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Moderate versus ultra-hypofractionated locoregional breast radiotherapy: Results of a retrospective study during the covid-19 era

Radiothérapie mammaire locorégionale modérée ou ultra-hypofractionnée : résultats d'une étude rétrospective durant l'ère de la covid-19

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ABSTRACT

Purpose. – The use of ultra hypofractionated adjuvant breast radiotherapy for elderly patients was extended during the covid-19 pandemic. We compared its efficacy and safety versus moderate hypofractionation in elderly patients with breast cancer receiving locoregional radiotherapy at a single radiotherapy centre.
Methods. – This retrospective analysis utilized routine patient data. Inclusion criteria comprised women aged 65 years or older with non-metastatic breast cancer, positive axillary nodes, and treated with locoregional radiotherapy following the ultra or moderate hypofractionation protocols. Outcomes studied included overall survival, disease-free survival, late normal tissue effects, and acute toxicity. Comparative analysis employed logistic regression and survival analysis with covariate adjustments.
Results. – Two hundred and twenty-one patients were included, with a median age of 72.5 years (interquartile range [IQR]: 67.9–77.7 years) and a median follow-up of 36.3 months (IQR: 25.4–47.8 months). No significant differences were found in overall and disease-free survival rates between ultra and moderate hypofractionation protocols (adjusted hazard ratio [HR] for death: 0.81, 95 % confidence interval [CI]: 0.27–2.46, $P = 0.712$; adjusted HR for relapse or death: 0.96, 95 % CI: 0.39–2.37, $P = 0.923$). Although ultra-hypofractionation showed an increase in moderate late-onset breast oedema, no significant differences were observed regarding other more common moderate adverse events, such as acute dermatitis and late-onset homolateral arm oedema.
Conclusion. – Our retrospective analysis suggests that the ultra-hypofractionation protocol for locoregional irradiation in elderly patients with breast cancer maintains an acceptable safety profile and shows no significant difference in efficacy compared to the moderate hypofractionation schedule. Prospective confirmation is awaited.

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RÉSUMÉ

Objectif de l'étude. – L'utilisation de la radiothérapie ultra-hypofractionnée adjuvante du cancer du sein pour les patientes âgées a été élargie pendant la pandémie de covid-19. Nous avons comparé son efficacité et sa sécurité par rapport à l'hypofractionnement modéré chez les patientes âgés atteintes d'un cancer du sein recevant une radiothérapie locorégionale dans un centre de radiothérapie.

Méthodes. – Cette analyse rétrospective a utilisé des données de routine de patients. Les critères d'inclusion comprenaient les femmes âgées de 65 ans ou plus atteintes d'un cancer du sein non métastatique avec des ganglions axillaires et prises en charge par radiothérapie locorégionale avec les protocoles ultra- et modérément hypofractionnés. Les résultats étudiés comprenaient la survie globale, la survie sans maladie, les effets tardifs sur les tissus normaux et la toxicité aiguë. L'analyse comparative a utilisé la régression logistique et l'analyse de survie avec ajustements de covariables.

Résultats. – Deux-cent-vingt-et-une patientes ont été incluses, avec un âge médian de 72.5 ans [écart interquartile (IQR): 67.9–77.7 ans] et un suivi médian de 36.3 mois (IQR: 25.4–47.8 mois). Aucune différence significative n'a été trouvée dans les taux de survie globale et de survie sans maladie entre les protocoles ultra et modérément hypofractionnés [*hazard ratio* (HR) ajusté pour le décès: 0.81, intervalle de confiance (IC) à 95 %: 0.27–2.46, $p = 0.712$; HR ajusté pour la rechute ou le décès: 0.96, IC à 95 %: 0.39–2.37, $p = 0.923$]. Bien que l'ultra-hypofractionnement ait montré une augmentation de l'œdème modéré du sein tardif, aucune différence significative n'a été observée concernant d'autres événements indésirables modérés plus fréquents, tels que la dermatite aiguë et l'œdème du bras homolatéral tardif.

Conclusion. – Notre analyse rétrospective suggère que le protocole ultra-hypofractionné pour l'irradiation locorégionale chez les patientes âgées atteintes d'un cancer du sein maintient un profil de sécurité acceptable et ne montre aucune différence significative en termes d'efficacité par rapport au schéma d'hypofractionnement modéré. Une confirmation prospective est attendue.

1. Introduction

Regional nodal radiotherapy for node-positive patients with breast cancer improves disease-free and overall survival [1–6]. Randomized controlled trials have shown that moderate hypofractionation as the protocol of the UK Standardisation of Breast Radiotherapy trial (START) B offers comparable efficacy and often better safety profiles compared to conventional fractionation [7,8], and is increasingly adopted and is our current standard of care for most patients. Hypofractionation, involving fewer but larger doses, reduces patient hospital visits, enhances convenience, and optimizes machine and staff resources, thus reducing costs and alleviating pressure on services.

The covid-19 pandemic precipitated a notable transition from moderate hypofractionation to more extreme hypofractionation protocols, such as ultra-hypofractionation [9,10]. This change was driven by constraints on hospital services, coupled with the reassuring publication of the 5-year follow-up data from the Fast Forward trial and the 10-year results of the FAST trial [11,12]. Most trials comparing hypofractionation protocols were conducted primarily in patients without regional nodal radiotherapy requirements. Due to limited evidence, European guidelines cautiously favour moderate hypofractionation over ultra-hypofractionation for regional nodal radiotherapy [13–15]. Nodal radiotherapy poses challenges due to potential significant side effects, including lymphoedema, brachial plexopathy, and impaired shoulder mobility [1].

Currently, there is a paucity of studies comparing ultra-hypofractionation to moderate hypofractionation for breast cancer, particularly in node-positive cases. While trials such as FAST-Forward and YO-HAI5 have shown promise for ultra-hypofractionation, their primary focus has been on patients without nodal involvement [11,16]. The ongoing extension of the FAST-Forward trial, known as the Fast Forward Nodal Sub-Study, is currently accruing data, with initial results from the 3-year follow-up showing promise [15]. At the University Hospital Centre (CHU) Université Catholique de Louvain (UCL) Namur, ultra-hypofractionation has been prescribed using the French radiotherapy scheme, delivering weekly doses of 5.5 Gy to nodal regions, particularly in geriatric or very elderly patients (aged 70 years and older) [17]. Ultra-hypofractionation following the FAST protocol has become the standard practice for patients over 70 requiring breast irradiation. In the context of the covid-19 pandemic, there has been an increasing trend in prescribing regional irradiation with ultra-hypofractionation FAST scheme, which is further reviewed in this paper.

Given the limited data on ultra hypofractionation's efficacy and safety in nodal radiotherapy, there is a pressing need for comparative studies against moderate hypofractionation. Hence, this study aimed to assess the efficacy and safety of the FAST protocol compared to the START-B protocol for breast cancer in elderly patients undergoing locoregional irradiation, utilizing real-world data from patients treated in a single regional radiotherapy centre.

2. Methods

This retrospective cohort study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for reporting purposes [18].

2.1. Study population

The source population consisted in patients with breast cancer receiving locoregional radiotherapy at CHU UCL Namur between 2018 and 2021.

Inclusion criteria were women aged 65 years or older at the time of treatment with invasive, non-metastatic breast cancer, and positive axillary nodes (either pre- or postoperative), and who have undergone locoregional radiotherapy targeting regional lymph nodes as well as the chest wall or breast, following either the START-B or FAST protocols.

Exclusion criteria were patients under 65 years old, males, those with a history of previous homolateral radiotherapy, individuals without an axillary procedure and with single irradiation of axillary level 1, lack of information on the end of treatment, and treatment discontinuation (e.g. due to rapid progression or concerns about hospital visits amid the covid-19 context).

The study included all eligible patients meeting the inclusion criteria without applying a specific sampling strategy.

2.2. Variables

2.2.1. Outcomes or dependent variables

The dependent variables in this study were overall survival, disease-free survival, local–regional relapse, local relapse, distant relapse, contralateral breast cancer, late normal tissue effects and acute toxicity.

Overall survival was defined as the time from radiotherapy to death from any cause, and disease-free survival as the time from radiotherapy to recurrence or death from any cause, whichever occurred first [19]. Additionally, locoregional relapse was defined as a relapse in the breast or chest wall, ipsilateral axilla, or supraclavicular fossa or internal mammary chain, within the irradiated target volume. Local relapse was defined as a relapse in the breast or chest wall, distant relapse as a relapse in non-irradiated organs, and contralateral breast cancer as the emergence of a new and separate breast cancer in the opposite (contralateral) breast.

Late normal tissue effects encompass breast atrophy, breast induration, telangiectasia, breast oedema, homolateral arm oedema, breast pain, homolateral arm pain, hyperpigmentation, and brachial plexopathy. Acute toxicity encompasses side effects that manifest within 6 months following radiotherapy and comprises acute dermatitis and dysphagia. Toxicity grading was conducted according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [20].

2.2.2. Exposures and covariates

Exposed patients were those treated with the FAST protocol: 28.5 Gy in five fractions of 5.7 Gy once a week for five weeks (FAST protocol). Non-exposed patients were those treated with the START-B protocol: 40 Gy in 15 fractions of 2.67 Gy 5 days a week for 3 weeks. The decision to administer a boost dose was based on clinical judgment for both protocols.

Baseline characteristics encompassed demographic, clinical and therapeutic factors. Based on the literature and clinical expertise, potential confounding factors were identified: i) for efficacy analysis, age, hormone receptor-expressing breast cancer, and Eastern Cooperative Oncology Group (ECOG) performance status; ii) for safety analysis, irradiated volume (clinical target volume for the regional lymph nodes or nodal clinical target volume), use of chemotherapy, and axillary lymph node dissection.

2.3. Study tool and data collection

The "FAST vs. START-B Database' records various patient data, including demographics, clinical information, treatments and outcomes. This information was extracted from the institutional electronic medical records system (OmniPro) and entered into a dedicated electronic case report form. The electronic case report forms were designed using the Research Electronic Data Capture (REDCap) platform [21,22]. Data collection was conducted by pairs of researchers who double-checked each other's work. In instances of discrepancies, an independent physician conducted a triple check to ensure accuracy.

2.4. Statistical analysis

All statistical analyses were performed utilizing STATA software. Quantitative variables were presented as median (interquartile range [IQR]), while categorical variables were expressed as frequency (percentage). Comparisons between radiotherapy protocols and baseline characteristics were conducted using the Wilcoxon rank-sum test for non-normally distributed quantitative variables, and Pearson's Chi^2 test or Fisher's exact test for categorical variables.

For the analysis of radiotherapy protocols and safety outcomes, associations were examined using logistic regression. Adverse events were defined as the worst grade reported during visits from the start of radiotherapy to the date of the analysis, with a focus on moderate adverse events (defined as grade 2 or higher). The variables were summarized as frequencies along with their crude and adjusted odds ratios (OR) and 95 % confidence intervals (CI).

In the analysis of radiotherapy protocols and efficacy outcomes, associations were explored using survival analysis methods. The time variable was computed as the time from radiotherapy initiation to the occurrence of the first event or the last follow-up assessment, whichever occurred first. Cox proportional hazards regression models were utilized to derive crude and adjusted hazard ratios (HR) along with 95 % confidence intervals. The duration of the follow-up was determined as the time from radiotherapy initiation to either death or the patient's last hospital visit, also referred to as the 'last news'.

The regression models were adjusted for previously described potential confounding factors. Additional variables, considered statistical confounders based on the 10 % rule (which suggests a variable should be included if its introduction causes a 10 % or greater change in the effect estimate), were incorporated in the models only if they significantly improved the goodness-of-fit, as determined by the likelihood ratio test. For efficacy outcomes, the additional variable tested was the radiotherapy year. For safety outcomes, each confounder — age, use of boost, and radiotherapy year — was tested individually to determine whether its inclusion improved the model fit. Statistical significance was determined based on *P*-values less than 0.05.

2.5. Ethical considerations

Access to the electronic medical records was authorized by the Ethics Committee of the CHU UCL Namur-Sainte-Élisabeth centre. Confidentiality in the handling of data and use of the resulting information was ensured.

3. Results

The original cohort for this study comprised 306 individuals who underwent locoregional irradiation at the CHU UCL Namur Network from 2018 to 2021. Among them, 85 individuals were excluded as they did not fulfil the inclusion criteria. A visual representation of the patient selection process is depicted in Fig. 1.

3.1. Patient characteristics

Baseline characteristics are detailed in Table 1. Most patients underwent breast-conserving surgery and axillary dissection, with a median of 11 axillary nodes removed during dissection. Notably, patients in the FAST group were older ($\Delta = 9.9$ years; $P < 0.001$), had higher rates of diabetes ($\Delta = 11.1$ %; $P = 0.027$), and worse ECOG performance status (0 versus 1–3: $\Delta = 28.6$ %; $P < 0.001$), while also showing lower rates of chemotherapy use ($\Delta = 18.4$ %; $P = 0.004$) compared to the START-B group. Additionally, the use of boost was more prevalent in patients receiving the START-B protocol

Table 1
Results of a study comparing ultra-hypofractionated protocol ('FAST') to moderate hypofractionated protocol ('START-B') for locoregional radiotherapy in elderly patients with breast cancer: baseline characteristics.

Characteristics	Total ($n = 221$)	FAST ($n = 89$)	START-B ($n = 132$)
Age ($n_T = 221$), years, median (IQR)	72.5 (67.9–77.7)	79.3 (74.8–84.8)	69.4 (66.7–72.5)
Referring centre ($n_T = 217$), *n* (%)			
Sainte-Élisabeth	112 (51.6)	43 (48.3)	69 (53.9)
Godinne	23 (10.6)	7 (7.9)	16 (12.5)
Dinant	13 (6.0)	6 (6.7)	7 (5.5)
CHR Namur	23 (10.6)	9 (10.1)	14 (10.9)
Saint-Luc Bouge	31 (14.3)	18 (20.2)	13 (10.2)
CHR Auvelais	15 (6.9)	6 (6.7)	9 (7.0)
Body mass index ($n_T = 196$), kg/m^2, median (IQR)	27.3 (23.7–31.2)	27.5 (23.3–31.4)	27.2 (23.9–30.9)
Tobacco consumption ($n_T = 221$), *n* (%)			
Past smoker	30 (13.6)	15 (16.9)	15 (11.4)
Active smoker	24 (10.9)	8 (9.0)	16 (12.1)
Diabetes ($n_T = 221$), *n* (%)	35 (15.8)	20 (22.5)	15 (11.4)
ECOG performance status ($n_T = 220$), *n* (%)			
0	77 (35.0)	16 (18.0)	61 (46.6)
1	127 (57.7)	60 (67.4)	67 (51.2)
2	13 (5.9)	10 (11.2)	3 (2.3)
3	3 (1.4)	3 (3.4)	0 (0.0)
Breast size [a] ($n_T = 75$), *n* (%)			
Small	24 (32.0)	10 (30.3)	14 (33.3)
Medium	47 (62.7)	22 (66.7)	25 (59.5)
Large	4 (5.3)	1 (3.0)	3 (7.1)
Tumour side ($n_T = 221$), *n* (%)			
Left	105 (47.5)	41 (46.1)	64 (48.5)
Right	115 (52.0)	47 (52.8)	68 (51.5)
Bilateral	1 (0.5)	1 (1.12)	0 (0.0)
Tumour location, quadrant ($n_T = 214$), *n* (%)			
Upper-inner	16 (7.5)	5 (5.8)	11 (8.7)
Upper-median	18 (8.4)	8 (9.2)	10 (7.9)
Upper-outer	62 (29.0)	24 (27.6)	38 (29.9)
Lower-inner	12 (5.6)	2 (2.3)	10 (7.9)
Lower-median	5 (2.3)	1 (1.2)	4 (3.2)
Lower-outer	14 (6.5)	5 (5.8)	9 (7.1)
Behind nipple	17 (8.0)	9 (10.3)	8 (6.3)
Outer-equatorial	11 (5.1)	3 (3.5)	8 (6.3)
Inner-equatorial	7 (3.3)	2 (2.3)	5 (3.9)
Central portion of the breast	1 (0.5)	1 (1.2)	0 (0.0)
All breast	5 (2.3)	2 (2.3)	3 (2.4)
Overlapping lesion	46 (21.5)	25 (28.7)	21 (16.5)
Histological type ($n_T = 220$), *n* (%)			
Infiltrating ductal	166 (75.5)	61 (69.3)	105 (79.6)
Infiltrating lobular	39 (17.7)	18 (20.5)	21 (15.9)
Mixed	11 (5.0)	6 (6.8)	5 (3.8)
Other	4 (1.8)	3 (3.4)	1 (0.8)
Tumour grade ($n_T = 211$), *n* (%)			
1	43 (20.4)	18 (21.7)	25 (19.5)
2	92 (43.6)	33 (39.8)	59 (46.1)
3	76 (36.0)	32 (38.6)	44 (34.4)
Receptor expression ($n_T = 221$), *n* (%)			
Hormone receptor positive	177 (80.1)	69 (77.5)	108 (81.8)
Triple negative	32 (14.5)	15 (16.9)	17 (12.9)
HER2 positive	36 (16.3)	12 (13.5)	24 (18.2)
Pathological tumour stage ($n_T = 217$), n (%)			
pT0: no evidence of primary tumour	20 (9.2)	5 (5.6)	15 (11.7)
pTis: DCIS	3 (1.4)	1 (1.1)	2 (1.6)
pT1: $\leq$ 2 cm	74 (34.1)	28 (31.5)	46 (35.9)
pT2: 2-5 cm	81 (37.3)	34 (38.2)	47 (36.7)
pT3: > 5 cm	33 (15.2)	17 (19.1)	16 (12.5)
pT4: any size with extension to the chest wall and/or the skin	6 (2.8)	4 (4.5)	2 (1.6)
Pathological nodal stage ($n_T = 217$), *n* (%)			
pNX: evaluation not possible	4 (1.8)	2 (2.3)	2 (1.6)
pN0: absence of involvement in axillary lymph nodes	30 (13.8)	8 (9.0)	22 (17.2)
pN1: involvement of 1–3 axillary lymph nodes	144 (66.4)	63 (70.8)	81 (63.3)
pN2: involvement of 4–9 axillary lymph nodes	29 (13.4)	12 (13.5)	17 (13.3)
pN3: involvement of more than 9 axillary lymph nodes	10 (4.6)	4 (4.5)	6 (4.7)
Neoadjuvant chemotherapy alone ($n_T = 221$), *n* (%)	31 (14.0)	12 (13.5)	19 (14.4)
Neoadjuvant endocrine therapy alone ($n_T = 221$), *n* (%)	18 (8.1)	11 (12.4)	7 (5.3)
Surgery ($n_T = 221$), *n* (%)			
None	10 (4.5)	3 (3.4)	7 (5.3)
Breast conserving surgery	115 (52.0)	40 (44.9)	75 (56.8)
Mastectomy	96 (43.4)	46 (51.7)	50 (37.9)
Nodal surgery ($n_T = 221$), *n* (%)			
None	10 (4.5)	3 (3.4)	7 (5.3)
Axillary lymph nodes dissection	160 (72.4)	67 (75.3)	93 (70.5)

Table 1 (*Continued*)

Characteristics	Total (*n* = 221)	FAST (*n* = 89)	START-B (*n* = 132)
Sentinel lymph node biopsy	51 (23.1)	19 (21.4)	32 (24.2)
Number of axillary nodes removed (n_T = 157)	11 (8–15)	10 (8–15)	11 (8–15)
Margin status (n_T = 187), *n* (%)			
Negative	169 (90.4)	77 (88.5)	92 (92.0)
Positive	18 (9.6)	10 (11.5)	8 (8.0)
Adjuvant chemotherapy alone (n_T = 221), *n* (%)	13 (5.9)	4 (4.5)	9 (6.8)
Adjuvant endocrine therapy alone (n_T = 221), *n* (%)	125 (56.6)	58 (65.2)	67 (50.8)
Adjuvant chemotherapy alone → endocrine therapy alone (n_T = 221), *n* (%)	31 (14.0)	4 (4.5)	27 (20.5)
Chemotherapy (n_T = 221), *n* (%)	69 (31.2)	18 (20.2)	51 (38.6)
Boost (n_T = 221), *n* (%)	97 (43.9)	12 (13.5)	85 (64.4)
Regional nodal radiotherapy extent (n_T = 221), *n* (%)			
Internal mammary chain	91 (41.2)	33 (37.1)	58 (43.9)
Axillary level 1	117 (52.9)	48 (53.9)	69 (52.3)
Axillary level 2	213 (96.4)	85 (95.5)	128 (97.0)
Axillary level 3	212 (95.9)	85 (95.5)	127 (96.2)
Supraclavicular level 4	211 (95.5)	85 (95.5)	126 (95.5)
Nodal clinical target volume (n_T = 204), cm^3, median (IQR)	61.8 (43–111)	59.2 (41–103)	66.2 (44–113)
Radiotherapy year, *n* (%)			
2018	58 (26.2)	15 (16.9)	43 (32.6)
2019	60 (27.2)	10 (11.2)	50 (37.9)
2020	60 (27.2)	28 (31.5)	32 (24.2)
2021	43 (19.5)	36 (40.5)	7 (5.3)

CHR: centre hospitalier régional; DCIS: ductal carcinoma in situ; ECOG: Eastern Cooperative Oncology Group; HER2: Human epidermal growth factor 2; IQR: interquartile range; n_T: number of patients with available information.

[a] Breast size was defined as small for cup size A or B, medium for cup size C or D, and large for cup size E.

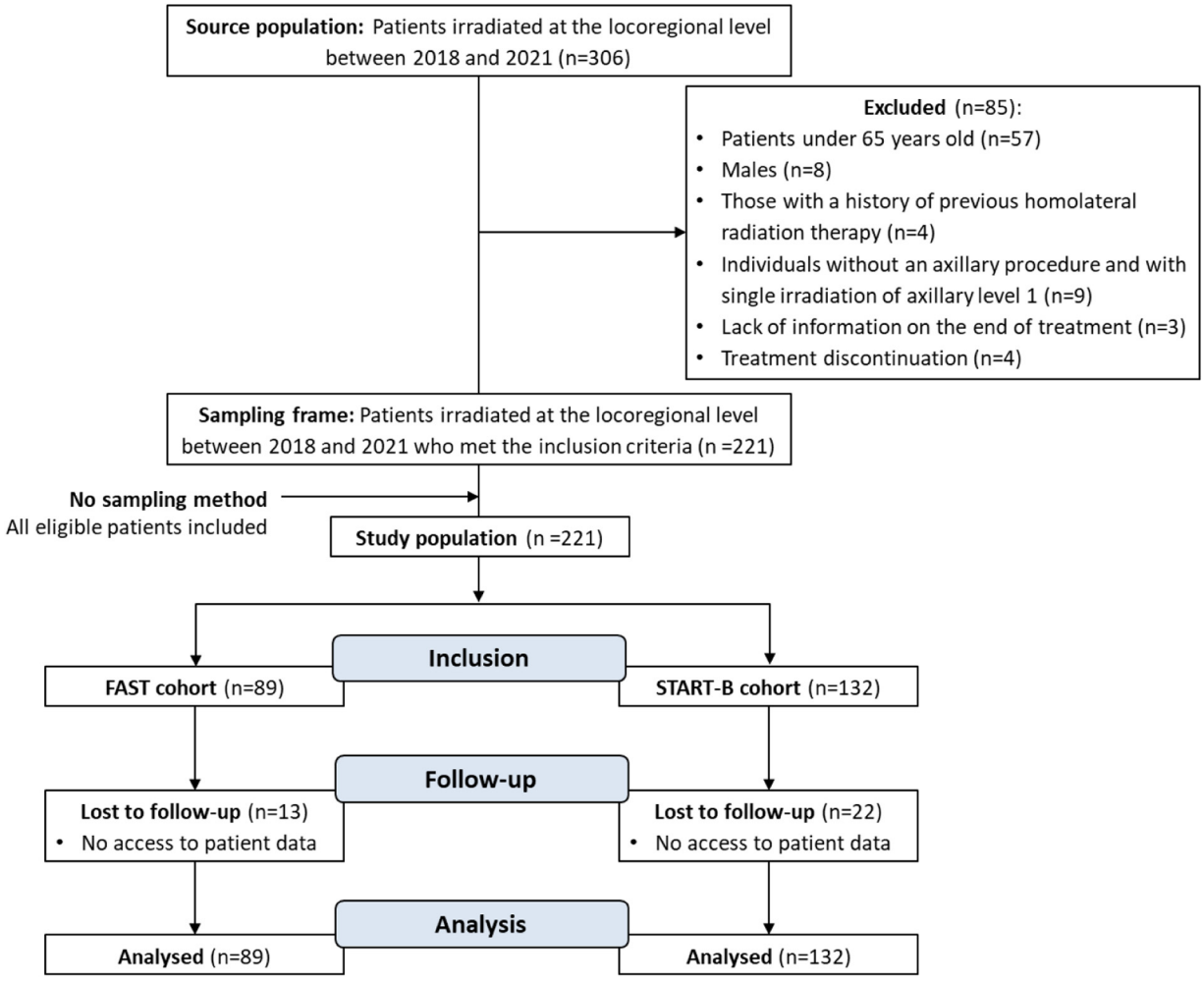

Fig. 1. Study comparing ultra hypofractionated protocol to moderate hypofractionated protocol for locoregional radiotherapy in elderly patients with breast cancer: flow diagram of patient selection.

Table 2
Results of a study comparing ultra-hypofractionated protocol ('FAST' [a]) to moderate hypofractionated protocol ('START-B' [b]) for locoregional radiotherapy in elderly patients with breast cancer: Cox regression analysis for relapse and mortality.

	Cumulative incidence, *n* (%)	Crude hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI) [c]	*P*
All-cause mortality					
FAST	16 (18.0)	2.18 (1.07–4.47)	**0.033**	0.81 (0.27–2.46)	0.712
START-B	15 (11.4)	1.00		1.00	
Relapse or death					
FAST	23 (25.8)	2.46 (1.34–4.50)	**0.004**	0.96 (0.39–2.37)	0.923
START-B	21 (15.9)	1.00		1.00	
Distant relapse					
FAST	14 (15.7)	2.00 (0.96–4.19)	0.065	1.43 (0.50–4.06)	0.506
START-B	15 (11.4)	1.00		1.00	
Local-regional relapse					
FAST	6 (6.7)	5.52 (1.07–28.35)	**0.041**	1.52 (0.18–12.59)	0.696
START-B	2 (1.5)	1.00		1.00	
Local relapse					
FAST	6 (6.7)	11.80 (1.36–102.10)	**0.025**	2.62 (0.20–34.20)	0.462
START-B	1 (0.8)	1.00		1.00	
Contralateral breast cancer					
FAST	3 (3.4)	7.11 (0.69–73.26)	0.099	3.11 (0.22–44.86)	0.405
START-B	1 (0.8)	1.00		1.00	

CI: confidence interval.
[a] FAST protocol: 89 patients.
[b] START-B protocol: 132 patients.
[c] Models were adjusted for age at radiotherapy, hormone receptor-positive breast cancer, and Eastern Cooperative Oncology Group (ECOG) performance status.

(Δ = 50.9 %; $P < 0.001$). Furthermore, significant differences were observed in the years of radiotherapy delivery, with a higher number of patients being irradiated in recent years in the FAST group (2018–2019 versus 2020–2021: Δ = 42.4 %; $P < 0.001$).

At the time of analysis, the median follow-up for the entire cohort was 36.3 months (IQR: 25.4–47.8 months), with the FAST cohort having a median follow-up of 25.8 months (IQR: 18.7–35.9 months), and the START-B cohort with a median follow-up of 44.0 months (IQR: 34.7–52.3 months). Thirty-five surviving patients from two referring hospitals were lost to follow-up due to a database hacking incident. The median follow-up in this group was 30.5 months (IQR: 17.6–47.8 months) for the entire cohort ($N = 35$, 15.8 %), 17.6 months (IQR: 11.7–25.4 months) for the FAST cohort ($N = 13$, 14.6 %), and 40.3 months (IQR: 29.0–48.1 months) for the START-B cohort ($N = 22$, 16.7 %).

3.2. Survival outcomes

3.2.1. Overall survival

At the time of analysis, 31 out of 221 patients had died (14.0 %). When adjusting for confounding variables such as age, ECOG performance status, and expression of hormone receptors, the adjusted HR revealed no statistically significant difference in overall survival between protocols (Table 2). Including the variable "radiotherapy year' to account for differences in follow-up between groups did not result in significant changes to the effect estimate, as indicated by the goodness-of-fit test, and therefore, it was not retained. Similar results were observed when adjusting for only age and ECOG performance status (HR: 0.86, 95 % CI: 0.28–2.68; $P = 0.800$).

3.2.2. Disease-free survival

At the time of analysis, 44 out of 221 patients had experienced a relapse or died (19.9 %). The results of the Cox regression analysis for relapse or death are reported in Table 2. There was no difference in the hazard or risk of relapse or death between the two groups. The inclusion of "radiotherapy year' in the model did not meaningfully alter the effect estimate, as confirmed by the goodness-of-fit test, and was consequently excluded.

3.2.3. Relapse patterns

Concerning distant relapse, 29 out of 221 patients experienced an event in the entire cohort (13.1 %). The results of the Cox regression analysis for distant relapse are reported in Table 2 and indicated no statistically significant difference between protocols.

Similar trends were observed for local and locoregional relapse, as well as contralateral breast cancer, although numbers were limited (Table 2). The analysis of contralateral breast cancer was limited by only four events, making it difficult to draw meaningful conclusions (Table 2). Adding "radiotherapy year' to all the relapse models did not result in meaningful changes to the effect estimates, as confirmed by the goodness-of-fit test, and this variable was therefore excluded from the final models.

3.3. Adverse events

The summaries of adverse events, categorized by grade, are detailed in Supplementary Tables 1, 2, and 3. Within the total cohort, instances of grade 3 or more adverse events were rare, with only four cases of grade 3 acute dermatitis observed in the START-B group. Importantly, for all other adverse events listed, encompassing both acute and late toxicity, there were no instances of grade 3 or higher adverse events recorded. Most reported adverse events fell into grade 1 or grade 2 categories. Concerning acute toxicity, among the 221 patients evaluated, 25 (11.3 %) had moderate acute dermatitis, while there were no occurrences of moderate dysphagia. In terms of late toxicity, the most common moderate late normal tissue effects were homolateral arm oedema (10.9 %) and breast oedema (7.2 %), with other moderate late normal tissue effects affecting less than 5 % of patients. Notably, there were no instances of moderate breast atrophy and telangiectasia. Furthermore, the study did not detect any cases of plexopathy.

3.4. Acute toxicity

Moderate dermatitis was reported in five patients (all grade 2) in the FAST group and 20 patients (16 grade 2 and four grade 3) in the START-B group. The odds of moderate dermatitis were lower in the FAST group compared to the START-B group, although statistical significance was lost when adjusting the model for irradiated volume, use of chemotherapy, axillary lymph node dissection, and

Table 3
Results of a study comparing ultra-hypofractionated protocol ('FAST' [a]) to moderate hypofractionated protocol ('START-B' [b]) for locoregional radiotherapy in elderly patients with breast cancer: logistic regression analysis for moderate adverse events.

	Cumulative incidence, *n* (%)	Crude odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI) [c]	*P*
Acute toxicity: dermatitis					
FAST	5 (5.6)	0.33 (0.12–0.92)	**0.035**	0.85 (0.25–2.92)	0.798
START-B	20 (15.2)	1.00		1.00	
Late toxicity					
Homolateral arm oedema					
FAST	10 (11.2)	1.07 (0.45–2.52)	0.883	0.63 (0.23–1.75)	0.376
START-B	14 (10.6)	1.00		1.00	
Breast oedema					
FAST	10 (11.2)	2.66 (0.93–7.60)	0.068	3.81 (1.12–12.98)	**0.033**
START-B	6 (4.6)	1.00		1.00	
Breast pain					
FAST	2 (2.3)	1.49 (0.21–10.81)	0.691	1.19 (0.15–9.13)	0.868
START-B	2 (1.5)	1.00		1.00	
Breast induration					
FAST	3 (3.4)	4.57 (0.47–44.65)	0.191	3.72 (0.36–38.33)	0.270
START-B	1 (0.8)	1.00		1.00	
Homolateral arm pain					
FAST	1 (1.1)	1.49 (0.09–24.11)	0.779	0.44 (0.01–14.78)	0.647
START-B	1 (0.8)	1.00		1.00	

CI: confidence interval.
[a] FAST protocol: 89 patients.
[b] START-B protocol: 132 patients.
[c] Models were adjusted for irradiated volume, use of chemotherapy, and axillary lymph node dissection, with the exception of the variables dermatitis and homolateral arm oedema, which were additionally adjusted for the use of boost.

use of boost (Table 3). Including the variables "radiotherapy year' and "age' in the model did not result in significant changes to the effect estimate; therefore, they were not retained.

3.5. Late toxicity

Moderate breast oedema occurrences were all grade 2 in both study groups. Following adjustment for potential confounders, logistic regression analysis revealed that the odds of moderate breast oedema were significantly higher in the FAST group compared to the START-B group when adjusting for irradiated volume, use of chemotherapy, and axillary lymph node dissection (Table 3). The addition of "use of boost', "radiotherapy year', and "age' did not meaningfully alter the effect estimate, so these variables were excluded from the final model.

Moderate homolateral arm oedema occurrences were all grade 2 in both study groups. No significant difference was observed in the odds of moderate homolateral arm oedema between the two groups when accounting for irradiated volume, use of chemotherapy, axillary lymph node dissection, and use of boost (Table 3). Adding "radiotherapy year' and "age' to the model did not noticeably affect the effect estimate, and as such, these variables were excluded from the final model. Notably, an exploratory analysis suggested that patients undergoing more extensive axillary lymph node dissection, regardless of the RT protocol used, may have a higher likelihood of experiencing late homolateral arm oedema following locoregional irradiation (OR: 1.73 in patients with at least eight nodes removed compared to those with less than eight nodes removed). However, our study reveals a balanced distribution of axillary lymph node removal between both groups, suggesting that this factor did not significantly influence our results.

Other associations between adverse events and radiotherapy protocol, including moderate breast pain, breast induration, and homolateral arm pain, were inconclusive due to the low number of events (four or fewer events for each outcome; Table 3).

4. Discussion

To our knowledge, this study is the first to compare the efficacy and safety of the FAST (weekly ultra-hypofractionation) and START-B (moderate hypofractionation) protocols for node-positive breast cancers in patients undergoing locoregional irradiation. Our findings reveal no significant differences in overall- and disease-free survival between the two protocols. Besides, no significant disparities were noted in common moderate adverse events, including acute dermatitis and late onset homolateral arm oedema.

Two large-scale trials, the FAST and START-B trials, form the current basis for the use of weekly ultra-hypofractionated and moderate hypofractionated schedules for regional node irradiation, respectively [7,12]. However, these trials did not fully represent our target population, which consists of patients with node-positive disease requiring regional node radiotherapy. Although extrapolating their results to elderly patients with node-positive disease is common, there remains a lack of trials in this specific population. Notably, our study population exhibited significant poor prognostic factors that may influence outcomes, necessitating caution in data extrapolation. Elderly breast cancer patients are prone to unfavourable outcomes due to factors such as delayed diagnosis, comorbidities, and disparities in treatment [23–25]. Despite radiation therapy exclusion in some cases, our study provides valuable insights for tailored care approaches in this vulnerable population [26].

In this cohort of elderly patients with node-positive breast cancer undergoing locoregional radiotherapy, our findings suggest no statistically significant disparities in overall- and disease-free survival between the FAST and START-B protocols after adjusting for confounding variables. While our study may have lacked statistical power to detect differences in these outcomes, the evidence presented does not support rejecting the null hypothesis of similarity between the protocols.

Regarding toxicity, specifically moderate acute dermatitis, our study initially favoured the FAST protocol. However, after adjustment, the statistical significance was lost (Table 3), likely due to limited statistical power. This observation is consistent with findings from the YO-HAI5 trial, which reported a lower incidence of moderate acute dermatitis with an ultra-hypofractionated regimen of 28.5 Gy in five fractions over 10 to 12 days compared to the START-B protocol in node-negative breast cancer patients (median age 59 years) [16]. The trial authors attributed the expected decrease in acute toxicity rates to the lower total dose administered

in the five-fraction regimen (28.5 Gy) compared to the 15-fraction regimen (40 Gy). They emphasized that acute skin reactions are primarily influenced by the total dose and show less sensitivity to fraction size when compared to late normal tissue effects.

Additionally, our study observed a higher likelihood of moderate breast oedema with the FAST protocol, consistent with the FAST-Forward trial [11]. This can be attributed to the higher radiation dose per fraction in the FAST protocol (5.7 Gy per fraction compared to 2.67 Gy per fraction with the START-B protocol), leading to more extensive DNA damage and increased risk of late normal tissue effects in the breast [27,28]. However, we cannot dismiss a falsely significant difference in this adverse event, considering the multiple comparisons.

We also found a comparable incidence of moderate homolateral arm oedema between both protocols. Although an exploratory analysis suggested that patients who undergo more extensive axillary lymph node dissection may have a higher likelihood of experiencing moderate homolateral arm oedema following locoregional irradiation, in our study, the number of axillary lymph nodes removed was balanced between both groups, indicating that our results were not influenced by this potential confounder.

Compared to the FAST-Forward Nodal Sub-Study, with similar follow-up duration, we observed comparable rates of acute dermatitis (11.3 % versus 10.7 %) and homolateral arm oedema (10.9 % versus 8.8 %) [29]. However, our study exhibited higher rates of breast oedema (7.2 % versus 2.5 %).

Although the follow-up durations differed significantly between the FAST and START-B groups, the inclusion of this confounding factor, represented by the variable "year of radiotherapy,' in the final models did not alter the outcomes in terms of efficacy or safety. This suggests that differences in follow-up time between the two protocols did not significantly influence the adjusted hazard ratios or odds ratios in the survival and adverse event analyses.

Despite its observational retrospective design, this study contributes valuable insights into the efficacy and safety of ultra hypofractionated radiotherapy in elderly breast cancer patients. While recognizing its limitations, including lack of randomization, retrospective grading of toxicities, and limited statistical power, combined evidence from observational studies and randomized controlled trials can inform clinical decision-making.

The FAST protocol, with its weekly ultra hypofractionated radiotherapy, offers a promising alternative for locoregional irradiation in elderly breast cancer patients. Its condensed schedule enhances compliance and reduces logistical challenges, benefiting both patients and healthcare facilities.

5. Conclusion

Our findings suggest that the FAST protocol for locoregional irradiation in elderly breast cancer patients does not significantly increase the risk of mortality, recurrence, or common moderate adverse events, such as acute dermatitis and late onset homolateral arm oedema. Further follow-up and prospective confirmation of these results is awaited.

Author contributions

AEY: methodology, investigation, data curation, writing–review & editing, visualization; PAR: methodology, formal analysis, investigation, data curation, writing–original draft, visualization; AD, VR: methodology, resources, writing–review & editing, supervision, project administration; ÉBo: investigation, data curation; ÉBr, JS: methodology, investigation, data curation; LD: methodology, investigation, writing–review & editing; MS, JV: methodology, investigation; BB, MR: methodology, software, formal analysis, data curation.

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Online Supplement. Supplementary data

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Disclosure of interest

The authors declare that they have no competing interest.

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