}Pd and especially to ^{125}I. With the short half-life of ^{131}Cs, the initial dose rate is high and the effective treatment time is short compared with sources with longer half-lives. Beyond the short effective treatment time, the influence of the tumor repopulation rate decreases and the curve flattens. Similar flattening of the BED $Gy_{1.4}$ curves for prostate cancer occurs with decreasing tumor repopulation rates.

For tumors like typical SCCs of the head and neck, ^{131}Cs and ^{103}Pd have similar effects; any advantage of ^{131}Cs occurs with the most rapidly repopulating tumors. Both have advantages over ^{125}I in terms of tumor BED using stromal tolerance doses. For prostate (α/β = 1.48 Gy) tumors, ^{131}Cs has an advantage over ^{103}Pd, and again both have a higher effect than ^{125}I. As figure 3.6 shows, a particular advantage for ^{131}Cs may be for rapidly growing prostate cancer. Because of uncertainty regarding RBE values and the lack of clinical data, these guidelines for ^{131}Cs seeds are, at best, tentative guidelines to likely trends.

3.5 Summary

In recent times, with the development of improved implanting equipment, interest in the use of permanently implanted radioactive seeds has been rekindled. Currently, the main radionuclides of interest are ^{125}I and ^{103}Pd, and ^{131}Cs sources, which have recently been manufactured.

This chapter has examined the radiobiological and physical basis of seed implants and permanent seed implant models have been derived. These models include relative biological effects because the very low dose rate delivered by decaying seeds causes a substantial RBE that is frequently ignored.

The models developed are available on the accompanying CD, making calculations simple. Model KI2FIG35 calculates tumor and stromal BED values following treatment. Model KI2RECIPIOD compares BED values for decaying sources of tumor and stroma using monoexponential and reciprocal repair and compares this with alternative LDR continuous repair models. Guidelines to simplify the use of these models can be found in chapter 8. By using these models, comparisons can be made between the use of ^{103}Pd, ^{125}I, and ^{131}Cs and between seed implants and fractionated radiotherapy.

It is apparent that resistant and rapidly growing tumors are best treated with ^{103}Pd, which delivers an effective dose faster than ^{125}I. The disadvantage of ^{125}I for fast-growing tumors decreases as tumor-doubling times increase, but ^{103}Pd remains superior for all tumor-doubling times.

It is emphasized that these models provide guidelines only but may be useful to explore the likely consequences of changes in parameter values.