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Radiobiological Aspects of Intraoperative Radiotherapy (IORT) with Isotropic Low-Energy X Rays for Early-Stage Breast Cancer

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The purpose of this study was to model the distribution of biological effect around a miniature isotropic X-ray source incorporating spherical applicators for single-dose or hypofractionated partial-breast intraoperative radiotherapy. A modification of the linear-quadratic formalism was used to calculate the relative biological effectiveness (RBE) of 50 kV X rays as a function of dose and irradiation time for late-reacting normal tissue and tumor cells. The response was modeled as a function of distance in the tissue based on the distribution of equivalent dose and published dose–response data for pneumonitis and subcutaneous fibrosis after single-dose conventional irradiation. Furthermore, the spatial distribution of tumor cell inactivation was assessed. The RBE for late reactions approached unity at the applicator surface but increased as the absorbed dose decreased with increasing distance from the applicator surface. The ED_{50} for pneumonitis was estimated to be reached at a depth of 6–11 mm in the tissue and that for subcutaneous fibrosis at 3–6 mm, depending on the applicator diameter and whether the effect of recovery was included. Thus lung tissue would be spared because of the thickness of the thorax wall. The RBE for tumor cells was higher than for late-reacting tissue. The applicator diameter is an important parameter in determining the range of tumor cell control in the irradiated tumor bed. © 2005 by Radiation Research Society

INTRODUCTION

Over the last decade, breast-conserving surgery has become the preferred treatment for early-stage breast cancer (*1*), usually with post-operative radiotherapy of the whole breast as part of the adjuvant therapy since this significantly reduces the rate of ipsilateral recurrence (*2–4*). However, the majority of recurrences are found near the tumor bed while recurrences further away may be considered new primary tumors (*5, 6*). Therefore, it has been argued that whole-breast irradiation may be replaced by partial-breast irradiation in a subgroup of patients (*5, 7, 8*). A number of clinical trials have been initiated to test this hypothesis, most of these employ brachytherapy (*9–15*), but intraoperative radiotherapy (IORT) has received increasing attention. Preliminary clinical studies have demonstrated the feasibility of IORT for breast cancer treatment (*5, 8, 16–18*), and the efficacy is now being studied in randomized clinical trials on selected patients.

While the clinical benefit of local tumor bed irradiation awaits verification in long-term follow-up, the potential advantages with respect to the quality of life of patients (less normal-tissue reactions, improved cosmesis, avoiding daily travel to the radiotherapy center) and the reduced cost of treatment (*8*) constitute a considerable incentive for adopting such techniques. In view of this, the radiobiological implications for normal and tumor tissue should be carefully considered before new techniques are introduced on a broader scale.

The use of low-energy X rays makes it possible to deliver a highly localized dose of radiation and, at the same time, greatly simplifies radiation protection during IORT. The photon radiosurgery system (PRS) is a mobile miniature X-ray machine operated at 30–50 kV featuring a thin drift tube with a target at the tip emitting a nearly isotropic field of low-energy photons (*19*). This system has been used in the radiosurgical treatment of brain tumors (*20*). For irradiation of the excised tumor site in patients treated with breast-conserving surgery, spherical applicators of different diameters (2–5 cm) have been developed. Results from a pilot study in which most of the patients received external radiotherapy in addition to IORT showed that the treatment was, in general, well tolerated at a median follow-up time of 24 months (*8*). IORT with the photon radiosurgery system is currently being compared with conventional external-beam radiotherapy after breast-conserving surgery in a randomized clinical trial.

In radiotherapy, the dose that can be given to eradicate residual tumor cells is limited by late effects in irradiated normal tissue which, in conventional fractionated radiotherapy, is spared by giving the total radiation dose in multiple smaller fractions. The effect of changing the fraction

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size can be described by the linear-quadratic model in which the α/β ratio is a central parameter (e.g. ref. *21*). Because late-reacting tissues have lower α/β values than early-reacting or tumor tissue (*22*), late effects are expected to be more strongly affected by giving the total dose in a few large fractions or a single fraction such as in IORT. Frequently, calculation of the biologically effective dose (BED) is used to compare the effect of different fractionation schemes (e.g. ref. *21*). However, the classical expression for BED cannot be used to calculate the fractionation effect of low-energy X rays from data obtained with conventional high-energy photon irradiation because this requires that other parameters, in particular the radiation quality, be kept constant (see the Discussion).

The relative biological effectiveness (RBE) of the absorbed dose depends on the radiation quality. The RBE increases with decreasing photon energy and thus the RBE for the photon radiosurgery system source should be higher than for high-energy photons. Furthermore, RBE depends on the biological end point and in general increases with decreasing dose per fraction. Brenner and coworkers used the linear-quadratic (LQ) formalism to calculate RBE as a function of dose for different low-energy X-ray spectra emitted by miniature X-ray devices and estimated RBEs in the range 1.40–3.05 for tumor and early-reacting tissue (*23*). Experimental determination of RBE for inactivation of Chinese hamster ovary (CHO) cells gave values in the range 1.9–3.3 (*24*). However, estimates of RBE for late-reacting tissues with low α/β values have not been published.

Although the increase in RBE with decreasing dose will tend to enhance the biological effect at greater distances from the photon radiosurgery system source, cellular recovery during irradiations with a typical duration of 20–50 min would tend to reduce the biological effect. The net result of these contrary effects has not been assessed formally up until now. In the present work, we model the biological effect around the photon radiosurgery system applicator for the clinical dose distribution and irradiation times used in IORT for breast cancer. A modification of the LQ formalism by Brenner *et al.* (*23*) was used to calculate RBE values as a function of dose and irradiation time. Based on published dose–response data for single-dose irradiation, late effects in lung and connective tissue were estimated as a function of distance from the source. Furthermore, the spatial distribution of biological effect on tumor cells in the tumor bed was assessed. Although the absolute values should not be used uncritically in the clinical setting, the results provide a framework for understanding changes of biological effects upon variation of the physical treatment parameters and for designing biological experiments to validate this novel treatment.

MATERIALS AND METHODS

Dose Response for Single-Dose Irradiation

The dose–effect relationship for radiation-induced pneumonitis was determined previously for 303 patients receiving single doses of thoracic irradiation given at 0.5–4 Gy/min (*25*). Fifty-two of the patients developed pneumonitis with the onset occurring 1–7 months after irradiation in 90% of the cases (median 3 months). For the present analysis, the sigmoidal dose–response curve was approximated by a logistic function with an ED_{50} of 9.3.

Subcutaneous fibrosis after single-dose irradiation of pig skin with β-particle-emitting ^{90}Sr sources suggested an ED_{50} value of approximately 14–15 Gy (*26, 27*). In radiotherapy patients, dose–response curves for fractionated irradiation with 12 fractions given twice weekly or 22 fractions given at five fractions per week[2] (*28*) suggest a single-dose ED_{50} of approximately 13.5 Gy (assuming $\alpha/\beta = 3$ Gy). This would be consistent with the impression that ED_{50} values for humans are slightly lower than in the pig model (*29*). Therefore, as a conservative estimate, ED_{50} of 13.5 Gy was used, and the dose–response curve for fibrosis of the breast was approximated by a logistic function using the same exponent as for pneumonitis.

RBE Calculation

The variation of RBE as a function of dose was calculated using a modification of the method by Brenner *et al.* (*23*). In this model, the yield of lethal lesions is represented by the LQ formalism and the effect of dose protraction is accounted for by the generalized Lea-Catcheside time factor G for the simultaneous build-up and decay of radiation damage during continuous irradiation (*30*),

$$G = [2/(\lambda T)^2]\ (\theta - 1 + \lambda T), \tag{1}$$

where $\theta = \exp(-\lambda T)$ and $\lambda = \ln(2)/T_{1/2}$, and $T_{1/2}$ is the half-time for sublethal damage repair.

In contrast with the work by Brenner *et al.* (*23*), in which the same duration was assumed for test and reference radiation, the present calculations consider the effect of protracted low-energy photon irradiation compared to acute irradiation with high-energy photons to use published dose–response data. Therefore, the isoeffect equation for radiations of high (H) and low (L) biological effectiveness [Eq. 6 in ref. (*23*)] is modified:

$$\zeta_H D_H + G D_H^2 = \zeta_L D_L + D_L^2, \tag{2}$$

where ζ_H and ζ_L are the α/β ratios for the test and reference radiation, respectively.

This equation is solved for D_L and divided by D_H to obtain RBE

$$\mathrm{RBE}(D_H) = \frac{\zeta_L}{2D_H}\left[\sqrt{1 + \frac{4}{\zeta_L}\left(\frac{\alpha_H}{\alpha_L}D_H + \frac{G}{\zeta_L}D_H^2\right)} - 1\right]. \tag{3}$$

For late-reacting tissue, $\zeta_L = \alpha_L/\beta$ is assumed to be 3.0 Gy (*22*), whereas for tumor cells, typical values are in the range 7–10 Gy (*22, 31*). In the following, where appropriate, ''PRS'' represents the test radiation (H) and ''ref'' the reference radiation (L).

Dose–Volume Histograms

To be able to assess volume effects by comparison with data obtained with conventional radiation sources, doses were converted to equivalent acute doses of the reference radiation. Dose–volume histograms were calculated from concentric spherical shells assuming the radiation field to be perfectly isotropic.

PRS Source and Dose Distribution

The photon radiosurgery system source used for IORT (INTRABEAM®, Carl Zeiss AG, Oberkochen) has been described previously (*19, 32, 33*). For intraoperative breast irradiation, spherical applicators with

[2] J. Johansen, Relationship between *in vitro* radiosensitivity of normal human skin fibroblasts and the occurrence of late normal tissue reactions after radiotherapy. Ph.D. Thesis, Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, 1995.

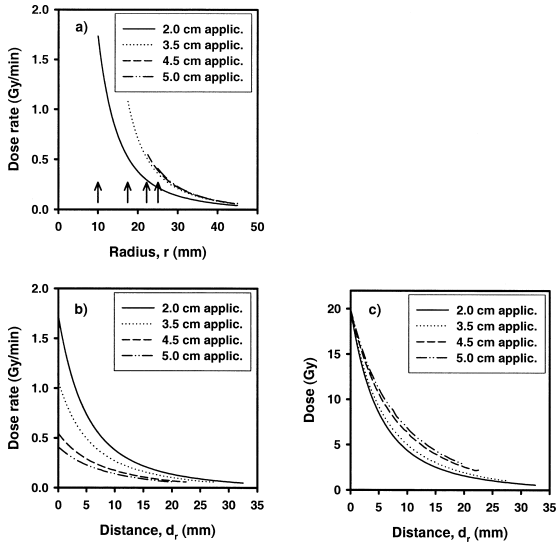

FIG. 1. Panel a: Dose rate as a function of the spherical radius in tissue with the photon radiosurgery system source in the center operated at 50 kV and with different applicators: 2.0, 3.5, 4.5 and 5.0 cm in diameter. The radii of the applicators are indicated by arrows. The curves for 3.5–5.0-cm applicators are very similar and the applicator material differs from that of the 2.0-cm applicator. Panel b: Dose rate in tissue shown as a function of distance from the applicator surface. Panel c: Dose as a function of distance in tissue, i.e. depth–dose curves, for different applicators normalized to a dose of 20 Gy at the applicator surface.

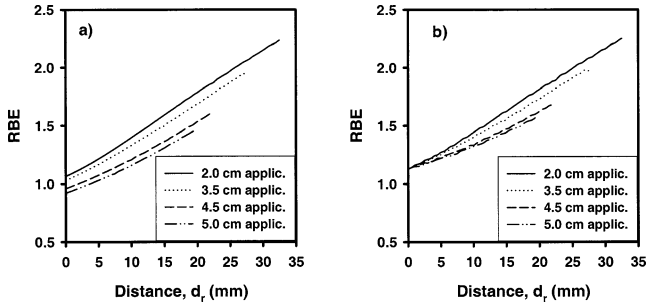

FIG. 2. Panel a: RBE as a function of distance from the applicator surface calculated from Eq. (3) including recovery during protracted irradiation with a dose of 20 Gy at the applicator surface. Panel b: Same as panel a except that the effect of recovery was excluded. The effect of recovery is greater for large applicator diameters and at high doses, i.e. close to the applicator surface.

diameters ranging from 2 to 5 cm are available. The radial dose distribution in tissue was calculated from the dose distribution obtained in a water phantom without the applicator by multiplication by so-called transfer functions (TF), defined as the ratio between the dose rates in the presence and in the absence of the applicator as a function of the radius, r (distance from the target). For each applicator diameter, the TF may be fitted by the general function $\mathrm{TF}(r) = \exp(a + b\, r^{0.5} + c\, r^{-1.5})$ with parameters a, b and c determined by fitting the function to the ratio of the measured doses. TF tables for each specific applicator were supplied by the manufacturer.

RESULTS

The dose distribution around the applicator is determined by the geometrical decrease $\propto r^{-2}$ with increasing distance, r, from the source at the center of the spherical applicator and by the attenuation of the photons with distance in the tissue. Figure 1a shows the dose rates in tissue for four different applicator diameters ranging from 2 to 5 cm. From a clinical point of view, the depth in the tissue, i.e. the radial distance, d_r, from the applicator surface, is an important variable. The variation of the dose rate with d_r is shown in Fig. 1b. Under these conditions, the attenuation in the tissue should be the same for all applicators. For tumor bed IORT of the breast, a prescribed dose of 20 Gy at the applicator surface was assumed, and Fig. 1c shows the dose distributions normalized to this value. As seen from this figure, the radial depth–dose curves become more shallow with increasing applicator diameter.

The estimated variation of RBE with dose was calculated for each of the four selected applicators using the formalism of Brenner *et al.* (*23*) with the exception that the reference radiation dose was assumed to be delivered acutely at high dose rate. An α_{ref}/β ratio of 3.0 Gy was assumed for late-reacting normal tissue and the ratio $\alpha_{PRS}/\alpha_{ref}$ for 50 kV X rays and high-energy reference photons was assumed to be 3. In the present calculations, the half-time for recovery from sublethal damage was assumed to be 15 min for irradiation with the photon radiosurgery system. Using a longer half-time would reduce the effect of recovery during irradiation. Recent clinical studies suggest the existence of a slow component in the recovery of late damage, which for subcutaneous fibrosis in head and neck patients was estimated to have a half-time of approximately 4.4 h (*34*). However, during the early phase of recovery, the fast component should dominate and the slow component can probably be neglected.

Figure 2a shows the results plotted as function of d_r. For the largest applicator, the RBE varies between 0.92 at the applicator surface and 1.45 at a distance of 20 mm. The effect of cellular recovery during protracted irradiation is greater for the large applicators owing to longer irradiation times. Figure 2b shows the variation in RBE in the absence of recovery. Comparison with Fig. 2a shows that the effect of recovery is more pronounced close to the applicator where doses are higher and the contribution from the repairable β component is greater.

The expected response for pneumonitis as a function of distance from the applicator surface is shown in Fig. 3a. According to this estimate, the ED_{50} is reached at a distance of 5.9–7.8 mm depending on the diameter of the applicator. The steep decrease reflects the steepness of single-dose–response curves combined with the slope of the depth–dose curve. Figure 3b shows a comparison of the distances d_r, where ED_{50} and ED_{10} are reached under different assumptions: in the presence of recovery, in the absence of recovery, and for a constant RBE of 1.5, respectively. In the absence of recovery, the curves are displaced away from the applicator surface and the displacement is greater for the larger diameters. A further displacement occurs if RBE is assumed to be constant equal to 1.5. Figure 3c–d shows

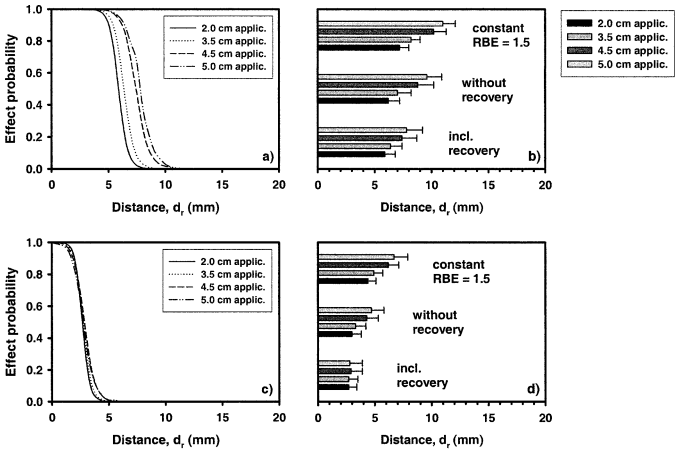

FIG. 3. Estimated distribution of the probability of developing late effects as a function of distance in the tissue from the applicator surface for different applicators. Panel a: The probability of developing pneumonitis calculated as function of distance, including the effect of recovery during irradiation assuming a repair half-time of 15 min in the RBE calculation. Panel b: Distance from surface of applicator where the ED_{50} (bar) and the ED_{10} (error flag) for pneumonitis are reached. Data were obtained from calculations similar to the curves in panel a under different assumptions as indicated: with recovery during irradiation (from panel a), without recovery or assuming a constant RBE of 1.5 in the RBE calculation. Panel c: The probability of developing subcutaneous fibrosis calculated as function of distance including the effect of recovery during irradiation assuming a repair half-time of 15 min in the RBE calculation. Panel d: Distance from surface of applicator where the ED_{50} (bar) and the ED_{10} (error flag) for subcutaneous fibrosis are reached under different assumptions as indicated similar to panel b.

similar curves for radiation-induced subcutaneous fibrosis. Because this end point requires higher doses than pneumonitis, the volume at risk for developing fibrosis is smaller than that for pneumonitis.

To assess the volume of normal tissue receiving a given critical dose level, dose–volume histograms were calculated from the distribution of absorbed dose around the photon radiosurgery system as well as after conversion to equivalent acute doses of high-energy photons using the calculated RBE values. Figure 4a and b shows that the volume exceeding a given dose depends strongly on the size of the applicator. In general, however, the volumes exceeding the equivalent reference ED_{50} of 9.3 Gy for pneumonitis and 13.5 Gy for fibrosis are relatively small. Thus, for 3.5–5.0-cm applicators, the ED_{50} for pneumonitis is exceeded only in a spherical shell with a volume of 30–85 cm^2 around the applicator and the ED_{50} for fibrosis is exceeded only in 13–27 cm^2. In general, the actual volume of exposed tissue will be smaller than these values owing to the anatomical shape of the patient. For example, lung tissue does not surround the photon radiosurgery system applicators but is found only at a distance and in certain directions.

The steep dose gradient around the photon radiosurgery system source implies that the number of tumor cells that can be eradicated depends on the distance from the applicator. Assuming $\alpha_{ref}/\beta = 10$ Gy for tumor cells and including recovery, Fig. 5a shows that over a distance 0–20 mm

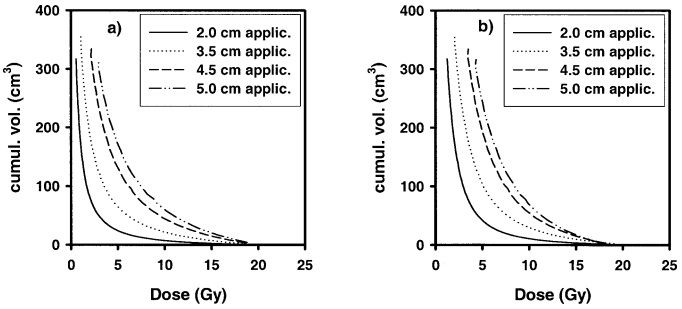

FIG. 4. Cumulative distribution of volume receiving a physical dose of radiation exceeding a given level. Panel a: dose of 50 kV X rays from photon radiosurgery system. Panel b: Cumulative distribution of volume receiving equivalent acute dose of high-energy photons (reference radiation) using RBE values calculated from Eq. (3) for late-reacting tissue.

from the applicator surface RBE varies in the range 1.28–2.21 for the 3.5-cm applicator and 1.20–1.98 for the 5.0-cm applicator. For $\alpha_{ref} = 0.3\ Gy^{-1}$ and $\beta = 0.03\ Gy^{-2}$ (yielding SF2 = 0.49 for the reference radiation), the surviving fraction was calculated as a function of distance as shown in Fig. 5b. With the chosen parameters, the value SF = 0.01 would be reached at a distance of 10.8 mm for the 3.5-cm applicator and at 14.0 mm for the 5-cm applicator. At 10 mm from the applicator, calculated values of SF would be equal to 0.0062 and 0.0010 for the 3.5-cm and 5-cm applicators, respectively.

DISCUSSION

Intraoperative irradiation of the tumor bed with low-energy X rays is currently being compared with conventional external-beam irradiation in randomized clinical trials on early-stage breast cancer patients treated with breast-conserving therapy. Results from a pilot study in which most of the patients received external radiotherapy in addition to IORT showed that the treatment was generally well tolerated at a median follow-up time of 24 months (*8*). Nevertheless, it may be argued that high single doses combined

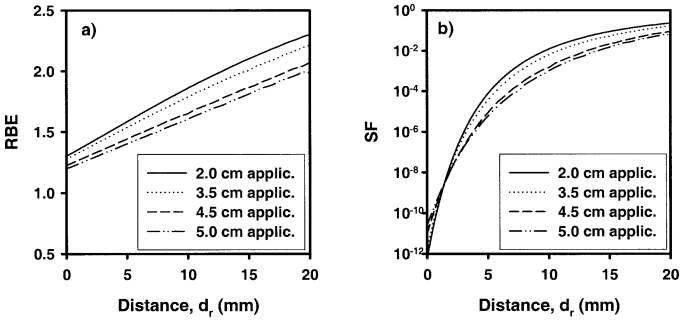

FIG. 5. Panel a: RBE as a function of distance from the applicator surface calculated from Eq. (3) for tumor cells, including recovery with an assumed repair half-time of 15 min during protracted irradiation with a dose of 20 Gy at the applicator surface. Panel b: Model calculations of the surviving fraction for tumor cells as a function of distance from the applicator surface, assuming $\alpha_{ref} = 0.3\ Gy^{-1}$ and $\beta = 0.03\ Gy^{-2}$ (yielding an SF2 of 0.49) for the reference radiation.

with an increased RBE for low-energy photons may cause greater than expected late reactions in the normal tissue which normally benefits from conventional fractionated irradiation owing to the lower α/β values compared with tumor and early-reacting normal tissue.

The biologically effective dose (BED) is a useful concept based on the LQ model for comparing the biological effect of different fractionation schemes (e.g. ref. *21*). The BED represents the dose that is calculated to be required to reach a certain level of effect when the total dose, *D,* is given in very small fractions ($d << \alpha/\beta$, with *d* being the dose per fraction) assuming full recovery and no proliferation between fractions: $\text{BED} = E/\alpha = D[1 + d/(\alpha/\beta)]$. The advantage of BED is that BED values are additive as long as only the fractionation parameters, *D* and *d,* are varied. However, the derivation of the BED expression requires α to be constant to compare BED values. Therefore, the classical BED expression is not applicable for comparing fractionation schemes obtained with different radiation qualities involving different values of α and RBE. A modification has been suggested to include the effect of RBE (*35*), but further modification would be required to take into account the effect of recovery during protracted irradiation.

In the present work, we have employed a modification of the LQ formalism used by Brenner *et al.* (*23*) to estimate RBE values as a function of dose and irradiation time. These values were used to estimate the dose–effect relationship for low-energy photons based on clinical and experimental data obtained with high-energy photons or electrons after single-dose irradiation, where available. The expected spatial distribution of late reactions was then calculated from the dose distribution and the estimated dose–response curves.

In calculating RBE, it was assumed that changes in radiation quality affect mainly the linear coefficient α. Previous studies have found values of α_H/α_{ref} (equivalent to RBE at the zero dose limit) in the range 1.3–1.8 for V79 or CHO cells irradiated with 50–55 kV X rays (*36, 37*). On the other hand, estimates based on photon spectra from the photon radiosurgery system suggested α_H/α_{ref} values in the range 2.44–3.05 for 40 kV X rays from the photon radiosurgery system (*23*). For 50 kV operating voltage, lower values would be expected. Experimentally, an RBE of 3.3 was found for CHO cells at 50% survival with the PRS operated at 40 kV (*24*). The reason for the difference between the experimental values for photon radiosurgery system and 50–55 kV X rays from other machines may be related in part to differences in the photon spectra owing to the operating voltage and beam filtration. However, the survival curves for 50–55 kV in the previous studies showed a pronounced curvature (*36, 37*) which, in this range of surviving fraction, is also a feature of ultrasoft X rays, even down to energies of 0.3–1.5 keV (*38–41*). By contrast, the survival curve of CHO cells determined for photon radiosurgery system at 4 mm depth in tissue-equivalent material was essentially linear (*24*). Furthermore, at shorter distances where less filtering of the low-energy part of the PRS spectrum should occur, the survival curve unexpectedly showed a strongly reduced RBE at all doses and the appearance of a curvature. It cannot be excluded that the high RBE for the PRS at 4 mm depth may be related in some way to this unexplained reverse effect of beam hardening on the RBE.

In the present calculations, the value of $\alpha_{PRS}/\alpha_{ref}$ was assumed to be equal to 3, which may be a slight overestimation but is likely to be on the conservative side with respect to normal-tissue effects. As a result of the dose dependence of RBE, the estimated RBE increase as the dose decreases with increasing distance from the applicator. However, it should be noted that the numerical variation depends on $\alpha_{PRS}/\alpha_{ref}$ and on the assumption that β depends only on the biological end point and not on the radiation quality.

The effect of cellular recovery during irradiation was incorporated into the RBE calculations and resulted in a reduction of the effective RBE. The published dose–response data for the reference radiation were obtained for short irradiation times, whereas for the photon radiosurgery system with applicator diameters of 3.5–5.0 cm, irradiation times are in the range 20–50 min. The assumed half-time for recovery from sublethal damage of 15 min was chosen to estimate the possible size of the effect, and calculations were compared with the hypothetical situation in which no recovery takes place. The absence of recovery would be expected to increase the distance within which normal tissue reaction might develop by 1–2 mm for 3.5–5.0-cm applicators. The existence of a slow recovery component for late damage with a half-time of approximately 4.4 h has been implicated (*34*), but a slow component can probably be neglected during the early phase of recovery. Thus the half-time of the fast component is likely to determine the effect of recovery during intraoperative radiotherapy with the photon radiosurgery system source.

The effect of recovery was to decrease the spatial extent of late damage that would extend to larger depths if recovery were neglected. Recovery is more important for long irradiation times, i.e. for large applicators, and for higher doses. At high doses, recovery may even counteract the increased range of the depth–dose curve in tissue for increasing applicator size as is evident in the case of fibrosis (Fig. 3c–d). On the other hand, if a constant RBE of 1.5 is assumed (i.e. RBE is independent of dose and irradiation time), late effects extend to a larger depth in the normal tissue and the dependence on applicator size becomes more pronounced.

It might have been expected that the increase in RBE with decreasing dose would result in more shallow curves of the effect as a function of distance. However, the steepness of the dose–response curves for late reaction implies that the change in RBE is relatively small over the narrow dose range where the increase in response is steep. Thus the probability of effect increases from 10% to 90% over

a distance of a couple of millimeters. Furthermore, the effect of beam hardening on RBE was neglected because the major change in the photon spectrum is expected to occur over the first few millimeters of applicator material near the gold target.

While radiation-induced subcutaneous fibrosis would impair cosmesis after breast-conserving surgery, a more serious late effect to be considered in relation to IORT is radionecrosis. Dermal necrosis in the pig model has been found to occur with an $ED_{50} \sim 19.5$–20.5 Gy (*42, 43*). Following the argument above (see the Materials and Methods), a slightly lower value of $ED_{50} \sim 18.0$ Gy for the reference irradiation might be expected in humans. With RBE values of approximately 1.0–1.2 at high doses, ED_{50} is expected to be reached at a depth of 2–3 mm. Although some data suggest that the dose–response curve for radiation-induced necrosis may be less steep than for fibrosis [cf. (*25, 43*)], necrosis would be expected to be limited to a narrow shell around the applicator. In accordance with this, dermal necrosis was observed only in a small area near the applicator surface in 1 out of 25 patients in the pilot study (*8*). It is conceivable that healing processes from the surrounding tissue, possibly stimulated by the surgery, may permit some regeneration in small volumes of tissue.

Volume effects may help reduce adverse effects in the lung since partial lung irradiation is considered to be better tolerated than irradiation of the whole lung (*44, 45*). However, there are few published data on the biological effects in very small irradiated lung volumes. The absorbed dose as a function of distance from the applicator, i.e. depth in the normal tissue, decreased for all applicators, but the steepness was less for the large applicator sizes, thus increasing the isodose volumes. Lung tissue, however, is present at only one side of the applicator. More importantly, even in the thinnest patients the thorax wall is thicker than 11 mm, and thus doses are reduced to less than the ED_{50} before reaching the lung.

While a main objective of the present work was to estimate the extent of late reactions in normal tissues, the formalism can also be used to estimate RBE for tumor cell inactivation. The higher RBE values for tumor cells compared with late reactions are a consequence of the higher α/β value, which was assumed to be equal to 10 Gy for the reference radiation. The change in SF with distance in the tumor bed was approximated by calculating SF from the LQ model with the coefficients $\alpha_{ref} = 0.30$ Gy^{-1}, $\beta = 0.03$ Gy^{-2} and the dose multiplied by RBE, yielding an $SF2_{ref}$ of 0.49. However, the absolute values of the calculated surviving fractions depend strongly on the chosen values of α and β. *In vitro* studies yielded SF2 values of 0.3 for MFC7 breast tumor cells and 0.38 ± 0.09 (mean $\pm$ SD; range: 0.23–0.54) for eight breast cancer cell lines including MCF7 (*46, 47*). A hormone-dependent cell line showed an SF2 of 0.33 under proliferating conditions and an SF2 of 0.68 under estrogen-depleted, growth-restricted conditions, whereas two hormone-independent cell lines showed an SF2 of 0.51 and 0.65 irrespective of the growth conditions (*48*).

The LQ coefficients used for the present estimates were chosen to yield an SF2 that is representative of the upper range of the published *in vitro* studies. Although the absolute values of α and β in the clinical setting are not known, the plot of SF as a function of distance in the tissue emphasizes the highly localized nature of irradiation with the photon radiosurgery system. Furthermore, it shows that the distance in tissue where a given level of tumor cell inactivation can be achieved is markedly greater for large than for small-diameter applicators. Very close to the applicator surface, i.e. at high doses and small values of SF, this relationship may be reversed owing to the effect of recovery during protracted irradiation.

The probability of tumor control depends on the actual distribution of tumor cells in the tumor bed. However, for a single cluster of tumor cells, a simple calculation can be made assuming that the number of surviving cells is distributed according to the Poisson distribution. In this case, the probability of finding no survivors among N clonogenic cells irradiated to a survival level, SF, is determined by $P(0) = \exp[-(N \cdot SF)]$. Thus, if the probability of controlling the cluster is required to be 90%, i.e. $P(0) = 0.9$, then the number of cells in the cluster should be smaller than $N = -\ln(0.9)/SF = 0.105/SF$. For more accurate modeling, experimental data for tumor cell inactivation with the photon radiosurgery system and for the distribution of clonogenic cells in the tumor bed are required.

In conclusion, calculations using the LQ formalism yield RBE values for late normal tissue reaction that are lower than for tumor cell inactivation and may even reach unity at high doses when recovery is considered. For pneumonitis, the extent of normal tissue reaction was estimated to be limited to a depth of 6–11 mm in the tissue, which is less than the thickness of the thorax wall. Subcutaneous fibrosis was estimated to be confined to a depth of 3–6 mm while radionecrosis should be restricted to even smaller depths of tissue. Owing to the small volumes exposed to critical dose levels, late reactions may be further reduced by regeneration from surrounding tissue, although the influence on the regenerative capacity of lower doses to the surrounding tissue may have to be considered. The diameter of the applicator can significantly influence the spatial extent of the level of biological effect in the surrounding tissue. The influence is greater at low doses, i.e. for normal tissue reactions with a low ED_{50}, while at higher doses it may be partly compensated by recovery during long irradiation times. For tumor cells, the applicator diameter should be considered a major treatment-related factor in determining the range of tumor cell control in the irradiated tumor bed.

The present calculations may contribute to an understanding of the low level of normal tissue reaction observed clinically in a pilot study on IORT with the PRS in breast cancer patients treated with breast-conserving surgery (*8*).

Further experimental data from cell culture and large animal models are required to validate these estimates and to provide a basis for modeling biological effect as part of treatment planning for individual patients. Continued attempts to monitor and characterize any fibrosis or necrosis observed clinically in patients treated with this new modality will be equally essential.

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