Autologous fat transfer after breast cancer surgery: An exact-matching study on the long-term oncological safety

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A B S T R A C T

Introduction: Autologous fat transfer (AFT) is widely adopted for breast reconstruction, but its long-term oncologic safety is still not clearly established. The aim of the present study was to compare the 10-year loco-regional recurrence (LRR)-free and distant metastases (DM)-free survival probabilities in AFT vs. control patients, also evaluating the impact of AFT in different intrinsic molecular subtypes of breast cancer.
Materials and methods: 464 AFT patients were exactly matched with a cohort of 3100 control patients treated between 2007 and 2017. A multivariate survival analysis was performed accounting for all variables related to LRR and DM, including adjuvant/neoadjuvant treatments. End-points were analyzed both overall and in each molecular subtype.
Results: LRR occurred in 6.4% of AFT and in 5.0% of control patients (p = 0.42), while DM were observed respectively in 7.7% and 5.4% of cases (p = 0.20). AFT showed no effect on the 10-year LRR-free survival probability (adjusted HR 0.87, 95%CI 0.43–1.76, p = 0.69) or the 10-year DM-free survival probability (adjusted HR 0.82, 95%CI 0.43–1.57, p = 0.55). Luminal A patients treated by AFT showed a decreased LRR-free survival probability (HR 2.38, 95%CI 0.91–6.17, Log-Rank p = 0.07), which was significantly lower than controls after 80 months (Log-Rank p = 0.02). No differences in the 10-year event-free survival probability were found in Luminal B, HER2-positive or triple-negative patients.
Conclusion: AFT does not increase breast cancer recurrence, with the possible exception of late LRRs for Luminal A patients, but further clinical and preclinical data are required to better clarify this data. The use of AFT should not be discouraged.

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Introduction

Autologous fat transfer (AFT) consists in adipose fat tissue liposuction from donor sites, its purification and its relocation to breast sites, to refill a volume defect or to correct other asymmetries or irregularities after breast-conserving surgery or mastectomy [1,2]. This technique is widely adopted by breast surgeons, and its use has risen over time [3]. However, concerns about an increased risk of cancer recurrence have been raised, and the oncological safety of AFT has been questioned [4–7]. Indeed, adipose-derived mesenchymal stem cells are transferred together with adipose tissue during AFT, stimulating angiogenesis and stroma remodeling, thus being responsible for the cosmetic success of lipofilling [8,9]. On the other hand, preclinical studies showed that adipocytes and adipokines, being part of the tumor microenvironment, may play a role in cancer occurrence and progression, possibly being related to recurrence [10–13]. A few case-control studies based on large populations are available today, which suggest that local recurrence rates do not seem increase after AFT [7,14]. At the same time, rigorous evidence analyzing long-term oncologic outcomes and which also considers adjuvant treatments and biomolecular

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subtypes (BMS) of breast cancer are still scarce [14]. The aim of the present study was to assess the long-term oncologic impact of AFT, by comparing the 10-year loco-regional and distant recurrence-free survival probability in patients treated for breast cancer with or without AFT, also evaluating the correlation with BMS and adjuvant therapies in a long-term follow up.

Material and methods

Study population

Patients were retrospectively collected from the prospectively-maintained database of the EUSOMA-accredited Breast Unit of ICS Maugeri Hospital from January 2007 to December 2017. The 464 patients who received at least one AFT were selected and exactly matched with a cohort of control patients extracted from the remaining 3100 women who were not subjected to AFT. Inclusion criteria were: proven diagnosis of breast cancer and any surgery including lumpectomy, nipple-sparing mastectomy or skin-sparing mastectomy with reconstruction. Patients with benign diseases, distant metastases at diagnosis, a previous diagnosis of breast cancer or other cancer, or with relevant data missing were excluded from the study.

Study design and endpoints

Due to the non-random design of the study, an exact match of categorical variables and a range of values for continuous variables were designated, matching patients treated with AFT and control patients according to the subsequent variables: age, histopathology, staging, BMS and grading. BMS were approximated as follows, based on the histopathological features of breast cancer: luminal A (positive hormone receptors and negative HER2, Ki67 < 14%), luminal B (positive hormone receptors and any HER2 status, Ki67 $\geq$ 14%), HER2-enriched (negative hormone receptors and positive HER2), and triple-negative (negative hormone receptors and negative HER2). AFT patients and controls were matched allowing a 1:4 ratio at most. To provide a reliable comparison between AFT and control patients in terms of follow-up, each selected control had an event-free follow-up for at least as long as the period between breast cancer surgery and the AFT of the matched case. The main endpoints were 1) the 10-year loco-regional recurrence (LRR)-free survival probability and 2) the 10-year distant metastases (DM)-free survival probability in patients treated with AFT vs. controls. LRR was defined as the occurrence of ipsilateral breast cancer or nodal disease at axillary, internal mammary and/or supraclavicular level, proven on core biopsy. DM was defined as the occurrence of distant lesions with computed tomography and positron emission tomography features suggestive of malignancy, even if not biopsy-proved. A multivariate survival analysis was performed accounting for all variables related to LRR and DM, including adjuvant or neoadjuvant treatments and BMS. Secondary endpoints were: 1) cancer-related death rate, 2) impact of AFT on LRR and DM stratified by number of AFT procedures, time between breast cancer surgery and AFT, and type of surgery, and 3) evaluation of long-term oncologic safety of AFT according to each BMS.

AFT technique

Indications for AFT were: contour defects, asymmetry, scar retraction and fibrosis, or volume defect after any type of breast cancer surgery; thinning of peri-prosthetic tissues after mastectomy and breast reconstruction, particularly in the case of increased risk of implant exposure; capsular contracture after implant reconstruction. Preferred donor sites were abdominal subcutaneous tissue or fatty tissue from thighs. The chosen area was infiltrated with Klein's solution (average 200 mL) prepared as follows: 60 mg of lidocaine, 7.5 mg of ropivacaine and 1 mg of adrenaline mixed in 1 L of cold saline solution at 0.9%. Infiltration was performed through the subdermal tissue of the donor site using an 18G needle connected to a 50 mL syringe. After infiltration, a 5 mm skin incision was performed on the donor site and a blunt-tipped Coleman cannula with a diameter of 4 mm was inserted. Liposuction by negative pressure was then started. The aspirated adipose tissue was then centrifuged (IEC Medispin-6 Krackeler Scientific Inc., Albany, NY) at 2700×g for 3–4 min to separate adipocytes from erythrocytes, lysed cells and serum. The purified fat tissue was then collected and slowly injected into the subdermal space of the receiving breast site.

Statistical analysis

Differences between AFT and control patients after exact matching were assessed to verify the heterogeneity of the study population. Variables were reported as mean ± standard deviations or as absolute numbers and percentages. Categorical variables were compared using a χ^2 test or Fisher exact test when the sample size was less than or equal to 5, while continuous variables were compared using a Student's T test or non-parametric Wilcoxon test in case of the variable's non-normal distribution. AFT and control patients were compared by a Cox proportional hazards regression model, including variables significantly associated with the outcomes, such as the type of adjuvant/neoadjuvant therapy (hormone therapy, chemotherapy and radiation therapy) and BMS to avoid any bias. The 10-year LRR-free and DM-free survival probabilities were estimated by the Kaplan-Meier method, both globally and in each BMS. Statistical significance was set at p < 0.05 (two-tailed). Data analysis was performed using SAS software (v. 9.4, SAS Institute Inc., Cary, USA).

Results

Distribution of baseline variables and type of adjuvant treatments after exact matching

After exact matching, 830 patients were included for outcomes analyses: 233 AFT (28.1%) and 597 control patients (71.9%). The distribution of baseline variables and BMS were balanced between groups, as reported in Table 1. AFT patients were treated more frequently by mastectomy when compared to controls (76.8% vs. 25.6%, p < 0.0001). Consequently, control patients were more likely to receive radiation therapy when compared to AFT cases (74.9% vs. 45.9%, p < 0.0001). In particular, whole breast radiotherapy with or without boost was offered to 45.8% of AFT patients and to 53.6% of the control group, thoracic wall and/or loco-regional radiotherapy were performed respectively in 38.3% and 25.4% of cases, and other types of radiotherapy were delivered in 15.9% and 21.0% of patients (p = 0.053), Table 1. Chemotherapy was administered in 54.1% of AFT patients vs. 44.6% of control patients (p = 0.04); neoadjuvant treatment was proposed respectively in 12.0% and 8.4% of cases (Table 1). Chemotherapy regimen was based on anthracyclines with or without taxanes in 64.7% of AFT vs. 57.1% of control patients, and trastuzumab was administered respectively in 26.1% and 34.8% of cases; in the remaining cases, cyclophosphamide with methotrexate and fluorouracil (5.9% vs. 5.0%) or other regimens (3.4% vs. 3.1%) were offered (p = 0.48).

Table 1
Distribution of baseline variables after exact matching.

	AFT (n = 233)	No AFT (n = 597)	p-value
Age at diagnosis (years)	49.4 (±9.0)	50.7 (±8.9)	0.07
Body mass index (mean, Kg/m^2)	23.8 (±4.8)	24.5 (±4.9)	0.09
Menopausal status			
Pre-menopausal	134 (57.5%)	342 (57.3%)	0.95
Post-menopausal	99 (42.5%)	255 (42.7%)	
Type of surgery			
Lumpectomy	54 (23.2%)	444 (74.4%)	<0.0001
Mastectomy	179 (76.8%)	153 (25.6%)	
Histological Type			
DCIS	26 (11.2%)	62 (10.4%)	0.84
Ductal invasive carcinoma	173 (74.2%)	455 (76.2%)	
Lobular invasive carcinoma	34 (14.6%)	80 (13.4%)	
Grading			
G1	23 (9.9%)	72 (12.1%)	0.23
G2	126 (54.1%)	345 (57.8%)	
G3	84 (36.0%)	180 (30.1%)	
Staging			
Stage 0	31 (13.3%)	72 (12.1%)	0.05
Stage I	94 (40.3%)	289 (48.4%)	
Stage II	71 (30.5%)	178 (29.8%)	
Stage III	37 (15.9%)	58 (9.7%)	
Biomolecular subtype			
Luminal A	120 (51.5%)	336 (58.3%)	0.48
Luminal B	75 (32.2%)	181 (30.3%)	
HER2+	16 (6.9%)	28 (4.7%)	
TNBC	22 (9.4%)	52 (8.7%)	
Hormone therapy			
Yes	186 (79.8%)	475 (79.6%)	0.93
No	47 (20.2%)	122 (20.4%)	
Chemotherapy			
No	107 (45.9%)	331 (55.4%)	0.04
Yes, neoadjuvant	28 (12.0%)	50 (8.4%)	
Yes, adjuvant	98 (42.1%)	216 (36.2%)	
Radiation therapy			
Yes	107 (45.9%)	447 (74.9%)	<0.0001
No	126 (54.1%)	150 (25.1%)	

Long-term outcomes and event-free survival probabilities between AFT vs. no AFT patients

Mean follow-up after breast cancer surgery was 74.1 (±40.4) months in AFT patients vs. 63.8 (±37.1) months in controls (p = 0.0015). In the AFT group, the mean time interval from breast cancer surgery to the first lipofilling procedure was 22.9 (±19.7) months, matched with an event-free interval which was at least equal in control patients. The, mean follow-up period after the first lipofilling procedure was 51.2 (±35.0) months. LRR occurred in 6.4% of AFT patients and in 5.0% of control patients (p = 0.42), while DM were observed respectively in 7.7% and 5.4% of cases (p = 0.20). Furthermore, no difference was observed in cancer-related death rates, being 5.1% in AFT vs. 3.4% in controls (p = 0.23). All these data are reported in Table 2. AFT and control patients showed comparable 10-year LRR-free survival probability curves, with a hazard

Table 2
Long-term outcomes between lipofilled vs. non-lipofilled patients.

	AFT (n = 233)	No AFT (n = 597)	p-value
Loco-regional recurrence			
Yes	15 (6.4%)	30 (5.0%)	0.42
No	218 (93.6%)	567 (95.0%)	
Distant metastases			
Yes	18 (7.7%)	32 (5.4%)	0.20
No	215 (92.3%)	565 (94.6%)	
Cancer-related death			
Yes	12 (5.1%)	20 (3.4%)	0.23
No	221 (94.9%)	577 (96.6%)	

ratio (HR) for AFT vs. no AFT equal to 0.96 (95%CI 0.52—1.80, Log-Rank test p = 0.91), see Fig. 1a. Also, 10-year DM-free survival probabilities were similar between AFT and control patients (HR 1.24, 95%CI 0.69—2.21, Log-Rank test p = 0.47), as shown in Fig. 1b.

Multivariate survival analysis of AFT vs. no AFT on LRR-free and DM-free survival probabilities

After adjusting for potential confounding variables by means of the Cox regression model, AFT confirmed no effect on 10-year LRR-free survival probability, with a HR equal to 0.87 (95%CI 0.43—1.76, p = 0.69). No variable resulted to be independently associated with LRR. AFT was not associated with decreased 10-year DM-free survival probability (HR 0.82, 95%CI 0.43—1.57, p = 0.55). The only factor independently associated with DM was the need for adjuvant (HR 2.81, 95%CI 1.10—7.14, p = 0.03) or neoadjuvant (HR 5.63, 95%CI 2.01—15.75, p = 0.001) chemotherapy. Menopausal status and body mass index showed no significant association with LRR or DM. The Cox multivariate analysis is reported in Table 3.

Impact of number of AFT procedures, time between oncologic surgery and AFT and type of surgery on outcomes

Taking all AFT patients (n = 464) into consideration, no correlation was found between the number of lipofilling procedures and the occurrence of LRR or DM (respectively Log-rank p = 0.28 and p = 0.45), as reported in Table 4. Performing AFT early (<1 year from oncologic surgery) was not associated with increased events (for LRR Log-rank p = 0.44, for DM Log-rank p = 0.74), despite a higher proportion of early AFT observed among recurrent patients (36.0% vs. 24.2%). Use of AFT after breast-conserving surgery, nipple-sparing mastectomy or skin-sparing mastectomy was not related to LRR (Log-rank p = 0.85) or DM (Log-rank p = 0.33).

Impact of AFT on outcomes in different BMS of breast cancer

A sub-analysis was performed comparing the effect of AFT vs. no AFT on 10-year LRR-free and DM-free survival probabilities in different BMS of breast cancer (Fig. 2). AFT was not associated with increased frequency of LRR (HR 2.38, 95%CI 0.91—6.17, Log-Rank p = 0.07) and DM (HR 2.18, 95%CI 0.94—5.06, Log-Rank p = 0.06) in Luminal A patients, considering the overall follow-up. However, starting from 80 months, survival probability curves were different between the remaining AFT patients (n = 45) and controls (n = 100) for LRR (Log-Rank p = 0.02, Fig. 2a) but not for DM (Log-Rank p = 0.06, Fig. 2b). No differences were observed for Luminal B (LRR: HR 0.51, 95%CI 0.16—1.60, Log-Rank p = 0.24, Fig. 2c; DM: HR 1.05, 95%CI 0.39—2.81, Log-Rank p = 0.91, Fig. 2d) and HER2-positive breast cancers (LRR: HR 1.97, 95%CI 0.33—11.89, Log-Rank p = 0.45, Fig. 2e; DM: HR 0.79, 95%CI 0.08—7.76, Log-Rank p = 0.84, Fig. 2f). Also, no differences were found in triple-negative breast cancers, where no events were encountered among AFT patients (LRR: Log-Rank p = 0.07, Fig. 2g; DM: Log-Rank p = 0.12, Fig. 2h).

Discussion

At least 41 non-overlapping studies have previously reported LRR and DM rates after AFT, but the oncologic safety of lipofilling still remains debated, despite the fact that the great majority of evidence suggests similar outcomes between AFT and control patients [7]. We observed that LRR and DM rates were similar between AFT and control patients after exact matching according to baseline cancer-related features. After adjusting for confounders in a regression model accounting for adjuvant treatments and BMS,
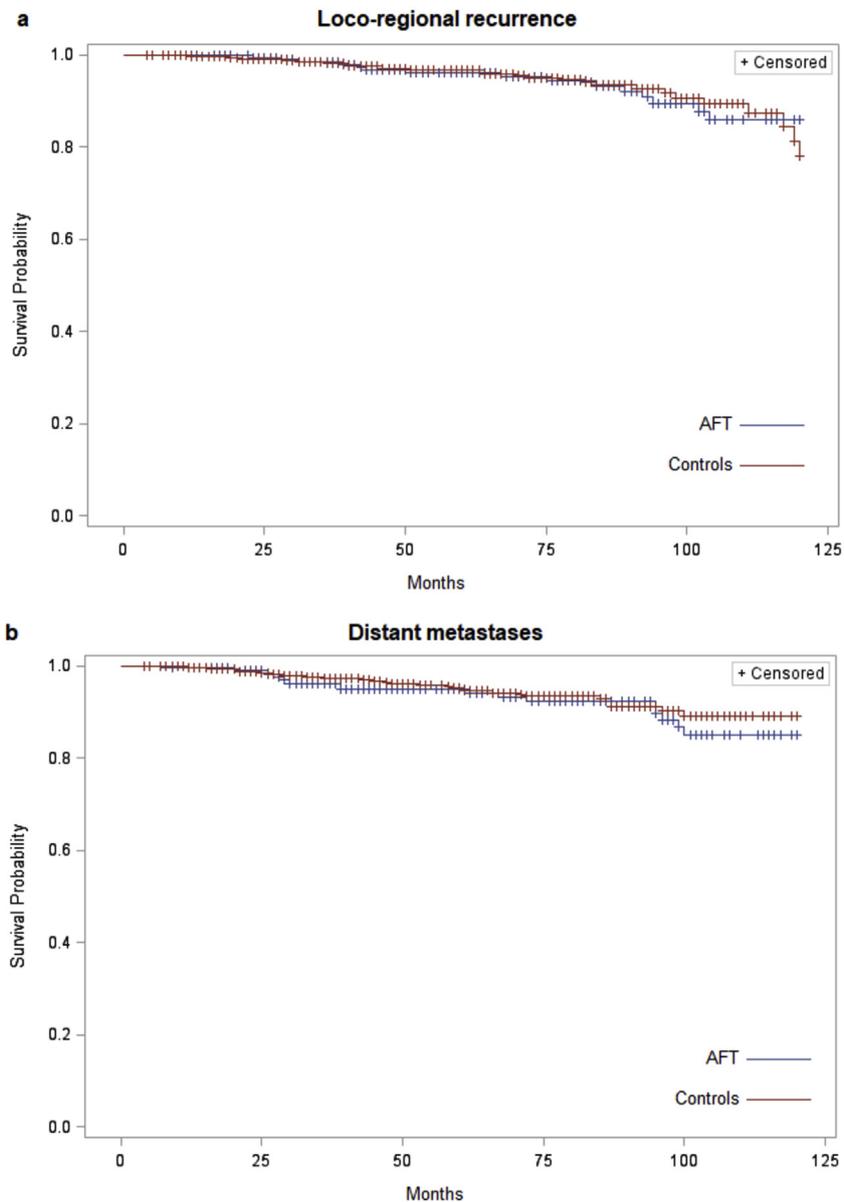
Fig. 1. Survival probability curves of AFT vs. control patients. a) 10-year loco-regional recurrence-free survival probability; b) 10-year distant metastases-free survival probability. AFT, autologous fat transfer.

AFT was still not associated with increased LRR (HR 0.87, p = 0.69) or DM (HR 0.82, p = 0.55). Recently, a large meta-analysis on 4292 patients demonstrated a non-significant incidence rate difference in LRR of −0.15% per year between AFT and control patients, providing robust evidence of AFT safety after breast cancer [7]. However, the mean follow-up from AFT procedure was only 2.7 years for included studies. Considering the long-lasting natural history of breast cancer, such a short follow-up is a common concern due to the risk of under-estimation in cumulative incidence of events [15,16]. In the present study, a longer follow-up is available for AFT patients, with a mean of 51.2 months after the first lipofilling procedure. As can be expected, a longer overall follow-up was available for AFT patients (74.1 vs. 63.8 months, p = 0.0015), since AFT is generally reserved for patients after a certain disease-free interval. To better control for this bias, we matched control patients with a disease-free period at least equal to the period from breast cancer surgery to the first lipofilling in AFT patients. This

solution was first proposed by Petit and colleagues in their landmark study on 321 AFT patients, providing a reliable comparison which showed no impact of AFT on LRR (HR 1.11, p = 0.792) [17]. Also, Krastev et al. reported a longer overall follow-up for AFT patients compared to control, being respectively 9.3 vs. 8.6 years but again, the LRR-free interval of control patients was matched with the period between breast cancer surgery and exposure to AFT [15]. No effect of AFT on LRR was found, with a HR of 0.63 (p = 0.33), confirming that evidence of higher risk after AFT is lacking.

A major point of concern is the unbalanced proportion of patients who underwent mastectomy vs. breast-conserving surgery in the two groups, with mastectomy performed in 76.8% of AFT patients vs. only 25.6% of controls (p < 0.0001) after exact matching. Since AFT can correct soft tissue deformities, skin flap thinning, capsular contracture and post-mastectomy pain syndrome [18,19], it is not surprising that AFT was adopted after mastectomy in the great majority of patients in this study and in previous literature

Table 3
Multivariate survival analysis of AFT vs. no AFT on 10-year LRR-free and DM-free survival probabilities.

	Loco-regional recurrence			Distant Metastases		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95%CI	p-value
Age at diagnosis	1.03	(0.98—1.08)	0.29	1.02	(0.98—1.07)	0.35
Body mass index	0.95	(0.88—1.03)	0.19	0.93	(0.86—1.00)	0.05
Menopausal status						
Pre-menopausal vs. post-menopausal	1.58	(0.66—3.79)	0.31	1.35	(0.58—3.12)	0.49
Type of surgery						
Lumpectomy vs. mastectomy	0.84	(0.34—2.10)	0.71	1.09	(0.47—2.51)	0.84
AFT						
Performed vs. not performed	0.87	(0.43—1.76)	0.69	0.82	(0.43—1.57)	0.55
pT stage						
Early vs. locally-advanced breast cancer	1.47	(0.65—3.33)	0.36	0.61	(0.33—1.13)	0.12
pN stage						
pN0 vs. pN2-3	1.14	(0.35—3.76)	0.83	0.42	(0.16—1.07)	0.07
pN1 vs. pN2-3	1.45	(0.45—4.67)	0.54	0.54	(0.23—1.30)	0.17
Biomolecular subtype						
Luminal A vs. TNBC	0.63	(0.16—2.54)	0.51	0.47	(0.10—2.25)	0.34
Luminal B vs. TNBC	1.00	(0.27—3.78)	1.000	0.41	(0.09—1.92)	0.26
HER2+ vs. TNBC	1.54	(0.46—5.22)	0.49	1.27	(0.34—4.71)	0.72
Chemotherapy						
Yes: adjuvant vs no	0.91	(0.39—2.11)	0.83	2.81	(1.10—7.14)	0.03
Yes: neoadjuvant vs. no	2.62	(0.97—7.09)	0.06	5.63	(2.01—15.75)	0.001
Hormone therapy						
Performed vs. not performed	0.70	(0.24—2.04)	0.51	2.41	(0.58—9.97)	0.22
Radiation therapy						
Performed vs. not performed	1.04	(0.45—2.42)	0.93	0.71	(0.31—1.60)	0.40

Table 4
Impact of number of AFT procedures, time between oncologic surgery and AFT and type of surgery on LRR and DM.

All AFT patients (n = 464)	Loco-regional recurrence			Distant metastases		
	No (n = 439)	Yes (n = 25)	Log-rank p-value	No (n = 425)	Yes (n = 39)	Log-rank p-value
Number of AFT procedures						
1	165 (37.6%)	5 (20.0%)	0.28	159 (37.4%)	11 (28.2%)	0.45
2	213 (48.5%)	16 (64.0%)		206 (48.5%)	23 (59.0%)	
≥3	61 (13.9%)	4 (16.0%)		60 (14.1%)	5 (12.8%)	
Time from cancer surgery to first AFT						
<1 year	106 (24.2%)	9 (36.0%)	0.44	107 (25.2%)	8 (20.5%)	0.74
1—3 years	198 (45.1%)	11 (44.0%)		190 (44.7%)	19 (48.7%)	
>3 years	135 (30.7%)	5 (20.0%)		128 (30.1%)	12 (30.8%)	
Type of surgery						
Lumpectomy	116 (26.4%)	5 (20.0%)	0.85	115 (27.1%)	6 (15.4%)	0.33
Skin-sparing mastectomy	254 (57.9%)	15 (60.0%)		243 (57.2%)	26 (66.7%)	
Nipple-sparing mastectomy	69 (15.7%)	5 (20.0%)		67 (15.8%)	7 (17.9%)	

[7,16,20—22]. Due to the different distribution of types of surgery in the two groups, AFT patients received significantly less radiotherapy when compared to controls (45.9% vs. 74.9%, p < 0.0001). Apparently, such differences could represent a bias for our findings. However, it is currently well-established that lumpectomy with radiotherapy carries a similar LRR risk when compared to mastectomy [23,24], and that biological features of breast cancer together with adjuvant treatments predict LRR better than the extent of surgery [25]. Therefore, the difference in the type of surgery is conceptually irrelevant in terms of the LRR rate, considering that the clinical, pathological and biological characteristics of patients were exactly matched and taken into account in the multivariate analysis. Furthermore, the type of surgery was in any case included in the multivariate survival analysis together with the use of AFT, and it confirmed that there was no association with LRR (HR 0.84, p = 0.71) or DM (HR 1.09, p = 0.84).

In our institution, loco-regional irradiation is proposed only in patients with >3 positive nodes irrespective of the type of surgery, thus avoiding post-mastectomy radiotherapy in N1 patients. Since the stage was similar between groups, no significant differences were found in the type of irradiation, being loco-regional radiotherapy offered in 38.3% of AFT patients vs. 25.4% of controls (p = 0.053). Moreover, the use of radiotherapy was considered in multivariate analysis, but it was not related to LRR (HR 1.04, p = 0.93) or DM (HR 0.71, p = 0.40). Consequently, it is unlikely that loco-regional irradiation in AFT patients could have biased survival analyses.

Indeed, some studies suggest that in AFT after breast-conserving surgery, adipose tissue may cross-talk with surrounding dormant residual cancer cells, thus promoting LRR [26,27]. In this study, the type of surgery was equally distributed among AFT patients with and without LRR (p = 0.72), and breast-conserving surgery was performed respectively in 26.4% and 20.0% of cases. This further excludes the role of the type of surgery in LRR and confirms the safety of AFT after breast-conserving surgery. The largest population of patients undergoing breast-conserving surgery followed by AFT comes from a recent study by Petit, which confirmed that AFT is a safe procedure even after lumpectomy [28]. Petit and Silva-Vergara suggested that AFT performed within 3 years after breast cancer surgery is related to increased risk of LRR [22,26]. In the present study, the great majority of patients (about 70%) received the first AFT procedure within 3 years from oncologic surgery, but
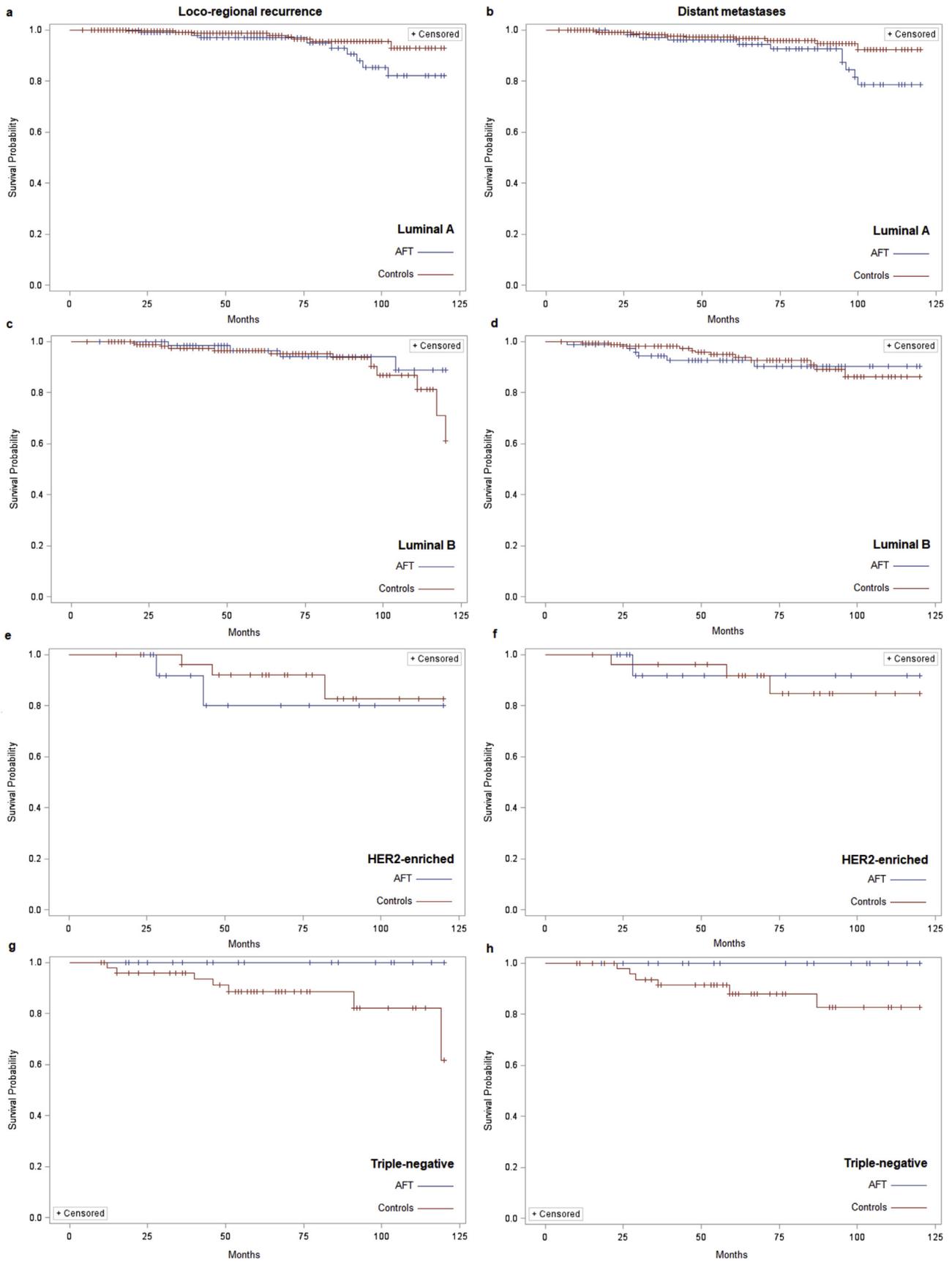
Fig. 2. 10-year survival probability curves of AFT vs. control patients for each biomolecular subtype of breast cancer. a) loco-regional recurrence and b) distant metastases in Luminal A; c) loco-regional recurrence and d) distant metastases in Luminal B; e) loco-regional recurrence and f) distant metastases in HER2-positive; g) loco-regional recurrence and h) distant metastases in triple-negative breast cancer.

this has not resulted in an increased event rate (p = 0.44 for LRR and p = 0.74 for DM).

No study is known to have specifically addressed the risk of AFT on LRR or DM in relation to fundamental predictors of outcome such as BMS [7,15–17,22,26]. Luminal cancers are related to late recurrences and HER2-positive or triple-negative cancers to early events [29–32]. Considering the global follow-up of Luminal A, no significant decrease in LRR-free (HR 2.38, p = 0.07) or DM-free (HR 2.18, p = 0.06) survival probabilities was observed in AFT patients. However, after 80 months a significant trend toward a lower LRR-free survival probability seems to be observed in AFT patients affected by Luminal A cancers (p = 0.02). Despite this intriguing finding, it should be noted that after 80 months only 145 Luminal A patients were still on follow-up, representing less than one-third of the initial Luminal A population. Therefore, no definitive conclusions on the impact of AFT on the Luminal A subtype may be drawn. There is no previous study which reports this effect of AFT on late LRR in Luminal A cancers, and this could be related to the shorter mean follow-up available in other studies, which could lead to missing late LRR typically associated with Luminal cancers [7]. Kronowitz et al. demonstrated that AFT patients undergoing hormone therapy had a three-fold risk of LRR when compared to controls [16]. The authors suggested that hormone-related pathways could somehow crosstalk with adipose-derived mesenchymal stem cells promoting recurrence, but no clear explanation could be offered. Also Petit described that LRRs significantly increased after AFT in DCIS [26]. Notably, 80% of tumors were estrogen receptor-positive. Therefore, in both Kronowitz and Petit studies, it is not clear whether the different outcome of AFT reported in those patient subsets might be better related to a Luminal-type BMS. Another finding of the present study is the unexpectedly low rate of LRR among lipofilled triple-negative patients (p = 0.07). This data could be explained by the fact that triple-negative breast cancer typically recurs with early events, thus excluding the indication for AFT [31]. Therefore, triple-negative AFT patients were mostly represented by cases with a longer disease-free survival compared to controls.

Study limitations

This study presents some limitations. First, it is not a randomized clinical trial therefore, patients were retrospectively allocated into two groups (AFT vs. no AFT) potentially associated with different LRR and DM risks. Indeed, AFT is often performed on young patients undergoing mastectomy for locally-advanced tumors at presentation, with higher T stages and more frequent axillary involvement [33]. This main difference accounts for the unbalanced distribution of variables observed in Table 1, particularly the overwhelming use of mastectomy in the AFT group, despite the matching of preoperative variables. However, exact matching and subsequent multivariate analysis were performed to properly address these biases. Second, radiotherapy was used differently between groups and loco-regional irradiation was favored slightly in AFT patients. Therefore, radiotherapy's possible role in biasing LRR analysis may remain unclear. Third, the exact matching of AFT and control patients greatly reduced the study population, thus flawing the study's statistical power. In particular, data on the impact of AFT on Luminal A patients after 80 months might not be robust enough to support relevant conclusions.

Conclusions

AFT could be safely proposed in the setting of multi-modal adjuvant treatment. A possible increase in late LRRs for Luminal A patients undergoing AFT cannot be excluded however, further clinical and preclinical data are required to better elucidate this point.

Conflict of interest statement

None declared.

Declarations of interest

None.

Role of the funding source

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.013.

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