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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Comparing hypofractionated and conventionally fractionated whole breast irradiation for patients with ductal carcinoma in situ after breast conservation: a propensity score-matched analysis from a national multicenter cohort (COBCG-02 study)

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Abstract

Background and purpose Randomized trials confirmed the efficacy and the safety of hypofractionated whole breast irradiation (HF-WBI) in patients with early-stage breast cancer. However, the role of HF-WBI in patients with DCIS after breast conserving surgery has not yet been clearly established in prospective randomized trials. The aim of this study was to evaluate if HF-WBI can be considered comparable to conventionally fractionated (CF)-WBI in DCIS patients.

Materials and methods The analysis included DCIS patients from four Italian centers treated with CF-WBI 50 Gy/25 fractions or HFRT 40.5 Gy/15 fractions, without tumor bed boost. A propensity score matching (PSM) analysis was performed using a logistic regression that considered age, grading, presence of necrosis, resection margin status and adjuvant endocrine therapy.

Results Five hundred twenty-seven patients was included (367 in the CF-WBI-group and 160 in the HR-WBI group). After 1:1 matching, 101 patients were allocated to the CF-WBI-group and 104 to the HF-WBI group. No correlation was observed between the type of RT schedule and LRFS (HR 1.68, 95% CI 0.82–3.45; $p = 0.152$). After PSM, no statistical difference was observed between the two RT group (HR 1.11, 95% CI 0.40–3.04; $p = 0.833$), with 3- and 5-years LRFS rates of 100% and 97.9% for CF-WBI and 95.6% and 94% for HF-WBI.

Conclusion A short course of radiation therapy seems to be comparable to CF-WBI in terms of clinical outcomes. These data support the use of hypofractionated schedules in DCIS patients, but considering the remaining uncertainties.

Keywords Ductal carcinoma in situ · Breast cancer · Hypofractionated radiotherapy · Multicenter study · Propensity score matching

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Introduction

The increasing use of diagnostic screening and advances in breast imaging led to a progressive increase of detection rate of ductal carcinoma in situ (DCIS) (Kerlikowske 2010). DCIS is a noninvasive variant of breast cancer with a negligible likelihood to develop regional lymph nodes localization or distant metastases (Sanders et al. 2005). However, the natural history of this clinical entity is unclear: certain cases are indolent but others can progress into invasive disease (Wallis et al. 2012). Historically, the conservative management of DCIS included breast conserving surgery (BCS) and whole breast irradiation (WBI) as postoperative treatment to achieve a significant local control benefit (Cuzick et al. 2011; Donker et al. 2013; McCormick et al. 2015; Wapnir et al. 2011; Warnberg et al. 2014). The major randomized trials adopted conventionally fractionated WBI (CF-WBI), and the schedule of 50 Gy in 25 fractions (5 fractions a week over 5 weeks) represented for decades the standard treatment for these patients.

The role of hypofractionation (HF) was investigated in patients with early-stage invasive breast cancer and the long-term results of the major clinical studies showed no significant differences in efficacy and toxicity as compared to CF-WBI (Haviland et al. 2013; Whelan et al. 2010). Therefore, HF-WBI has become the preferred radiation scheme for the treatment of early-stage invasive breast cancer (Smith et al. 2018).

Even more, after the recent publication of the results of the FAST-Forward trial (Murray Brunt et al. 2020), 1-week regimen instead of a standard 3-weeks schedule may be considered for a substantial group of patients. Considering the available literature data, the radiobiological bases common to both invasive and in situ breast cancer (Owen et al. 2006; Yarnold et al. 2005), and the standard use of HF-WBI in invasive breast carcinoma, the rationale to offer HF-WBI to breast cancer patients affected with DCIS is getting stronger.

Nevertheless, the role of HF-WBI in this setting is still debated, since data from randomized trials are pending and the level of evidence is low (Isfahanian et al. 2017; Lalani et al. 2014; Nilsson and Valachis 2015; Williamson et al. 2010).

We therefore performed a propensity score matching analysis (PSM) to evaluate whether HF-WBI can be considered comparable to CF-WBI in DCIS patients after breast conservation, based on a multicentric database.

Materials and methods

Study design and participants

We collected data from four Italian centers on women with DCIS and treated with BCS and postoperative radiation therapy (RT). Adjuvant endocrine therapy (ET) administration, RT fractionation, and delivery of a boost dose to the tumor bed followed the local policy of each Institution. The CF-WBI schedule was 50 Gy in 25 fractions over 5 weeks; the HF-WBI regimen was 40.5 Gy, 2.7 Gy per fraction in 15 fractions over 3 weeks.

Statistical analysis and propensity score matching

Distribution of clinical characteristics was analyzed using percentiles for continuous variables, and percentages and frequencies for categorical variables. Local recurrence free survival (LRFS) was defined as the time between the day of surgery and the date of locoregional recurrence, death from any cause or last follow-up. Distant metastases-free survival (DMFS) was considered as the time between surgery and diagnosis of metastases, death from any cause or last follow-up. Overall survival (OS) was defined as the time between date of surgery RT and death from any cause or last follow-up. We used Kaplan–Meier method to assess survival and log-rank statistic to test for differences between the patient and treatment's characteristics. All the analyses were performed using STATA V13 software (STATA Corp, College Station, TX).

We aimed to standardize the groups based on propensity to receive one RT treatment schedule over another. The following variables were selected: age (> or < 50 years), grading, presence of necrosis, resection margin status (negative vs close/positive) and endocrine therapy administration. A small subgroup of patients that received a radiotherapy boost to the lumpectomy cavity was excluded from the present analysis.

To minimize selection bias inherent in treatment group allocation, propensity score modeling was used to match the two groups using a logistic regression approach. An absolute standard bias measure < 0.20 is considered small, and sufficient overlap is required for the propensity scores (Austin 2011; Cohen 1988).

Results

Patients

Data on 527 DCIS patients treated with BCS and postoperative RT between 1989 and 2017 were analyzed (DCIS

Table 1 Patients characteristics of the whole cohort

	All patients 527 pts	CF-WBI 367 pts	HF-WBI 160 pts
Age years, median (range)	57 (31–83)	58 (30–87)	57 (30–87)
Family history			
No	344 (65.3)	240 (65.4)	104 (65)
Yes	180 (34.2)	124 (33.8)	56 (35)
ND	3 (0.5)	3 (0.8)	0
Radiological presentation			
No	41 (7.8)	27 (7.3)	14 (8.7)
Yes	484 (92.0)	339 (92.4)	145 (90.6)
ND	1 (0.2)	1 (0.3)	1 (0.6)
Menopausal state			
Premenopausal	152 (28.8)	100 (27.2)	52 (32.5)
Postmenopausal	375 (71.2)	267 (72.8)	108 (67.5)
N° excision			
0	15 (2.8)	11 (3.0)	4 (2.5)
1	511 (97.0)	355 (96.7)	156 (97.5)
2	1 (0.2)	1 (0.3)	0
Grading			
1	97 (18.1)	79 (21.5)	18 (11.2)
2	181 (33.8)	102 (27.8)	79 (49.4)
3	249 (46.4)	186 (50.7)	63 (39.3)
Necrosis			
No	272 (51.6)	155 (42.2)	117 (73.1)
Yes	255 (48.4)	212 (57.8)	43 (26.9)
Margins			
Negative	451 (85.4)	311 (84.7)	140 (87.5)
Positive	76 (14.6)	56 (15.3)	20 (12.5)
Endocrine therapy			
No	398 (75.5)	254 (69.2)	144 (90)
Yes	129 (24.5)	113 (30.8)	16 (10)

CF-WBI conventionally fractionated WBI, *HF-WBI* hypofractionated WBI

patients that received HF-WBI were treated from 2013 to 2017). Before PSM 367 were allocated to the CF-WBI and 160 to the HF-WBI groups, respectively. Patient characteristics of the whole cohort are reported in Table 1. After 1:1 matching, 101 patients were comprised in the CF-WBI group and 104 in the HF-WBI group. Prognostic variables before and after PSM are summarized in Table 2.

Median follow-up time was 128.1 months (range 6–352.4) for the whole sample. Median follow-up was 151.2 months for the CF-WBI group and 44.9 months for the HF-WBI group.

Local recurrence-free survival analysis

Among all patients, 58 (11.01%) had local relapse (48 in the CF-WBI group and 10 in the HF-WBI group). Median LRFS was not reached. Rates of LRFS at 3 and 5 years were 97.9% (95% CI 96.2–98.9) and 95.9% (95% CI 93.6–97.3), respectively. At analysis of correlation of risk factors with LRFS, higher grade (HR 1.85, 95% CI 1.23–2.77; $p=0.003$) and positive margins (HR 1.99, 95% CI 1.06–3.73; $p=0.031$) were correlated with worse LRFS. No correlation was observed between RT schedule and LRFS (HR 1.68, 95% CI 0.82–3.45; $p=0.152$). For CF-WBI, 3 and 5 year LRFS were 98.6% (95% CI 96.7–99.4) and 97.2% (95% CI 94.9–98.5), respectively, while they were 95.8% (95% CI 90.2–98.2) and 91.3% (95% CI 83.3–95.4) for HF-WBI (Fig. 1a). After PSM, no statistical difference was observed between the two RT group (HR 1.11, 95% CI 0.40–3.04; $p=0.833$) as well. Three and 5 years LFRS rates were 100% and 97.9% (95% CI 92.2–99.4) for CF-WBI and 95.6% (88.7–98.3) and 94% (95% CI 86–97.5) for HF-WBI (Fig. 1b), respectively.

Overall survival analysis

Rates of OS at 3 and 5 years were 99.5% (95% CI 98.3–99.9) and 99.1% (95% CI 97.6–99.6). At univariate analysis, only positive resection margin was correlated with worse OS (HR 2.67, 95% CI 1.31–5.43; $p=0.006$). No statistical difference was demonstrated for RT treatment (HR 0.62, 95% CI 1.47–2.62; $p=0.519$). According to treatment group, 3 and 5 years rates were 99.7% (95% CI 98–99.9) and 99.1% (95% CI 97.4–99.7) for CF-WBI and 98.9% (95% CI 93–99.8) and 98.9% (95% CI 93–99.8) for HF-WBI (Fig. 2a). After PSM, there were no difference (HR 0.50; 95% CI 0.1–2.26; $p=0.371$) in terms OS between the two groups with 3- and 5-years rates of 100% for CF-WBI, and 98.7% (95% CI 91.4–99.8) for HF-WBI (Fig. 2b).

Distant metastasis-free survival analysis

Median DMFS was not reached. DMFS rate was 99.5% (95% CI 98.3–99.9) and 99.3% (95% CI 98–99.7) at 3 and 5 years. At univariate analysis, none of the analyzed factors was correlated with DMFS. Rates of DMFS were 100% at 3 and 5 years for CF-WBI and 98.4% (95% CI 93.8–99.6) and 97.2% (95% CI 91.6–99.1) for HF-WBI (Fig. 3a). After PSM, RT treatment was not correlated with DMFS (HR 1.44, 95% CI 0.22–9.28; p = 0.701) (Fig. 3b).

Discussion

Large randomized trials confirmed with a considerable follow-up the equivalence of CF-WBI and HF-WBI in terms of efficacy and toxicity for patients with early-stage breast cancer (Haviland et al. 2013; Whelan et al. 2010).

Table 2 Prognostic variables before and after propensity score matching (PSM)

	Before PSM			After PSM		
	CF-WBI	HF-WBI	*P* value	CF-WBI	HF-WBI	*P* value
	367 pts	160 pts		101 pts	104 pts	
Age			0.052			0.898
≤50	79	47		27	28	
>50	288	113		73	76	
Grading			0.000			0.991
1	79	18		17	17	
2	102	79		45	46	
3	186	63		39	41	
Necrosis			0.000			0.872
No	155	117		63	66	
Yes	212	43		38	38	
Margins			0.407			0.942
Negative	311	140		90	93	
Positive	56	20		11	11	
Endocrine therapy			0.000			0.939
No	254	144		89	92	
Yes	113	16		12	12	

CF-WBI conventionally fractionated WBI, *HF-WBI* hypofractionated WBI

These data led radiation oncologist to evaluate HF-WBI as postoperative treatment for DCIS patients in their clinical practice.

There are retrospective and observational studies on series of DCIS patients treated with hypofractionated schemes that reported local recurrence rates ranging between 0 and 4.1% at 2–5 years (Cante et al. 2014; Ciervide et al. 2012; De Rose et al. 2018; Guenzi et al. 2013; Hathout et al. 2013).

Recently, the long-term results of Danish Breast Cancer Group (DBCG) HYPO trial, including 246 patients with DCIS, showed the non-inferiority of moderate hypofractionated schedule compared with conventional scheme in terms of breast induration or locoregional recurrence, but this was not the primary end-point of this trial (Offersen et al. 2020). However, these are the first encouraging data on the largest cohort of randomly assigned patients with DCIS.

An international, multicenter, randomized, phase 3 trial (BIG 03–07/TROG 07.01) is ongoing to evaluate the role of tumor bed boost and hypofractionation in patients with non-low-risk DCIS. The effects of diagnosis and treatment on health-related quality of life (HRQoL) at 2 years were recently published (King et al. 2020; Olivotto et al. 2020), but the results in terms of time to local recurrence (primary endpoint of the study) are still pending.

Waiting for mature randomized data, different authors reported retrospective analyses of DCIS patient series comparing HF-WBI and CF-WBI (Isfahanian et al. 2017; Lalani et al. 2014; Williamson et al. 2010) and all confirmed a substantial equivalence in terms of LC rates. Particularly, the Canadian group (Lalani et al. 2014) published comparative data on the largest DCIS population cohort that reported a not significant difference in local recurrence in HF-WBI group.

In 2015, a meta-analysis of observational studies confirmed HF-WBI as a safe option in patients with DCIS (Nilsson and Valachis 2015). More recently, the American Society of Radiation Oncology recommended with a moderate quality of evidence HF-WBI as an alternative to CF-WBI in patients with DCIS (Smith et al. 2018).

In this context, we aimed to compare clinical outcomes of two cohort of DCIS patients treated with CF-WBI or HF-WBI from an Italian multicenter database, using a propensity score matching to reduce the selection bias.

During the last decades, clinical, histopathological and treatment-related features were identified and included into nomograms to predict local recurrence risk (Meattini et al. 2019; Mokbel and Cutuli 2006; Rakovitch et al. 2007).

In our study, higher grade and positive surgical margins were confirmed to be correlated with worse LRFS.

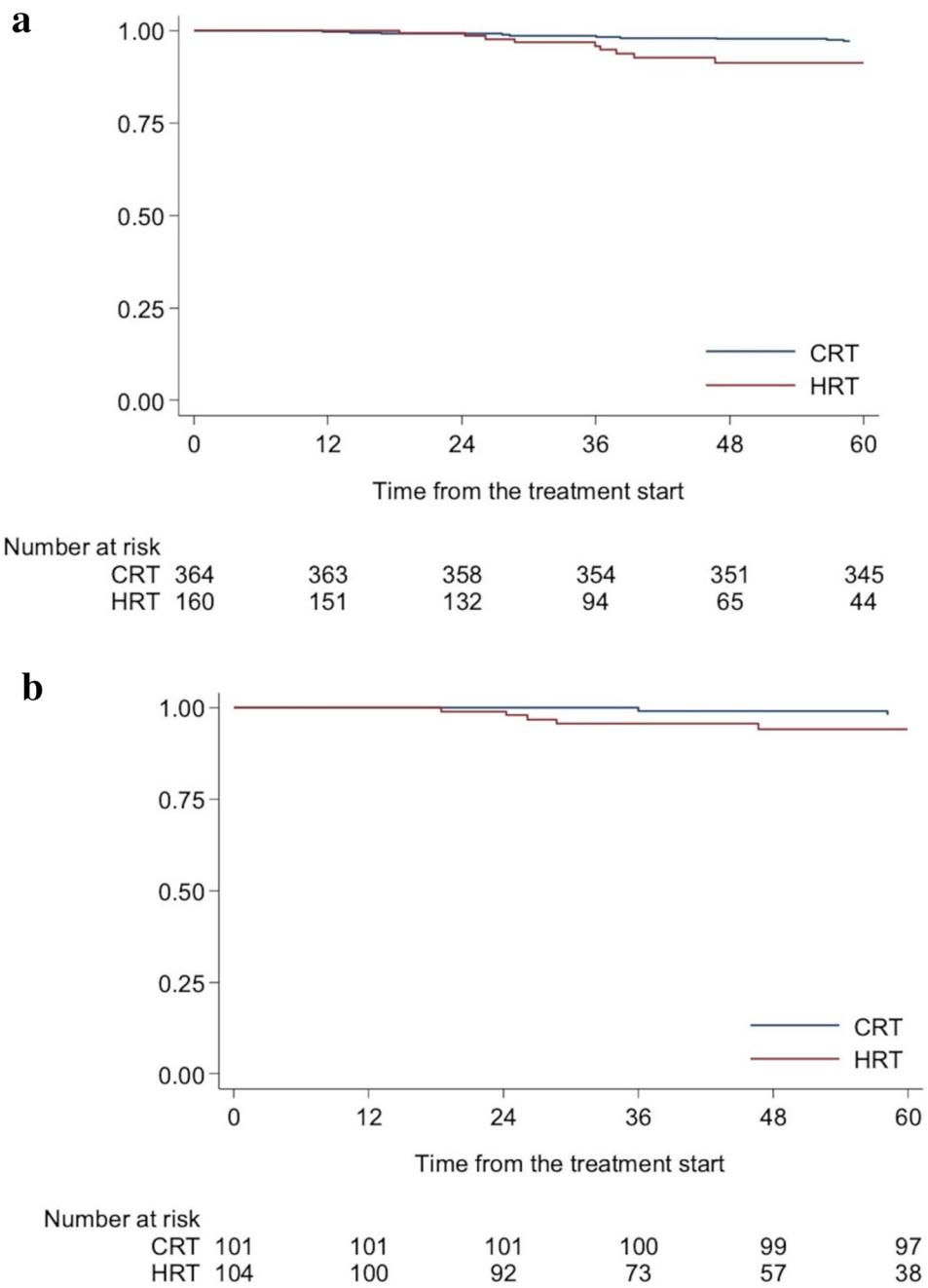
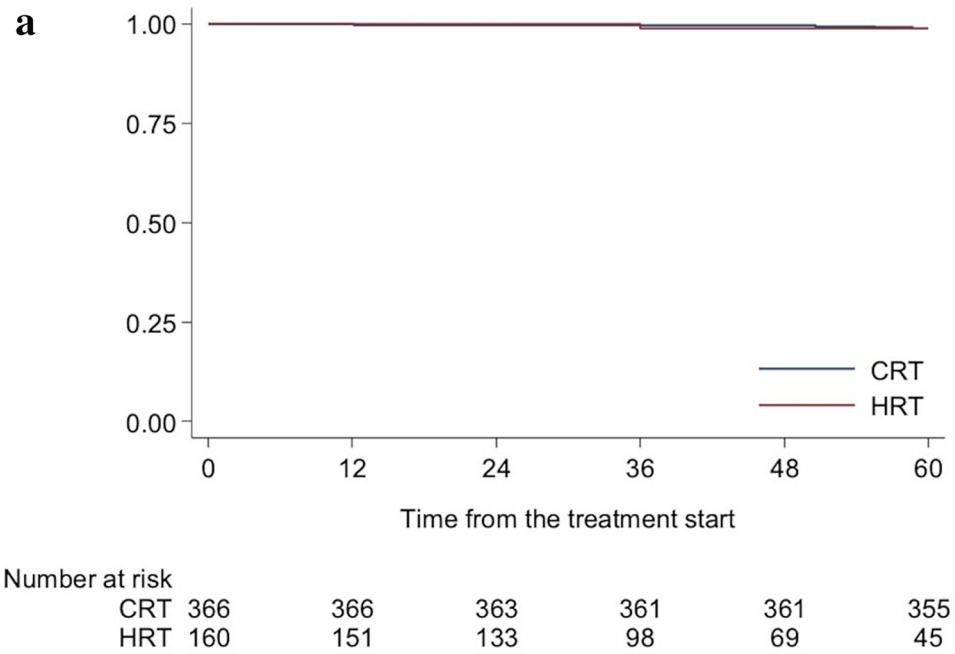


Fig. 1 **a** LRFS Kaplan–Meier curves before PSM**.** *CRT* conventionally fractionated radiotherapy, *HRT* hypofractionated radiotherapy. **b** LRFS Kaplan–Meier curves after PSM. *CRT* conventionally fractionated radiotherapy, *HRT* hypofractionated radiotherapy

After the application of PSM, the distribution of the main prognostic factors, such as age, grading, resection margin status, was comparable in the two RT treatment groups confirming the homogeneity of the analyzed samples.

In both arms, we excluded patients that received a tumor bed boost (TBB), whereas endocrine therapy was administered to a small numbers of patients (13% of each cohort after PSM). In the previously cited publications, the use of boost dose and the administration of tamoxifen were different in the HF-WBI and CF-WBI groups. Williamson (Williamson et al. 2010) included TBB only in one of the two hypofractionated schedules; whereas, endocrine therapy,



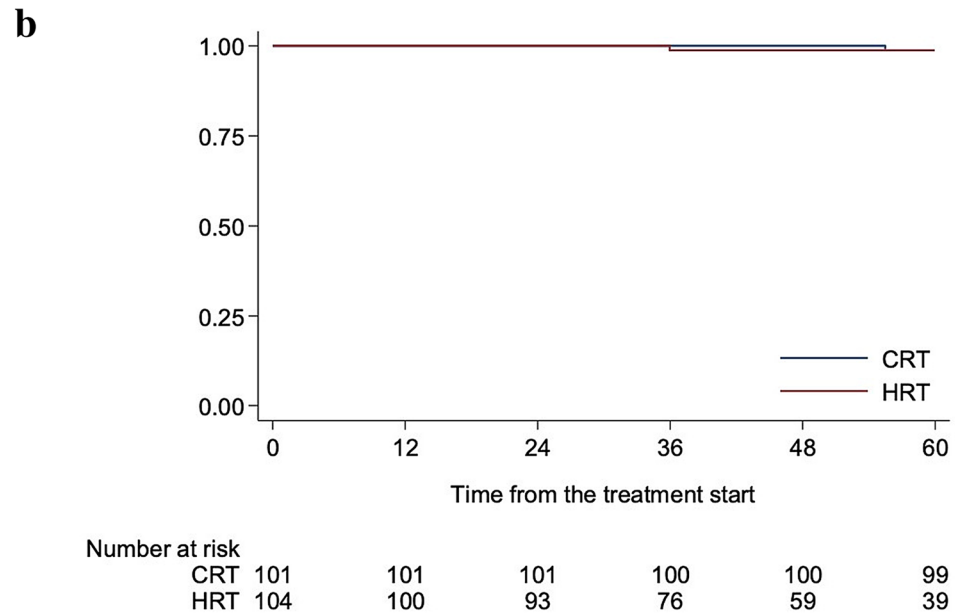


Fig. 2 **a** OS Kaplan–Meier curves before PSM. *CRT* conventionally fractionated radiotherapy, *HRT* hypofractionated radiotherapy. **b** OS Kaplan–Meier curves after PSM. *CRT* conventionally fractionated radiotherapy, *HRT* hypofractionated radiotherapy

administered in 15.7% of patients, resulted well balanced in both cohorts. In the study by Lalani et al. (2014), TBB was more frequently prescribed in the HF group, although they use propensity score matching to mitigate this imbalance. Moreover, the authors declared the absence of information about tamoxifen use for women younger than 65 years as an important limitation of their study. On the other hand, Isfahanian and colleagues (2017) reported comparable rate of TBB in HF (31%) and CF (23%) cohorts; similarly, endocrine therapy was administered in 27% of HF group and in 22% of CF group.

Regarding clinical outcomes, our study did not show any significant differences in terms of LRFS, DMFS and OS at 3 and 5 years in both unmatched and matched population, according to the literature. We found that 3 and 5 years LRFS rate were slightly lower in women treated with HF-WBI than in those treated with CF (95.6–94% vs 100–0.97.9%). However, 5-years LRFS rate of our HF cohort was substantially comparable with those reported for the same group (HF) in the aforementioned studies (Isfahanian et al. 2017; Lalani et al. 2014).

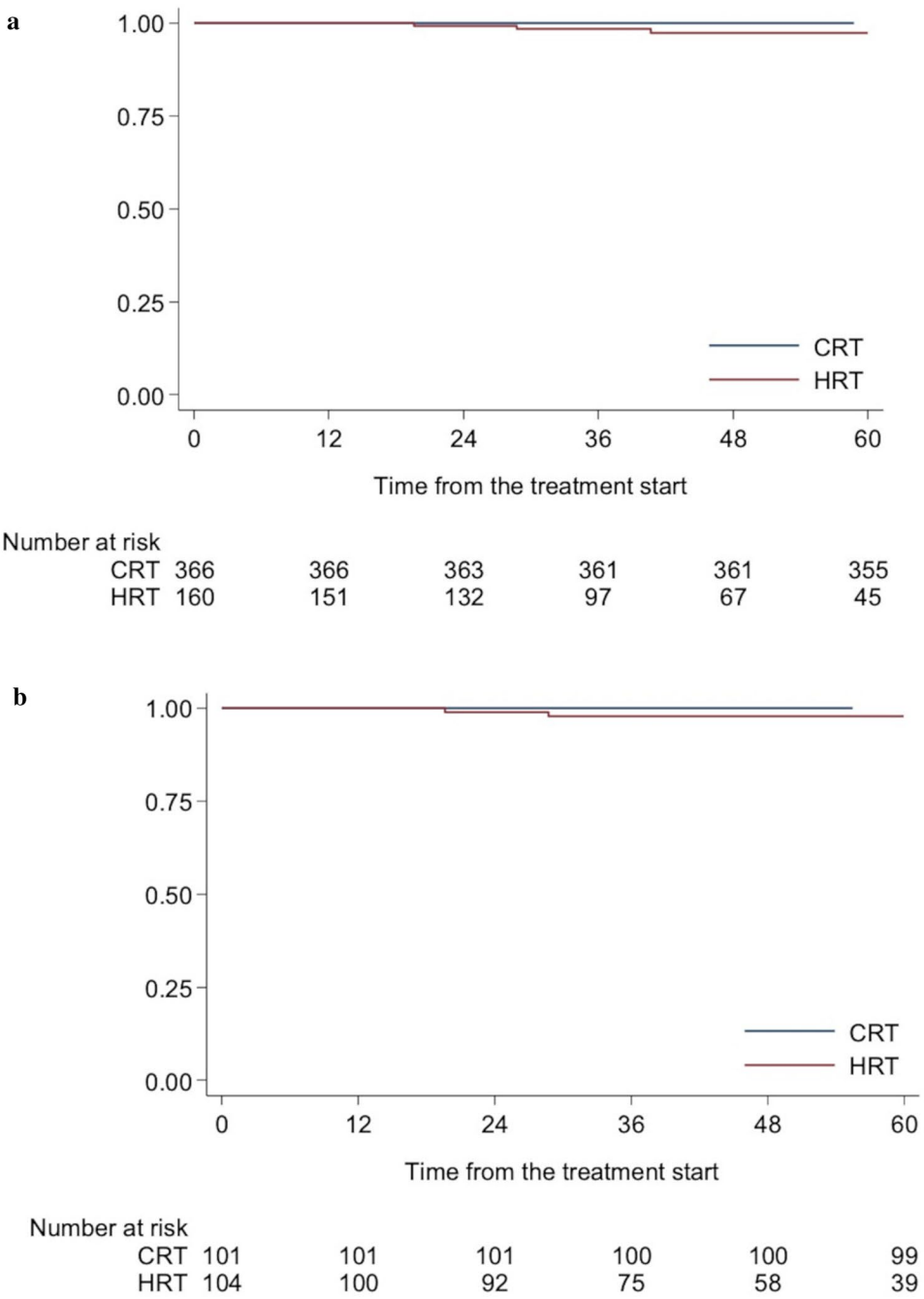


Fig. 3 **a** DMFS Kaplan–Meier curves before PSM. *CRT* conventionally fractionated radiotherapy; *HRT* hypofractionated radiotherapy. **b** DMFS Kaplan–Meier curves after PSM. *CRT* conventionally fractionated radiotherapy; *HRT* hypofractionated radiotherapy

Previously, Lalani et al. made a comparison between the two treatments using a propensity score adjustment approach (Austin 2011). To the best of our knowledge, our study is the first to use a propensity score matching method to compare two different radiotherapy schedules for DCIS patients. In this case, matched sets of treated subjects who share a similar value of the propensity score were defined (Rosenbaum and Rubin 1983), to minimize the selection bias thus well balanced in the studied cohorts.

As our analysis inevitably has some limitations (above all the retrospective nature of the collected data, then the limited number of the HF-WBI sample and finally the short follow-up period of the HF-WBI cohort) there is still some uncertainty about the long-term outcome which is relevant in a patient cohort with high longevity as it is the case for DCIS patients. The pending phase III results will further solidify the data basis for this disease paradigm.

Conclusion

Our PSM analysis confirmed that a HF-WBI schedule is comparable to CF-WBI in terms of efficacy for DCIS patients undergoing BCS. Waiting for the results of ongoing phase III randomized trials, these data support the use of hypofractionated schedules in DCIS patients, but considering the remaining uncertainties. The appropriate total dose and the necessity for a tumor bed boost will also be further elucidated by the pending phase III results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics Committee was not consulted because of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed consent Informed consent was obtained from all individual patients.

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