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Breast radiobiology

Is α/β for breast cancer really low?

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ABSTRACT

Purpose: Low α/β ratio for breast cancer has drawn a growing interest for exploring hypofractionation for breast irradiation. This work is to confirm the low α/β ratio based on large randomized clinical trials of breast irradiation.

Methods and materials: A model based on the generalized linear-quadratic (LQ) model and Poisson statistical model was developed to calculate disease-free survival with consideration of clonogen proliferation during the course of radiation treatment and exponential behavior of survival rate with follow-up time. Outcome data from a series of randomized clinical trials of early-stage breast radiotherapy were fitted to estimate the model parameters. Other clinical outcomes, including treatments with surgery alone or radiotherapy alone were used to validate the model and the estimated parameters. Hypofractionation regimens were proposed based on the newly estimated LQ parameters.

Results: Plausible population averaged radiobiologic parameters for breast cancer (95% confidence level) are $\alpha/\beta = 2.88$ (0.75–5.01) Gy; $\alpha = 0.08 \pm 0.02$ Gy^{-1}; potential doubling time $T_d = 14.4 \pm 7.8$ day. The analysis of the radiation-alone data suggested an α/β ratio of 3.89 ± 6.25 Gy, verifying the low α/β ratio based on the post-lumpectomy irradiation data. The hypofractionation regimens that are equivalent to the conventional regimen of 2.0 Gy × 25 in 5 weeks include 2.26 Gy × 20, 3.34 Gy × 10, 4.93 Gy × 5 or 3.39 Gy × 10 (BID).

Conclusions: The analysis of the available clinical data from multiple institutions support that breast cancer has a low ratio of α/β, encouraging hypofractionated radiotherapy regimens for breast cancer.

Breast carcinoma is the leading cancer in women [1]. Over the past several decades, breast-conservation treatment (BCT) has become the standard therapy for the early-stage breast cancer. Postoperative radiotherapy (RT) after lumpectomy is widely used to reduce local recurrence of breast cancer. Conventionally, a dose per fraction of 1.8–2.0 Gy in 25 fractions over 5–6 week treatment duration has been widely used.

Recently, it has been argued that the α/β ratio for breast cancer may be lower than previously considered [2–5]. This has resulted in a growing interest for exploring hypofractionation for breast irradiation. Hypofractionation schemes for breast treatment, which uses larger than 2 Gy per fraction and a shorter treatment period while maintaining cosmetic and patient disease-free survival rates, are attractive for early-stage breast irradiation. In this context, various clinical hypofractionated radiation therapy trials [3–10], in comparison of the clinical outcomes from the standard fraction scheme, are compiled and analyzed. The purpose of the work is to confirm the low α/β ratio for breast cancer based on available clinical data from large randomized trials of whole breast irradiation.

Method and materials

Clinical outcome data

A number of clinical outcomes for early-stage breast cancer treatment, including (1) breast conserving therapy (BCT), (2) radiotherapy alone and (3) breast-conservation surgery (BCS) alone were carefully analyzed. Table 1 shows the selected clinical outcome data used in this analysis, including study group, study size, fractionation schedule and local recurrence rate at specified follow-up times. Other clinical outcomes from different treatment regimens, such as surgery alone [8] and radiotherapy alone [9], were used to validate the model and/or the estimated model parameters.

Breast conversation surgery plus radiotherapy

Whelan et al. [6] compared two fractionation schedules: short term (42.5 Gy in 16 fractions over 22 days) and long term (50 Gy in 25 fractions over 35 days) based on a randomized trial of 1234 patients with early stage lymph node-negative breast cancer.

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Table 1
List of the clinical outcome data analyzed in this analysis.

Study	Study size	No. of fraction/ treatment duration/dose per fraction	Boost dose (% patient)	Follow-up (yr)	Local recurrence (%)
BCS + Radiation					
Whelan et al. (2002)					
50 Gy	612	25/35d/2.0 Gy	no	5	3.2
42.5 Gy	622	16/22d/2.66 Gy	no	5	2.8
Owen et al. (2006)					
50 Gy	471	25/35d/2.0 Gy	15.5 Gy (74%)	10	12.1
42.9 Gy	466	13/35d/3.3 Gy	15.5 Gy (75%)	10	9.6
39 Gy	474	13/35d/3.0 Gy	15.5 Gy (74%)	10	14.8
Shelley et al. (2000)					
40 Gy	294	16/22d/2.5 Gy	no	5	3.5
Clark et al. (1996)					
40 Gy	416	16/22d/2.5 Gy	12.5 Gy	3.6	5.5
Start A (2008)					
50 Gy	749	25/35d/2.0 Gy	10 Gy (60.4%)	5	3.6
41.6 Gy	750	13/35d/3.2 Gy	10 Gy (61.0%)	5	3.5
39 Gy	737	13/35d/3.0 Gy	10 Gy (60.5%)	5	5.2
Start B (2008)					
50 Gy	1105	25/35d/2.0 Gy	10 Gy (41.4%)	5	3.3
40 Gy	1110	15/15d/2.67 Gy	10 Gy (43.8%)	5	2.2
Radiotherapy alone					
Arriagada et al. (1985)					
40–45 Gy	242	16/21d/2.5 Gy or 20/28d/2.25 Gy	0–15 Gy or 20–35 Gy	3	78
45 Gy	221	18/30d/2.5 Gy	0–15 Gy or 20–35 Gy		
No radiation					
Clark et al. (1996)	421			3.6	25.7
Fisher et al. (2002)	634			20	39.2
Forrest et al. (1996)	294			5.7	24.5

Five-year local recurrence-free survival rates were 97.2% and 96.8% in the short and long arms, respectively, and no difference in disease-free or overall survival rates was seen.

Owen et al. [3] studied the effectiveness of fractionation schemes in early-stage breast treatment with a long-term follow-up. They randomly assigned 1410 women into three groups: 50 Gy given in 25 fractions, 39 Gy given in 13 fractions and 42.9 Gy given in 13 fractions, all doses were given over 5 weeks. After a median follow-up of 9.7 years, the risk of ipsilateral tumor relapse after 10 years was 12.1%, 14.8% and 9.6% in the groups of 50 Gy, 42.6 Gy and 39 Gy, respectively. An α/β ratio of 4.0 Gy for breast cancer was estimated from this study.

Most recently available outcome data were from two large randomized trials in the United Kingdom Standardization of Breast Radiotherapy (UK START) trial A and trial B [4,5]. A total of 2236 patients were enrolled in the START trial A, which includes randomized comparisons of 41.6 Gy in 13 fractions of 3.2 Gy and 39.0 Gy in 13 fractions of 3.0 Gy over 5 weeks with a control schedule of 50 Gy in 25 fractions of 2.0 Gy over 5 weeks. The rate of local–regional tumor relapse at 5 years was 3.6% in the 50 Gy group, 5.2% in the 39 Gy group, and 3.5% in the 41.6 Gy group. In the START Trial B, 2215 women were randomly assigned to 40 Gy in 15 fractions over 3 weeks or to 50 Gy in 25 fractions over 5 weeks. The rates of local–regional tumor relapse and late adverse effects for 40 Gy in 15 fractions were comparable to the standard schedule of 50 Gy in 25 fractions. In both trials adjuvant chemotherapy and tamoxifen were allowed per clinical practice, and a boost irradiation of 10 Gy was optional.

Breast cancer with radiotherapy alone

Arriagada et al. [9] retrospectively analyzed the data for a total of 463 breast cancer patients treated by RT alone from two cancer institutions. These patients either had inoperable tumors or were unsuitable for general anesthesia. The fractionation schedules include 40 Gy in 16 fractions over 21 days, 45 Gy in 20 fractions over 28 days, or 45 Gy in 18 fractions over 30 days. The boost dose to the tumor varied from 0 to 15 Gy or 20–35 Gy. This analysis clearly shows that tumor dose was the most significant factor on local control.

Breast cancer with no radiotherapy treatment

Clark et al. [8] reported a randomized clinical trial of breast conserving surgery with and without radiation treatment. All patients went through lumpectomy and axillary lymph node dissection. Patients (416) treated with 40 Gy with 16 fractions in 3 weeks were compared with 421 patients randomly assigned to no radiation therapy group. A dose of 12.5 Gy in five fractions was followed to the primary site in radiation group. The study showed that at a median follow-up of 7.6 years breast irradiation significantly reduced the local recurrence to 11% compared to 35% without treatment. There was no impact on overall survival; however there was a lower distant metastatic rate (23% versus 30%) in the irradiated arm.

Radiobiological models and fitting

The generalized linear-quadratic (LQ) model [11,12] with consideration of clonogen proliferation during the course of radiation treatment expresses as:

$$S = e^{-E} \tag{1}$$

$$E = \alpha D + \beta G D^2 - \gamma T \tag{2}$$

where S is the cell surviving fraction. The parameters α and β characterize intrinsic radiosensitivity for tumor, G is the dose protraction factor. For external beam radiation, the dose delivery time is generally shorter than the repair half-time of tumor cells, the total dose $D = nd$ and $G = 1/n$, where n is the number of fractions, d is

the dose per fraction. The quantity γ is the effective tumor-cell repopulation rate: $\gamma = \ln 2/T_d$, where T_d is the potential tumor cell doubling time. The total treatment duration T can be simply calculated as the number of treatment fractions multiplied by 1.4 (assuming five fractions per week).

The local disease-free survival rate (LSR) for breast radiation treatment is calculated from the cell surviving fraction S shown in Eq. (1) using the Poisson hypothesis [13]:

$$LSR(D) = e^{-k \cdot S} \tag{3}$$

Where, k is the number of tumor clonogens. S is the cell surviving fraction which can be calculated from Eqs. (1) and (2).

To simulate the relationship between prescription dose (D) and patient LSR at any elapsed time after radiation treatment ($\tau > T$), an exponential behavior of survival rate with elapsed time (τ) can be assumed and calculated by the following empirical equation [14,15]:

$$LSR(D,\tau) = e^{-k \cdot e^{-(\alpha D + \beta G D^2 - \gamma T)} \cdot e^{a(\tau - T - T_0)^b}} \quad (\tau > T) \tag{4}$$

A new term of $e^{a(\tau - T - T_0)^b}$ was introduced in Eq. (4), which is used to simulate the LSR evolution after radiation therapy completion at any elapsed time; it can be also understood to account for the tumor clonogenic cell repopulation according to Gompertz tumor growth model [16,17]. T_0 is the time for the tumor cells to start to grow exponentially after radiation treatment completion. In this study, we assume $T_0 = 0$ (see Discussion).

Under the initial situation such as breast conserving surgery without radiation treatment involved, say in Eq. (4), let $D = 0$ and $T = 0$, the equation can be rewritten as

$$LSR(D,\tau)|_{D=0} = e^{-k \cdot e^{a\tau^b}} \tag{5}$$

Thus, Eq. (5) is the relationship between the LSR and the elapsed time if no radiation is given, which also can be understood as tumor clonogenic cell repopulation with the elapsed time τ.

The Function Minimization and Error Analysis package (MINUIT) from the CERN program library (Geneva, Switzerland) was employed to fit the clinical outcome data using Eq. (4). A total of six fitting parameters, as shown in Eq. (4), are: α, β, the clonogenic number (k), the potential tumor doubling time (T_d) and tumor regrowth rate after radiation treatment, characterized by parameter a and b. All these parameters are independent variables and constrained to be positive. The idea of the fitting is to find the best-fit curve for a given clinical data set. The best-fit curve is defined as the parameter set that has the minimal sum of the deviations squared (least χ^2 error). The sum of the deviations is defined as:

$$\chi^2 = \sum_{j=1}^{n} \frac{[LSR^{Calc}(D_j,\tau) - LSR^{Obs}(D_j,\tau)]^2}{\sigma_j^2}, \tag{6}$$

where, $LSR^{Calc}(D_j, \tau)$ is the j-th patient survival rate calculated from Eq. (4); $LSR^{obs}(D_j, \tau)$ is the observed survival rate for the given dose D_j at time τ after the treatment; σ_j^2 is the error for the j-th data point. The statistical error σ_j can be calculated by Eq. (6) according to [17]:

$$\sigma_j = LSR(D_j,\tau) \cdot \sqrt{(1 - LSR(D_j,\tau))/N_j} \tag{7}$$

where N_j is the number of patient at risk during the interval j. The goodness of data fitting is evaluated by χ^2/dof, where dof is the degree of freedom, which is defined as the total number of clinically observed survival data points minus number of free parameters in the fitting function. For an acceptable fitting result, χ^2/dof should be around 1.0.

Weighted least-square method

Since the estimated parameters from different groups are uncorrelated, a plausible radiobiologic parameter based on a population of trials is calculated by:

$$\bar{x} \pm \delta\bar{x} = \frac{\sum_i \omega_i x_i}{\sum_i \omega_i} \pm \left(\sum_i \omega_i\right)^{-1/2} \tag{8}$$

where

$$\omega_i = 1/(\delta x_i)^2 \tag{9}$$

Here x_i and δx_i are the value and error yielded by fitting the i-th clinical trial. The weighting factor ω_i is calculated by the inverse square of the error of each measurement (δ_i). The weighting factor determines the relative importance of each quantity when considering a series of experimental data.

The fractionation regimen design

The newly derived parameter set was used to design new fractionation schemes that are radiobiologically equivalent to the current breast treatment schedules. For the target, the parameter set from this study is applied, while for the normal structures (e.g., heart and lung), the α/β ratio of 3 was assumed. The biological effective dose (BED) is defined as

$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\ln 2/T_d}{\alpha} T \tag{10}$$

To compare new regimens with the standard fraction regimen, the concept of normalized total dose (NTD) was used. The NTD, defined in 2 Gy fraction, is biologically equivalent to the standard fractionated dose [18–20], i.e.,

$$NTD = \frac{BED}{\left(1 + \frac{2.0}{\alpha/\beta}\right)} \tag{11}$$

Here, the NTD is the dose for a suggested fractionation scheme determined with the α/β ratio for the target to keep the same biological effect (as compared to the standard fraction regimen).

Results

Fig. 1 shows the fitting results of local disease-free survival rates from the selected individual clinical outcome data with follow-up times up to 16 years [3–7]. The estimated radiobiological parameters are summarized in Table 2.

Fig 2 displays local disease-free survival rates based on Arriagada et al. [9], where radiation alone was given in this group of patients. The analysis of the radiation-alone data suggested an α/β ratio of 3.89 (0.0–10.14) Gy, $\alpha = 0.04 \pm 0.04$ Gy^{-1} and $T_d = 11.0 \pm 12.2$ day (95% confidence level (CL)), verifying the lower α/β ratio estimated based on the data from post-lumpectomy irradiation. Fig. 3 shows the fitting results based on Clark et al. [8]. Local disease-free survival rates for BCT and lumpectomy alone data were considered and fitted simultaneously using Eq. (4). The fitter yields a similarly low α/β ratio of 3.34 (1.27–4.61) Gy. Other radiobiological parameters, such as $\alpha = 0.03 \pm 0.10$ Gy^{-1}, $T_d = 10.8 \pm 48.6$ day and $k = 14.5$ in 95% CL were obtained.

Fig. 4 shows the graphical comparison of the estimated α/β ratio (a) and α (b) derived from different regimens and/or different clinical outcome data sets: (1) lumpectomy plus radiation (BCT) (▲); (2) with/without radiation (○) and (3) surgery alone (Δ). All error bars show 95% CL. The fitting results from different groups (and/or regimens) are consistent within the uncertainty. The weighted average α/β ratios for breast PTV estimated based on the outcome

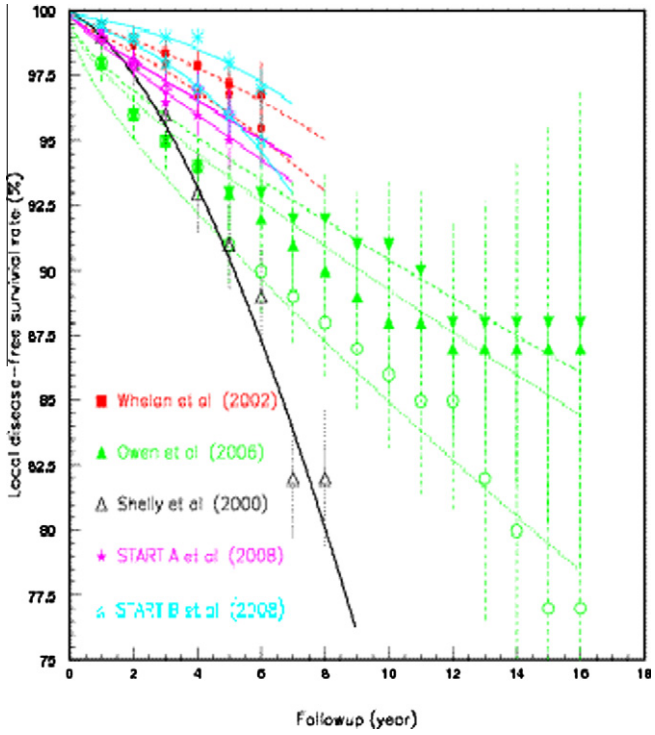

Fig. 1. Fitting results of local disease-free survival rates from multiple randomized clinical trials [3–7] with follow-up times up to 16 years. The curves represent the fitting (calculated based on proposed model) to the data points (from the literatures). Different dose fractionation schedules from the same clinical trial are shown in the same color with different line types.

Table 2
The estimated radiobiological parameters from different clinical data (95% CL).

	α/β (Gy)	$\Delta(\alpha/\beta)$	α (Gy^{-1})	$\Delta(\alpha)$	T_d (day)	$\Delta(T_d)$
Whelan	3.21	3.86	0.16	0.10	10.4	17.1
Owen	4.39	7.45	0.05	0.04	12.2	26.2
Shelley	2.21	1.59	0.13	0.06	21.3	71.5
START A	3.91	3.47	0.02	0.06	17.1	58.5
START B	2.49	1.63	0.09	0.02	15.9	9.7
Clark	1.44	1.27	0.03	0.10	10.8	48.6
Arriagada	3.89	6.25	0.04	0.04	11.0	12.2

data from the available randomized clinical trials (95% CL), are $\alpha/\beta = 2.88$ (0.75–5.01) Gy (ranging from 2.21 (0.62–3.82) Gy^{-1} [7] to 4.39 (0.0–11.84) [3]). The parameter of breast PTV radiosensitivty $\alpha = 0.08 \pm 0.02$ Gy^{-1} (ranging from 0.03 (0.0–0.08) Gy^{-1} [4] to 0.16 (0.06–0.26) Gy^{-1} [6]). The potential doubling time $T_d = 14.4$ (6.6–23.2) day (ranging from 10.4 (0.0–27.5) day [6] to 21.3 (0.0–92.8) day [7]). Noted that all the parameters were required to be positive, thus the lower bounds were all truncated at zero.

For the series data we studied, the parameter a and b are found to be in the range of (0.9–8.49)/yr and (0.07–0.46), respectively, indicating a slowing down pattern for breast tumor re-growth with time.

The fractionation regimen design

Based on the presently derived parameter set, we have calculated a series of fractionation schemes for whole breast cancer radiation treatment assuming different α/β ratios, including $\alpha/\beta = 10$ Gy (nominal α/β ratio for tumor), $\alpha/\beta = 2.88$ Gy (average from this analysis), 0.75 Gy (the lower bound from this analysis)

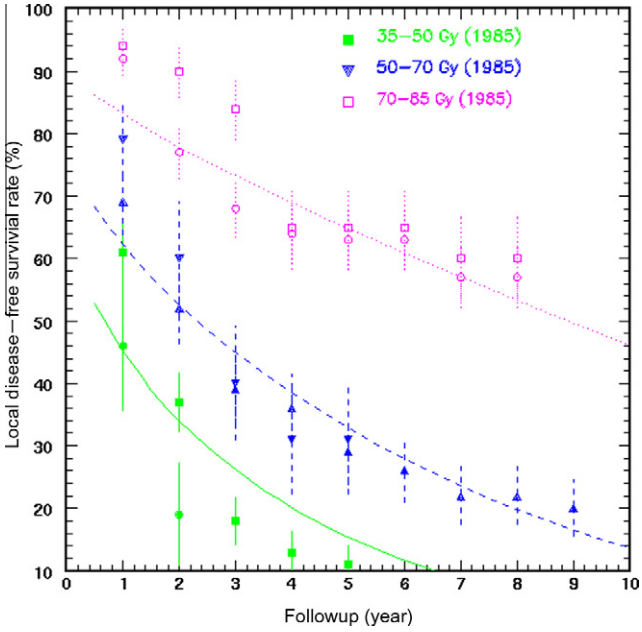

Fig. 2. Fitting results for radiation-alone data based on Arriagada et al. [9].

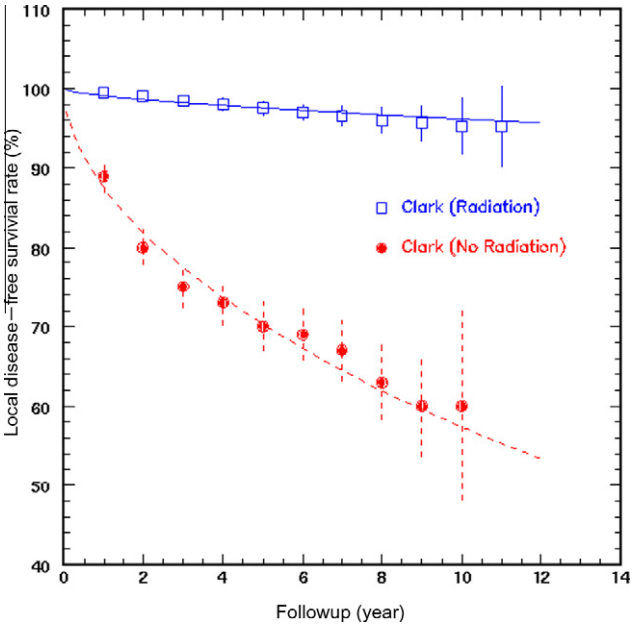

Fig. 3. Fitting results for radiation-alone data based on Clark et al. [8].

and 5.01 Gy (the upper bound from this analysis). The same α/β ratio is assumed in each group that achieved the same biological effectiveness for the target. Starting from the standard breast radiotherapy schedule (first row in each group), the possible hypofractionated schemes were calculated and tabulated in Table 3. The new fractionation regimens were designed (assuming different α/β ratios for breast cancer) that are biologically equivalent (for target) to the standard 2 Gy per fraction to 50 Gy in 35 days. The dose regimens for 20, 15, 10, 5, and 3 fractions and for 10 fractions given twice daily (BID) were calculated. As an example, if assuming the $\alpha/\beta = 2.88$ Gy for breast cancer, a fractionation scheme of 2.26 Gy × 20, 3.34 Gy × 10, 4.93 Gy × 5 or 3.39 Gy × 10 (BID) may be considered in order to achieve the same local control for breast cancer as the standard 2 Gy × 25 schedule. If the $\alpha/\beta = 5.01$ Gy, then the fraction dose of 2.26 × 20 Gy,

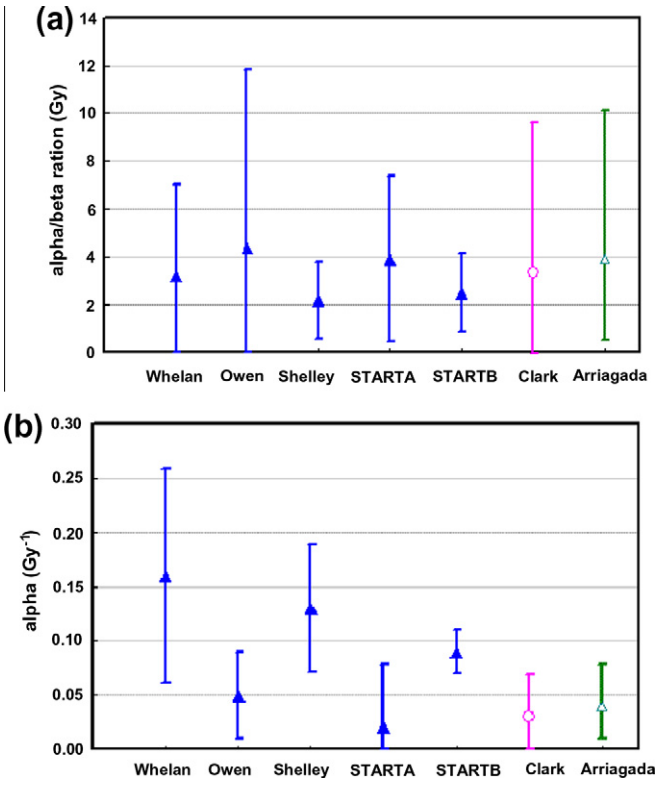

Fig. 4. Comparison of the α/β ratio (a) and the parameter α (b) derived from different clinical trials. Error bars represent 95% CL.

3.41 × 10 Gy, 5.13 × 5 Gy and 3.59 Gy × 10 (BID) may be considered. The NTDs for the target and OARs (assuming the $\alpha/\beta = 3$ for OARs) were also calculated. The advantage of a hypofractionated regimen may be seen from the BEDs for OARs if α/β ratio for breast cancer is less than 10 Gy. From the top to bottom in each group (excluding BID), the BEDs for OARs in each α/β group decrease with fewer fractions while BEDs for the targets are the same, indicating less complication for normal structures may be expected in hypofractionated schemes. For example, in the $\alpha/\beta = 2.88$ Gy series, a 27.7% decrease of BED (OAR) was seen in 4.93 Gy × 5 regimens (compared to the standard 2 Gy × 25 fraction) while the same biological equivalent dose to target was maintained. To achieve the same NTD for target as the current BID scheme of 3.85 Gy × 10 fractions, the fraction doses of 3.07 Gy, 3.39 Gy and 3.59 Gy should be considered assuming the α/β ratios of 0.75, 2.88 and 5.01 Gy, respectively.

Fig. 5 illustrates the NTD ratios of the target to OAR for different fractionated regimens with α/β ratios of 10, 2.88, 0.75 and 5.01 Gy for breast cancer respectively. Regimens with 3, 5, 10, 15, 20 and 25 were shown. It seems that when the α/β ratio for breast cancer is low (<10 Gy), fewer fractionation regimens tend to result in less BED for OARs while keeping the similar biological effectiveness for the target. Greater NTD ratios of target to OAR were clearly seen in hypofractionated schemes.

Discussion

Adjuvant whole breast irradiation after BCS has been proven appropriate for early-stage breast cancer yielding comparable local control and equivalent survival to mastectomy [21–22]. The standard radiation scheme using a dose per fraction of 2.0 Gy 25

Table 3
The dose per fraction, total dose, NTD for a series of fractionation schemes that lead to the same BEDs for the target. Four different α/β ratios for target were calculated and compared. For the organ-at-risk (OAR), the $\alpha/\beta = 3$ Gy was assumed.

	No. of fractions	Dose/fx (Gy)	Total dose (Gy)	T_d (d)	Target NTD (Gy)	OAR NTD (Gy)	NTD(Target)/NTD(OAR)	BED^{Target} (Gy)	BED^{OAR} (Gy)
$\alpha/\beta = 10$ Gy									
	25	2.00	50.0	35.0	32.5	50.0	0.65	38.9	83.3
	20	2.27	45.4	28.0	32.4	47.9	0.68	38.9	79.8
	15	2.70	40.5	21.0	32.3	46.2	0.70	38.8	77.0
	10	3.50	35.0	14.0	32.4	45.5	0.71	38.8	75.8
	5	5.42	27.1	5.0	32.3	45.6	0.71	38.8	76.1
	3	7.66	23.0	3.0	32.3	49.0	0.66	38.8	81.7
BID	10	3.85	38.5	5.0	41.9	52.7	0.79	50.3	87.9
$\alpha/\beta = 2.88$ Gy									
	25	2.00	50.0	35.0	37.6	50.0	0.75	63.7	83.3
	20	2.26	45.2	28.0	37.7	47.6	0.79	63.8	79.3
	15	2.65	39.8	21.0	37.6	44.9	0.84	63.7	74.9
	10	3.34	33.4	14.0	37.6	42.4	0.89	63.7	70.6
	5	4.93	24.7	5.0	37.7	39.1	0.96	63.8	65.2
	3	6.62	19.9	3.0	37.6	38.2	0.98	63.7	63.7
BID	10	3.39	33.9	5.0	41.8	43.3	0.96	70.8	72.2
$\alpha/\beta = 0.75$ Gy									
	25	2.00	50.0	35.0	44.3	50.0	0.89	162.3	83.3
	20	2.25	45.0	28.0	44.5	47.3	0.94	163.2	78.8
	15	2.61	39.2	21.0	44.4	43.9	1.01	162.8	73.2
	10	3.22	32.2	14.0	44.2	40.1	1.10	162.0	66.8
	5	4.62	23.1	5.0	44.3	35.2	1.26	162.4	58.7
	3	6.04	18.1	3.0	44.2	32.8	1.35	162.2	54.6
BID	10	3.07	30.7	5.0	41.8	37.3	1.12	153.4	62.1
$\alpha/\beta = 5.01$ Gy									
	25	2.00	50.0	35.0	35.0	50.0	0.70	48.9	83.3
	20	2.26	45.2	28.0	34.8	47.6	0.73	48.7	79.3
	15	2.67	40.1	21.0	34.8	45.4	0.77	48.8	75.7
	10	3.41	34.1	14.0	34.9	43.7	0.80	48.9	72.9
	5	5.13	25.7	5.0	35.0	41.7	0.84	48.9	69.5
	3	7.04	21.1	3.0	35.0	42.4	0.83	49.0	70.7
BID	10	3.59	35.9	5.0	41.9	47.3	0.89	58.6	78.9

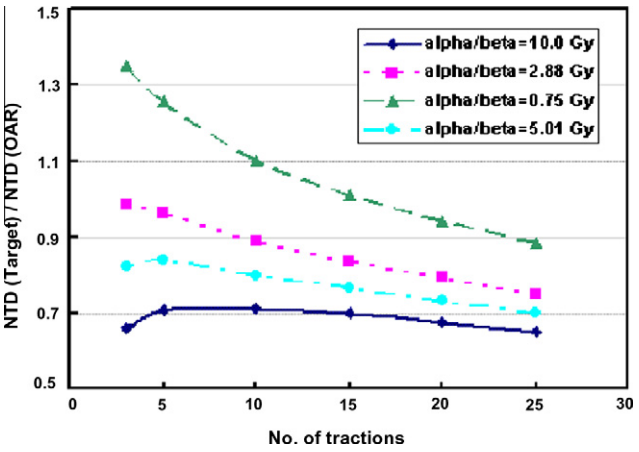

Fig. 5. The NTDs ratios of the target and OARs for different fractionated regimens calculated based on α/β ratios of 10, 2.88, 0.75 and 5.01 Gy for breast cancer. Fractionation regimens with 3, 5, 10, 15, 20 and 25 fractions are included.

fractions is set based on an assumption of the α/β ratio of 10 Gy for breast cancer. The α/β ratio of breast cancer has been under study with more recent data suggesting it to be around 4 [2,3], which implies the hypofractionated regimens should perhaps be more effective for local control of breast cancer as compared with the conventional 2 Gy fraction schedule. As a matter of fact, four randomized clinical trials [3–8] have so far demonstrated similar in breast local control and normal tissue damage in fewer fractions in comparison with the standard fractionation schedule. For example, based on the most recent publication from the United Kingdom group with the hypofractionated regimens (START A), the rate of local–regional tumor relapse at 5 years using hypofractionated schedule was comparable to that of in the 50 Gy group [5]. Similarly, Whelan et al. [6] reported a 5-year local relapse-free survival of 96.8% after 50 Gy in 25 fractions and 97.2% after 42.5 Gy in 16 fractions, respectively. They concluded that no statistical difference was found between hypofractionation and conventional schemes. Ongoing hypofractionation clinical trials for breast, such as the randomized United Kingdom FAST trial [10], are designed to compare late normal tissue responses and tumor control using fraction doses of 6 Gy and 5.7 Gy in five fractions over 5 weeks with the standard dose of 50 Gy in 25 fractions.

In this work, we have analyzed the outcome from a series of clinical trials to confirm the lower α/β ratio for breast cancer. A modified LQ model was employed to calculate LSR. The reported LSR from different groups was used directly to derive the radiobiologic parameters, therefore the concept of iso-effect which somewhat could be arbitrary is not needed in the α/β ratio determination. The α/β ratio for breast cancer was found in the ranges of 0.75–5.01 Gy using the least chi-square fitting technique. This finding confirmed with other literatures [3,4] that breast cancer may have a smaller α/β ratio, which, thus, suggests that a lower total dose in fewer fractions may be more effective than the conventional fractionation schemes. It is known that the lower α/β ratio (late-response tissue) is strongly dependent on dose per fraction, so the higher the dose per fraction, the greater the susceptibility of healthy tissues to radiation therapy. Given the fact that radiation induced cardiovascular disease for breast cancer may appear long (10–15 years) after radiotherapy, long-term follow up (for the current hypofractionation trials) on late lung and cardiac morbidity as well as survival rates are yet needed to evaluate the newly derived radiobiologic parameters.

The novelty of this work is using the analytic method. However, a resulting weakness is the introduction of additional parameters and assumption. For example, this analysis is based on the assumption that the dose and dose fractionation are the determining factors for LSR for breast cancer treatment. Therefore, the model we derived is a simplified empirical radiobiological model. Given the purpose of the study is not to investigate the dynamics of tumor growth (but to fit the clinical data and derive the population-based biological parameters), we consider our model in the first approximate is sufficient for that purpose. As shown in Fig. 1–3, the model is capable of simulating the LSR for breast cancer treatment up to 16 years for many randomized clinical trials. However, we need to mention the current analysis is limited by the following constraints: (1) Other than the prescription dose and dose fractionation, many prognostic factors have impact on the overall LSR but are not explicitly considered in the current study, such as tumor size, tumor staging, surgery extent (BCS with macroscopic excision or mastectomy, etc.), margin status, nodal status, adjuvant therapy (such as Tamoxifen and/or chemotherapy), etc. (2) Large variations exist in clinical data from different institutes. For example, the percentages of the patients who received boost treatment to tumor bed lead to different overall LSR, and the LSR for the patients with and without boost is not available separately from the literatures, which, in turn, resulted in the uncertainty of LSR and affected accuracy of the derived parameters. In particular, ~60% of BCS patients had a boost of 10 Gy in START A group, while only 42% of BCS patients received a boost dose of 10 Gy in START B. To account for different percentages of the patients who received boost treatment, the averaging boost dose (ABD) weighted by the proportion of patients receiving a boost dose is calculated by

$$ABD = \frac{\sum C_i \times D_i}{N}$$

Where C_i is the number of patients receiving a boost dose of D_i, and N is the total number of patients in the trial. For START B, the ABDs are calculated to be 4.14 and 4.38 Gy for the arms of 50 and 40 Gy, respectively. Considered the total doses delivered to the tumor bed, our fitting yields: $\alpha/\beta = 2.19 \pm 1.36$ Gy, $\alpha = 0.09 \pm 0.03$ and $T_d = 10.49 \pm 4.77$ day for START B, and $\alpha/\beta = 3.44 \pm 3.86$ Gy, $\alpha = 0.01 \pm 0.03$ and $T_d = 24.5 \pm 54.9$ day for START A. The parameters estimated using the total delivered doses are slightly different from the parameters estimated by using large field dose only (Table 2), however, they are consistent within the uncertainties. (3) The clinical data used are from the published articles, the individual patient data (censor data) are not reported from the literatures, which prevents us from using more robust analysis method such as maximal likelihood method. However, the methodology of the current study is general. The results for different prognosis factors (such as tumor size, tumor grading, etc.) can be done similarly once the clinical data become available.

Caution needs to be exercised when using the parameters for clinical purpose. The uncertainty in the analysis may be underestimated due to the complicated clinical situations. For example, the estimated potential doubling time of 14.4 (6.6–23.2) day was based on disease-free survival rate that includes not only the patients who have been cured but also the patients who have not been cured, but whose residual disease has not yet been detected at the follow-up time. Generally, tumors are unlikely to be detected until they grow to certain size (i.e., 1 gram or 10^9 cells) [16]. However, the clinical detection of tumor recurrence may vary significantly in literatures: some of patients are grossly palpable, some are found with mammogram or other imaging. In addition, differences in time to detection of recurrence may result from many factors, including significant differences in the follow-up intervals, and differences in the repopulation rate of surviving clonogens, therefore the data will not necessarily represent the same tumor size for all patients at the time of local recurrence. The model is only a partial reflection of what actually is represented in the data. Also, it is generally known that the tumor cells grow in

nonlinear fashion. According to Gompertz tumor growth model [16], starting with exponentially growth, the tumor growth decelerates and eventually stops. Tumor growth is more rapidly in preclinical phase for breast cancer, and progressive slowing at large size due to increasing cell death and decreasing cell proliferation as tumor nutrition deteriorates [15,16]. In this study, a time dependent tumor re-growth term $e^{\alpha(\tau-T-T_0)^b}$ is introduced to simulate tumor re-growth after radiation completion based on the clinical data. As a matter of fact, many questions remain to be answered, such as (1) when the tumor cells start to have exponential growth. In this work, due to the limited clinical data points, an implication is made that the tumor re-growth starts right after the radiation treatment completion ($T_0 = 0$); (2) Tumor doubling is assumed to be a constant. The tumor growth process is a complicated and unknown process. The detailed kinetic and mathematical formula of tumor re-growth is lacking and outside of scope of this study. However, our model shows similar trend in terms of tumor growth as in Gompertz model. Once the related data become available, the current method and model can be easily applied and modified to fit the clinical data.

The radiobiologic parameters derived from each individual trial are different, which may be understood as prognostic factor variations from institution to institution, the potential influence of chemotherapy on radiation response and on intra-treatment repopulation, etc. However, the presently estimated α/β ratio, the tumor sensitivity α and the potential doubling time T_d (95% CL) are all consistent within the uncertainty. All data analyzed in this analysis indicates a plausible low α/β ratio (<10 Gy) for breast cancer, which suggests that fraction size regimens using >2 Gy may be more suitable for breast cancer irradiation. The presently derived radiobiologic parameters may be useful in the design of new hypofractionated schemes for breast cancer radiation treatment. Larger fraction dose in fewer fractions could offer at least equivalent or more effective treatment in more convenient fashion for breast irradiation.

Conclusion

Based on large randomized clinical trials of whole breast irradiation, the analysis from multiple institutions yields α/β ratios in the range of 0.75–5.01 Gy (95% CL), supporting that breast cancer has a low α/β ratio. Such a low α/β ratio suggests that hypofractionated radiotherapy regimens may be advantageous for breast cancer. Using the α/β ratio derived above, selected possible fractionated regimens that are radiobiologically equivalent to the conventional 2.0 Gy $\times$ 25 regimens are calculated.

Conflict of interest

There is no conflict of interest for all authors.

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