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ORIGINAL ARTICLE

Large scale experience of two ultrahypofractionated 5 fractions regimes after breast conserving surgery from a single centre

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ABSTRACT

Purpose: Ultra-hypofractionation breast radiotherapy is a safe alternative to moderate hypofractionation. This study reports the results of two ultrahypofractionated regimens used in clinical practice in a high-volume radiotherapy center in terms of efficacy and of tolerance.

Methods: we included all patients treated in an adjuvant setting with five fractions after breast conserving surgery (BCS), for a histologically-confirmed invasive or *in situ* breast carcinoma. Radiotherapy regimens after BCS were either a 5-week schedule with 5 weekly fractions of 5,7 Gy or a one-week schedule with 5 daily fractions of 5,2 Gy. Adverse events were recorded and local-relapse free survival (LRFS), locoregional-relapse free survival (LRRFS), metastasis-free survival (MFS), for breast-cancer specific survival (BCSS) and overall survival (OS) were evaluated.

Results: Between December 2014 and December 2022, 396 patients (400 breasts) were treated with ultrahypofractionated radiotherapy. Five-year LRFS was 98.8% (95% confidence interval: 97.1%–100%), and 5-year OS was 96.0% (95%CI: 92.6–99.5%). Age was statistically associated with OS in univariate analysis (HR: 1.16, 95%CI: 1.04–1.42, $p = .01$). Four patients (1.0%) experienced acute grade 3 radiation-induced adverse events, and 8 patients (2.3%) acute grade 2 toxicities. Twenty-three patients (5.8%) experienced late toxicity, all of them being graded as grade 1. The use of the 5.7 Gy-weekly-fraction regimen and the delivery of a tumor bed boost were significantly associated with acute radiodermatitis ($p < .01$; $p = .02$; respectively) and late fibrosis ($p < .01$; $p = .049$; respectively).

Conclusions: ultrahypofractionated radiotherapy was associated with an excellent tumor control rate in our 'real-life' cohort with low-risk breast cancer patients. However, delivery of a tumor bed boost and using weekly 5.7-Gy fractions were associated with an increased risk of acute and late cutaneous toxicities.

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Introduction

Breast cancer is the most common cancer in women worldwide, accounting for 2.3 million cases in 2020 [1], with an expected increase of nearly 35% by 2040 [2]. Radiation therapy is an integral part of breast cancer multidisciplinary management because it improves local control and overall survival in patients after breast conserving surgery (BCS) or after total mastectomy in case of risk factors [3,4]. The classical radiation fractionation regimen was the normofractionated radiotherapy to a total dose of 50 Gy delivered in 25 fractions over 5 weeks, with or without an additional boost to the tumor bed depending on clinical presentation and patients' age [5]. During the last decade, with the long term results of multiple hypofractionation phase III trials (START A and B, RMH/GOC, CONSORT, RTOG 1005), moderate hypofractionation became a new standard of care in whole breast irradiation [6–10]. Moderate hypofractionation in cases of aggressive presentation with lymph node involvement or in very young patients is under investigation [11]. Ultrahypofractionation is an attractive perspective in order to reduce treatment time and a number of fractions and has been relatively less evaluated compared with moderate hypofractionation and is a part of the optimisation of the treatment strategy and individualisation of the patients' treatment. Such ultrahypofractionated usually regimens delivered 5 fractions, either on a weekly schedule [12–14] or with daily fraction [15]. The FAST Forward (FF) phase III trial demonstrated that there was no difference in terms of local control and toxicities when the whole breast radiotherapy was treated to a total dose of 26 Gy in 5 daily fractions in a population with low risk breast cancer, without regional lymph node irradiation [15,16]. In the Department of Radiation Oncology of the Institut Curie (Paris, France), the protocol delivering 26 Gy in 5 daily fractions was routinely adopted for the treatment of low risk patients older than 70 years, after a preliminary monocentric tolerance evaluation [16]. It represents an alternative to the previously implemented regimen of 28.5 Gy in 5 weekly fractions FAST (F) protocol based on a French national protocol of 5 weekly fractions of 6.5 Gy to a total dose of 32.5 Gy [12,13].

The purpose of this work is to report the real life experience of two ultrahypofractionated regimens used in every

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day clinical practice in our department (26 Gy in 5 daily fractions or 28.5 Gy in 5 weekly fractions) in terms of efficacy and of tolerance on a large patient cohort and also to evaluate our very first results of the use of Fast Forward regimen.

Materials and methods

Study design

This single centre retrospective study was conducted in the Department of Radiation Oncology of the Institut Curie, Paris, France and included all registered patients who were treated in an adjuvant setting with five fractions after breast conserving surgery, for a histologically confirmed invasive or *in situ* breast carcinoma without lymph node involvement. Patients presenting with metastatic breast cancer, treated in a palliative intent or requiring regional lymph node irradiation were excluded. The age limit was 70 years old except for a few patients who had major comorbidity with poor life expectancy. This study was conducted with the approval of the Institutional Radiation Oncology Review Board.

Treatment

Evaluated adjuvant ultrahypofractionated radiotherapy regimens after breast conserving surgery were either a 5 week-schedule with 5 weekly fractions of 5.7 Gy or a 1 week-schedule with 5 daily fractions of 5.2 Gy. Patients could additionally receive a sequential boost to the tumor bed in case of risk factors (grade 3, incomplete resection, triple negative tumors, lymphovascular invasion (LVI) or high grade ductal carcinoma *in situ* (DCIS)), according to institutional guidelines. For the boost, we used one or two supplementary fractions of 5.2 Gy or 5.7 Gy according to the initial fractionation, at the physician discretion. The clear margins were defined as no tumor for invasive carcinomas and a 2 mm margin for the ductal carcinoma *in situ* following institutional guidelines. The 1 week-schedule as the Fast Forward protocol was proposed after the publication of the study to all patients older than 70 years with low risk tumors who needed only whole breast irradiation and in some cases of patients who were younger but with heavy comorbidities.

Radiotherapy techniques

Patients were treated either in dorsal decubitus or isocentric lateral decubitus positions [17,18]. Deep inspiration breath hold (DIBH) was used for cardiac sparing and respecting the dose constraints to heart and lung in patients capable to keep the deep inspiration. The delineation of the breast clinical target volume (CTV) on the simulation computed tomography (CT) scanners was realized using ESTRO recommendations in cases of dorsal decubitus positioning or using the institutional recommendations in cases of isocentric lateral decubitus, previously reported [19]. At least 95% of the prescribed dose has to be delivered to the planned target volume (PTV). The published recommended constraints of doses to organs at risk of the Fast Forward protocol were used and respected for 1 week-schedule [15] and those of the national French protocol for the 5 week-schedule [12,13].

Outcome measures

All patients treated with ultrahypofractionated radiotherapy were seen at the end of treatment and when needed 2 weeks after the end of the radiotherapy, then every 6 months clinical examination with an annual mammogram for the first 5 years after the end of the radiotherapy, then annually with clinical examination and mammogram as the other patients treated for breast cancer. The toxicity was evaluated using the Common Terminology Criteria for Adverse Event (CTCAE) v5 scale.

Statistical analyses

Local-relapse free survival (LRFS), locoregional-relapse free survival (LRRFS), metastasis-free survival (MFS), cause-specific free survival (CSS), and overall survival (OS) were defined from the date of diagnosis, and analyzed using the Kaplan-Meier method. Non-adjusted hazard ratios were performed using the Cox proportional model and multivariate analysis was carried out to assess the adjusted influence of prognostic factors using the Cox stepwise procedure. The covariates selected for multivariate analysis were those with a p-value less or equal to 0.25 on univariate analysis. Identification of statistical correlations between clinical and treatment variables and treatment-related toxicity was performed using logistical regression. The statistical significance threshold was set at 0.05. Statistical analysis were conducted with the R software (version 4.0.2).

Results

Population

Between December 2014 and December 2022, 396 consecutives patients (with 400 treated breasts) have been treated with ultrahypofractionated whole breast radiotherapy in an adjuvant setting in our Department. Patient characteristics are presented in Table 1. Median age was 78 years (range, 57–94 years). Performance Status (PS) was 0 or 1 in 81.5% of patients. Tumors corresponded to invasive carcinoma in 377 cases (94%) and were staged if applicable as T1 or T2 in 91.7% of the time. Thirty-nine (9.8%) patients had a history of contralateral breast irradiation.

Treatment

Radiation schedules are summarized in Table 2. 256 (64%) treatments were performed with the regimen delivering 26 Gy in 5 daily fractions and 144 (36%) with the protocol delivering 28.5 Gy in 5 weekly fractions. There were 250 (62.5%) right-sided tumors, 150 (37.5%) left-sided tumors. Of them, 155 (39.1%) patients have been treated in supine and 241 (60.9%) in lateral isocentric position. The lateral position

Table 1. Patients and tumor characteristics.

	Number (%)
Performance status	
0	184 (46.5)
1	139 (35.1)
2	71 (17.9)
3	2 (0.5)
Side	
Right	250 (62.5)
Left	150 (37.5)
Pathology	
Invasive Ductal Carcinoma (IDC)	300 (75)
Invasive Lobular Carcinoma (ILC)	59 (14.7)
Ductal Carcinoma *in situ* (DCIS)	23 (5.7)
Other	18 (4.5)
N stage at pathology	
0	392 (98.0)
1(mi)	3 (0.7)
1	5 (1.3)
T stage at pathology[a]	
1a	23 (6.1)
1b	110 (29.2)
1c	189 (50.1)
2	51 (13.5)
3	0 (0)
Unknown	4 (1.1)
Grade[a]	
1	126 (33.4)
2	219 (58.1)
3	31 (8.2)
Unknown	1 (0.3)
Lympho-vascular invasion (LVI)[a]	
Yes	22 (5.8)
No	355 (94.2)
Tumor phenotype	
Luminal A	279 (74.0)
Luminal B	60 (15.9)
Triple negative	18 (4.8)
HER2	15 (4.0)
Unknown	5 (1.3)
Neo-adjuvant treatment[a]	
Yes	23 (6.1)
No	354 (93.9)
Adjuvant chemotherapy	
Yes	19 (4.75)
No	481 (95.25)

[a]Among Infiltrative tumors. Hormonal therapy or chemotherapy.

Table 2. Treatment characteristics.

	Number (%) or value (SD)
Position	
Supine	158 (39.5)
Lateral	242 (60.5)
Schedule	
Fast-Forward	256 (64.0)
Fast	144 (34.0)
Radiotherapy technics	
3D conformal, including lateral decubitus and field in field	272 (67.5)
IMRT	60 (15.0)
VMAT	68 (17.0)
Boost	
Yes	8 (2.0)
No	392 (98.0)
Systemic treatment drug during radiotherapy	
Yes	18 (4.5)
No	382 (95.5)
Adjuvant endocrine therapy	333 (84.1)

SD: standard deviation; 3D: three dimensional; IMRT: Intensity Modulated Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy.

was used in 80% of left side treament as shown in Figure 1. Eight patients (only 2% of all treated patients) received a tumor bed boost. Dosimetric data is provided in Table 3. Median mean heart dose (MHD) was 0.39 Gy (Interquartile range: 0.25–1.13 Gy).

Efficacy outcomes

With a median follow up of 15 months (range: 0–102 months), 5 patients experienced tumor recurrence: three patients experienced local failure (at 17, 23 and 81 months), one patient was diagnosed with a regional axillary relapse at 8 months followed by a metastatic evolution at 13 months and patient death at 19 months, and one patient had directly a distant relapse after 47 months. Overall, 9 patients died during follow-up, among which only one was related to disease progression (other death: car accident, COVID pulmonary disease, neurocognitive degenerescence, ovary cancer, or unknown). Five years local-relapse free survival was 98.8% (95% confidence interval (CI): 97.1%–100%), 5-year locoregional-relapse free survival was 98.5% (95% CI: 96.7%–100%), 5-year metastasis free survival was 98.0% (95.0%–100%), 5-year cancer specific survival was 99.4% (98.3%–100%) and 5-year overall survival was 96.0% (95% CI: 92.6–99.5%). Age was statistically associated with overall survival in univariate analysis (HR: 1.16, 95% CI: 1.04–1.42, $p = .01$), but no other variable were related to patient survival, in particular the fractionation regimen. Figure 2 shows local-relapse free survival, locoregional-relapse free survival, overall survival and metastasis free survival curves.

Median follow-up was 46 months for the FAST (F) regimen [range: 3–102] and 10 months [range: 0–35]. for the FAST FORWARD (FF). To compare both regimes, which are biologically different, we report our results at 2 years, the median follow-up for both regimens, as following: LRFS: 98.2[94.7–100] for Fast Forward vs 99.2 [97.6–100] for FAST; LRRFS: 98.2[94.7–100] for FF vs 98.5 [96.4–100] for F; MFS: 100 for FF vs 99.2 [97.6–100] for F; CSS: 100 for FF vs 99.2 [97.7–100] for F, and OS: 100 for FF vs 97.0 [94.1–99.9] for F.

Toxicity

Radiodermatitis was reported in 146 patients (36.8%), the majority being graded as grade 1 ($n = 139$, 95.2%). Four patients (1%) experienced grade 3 radiation-induced adverse events, all corresponding to radiodermatitis, and 8 patients (2.0%) grade 2 toxicities (7 radiation dermatitis and one oedema). The use of the 5.7 Gy-weekly-fraction regimen (compared with the 5.2 Gy daily fraction regimen) and the delivery of a tumor bed boost were significantly associated with acute radiodermatitis (HR = 1.16 [1.06–1.29], $p < .01$; and HR = 1.48 [1.06–2.07], $p = .02$; respectively). Twenty-three patients (5.8%) experienced late toxicity, all of them being graded as grade 1; edema was reported in 8 patients (2.0%), persistent skin pigmentation in 7 patients (1.8%), and late breast fibrosis in 9 patients (2.3%). The use of the 5.7 Gy weekly fraction regimen and the delivery of a tumor bed boost were significantly associated with late fibrosis (HR = 1.05 [1.02–1.09], $p < .01$; and HR = 1.11 [1.00–1.23], $p = .049$; respectively).

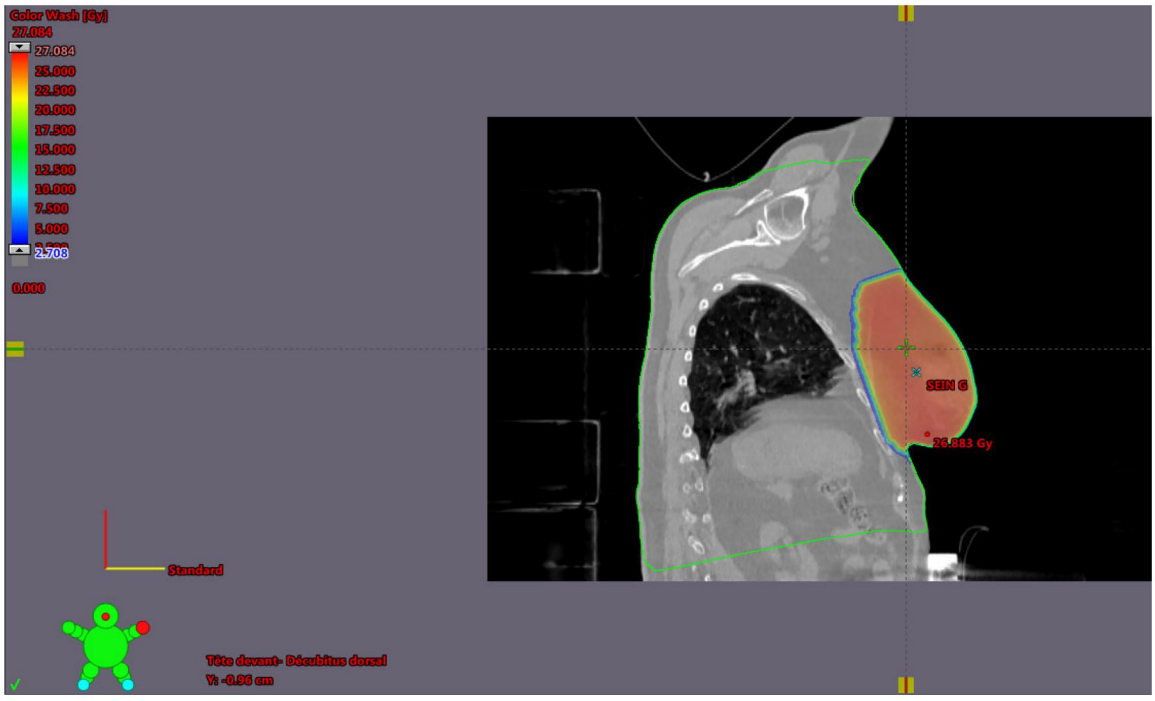

Figure 1. Example for the dosimetry of 77 years old patient treated in lateral position for left side breast cancer, patient with problems of obesity and cardiac dysfunction: in red: the breast volume receiving 26 Gy/5fractions and the mean heart dose is 0.18 Gy, and the mean dose to ipsilateral lung is 0.25 Gy and 0 Gy for contralateral lung.

Table 3. Dosimetric characteristics.

	Right side	Left side	Decubitus Dorsal	Decubitus Lateral	Total
Heart					
Dmean (Gy)	0.8 (0.7)	0.8 (0.8)	0.8 (0.7)	0.8 (0.8)	0.77 (0.4)
Dmax (Gy)	3.2 (3.4)	8.6 (9.3)	7.0 (7.0)	4.2 (6.5)	5.27 (2.2)
V1.5 Gy (%)	6.2 (11.3)	4.3 (7.6)	12.0 (13.4)	1.0 (0.0)	5.5 (10.1)
V5 Gy (%)	0.1 (0.5)	0.8 (2.3)	0.7 (2.3)	0.0 (0.0)	0.4 (1.5)
V7 Gy (%)	0.0 (0.2)	0.6 (1.9)	0.5 (1.7)	0.0 (0.0)	0.3 (1.2)
Homolateral lung					
Dmean (Gy)	2.2 (2.0)	0.9 (1.30)	3.4 (1.76)	0.23 (0.3)	1.7 (1.9)
V5 Gy (%)	11.1 (12.5)	1.9 (5.3)	17.4 (12.0)	0.3 (0.9)	7.6 (11.3)
V10 Gy (%)	5.8 (6.7)	2.2 (4.7)	9.1 (6.6)	0.2 (0.5)	4.5 (6.3)

Dmean: mean dose; Dmax: maximum dose; Vx: volume receiving × Gy.

Discussion

Our single centre study demonstrated excellent real-life outcomes using ultra hypofractionated radiotherapy for breast cancer.

We found that the tumor control was excellent. Only 5 patients (1.0%) experienced tumor control failure which is consistent with other published studies in this low risk population [12,14,15,20,21] and the fact that the FAST Forward trial demonstrated a non-inferiority of ultrahypofractionation compared with a moderately hypofractionated regimen delivering 40 Gy in 15 fractions. Nevertheless, it is important to remember that the follow-up in this trial at the time of publication was limited to 5 years, which might be kept in mind when proposing this treatment to young patients. Therefore this population of patients was not included in the study.

Hypofractionation regimens in 5 fractions have a long history in France and have been used mostly in elderly in elderly patients and patients with poor performance status [12,13].

The excellent tolerance reported in these series was also related probably to the use of individualized irradiation techniques adapted to every patient anatomy.

Treatment was safe with only 2.3% grade 2 and 1.0% grade 3 acute toxicity, which is comparable with what was observed in the prospective trials [22]. As most of the patients were seen only at 6 months, we might have missed acute toxicity but patients were educated to come back at the centre in case of any problem, and it should be noted that using a FAST Forward regimen, Nugent and al [23] evidenced that the maximum incidence of toxicity appeared at week 1, and decreased by 3% per week. Late toxicity was also very limited in our cohort and slightly lower than in the FAST-Forward trial that reported 4% of breast induration and 6% of breast shrinkage. We found that while the tumor control was excellent and did not significantly differed between 5 daily fractions of 5.2 Gy and 5 weekly fractions of 5.7 Gy,

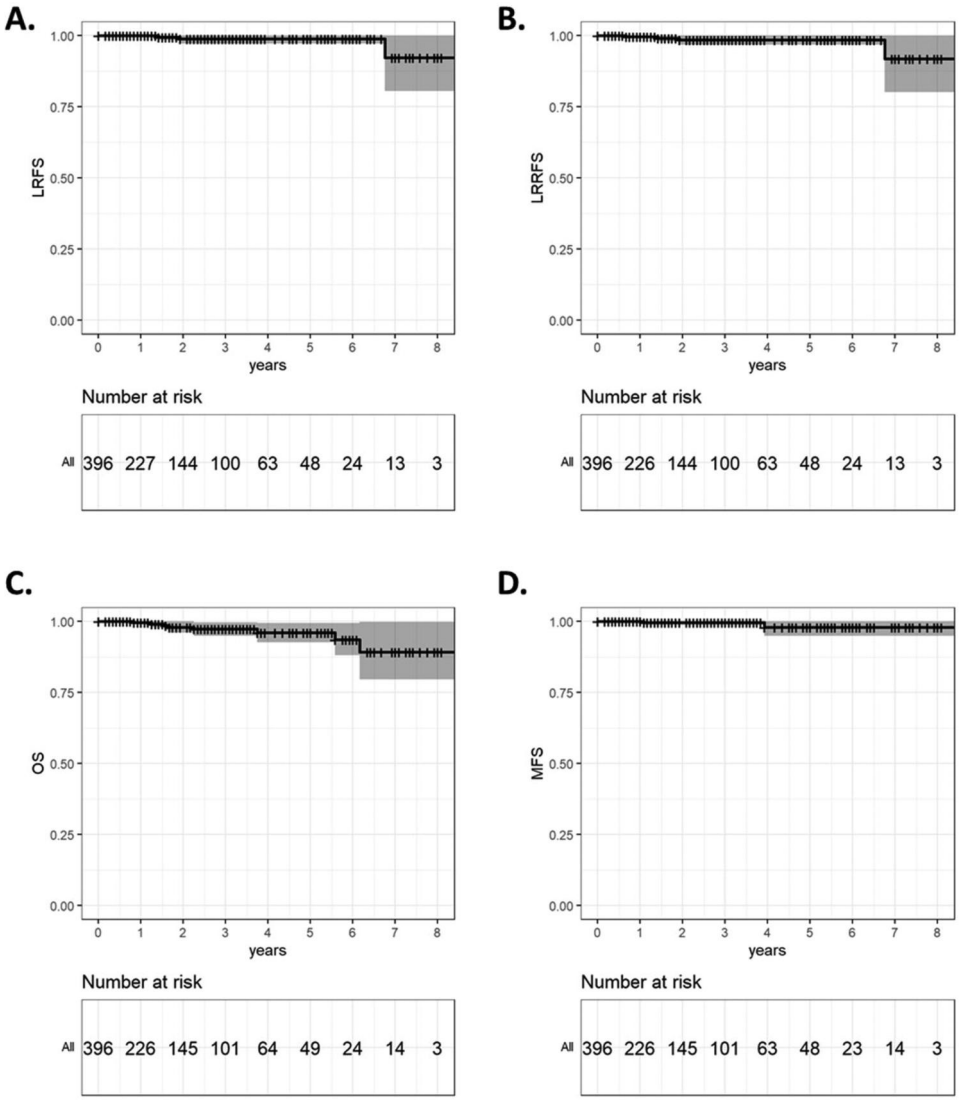

Figure 2. Local relapse free survival (LRFS), (A) loco regional relapse free survival (LRRFS), (B) overall survival (OS), (C) and metastasis free survival (MFS), (D) of patients treated with ultra-hypo fractionated breast radiotherapy at Institut Curie (Paris, France).

the latter regimen was associated with significantly more acute radiodermatitis and late breast fibrosis. This difference between both regimens might be explain by a longer follow-up for patients treated by a 5 week-schedule because it was the first schedule used before the publication of the FAST Forward protocol. Nevertheless, our results confirm the results of the FAST Forward trial, which demonstrated that an ultrahypofractionated regimen using 5.4 Gy per fraction lead to inferior cosmetic results compared with 5.2 Gy per fraction.

It should be noted that no pulmonary or cardiac adverse events were observed. The use of isocentric lateral decubitus for left-sided breast cancer irradiation (Figure 1) is a simple alternative to the deep inspiration breath hold to achieve low pulmonary and cardiac radiation exposure, while limiting treatment time and improving dose homogeneity target volumes [18]. Mean cardiac dose and mean heart V5% for left side breast treatments were very low in our cohort, probably owing to the use of lateral position for 80% of left-side breast treatments. The same technique obviously can be used in right side breast tumors. Indeed, doses constraints in the heart might be difficult to stand without DIBH notably because of V5% [24].

There is also the problem of the use of deep inspiration breath hold in the elderly because the difficulties with some patients to keep the deep inspiration because the presence of comorbidities.

On the other hand, the Fast Forward weekly protocol is very attractive for elderly patients who have difficulties to attend the hospital daily for their radiotherapy sessions. It is better than the protocols of accelerated partial breast irradiation using in most cases 10–15 fractions.

Adding a tumor bed boost improves local control [25,26], but its benefit and its tolerance have never been specifically evaluated in ultrahypofractionation trials. The FAST Forward protocol specified the use of a sequential boost and eight of our patients had a sequential tumor bed boost; while none of them had a tumor relapse, it was statistically associated with an increased risk of late fibrosis. The question of boost is still not resolved in ultrahypofractionation trials because in some cases normofractionated boost of 10 Gy in 5 fractions was used in Fast Forward Trial. If the question is how to

reduce the treatment time and number of fractions, a single fraction of 5.2 Gy daily or 5.7 Gy weekly fraction could be an interesting therapeutic option and this is a possible option for future studies.

On the other hand, the increased fibrosis after the boost is well known well known already a fact and perfectly described and documented in the EORTC 'Boost versus no boost' trial. Bartelink et al. reported with follow up of 20 years that the cumulative incidence of severe fibrosis at 20 years was 1.8% (99% CI 1.1–2.5) in the no boost group versus 5.2% (99% CI 3.9–6.4) in the boost group ($p < .0001$). The authors concluded that radiation boost after whole-breast irradiation has no effect on long-term overall survival, but can improve local control, with the largest absolute benefit in young patients, although it increases the risk of moderate to severe fibrosis [27].

Registries has evidenced that simultaneous integrated boost using 5 fractions of 5.8 Gy, implemented with a FAST Forward protocol for whole breast irradiation, was well tolerated [28] and this approach is currently being prospectively evaluated in a randomized phase III trial [29].

With this kind of de-escalation treatment protocols with a small number of fractions, low toxicity and good quality of life, probably account for the increased recurrence rate reported recently in the phase 3 randomized trial of the omission of irradiation by Kunkler and colleagues [30]. Despite the similar survival, the cumulative incidence of local breast cancer recurrence within 10 years was 9.5% (95% confidence interval [CI], 6.8–12.3) in the no-radiotherapy group *vs* 0.9% (95% CI, 0.1–1.7) in the radiotherapy group (hazard ratio, 10.4; 95% CI, 4.1–26.1; $p < .001$). These recurrences can be avoid using 5 fractions hypofractionated regimens which are reported with excellent tumor control, local recurrence free survival and low toxicity [7,12,15].

The limitation of our study is that it is a retrospective analysis of all patients treated in our Department with the Fast Forward treatment protocol is with a short follow up period; the median follow up is too short at 15 months to see late cardiac events, which tend to occur at 10 years post RT.

At the same time, the positive point is that it is a homogeneous study because its single centre nature and the use of adapted to patients' anatomy techniques with a respect of the constraints at the organs at risk (OAR). It has shown that the Fast Forward protocol is an attractive treatment regimen, reducing the time of radiotherapy adapted for patients treated to the whole breast, used especially in the elderly. This protocol used in a selected population of patients is an example of treatment de-escalation and a perfect example of personalized radiotherapy for improved clinical benefit. This could be an interesting option to optimize the treatment strategy and share the treatment decision with the patients. At the same time, longer long term results are needed to generalize this treatment to younger patients.

Conclusions

In conclusion, this large-size real-life cohort study evaluating two five fractions regimens for adjuvant breast radiotherapy (5.7 Gy weekly fractions or 5.2 Gy daily fractions) demonstrated that ultrahypofractionated radiotherapy was associated with an excellent tumor control rate in low-risk breast cancer patients. However, delivery of a tumor bed boost and using weekly 5.7 Gy fractions were associated with an increased risk of acute and late cutaneous toxicities. Longer follow-up is needed to confirm the results.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Nons

Data availability statement

Data is available in case of questions.

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