Radiobiological Comparison of Hypofractionated Accelerated Partial-Breast Irradiation (APBI) and Single-Dose Intraoperative Radiotherapy (IORT) with 50-kV X-Rays

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Background and Purpose: Intraoperative radiotherapy (IORT) of the tumor bed in early breast cancer is presently performed with a single dose of 50-kV X-rays from a miniaturized X-ray machine using spherical applicators. The purpose was to model the biological effect of hypofractionated accelerated partial-breast irradiation (APBI) with ten fractions.
Material and Methods: The relative biologic effectiveness (RBE) was estimated from the linear-quadratic (L-Q) formalism including repair of sublethal damage or assuming a constant RBE = 1.2–1.5. The radial distribution of biological effect was assessed from clinical dose-response curves. In accordance with clinical convention, the dose for APBI was prescribed at 1 cm depth in the tumor bed, whereas for IORT it was prescribed at the applicator surface.
Results: The fraction size was fitted to give the same risk of late normal-tissue reaction (fibrosis) as single-dose IORT with a maximum dose of 20 Gy. The isoeffective fraction size at 1 cm depth varied between 1.01 Gy for RBE estimated from the L-Q model and 1.64 Gy for constant RBE. The applicator size and dose prescription point influenced the radial dose distribution. The "sphere of equivalence" within which the risk for local recurrence is the same for whole-breast radiotherapy was predicted to extend to 11–15 mm distance from the applicator for α/β = 10 Gy and 9–13 mm for α/β = 4 Gy for hypofractionated APBI, representing an increase of the sphere of equivalence by 2.5–6 mm relative to single-dose IORT.
Conclusion: An increase of the therapeutic window with hypofractionated APBI relative to single-dose IORT should be feasible.

Key Words: Breast · Radiotherapy · Fractionation · APBI · Modeling

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Strahlenbiologischer Vergleich hypofraktionierter, akzelerierter Teilbrustbestrahlung (APBI) und einzeitiger intraoperativer Radiotherapie (IORT) mit 50-kV-Röntgenstrahlen

Hintergrund und Ziel: Die intraoperative Radiotherapie (IORT) des Tumorbetts bei frühen Mammatumoren mit 50-kV-Röntgenstrahlen von einem miniaturisierten Röntgengerät wird derzeit als Einzeitbestrahlung mit sphärischen Applikatoren durchgeführt. Das Ziel war, die biologische Wirkung einer hypofraktionierten, akzelerierten Teilbrustbestrahlung (APBI) mit zehn Fraktionen zu modellieren.
Material und Methodik: Die relative biologische Wirksamkeit (RBE) wurde mit dem linear-quadratischen Formalismus einschließlich Reparatur subletaler Schäden veranschlagt, alternativ wurde ein konstanter Wert von RBE = 1,2–1,5 angenommen. Die radiale Risikoverteilung biologischer Wirkung wurde mit Hilfe von klinischen Dosis-Wirkungs-Kurven bestimmt (Abbildung 1). Die Dosis für APBI wurde anhand der klinischen Verschreibungskonventionen in 1 cm Tiefe des Tumorbetts festgelegt, während die Dosis für IORT an der Oberfläche verschrieben wurde.
Ergebnisse: Die Fraktionsgröße wurde angepasst, bis das gleiche Risiko später Normalgewebsreaktion (Fibrose) wie nach Einzeit-IORT mit einer maximalen Dosis von 20 Gy erreicht wurde (Abbildung 2). Die isoeffektive Fraktionsgröße in 1 cm Tiefe war 1,01 Gy, wenn RBE mit dem linear-quadratischen Modell bestimmt wurde, und 1,64 Gy für konstante RBE (Tabelle 1). Die Applikatorgröße und der Dosisverschreibungspunkt beeinflussten die radiale Dosisverteilung (Abbildung 3). Die Äquivalenzkugel, innerhalb welcher das Rezidivrisiko gleich groß wie bei Ganzbrustbestrahlung ist, erstreckte sich bis 11–15 mm Abstand von der Applikatoroberfläche für α/β = 10 Gy und bis 9–13 mm für α/β = 4 Gy (Abbildung 4). Dies entspricht einer Vergrößerung um 2,5–6 mm im Vergleich zur Einzeit-IORT.

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Schlussfolgerung: Eine Vergrößerung des therapeutischen Fensters durch hypofraktionierte APBI gegenüber Einzeit-IORT sollte möglich sein.

Schlüsselwörter: Teilbrustbestrahlung · Strahlentherapie · Fraktionierung · Modellierung

Introduction

Interest in accelerated partial breast radiotherapy (APBI) is rising rapidly worldwide [18, 20, 22, 24, 27, 33, 34, 38]. Although the rationale varies between different studies [16], it is generally assumed that recurrences after breast-conserving surgery occur near the site of a tumor and that part of the patients may not need adjuvant radiotherapy to the whole breast [6, 15].

APBI may be applied by interstitial brachytherapy, brachytherapy applicators, and intensity-modulated external-beam radiotherapy [19, 21, 25, 32, 36]. Furthermore, intraoperative radiotherapy (IORT) with high-energy electrons or low-energy X-rays is used either as a boost in combination with postoperative WBRT [13, 23, 28, 35] or as sole treatment [11, 13, 17, 27, 29, 31].

Isotropic 50-kV X-rays from the Intrabeam® machine are presently applied as single-dose IORT to the tumor bed. Spherical applicators 4.0–5.0 cm in diameter are inserted into the cavity left after excision of the tumor with a 1-cm margin. This source is characterized by an increased relative biologic effectiveness (RBE), a nonuniform dose distribution, and a dose rate which depends on the applicator size, requiring typically 30–50 min to deliver a dose of 20 Gy at the applicator surface. Single doses of 6–7 Gy are achieved at 1 cm distance from the applicator surface. The RBE is influenced by the radiation quality, the dose per fraction, and the effect of sublethal damage (SLD) repair during irradiation.

An international, multicentric phase III trial, TARGIT (TARGeted Intraoperative radioTherapy), is testing a risk-adapted approach to IORT with Intrabeam® in highly selected patients [29]. Previous modeling of the risk of late normal-tissue reaction estimated radiation-induced fibrosis to be limited to a few millimeters distance from the applicator [8]. Modeling the risk of local recurrence suggested the existence of a "sphere of equivalence" within which the integrated risk after IORT would be identical to that after whole-breast radiotherapy (WBRT) [7]. Thus, in a cohort of patients, increased control of tumor foci close to the applicator surface partly compensates the decrease of control at larger distances. Quantitative calculation indicated that the "sphere of equivalence" may be close to 1 cm of tumor bed tissue targeted by IORT.

Fractionation can increase the therapeutic window between local tumor control and late normal-tissue reaction. The purpose of the present study was to model the risk of recurrence for hypofractionated APBI and single-dose IORT at isoeffective doses for late reaction.

Material and Methods

Radiation Source and Dose Distribution

Doses of 50-kV X-rays from the Intrabeam® PRS400 miniaturized X-ray machine (Carl Zeiss Surgical GmbH, Oberkochen, Germany) with spherical applicators for tumor bed irradiation were determined as function of distance from the source [8].

Modeling of RBE

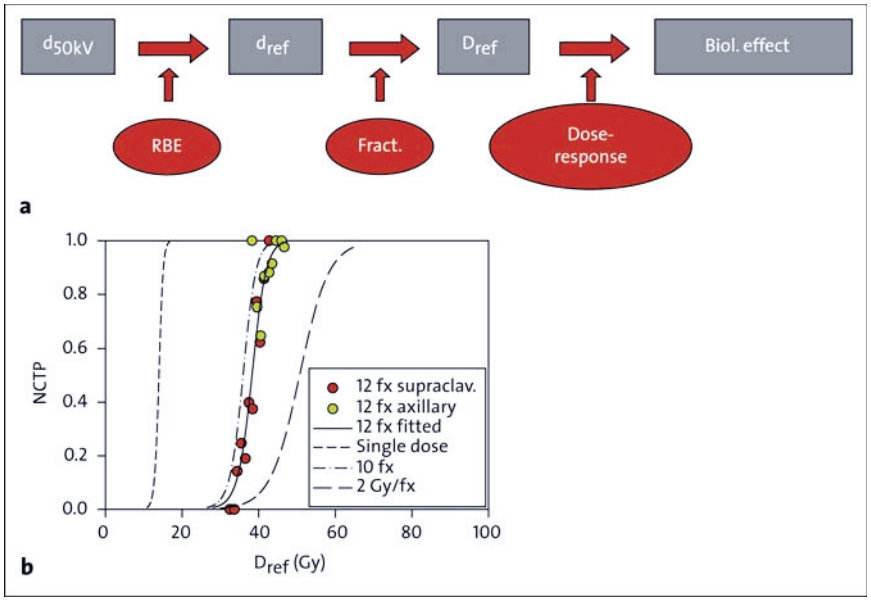
The RBE was estimated by the linear-quadratic (L-Q) formalism including the effect of continuous induction and decay of SLD during protracted irradiation [4, 8]. The modeling strategy for hypofractionated APBI is shown schematically in Figure 1a. For late reaction of normal tissue, the ratio of the linear and quadratic coefficients (α and β, respectively) was assumed to be $\alpha/\beta = 3$ Gy, whereas for local tumor control, values of 10 Gy and 4 Gy were applied as indicated. The ratio of the linear coefficients, α_{50kV} for X-rays from Intrabeam® and α_{ref} for reference radiation (high-energy X-rays), was assumed to be $\alpha_{50kV}/\alpha_{ref} = 3$, and the repair half-time of SLD $T_{1/2} = 15$ min as previously described [7, 8]. Alternatively, RBE was assumed to be constant equal to 1.2 or 1.5.

Calculation of Isoeffective Doses

The dose per fraction of reference radiation, d_{ref}, which would be isoeffective with the biological effect of the physical dose of 50-kV X-rays, d_{50kV}, was calculated by multiplying the physical dose by RBE: $d_{ref} = RBE \times d_{50kV}$. The total dose, $10 \times d_{ref}$, was converted to the isoeffective total dose, D_{ref}, for the appropriate fractionation scheme using the L-Q model for fractionation [12].

Dose-Response Relationships

The biological effect (risk of late reaction or local recurrence) was estimated from clinical dose-response data. Subcutanous fibrosis after postmastectomy radiotherapy with twelve fractions [2] was used to estimate the clinical risk of fibrosis for hypofractionated APBI (Figure 1b). A weighted, least-squares fit of a logistic dose-response curve yielded $ED_{50} = 38.2$ Gy (neglecting differences in follow-up time). Conversion to other fractionation schemes was done using $\alpha/\beta = 3$ Gy for late reaction [14], which was within the confidence interval of a detailed analysis including 22 fractions [3]. Conversion of the total doses, D_{ref}, to EQD2 given in 2 Gy/fraction yielded a curve with $ED_{50} = 47.3$ Gy. For single-dose irradiation, the L-Q model yielded $ED_{50} = 14.0$ Gy, consistent with the im-



Figures 1a and 1b. a) Schematic diagram of the modeling strategy for biological effect of hypofractionated APBI. For explanation, see text. b) Clinical dose-effect relationship for subcutaneous fibrosis after twelve fractions delivered twice weekly [2] was used to estimate the risk of fibrosis for different doses. A logistic function was fitted to the clinical data weighted by the number of patients as provided in the original publication. This curve was converted to other fractionation schemes (single dose, ten fractions, 2 Gy/fx) using the L-Q model with $\alpha/\beta = 3$ Gy.

Abbildungen 1a und 1b. a) Schematische Darstellung der Modellierungsstrategie für die biologische Wirkung der hypofraktionierten, akzelerierten APBI. Erklärung s. Text. b) Die klinische Dosis-Wirkungs-Beziehung für subkutane Fibrose nach zwölf Fraktionen zweimal pro Woche [2] wurde für die Abschätzung des Fibroserisikos verwendet. Eine logistische Funktion wurde den klinischen Daten angepasst, mit Wichtung nach Anzahl von Patientinnen wie in der Originalarbeit angegeben. Die Kurve wurde für andere Fraktionsschemata (Einzeitdosis, zehn Fraktionen, 2 Gy/Fx) mittels des linear-quadratischen Modells mit $\alpha/\beta = 3$ Gy umgewandelt.

pression that ED_{50} may be slightly lower in humans than in the pig model [8, 9].

The risk of pneumonitis was determined by converting the total dose to the isoeffective single dose and using dose-response relationship for single-dose irradiation of human patients (ED_{50} = 9.3 Gy) [8, 30].

A dose-response relationship for control of local recurrence was previously derived from clinical radiotherapy with daily fractions of 2 Gy given five times per week with a modification to account for the effect of absent repopulation of tumor cells between surgery and IORT [7].

Results

Previous modeling for single-dose IORT [8] estimated 50% risk of fibrosis at a distance of approximately 2.8 mm from the surface of a 4.5-cm applicator when RBE was calculated by the L-Q formalism including SLD repair, and at approximately 6.2 mm for constant RBE = 1.5. In the following, the isoeffective fraction size for hypofractionated APBI, which would yield the same amount of fibrosis as single-dose IORT with 20 Gy at the applicator surface, was determined.

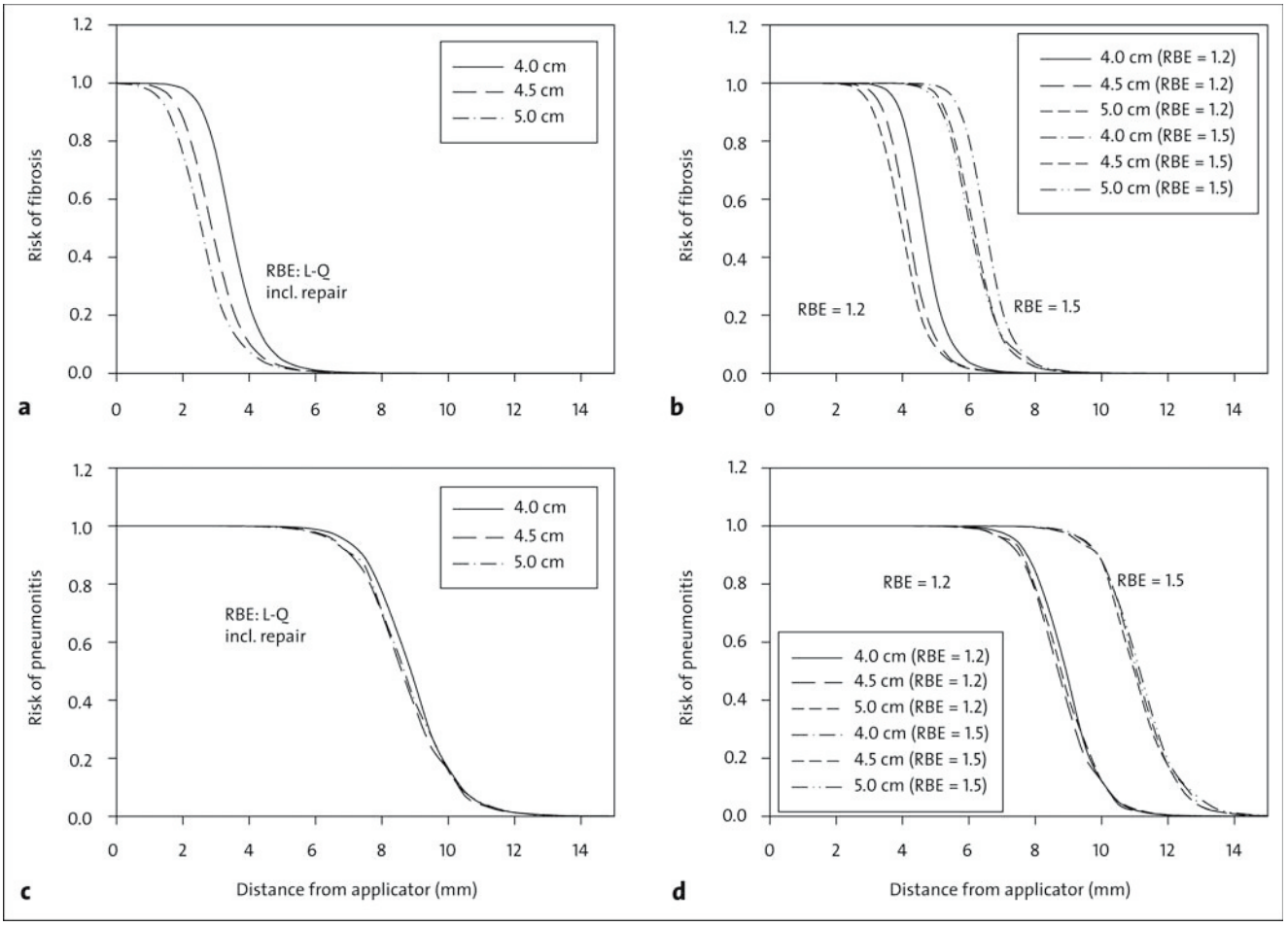
For nonuniform dose distributions such as in brachytherapy, clinical practice is to prescribe the dose to a reference point at a defined distance from the source. Therefore, the radial extent of fibrosis was modeled for ten fractions of hypofractionated APBI with dose prescribed at 1.0 cm distance from the applicator surface. The dose was varied until the distance from the applicator at which 50% risk is reached fitted the curve for single-dose IORT.

Table 1 shows the isoeffective dose per fraction, d_{50kV}, for each applicator. The isoeffective dose was 7–11% lower for a 4.0-cm applicator diameter and 3–7% higher for 5.0 cm compared with 4.5 cm. Thus the isoeffective dose per fraction is determined mainly by the assumptions regarding RBE, whereas the effect of applicator size on the radial extent of fibrosis will be small. Using a different prescribed dose for each applicator size, therefore, hardly seems clinically important. The radial distribution of fibrosis was calculated for all three applicator sizes (4.0–5.0 cm diameter) using the fraction sizes determined for the intermediate diameter, 4.5 cm (Figures 2a and 2b). The distribution of risk of pneumonitis for the two dose fractions (Figures 2c and 2d) estimated ED_{50} to be limited to 9–11 mm distance from the applicator.

Table 1. Isoeffective fraction size, d, at 1.0 cm distance from the applicator surface for accelerated partial-breast irradiation (APBI) with ten fractions of 50-kV X-rays from Intrabeam®. The fraction size was determined by radiobiological modeling to be isoeffective with single dose intraoperative radiotherapy (20 Gy at the applicator surface) for radial extent of fibrosis. The calculations were performed for different assumptions regarding the relative biological effectiveness (RBE). fx: fraction.

Tabelle 1. Isoeffektive Fraktionsgröße, d, in 1,0 cm Abstand von der Applikatoroberfläche für akzelerierte Teilbrustbestrahlung (APBI) mit zehn Fraktionen Intrabeam®-50-kV-Röntgenstrahlen. Die Fraktionsgröße wurde durch strahlenbiologische Modellierung so bestimmt, dass Fibrose nach APBI das gleiche radiale Ausmaß wie nach Einzeit-IORT (intraoperative Radiotherapie) mit 20 Gy an der Applikatoroberfläche haben sollte. Die Berechnungen wurden unter verschiedenen Annahmen bezüglich der relativen biologischen Wirksamkeit (RBE) durchgeführt. fx: Fraktion.

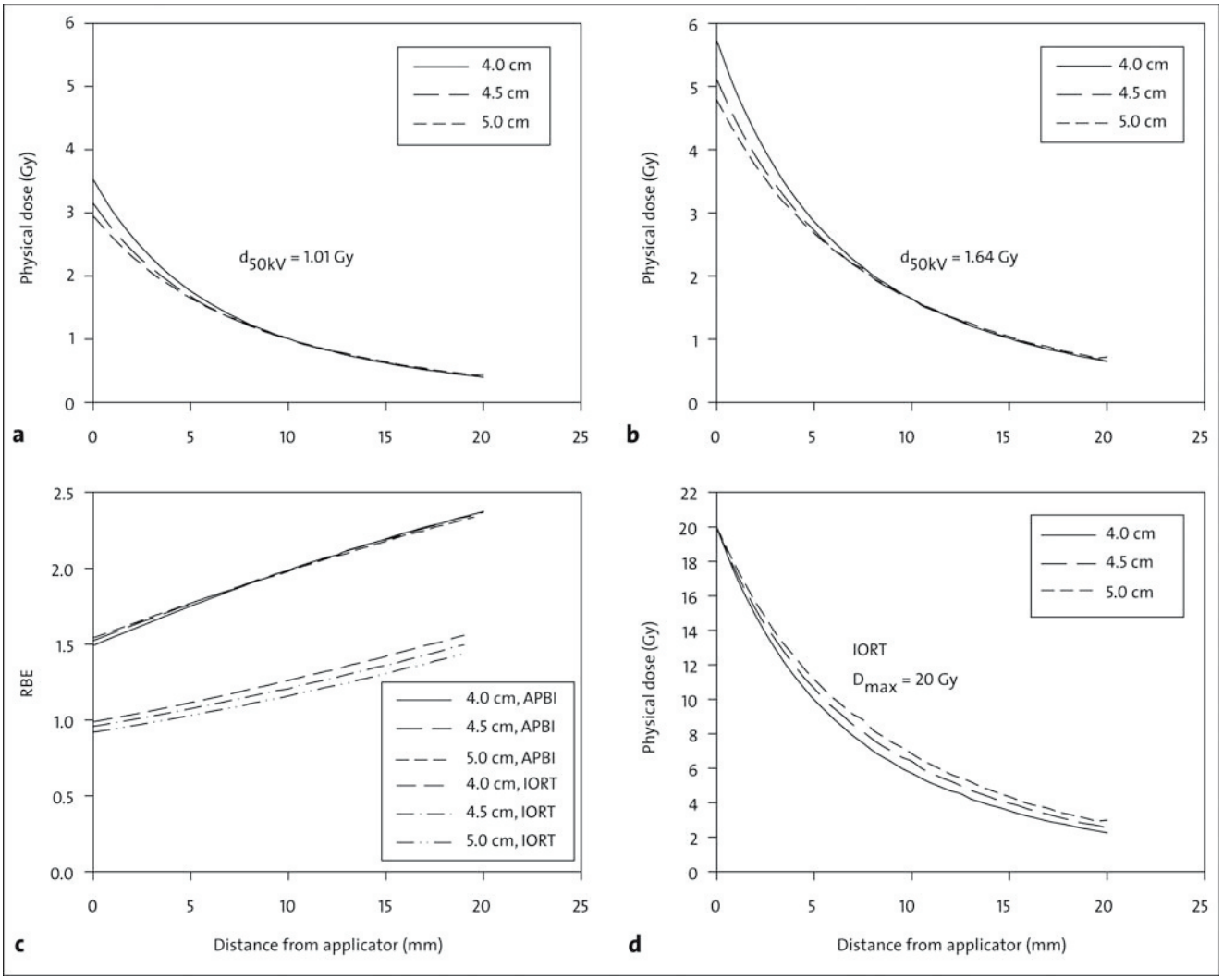
Applicator diameter (cm)	RBE assumption including repair	Constant = 1.2	Constant = 1.5
4.0	0.936 Gy/fx	1.46 Gy/fx	1.47 Gy/fx
4.5	1.01 Gy/fx	1.64 Gy/fx	1.64 Gy/fx
5.0	1.04 Gy/fx	1.76 Gy/fx	1.75 Gy/fx



Figures 2a to 2d. Radial distribution of risk of fibrosis (a, b) and pneumonitis (c, d) after ten fractions of size d_{50kV} at 1.0 cm distance from the surface of applicators 4.0–5.0 cm in diameter. The fraction sizes were chosen to be isoeffective with single dose IORT for fibrosis using a 4.5-cm applicator. Modeling calculations were performed for different assumptions regarding RBE: L-Q formalism including the effect of SLD repair, d_{50kV} = 1.01 Gy (a, c), and constant RBE = 1.2 or 1.5, d_{50kV} = 1.64 Gy (b, d).

Abbildungen 2a bis 2d. Radiale Verteilung des ermittelten Risikos für Fibrose (a, b) bzw. Pneumonitis (c, d) nach zehn Fraktionen der Fraktionsgröße d_{50kV} in 1,0 cm Abstand der Oberfläche von Applikatoren mit 4,0–5,0 cm Diameter. Fraktionsgrößen, isoeffektiv mit Einzeit-IORT bezüglich Fibrose, wurden für einen Applikatordiameter von 4,5 cm gewählt. Die Modellberechnungen wurden unter verschiedenen Annahmen bezüglich RBE durchgeführt: linear-quadratischer Formalismus einschließlich Reparatur subletaler Schäden (a, c) bzw. konstante RBE = 1,2 bzw. 1,5 (b, d).

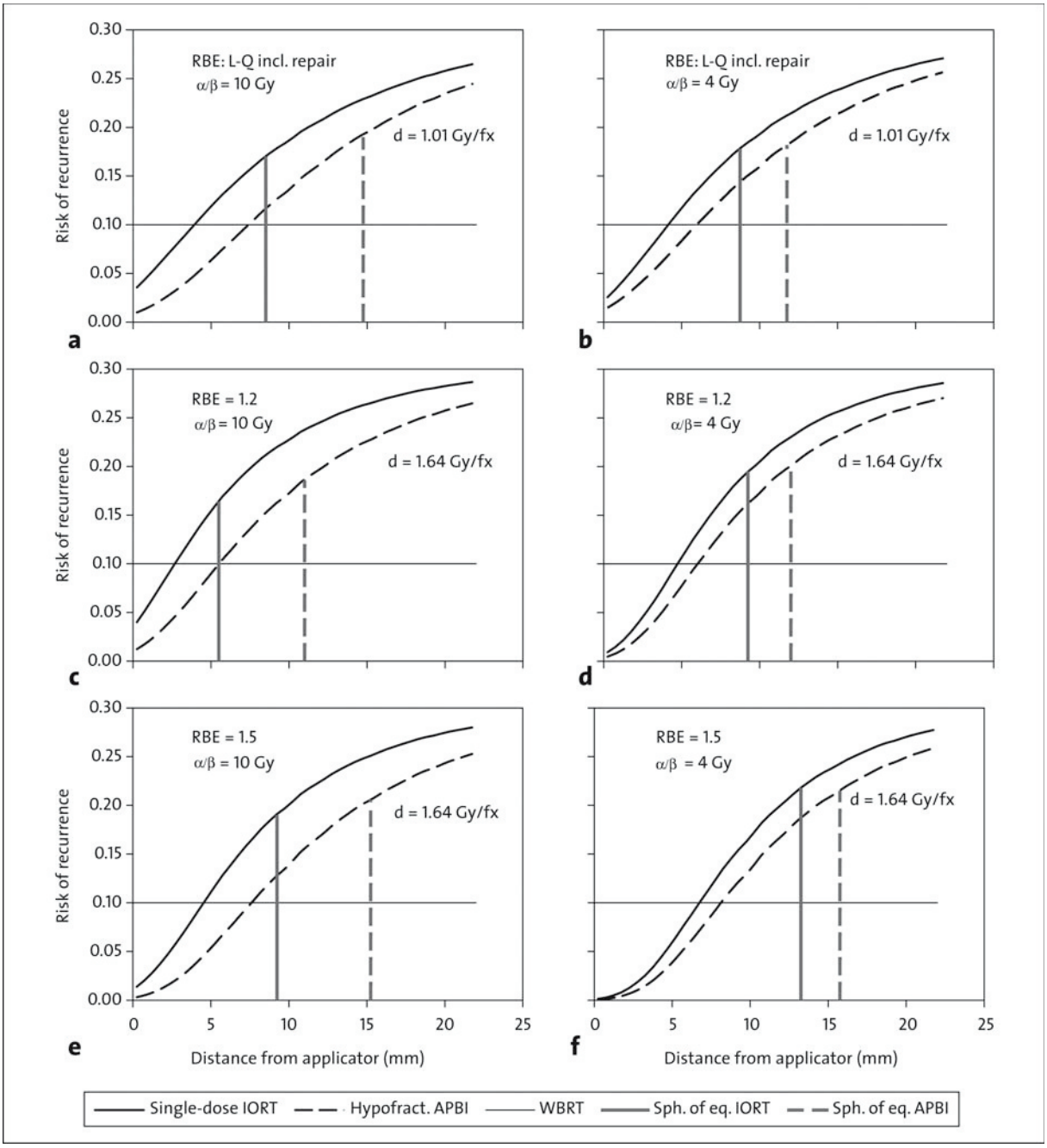
Doses at the applicator surface can vary in the range of 3.0–5.7 Gy/fraction, depending on d_{50kV} and applicator size (Figures 3a and 3b). Owing to the dose-squared law for isotropic radiation sources, the slope of the normalized dose versus distance from the applicator surface decreases with increasing radius of the applicator [8]. For dose prescription with APBI at 1 cm distance, the physical dose of 50-kV X-rays will increase with decreasing applicator size at distances closer to the applicator (Figures 3a and 3b). Since the applicator size is predicted to have little influence on RBE for APBI (Figure 3c), the equivalent fraction size of reference radiation, $d_{ref} = RBE \times d_{50kV}$, should increase with decreasing applicator size. Fibrosis is limited to short distance from the applicator, whereas induction of pneumonitis occurs at larger distance [8]. Therefore, the radial extent of fibrosis was predicted to increase with decreasing applicator diameter, while the radial extent of pneumonitis (close to the prescription point at 1 cm) will be essentially independent of the applicator size. Dose prescription at the applicator surface in the TARGIT protocol for single-dose IORT implies that the dose at a given distance from the applicator increases with increasing applicator diameter (Figure 3d). However, since RBE modeled by the L-Q formalism including SLD repair decreases with increasing applicator diameter (Figure 3c), the two opposing effects essentially cancel each other rendering the extent of fibrosis nearly independent of the applicator diameter. For constant RBE, on the other hand, the equivalent dose of reference radiation will be proportional to physical dose and thus the radial extent of fibrosis should increase with applicator size [8].



Figures 3a to 3d. The slope of the radial physical dose distribution of 50-kV X-rays increases with decreasing applicator diameter. Dose prescription at 1 cm distance from the applicator surface for APBI implies that the physical dose increases with decreasing applicator size for distances < 1 cm. d_{50kV} = 1.01 Gy for RBE estimated by the L-Q formalism including SLD repair (a); d_{50kV} = 1.64 Gy for constant RBE = 1.2–1.5 (b). RBE for normal tissue reaction (α/β = 3 Gy) was modeled by the L-Q formalism including repair increases with increasing distance (decreasing dose per fraction) and shorter irradiation times (smaller applicator diameter). The effect of applicator size was negligible for hypofractionated APBI (short irradiation time), but not for single-dose IORT with longer irradiation times (c). For comparison, prescription of dose at the applicator surface as for IORT (D_{max} = 20 Gy) results in an increase of physical dose with increasing applicator size (d).

Abbildungen 3a bis 3d. Die Steigung der radialen physikalischen Dosisverteilung für 50-kV-Röntgenstrahlen nimmt mit kleineren Applikatorgrößen zu. Die Dosisverschreibung in 1 cm Abstand von der Applikatoroberfläche für APBI bedeutet eine Zunahme der physikalischen Dosis von 50-kV-Röntgenstrahlen mit abnehmender Applikatorgröße bei Abständen < 1 cm. d_{50kV} = 1,01 Gy für RBE berechnet mit dem linear quadratischen Formalismus einschließlich Reparatur (a); d_{50kV} = 1,64 Gy für konstante RBE = 1,2–1,5 (b). Bei Modellierung mit dem linear-quadratischen Formalismus einschließlich Reparatur nimmt RBE für Normalgewebsreaktion (α/β = 3 Gy) mit zunehmenden Abstand (kleinere Dosen) und kürzeren Bestrahlungszeiten (kleineren Applikatorgrößen) zu. Der Einfluss der Applikatorgröße war vernachlässigbar für hypofraktionierter APBI (kurze Bestrahlungszeit), nicht aber für Einzeit-IORT mit längeren Bestrahlungszeiten (c). Die Dosisverschreibung an der Applikatoroberfläche bei Einzeit-IORT (D_{max} = 20 Gy) führt zu einer Zunahme der Dosis mit zunehmender Applikatorgröße (d).

The distribution of risk of recurrence was compared for hypofractionated APBI and single-dose IORT at isoeffective doses for late reactions (Figures 4a to 4f). The size of the "sphere of equivalence" was influenced by the RBE model and by the α/β value for local control, but fractionation was predicted to increase its size in all cases. Thus the radius would be expected to increase by 5–6 mm for α/β = 10 Gy and by 2.5–3 mm for α/β = 4 Gy. The volume of tumor bed within the "sphere of equivalence" would be increased 1.3- to 2.5-fold.



Figures 4a to 4f. Modeled distribution of risk of recurrence as function of the distance from the applicator surface for hypofractionated APBI with ten equal fractions for 4.5 cm applicator diameter. The position of the sphere of equivalence (sph. of eq.) is indicated by the vertical lines. The calculations were performed for isoeffective doses per fraction with respect to fibrosis after single-dose IORT. The dose per fraction was d_{50kV} = 1.01 Gy for RBE calculated by the L-Q formalism including repair (a, b), and d_{50kV} = 1.64 Gy for constant RBE = 1.2 (c, d) or 1.5 (e, f). Calculations were performed assuming α/β = 10 Gy (a, c, e) or α/β = 4 Gy (b, d, f) for local tumor control.

Abbildungen 4a bis 4f. Die modellierte Verteilung des Rezidivrisikos als Funktion des Abstands von der Applikatoroberfläche für hypofraktionierte APBI mit zehn gleich großen Fraktionen bei einem Applikatordiameter von 4,5 cm. Die Position der Äquivalenzkugel (Sph. of eq.) ist durch die senkrechten Linien markiert. Die Berechnungen wurden für isoeffektive Fraktionsgrößen in Bezug auf Fibrose nach Einzeit-IORT durchgeführt. Die Dosis pro Fraktion war d_{50kV} = 1,01 Gy für RBE nach dem linear quadratischen Formalismus einschließlich Reparatur (a, b) bzw. d_{50kV} = 1,64 Gy für konstante RBE = 1,2 (c, d) bzw. 1,5 (e, f). Die Berechnungen wurden unter der Annahme von α/β = 10 Gy (a, c, e) bzw. α/β = 4 Gy (b, d, f) für lokale Tumorkontrolle durchgeführt.

Discussion

The present model calculations support that hypofractionated APBI with 50-kV X-rays from Intrabeam® might increase local control in the tumor bed without increasing the risk of late fibrotic reaction, thus potentially increasing the therapeutic window.

Radiobiological modeling involves a number of assumptions and estimates of model parameters. In the L-Q formalism, RBE $\rightarrow \alpha_{50kV}/\alpha_{ref}$ for D $\rightarrow$ 0 and thus the assumption regarding the numeric value of this ratio becomes increasingly important, as the dose per fraction is reduced. Furthermore, the time to deliver each dose fraction is shorter than for IORT, so the effect of SLD repair during protracted irradiation is considerably smaller than for single-dose irradiation. Both factors contribute to increasing the estimated RBE demonstrated by values in the range of 1.5–2 for small dose fractions compared with 0.9–1.3 for single-dose IORT within the first 10 mm distance from the applicator surface. To reduce the dependence on model parameters, constant values of RBE of 1.2–1.5 were included in the modeling calculations.

Owing to the difference in RBE, the isoeffective doses per fraction estimated from the L-Q formalism including the effect of SLD repair resulted in a smaller dose fraction (d_{50kV} = 1.01 Gy/fraction at 1.0 cm depth) than for constant RBE (d_{50kV} = 1.64 Gy/fraction in 1.0 cm depth). This follows from the fact that the physical dose yielding a given equivalent dose of reference radiation (e.g., resulting in 50% risk) is inversely proportional to RBE (because $d_{ref} = RBE \times d_{50kV}$). For constant RBE, fibrosis extended to larger distance (greater depth in the tumor bed) for RBE equal to 1.5 compared with 1.2. However, the isoeffective dose per fraction was the same for the two values, because RBE influenced the spatial extent of fibrosis after single-dose IORT similarly.

Because of the different reference points for dose prescription, the dependence of the extent of fibrosis on applicator size was reversed for APBI compared with IORT. However, the difference in isoeffective dose for different applicator sizes was modest and caused only a small variation of the extent of fibrosis, which did not justify using different prescribed doses for different applicator sizes. Furthermore, the applicator size had essentially no influence on the predicted risk of pneumonitis, because the radial extent was close to the dose prescription point. Importantly, the predicted extent of pneumonitis after hypofractionated irradiation was comparable to that after IORT with a single dose. Thus the thickness of the chest wall should shield the lung tissue against the risk of pneumonitis after hypofractionated irradiation as already found for single-dose IORT.

As expected, the size of tumor bed volume within the "sphere of equivalence" for recurrence was increased by fractionation compared with single-dose IORT by a factor of 1.3–2.5. The size was increased irrespective of the assumptions regarding RBE. Importantly, the effect depends on the differential in α/β between tumor and normal tissue. Usually, a value of α/β = 10 Gy is assumed for most tumor cells in vivo and in vitro [12, 26, 37], but recent hypofractionation trials yielding α/β = 4.6 Gy (confidence interval 1.1–8.1) adjusted for known prognostic factors [1], strongly suggested that values of α/β may be lower than 10 Gy.

Delays between surgery and the start of radiotherapy significantly influence local control, implicating that proliferation of residual tumor cells in this time interval plays an important role [5, 10]. For IORT, the time interval is reduced to zero, thus completely eliminating any proliferation of tumor cells between surgery and irradiation. In the present calculations, the same assumption was made, i.e., that APBI was started immediately after surgery, so that proliferation can be neglected. Therefore, an important prerequisite for transferring the present model calculations into the clinical situation is that the time interval between surgery and APBI is kept short.

Conclusion

Hypofractionated APBI with Intrabeam® should be able to increase the therapeutic window between tumor control and late normal-tissue reaction. In any case, the fraction sizes determined here strongly depend on the true value of RBE. Because of the increased dose per fraction at the applicator surface, the isoeffective dose per fraction in the range of 1.0–1.6 Gy should be used only as a first estimate for a phase I/II study to determine safe doses. Close long-term monitoring of late reaction and local control is mandatory.

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