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Ultra-hypofractionated one-week locoregional radiotherapy for patients with early breast cancer: Acute toxicity results

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ABSTRACT

Purpose: Moderate hypofractionated radiotherapy is the standard of care for all patients with breast cancer, irrespective of stage or prior treatments. While extreme hypofractionation is accepted for early-stage tumours, its application in irradiating locoregional lymph nodes remains controversial.
Materials and methods: A prospective registry analysis from July 2020 to September 2023 included 276 patients with early-stage breast cancer treated with one-week ultra-hypofractionation (UHF) at 26 Gy in 5 fractions on the whole breast (58.3 %) or thoracic wall (41.7 %) and ipsilateral regional lymph nodes and simultaneous integrated boost (58.3 %). Primary endpoint was assessment of acute adverse events (AEs). Secondarily, onset of early-delayed toxicity was assessed. A minimum 6-month follow-up was required for assessing potential treatment-related early-delayed complications. Acute or late complications attributable to treatment were assessed at inclusion using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.
Results: With a median follow-up of 19 months (range 1–49 months), 159 (57.6 %) patients reported AEs, predominantly grade (G) 1 (n = 139, 50.4 %) and G2 (n = 20, 7.8 %). Skin acute toxicity was common (G1/2: 134, G3: 14), while breast oedema occurred in 10 patients (G1: 9, G2: 1), and 15.9 % reported breast pain (G1: 42, G2: 2). Ipsilateral arm oedema was observed in 1.8 % patients. For patients with a follow-up beyond 6 months (n = 213), 23.4 % patients reported G1/G2 skin AEs, 8.8 % had G1/G2 breast/chest wall oedema, and 8.9 % experienced arm lymphedema. There were no cases of brachial plexopathy or G3 toxicity in this group of patients.
Conclusions: One-week UHF adjuvant locoregional radiation is well-tolerated, displaying low-toxicity profiles comparable to other studies using similar irradiation schedules.

Introduction

Radiotherapy is pivotal in treating breast cancer, impacting long-term survival. Regional node irradiation (RNI) reduces breast cancer death risk by 1 to 5 %, varying with lymph node status [1]. Moderately hypofractionated radiation therapy (MHF), typically prescribed as a 2.67 Gy daily dose to the breast/chest wall with or without irradiation of the regional lymph nodes, delivered in 15 to 16 daily fractions, is standard after breast surgery, offering comparable efficacy to longer regimens but with shorter treatment times [2–5]. Simultaneous integrated boost (SIB) is safe and well-tolerated, reducing treatment duration without compromising outcomes. Studies like IMPORT HIGH demonstrate similar rates of breast induration with SIB compared to sequential boost techniques [6].

The FAST and FAST-Forward studies explored hypofractionated radiotherapy (HFRT) beyond moderately hypofractionated schedules

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[4–8]. In FAST, 28.5 Gy or 30 Gy in 5 fractions showed similar cosmetic outcomes to 50 Gy in 25 fractions for low-risk breast cancer [9]. FAST-Forward investigated ipsilateral breast tumor relapse (IBTR), with 26 Gy in 5 fractions over a week demonstrating comparable outcomes to longer regimens [10]. Clinician-assessed normal tissue effects were 9.9 %, and 11.9 % for 40 Gy, and 26 Gy, respectively. The results from FAST-Forward nodal sub-study (ISRCTN19906132) indicate that at 2–3 years' follow-up there is no early indication that outcomes relating to arm or shoulder AEs are different for 26 Gy compared with the standard 40 Gy [11].

Since the results of the FAST trials have been published, ultra-hypofractionated (UHF) 1-week schedules have gained support from various studies, showing comparable toxicity and tumor control rates to conventional schedules [7,12–15]. UHF (26 Gy in 5 fractions over a week) is emerging as a new standard for certain breast irradiation scenarios, though data supporting nodal or boost irradiation and in reconstruction cases are limited [2,4]. Despite this, UHF is preferred for low-risk cases [16,17]. We adopted it for early breast cancer patients post-pandemic, continued this practice based on strong clinical experience and decided to collect data in a prospective registry. The objective of this research was to evaluate the acute toxicity rates in patients undergoing postoperative UHF irradiation and regional nodal irradiation (RNI) over one week.

Materials and methods

Patients

A prospective database was utilized to identify consecutive eligible patients with early invasive breast cancer who received postoperative radiotherapy to the breast or chest wall with RNI between July 2020 and September 2023. The study was approved by the Local Ethics and Clinical Research Committee (Ref.: 21.09.1880-GHM) and patients provided informed consent. Clinical and pathological data, including molecular breast cancer subtypes, were collected retrospectively from medical records. Clinical staging was based on physical examination and imaging modalities. Systemic treatment was not an exclusion criterion. All patients were discussed in the breast multidisciplinary committee and the intra-departmental clinical session, where clinical indications and the accomplishment of the dosimetric outcomes of the proposed treatment were reviewed. Patients with distant metastasis, previous ipsilateral radiotherapy, or synchronous bilateral breast carcinoma were excluded. The study cut-off date was December 12, 2023.

Radiation treatment

Patients underwent CT-based simulation in the supine position, with the ipsilateral arm raised, using either free breathing or deep inspiration breath hold (DIBH) with the Catalyst™ (C-RAD AB, Uppsala, Sweden) system. Target volumes and organ-at-risk (OAR) delineations were performed following European Society for Radiotherapy and Oncology (ESTRO) guidelines [18–21], including whole breast/chest wall post-operative clinical target volume (CTVp_breast), SIB volume (CTVp_SIB) and lymph node clinical target volumes contours (CTVn_L1–2, CTVn_L3–4 and CTVn_IMN). For the dosimetric evaluation, planning target volume was cropped 3 mm below skin (PTVp_eval) and PTVs for lymph node areas were generated by adding a 5 mm isotropic margin to CTVs. OAR delineations included heart, ipsilateral and contralateral lungs, contralateral breast, skin and brachial plexus. A 1-week schedule of 26 Gy in 5.2 Gy/fraction was prescribed to the breast/chest wall and lymph node areas. Patients receiving breast-conserving surgery (BCS) also received a simultaneous integrated boost (SIB) to a cumulative dose of 29–31 Gy in 5 fractions. Daily image-guided radiation therapy verification was conducted using LINAC-kV-cone-beam CT and surface guided radiation therapy. Treatment utilized 6 and 15 MV photons from an Elekta Versa HD (Elekta Solutions AB, Stockholm, Sweden) linac.

Table 1
Patient and breast cancer characteristics at diagnosis.

Parameter	Total n (%)
Gender	
Female	273 (98.9)
Male	3 (1.1)
Breast side	
Left	61 (22.1)
Right	215 (77.9)
Clinical stage	
Stage I	96 (34.8)
Stage II	133 (48.2)
Stage III	47 (17.0)
Pathological tumour stage	
pT0	1 (0.4)
pT1	96 (34.8)
pT2	63 (22.8)
pT3	6 (2.1)
pT4	1 (0.4)
ypT0	37 (13.4)
ypT1	48 (17.4)
ypT2	14 (5.1)
ypT3	2 (0.7)
ypTx	8 (2.9)
Pathological lymph node stage	
pN0	58 (21.0)
pN1	89 (32.2)
pN2	9 (3.3)
pN3	2 (0.7)
pNx	12 (4.4)
ypN0	66 (24)
ypN1	24 (8.7)
ypN2	10 (3.6)
ypN3	4 (1.4)
ypNX	2 (0.7)
Lymph node extracapsular extension	
Present	45 (16.3)
Absent	191 (69.2)
Unknown/Not reported	40 (14.5)
Lympho-vascular invasion	
Present	104 (37.7)
Absent	137 (49.6)
Unknown/Not reported	35 (12.7)
Histology	
Invasive ductal carcinoma	233 (84.4)
Invasive lobular carcinoma	27 (9.8)
Other types	16 (5.8)
Grading	
G1	43 (15.6)
G2	158 (57.2)
G3	66 (23.9)
Unknown/Not reported	9 (3.3)
Clinical subtype	
HR+/HER2-	200 (72.5)
HR+/HER2+	20 (7.2)
HR-/HER2+	8 (2.9)
HR-/HER2-	46 (16.7)
Unknown	2 (0.7)

Abbreviations: n = Number, G = Grade, T = Tumour, N = Node, HR = Hormonal receptor, HER2 = Human Epidermal Growth Factor Receptor 2.

Patients were treated with volumetric modulated radiation therapy (VMAT) or three-dimensional conformal radiotherapy (3D-CRT) with optimized dose distributions meeting specified constraints outlined in Appendix A (Table A1).

Endpoints and statistical methods

The primary endpoint was acute toxicity assessment, conducted by physicians and nurses on the last day of treatment, one week, and one month post-radiotherapy, with subsequent evaluations every three months. Additional assessments occurred at patients' discretion if they experienced symptoms possibly related to treatment. Treatment-related complications were graded using the Common Terminology Criteria for

Table 2
Surgery and systemic treatment characteristics.

Type of treatment / Parameter	Total n (%)
Breast conserving surgery	161 (58.3)
Mastectomy	115 (41.7)
Reconstruction type	
No reconstruction	198 (71.7)
Previous breast augmentation with implants	5 (1.8)
Reconstruction with tissue expander	63 (22.8)
Reconstruction with immediate silicone prosthesis	6 (2.2)
Reconstruction with delayed DIEP	4 (1.5)
Type of axillary surgery	
SLNB	176 (63.8)
ALND	96 (34.8)
Not performed	4 (1.4)
Median number of lymph nodes removed (range)	2 (0–30)
Median number of positive lymph nodes (range)	1 (1–29)
Primary systemic therapy	
Yes	106 (38.4)
No	170 (61.6)
Adjuvant chemotherapy	
Yes	109 (39.5)
No	167 (60.5)
Adjuvant targeted therapies or immunotherapy	
Anti-HER2*	27 (9.8)
CDK4/6i	7 (2.5)
Immunotherapy	5 (1.8)
Other**	19 (6.9)
No	218 (79.4)
Adjuvant endocrine Therapy	
Yes	223 (80.8)
No	53 (19.2)

*Includes Trastuzumab, Pertuzumab and Trastuzumab emtansine (T-DM1); **Includes Olaparib and investigational drugs. Abbreviations: n = Number, SLNB = sentinel lymph node biopsy, ALND = Axillary Lymph Node Dissection, DIEP = Deep inferior epigastric artery perforatorflap, HER2 = Human Epidermal Growth Factor Receptor 2, CDK4/6i = cyclin-dependent kinase 4/6 inhibitors.

Adverse Events (CTCAE) v5.0 scale [22]. Acute toxicity rates were reported as the highest grade within the first three months post-radiotherapy. Secondary endpoints included early-delayed toxicity assessment, requiring a minimum 6-month follow-up. Disease recurrence was analyzed from the time of breast cancer diagnoses. Statistical analysis involved descriptive statistics, Kruskal-Wallis test for continuous variables, chi-squared test for categorical variables, binomial logistic regression for associated factors with AEs, and Kaplan-Meier method for actuarial rates. Data were expressed as median with a range for continuous variables, and as counts with frequencies for categorical data. Median values were chosen as cut-offs for age and breast volume calculations. All tests were two-sided with a significance level of $p = 0.05$ using IBM SPSS Statistics software version 29.0.0.

Results

Patients

In total, 276 patients with invasive early breast cancer who received postoperative radiotherapy to the breast/chest wall and lymph nodes were included in the study. Median age at breast cancer diagnosis was 52 years (range31–89 years). The majority of patients had HR+/HER2- right-sided breast cancer. The median follow-up was 19 months (range 1–49 months). Details on the patients' and breast cancers' characteristics at diagnosis are presented in Table 1. Surgical procedures, types of reconstruction and systemic treatment characteristics are presented in Table 2.

Table 3
The percentage of any ≥ grade 1 adverse events, related to locoregional therapy within first 3 months or ≥ 6 months following completion of radiotherapy, in relation to demographics, locoregional technique or systemic therapy.

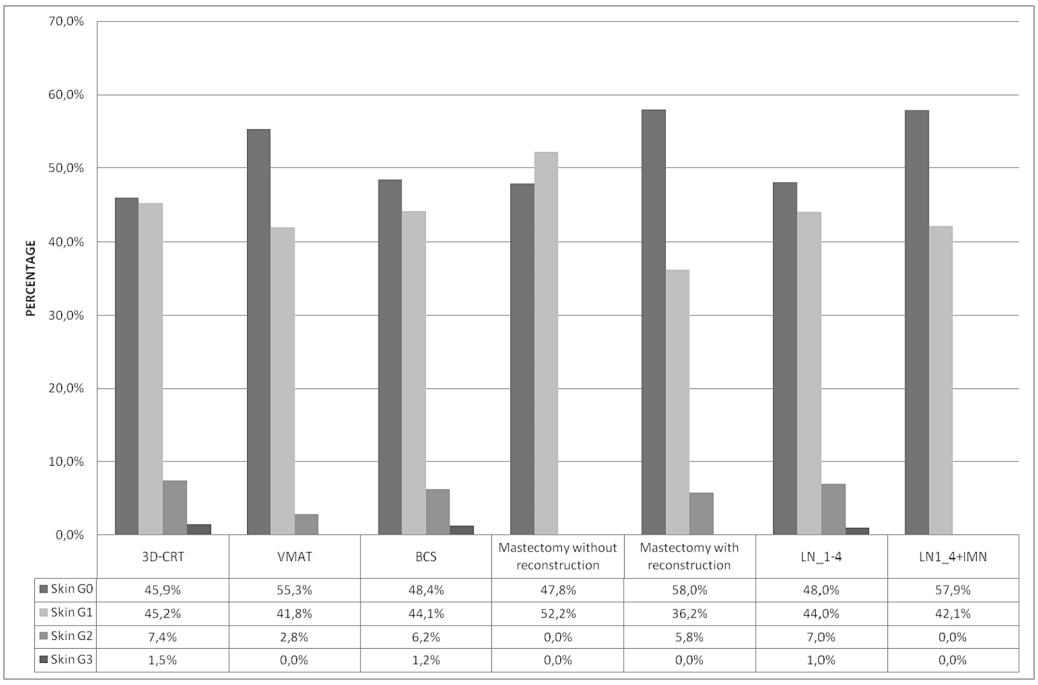
	Any locoregional therapy related toxicity ≤ 3 months(n = 276)	p value	Any locoregional therapy related toxicity ≥ 6 months(n = 213)	p value
Age: <52 vs ≥ 52 years	55.6 % vs 59.8 %	0.542	53.8 % vs 44.1 %	0.158
Surgery: BCS vs mastectomy	62.1 % vs 51.3 %	0.084	52.5 % vs 43.7 %	0.196
Reconstruction: Yes vs No	50.0 % vs 60.6 %	0.137	43.3 % vs 50.8 %	0.317
RT technique: 3D-CRT vs VMAT	62.2 % vs 53.2 %	0.144	52.4 % vs 45.0 %	0.252
IMN RT: Yes vs No	47.4 % vs 61.5 %	0.041	43.8 % vs 50.6 %	0.384
Breast/chest wall PTV: <740 cm^3 vs ≥ 740 cm^3	55.1 % vs 60.1 %	0.465	49.2 % vs 48.4 %	1.000
Breast/chest wall PTV: <105 % vs ≥ 105 % PD	58.3 % vs 56.2 %	0.795	46.7 % vs 53.2 %	0.409
PST: Yes vs No	52.8 % vs 60.6 %	0.213	50.0 % vs 48.0 %	0.794
Postoperative chemotherapy: Yes vs No	59.6 % vs 57.7 %	0.482	56.0 % vs 44.5 %	0.121
Postoperative targeted therapy: Yes vs No	42.9 % vs 61.4 %	0.043	42.9 % vs 51.0 %	0.464
Postoperative endocrine therapy: Yes vs No	59.6 % vs 53.4 %	0.362	50.3 % vs 44.3 %	0.461

Abbreviations: RT = Radiotherapy, PD = Prescribed dose (26 Gy), PTV = Planning target volume, 3D-CRT = Three-dimensional conformal radiotherapy, BCS = Breast conserving surgery, IMN = Internal mammary lymph nodes, PST = Primary systemic therapy.

Radiotherapy

All patients received 26 Gy in 5 fractions to the CTVp_breast and CTVn_L1–4 with or without CTVn_IMN. Patients who were treated with BCS (N = 160, 58.0 %) also received SIB with a median dose of 6.0 Gy (range, 5.8–6.2 Gy) in 5 fractions. With respect to lymph node CTVs, 200 (72.5 %) patients received radiotherapy to the axillary lymph node levels I-IV and 76 (27.5 %) patients received comprehensive nodal irradiation (CTVn_L1–4 and CTVp_IMN), 41 (54 %) of them had left breast tumors and 35 (46 %) had right breast tumors. Five-fraction radiotherapy was delivered within a median time of 7 days (range, 5–8. Treatment technique was either 3D-CRT in 135 (48.9 %) or VMAT in 141 (51.1 %) patients. In 30 (10.9 %) patients,3D-CRT or VMAT were combined with deep DIBH. All patients who received comprehensive nodal irradiation were treated with VMAT technique. Median PTVp_breast volume was 740.5 cm^3 (range, 153–2,800.7 cm^3), PTVn_L1–2 104.9 cm^3(range, 18.8–293.6 cm^3), PTVn_L3–4 59.9 cm^3(range, 1.9–196 cm^3) and PTVn_IMN9.9 cm^3(range, 1.8–25.4 cm^3).

Treatment planning parameters for target volumes and OARare presented in **Appendix A** (Table A2). Compared to patients treated with mastectomy, patients, who had BCS, had a higher percentage of PTVp_breast_eval, receiving ≥ 105 % of the prescribed dose (0.5; range: 0–5,6 vs. 15.3, range: 0–45.2; $p < 0.001$).Patients with left-sided left breast cancer had a higher mean absorbed dose to the heart (heart-D_{mean}) compared to patients with right-sided breast cancer (2.4 Gy, range: 0.4–4.4 Gyvs 0.9, range: 0.2–5.6 Gy, $p < 0.001$). Higer heart-D_{mean}were observed in treatment plans for patients receiving additional irradiation to the IMN, compared to patients, who were irradiated only axillary lymph node levels I-IV (2.5 Gy, range: 1.1–4.4 Gy vs 0.9 Gy, range: 0.2–5.6 Gy;$p < 0.001$). Irradiation to the IMN did not result in



	3D-CRT	VMAT	BCS	Mastectomy without reconstruction	Mastectomy with reconstruction	LN_1-4	LN1_4+IMN
Skin G0	45,9%	55,3%	48,4%	47,8%	58,0%	48,0%	57,9%
Skin G1	45,2%	41,8%	44,1%	52,2%	36,2%	44,0%	42,1%
Skin G2	7,4%	2,8%	6,2%	0,0%	5,8%	7,0%	0,0%
Skin G3	1,5%	0,0%	1,2%	0,0%	0,0%	1,0%	0,0%

Fig. 1. Acute skin toxicity. Abbreviations: 3D-CRT = Three-dimensional conformal radiotherapy, VMAT = Volumetric modulated radiation therapy, BCS = Breast conserving surgery, LN = Lymph nodes, IMN = Internal mammary lymph nodes, G = grade.

higher ipsilateral lung-D_{mean} (6.0 Gy, range:7–7.7 Gy vs 5.9 Gy, range: 2.2–7.7 Gy; p = 0.406).

Acute toxicity outcomes

Within first 3 months after the completion of radiation therapy, 159 (57.6 %) patients experienced any AEs (Table 3). Approximately, half of the patients (n = 139, 50.4 %) experienced ≥ grade 1 (G1) and 20 (7.8 %) experienced ≥ G2 toxicity (**Appendix A, Fig. A1**).

The most common acute effect was the development of radiation dermatitis, which manifested as erythema and/or desquamation. In total, 120 (43.5 %) patients had G1, 14 (5.1 %) patients had G2, and 2 (0.7 %) patients had G3 skin AEs. When 3D-CRT was compared to VMAT, there was no statistically significant difference in skin toxicity (0.148) or for patients receiving BCS versus mastectomy with or without reconstruction (p = 0.335). Similarly, there was no statistically significant difference in acute skin AEs for patients receiving radiotherapy to axillary lymph nodes I–IV or axillary lymph nodes I–IV with IMN (p = 0.178) (Fig. 1).

Nine (3.3 %) patients experienced G1, and one (0.4 %) patient experienced G2 breast oedema. Altogether 44 (15.9 %) patients reported pain in the treated breast/chest wall (G1: 42, 15.2 %; G2: 2, 0.7 %). Breast pain was more commonly reported by patients receiving BCS compared to mastectomy (18.6 % vs 12.2 %, p = 0.047). Ipsilateral arm oedema was observed in 21 patients (G1: 13, 4.7 %; G2: 8, 2.9 %). We have observed one (0.4 %) G2 lung toxicity. All patients completed planned treatment and there was no heart, oesophageal or brachial plexus toxicity. There was no relationship between treatment planning parameters and the occurrence of skin toxicity of any grade, the occurrence of breast oedema or breast pain.

Two thirds of patients (n = 213, 77.2 %) were followed by at least 6 months (median 17.4, range: 6–39.1 months) and were evaluated for early-delayed toxicity. G1 AEs were experienced by 85 (39.9 %) patients, while G2 AEs were experienced by 19 (8.9 %) patients, as follows: G1 and G2 skin AEs in 44 (20.6 %) and 6 (2.8 %) patients, G1 and G2 breast/chest wall oedema in 15 (7 %) and 4 (1.8 %) patients, respectively, G2 breast pain in one (0.5 %) patient, G1 asymptomatic lung radiologic changes in 23 (10.7 %) patients, and G2 lung toxicity in one (0.5 %) patient. In addition, 19 (8.9 %) individuals had arm lymphedema (14 in axillary lymphadenectomy arm and 5 in sentinel lymph node biopsy arm, p < 0.005) and 15 (7.0 %) patients had ipsilateral shoulder discomfort or restricted movement. No G3 toxicity was observed in this group of patients (**Appendix A, Fig. A2**).

A logistic regression model, to ascertain the effects of age, type of surgery, radiotherapy volumes and techniques, as well as systemic treatment received pre- or post-operatively on the likelihood that the patients would experience early or late (≥6 months of follow-up) AEs of any grade was not statistically significant: $\chi 2 = 6.183$, p = 0.627 and $\chi 2 = 8.067$, p = 0.427, respectively. However, in the early-delayed toxicity model, receiving postoperative chemotherapy (p = 0.017) or receiving ≥ 105 % of the prescribed dose to the breast/chest wall PTV (p = 0.011) added significantly to the model/prediction.

Disease outcomes

All patients remained alive at the study's conclusion. Local relapse occurred in 3 patients (1.1 %), while no regional relapses cases or contralateral breast relapse were observed. The three patients experiencing local relapse had HR-/HER2- clinical subtype, while distant relapse occurred in 7 patients (2.5 %), including 2 with HR-/HER2 + and 5 with HR+/HER2- clinical subtypes. The actuarial rates of ipsilateral breast recurrence-free survival (IBRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) at 1, 2, and 3 years are 100 %, 98.4 %, and 98.4 %; 98.7 %, 97.6 %, and 94.6 %; 98.7 %, 96.6 %, and 98.7 %, respectively.

Discussion

We present acute toxicity outcomes in 276 breast cancer patients receiving 1-week UHF therapy to the breast/chest wall with RNI, with or without IMN irradiation. Within 3 months post-treatment, 5.7 % (n = 16/273) reported ≥ Grade 2 AEs, consistent with rates at 6 months (5.6 %, n = 12/213). Arm lymphedema occurred in up to 8.9 % of patients, with 7 % reporting joint stiffness. Early toxicity rates in similar studies

Table 4
. Acute toxicities reported with ultra-hypofractionated locoregional radiotherapy.

Author	Patients and follow-up	N	WBI/chest wall	RNI	Tumor bed boost	Results
Monten 2017 [23] HAI-5, Prospective phase I-II.	Mean age: 73.6 years. MFU: 5.6 months	**95** RNI 41 % IMN: 0 % Boost: 66 %	5F: 5 x 5.7 Gy (every other day)	5F: 5 x 5.4 Gy (every other day)	5F: 5 x 6.5–6.9 Gy (every other day)	Acute toxicity ≥ G2 in 11.6 % patients Radiodermatitis ≥ G2: 17.5 % vs 0 % (no SIB) (One case G3)
Van Hulle 2019 [24]Matched case analysis.	Mean age: 73 (5F) vs 70(15F) years. MFU: NA	**122** RNI: 25 %, IMN: NA Boost: 90 %	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 5.4 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 6.5–6.9 Gy (every other day) 15F: 4–6 x 2.5–2.48 Gy or SIB 15 x 3.12 Gy	Acute toxicity, 5F vs 15F: Breast oedema: 60.6 % vs 83.6 %** Dermatitis: 16.4 % vs 32.8 % Desquamation: 3.3 % vs 9.8 % Pain: 60.6 % vs. 63.9 %
Van Hulle 2020[25]Retrospective match-control.	Mean age: 73 (5F) vs 65(15F) years. FU: 2 years	**71** RNI28% IMN: NABoost:90 %	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 5.4 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 6.2–6.5 Gy, SIB (every other day) 15F: 4–6 x 2.5–2.48 Gy or SIB 15 x 3.12 Gy	5F vs 15F: Telangiectasia: 4 % vs 17 %** Breast oedema: 15 % vs 30 % Fibrosis in tumor bed: 18 % vs 21 % Fibrosis out of tumor bed: 20 % vs 7 %** Breast retraction: 20 % vs 38 %** Pigmentation: 23 % vs 28 % Breast pain: 6 % vs 17 %**
Van Hulle 2020[26]Retrospective comparison.	Mean age: 63 (5F) vs 61(15F) years. FU: 1 year	**779** 5F: **186** RNI 27 % IMN: NA Boost90% 15F: **593** RNI 23 % IMN: NA Boost 84 %	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: Arm: 5 x 6.2–6.5 Gy (every other day) 15F: 4–6 x 2.5–2.48 Gy or SIB 15 x 3.12 Gy	2–4 weeks after RT, 5F vs 15F: Arm symptoms:16.1 % vs 20.6 %** Breast symptoms: 18.9 % vs. 20.8 %** 1 yearafter RT, 5F vs 15F: Arm symptoms:13.7 % vs 16.4 % Breast symptoms: 15.6 % vs. 11.9 %**
Vakaet 2022[27]Randomized 5F vs 15F and prone vs. supine RT.	Mean age: 54 years. FU: NA	**57** RNI: 100 % IMN: 0 % Boost: 98 %	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 5.7 Gy (every other day) 15F: 15 x 2.67 Gy (1-week)	5F: 5 x 6.2–6.5 Gy (every other day) 15F: 4–6 x 2.5–2.48 Gy or SIB 15 x 3.12 Gy	Acute toxicity: 5F vs. 15F: 15 % vs 41 %** No difference regarding position.
Wheatley 2022[11,28] *RandomisedFAST-Forward sub-study.	Median age: 60 years. FU: 2–3 years	**261**(26 Gy: 134, 40 Gy: 127) RNI: 100 % IMN: 0 % Boost: 26 %	5F: 5 x 5.2 Gy (1-week) 15F: 15 x 2.67 Gy (3 weeks)	5F: 5 x 5.2 Gy (1-week) 15F: 15 x 2.67 Gy (3 weeks)	NA	2-year moderate/marked toxicity: 5F vs 15F: Arm/hand swelling:7% vs 10 % Pain arm/shoulder: 15 % vs 18 % Difficulty rising arms: 7 % vs 12 % Shoulder stiffness:12 % vs 10 % 3-year arm lymphedema: 12 % vs 8 %
Chakraborty 2022 [29] HYPORTRandomized Controlled Study.	Median age: NA. FU: 3 months.	**271** RNI: 72 %	5F: 5 x 5.2 Gy (1-week) 15F: 15 x 2.67 Gy (3-weeks)	5F: 5 x 5.2 Gy (1-week) 15F: 15 x 2.67 Gy (3-weeks)	5F: 5 x 6.0 GySIB(1-week) or 4 x 3 Gy 15F: 4 x 3 Gy or SIB 15 x 3.2 Gy	Acute toxicity, 5F vs 15F: Radiodermatitis G2: 2.2 % vs 9.6 %

(*continued on next page*)

Table 4 (*continued*)

Author	Patients and follow-up	N	WBI/chest wall	RNI	Tumor bed boost	Results
		IMN: 4 % Boost: 38 %				Radiodermatitis G3: 0.7 % vs 1.5 % Dysphagia ≥ G2: 0 vs 0 Cough G2: 0 vs 1.5 %
Potdevin-Stein 2023 [30] *Prospective registry.	Median age: 60 years. MFU: 20 months.	**242** (26 Gy: 123) RNI: 100 % IMN: 100 % Boost: 76 %	5F: 5 x 5.2 Gy (1-week)	5F: 5 x 5.2 Gy (1-week)	5F: 5 x 5.8 Gy SIB (1-week)	Acute toxicity: Radiodermatitis G2: 27 % Esophagitis G2: 0.8 % (RNI) Toxicity > 3 months: Skin G2: 0.9 % Pain G2: 1.8 %
Giridhar 2023[31] Retrospective cohort.	Median age: 49 years. MFU: 25 months (75 % patients).	**172** RNI: 97 % IMN: 0 % Boost:14 %	5F: 5 x 5.2 Gy (1-week)	5F: 5 x 5.2 Gy (1-week)	5 x 2.5 Gy (1-week, sequentially).	Acute toxicity Radiodermatitis G2: 2.9 % Radiodermatitis G3: 1.7 % Esophagitis G2: 6.9 %
Pathak 2023 [32]*	Median age: 49 years. MFU: 25 months.	**1435** RNI: 70 % IMN: 11.7 % Boost: 24 %	5F: 5 x 5.2 Gy (1-week) in 53 % or 5 x 5.7 Gy (once weekly) in 47 %	5F: 5 x 5.2 Gy (1-week) in 53 % or 5 x 5.7 Gy (once weekly) in 54 %	5 x 6.4 Gy (1-week) or 5 x 6.6 Gy (once weekly)	Acute toxicity in RNI: Skin G2: 7.2 % Esophagitis G2: 8.1 %
Current study 2023 Prospective registry	Median age: 52 years. MFU: 13 months.	**276** RNI: 100 % IMN: 28 % Boost: 58 %	5F: 5 x 5.2 Gy (1-week)	5F: 5 x 5.2 Gy (1-week)	5F: 5 x 5.8–6.2 Gy SIB (1-week)	Acute toxicity: Radiodermatitis G2: 5.1 % Radiodermatitis G3: 0.7 % Breast oedema G2: 0.4 % Breast pain G2: 0.7 % Lung G2: 0.4 % 6-month shoulder stiffness: 7.0 % 6-month arm lymphedema: 8.9 %

Abbreviations: MFU = Median follow-up, FU = Follow up, NA = Not available, N = number, WBI = Whole breast irradiation, RNI = Regional nodes irradiation, SIB = Simultaneously integrated boost; F = Fraction(s), G = Grade, IMN = Internal mammary lymph nodes, *Reported as a conference proceeding, **Statistically significant.

align with ours (Table 4), with no notable cardiac events or brachial plexopathy reported, and few instances of radiation pneumonitis. The FAST-Forward nodal sub-study reported 15 % of patients on a 5-fraction regimen experiencing moderate or significant toxicity after two years [11], offering valuable long-term data in this context.

We observed no increase in acute toxicity rates within the first three months post-radiation in patients undergoing regional nodal irradiation (RNI) compared to our previously published cohort treated with ultra-hypofractionated whole breast irradiation (WBI) [7]. Notably, since implementing the ultra-hypofractionated regimen in March 2020, all diagnosed breast cancer patients in our department received the 5-fraction regimen, irrespective of clinical factors. The imbalance between right and left treated breasts remains unexplained but as far as our knowledge reaches it was not due to known patient selection bias, albeit given that the final decision regarding radiotherapy schedule corresponded to the responsible physician in each case, we cannot completely exclude the possibility of case selection, especially at the beginning with ultra-hypofractionated treatments. Approximately one-third of our series IMN irradiation, and a similar proportion underwent breast reconstruction, with no increased AEs observed. Discrepancies in reported AEs among studies may stem from global variations in lymph node target delineation guidelines, particularly for IMN and level III-IV lymph nodes [33]. With modern radiotherapy techniques, long-term severe toxicity rates are low. In our patients undergoing 3D-CRT we utilized a multisegmented technique with a minimum of three fields for SIB, contributing to comparable tolerance between VMAT and 3D-CRT treatments. Ongoing research aims to analyze acute and late toxicity rates, disease outcomes, and patient-reported outcomes (Table 5).In our study, the one-year local recurrence rate was 0.4 %, within the target range of 0.5 % per year [5]. Comparing 5-day to 15-day schedules, data show no difference in ipsilateral breast tumor recurrence (IBTR) rates up to 10 years of follow-up [9–11,13]. In FAST trials, the one-week UHF schedule of 26 Gy showed no difference in IBTR or normal tissue effects compared to traditional schedules [10,34].

Employing UHF schedule in breast cancer radiotherapy offers numerous benefits. It allows for shorter time from post-neoadjuvant chemotherapy to targeted treatments, thereby reducing locoregional treatment duration. This reduction facilitates quicker completion of specific locoregional treatment after surgery, and in certain cases, it may enable earlier administration of necessary radiotherapy in patients undergoing genomic profiling for adjuvant chemotherapy, leading to an overall reduction in treatment duration. Fewer treatment fractions streamline healthcare logistics, decrease expenses, minimize waiting times, lower the risk of treatment interruption, and enhance patient comfort by reducing in-hospital time and treatment burden. This ultimately improves patient access to advanced radiation therapy [35–37].

We recognize the limitations of our study, including the absence of randomization and a control arm, which may introduce biases affecting data interpretation. However, comparisons with historical series suggest comparable tolerance with ultra-hypofractionation for whole breast/chest wall and RNI, regardless of breast reconstruction. While our patient population predominantly consisted of right-sided, Stage I-II, G1-2, HR+/HER2- cases, caution is advised in generalizing these findings to other patient categories underrepresented in our cohort. Additionally,

Table 5
Ongoing prospective studies employing ultra-hypofraction in locoregional breast cancer radiotherapy.

Study Study type	Patients	Type of surgery	Treated volumes	Standard RT arm	Experimental RT arm	Outcome measures
NCT04434677 Randomized controlled trial. Estimated enrolment = 100.	≥50 years old, invasive early BC, pT1–3 pN0–2 Main exclusion criteria: cT4, pT4, M0 positive margins, prior RT.	BCS or mastectomy.	WBI/Chest wall + RNI	40 Gy in 15F (3 weeks) ± boost 3D-CRT	26 Gy in 5F (every other day) 3D-CRT	Rate of acute and chronic toxicity ≥ G2(NCI-CTCAE). Rate of IBTR, Compliance to treatment (number of interrupted days of radiation) and OS.
NCT05912231 Randomized controlled trial, phase II. Estimated enrolment = 60.	≥18 years old, invasive early BC, stage II-III, scheduled to receive conventional left-sided or bilateral breast/chest wall RT inclusive of treatment to the IMN or unfavourable cardiac anatomy with respect to the target volumes. Main exclusion criteria: M0, contraindication to RT, contraindication to gadolinium contrast	BCS or mastectomy.	WBI/Chest wall + RNI + IMN	None.	Two experimental arms: Accelerated PBT 1 x daily for 5 days (1- week). OR Accelerated XRT 1 x daily for 5 days (1- week).	Change in myocardial fibrosis from baseline in PBT, change in global longitudinal strain (on cardiac magnetic imaging) from baseline, stability of cardiac biomarkers from baseline, body image evaluation and change in shoulder function from baseline.
NCT05150535 Randomized controlled trial. Estimated enrolment = 100.	≥45 years old, invasive early BC, pTX–4 pN0–3 ±PST and following surgery with adequate axillary clearance and a negative margin. Main exclusion criteria: M0, recurrent BC, synchronous bilateral BC, stages T1–2 N0, T1N1.	BCS (including oncoplastic breast surgery) or mastectomy.	WBI/Chest wall + RNI ± IMN for cN2 or cN3 BC	40 Gy in 15F (3 weeks) ± SIB 48 Gy in 15F or sequential boost 14 Gy in 4F.	26 Gy in 5F (1-week) ± SIB 30 Gy in 5F or sequential boost 14 Gy in 4 fractions.	Rate of acute and chronic toxicity ≥ G2(NCI-CTCAE), local recurrence, patient compliance and OS.
NCT04472845 **HYPART** A Non-inferiority, Open-label, Phase III Randomized Trial. Estimated enrolment = 1018.	≥18 years old, invasive early BC, pT3–4pN2–3 M0 Main exclusion criteria: Breast reconstruction with implants, contralateral BC.	BCS or mastectomy, reconstruction with autologous tissue or tissue-expander allowed.	WBI/Chest wall + axilla levels III and IV in G3, N2, T3–4	None.	Two experimental arms: 26 Gy in 5F (1-week) ± SIB 34 Gy in 5F or sequential boost 8 Gy in 2F. OR 34 Gy in 10F (2-weeks) ± SIB 42 Gy in 10F or sequential boost 8 Gy in 2F.	Loco-regional recurrence, DFS, OS, acute radiation toxicity and late adverse events (RTOG grading system) and QoL.
NCT04550910 Randomized controlled trial. Estimated enrolment = 166.	≥18 years old, invasive BC, cT3–T4 and/or N + following PST or cT3–T4 ± N+	BCS or mastectomy.	WBI/Chest wall + RNI	40 Gy in 15F (3 weeks)	28.5 Gy in 5F (once weekly)	Chest wall pain, Dysphagia, Skin toxicity, Pulmonary Toxicity, Brachial plexopathy (all by RTOG grading system), Lymphedema (CTCAE v.5.0) and local control.

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Table 5 (*continued*)

Study Study type	Patients	Type of surgery	Treated volumes	Standard RT arm	Experimental RT arm	Outcome measures
NCT03788213 **HYPORT**Adjuvant An Open Label Randomised Controlled Study. Estimated enrolment = 2100.	≥18 years old, invasive BC, surgery with ALND, cT0–T4 and/or N + with indication for RT Main exclusion criteria: Pathologically proven residual cN3 disease, prior RT, concurrent chemotherapy.	BCS or mastectomy with ALND.	WBI/Chest wall ± RNI ± IMN (according to institutional policy)	40 Gy in 15F (3 weeks) ± SIB 48 Gy in 15F or sequential boost 12 Gy in 4F.	26 Gy in 5F (1-week) ± SIB 30 Gy in 5F or sequential boost 12 Gy in 4F.	Locoregional Recurrence Rate, OS, iDFS, Adverse events, QoL.
NCT05850637 Prospective phase II non-randomized single arm. Estimated enrolment = 60.	≥65 years old, invasive BC with indication for RT Main exclusion criteria: prior RT,bilateral breast RT, any breast reconstruction, positive resection margins.	BCS or mastectomy.	WBI/Chest wall ± RNI	None.	Single arm: 28.5 Gy in 5F (every other day)	Acute toxicity (CTCAE v.5.0) and late toxicity (RTOG grading system), Locoregional free survival, DFS, OS, and cosmesis change (Harvard/NSABP/RTOG scale).
NCT04648904 **FAST-R Trial** Single-arm, single-site, prospective non-inferiority trial. Estimated enrolment = 72.	≥65 years old, invasive BC stage IIa–IIIa, with indication for RT, with breast reconstruction. Main exclusion criteria: positive resection margins, M0, c/pT3–T4 or involved internal mammary disease (N1b, N1c, and N2b).	Mastectomy with reconstruction.	PMRT	None.	Single arm: 26 Gy in 5F (1-week (or within 10 consecutive weekdays to allow for treatment delays) ± sequential boost of of 5.2 Gy for 1–2For an alternate boost schedule of 2.5 Gy for 1–4F.	Local recurrence, regional recurrence, complications (CTCAE v.5.0).
NCT04509648 **ARROW** Prospective, single-arm trial. Estimated enrolment = 197.	≥18 years old, invasive BC, surgery with ALND, pT1–3 pN +. Main exclusion criteria: positive resection margins, pathologically positive ipsilateral supraclavicular lymph node or involved internal mammary disease, prior RT, synchronous bilateral BC, cT4, M0.	BCS or mastectomy with ALND.	WBI/Chest wall + RNI + IMN	None.	Single arm: 26 Gy in 5F (1-week ± sequential boost of of 5.2 Gy in 2F.	Rate of acute ≥ G2 (CTCAE v.3.0) and late ≥ G2 (RTOG grading system) toxicity, Cosmesis outcomes (Harvard/NSABP/RTOG scale), locoregional recurrence, DMFS, iDFS, OS and QoL.
NCT04228991 **RHEAL** An Open Label Randomised Controlled Study.	≥18 years old, invasive BC, candidate for locoregional RT, T3N0, T1–3 N1–2, M0. Main exclusion criteria: cT4 or N3, bilateral breast RT, breast reconstruction, prior RT.	BCS or mastectomy with SLNB or ALND.	WBI/Chest wall + RNI	40 Gy in 15F (3 weeks)	26 Gy in 5F (1-week)	Rates of lymphedema, breast cancer recurrence, mortality, acute and late radiation toxicity, arm mobility, QoL, perception of lymphedema, perception of breast cosmesis, health care resource utilization and patient costs.

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Table 5 (*continued*)

Study Study type	Patients	Type of surgery	Treated volumes	Standard RT arm	Experimental RT arm	Outcome measures
Estimated enrolment = 588.						
NCT03280719 **PRO-SURF** An Open Label Randomised Controlled Study. Estimated enrolment = 61.	≥18 years old, invasive BC, following BCS, candidate for locoregional RT. Main exclusion criteria: M0, bilateral breast RT, prior RT.	BCS	WBI + RNI	40 Gy in 15F (3 weeks) + SIB 46.8 Gy in 15F Prone vs. supine.	WBI: 28.5 Gy in 5F (over 12 days) + SIB 31 Gy in 5F; RNI: 27 Gy in 5F (over 12 days) Prone vs. supine	Breast retraction, acute toxicity (CTCAE v4.03), cosmesis (Photographic image analysis using BCCT.core), QoL, locoregional and distant tumour control, treatment duration, dose parameters of target volumes and organs-at-risk, setup accuracy, treatment cost.
NCT04098926 **HAI-5** Single-arm, single-site, prospective non-randomised trial. Estimated enrolment = 70.	≥70 years old, invasive BC, candidate for locoregional RT. Main exclusion criteria: M0, bilateral breast RT.	BCS or mastectomy.	WBI/Chest wall ± RNI	None.	Single arm: WBI/Chest wall: 28.5 Gy in 5F ± SIB 32.5 Gy in 5F (R0) or SIB 34.5 Gy in 5F (R1) RNI: 27 Gy in 5F (every other day, over 10 days)	Breast retraction (LENT-SOMA), acute (CTCAE v. 4.0) and late radiation toxicity, locoregional and distant tumour control, breast cancer specific survival and OS.
NCT03121248 **HAI-5-III** A Partially Randomized patient preference trial. Estimated enrolment = 798	≥65 years old, invasive BC, candidate for locoregional RT. Main exclusion criteria: M0, bilateral breast RT, reconstructive breast surgery.	BCS or mastectomy.	WBI/Chest wall ± RNI	Randomised or observational arm. WBI/Chest wall: 40 Gy in 15F ± SIB 32.5 Gy in 5F (R0) or SIB 34.5 Gy in 5F (R1) ± RNI: 27 Gy in 5F	Randomised or observational arm. WBI/Chest wall: 28.5 Gy in 5F ± SIB 32.5 Gy in 5F (R0) or SIB 34.5 Gy in 5F (R1) ± RNI: 27 Gy in 5F (every other day, over 10 days)	Breast retraction (LENT-SOMA), acute (CTCAE v. 4.0) and late radiation toxicity, including Chronic toxicity - prevalence of radiation induced brachial plexopathy, locoregional and distant tumour control, breast cancer specific survival, OS, patient preference, QoL, Cost effectiveness analysis, technical feasibility of prone positioning and deep inspirational breath-hold in prone position
NCT05665920 **HYPHEN** Prospective, interventional, exploratory, controlled, randomized study. Estimated enrolment = 36	≥18 years old, invasive BC, except invasive lobular carcinoma, following BCS, pT1–3 and pN1–3a, candidate for locoregional RT. Main exclusion criteria: M0, concomitant chemotherapy, histology of metaplastic carcinoma, prior RT.	BCS	WBI + RNI	40 Gy in 15F (3 weeks)	26 Gy in 5F (1-week)	Locoregional recurrence, OS, DFS, locoregional control, acute toxicity (RTOG grading system) and late toxicity, QoL and body image scale.
NCT04443413 Phase III randomised controlled trial.	≥18 years old, invasive BC, T1–T4c, N0–3, candidate for locoregional RT. Main exclusion criteria: M0, cT4d, severe co-morbidity, recurrent BC, prior RT, bilateral BC RT.	BCS or mastectomy	WBI/Chest wall + RNI	40 Gy in 15F (3 weeks) X.rays or protons	26 Gy in 5F (1-week) X.rays or protons	Complication rate, Incidence of acute adverse events and late toxicity, locoregional control, iDFS, DFS, cause-specific survival, OS, QoL, clinical features, dose-volume parameters, technique, associated

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Table 5 (*continued*)

Study Study type	Patients	Type of surgery	Treated volumes	Standard RT arm	Experimental RT arm	Outcome measures
Estimated enrolment = 98						with fair and poor cosmetic outcomes or unplanned surgical intervention and costs and comparative effectiveness of treatment

Abbreviations: BC = Breast cancer, BCS = Breast conserving surgery, T = Tumour, N = Nodes, M = Metastases, RT = Radiotherapy; 3D-CRT = Three-dimensional conformal radiotherapy, WBI = Whole breast irradiation, RNI = Regional nodes irradiation, IMN = Internal mammary lymph nodes irradiation, G = Grade, NCI-CTCAE = The National Cancer Institute - Common Terminology Criteria for Adverse Events, IBTR = Ipsilateral local tumourrecurrence, OS = Overall Survival, DFS = Disease-free survival, iDFS = Invasive Disease Free Survival, DMFS = Distant metastasis free survival, PBT = Proton beam radiation therapy, XRT = Photon radiation therapy, PST = Primary systemic therapy, F = fraction(s), RTOG = Radiation Therapy Oncology Group, NSABP = National Surgical Adjuvant Breast and Bowel Project, LENT-SOMA = Late Effects Normal Tissue Task Force - Subjective, Objective, Management, Analytic, ALND = Axillary lymph node dissection, SLNB = Sentinel lymph node biopsy, QoL = Quality of life, PMRT = Postmastectomy radiation therapy.

retrospective data collection may introduce biases. Limited follow-up and cohort size may obscure certain results and prevent definitive long-term tolerance assessment. The decision to deliver a boost to all patients following BCS may be open to discussion. While existing evidence supports its efficacy in reducing local failure for all treated patients, the advancements in local control achieved in recent decades, coupled with the potential negative impact of a boost on cosmetic outcomes, underline a growing inclination to reserve it for patients at high risk of local recurrence. Our analysis of late toxicity focused on patients with a minimum of 6 months of follow-up, recognizing that an extended duration is pivotal for a comprehensive evaluation of potential late complications. Albeit complications were assessed by experienced medical and nursing staff, incorporating Patient-reported Outcome Measures (PROMs) could enhance the depth and breadth of our results. Future investigations should prioritize detailed quality-of-life analysis. Strengths include analyzing one of the largest real-world cohorts of breast cancer patients undergoing breast/chest wall and RNI, encompassing patients receiving IMN irradiation, younger patients (median age 52 years), and those with breast reconstruction. In conclusion, based on our cohort's analysis, one-week UHF postoperative locoregional radiation has low acute and early-delayed toxicity profiles in selected breast cancer patients. If appropriate dose constraints are achieved, similar toxicity profiles are displayed postmastectomy, breast reconstruction, SIB, or RNI, including IMN.

Author contributions

The work reported in the paper has been performed by the authors, unless clearly specified in the text: Conceptualization: AML, IR, RC; Data curation: IR, AML; Formal Analysis: IR, AML; Funding acquisition: none; Investigation: none; Methodology: AML,IR, RC; Project administration: IR, AML, RC; Resources: AML,IR, RC; Software: none; Supervision: AML, RC; Validation: AML, IR, RC; Visualization: none; Writing – original draft: IR, AML, RC; Writing – review & editing: All authors; All authors read, provided feedback and approved the final protocol and manuscript.

Declaration of interests

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CRediT authorship contribution statement

Ivica Ratosa: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Angel Montero:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Raquel Ciervide:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Beatriz Alvarez:** Writing – review & editing. **Mariola García-Aranda:** Writing – review & editing. **Jeannette Valero:** Writing – review & editing. **Xin Chen-Zhao:** Writing – review & editing. **Mercedes Lopez:** Writing – review & editing. **Daniel Zucca:** Writing – review & editing. **Ovidio Hernando:** Writing – review & editing. **Emilio Sánchez:** Writing – review & editing. **Miguel Angel de la Casa:** Writing – review & editing. **Rosa Alonso:** Writing – review & editing. **Pedro Fernandez-Leton:** Writing – review & editing. **Carmen Rubio:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Access to the de-identified data on a secure web application REDCap (Research Electronic Data Capture) platform can be made available to qualified researchers upon reasonable request. Further information is available from the corresponding author upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100764.

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