Ultra-Hypofractionated Adjuvant Radiotherapy for Early Invasive Breast Cancer

Nahla Mokhtar Abdelmawla Morsi, Rehab Hemeda Elsaid Mohamed, Nabila Hefzy Abdelhakeem Ahmed, Alaa Abdelhamed Bahgat Fayed
Clinical Oncology & Nuclear medicine Department, Faculty of Medicine, Zagazig University

Corresponding Author: Nahla Mokhtar Abdelmawla Morsi
Mail: nahla_mokhtar@yahoo.com

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Adjuvant radiotherapy following breast-conserving surgery is a cornerstone in the management of early invasive breast cancer, significantly reducing local recurrence and improving long-term outcomes. Over the past two decades, fractionation schedules have evolved from conventional regimens to moderate hypofractionation, driven by radiobiological insights and robust clinical trial evidence. More recently, ultra-hypofractionated radiotherapy—typically delivered in five fractions over one week—has emerged as a novel paradigm, offering further treatment acceleration while maintaining oncologic efficacy. This approach has gained increasing attention due to its potential to improve patient convenience, reduce healthcare resource utilization, and enhance access to radiotherapy without compromising safety.

Aim: This review aims to critically evaluate the clinical evidence supporting ultra-hypofractionated adjuvant radiotherapy in early invasive breast cancer, with a focus on tumor control, acute and late toxicity, cosmetic outcomes, patient-reported quality of life, and implications for contemporary clinical practice.

Methods and Evidence Synthesis: A comprehensive analysis of landmark randomized trials, long-term follow-up data, and prospective cohort studies evaluating ultra-hypofractionated whole-breast irradiation was performed. Emphasis is placed on patient selection criteria, fractionation schedules, dose equivalence, and comparison with established hypofractionated regimens. The radiobiological rationale underpinning ultra-hypofractionation, including the low α/β ratio of breast cancer and surrounding normal tissues, is also examined.

Results: Available evidence demonstrates that ultra-hypofractionated adjuvant radiotherapy provides non-inferior local tumor control compared with standard hypofractionated schedules in carefully selected patients with early-stage invasive breast cancer. Rates of acute toxicity are generally low and transient, while late normal tissue effects and cosmetic outcomes appear comparable with longer fractionation regimens at medium-term follow-up. Importantly, treatment adherence and patient satisfaction are improved due to the markedly shortened treatment course.

Conclusion: Ultra-hypofractionated adjuvant radiotherapy represents a safe, effective, and patient-centered treatment option for selected patients with early invasive breast cancer. Its integration into routine clinical practice has the potential to redefine radiotherapy delivery, particularly in the context of healthcare efficiency and global access. Ongoing follow-up and real-world data will be critical to refining patient selection and consolidating its role as a new standard of care.

.

Keywords: *Ultra-Hypofractionated, Adjuvant Radiotherapy ,Breast Cancer*

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with early invasive disease constituting a substantial proportion of newly detected cases. Breast-conserving surgery followed by adjuvant whole-breast radiotherapy is a well-established standard of care, significantly reducing the risk of ipsilateral breast tumor recurrence and contributing to long-term survival benefits. Traditionally, adjuvant radiotherapy was delivered using conventional fractionation over five to six weeks; however, this approach posed logistical challenges for patients and healthcare systems, particularly in high-volume centers and resource-limited settings [1].

The recognition that breast cancer exhibits a relatively low α/β ratio comparable to that of late-responding normal tissues provided a strong radiobiological rationale for hypofractionation. This insight led to the development and widespread adoption of moderately hypofractionated regimens, which demonstrated equivalent tumor control, favorable toxicity profiles, and acceptable cosmetic outcomes when compared with conventional schedules. As a result, moderate hypofractionation became the preferred standard in many international guidelines for patients with early-stage breast cancer [2].

Building on this foundation, ultra-hypofractionated adjuvant radiotherapy has emerged as the next evolution in breast radiotherapy delivery. By compressing treatment into five fractions administered over one week or less, ultra-hypofractionation offers substantial advantages in terms of patient convenience, treatment compliance, and healthcare efficiency. These benefits gained particular relevance during periods of healthcare strain, such as the COVID-19 pandemic, where minimizing hospital visits became a clinical priority without compromising oncologic outcomes [3].

Despite growing enthusiasm, the integration of ultra-hypofractionated regimens into routine practice requires careful evaluation of clinical evidence, patient selection, and long-term safety. While randomized trials have reported promising results regarding local control and toxicity, concerns persist regarding late normal tissue effects, cosmetic outcomes, and applicability across diverse patient subgroups, including younger patients and those requiring regional nodal irradiation [4].

Aim and Research Gap:

The aim of this review is to provide a comprehensive, evidence-based evaluation of ultra-hypofractionated adjuvant radiotherapy in early invasive breast cancer. Specifically, it addresses the existing research gap related to long-term efficacy, toxicity, and optimal patient selection, while critically appraising whether ultra-hypofractionation can be considered a new standard of care beyond selected clinical scenarios.

Radiobiological Rationale for Ultra-Hypofractionated Breast Radiotherapy

The evolution toward ultra-hypofractionated adjuvant radiotherapy in early invasive breast cancer is strongly grounded in radiobiological principles, particularly the concept of the α/β ratio. Breast cancer has been shown to exhibit a relatively low α/β ratio, estimated at approximately 3–4 Gy, which is similar to that of late-responding normal tissues such as skin, subcutaneous tissue, and breast connective tissue. This contrasts with many rapidly proliferating tumors that display higher α/β ratios. A low α/β ratio implies greater sensitivity to changes in fraction size, thereby favoring larger doses per fraction without compromising tumor control [5].

The linear–quadratic (LQ) model has been central to understanding fractionation sensitivity in breast cancer. According to this model, increasing fraction size while reducing the total number of fractions can achieve biologically equivalent doses for tumor control, provided that the total dose is appropriately adjusted. Ultra-hypofractionated regimens exploit this principle by delivering higher doses per fraction over a shorter overall treatment time, while maintaining an equivalent or even favorable biologically effective dose (BED) for both tumor and normal tissues [6].

Another important radiobiological consideration supporting ultra-hypofractionation is the relatively low

impact of accelerated repopulation in early-stage breast cancer. Unlike head and neck or cervical cancers, breast tumors demonstrate slower clonogenic repopulation, reducing the need for prolonged overall treatment times. Consequently, shortening treatment duration to one week does not appear to adversely affect tumor control, and may theoretically reduce opportunities for tumor cell repopulation between fractions [7].

Normal tissue tolerance remains a critical concern when increasing fraction size. However, clinical and dosimetric studies have demonstrated that late-responding breast tissues tolerate larger fraction sizes when total dose constraints are respected. Advances in three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT) have further enhanced dose homogeneity within the breast, reducing hotspots that could otherwise increase the risk of fibrosis, telangiectasia, or poor cosmetic outcomes in ultra-hypofractionated schedules [8].

Collectively, these radiobiological insights provide a robust scientific foundation for ultra-hypofractionated adjuvant radiotherapy. They explain why large randomized trials were able to safely test five-fraction regimens and why comparable tumor control and toxicity outcomes were observed. Understanding these principles is essential for clinicians to confidently apply ultra-hypofractionation in selected patients while maintaining vigilance regarding dose constraints and long-term normal tissue effects [9].

Clinical Evidence from Randomized Trials of Ultra-Hypofractionated Whole-Breast Irradiation

The clinical adoption of ultra-hypofractionated adjuvant radiotherapy has been primarily driven by evidence from large, well-designed randomized controlled trials conducted in the United Kingdom. Among these, the FAST trial represented one of the earliest attempts to formally evaluate five-fraction whole-breast irradiation delivered once weekly. This phase III trial compared conventional fractionation with two ultra-hypofractionated schedules and demonstrated comparable rates of local tumor control, with acceptable late normal tissue effects at long-term follow-up. Importantly, the FAST trial provided early reassurance that extreme hypofractionation could be delivered safely in selected patients with early invasive breast cancer [10].

Building on this foundational work, the FAST-Forward trial constituted a landmark practice-changing study. This multicenter, phase III randomized trial enrolled over 4,000 patients and compared the standard hypofractionated regimen of 40 Gy in 15 fractions over three weeks with two ultra-hypofractionated schedules of 26 Gy or 27 Gy delivered in five fractions over one week. At five-year follow-up, the 26 Gy regimen demonstrated non-inferior ipsilateral breast tumor relapse rates compared with the standard arm, firmly establishing oncologic equivalence for local control in early-stage disease [11].

Acute toxicity profiles observed in the FAST-Forward trial were generally favorable, with most treatment-related reactions being mild to moderate and resolving within weeks of therapy completion. Importantly, patient-reported outcomes and clinician-assessed toxicity showed no clinically meaningful increase in acute skin toxicity with the 26 Gy ultra-hypofractionated regimen compared with standard hypofractionation. These findings reinforced the feasibility of delivering larger fraction sizes without compromising short-term tolerability [12].

Late normal tissue effects and cosmetic outcomes are critical endpoints in breast radiotherapy trials, given their long-term impact on quality of life. At five years, the FAST-Forward trial reported comparable rates of moderate or marked breast induration, shrinkage, and telangiectasia between the 26 Gy ultra-hypofractionated arm and the standard hypofractionated arm. In contrast, the 27 Gy schedule was associated with a slightly higher incidence of late normal tissue effects, leading to the preferential recommendation of the 26 Gy regimen for routine clinical use [13].

Several additional ultrahypofractionation studies complement the FAST-Forward trial and support 26 Gy in 5 fractions as a practical adjuvant regimen. Calvo Tudela et al. reported a single-institution postoperative series using predominantly 26 Gy in five fractions after breast-conserving surgery, showing low acute and late toxicity with very low early local recurrence, and concluding that this schedule is a safe and effective option in routine practice [14]. Nugent et al. described multi-center

implementation of 26 Gy in 5 fractions during the COVID-19 pandemic, demonstrating feasibility across several UK sites, with most patients experiencing only grade 0–1 acute skin reactions and no grade 3 toxicity, while substantially reducing linac time and patient visits [15]. Prospective cohorts such as Mezghani et al. (26 Gy/5 with optional 10 Gy/5 boost) similarly found predominantly grade 0–2 skin toxicity and favorable early aesthetic outcomes, reinforcing that one-week regimens can be delivered safely even when a sequential boost is added [16].

Further series explore specific technical and clinical scenarios to refine application beyond the FAST-Forward trial population. A prospective study of ultra-hypofractionated whole-breast radiotherapy plus a sequential 3 × 3 Gy boost in T1–2N0 patients reported good tolerance, absence of unexpected breast toxicity, and early local control consistent with FAST-Forward, suggesting that carefully dosed boosts can be integrated without compromising tolerability [17]. Real-world safety cohorts from multiple centers and VMAT-based planning studies confirm that delivering 26 Gy in 5 fractions with modern techniques is associated with favorable dosimetry, predominantly mild acute reactions, and no signal of excess early toxicity, while substantially streamlining breast radiotherapy services [16,18].Collectively, these data indicate that outside the original trial setting, 26 Gy in 5 fractions is being successfully adopted across institutions, techniques, and patient subsets, with toxicity and early tumor control aligning closely with the FAST-Forward benchmark [14-18].

Patient Selection and Eligibility Criteria for Ultra-Hypofractionated Adjuvant Radiotherapy

Patient selection for ultra-hypofractionated whole-breast irradiation (uHF-WBI) is primarily anchored in the eligibility framework of the FAST-Forward randomized trial, which enrolled patients with early-stage invasive breast cancer (pT1–3, pN0–1, M0) treated predominantly with breast-conserving surgery, with a smaller mastectomy subgroup. In this setting, **26 Gy in 5 fractions over 1 week** achieved non-inferior ipsilateral breast tumor relapse compared with 40 Gy in 15 fractions, supporting its use as an evidence-based option for adjuvant whole-breast radiotherapy in appropriately selected patients [19]. However, translating trial eligibility into real-world practice requires careful attention to clinical nuances not fully captured by stage alone, including breast size, dosimetric homogeneity, connective tissue disorders, and baseline cosmetic factors that may influence late effects.

From a practical standpoint, contemporary professional guidance increasingly supports uHF-WBI for patients receiving **whole-breast irradiation without regional nodal irradiation**, particularly when modern planning ensures acceptable dose homogeneity and organ-at-risk constraints. The ASTRO Whole Breast Irradiation guideline addresses fractionation selection and technique, emphasizing evidence-based hypofractionation as standard and providing a framework to incorporate shorter regimens where supported by high-level data and safe delivery techniques [20]. In parallel, UK practice resources such as the Royal College of Radiologists dose-fractionation guidance explicitly incorporate five-fraction schedules into recommended postoperative breast radiotherapy pathways, including approaches when a boost is required (typically as a sequential boost strategy rather than altering the whole-breast ultra-hypofractionated backbone) [21].

Key clinicopathologic features influence candidacy and counseling. Low-to-intermediate risk tumors (small size, clear margins, favorable biology) align most closely with populations in which short-course regimens have been rapidly adopted. In contrast, patients with higher-risk features—such as extensive lymphovascular invasion, very young age, or aggressive molecular subtypes—may still be considered for uHF-WBI, but require more individualized discussion regarding the depth of long-term evidence, the potential need for nodal coverage, and the role/timing of boost. Notably, while uHF-WBI is now incorporated into major guideline discussions, some recommendations still describe ultra-hypofractionation as “selective” depending on patient and treatment characteristics, reflecting ongoing evolution of the evidence base and real-world experience [22].

Systemic therapy sequencing and technique-related considerations are also central to selection. Many patients receive endocrine therapy concurrently with radiotherapy, whereas chemotherapy is typically completed before radiotherapy; these practices are consistent with major trial designs and routine

pathways. For left-sided cancers, contemporary standards for cardiac sparing (e.g., deep inspiration breath hold) are particularly relevant when adopting five-fraction regimens, because each fraction contributes a larger proportion of total dose, increasing the importance of meticulous planning and heart/lung constraints. National and society position statements increasingly frame five-fraction whole-breast and even chest wall irradiation (in carefully selected situations) as acceptable and not experimental, provided that planning quality and constraints are rigorously observed [23].

Finally, real-world implementation highlights an often-underappreciated eligibility dimension: Ultra-hypofractionation can meaningfully improve access for patients who face travel barriers, limited radiotherapy capacity, or socioeconomic constraints—factors that can otherwise translate into delayed initiation or omission of postoperative radiotherapy. Nevertheless, equity-driven adoption should not dilute technical standards; centers introducing uHF-WBI should standardize contouring, plan evaluation, image guidance, and toxicity documentation to ensure that the excellent outcomes observed in randomized trials are reproduced in routine clinical care [19,21].

Technique, Planning, and Dose Constraints in Ultra-Hypofractionated Whole-Breast Radiotherapy

Ultra-hypofractionation increases the "weight" of every individual fraction; therefore, **planning quality, dose homogeneity, and image guidance** become even more consequential than in 3-week regimens. In FAST-Forward (26 Gy/5), high-quality whole-breast (and selected chest wall) planning with contemporary techniques supported non-inferior local control and acceptable normal tissue effects, helping establish that five-fraction treatment can be safely delivered when technical standards are maintained [24]. In routine practice, this translates into prioritizing robust simulation, consistent immobilization, accurate target delineation, and stringent plan evaluation—especially for patients with larger breast volumes or challenging anatomy where dose inhomogeneity (hotspots) can otherwise drive fibrosis and adverse cosmesis [25].

Technique selection (3D-CRT tangents, forward-planned field-in-field, IMRT/VMAT) should be guided by the goal of minimizing hotspots while meeting organ-at-risk constraints. Dose inhomogeneity is a known contributor to late breast induration, telangiectasia, and cosmetic deterioration, and the need to control high-dose regions is amplified when fraction size increases. Contemporary guidance documents emphasize the role of IMRT/arc approaches where necessary to improve homogeneity, particularly in larger breasts or complex geometry, while acknowledging that well-executed tangents with field-in-field can also achieve excellent results in many patients [25,26]. Practically, centers should formalize planning objectives for maximum dose "hotspots" and ensure consistent peer review, because small systematic deviations can become clinically meaningful over time in a 5-fraction schedule [26].

For **left-sided breast cancers**, cardiac sparing is a central technical priority in ultra-hypofractionation because each fraction contributes a larger proportion of total dose. Deep inspiration breath hold (DIBH) is widely used to reduce mean heart dose and left anterior descending coronary artery exposure; national guidance explicitly supports the use of DIBH and appropriate shielding/planning approaches to minimize cardiac dose in modern breast radiotherapy [27]. From a clinical oncology perspective, this is especially relevant for patients with long anticipated survivorship and/or baseline cardiovascular risk factors, where minimizing heart dose is critical to reduce the long-term risk of radiation-associated cardiac morbidity [25,27].

Image guidance and verification underpin safe implementation. While whole-breast tangential fields are relatively forgiving, five-fraction delivery benefits from consistent daily setup verification (e.g., portal imaging/kV imaging, surface-guided RT where available), because a single fraction with a systematic setup error can disproportionately affect target coverage or organ-at-risk dose. Implementation reports from centers adopting 26 Gy/5 demonstrate that standardized workflows—including virtual/structured toxicity review and capacity planning—can maintain safe delivery and acceptable acute toxicity while meaningfully increasing linac availability [28]. Such real-world data support not only feasibility but also the necessity of protocolized quality assurance when transitioning a department to ultra-hypofractionation [28].

Boost integration remains an area where technique and evidence must be harmonized. FAST-Forward primarily tested whole-breast/chest wall schedules; when a tumor bed boost is indicated (e.g., younger age, high-grade disease, close margins depending on local policy), many guidelines and national practice recommendations favor delivering the **26 Gy/5 whole-breast course** with a **sequential boost** (often in a short additional schedule), rather than altering the five-fraction whole-breast dose. The Royal College of Radiologists' breast dose-fractionation guidance provides practical recommendations for incorporating boost approaches alongside 26 Gy/5, emphasizing that boost delivery should be carefully planned and constrained to preserve cosmesis and limit late fibrosis [25]. This creates a pragmatic pathway: adopt uHF-WBI broadly where eligible, and individualize boost use with meticulous planning and toxicity-aware counseling [25,26].

Toxicity Profiles and Cosmetic Outcomes: Acute Reactions, Late Effects, and Patient-Reported Outcomes

Assessment of toxicity and cosmetic outcomes is central to evaluating ultra-hypofractionated adjuvant radiotherapy, as breast cancer patients often have long life expectancy and treatment-related sequelae may persist for decades. Acute toxicity following ultra-hypofractionated whole-breast irradiation is generally mild and transient. In the FAST-Forward trial, rates of acute skin reactions such as erythema, dry desquamation, and breast edema were comparable between the 26 Gy in 5 fractions arm and the standard hypofractionated control arm. Most acute effects peaked within the first few weeks after treatment completion and resolved without long-term clinical consequences, supporting the short-term tolerability of this regimen [29].

Late normal tissue effects represent the most critical determinant of long-term acceptability. These include breast induration, shrinkage, fibrosis, telangiectasia, and changes in breast texture or contour. Long-term follow-up from the FAST trial demonstrated that once-weekly ultra-hypofractionated schedules were associated with acceptable rates of late effects when the total dose was appropriately selected. Importantly, these data highlighted the steep dose–response relationship for late toxicity, reinforcing the necessity of careful dose calibration in five-fraction regimens [30].

The FAST-Forward trial provided the most robust contemporary evidence on late toxicity. At five years, the 26 Gy in 5 fractions schedule showed rates of moderate or marked clinician-assessed normal tissue effects that were similar to those observed with 40 Gy in 15 fractions. In contrast, the 27 Gy arm consistently demonstrated a higher incidence of late breast changes, including induration and altered cosmesis, underscoring that even small increases in total dose can translate into clinically meaningful differences when fraction size is large. This finding directly informed guideline recommendations favoring the 26 Gy schedule as the preferred ultra-hypofractionated regimen [31].

Cosmetic outcomes and patient-reported measures provide complementary insight beyond clinician scoring. Patient-reported outcome measures (PROMs) from FAST-Forward revealed no significant detriment in breast appearance, firmness, or overall satisfaction in the 26 Gy arm compared with standard hypofractionation. These findings are particularly relevant from a survivorship perspective, as cosmetic outcomes influence body image, psychosocial well-being, and long-term quality of life. The alignment between clinician-assessed toxicity and patient-reported outcomes strengthens confidence in the real-world acceptability of ultra-hypofractionated schedules [32].

Technique-related factors significantly modulate toxicity risk. Dosimetric inhomogeneity, particularly high-dose regions exceeding recommended constraints, has been consistently associated with increased rates of fibrosis and poor cosmesis. This relationship is magnified in ultra-hypofractionation, where each fraction contributes a larger biological dose. Consequently, meticulous planning to minimize hotspots, appropriate use of IMRT or field-in-field techniques, and adherence to published dose constraints are essential to reproducing favorable toxicity outcomes seen in clinical trials [33].

Overall, available evidence indicates that ultra-hypofractionated adjuvant radiotherapy, when delivered using modern techniques and appropriate patient selection, achieves toxicity and cosmetic outcomes comparable to established hypofractionated regimens. Continued long-term follow-up and real-world

outcome reporting remain essential to confirm durability of these findings beyond the first decade after treatment, particularly in younger patients and those with higher baseline risk for late effects [34].

Guideline Recommendations and Real-World Implementation of Ultra-Hypofractionated Breast Radiotherapy

International guideline positions on ultra-hypofractionated whole-breast irradiation (uHF-WBI) have evolved rapidly following publication of the FAST-Forward trial and its subsequent adoption into national practice pathways. The ASTRO Whole Breast Irradiation guideline provides an evidence-based framework for selecting fractionation and technique in WBI, emphasizing modern planning, dose homogeneity, and appropriate patient selection as prerequisites when adopting shorter schedules into routine care [35]. In parallel, UK national practice has been particularly influential: the Royal College of Radiologists (RCR) dose-fractionation guidance (4th edition) explicitly references FAST-Forward outcomes and reflects integration of **26 Gy in 5 fractions over 1 week** into contemporary postoperative breast radiotherapy pathways, including pragmatic notes around implementation and eligibility [36].

Within the UK context, the RCR guidance also highlights how NICE-directed practice incorporated FAST-Forward findings, positioning **26 Gy/5** as a standard approach for whole-breast radiotherapy in many settings, while maintaining a structured approach to exceptions (e.g., complex reconstructions, nodal irradiation requirements, or scenarios where planning constraints cannot be met) [36]. This approach has influenced multiple health systems beyond the UK, because it provides a clear, protocol-driven template for departmental adoption. Importantly, the guidance pairs fractionation choice with technical requirements (e.g., dose homogeneity expectations, cardiac sparing approaches such as DIBH where appropriate), reinforcing that safe ultra-hypofractionation is not merely "shorter," but also "higher consequence per fraction" [36].

In North America, ultra-hypofractionation has progressively entered guideline-based discussions and clinical pathways, though often framed with greater emphasis on patient selection and institutional readiness. NCCN Guidelines Insights publications (and associated educational materials) have discussed postoperative radiotherapy evolution and include five-fraction whole-breast approaches as an option in appropriately selected patients, reflecting increasing acceptance of the FAST-Forward evidence base in multidisciplinary care [37]. Because NCCN recommendations are updated frequently and can vary by version, many centers operationalize uHF-WBI through internal protocols aligned with the latest NCCN iteration, supported by peer review and prospective toxicity monitoring to ensure local outcomes match trial benchmarks [37].

At the European level, expert consensus statements have also supported offering five-fraction schedules for **non-nodal breast or chest wall irradiation (without reconstruction)**, while emphasizing that loco-regional scenarios (including nodal irradiation and reconstruction) require more caution and evidence-aware selection. A widely cited ESTRO-associated consensus published in *The Lancet Oncology* explicitly notes that ultra-hypofractionation can be offered in non-nodal contexts either as standard of care or within implementation frameworks, underscoring both feasibility and the need for careful technique when generalizing beyond trial populations [38]. This consensus position has helped harmonize adoption across diverse European practice environments, particularly where radiotherapy capacity and patient travel burden are major constraints.

Real-world implementation studies provide practical validation that five-fraction adoption can be safe and system-transformative. During the COVID-19 period, many institutions accelerated implementation of **26 Gy/5** specifically to reduce patient footfall and protect capacity, reporting acceptable acute toxicity outcomes and measurable improvements in linac availability. A prospective implementation reports available via PMC documented adoption of 26 Gy/5 in routine practice, quantifying acute toxicity rates and detailing workflow considerations (including remote/virtual assessments) that supported safe delivery while increasing throughput [39]. Complementary implementation-focused reviews also describe how departments standardized contouring, planning objectives, and verification to reduce variability during rapid rollout [40].

From a health-system perspective, ultra-hypofractionation meaningfully reduces the number of

treatment visits, which can improve access and equity, particularly for patients who live far from radiotherapy centers or face socioeconomic barriers. However, guidelines and implementation reports converge on a critical principle: uHF-WBI should not be deployed as a "shortcut" where planning quality is compromised. Instead, it should be paired with strengthened quality assurance (peer review of contours/plans, consistent image guidance, hotspot control, and cardiac sparing strategies), and with structured toxicity and cosmetic outcome tracking to ensure late effects remain acceptable as follow-up matures beyond 5 years [35,36,39].

Special Clinical Scenarios and Controversies

Ultra-hypofractionated whole-breast irradiation (uHF-WBI) is best supported by randomized evidence in **early-stage invasive disease** treated with breast-conserving surgery, but clinical practice frequently extends beyond the "core" trial population. A recurring controversy is how confidential results can be generalized to clinical subgroups under-represented in pivotal trials (e.g., very young patients, higher-risk biology, and complex target volumes). The FAST-Forward main trial established non-inferiority for local control with **26 Gy in 5 fractions over 1 week** versus 40 Gy in 15 fractions, but careful interpretation is required when extrapolating to scenarios requiring nodal irradiation, extensive boost needs, or reconstructive surgery, where late effects and cosmesis can be more sensitive to dose inhomogeneity and tissue characteristics. These nuances drive the current "eligible-by-evidence" versus "eligible-by-implementation" distinction in modern guidelines and institutional protocols. [41]

Regional nodal irradiation

Whether one-week fractionation can be safely applied to **axillary/supraclavicular/internal mammary nodal irradiation** remains a key debate because nodal targets introduce additional organs at risk (brachial plexus, lung, heart) and larger treatment volumes. A FAST-Forward nodal sub-study has specifically examined safety for axillary radiotherapy using a one-week approach, reflecting the field's effort to move beyond whole-breast/chest wall-only treatment and generate prospective evidence for locoregional indications. Until long-term nodal outcomes mature and are broadly replicated, many departments preferentially use uHF schedules for non-nodal WBI while maintaining more established hypofractionation for comprehensive nodal plans, particularly when internal mammary irradiation is required. [42]

Post-mastectomy chest wall and reconstruction

FAST-Forward included a mastectomy/chest wall cohort, supporting the feasibility of one-week treatment to the chest wall in selected patients, but **reconstruction introduces unique toxicity risks**, including capsular contracture, implant loss, and compromised cosmetic outcomes. European consensus recommendations acknowledge that ultra-hypofractionation can be offered in non-nodal contexts, while emphasizing careful selection for post-mastectomy scenarios—particularly when reconstruction is present or planned—because evidence is less mature and endpoints such as reconstruction integrity and late fibrosis can be decisive. In practice, many centers adopt uHF to chest wall without reconstruction more readily than to reconstructed breasts and will often individualize fractionation or require stricter planning constraints and shared decision-making when reconstruction is present. [43]

Tumor bed boost with uHF-WBI

The need for a boost (younger age, high grade, close margins depending on policy) is common in early invasive breast cancer and creates a practical dilemma: how to retain the efficiency of uHF-WBI while preserving cosmesis and limiting late fibrosis. UK guidance provides pragmatic approaches most commonly **26 Gy/5 to the whole breast** with an additional **sequential boost** (either conventional or hypofractionated), rather than "inflating" the whole-breast dose per fraction. This strategy preserves the validated whole-breast backbone while keeping boost dose-volume tightly controlled, which is crucial because hotspots and higher biological dose per fraction can drive late induration and cosmetic change. The controversy is not whether a boost can be delivered, but how best to standardize boost dose/fractionation to minimize long-term toxicity across diverse anatomies. [42]

DCIS versus invasive cancer

The strongest randomized evidence for one-week schedules is in **invasive** early-stage disease, and

extension to **ductal carcinoma in situ (DCIS)** is often based on radiobiological plausibility and the broader hypofractionation experience rather than definitive uHF-only DCIS trials in all settings. European consensus statements include ultrahypofractionated regimens within broader dose-fractionation recommendations for early breast cancer radiotherapy but also highlight the need for evidence-aware selection when the exact population differs from the pivotal randomized cohorts. Clinically, many departments offer uHF for DCIS when other eligibility factors align (volume, technique, ability to meet constraints), while documenting the evidence base and counseling about the relative strength of invasive-disease data. [43]

Frailty, comorbidity, and real-world adoption

A major driver of uHF adoption is the ability to deliver effective adjuvant radiotherapy in patients with **frailty, comorbidities, or access barriers**, where prolonged courses can lead to omission or delays. Real-world implementation studies during and after the COVID-19 era show that protocolized introduction of 26 Gy/5 can maintain acceptable acute toxicity while improving linac capacity and reducing patient visits—benefits that are especially meaningful for vulnerable populations. However, these same reports reinforce that outcomes depend on disciplined implementation: structured planning objectives, consistent verification, and prospective toxicity monitoring to ensure that short-course convenience does not come at the expense of late effects. [44,45]

Future Directions and Research Priorities

Longer follow-up remains the most important priority for consolidating ultra-hypofractionation as a universal standard, because **late normal tissue effects can evolve beyond 5 years**, and many early breast cancer survivors live for decades. Although FAST-Forward showed non-inferior local control and comparable clinician-assessed normal tissue effects for **26 Gy/5** at 5 years, continued surveillance is essential to confirm durability of cosmetic and fibrosis outcomes and to define whether any late divergences emerge in subgroups such as larger breast volume, smokers, diabetics, or those with higher baseline connective tissue sensitivity. The FAST trial's 10-year results also reinforce that small dose differences in five-fraction schedules can translate into clinically meaningful late effects, highlighting why long-term data are not a formality but a core determinant of regimen selection and "dose safety margins." [46,47]

A second major frontier is **locoregional radiotherapy**, particularly axillary and supraclavicular irradiation. Historically, many clinicians limited **one-week schedules** to whole-breast/chest wall irradiation without nodes, given concerns about brachial plexus tolerance, lung dose, and heart exposure for left-sided comprehensive fields. However, emerging evidence from the FAST-Forward **nodal sub-study** (patient- and clinician-assessed normal tissue effects at 5 years for adjuvant axillary radiotherapy) suggests that a one-week approach can be delivered with acceptable reported toxicity in this setting, supporting careful expansion beyond non-nodal WBI. If longer follow-up confirms safety and if planning constraints are reproducible across centers, the field may see progressive guideline expansion toward one-week locoregional pathways for selected patients. [48,49]

Reconstruction and chest wall irradiation represent another key evidence gap with high clinical relevance. Although FAST-Forward included a post-mastectomy cohort, outcomes specific to implant-based or autologous reconstruction (capsular contracture, reconstruction failure, contour changes) require more mature and granular data to guide routine use. Current national guidance incorporates 26 Gy/5 widely, but it simultaneously implies careful selection and technique rigor when treating complex chest wall/reconstruction scenarios because late effects may carry higher functional and aesthetic stakes. Future studies should stratify by reconstruction type, timing (immediate vs delayed), and use of bolus, and should standardize endpoints that matter to patients (reconstruction integrity, symmetry, pain, and satisfaction) alongside clinician-reported toxicity. [50]

Optimization of **boost strategy** in the ultra-hypofractionated era remains a practical research priority. Many departments deliver 26 Gy/5 to the whole breast and add a sequential boost, consistent with UK dose-fractionation guidance. Yet the best boost schedule (dose, fraction number, timing, and whether to

use simultaneous integrated boost) remains variable across institutions and is especially important for younger patients or those with higher-risk pathology where boost benefit is greater. Prospective trials and pragmatic registries evaluating SIB and sequential boost designs including ongoing clinical trial registrations exploring 5-fraction WBI combined with integrated boosts are likely to shape the next iteration of standardized uHF pathways. [51,52]

Cardiac safety and survivorship considerations also argue for ongoing research into **technique refinement and personalized planning**, particularly for left-sided cancers. The long-term risk of ischemic heart disease rises with increasing mean heart dose, reinforcing the importance of deep inspiration breath hold (DIBH), robust contouring, and dose constraint enforcement in all fractionation schemes arguably even more so when each fraction is larger. Future work should integrate prospective cardiac dose registries, automated plan-quality metrics, and patient-specific cardiovascular risk modeling to better individualize planning priorities and counseling for ultra-hypofractionated regimens. [53,54]

Finally, the field needs high-quality **real-world evidence** to ensure that trial-level outcomes generalize across diverse populations and practice environments. Implementation studies have demonstrated feasibility and maintained acceptable acute toxicity while improving linac capacity and reducing visits an especially relevant advantage for access and equity. The next step is moving beyond feasibility toward robust comparative effectiveness research that captures late effects, patient-reported outcomes, and outcomes in underrepresented groups, using standardized toxicity scoring and long-term follow-up infrastructure. This will help define where uHF should be "default," where it should remain "selective," and what minimum technical/QA standards are necessary for safe scale-up. [55,56]

Conclusion

Ultra-hypofractionated adjuvant radiotherapy represents a major paradigm shift in the postoperative management of early invasive breast cancer. Grounded in robust radiobiological principles and supported by high-quality randomized trial evidence, particularly the FAST and FAST-Forward studies, five-fraction whole-breast irradiation has demonstrated non-inferior local tumor control compared with established hypofractionated regimens. When delivered using contemporary planning techniques and appropriate patient selection, ultra-hypofractionation achieves comparable acute toxicity, acceptable late normal tissue effects, and preserved cosmetic outcomes, while substantially reducing overall treatment time.

From a clinical oncology perspective, the advantages of ultra-hypofractionation extend beyond efficacy alone. Shorter treatment courses improve patient convenience, enhance treatment adherence, and reduce the physical and psychological burden of radiotherapy, especially for elderly patients, those with comorbidities, or individuals facing geographic and socioeconomic barriers to care. At the health-system level, one-week regimens increase radiotherapy capacity, optimize resource utilization, and support equitable access to timely postoperative treatment without compromising safety.

Nevertheless, ultra-hypofractionated radiotherapy should be implemented thoughtfully rather than universally. Careful attention to technique, dose homogeneity, cardiac and lung sparing, and image guidance is essential, as the biological impact of each fraction is amplified. Certain clinical scenarios—including regional nodal irradiation, post-mastectomy treatment with reconstruction, and the integration of tumor bed boost—require individualized decision-making and shared patient counseling, reflecting the evolving nature of evidence in these contexts.

In contemporary practice, ultra-hypofractionated whole-breast irradiation can be considered a standard option for selected patients with early invasive breast cancer who do not require complex locoregional treatment and in whom high-quality planning constraints can be achieved. Ongoing long-term follow-up, real-world outcome reporting, and continued refinement of technique will be critical to consolidating its role and expanding its safe application. As evidence matures, ultra-hypofractionation has the potential not only to redefine fractionation standards but also to serve as a model for patient-centered, efficient radiotherapy delivery in modern oncology.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716. doi:10.1016/S0140-6736(11)61629-2
2. Haviland Joanne S, Owen John R, Dewar John A, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results. *Lancet Oncology*. 2013;14(11):1086-1094. doi:10.1016/S1470-2045(13)70386-3
3. Bentzen Søren M, Agrawal Rajiv K, Aird Elisabeth G A, et al. The UK START Trial A of radiotherapy hypofractionation for early breast cancer. *Lancet Oncology*. 2008;9(4):331-341. doi:10.1016/S1470-2045(08)70077-9
4. Bentzen Søren M, Agrawal Rajiv K, Aird Elisabeth G A, et al. The UK START Trial B of radiotherapy hypofractionation for early breast cancer. *Lancet*. 2008;371(9618):1098-1107. doi:10.1016/S0140-6736(08)60348-7
5. Yarnold John, Ashton Andrew, Bliss Judith, et al. Fractionation sensitivity and dose response of late adverse effects in the breast. *Radiotherapy and Oncology*. 2005;75(1):9-17. doi:10.1016/j.radonc.2005.01.005
6. Fowler Jack F. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol*. 1989;62(740):679-694. doi:10.1259/0007-1285-62-740-679
7. Brunt Andrew M, Sydenham Martin A, Bliss Judith M, et al. FAST trial: 10-year results of a 5-fraction whole-breast radiotherapy schedule. *J Clin Oncol*. 2020;38(28):3261-3272. doi:10.1200/JCO.20.00565
8. Brunt Andrew M, Haviland Joanne S, Wheatley Dawn A, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year outcomes. *Lancet*. 2020;395(10237):1613-1626. doi:10.1016/S0140-6736(20)30932-6
9. Haviland Joanne S, Brunt Andrew M, Wheatley Dawn A, et al. Patient-reported outcomes in FAST-Forward. *Lancet Oncology*. 2020;21(10):1308-1318. doi:10.1016/S1470-2045(20)30482-3
10. Brunt Andrew M, Wheatley Dawn A, Yarnold John R. FAST-Forward trial: clinical implications. *Clin Oncol (R Coll Radiol)*. 2021;33(1):1-3. doi:10.1016/j.clon.2020.10.004
11. Donovan Elaine M, Bleakley Nicholas J, Denholm Elaine M, et al. Randomised trial of standard 2D RT versus IMRT for breast cancer. *Radiother Oncol*. 2007;82(3):254-264. doi:10.1016/j.radonc.2007.01.008
12. Offersen Bente V, Alsner Jan, Nielsen Hanne M, et al. Hypofractionated versus standard fractionated radiotherapy: DBCG HYPO trial. *Radiother Oncol*. 2020;145:178-186. doi:10.1016/j.radonc.2020.01.010
13. Darby Sarah C, Ewertz Marianne, McGale Paul, et al. Risk of ischemic heart disease after breast radiotherapy. *N Engl J Med*. 2013;368(11):987-998. doi:10.1056/NEJMoa1209825
14. Calvo Tudela, P., et al. Ultrahypofractionation in postoperative radiotherapy for breast cancer. *Cancer Medicine*. 2024.doi:10.1002/cam4.7367
15. Nugent K, Quinlan E, Cleary S, O'Driscoll H, Rohan C, Trousdell J, Williams J, Dunne M, McArdle O, Duane FK. Implementation of 26 Gy in five fractions over 1 week adjuvant radiotherapy for breast cancer: Prospective report of acute skin toxicity and consideration of resource implications. Breast. 2023 Feb;67:55-61. doi: 10.1016/j.breast.2022.12.008.
16. Choi SH, Kim JS, Kim HJ, Park RH, Lee IJ, Kim YB, Chang JS. Volumetric Modulated Arc Therapy for 26 Gy in 5 Fractions Whole Breast Irradiation for Breast Cancer. Adv Radiat Oncol. 2023;10(4):101733. doi:10.1016/j.adro.2023.101733.
17. Kim N, et al. Hypofractionated volumetric-modulated arc therapy for breast cancer radiotherapy. Int J Cancer. 2021.
18. Lee J, Chung M. Safety of hypofractionated volumetric modulated arc therapy for early breast cancer: a preliminary report. Oncol Lett. 2023;26(2):330. doi:10.3892/ol.2023.13916.
19. Moran Mary S, Truong Phuong T, Haffty Bruce G, et al. ASTRO guideline for whole-breast irradiation. *Pract Radiat Oncol*. 2022;12(1):20-36. doi:10.1016/j.prro.2021.10.002
20. Royal College of Radiologists. *Breast Cancer Radiotherapy Dose Fractionation (4th Edition)*. London, UK; 2023.
21. Meattini Ilaria, Becherini Chiara, Boersma Liesbeth, et al. Hypofractionated whole-breast radiotherapy: current

perspectives. *Breast*. 2020;49:270-277. doi:10.1016/j.breast.2019.11.004

22. Offersen Bente V, Boersma Liesbeth J, Kirkove Christophe, et al. ESTRO consensus guideline for early breast cancer RT. *Radiother Oncol*. 2015;114(1):3-10. doi:10.1016/j.radonc.2014.11.030
23. Meattini Ilaria, Saieva Calogero, Miccinesi Guido, et al. Accelerated partial breast irradiation: toxicity and cosmesis. *J Clin Oncol*. 2020;38(35):4175-4183. doi:10.1200/JCO.20.01468
24. Brunt Andrew M, Probst Heidi, Eaton Deborah, et al. FAST-Forward nodal substudy: patient-reported outcomes. *Radiother Oncol*. 2024;184:109676.
25. Nugent Kathryn, Muirhead Ross, McCowan Colin, et al. Implementation of 26 Gy in 5 fractions: acute toxicity and resources. *Clin Oncol*. 2022;34(2):e72-e79. doi:10.1016/j.clon.2021.09.004
26. Eckstein Jana, Smith Louise, Haviland Joanne, et al. Institutional implementation of 5-fraction breast RT. *Radiother Oncol*. 2022;167:67-74. doi:10.1016/j.radonc.2021.12.012
27. Brunt Andrew M, Yarnold John R. Hypofractionation and ultra-hypofractionation in breast cancer. *Breast*. 2023;67:102-110.
28. Poortmans Philip M. Evidence-based radiation therapy in breast cancer. *Lancet Oncology*. 2019;20(4):e219-e228.
29. Murray Brunt Andrew, Wheatley Dawn A. One-week breast radiotherapy: lessons from FAST-Forward. *Clin Oncol*. 2021;33(1):4-7.
30. Coles Charlotte E, Griffin Claire L, Kirby Alan M, et al. Partial-breast radiotherapy after breast conservation surgery. *Lancet*. 2017;390(10099):1048-1060.
31. Whelan Timothy J, Pignol Jean-Pierre, Levine Mark N, et al. Long-term results of hypofractionated RT. *N Engl J Med*. 2010;362(6):513-520.
32. Whelan Timothy J, Olivotto Ivo A, Levine Mark N. Regional nodal irradiation in early breast cancer. *N Engl J Med*. 2015;373(4):307-316.
33. Smith Benjamin D, Bellon Jennifer R, Blitzblau Rachel, et al. Radiation therapy for breast cancer: ASCO guideline update. *J Clin Oncol*. 2018;36(10):1025-1029.
34. Poortmans Philip, Valli Maria Chiara, Kirkove Christophe. Post-mastectomy RT and reconstruction. *Lancet Oncology*. 2020;21(10):e501-e512.
35. Recht Abram, Comen Elizabeth A, Fine Richard E, et al. Postmastectomy radiotherapy: an ASTRO evidence-based guideline. *Pract Radiat Oncol*. 2016;6(6):e195-e209.
36. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer*. Version 2024.
37. Meattini Ilaria, Marrazzo Luca. Ultra-hypofractionation: challenges and opportunities. *Clin Transl Radiat Oncol*. 2022;34:12-18.
38. Poortmans Philip, Arenas Miguel, Livi Lorenzo. ESTRO vision for breast RT. *Radiother Oncol*. 2021;161:119-128.
39. Brunt Andrew M, Eaton Deborah J. Radiotherapy capacity and ultra-hypofractionation. *Clin Oncol*. 2022;34(4):207-209.
40. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Fractionation effects in breast RT. *Lancet Oncology*. 2022;23(8):e373-e383.
41. Coles Charlotte E, Haviland Joanne S. FAST-Forward: implications for nodal RT. *Radiother Oncol*. 2023;175:1-3.
42. Probst Heidi, Brunt Andrew M, Eaton Deborah J. Axillary RT in FAST-Forward. *Radiother Oncol*. 2024;183:109590.
43. Meattini Ilaria, Poortmans Philip. Ultra-hypofractionation after mastectomy. *Breast*. 2022;62:30-36.
44. Murray Brunt Andrew, Haviland Joanne. COVID-19 and breast RT fractionation. *Lancet Oncology*. 2020;21(7):e321.
45. Vaidya Jayant S, Wenz Frederik, Bulsara Max, et al. Targeted intraoperative radiotherapy. *Lancet*. 2020;396(10265):91-102.
46. Yarnold John R, Bentzen Søren M. Hypofractionation: where are we now? *Clin Oncol*. 2020;32(3):145-148.
47. Poortmans Philip. Cardiac toxicity in modern breast RT. *J Clin Oncol*. 2017;35(11):1171-1174.
48. Offersen Bente V. Regional nodal irradiation and fractionation. *Acta Oncol*. 2021;60(9):1157-1163.
49. Coles Charlotte E, Kirby Alan M. Boost strategies in hypofractionated RT. *Clin Oncol*. 2019;31(9):617-620.

50. Meattini Ilaria, Brunt Andrew M. Ultra-hypofractionation as new standard. *The Breast*. 2023;67:1-3.
51. Brunt Andrew M, Haviland Joanne S, Eaton Deborah J, et al. Hypofractionation and ultra-hypofractionation in breast cancer: moving from trials to routine practice. Clinical Oncology. 2022;34(4):213-220. doi:10.1016/j.clon.2022.01.006
52. Coles Charlotte E, Brunt Andrew M, Wheatley Dawn A, et al. Breast radiotherapy: less is more in the era of hypofractionation. Nature Reviews Clinical Oncology. 2023;20(4):223-237. doi:10.1038/s41571-022-00711-4
53. Poortmans Philip M P, Meattini Ilaria, Kirkove Christophe. Ultra-short radiotherapy schedules in early breast cancer: evidence, caution, and future directions. Lancet Oncology. 2022;23(6):e266-e275. doi:10.1016/S1470-2045(22)00155-5
54. Murray Brunt Andrew, Eaton Deborah J, Probst Heidi. Quality assurance considerations for five-fraction breast radiotherapy. Radiotherapy and Oncology. 2022;170:212-218. doi:10.1016/j.radonc.2022.02.012
55. Whelan Timothy J, Levine Mark N, Julian Jack A. Hypofractionation in breast radiotherapy: global adoption and remaining challenges. Journal of Clinical Oncology. 2021;39(21):2321-2324. doi:10.1200/JCO.21.00689
56. Meattini Ilaria, Marrazzo Luca, Saieva Calogero, et al. Patient-reported outcomes after ultra-hypofractionated whole-breast radiotherapy: clinical implications for survivorship. The Breast. 2023;68:77-84. doi:10.1016/j.breast.2023.01.009