The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 706- 712

Hypo-Fractionation Radiotherapy in Breast Cancer Patients: Review Article

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ABSTRACT
In breast carcinoma management, radiation therapy (RT) is a necessary management. The typical therapeutic regimen for RT to the breast involves administering 25 fractions of 2.0 Gy per day over a five-week period. Breast cancer is more suitable
for greater fraction sizes than squamous carcinomas, according to datasupporting the use of fewer fractions of more than 2 Gy per day (hypo-fractionation). Consequently, it may exhibit similarly high fractionation sensitivity to the dose-limiting normal tissues, such as muscle, subcutaneous tissues, skin, and ribs. This article examins the literature that supports the hypo-fractionated radiation efficacy in breast cancer treatment, explore the radiobiological rationale that is unique to carcinomas of breast, and present a case for the regimen implementation of shorter, hypo-fractionated RT sessions when radiation administered on breast.
Keywords: Hypo-fractionation, breast cancer, radiotherapy, conventional fractionation, radiobiology.

INTRODUCTION
The most frequently detected cancer in women worldwide is breast cancer (BC). The typical approach to treating early-stage BC is breast conservation therapy (BCT). Accompanied by adjuvant radiation treatment (RT), which may or may not include adjuvant systemic agents breast conserving surgery (BCS) are approaches in the treatment. Locoregional recurrence after BCS can be decreased via utilizing RT in numerous, randomized controlled trials (RCT) of invasive BC performed over the past years. This has resulted in breast preservation and exceptional survival high rates [(1)].

Regarding to the Early Breast Cancer Trialists' Collaborative Group meta-analysis, after BCS RT decreased from 35.0% to 19.3% regarding 10-year recurrence possibility and from 25.2% to 21.4% in 10,801 regarding the 15-year mortality risk in women experienced invasive BC involved in 17 RCT. Traditionally, adjuvant RT the conventionally-fractionated whole breast irradiation (CF-WBI) has been employed for early-stage BC. This treatment involves the 45-50 Gray (Gy) application in 1.8-2.0 Gy fractions to the entire breast, without or with a further tumor bed boost, across a three to seven-week period [(2)].

In the past, it was assumed that for healthy tissue preservation the small fraction sizes delivery over a prolonged period was essential. Nevertheless, in the nineties, it was discovered that the late-reacting normal tissues and the BC were evenly susceptible to fraction size. These discoveries facilitated the of hypo-fractionated whole breast irradiation (HF-WBI) development, that is a sum dose that is radio-biologically comparable to a CF-WBI regimen. HF-WBI is characterized by fraction sizes that exceed 2 Gy and is administered to the entire breast, either beside or not an additional tumor bed increase [(3)].

The HF-WBI primary objective is to shorten the therapies duration by decreasing the individual fractions number, thereby establishing sessions that increase cases compliance. The potential to expand the BCT utilization and care access, whereas simultaneously reducing healthcare expenses, is also enhanced by the shortened courses advantages [(4)].

Regarding cosmetic findings and local recurrence, HF-WBI is comparable to most traditional WBI, as validated by randomized trials. Effective benefits to cases and health services are also a factor in the interest in hypo-fractionation (HF). Cases are afforded numerous benefits regarding convenience, cost, quality of life (QOL), and time, when treatment is administered with the fractions minimum number over the shortest feasible duration. Additionally, a shortened fractionation schedule would result in cost savings for the healthcare budget and a reduction in waiting lists at overcrowded RT centers, given the high prevalence of BC in our society [(5)].

Breast Cancer Epidemiology and Prevalence
The most frequently detected cancer in female globally is BC, which has surpassed pulmonary cancer. In 2020, the estimated number of new BC cases was 2.3 million, which accounted for 11.7% of all new malignancies. Additionally, 684,996 cases resulted in death. Egypt has a significant mortality rate from BC, with a prevalence of 21.3 per 100,000 occurrences. As many as 60 to 70% of BC cases in Egypt are diagnosed at an advanced stage. The 48.5 years in Egypt is standard age at diagnosis, that appears to be 10 years younger than in North America and Europe [(6)].

The BC prevalence is rising since the widespread mammography screening adoption and is projected to keep increasing as the general population ages. On a worldwide basis, the mortality rates for female BC were significantly decreased in developed countries than in developing countries (12.8 per 100,000 vs 15.0 per 100,000). Also, the BC mortality rate has dropped in the majority of western countries as a result of recent advancements in therapies and earlier diagnosis [(7)].

The BC primary risk factors are lifestyle risk factors, hormonal and reproductive risk factors (early

Received: 29/08/2024
Accepted: 23/10/2024

age at menarche, later age at menopause, genetic predisposition, menopausal hormone therapy, less breast feeding, older age at first birth, and oral contraceptives), in addition to high-penetrance genes germline mutations for example; breast cancer [BRCA1/2], TP53, BRCA2 [PALB2] partner and localizer, ATM, RAD51 homolog C [RAD51C], checkpoint kinase 2 [CHEK2], BRCA1 associated RING domain 1 [BARD1], and others[8].

Pathology

Adenocarcinomas comprise the preponderance of breast malignancies, with 15% from the lobular epithelium and 85% of cases originating from the breast ducts. The ductal pathology encompasses several conditions, involving invasive metastasized carcinomas into the adjacent breast parenchyma outside the basement membrane and ductal carcinoma in situ. Inflammatory breast malignancies, Breast Paget's disease, and papillary carcinomas are BC additional types [9].

Malignant phyllodes and angiosarcomas are uncommon sarcomas. The pathways that regulate cell proliferation and apoptosis dysregulation is the oncogenesis cause. HER2 receptors, progesterone receptors and estrogen receptors, presence or absence is a critical factor in deciding therapy plans [10].

Presentation

BC typically manifests as a lump in the breast and is typically asymptomatic. However, fibroadenomas, cysts, and fibrocystic change are benign in character, accounting for 90% of breast masses. Breast malignancies may manifest as [11].

- Hard, immobile, irregular or fixed mass detected in the breast and/or axillary lump.
- Nipple changes such as discharge, inversion, or skin changes.
- Changes in shape and size and swelling of the breast.
- Changes in skin involve ulceration, dimpling, erythema, peau d'orange, and pitting.

Despite its prevalence, breast discomfort that is not accompanied by any other symptoms is a rare indication of BC [11].

Factors related with breast cancer

BC elevated risk is linked to a variety of factors, both modifiable and non-modifiable. Obesity, a lack of activity, and contact with exogenous hormones are all preventable risk factors that can be altered or prevented. The individual's age and genetic susceptibility are unchangeable and cannot be altered [12] (Table 1).

Modifiable risk factors	■ Obesity ■ Increased alcohol consumption ■ Sedentary lifestyle ■ Exogenous hormone exposure including contraceptive pills, hormone replacement therapy ■ Radiation exposure
Non-modifiable risk factors	■ Increasing age ■ Genetic predisposition – including mutations in: ■ BRCA1 or BRCA2 ■ PALB2, TP53, PTEN, STK11, NF1 ■ Endogenous hormone exposure ■ Early menarche, late menopause ■ Nulliparity, late pregnancy
Protective factors	■ Lactation ■ Physical activity ■ Reduced alcohol consumption ■ Use of aspirin or non-steroidal anti-inflammatory drugs

Table (2): Risk and protective factors correlated to breast cancer [12].

Clinical breast examination

The breast clinical examination entails the regional lymph nodes (LN), both axillae and bilateral breasts evaluation. This comprises the following:

Inspection:

The patient should be seated on an examination couch that is adjusted to a 30–45° angle. Skin is visually inspected for any alterations, such as masses, erythema, tethering, scars, puckering, and nipple discharge or alterations. Subsequently, the case's arms above and behind their head should elevated and then compress their palms against the pelvis. The doctor is responsible for observing any resulting changes in skin that may be the consequence of these movements [(13)].

Palpation:

The physician can accurately assess the density of breast tissue by palpating each breast from the superior to inferior margins, in addition to from the medial to lateral aspects, to examine the four quadrants and nipple-areola complex [(14)].

In overall, benign masses do not induce variations in skin and are frequently mobile, well-defined and smooth. Nevertheless, fibroadenomas are firmly established [(15)].

Investigations

Radiological Investigations:

In order to evaluate distal metastases and LN involvement should use additional imaging, as a thorax, pelvis, and abdomen computed tomography scan. The most critical investigation for the abnormalities visualization and characterization is radiological imaging. An ultrasound scan enables a concentrated clinically palpable abnormality examination, while a mammogram examines breast tissue [(16)].

Digital breast tomosynthesis enhances the results of a mammogram by generating breast tissue three-dimensional X-ray images. Contrast magnetic resonance imaging may be necessary for certain patients to aid in deciding, such as, monitoring the case's response to neoadjuvant chemotherapy, figuring out whether to pursue BCS, or determining the tumor size when there is a difference in size between imaging modalities [(17)].

Histopathological Evaluation:

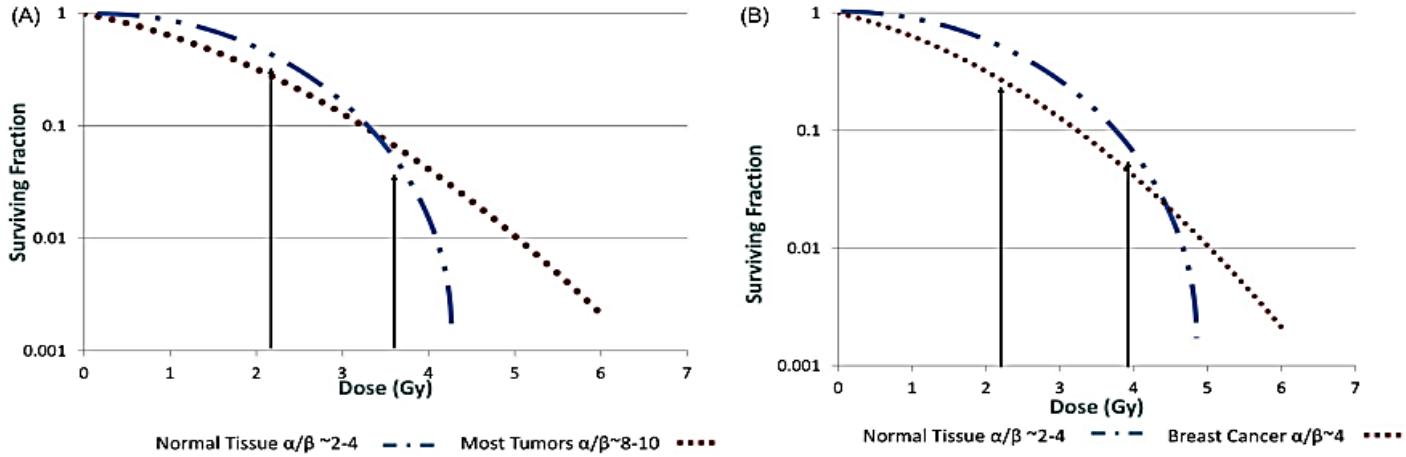
The American Joint Committee on Cancer classification is employed for disease staging. This entails anatomical staging, which is determined by metastasis (M), tumor extent (T), and the regional lymph nodes (N) [(18)] (Table 3).

Tumour (T)	Tis	Carcinoma in situ
	T1	Tumour <2 cm
	T2	Tumour 2–5 cm
	T3	Tumour >5 cm
	T4	Tumour with extension to skin or chest wall
Lymph node (N)	N0	No regional node involvement
	N1	Ipsilateral, movable axillary lymph node involvement
	N2	Ipsilateral, fixed axillary lymph node involvement or non-fixed ipsilateral internal mammary nodes
	N3	Ipsilateral infraclavicular or supraclavicular nodes, or ipsilateral internal mammary nodes in combination with axillary nodes
Metastases (M)	M0	No distant metastasis
	M1	Distant metastasis

(Table 4): A simplified table of the anatomical stages system for lymph nodes, clinical tumors, and metastases [(18)].

The rationale behind hypofractionation (HF) in breast cancer: the radiobiological foundation of conventional fractionation (CF)

It is essential to have a comprehension of the fundamental radiobiologic principles of fractionation in order to be able to understand and have certainty in HF validity and safety for BC. Initially, the optimum radiation fractionation schedule for any cancer is contingent upon the tumor pathological type and its adjacent location. It must strike a balance between minimizing late normal tissue morbidity and maximizing tumor cell death (referred to as local control). The overall dose administered, the therapy period, the daily fraction size, and the irradiated volume are the four primary factors that determine the radio-biologic dependencies of this intricate relationship [(19)]. Typically stated in RT as the therapeutic ratio, it delineates the maximum radiation dose that can be delivered for achieving controlled cancer cell mortality and the lowermost radiation dose that can be delivered to minimal morbidity in normal tissues. In order to quantify the intrinsic radiosensitivity of cells in cultures, mathematical radiobiological models have been developed, facilitating the therapeutic ratio enhancements prediction through the manipulation of these variable and the comparison of various approaches to therapy [(20)]. The most frequently utilized by radiation oncologists/radiobiologists is the linear-quadratic (LQ) radiobiologic model. It is the most effective in illustrating the rationale for CF and depicts the normal tissue and tumors sensitivity to alterations in fraction size. Despite the absence of consideration for the effect of total therapy period or tissue volume, the association among cellular responses to any specific fraction size and the distinctions between the normal cells and tumor cellular response is considered. A fundamental radiobiological historical premise has been that the normal late-reacting tissue is more affected whereas to larger fraction size most tumor types are comparatively less susceptible [(21)]. Although this model is expected to be an oversimplification, it employs the "α/β ratio" to denote the specific cell population sensitivity to variations in radiation dosage. by radiation cell survival curve for any cell type this radiation sensitivity is illustrated, whether it is a malignancy or normal ((Figure**)**. From a clinical perspective, most regular tissues (heart, spinal cord, and lung) have less α/β ratios (typically 1-5 Gy) and are perceived to be quite more sensitive to alterations in fraction size, with survival plots. Conversely, tumors have been perceived as being less susceptible to fractional changes, as evidenced by their survival graphs. Consequently, they exhibit high α/β ratios (typically 8-10 Gy) [(22)]. The original origins of these assumptions were experimental models that were performed on human squamous cell carcinomas cell lines from the neck and head and cervix. The high α/β ratio validity for BC was not questioned until the 1980s. BC cell lines demonstrate an α/β ratio that is considerably lower than anticipated and more comparable to the α/β ratio of the surrounding normal tissue, as demonstrated by the supplementary radiobiological modeling application specific to human breast tumors to the LQ equation [(23)]. Specific to BC the α/β ratios that were 3.5 Gy for telangiectasia, 4.7 Gy for breast edema, and 4.0 Gy for breast induration, according to early estimates. CF (40GY\15fx\3 weeks) may provide only minor advantages and may be shielding BC cells in the same way as normal tissues, as evidenced by the similar α/β ratios for BC and late effects. Expanding the daily fraction size (HF) should offer CF patients comparable tumor controlling and toxicity, assuming that the overall dose is lowered to compensate for the increased dose per fraction [(24)].



(Figure 1): Normal tissue and tumor cell survival curves, as determined by the LQ equation. Cell survival curves. The blue dashed line represents the surviving normal tissue fraction, while the red dotted line represents the surviving tumor fraction. **A:** rationale for conventional fractionation. The cell mortality rate is generally higher in the majority of tumors than in normal tissue when a daily fraction of 2 Gy is administered, assuming low α/β ratios for normal tissue (2-4 Gy) and high α/β ratios for tumors. The therapeutic ratio is significantly diminished by increasing the daily fraction size to 4Gy, as the frequency of cell death is typically higher in normal cells than in tumor cells. This leads to an increase in toxicity in comparison to tumor control. **B:** Hypofractionation's rationale. For breast cancer cells, the α/β ratios were observed to be comparable to those of normal tissue (2-4 Gy). Therefore, there is no additional therapeutic benefit to be gained from the 2 Gy or 4 Gy utilization [(24).]

Clinical evidence supporting hypofractionation in breast cancer

Multiple randomized BCTs were launched to evaluate the CF safety and effectiveness with HF, based on the radiobiological data previously discussed and released clinical trials that utilizing HF in BC from centers in the UK and Canada stated great local control and minimal morbidity. The Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) trial randomized 1410 women to either CF (50 Gy/25 fractions/2 Gy) or two HF experimental arms: (a) 42.9 Gy /13 fractions/3.3 Gy and (B) 39 Gy/13 fractions/3.0 Gy. In order to assess the repair-related factors (β and α) radio biologically and standardize the delivery (and recuperation) period, the treatment was performed over a five-week period [(25)].

The 42 Gy arm did not exhibit a substantial difference from the 50 Gy arm in terms of local control and later toxicity, despite the fact that the primary outcome was normal tissue alteration, and the secondary end point was local control. The 39 Gy arm exhibited marginally superior late toxicity than the 50-Gy arm, but it had inferior local control. The authors confirmed the radiobiological principles previously discussed by estimating the α/β ratio for normal late tissue impacts (muscle, breast, rib cage) to be 3.6 Gy and the α/β ratio for BC to be 4 Gy, considering these findings. The protocol two subsequent UK HF trials design; the START A and START B, was influenced by this pivotal trial [(26)].

Within the START A trial was conducted in which 2236 women with BC in early-stage were randomized to either the standard arm of 50 Gy/25 fractions/2 Gy or the two experimental arms of 39 Gy/13 fractions /3.0 Gy or 41.6 Gy/13 fractions/3.2 Gy. All participants were treated in a similar manner over a five-week period. Local control was the primary endpoint, while late tissue toxicity was the secondary endpoint. 39-Gy arm had less breast late toxicities, in local control insignificant differences were detected between the three arms at the 5-year median follow-up [(27)].

As a result of the RMH/GOC and START experiments combined analysis, the normal tissue α/β ratio has been determined to be 3.1 Gy (95% CI 2.0-4.2) and to be 3.5 Gy (95% CI 1.2-5.7) for BC. The START B, a clinically pragmatic trial that investigates the noninferiority of HF for both local control and adverse effects, randomized 2215 women with early-stage BC to receive either HF of 40 Gy/15 fractions/2.67 Gy over 3 weeks or CF of 50 Gy/25 fractions/2 Gy over 5 weeks. Local-regional control results were insignificantly different between the two arms at the 5-year initial report, and toxicity was similarly minimal [(27)].

The Canadian NCI trial, the fourth trial, supplied additional long-term follow-up data and clinical validation for HF-WBRT. This study randomized 1234 T1/T2, pN0 cases to receive WBRT provided as 42.5 Gy/16 fractions/2.66 Gy or 50 Gy/25 fractions/2 Gy. Between the therapy arms at the 5- and 10-year follow-up, as was observed in the UK trials cosmetic findings, grade II-III toxicities and local recurrence-free survival were comparable [(28)].

The Canadian NCI trial cohort was evenly treated low-risk T1/T2/N0 group that was early-stage and >50 years of age. All cases received WBRT (no regional nodal fields) without systemic chemotherapy. In contrast, the three UK trials include a broader patient's range, with the exception of those who received direct reconstruction or concurrent cytotoxic chemotherapy. Although the combined cohort of HF and CF exhibits variability, outcomes generally suggest that HF has less incidence of telangiectasia, chest /breast wall edema, fibrosis, and no long-term brachial plexopathy rates [(29)].

These trials have profoundly challenged a number of underlying radiobiological expectations about adjuvant breast radiotherapy, thereby providing Level I data that can be used to alter the radiation prescription paradigm that necessitates CF for breast cancer. The CF benefits as a standard in breast radiation delivery have been eliminated, as the BC sensitivity to variations in radiation fraction size is now comparable to that of the surrounding normal tissue. The HF-WBRT use needed to now be considered care standard in the adjuvant setting of BCT for early-stage BC, at a minimum, due to the consistent demonstration of HF regimens safety and efficacy in the long-term follow-up of these four trials [(25)].

Who should receive HF radiation?

The data body is unequivocally in favor of HF-WBRT for cases who are early-stage, node-negative, >50 years old, and post–BCS, as demonstrated by long-term results from randomized trials. As a result, it is recommended that these patients receive 40-42.6 Gy in 15-16 fractions HF-WBRT regimens on a regular basis. Despite the extensive research on HF-WBRT (breast alone), HF usage in local-regional RT context (breast/chest wall + regional nodes, either after BCS or mastectomy) remains more controversial [(24)].

Despite the fact that the ASTRO 2018 consensus guideline is based on the available published clinical literature, the UK has extensive clinical experience treating HF-WBRT and HF-PMRT ± regional nodes. In addition, the UK National Institute for Clinical Excellence (NICE) guidelines have required that most regional and local treatments following mastectomy or BCS be administered with HF since 2009. Hypo-fractionated local-regional RT is frequently employed at specific institutions in Canada, particularly in British Columbia province, as evidenced by the Canadian post-mastectomy randomized trial and the numerous large population-based outcome analyses [(30)].

Nevertheless, the utilization of HF local-regional RT is restricted in other regions of the world.

The four primary trials' underrepresentation of specific patient subgroups is frequently the basis for the arguments against the routine implementation of HF radiation for BC [30].

Future of hypo-fractionated radiation

The UK Trialists are currently evaluating a variety of shortened HF regimens for WBRT in order to ascertain the speed at which WBRT can be administered, following the demonstration of the HF regimens efficacy and safety of 15 or 16 fractions by Level I data. 915 women aged 50 years or older with pT1/pT2, pN0, and M0 disease after BCS were randomized to the traditional CF regimen of 50 Gy/25 fractions/2 Gy/5 weeks daily or to two experimental HF-WBRT arms in the UK FAST trial. (a) 30 Gy/6Gy/ once per week for 5 weeks and (b) 28.5 Gy/5.7Gy/ once per week for 5 weeks [31].

At a three-year follow-up, the 28.5 Gy arm was determined to be comparable to the 50 Gy arm and substantially less deleterious than the 30-Gy arm, as reported in their analysis. There were only two local relapses, both were in the CF-WBRT therapy arm. The FAST trial preliminary findings served as a foundation for the development of their subsequent protocol, the UK FAST FORWARD trial. In this trial, 4000 cases were randomly assigned to receive either their standard HF-WBRT of 40Gy/2.6 Gy/15 fractions/3 weeks or two HF-WBRT experimental regimens, which were both administered in a single week: 27 Gy/5.4 Gy/5 fractions/1 week and 26 Gy/5.2 Gy/5 fractions/1 week. It is envisaged that the long-term results of this trial will offer supplementary condensed delivery options for early-stage breast cancer [31].

CONCLUSION

RT is an indispensable weapon in the fight against BC. However, the treatment of BC is not a single approach, and the various alternatives are still being debated. By transitioning from the traditional five-week treatment regimen to a one-week schedule, the QOL of cases of all ages may be preserved or enhanced. This may also simplify the treatment process, particularly for elderly patients who require additional support and fragile patients in general. Altered fractionation may be implemented through HF (over one week), conclusive single-session intraoperative RTH, or accelerated partial breast irradiation. The former is now considered the standard approach, while the latter is currently being evaluated. Nevertheless, the preliminary findings appear to be promising.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

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