Breast cancer radiobiology: The renaissance of whole breast radiation fractionation (Review)

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Received July 4, 2024; Accepted September 30, 2024

DOI: 10.3892/mco.2024.2795

Abstract. Breast cancer radiotherapy has evolved significantly, driven by decades of research into fractionation schedules aimed at optimizing treatment efficacy and minimizing toxicity. Initial trials such as NSABP B-06 and EBCTCG meta-analyses established the benefits of adjuvant whole-breast irradiation in reducing local recurrence and improving survival rates. The linear-quadratic (LQ) model provided a framework to understand tissue response to radiation, highlighting the importance of the α/β ratio in determining fractionation sensitivity. The present scoping review aimed to identify and describe hypofractionation regimens for whole breast radiotherapy and evaluate dose differences using the LQ model across proposed α/β ratios. A comprehensive PubMed search for clinical trials published since 2010 on hypo-fractionated regimens was performed. Studies discussing α/β ratios for breast cancer have been also searched. Data on dose, fractions and α/β ratios were collected, and biologically effective dose (BED) and equivalent dose in 2 Gy fractions were calculated. The coefficient of variation for BED varied with α/β ratios, showing the lowest variability for an α/β ratio of ~3 without tumor repopulation and increased with repopulation (BED-kT; k is a constant that depends on the repopulation rate of the tumor, and T is the total treatment time in days). Significant differences in BED variances were observed across α/β ratios (F-statistic 219.6, P<0.0001). START trials (P, A, and B) established α/β ratios of 3-4 Gy for breast cancer and normal tissues, confirming that hypofractionation is as effective as standard fractionation with potentially fewer late toxicities. Subsequent trials, such as FAST and FAST-Forward, demonstrated that ultra-hypofractionation is equivalent in tumor compared with conventional regimens. Further research is needed to gain a stronger understanding of radiobiological properties of breast cancer cells. Advances in radiotherapy technologies and the integration of biomarkers, radiomics and genomics are transforming treatment, moving towards precision medicine.

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Key words: breast cancer, radiotherapy, radiobiology, review, α/β ratio

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1. Introduction

In radiation oncology, the tale of fractionation schedules unfolds with the precision of a carefully crafted narrative. In a realm where each trial and study form a piece of a larger puzzle, the journey of breast cancer treatment has shifted profoundly. Decades of meticulous research have unveiled pivotal insights, reshaping how the battle against what is increasingly becoming a chronic disease is approached.

Breast cancer is the most common malignancy in females worldwide, with 2.3 million new cases in 2020 (1). The role of adjuvant radiotherapy for breast cancer has been extensively studied and has gone through multiple turning points. The landmark NSABP B-06 trial showed a notable reduction in 20-year local recurrence rates-from 39 to 14%-with addition of adjuvant radiotherapy (2). Moreover, findings from the EBCTCG meta-analysis underscored that adjuvant radiotherapy significantly enhances survival. It lowered the 15-year mortality risk from breast cancer to 26% for node-negative patients and to 48% for those with lymph node involvement (3). The analysis introduced the concept of a '4:1 ratio', illustrating that preventing 4 local recurrences by year 5 potentially averts 1 breast cancer death by year 15 (3).

Historically, breast cancer treatment relied on delivering 50 Gy over 25 fractions spanning 5 weeks via radiotherapy. This method sought to achieve effective tumor control while mitigating harm to surrounding tissues using 2 Gy fractions. However, emerging research illuminated a common

responsiveness of both healthy tissues and cancerous breast tissues to the size of treatment fractions, as measured by the *α/β ratio* (4-6).

This has paved the way for clinical trials such as the START trials, which confirmed the safety and efficacy of hypofractionation in both early-stage breast cancer and post-mastectomy settings (7). More recent trials, such as FAST and FAST-Forward, have further explored the potential of ultra-hypofractionated regimens, aiming to deliver doses in just a few fractions (8,9).

The present scoping review seeks to synthesize current evidence on hypofractionation in breast cancer radiotherapy, focusing on the dose-fractionation regimens tested in clinical trials and the radiobiological implications of varying α/β ratios. By exploring biologically effective dose (BED) calculations across different fractionation schedules, the present review aims to provide insights into optimizing treatment protocols that maximize therapeutic efficacy while minimizing toxicity.

2. The linear quadratic (LQ) model and our understanding of hypofractionation

The LQ model is a foundational concept in radiobiology used to describe the effects of radiation on cells (10). It provides a mathematical framework to predict cell survival following exposure to different doses of radiation. The LQ model is expressed by the equation:

$$S = e^{-\alpha D - \beta D2}$$

Where: S is the surviving fraction of cells; D is the dose of radiation; α and β are parameters that describe the linear and quadratic components of cell elimination, respectively. The biologically effective dose (BED) is a measure that reflects the biological effect of a given radiation dose. It accounts for the total dose, dose per fraction, and the tissue response to radiation. BED is useful for comparing different fractionation schedules and is calculated using the formula derived from the LQ equation as follows:

For a treatment of N fractions:

$$S = e^{N(-\alpha D - \beta D2)}$$

Taking the natural logarithm:

$$-\mathrm{Ln}S = N(\alpha D + \beta D^2)$$

Dividing by α:

$$BED = \frac{-lnS}{\alpha} = \mathrm{Nd\ x}\left(1 + \frac{d}{\alpha/\beta}\right)$$

Thus:

$$BED = D\ \mathrm{x}\left(1 + \frac{d}{\alpha/\beta}\right)$$

Where: BED is the biologically effective dose; D is the total dose in Gy (Gray); d is the dose per fraction in Gy; α/β is the alpha/beta ratio, representing tissue sensitivity to fraction size.

If accounting for repopulation, the formula becomes:

$$BED = D\ \mathrm{x}\left(1 + \frac{d}{\alpha/\beta}\right) - kT$$

Where k is a constant that depends on the repopulation rate of the tumor, and T is the total treatment time in days.

The equivalent dose in 2 Gy fractions (EQD2) is a concept used to compare different radiation treatment regimens. It normalizes doses to an equivalent dose delivered in 2 Gy fractions, which is the 'standard fractionation' scheme in radiotherapy. The EQD2 is calculated using a formula derived from the BED equation as follows:

Normalizing the BED equation to an equivalent dose delivered in 2 Gy fractions; the fraction size d was set to 2 Gy. Let $D_{2\mathrm{Gy}}$ be the total dose in 2 Gy fractions:

$$BED_{2Gy} = D_{2Gy}\ \mathrm{x}\left(1 + \frac{2}{\alpha/\beta}\right)$$

Since the BEDs for both the original and 2 Gy fractionation regimens should be equivalent, the 2 BED expressions were equated:

$$D\ \mathrm{x}\left(1 + \frac{d}{\alpha/\beta}\right) = D_{2Gy}\ \mathrm{x}\left(1 + \frac{2}{\alpha/\beta}\right)$$

Solving for $D_{2\mathrm{Gy}}$:

$$D_{2Gy} = \frac{D\ \mathrm{x}\left(1 + \frac{d}{\alpha/\beta}\right)}{1 + \frac{2}{\alpha/\beta}}$$

Multiplying by $\frac{\alpha/\beta}{\alpha/\beta}$, the EQD2 equation is derived as:

$$EQD2 = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

D is the total dose; d is the dose per fraction; *α/β* is the tissue-specific ratio of the linear and quadratic coefficients.

Understanding and applying these concepts are crucial for optimizing hypofractionated regimens in breast radiotherapy, ensuring effective and safe treatment for patients.

Hypofractionation refers to radiation doses exceeding 2 Gy per fraction, and ultra-hypofractionation as doses of 5 Gy or more per fraction. Normal and malignant tissues have different sensitivities to the size of radiotherapy fractions, described by the α/β ratio. Lower α/β ratios (measured in Gy) indicate greater sensitivity to changes in fraction size.

Previous studies have indicated that breast cancer exhibits comparable sensitivity to fraction size as late-reacting normal tissues as discussed below (5,11). Hypofractionation involves more than just reducing the overall treatment duration. In breast radiotherapy trials, adjustments in the EQD2 and BED of experimental regimens aim for iso-effectiveness, particularly concerning late tissue toxicity. This justifies how early attempts of hypofractionation, which did not sufficiently lower the total dose, led to high normal tissue toxicity, increasing the inertia against moving towards hypofractionation.

Due to the typically higher α/β ratio for acute tissue toxicity endpoints, hypofractionated regimens often exhibit a lower

EQD2 for acute toxicity. However, this does not necessarily translate to reduced acute toxicity because acute tissue toxicity is sensitive to overall treatment time, often increasing as the overall treatment time decreases, as observed in hypofractionated schedules. Conversely, tumor cell repopulation strongly supports the rationale for accelerating treatment through hypofractionation.

Precisely estimating the α/β ratio is essential for anticipating toxicity in novel hypofractionated schedules, which is particularly highlighted in breast cancer hypofractionation trials. The consistent results across these trials have solidified the relevance of the LQ model, even for the most condensed fractionation regimens employed in breast radiotherapy, as discussed below.

3. Methods

The present study is a scoping review, aiming to identify and describe hypofractionation regimens for whole breast radiotherapy, and to evaluate how they differ in terms of calculated dose using the LQ model, with and without accounting for tumor repopulation, based on the different α/β ratios proposed in previous studies.

Searching for hypofractionation regimens. A comprehensive search of the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was performed to identify clinical trials on hypofractionated and ultrahypofractionated radiotherapy for breast cancer (Fig. 1). The following search query was used: ((‘breast neoplasms’[MeSH Terms] OR ‘breast cancer’[Title/Abstract]) AND (‘hypofractionation’[Title/Abstract] OR ‘hypofractionated’[Title/Abstract] OR ‘ultrahypofractionation’[Title/Abstract]) AND (‘randomized controlled trial’[Publication Type] OR ‘clinical trial’[Publication Type])) AND (‘2010’[Date-Publication]: ‘2024’[Date-Publication]).

Inclusion criteria. The inclusion criteria were as follows: i) Clinical trials published after 2010 involving patients with breast cancer receiving adjuvant radiotherapy. ii) Studies examining hypofractionated or ultra-hypofractionated radiotherapy. iii) Study design should be a clinical trial. iv) Trials reporting local or locoregional control as outcomes.

Exclusion criteria. The exclusion criteria were as follows: i) Studies with designs other than clinical trials. ii) Studies investigating fractionation regimens with a concomitant boost to the tumor bed. iii) Studies focusing on partial breast irradiation instead of whole breast irradiation. iv) Studies reporting only toxicity outcomes without local or locoregional control. For eligible studies, data were collected on total dose, number of fractions and fraction size.

Searching for α/β ratios. An additional search was conducted in PubMed to identify studies discussing or proposing α/β ratios for breast cancer cells (Fig. 2). The studies identified in the earlier search were included in this phase, as they typically mention α/β ratios to justify the hypofractionated regimens used. Also, a previous study that discussed possible α/β ratios for breast cancer cells was also reviewed (12). The following search query was applied: ((‘breast neoplasms’[MeSH Terms] OR ‘breast cancer’[Title/Abstract] OR ‘breast carcinoma’[Title/Abstract]) AND (‘alpha-beta ratio’[Title/Abstract] OR ‘alpha beta ratio’[Title/Abstract] OR ‘α/β ratio’[Title/Abstract] OR ‘radiobiological parameters’[Title/Abstract]) AND (‘dose-response relationship’[Title/Abstract] OR ‘radiotherapy’[Title/Abstract] OR ‘radiation therapy’[Title/Abstract])).

Inclusion criteria. Studies investigating, adopting, or suggesting an α/β ratio for breast cancer cells (*in vivo* or *in vitro*) were included.

Exclusion criteria. The exclusion criteria were as follows: i) Studies not reporting any discussion about α/β ratio for breast cancer cells. ii) Studies examining α/β ratio of normal cells only. iii) Studies discussing α/β ratios for cancers other than breast cancer. Data on the α/β ratios adopted, utilized, or proposed by the included studies were collected.

Selection. The study selection process was conducted as follows: First, titles and abstracts were screened to identify studies that potentially met the inclusion criteria. Full-text review was then carried out for selected articles to confirm their eligibility for inclusion in the scoping review.

Subsequently, BED was analyzed for different fractionation schedules based on the different α/β ratios.

Statistical analyses. Analysis was conducted via GraphPad Prism 10.2.2. The BED and EQD2 were calculated using various α/β ratios extracted from the literature. Calculated values were rounded for clarity and ease of interpretation. To evaluate the variability of BED across fractionation regimens, the coefficient of variation (CV) was computed for both BED and BED adjusted for tumor repopulation (BED-kT). The Brown-Forsythe ANOVA test was employed to assess differences in variances across various α/β ratios. Lastly, a discussion of different practice-changing hypofractionation trials and elaboration of the doses used to yield equivalent tumor control probabilities were provided.

4. Results

After identifying the relevant studies, all hypofractionated regimens described in the eligible studies were collected. EQD2 and BED were calculated using the different α/β ratios obtained. To present comprehensive and clear results, some of the calculated values were rounded. The calculated BED and EQD2 for all hypofractionated radiotherapy regimens, categorized by the relevant α/β ratios, are included in Tables I and II.

The purpose of determining the dose for different fractionation schedules was to ensure iso-effectiveness in terms of late tissue endpoints. Despite differences in BED between regimens, hypofractionated doses proved to be at least equivalent to conventionally fractionated doses.

BED differs significantly between fractionation regimens over the proposed α/β ratios. To appreciate such variability, the coefficient of variation (CV) for the BED values was computed with and without accounting for tumor repopulation (BED and BED-kT, Table III). As illustrated in Fig. 3, the CV is lowest for an α/β ratio of ~3 when repopulation is not considered but increases when repopulation is factored in BED calculation.

Across the various α/β ratios, there are significant differences in the variations of BED values for different fractionation

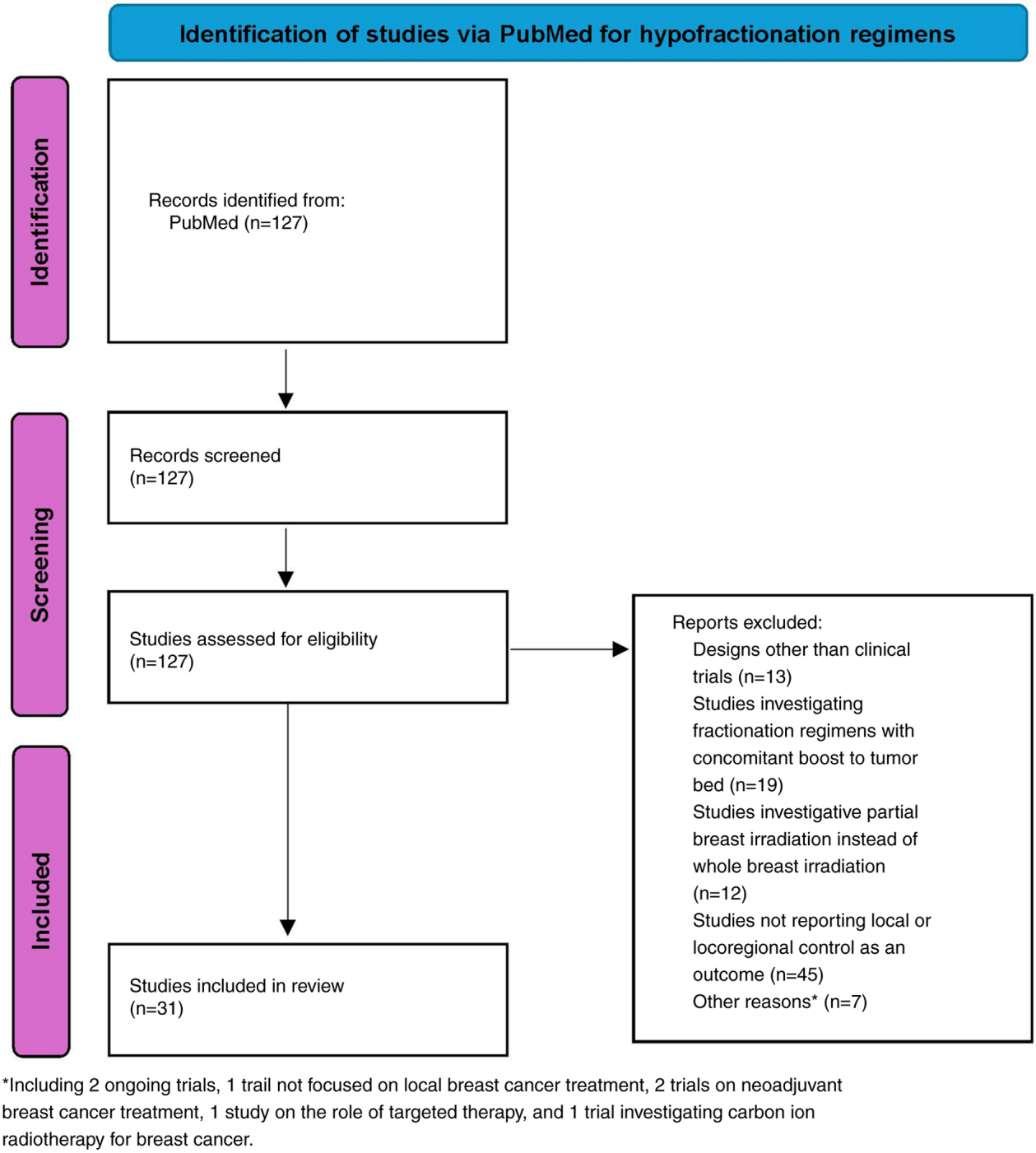

Figure 1. Adapted preferred reporting items for systematic reviews and meta-analyses flow diagram for identification of hypofractionation trials (39).

regimens. Such variations are not consistent across different α/β ratios. This is visually represented in Fig. 4. The Brown-Forsythe ANOVA test was utilized to assess the differences in variances. The test yielded an F-statistic of 219.6 with degrees of freedom (13.00, 85.11) and a P-value of <0.0001, indicating a highly significant result.

In Fig. 5, linear graphs show how BED and BED-kT (A and B, respectively) change across different α/β ratios for 3 common breast cancer fractionation regimens: 50 Gy/25 Fx, 40 Gy/15 Fx, and 26 Gy/5 Fx. Based on these figures, the α/β ratio that corresponds to an equivalent BED across the 50 Gy/25 Fx, 40 Gy/15 Fx and 26 Gy/5 Fx regimens appears to be <2. However, when accounting for tumor repopulation, the α/β ratio associated with equivalent BED-kT shifts to ~4 or slightly higher.

5. Discussion

Unraveling the α/β ratio puzzle in breast cancer and late toxicities. Starting with the data from clinical trials, from an analysis of 158 cases of ipsilateral local tumor recurrence, breast cancer α/β ratio was estimated at ~4.0 Gy (11). Yet, the estimation of this value has been evolving with the cumulative evidence of other altered fractionation trials and studies.

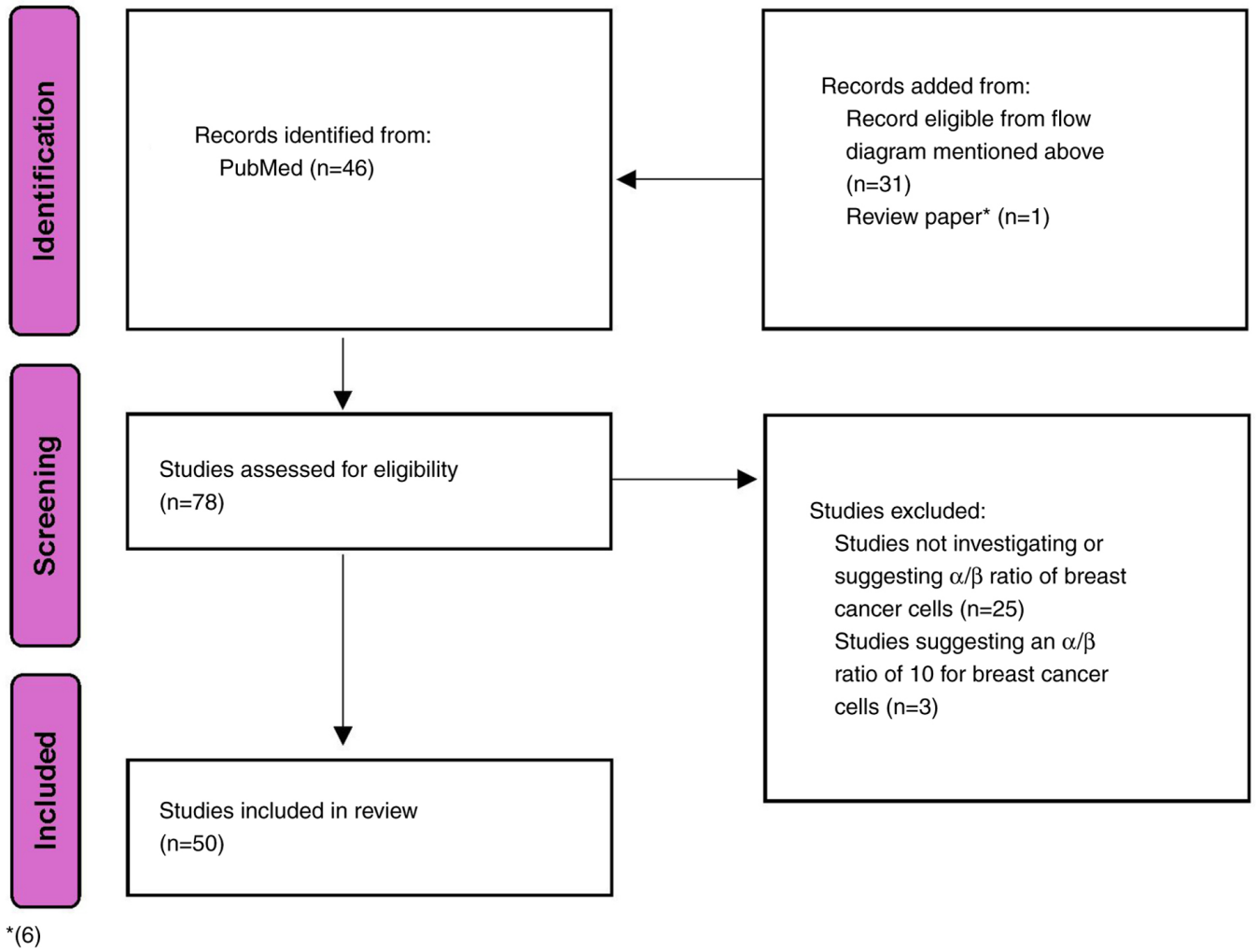

Figure 2. Adapted preferred reporting items for systematic reviews and meta-analyses flow diagram for identification of studies proposing values for breast cancer α/β ratio (39).

The START-P and START-A trials, spanning nearly two decades, have been pivotal in this journey. These trials were designed to directly assess the α/β ratio for tumor control and normal tissue effects (NTE) while standardizing overall treatment time (5-7). By comparing a standard 25-fraction regimen with two experimental 13-fraction hypofractionated regimens, all administered over 5 weeks, these trials provided valuable insights into the α/β ratios for both late toxicity endpoints and tumor control without the influence of varying overall treatment time.

START-P showed an estimated α/β value of 3.6 Gy [95% confidence interval (CI), 1.8-5.4] for any change in breast appearance, and an α/β value for palpable breast induration of 3.1 Gy (95% CI, 1.8-4.4) (5). Collectively, an α/β value of ~3 Gy for late normal tissue changes in the breast is inferred from the equivalence observed between 41.6 Gy delivered in 13 fractions and 50 Gy in 25 fractions over 5 weeks (5).

START-A trial randomized 2,236 patients to 50 Gy/25 Fx vs. 41.6 Gy or 39 Gy in 13 Fx every other day. With a median follow up of 9.3 years, no difference in 10-year locoregional control was found between the hypofractionated regimens and standard fractionation (41.6 Gy vs. 50 Gy: 6.3 vs. 7.4%; P=0.65 and 39 Gy vs. 50 Gy: 8.8 vs. 7.4%; P=0.41) (6).

The α/β ratio estimated for breast cancer based on local-regional relapse data in START Trial A is 4.8 Gy (95% CI, 0-16.3 Gy), bolstered by a meta-analysis including results from the pilot trial, yielding an α/β ratio estimate of 4.6 Gy (95% CI, 1.1-8.1) (7). This estimate aligns closely with the α/β ratio for NTE estimated at 3.4 Gy (95% CI, 2.3-4.5) from photographic assessments (6).

While uncertainties remain in precise fractionation sensitivity estimation, it was evident that breast cancer appears to differ from other cancers with higher α/β values, indicating potential variability in response to fraction size. As the story unfolded, START-B emerged as the next chapter, exploring how time influences treatment outcomes.

In START B trial, 1,105 women were allocated to the 50 Gy group and 1,110 to the 40 Gy group, with a median follow-up of 6.0 years (interquartile range, 5.0-6.2), the 5-year local-regional tumor relapse rate was 2.2 (95% CI, 1.3-3.1) in the 40 Gy group and 3.3% (95% CI 2.2-4.5) in the 50 Gy group (13). This represents an absolute difference of -0.7% (95% CI, -1.7 to 0.9%), suggesting that local-regional relapse could potentially be up to 1.7% lower or at most 0.9% higher after 40 Gy compared with 50 Gy. Both photographic assessments and patient-reported evaluations indicated fewer

Table I. Biologically equivalent dose for different radiotherapy regimens with relevant a/b ratios described in different studies.

Total dose/ fractions	Total dose	Fractional dose	Fractions	4.8	4.6	4	3.7	3.6	3.5	3.4	3.1	3	2.7	2.5	2	1.5	1
50/25	50.00	2.00	25	70.8	71.7	75.0	77.0	77.8	78.6	79.4	82.3	83.3	87.0	90.0	100.0	116.7	150.0
43.5/15	43.50	2.90	15	69.8	70.9	75.0	77.6	78.5	79.5	80.6	84.2	85.6	90.2	94.0	106.6	127.6	169.7
43.2/16	43.20	2.70	16	67.5	68.6	72.4	74.7	75.6	76.5	77.5	80.8	82.1	86.4	89.9	101.5	121.0	159.8
42.9/13	42.90	3.30	13	72.4	73.7	78.3	81.2	82.2	83.3	84.5	88.6	90.1	95.3	99.5	113.7	137.3	184.5
42.5/16	42.50	2.66	16	66.0	67.0	70.7	73.0	73.9	74.8	75.7	78.9	80.1	84.3	87.7	98.9	117.8	155.4
42/15	42.00	2.80	15	66.5	67.6	71.4	73.8	74.7	75.6	76.6	79.9	81.2	85.6	89.0	100.8	120.4	159.6
41.6/13	41.60	3.20	13	69.3	70.5	74.9	77.6	78.6	79.6	80.8	84.5	86.0	90.9	94.8	108.2	130.3	174.7
40/15	40.00	2.67	15	62.3	63.2	66.7	68.9	69.7	70.5	71.4	74.5	75.6	79.6	82.7	93.4	111.2	146.8
39/13	39.00	3.00	13	63.4	64.4	68.3	70.6	71.5	72.4	73.4	76.7	78.0	82.3	85.8	97.5	117.0	156.0
36.63/11	36.63	3.33	11	62.0	63.1	67.1	69.6	70.5	71.5	72.5	76.0	77.3	81.8	85.4	97.6	117.9	158.6
36.5/10	36.50	3.65	10	64.3	65.5	69.8	72.5	73.5	74.6	75.7	79.5	80.9	85.8	89.8	103.1	125.3	169.7
34/10	34.00	3.40	10	58.1	59.1	62.9	65.2	66.1	67.0	68.0	71.3	72.5	76.8	80.2	91.8	111.1	149.6
30/5	30.00	6.00	5	67.5	69.1	75.0	78.6	80.0	81.4	82.9	88.1	90.0	96.7	102.0	120.0	150.0	210.0
28.5/5	28.50	5.70	5	62.3	63.8	69.1	72.4	73.6	74.9	76.3	80.9	82.7	88.7	93.5	109.7	136.8	191.0
27/5	27.00	5.40	5	57.4	58.7	63.5	66.4	67.5	68.7	69.9	74.0	75.6	81.0	85.3	99.9	124.2	172.8
26/5	26.00	5.20	5	54.2	55.4	59.8	62.5	63.6	64.6	65.8	69.6	71.1	76.1	80.1	93.6	116.1	161.2

Table II. Equivalent dose in 2 Gy/Fx for different radiotherapy regimens with relevant a/b ratios described in different studies.

Total dose/ fractions	Total dose	Fractional dose	Fractions	4.8	4.6	4	3.7	3.6	3.5	3.4	3.1	3	2.7	2.5	2	1.5	1
50/25	50.00	2.00	25	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
43.5/15	43.50	2.90	15	49.3	49.4	50.0	50.4	50.5	50.6	50.8	51.2	51.3	51.8	52.2	53.3	54.7	56.6
43.2/16	43.20	2.70	16	47.6	47.8	48.2	48.5	48.6	48.7	48.8	49.1	49.2	49.6	49.9	50.8	51.8	53.3
42.9/13	42.90	3.30	13	51.1	51.4	52.2	52.7	52.9	53.0	53.2	53.8	54.1	54.8	55.3	56.8	58.8	61.5
42.5/16	42.50	2.66	16	46.6	46.7	47.1	47.4	47.5	47.6	47.7	48.0	48.1	48.4	48.7	49.5	50.5	51.8
42/15	42.00	2.80	15	46.9	47.1	47.6	47.9	48.0	48.1	48.2	48.6	48.7	49.1	49.5	50.4	51.6	53.2
41.6/13	41.60	3.20	13	48.9	49.2	49.9	50.4	50.5	50.7	50.8	51.4	51.6	52.2	52.7	54.1	55.9	58.2
40/15	40.00	2.67	15	43.9	44.1	44.5	44.7	44.8	44.9	45.0	45.3	45.4	45.7	46.0	46.7	47.7	48.9
39/13	39.00	3.00	13	44.7	44.9	45.5	45.8	46.0	46.1	46.2	46.6	46.8	47.3	47.7	48.8	50.1	52.0
36.63/11	36.63	3.33	11	43.8	44.0	44.7	45.2	45.3	45.5	45.7	46.2	46.4	47.0	47.5	48.8	50.5	52.9
36.5/10	36.50	3.65	10	45.4	45.6	46.5	47.1	47.3	47.5	47.7	48.3	48.5	49.3	49.9	51.6	53.7	56.6
34/10	34.00	3.40	10	41.0	41.2	41.9	42.4	42.5	42.7	42.8	43.3	43.5	44.1	44.6	45.9	47.6	49.9
30/5	30.00	6.00	5	47.6	48.2	50.0	51.1	51.4	51.8	52.2	53.5	54.0	55.5	56.7	60.0	64.3	70.0
28.5/5	28.50	5.70	5	44.0	44.5	46.1	47.0	47.3	47.7	48.0	49.2	49.6	50.9	51.9	54.9	58.6	63.7
27/5	27.00	5.40	5	40.5	40.9	42.3	43.1	43.4	43.7	44.0	45.0	45.4	46.5	47.4	50.0	53.2	57.6
26/5	26.00	5.20	5	38.2	38.6	39.9	40.6	40.9	41.1	41.4	42.3	42.6	43.7	44.5	46.8	49.8	53.7

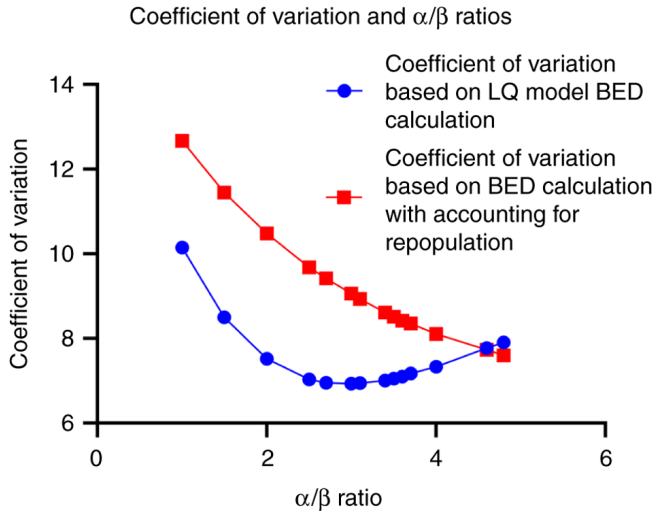

Figure 3. Line plot with data points showing the coefficient of variation of BED values for different fractionation regimens across α/β ratios, displayed without accounting for repopulation (blue) and with repopulation factored in (red). LQ, linear-quadratic; BED, biologically effective dose.

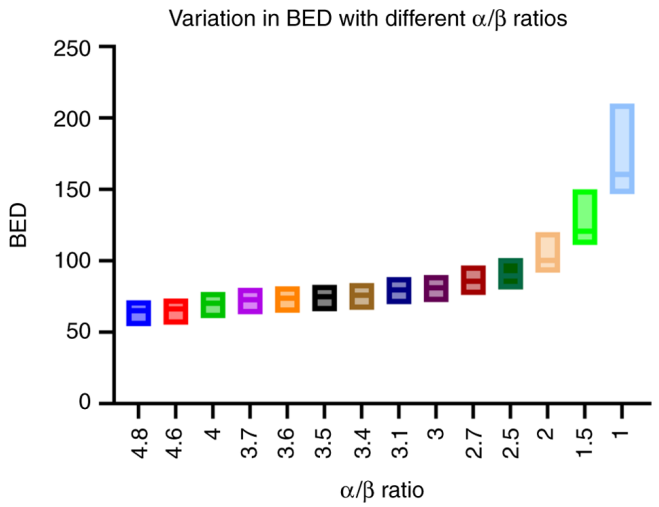

Figure 4. Bar graph illustrating the range of BED values for different fractionation regimens at each α/β ratio. BED, biologically effective dose.

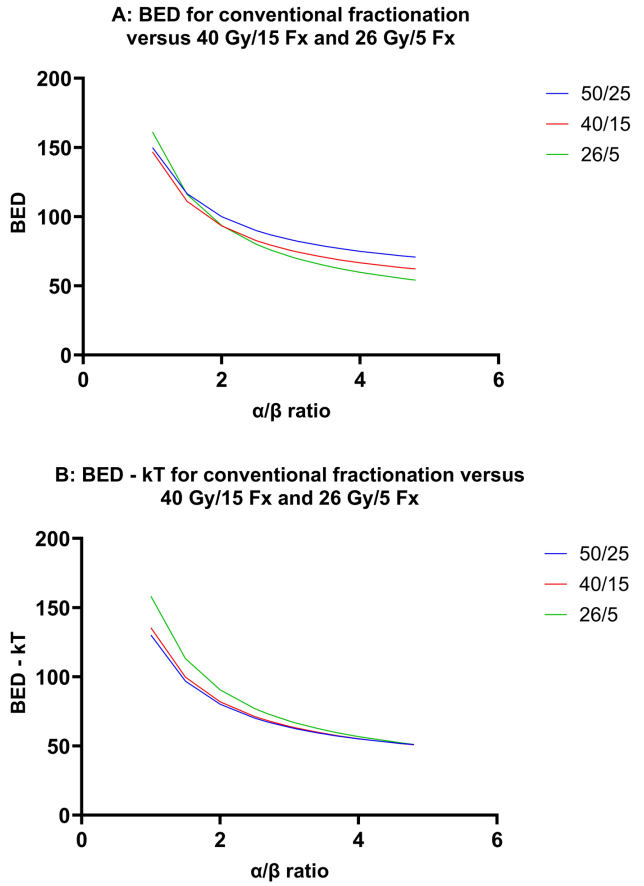

Figure 5. (A) Line plots for the 50 Gy/25 Fx, 40 Gy/15 Fx, and 26 Gy/5 Fx regimens displaying BED values across different α/β ratios. Plots converge around an α/β ratio below 2 Gy. (B) Same plots, but with tumor repopulation factored in (k is 0.6 BED/day; T is 33, 19 and 5 days for 25, 15 and 5 fractions, respectively). Plots converge around an α/β ratio above 4 Gy. BED, biologically effective dose.

late adverse effects following treatment with 40 Gy than with 50 Gy (side effects, including telangiectasia, breast shrinkage and edema were significantly less frequent in the hypofractionated regimen) (13).

Traditionally, it was anticipated that local-regional relapse rates would be higher with 40 Gy in 15 fractions than with 50 Gy in 25 fractions, based on an α/β point estimate of 3.5 Gy for local-regional tumor control derived from the START-P and START-A trials. Adjusting for the EQD2 (Table II), the 40 Gy regimen in START-B approximates closer to 45 Gy rather than 50 Gy, assuming no impact of treatment time.

In a Canadian randomized trial involving 1,234 patients, no significant difference in ipsilateral tumor recurrence was observed between schedules of 50 Gy in 25 fractions of 2.0 Gy over 35 days and 42.5 Gy in 16 fractions of 2.66 Gy over 22 days to the whole breast (11). While the comparison based on 44 events lacks precision, if both schedules are equally effective for tumor control, the α/β value for tumor response could potentially be as low as 3.0 Gy, aligning with the fractionation sensitivity observed in healthy tissues that develop adverse effects years later.

Following these pivotal trials, the American Society of Radiation Oncology recommends 15- or 16-fraction schedules as preferred options for whole-breast radiotherapy (14). These trials have not only reshaped the landscape of breast radiotherapy but also catalyzed a renaissance in altered fractionation strategies, paving the way for subsequent ultra-hypofractionation trials.

Ultra-hypofractionation trials for whole breast radiotherapy. The α/β values derived from the FAST trial align closely with those observed in the 10-year analysis of the START-A trial, indicating estimates ranging from 3-4 Gy for late NTE in the breast (8). This consistency underscores the applicability of the linear-quadratic model for fraction sizes up to 5.0-6.0 Gy.

However, there appears to be a slightly heightened sensitivity (lower α/β value) than initially predicted (reduced rates of moist desquamation and subsequent late skin damage) when larger fractions are utilized. For instance, the FAST trial randomized 915 patients with early stage invasive ductal breast cancer (pT1-2 pN0; age ≥50) to 50 Gy/25 Fx, 30 Gy/5 Fx

Table III. Biologically equivalent dose for different radiotherapy regimens with accounting for tumor repopulation (BED-kT).

Total dose/ fractions	Total dose	Fractional dose	Fractions	4.8	4.6	4	3.7	3.6	3.5	3.4	3.1	3	2.7	2.5	2	1.5	1
50/25	50.00	2.00	25	51.0	51.9	55.2	57.2	58.0	58.8	59.6	62.5	63.5	67.2	70.2	80.2	96.9	130.2
43.5/15	43.50	2.90	15	58.4	59.5	63.6	66.2	67.1	68.1	69.2	72.8	74.2	78.8	82.6	95.2	116.2	158.3
43.2/16	43.20	2.70	16	54.3	55.4	59.2	61.5	62.4	63.3	64.3	67.6	68.9	73.2	76.7	88.3	107.8	146.6
42.9/13	42.90	3.30	13	62.2	63.5	68.1	71.0	72.0	73.1	74.3	78.4	79.9	85.1	89.3	103.5	127.1	174.3
42.5/16	42.50	2.66	16	52.8	53.8	57.5	59.8	60.7	61.6	62.5	65.7	66.9	71.1	74.5	85.7	104.6	142.2
42/15	42.00	2.80	15	55.1	56.2	60.0	62.4	63.3	64.2	65.2	68.5	69.8	74.2	77.6	89.4	109.0	148.2
41.6/13	41.60	3.20	13	59.1	60.3	64.7	67.4	68.4	69.4	70.6	74.3	75.8	80.7	84.6	98.0	120.1	164.5
40/15	40.00	2.67	15	50.9	51.8	55.3	57.5	58.3	59.1	60.0	63.1	64.2	68.2	71.3	82.0	99.8	135.4
39/13	39.00	3.00	13	53.2	54.2	58.1	60.4	61.3	62.2	63.2	66.5	67.8	72.1	75.6	87.3	106.8	145.8
36.63/11	36.63	3.33	11	53.0	54.1	58.1	60.6	61.5	62.5	63.5	67.0	68.3	72.8	76.4	88.6	108.9	149.6
36.5/10	36.50	3.65	10	57.1	58.3	62.6	65.3	66.3	67.4	68.5	72.3	73.7	78.6	82.6	95.9	118.1	162.5
34/10	34.00	3.40	10	50.9	51.9	55.7	58.0	58.9	59.8	60.8	64.1	65.3	69.6	73.0	84.6	103.9	142.4
30/5	30.00	6.00	5	64.5	66.1	72.0	75.6	77.0	78.4	79.9	85.1	87.0	93.7	99.0	117.0	147.0	207.0
28.5/5	28.50	5.70	5	59.3	60.8	66.1	69.4	70.6	71.9	73.3	77.9	79.7	85.7	90.5	106.7	133.8	188.0
27/5	27.00	5.40	5	54.4	55.7	60.5	63.4	64.5	65.7	66.9	71.0	72.6	78.0	82.3	96.9	121.2	169.8
26/5	26.00	5.20	5	51.2	52.4	56.8	59.5	60.6	61.6	62.8	66.6	68.1	73.1	77.1	90.6	113.1	158.2

k is 0.6 BED/day; T is 33, 22, 19, 17, 15, and 5 days for 25, 16, 15, 13, 11, and 5 fractions, respectively.

(once weekly), or 28.5 Gy/5 Fx (once weekly). After a median follow up of 9.9, findings showed that patchy/confluent moist desquamation rates were 11.7, 2.7 and 2.8% after doses of 50.0 Gy, 30.0 Gy and 28.5 Gy, respectively (8).

With an α/β value estimated at 2.7 Gy, the 15-fraction regimen equates to ~45.7 Gy in 2.0 Gy equivalents (Table II). The FAST trial identifies a 5-fraction schedule that appears radio-biologically equivalent to the standard 25-fraction regimen with respect to late NTE.

The FAST-Forward trial demonstrated the non-inferiority, as measured by ipsilateral breast tumor relapse rates at 5 years, of 27 Gy and 26 Gy schedules delivered in 5 fractions compared with 40 Gy in 15 fractions for patients with early breast cancer [5-year ipsilateral breast recurrence was similar among the three arms; 2.1 (40 Gy), 1.7 (27 Gy) and 1.4% (26 Gy)] (9). The NTE observed over 5 years with the 26 Gy regimen were comparable to those with the 40 Gy regimen.

Late NTE show a steep dose-response curve, allowing for clinically and statistically significant differences in event rates between the 26 Gy and 27 Gy schedules. While a 3-4 Gy difference in EQD2 between these regimens might appear small for detecting toxicity differences, understanding repair time can elucidate its significance. Repair time, typically measured in half-lives where 5 half-lives equate to ~95% repair, is crucial in late toxicity. Previous studies proposed a half-life of ~40 days for skin telangiectasia, suggesting a slow repair mechanism that mitigates toxicity over time (15,16).

The 26 Gy in 5 fractions schedule, which is equally effective with 40 Gy in 15 fractions, provides a direct estimation of α/β for late NTE, consistent with values observed in other trials. The α/β value of 3.7 Gy (95% CI, 0.3-7.1) for tumor control in FAST-Forward is similar to the 3.5 Gy (1.2-5.7) estimated from the START-P and START-A trials. Assuming no time effect, 26 Gy in 5 fractions corresponds to 46.8 Gy and 53.7 Gy in 2 Gy fractions, assuming α/β values of 2 Gy and 1 Gy, respectively (Table II).

The 26 Gy dose level exhibits similar NTE as the 40 Gy in 15 fractions regimen, supporting its adoption as a new standard for adjuvant breast radiotherapy. Based on the findings of these practice-changing studies, the ultra-hypofractionated dose of 26 Gy/5 Fx was adopted in the radiotherapy clinical guidelines of the European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus (17) and the National Institute for Health and Care Excellence (18).

Although the LQ model has proven reliable for predicting late tissue toxicities, the present analysis reveals complexities when applying it to other critical endpoints, such as tumor control. These findings underscore the necessity for a more nuanced approach to radiobiological indices, particularly in the context of fractionation schedules. By rigorously examining BED variations across α/β ratios and incorporating considerations for tumor repopulation, it becomes clearer that further research is warranted to acquire stronger grasp on fundamental radiobiological properties of cancer cells.

Financial impact of hypofractionation and ultra-hypofractionation. The economic implications of hypofractionation and ultra-hypofractionation in breast cancer radiotherapy are substantial. Multiple studies have demonstrated the cost-effectiveness of these approaches (19-21). By reducing the number of treatment sessions, these fractionation schedules not only decrease the direct costs associated with fewer patient visits and less machine usage but also indirectly reduce expenses related to transportation and time off work for patients. These economic benefits make hypofractionated and ultra-hypofractionated regimens particularly appealing, especially in resource-limited settings. Resistance to adopting hypofractionation has even been revealed to add extra avoidable costs (22). Additionally, adding radiotherapy to hormonal therapy in older patients has been found to yield the highest clinical benefits and costs compared with hormonal therapy alone, indicating that radiotherapy combined with hormonal therapy is cost-effective in the US (23). Moreover, advancements in fractionation schedules have demonstrated that a 5-fraction regimen of radiotherapy is even more cost-effective than hormonal therapy in older patients (24). These findings suggested that future research should potentially shift practice towards this regimen, as omitting hormonal therapy might spare more side effects than omitting a 5-fraction schedule of radiotherapy, particularly for older patients.

Advancing radiotherapy techniques and predictive models in breast cancer treatment. Alongside advancements in fractionation schedules, the development of radiotherapy techniques such as three-dimensional conformal radiation therapy, intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) has transformed the landscape of breast cancer treatment. These technologies represent a significant leap forward in precision medicine, offering refined control over radiation dose distribution. IMRT and VMAT enable clinicians to achieve greater homogeneity in dose delivery within the target area while minimizing exposure to critical neighboring organs. Clinicians need to be mindful of the impact that such planning techniques can have on tumor and normal tissue radiation doses (25).

The equivalent uniform dose (EUD), pioneered by Niemierko (26), is a method used to address volume effects on normal tissue toxicity and tumor control by condensing dose distributions into a single dose level that yields equivalent biological effects. EUD is quantified as the uniform dose delivered in daily 1.8 Gy fractions, achieving an equivalent tumor control probability (TCP) compared with the original dose distribution, formulated as (26,27):

$$EUD = \frac{-\ln\{\sum_i v_i \exp[-(\alpha + \beta d_i)D_i + \gamma T_t\}}{\alpha + \beta 1.8 - \gamma 1.4/1.8}$$

Where:

v_i is the fraction of the target volume irradiated with dose D_i

d_i is the fractional dose. In each dose bin, d_i can be calculated as $d_i = \frac{D_i \mathrm{d}}{D}$.

γ is ln(2)/T_{pot}; T_{pot} is the potential doubling time; T_t is the treatment time.

The extent of irradiated normal tissue plays a critical role in predicting late toxicity. For example, IMRT has demonstrated potential improvements in the homogeneity index and EUD for

targets (28). Addressing the challenges posed by non-uniform dose distributions is crucial for optimizing radiation plans, with methodologies including EUD and models such as normal tissue complication probability and TCP playing pivotal roles in plan evaluation.

Looking ahead, the incorporation of radiomics may show potential for customizing radiation plans and techniques according to the unique characteristics of each breast cancer patient, with the goal of improving treatment outcomes on a personalized basis (29-33). Progress in biomolecular markers, radio-genomics and radiomics is crucial in addressing individual patient vulnerability to late toxicity (34-38). Integrating these genomic and radiomic findings into comprehensive clinical and dosimetric predictive models offers the possibility of enhancing the accuracy of predictions for normal tissue toxicity. This integrated approach also empowers radiation oncologists to refine fractionation regimens more precisely, thereby optimizing treatment outcomes for their patients.

As the present scoping review focused on the radiobiology and clinical implications of whole-breast radiotherapy, the exploration of accelerated partial breast irradiation (APBI) is beyond its scope. APBI represents a significant shift in radiotherapy by targeting only the tumor bed rather than the entire breast. The rationale behind APBI is to achieve improved geometric sparing of healthy breast tissues using brachytherapy, external beam radiotherapy and intraoperative radiotherapy, thereby reducing treatment-related toxicity and improving cosmetic outcomes. The potential of APBI to further reduce the treatment burden and enhance patient quality of life underscores the ongoing evolution and personalization of breast cancer radiotherapy. The extensive and intriguing radiobiology, as well as the clinical and cost-effectiveness aspects of APBI, were not discussed in the present study.

Ultimately, this narrative of discovery and innovation in radiotherapy underscores a transformative era. It is a story where science and compassion converge, promising tailored treatments that not only combat cancer but also enhance patients' quality of life. As these developments are put behind, the future holds promise for personalized radiotherapy paradigms that redefine standards of care, offering renewed hope to those battling breast cancers.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AA designed the overall concept and outline of the manuscript. AA, RA and FA collected the data and reviewed the literature. AA and FA contributed to the writing and editing of the manuscript. All authors read and approved the final version of the manuscript. AA and FA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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