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ORIGINAL ARTICLE – BREAST ONCOLOGY

Survival Impact of Locoregional Treatment of the Primary Tumor in De Novo Metastatic Breast Cancers in a Large Multicentric Cohort Study: A Propensity Score-Matched Analysis

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ABSTRACT

Introduction. Improvement in overall survival (OS) by locoregional treatment (LRT) of the primary tumor in de novo metastatic breast cancer (MBC) patients remains controversial.

Objective. The aim of our study was to evaluate the impact of LRT on OS in a large retrospective cohort of de novo MBC patients, with regard to immunohistochemical characteristics and pattern of metastatic dissemination.

Methods. We conducted a mu
lticentric retrospective study of patients diagnosed with de novo MBC selected from the French Epidemiological Strategy and Medical Economics MBC database (NCT03275311) between 2008 and 2014. Overall, 4276 women were included in the study. LRT comprised either radiotherapy, surgery, or both.

Results. LRT was used in 40% of patients. Compared with no LRT, patients who received LRT were younger

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($p < 0.0001$) and were more likely to have only one metastatic site ($p < 0.0001$) or bone-only metastases ($p < 0.0001$). LRT was associated with a significantly better OS based on landmark multivariate analysis at 1-year (hazard ratio 0.65, 95% confidence interval 0.55–0.76, $p < 0.001$). Similar results were observed in all sensitivity analyses, including propensity score matching. In subgroup analysis, LRT was associated with better OS in patients with hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative (61.6 vs. 45.9 months, $p < 0.001$) and HER2-positive tumors (77.2 vs. 52.6 months, $p = 0.008$), but not in triple-negative tumors (19 vs. 18.6 months, $p = 0.54$), and was also associated with a reduction in the risk of death in visceral metastatic patients ($p < 0.001$).

Conclusions. LRT was associated with a significantly better OS in de novo MBC patients, including patients with visceral involvement at diagnosis; however, LRT did not impact OS in triple-negative MBC.

In Western countries, approximately 3–8% of women with primary breast cancer (BC) show synchronous distant metastases at diagnosis (stage IV).[1–5] Stage IV treatment is palliative and aims to prolong survival and maintain quality of life (QoL). These goals are indisputably achieved with systemic therapies that are efficient to control disease burden, especially for human epidermal growth factor receptor 2-positive (HER2+) and hormone receptor-positive (HR+)/HER2-negative (HER2−) BCs.[6–8]

The benefit of locoregional treatment (LRT) with surgery and/or radiotherapy of the primary tumor in patients with de novo metastatic BC (MBC) is controversial and does not represent the standard of care.[9] LRT improves local disease control by slowing down the progression of the breast tumor[10]; however, the impact of LRT on overall survival (OS) is not clear. While some retrospective studies failed to show an improvement of OS,[10–14] other retrospective studies[15–25] and meta-analyses[26,27] suggested that a subset of patients could have a survival benefit. These studies present some limitations as they were mostly conducted before the recent systemic treatments and without the tumor's immunohistochemical (IHC) characteristics. They have disparate design in terms of patient numbers, indications of surgery, timing, and modalities of LRT. Moreover, they are likely biased as most of the patients who received LRT were young, with excellent performance status (PS), and limited metastatic disease, and thus with a better prognosis.[12,14] Only two prospective studies have been published, with contradictory results and different designs.[28,29] In the first study, conducted in India, patients were randomized for LRT after a response to induction systemic therapy. OS was not improved by LRT, regardless of metastatic sites involved or IHC subtype of the primary tumor. However, only 8% of patients with HER2+ MBC received anti-HER2 treatment (a much lower percentage than that received by patients, according to clinical practices), and systemic therapy was suspended following good response. In the second study, patients randomized in the LRT group received LRT before systemic therapy, and the hazard of death was 34% lower in the LRT group ($p = 0.005$).[29]

The UNICANCER Epidemiological Strategy and Medical Economics (ESME) MBC national cohort is a very large and good-quality cohort of MBC patients treated within the national network of 18 French Comprehensive Cancer Centers (FCCCs). The main objective of our study was to evaluate the impact of LRT (defined as surgery, radiotherapy, or both) on OS in women with de novo MBC. Secondary objectives were to evaluate the impact of LRT on OS among the three MBC subcohorts (HER2+, HR+/HER2−, and triple negative [TN]), and according to the pattern of metastatic dissemination.

PATIENTS AND METHODS

Data Source

We conducted a non-interventional, retrospective, comparative study in patients with de novo MBC selected from the ESME MBC database (NCT03275311). Patients had started treatment for MBC from 1 January 2008 to 31 December 2014. The database was authorized by the French data protection authority (authorization no. 1704113), was managed by R&D UNICANCER according to good clinical practice guidelines,[30] and was approved by an independent ethics committee (Comité de Protection des Personnes Sud-Est II 2015-79).

Patient Selection

Patients were considered to have de novo MBC (stage IV) if the diagnosis of metastases occurred within 90 days after the initial BC diagnosis. Of 16,703 MBC patients recorded in the ESME MBC database during the study period, 4507 had distant metastases at diagnosis, and 4276 were included in our study (Fig. 1).

Variables of Interest

Demographic information included age and menopausal status. Primary tumor characteristics included clinical size [$\leq$ 5 cm (T0/Tis/T1/T2) and $>$ 5 cm (T3–T4)] and clinical lymph node involvement (N0 or N-positive [N1/N2/N3]). The following pathology data were collected: (1) tumor

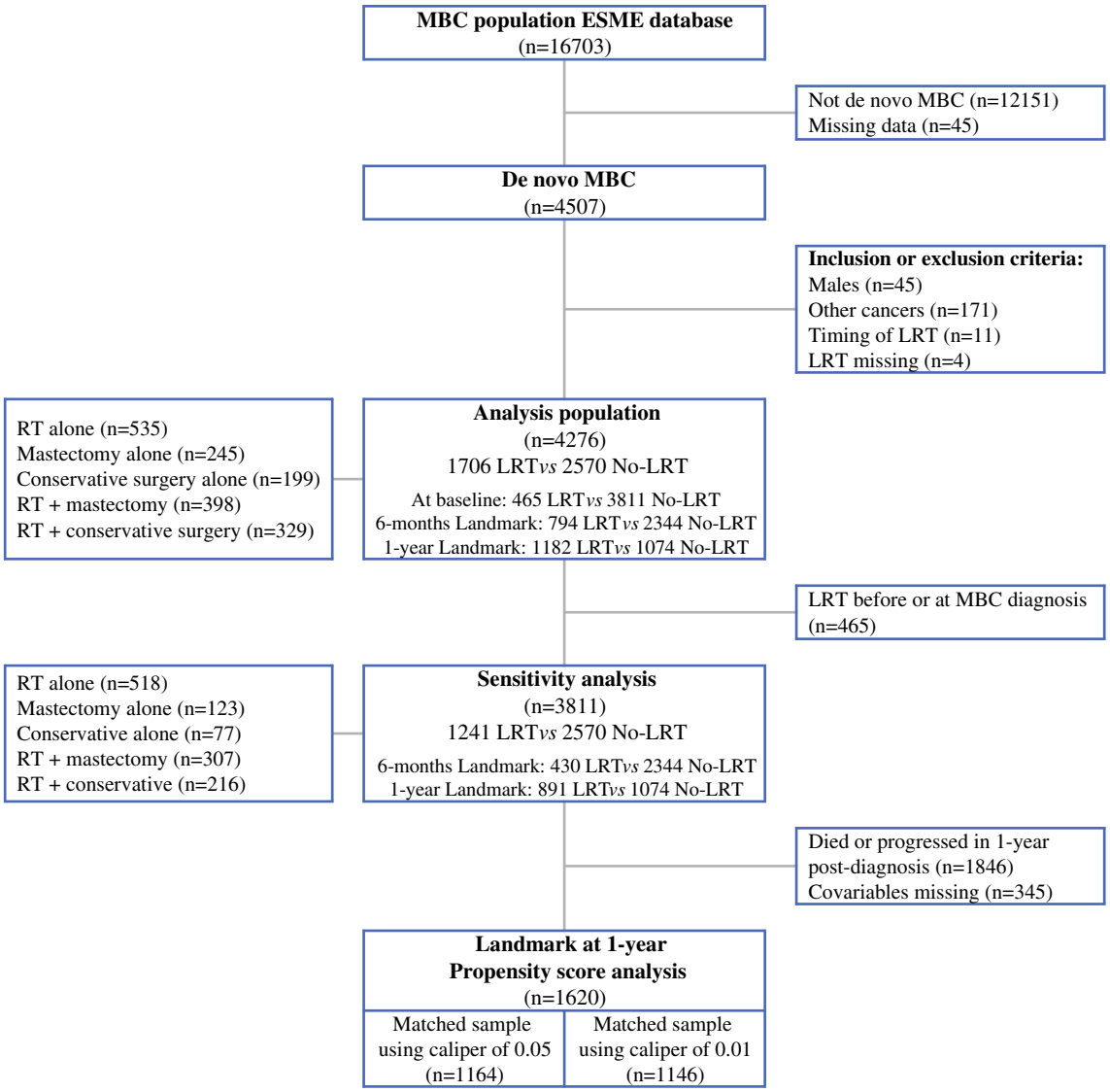

FIG. 1 Study design. *ESME* epidemiological strategy and medical economics, *LRT* locoregional treatment, *MBC* metastatic breast cancer, *n* number of patients, *RT* radiotherapy

grade; (2) estrogen receptors (ERs) and/or progesterone receptors (PRs), categorized as positive (≥ 10% of tumor cells expressed receptors), negative, or missing; (3) HR, categorized as positive if ER and/or PR were positive; and (4) HER2 status, categorized as positive or negative according to American Society of Clinical Oncology (ASCO) guidelines.[31] Regarding metastatic site involvement at diagnosis, three groups were identified: visceral non-central nervous system (CNS), non-visceral (lymph nodes, skin, bone, and pleura), and CNS (brain and/or cerebrospinal fluid) metastases. The number of metastatic organ sites involved at diagnosis was classified as one, two, or more than two. Women with an exclusive bone metastatic disease were studied separately. Patients were categorized as having received or not received LRT, defined as surgery (mastectomy or conservative), radiotherapy, or both. Treatment information included the use of systemic therapy (hormonal, chemotherapy, or targeted therapy).

Statistical Analysis

Continuous variables were presented as median and range (minimum–maximum), and categorical variables were summarized by frequencies and percentages. Comparisons between groups were assessed using the Chi square or Fisher's exact tests for categorical variables, and Kruskal–Wallis test for continuous variables. OS was defined as the time from MBC diagnosis to death from any cause, and was estimated using the Kaplan–Meier method with 95% confidence interval (CI). Patients still alive were censored at the cut-off date (15 January 2016) or at their

last available follow-up. Univariate and multivariate analyses were performed using the log-rank test and Cox proportional hazards model, respectively. To minimize survivor treatment selection bias, Cox model with time-dependent variable and landmark analyses at 6 months and 1 year (excluding patients who died or progressed in the first 6 months and 1 year post-diagnosis) were used to evaluate the effect of LRT on OS. A sensitivity analysis was performed after excluding women who underwent LRT before or at the time of diagnosis of MBC. A propensity score-matching analysis was performed on the sensitivity cohort to account for potential treatment selection bias at the 1-year landmark (more details in the electronic supplementary material). All tests were two-sided, and a p value < 0.05 was considered statistically significant. All analyses were conducted using Stata® version 13 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study Population

Of 4276 patients included in the final analysis, 1706 (40%) received LRT and 2570 (60%) did not. LRT consisted of surgery (26%), radiotherapy (31%), or a combination of both (43%) (Fig. 1). Surgery, either alone or combined, consisted of mastectomy (55%) and conservative surgery (45%). Median time between MBC diagnosis and LRT was 5.7 months (range 3.8–71.4). Patient baseline characteristics are summarized in Table 1. At diagnosis, patients in the LRT group, compared with those in the no-LRT group, were younger ($p < 0.0001$), had fewer metastatic sites ($p < 0.0001$), and were more likely to have non-visceral (52% vs. 36%) or bone-only (34% vs. 27%) metastases. There were no differences in HR status ($p = 0.6376$). Trastuzumab was used in 94% of patients with HER2+ disease, and endocrine therapy in 90% of patients with HR+ disease (as frontline or after). The median duration of frontline treatment was longer in the LRT group compared with the no-LRT group (16.4 vs. 7.8 months; $p < 0.0001$).

Overall Survival and Impact of Locoregional Treatment

The median follow-up was 45.3 months (95% CI 43.8–46.9) and the median OS was 45.2 months (95% CI 43.3–47.1). The OS rate at 5 years was 39% (95% CI 36.58–40.52). As expected, significant survival differences existed between subgroups of patients. Median OS was 19.0 months (95% CI 17.0–21.0) for patients presenting TN status, 47.4 months (95% CI 45.2–50.4) for patients presenting with HR+/HER2− status, and 53.3 months (95% CI 48.9–60.2) for patients presenting with HER2+ status.

Based on univariate analysis, several parameters significantly influenced OS, including age, stage of primitive tumor, histological grade, HR and HER2 status, presence of visceral metastases, and number of sites (electronic supplementary Table 1). LRT was associated with a significantly better OS based on a Cox model with a time-dependent variable (HR 0.51, 95% CI 0.46–0.56, $p < 0.001$). OS was also better according to landmark analysis at 6 months (HR 0.70, 95% CI 0.61–0.80, $p < 0.001$) and 1 year (HR 0.59, 95% CI 0.51–0.68, $p < 0.001$) (Fig. 2a). After adjustment for age, IHC tumor subtype, and number and type of metastatic sites involved, LRT was associated with a reduction in the risk of death (landmark multivariate analysis: HR 0.76, 95% CI 0.66–0.88, $p < 0.001$ at 6 months; HR 0.65, 95% CI 0.55–0.76, $p < 0.001$ at 1 year) (Fig. 2a and Table 2).

To prevent selection bias, patients who underwent LRT with curative intent before or at the time of diagnosis of MBC were excluded from the sensitivity analysis [465/4276 patients (11%)] (Fig. 1). LRT remained associated with OS (landmark multivariate analysis: HR 0.73, 95% CI 0.60–0.89, $p = 0.002$ at 6 months; HR 0.65, 95% CI 0.54–0.78, $p < 0.001$ at 1 year) (Fig. 2b and Table 2). Similar results were observed in all sensitivity analyses, including using a propensity score matching (caliper of 0.05: HR 0.60, 95% CI 0.49–0.74, $p < 0.001$) (electronic supplementary Fig. 1).

Subgroup Analyses

We then evaluated the effect of LRT in subgroups of patients classified by IHC subtypes, number and type of metastatic sites involved, and bone-only metastases. We performed these analyses at baseline and at the 1-year landmark, in both the overall and sensitivity cohorts (Table 3). Pattern of metastatic dissemination according to IHC subtype of the primitive tumor is presented in electronic supplementary Table 2. Regarding IHC characteristics, LRT did not improve OS in patients with TN tumor at baseline ($p = 0.54$) and at the 1-year landmark ($p = 0.38$). However, LRT was associated with better OS in patients with HR+/HER2− (up to 16 months, $p < 0.001$) and HER2+ tumors (up to 25 months, $p = 0.008$) (Table 3, electronic supplementary Fig. 2). LRT was also associated with a reduction in the risk of death in isolated bone metastatic patients ($p < .001$) and in visceral metastatic patients without CNS involvement ($p < 0.001$). Multi-metastatic disease (more than two sites involved) was not associated with better OS at baseline with LRT ($p = 0.15$), but was significant among patients with more than 1-year survival (43.9 vs. 63 months, $p = 0.006$). Results were similar in the sensitivity analysis (Table 3).

TABLE 1 Patient and tumor baseline characteristics in the entire cohort of de novo MBC patients

	All patients with de novo MBC	LRT group	No-LRT group	*p* value
No. of patients	4276 (100)	1706 (60)	2570 (40)	
Age at diagnosis, years [median (range)]	60 (19–97)	57 (19–94)	61 (23–97)	< 0.0001
Age at diagnosis, years				< 0.0001
< 50	1110 (26)	561 (32.9)	549 (21.4)	
50–70	2135 (49.9)	844 (49.5)	1291(50.2)	
> 70	1031 (24.1)	301 (17.6)	730 (28.4)	
Menopausal status				< 0.0001
No	1390 (32.5)	653 (38.3)	737 (28.7)	
Yes	2885 (67.5)	1052 (61.7)	1833 (71.3)	
NA	1	1	0	
Clinical tumor size, cm				< 0.0001
< 5	650 (32.5)	361 (39.6)	289 (26.5)	
≥ 5	1352 (67.5)	550 (60.4)	802 (73.5)	
Missing	2274	795	1479	
Clinical nodal status				0.0009
N0	432 (23.8)	232 (27.3)	200 (20.7)	
N+	1384 (76.2)	617 (72.7)	767 (79.3)	
Missing	2460	857	1603	
Tumor histological grade				< 0.0001
I	265 (7.1)	89 (5.8)	176 (8.1)	
II	2016 (54.4)	767 (50.3)	1249 (57.2)	
III	1428 (38.5)	669 (43.9)	759 (34.8)	
Missing	567	181	386	
HR status				0.6376
Positive	2991 (76.9)	1166 (77.3)	1825 (76.6)	
Negative	900 (23.1)	343 (22.7)	557 (23.4)	
Missing	385	197	188	
HER2 status				0.0388
Positive	918 (24.1)	387 (25.9)	531 (22.9)	
Negative	2893 (75.9)	1109 (74.1)	1784 (77.1)	
Missing	465	210	255	
IHC tumor classification				0.0447
TN	495 (13.1)	178 (12.1)	317 (13.8)	
HR+/HER2−	2356 (62.5)	903 (61.5)	1453 (63.1)	
HER2+	918 (24.4)	387 (26.4)	531 (23.1)	
Missing	507	238	269	
No. of metastatic sites				< 0.0001
1	2174 (50.8)	1084 (63.5)	1090 (42.4)	
2	1134 (26.5)	390 (22.9)	744 (28.9)	
> 2	968 (22.6)	232 (13.6)	736 (28.6)	
Bone-only metastases				< 0.0001
No	2999 (70.2)	1122 (65.8)	1877 (73.1)	
Yes	1276 (29.8)	584 (34.2)	692 (26.9)	
Missing	1	0	1	
Pattern of metastatic disease				< 0.0001
CNS	194 (4.5)	26 (1.5)	168 (6.5)	
Visceral non-CNS	2252 (52.7)	788 (46.2)	1464 (57)	
Non-visceral	1830 (42.8)	892 (52.3)	938 (36.5)	

TABLE 1 continued

	All patients with de novo MBC	LRT group	No-LRT group	*p* value
Hormonal therapy first-line				< 0.0001
No	1725 (40.3)	525 (30.8)	1200 (46.7)	
Yes	2551 (59.7)	1181 (69.2)	1370 (53.3)	
Chemotherapy, targeted therapy, or immunotherapy first-line				< 0.0001
No	1067 (25)	280 (16.4)	787 (30.6)	
Yes	3209 (75)	1426 (83.6)	1783 (69.4)	
Duration first-line, months [median (range)]	10.8 (1.1–95.0)	16.4 (1.2–95.0)	7.8 (1.1–89.0)	< 0.0001
Median time [months] between diagnosis and first systemic treatment (range)	0.7 (0–63.2)	0.6 (0–25.6)	0.7 (0–63.2)	0.3701

Data are expressed as *n* (%) unless otherwise specified

CNS central nervous system, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *IHC* immunohistochemical, *LRT* locoregional treatment, *MBC* metastatic breast cancer, *n* number of patients, *NA* not available, *TN* triple negative

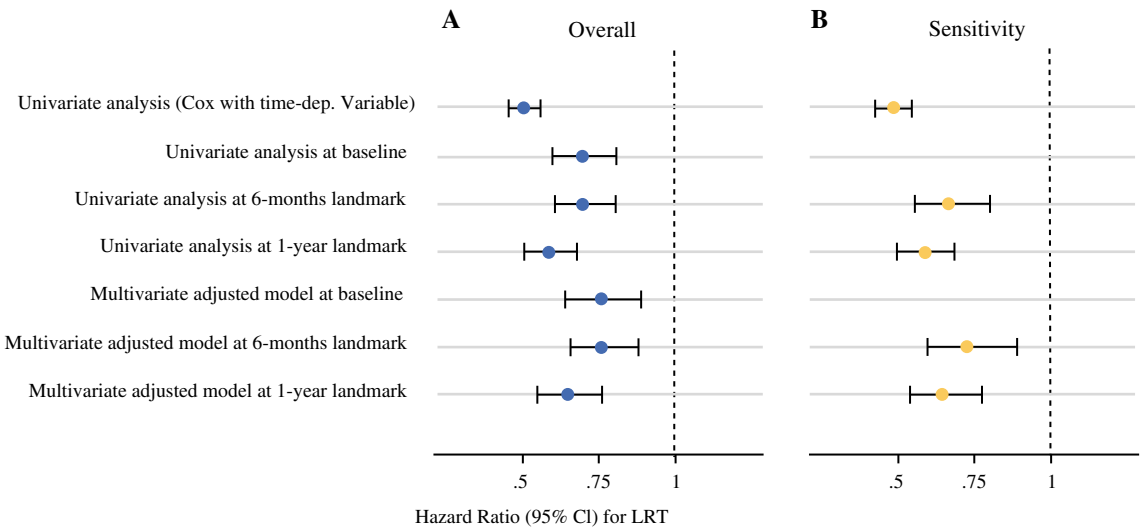

FIG. 2 Forest plot of univariate and multivariate OS analysis for LRT: summary of hazard ratios in the **a** overall and **b** sensitivity cohorts. Multivariate analysis adjusted for age at diagnosis, IHC subtype, and number and type of metastatic sites. *CI* confidence interval, *IHC* immunohistochemical, *LRT* locoregional treatment, *OS* overall survival, *time-dep.* time-dependent

DISCUSSION

The present study demonstrated that LRT was associated with a significant 35% reduction in the risk of death (95% CI 0.54–0.78) in de novo MBC patients with a controlled systemic disease for at least 1 year, based on robust statistical analysis, including propensity score, which controlled for several variables associated with the receipt of LRT. ESME MBC represents a very wide multicenter cohort, representative of current diagnostic and therapeutic management of patients in FCCCs. Similar to other published data,[15–17,20] patients who underwent LRT in our cohort were younger, and presented a less important tumor burden and less aggressive metastatic disease. Selection bias can be a major confounding factor in such retrospective studies; thus, we undertook extensive statistical analysis to limit the many biases. Indeed, LRT remained associated with improved OS after adjustment for confounding factors (hazard ratio 0.76, $p = 0.001$). In sensitivity analysis, patients who underwent LRT before diagnosis of metastatic spread (probably in a curative attempt) were excluded because the surgical decision could have been made with a curative objective and patients were more likely to have lower metastatic burdens than those diagnosed with metastases preoperatively. To avoid another major bias, we excluded patients who died (13% of patients) or progressed under systemic treatment in the first year because they were more likely to have not received

TABLE 2 Multivariate analysis of LRT adjusted for prognostic factors for OS in the overall and sensitivity cohorts, at baseline and 1-year landmark

Characteristics	Overall cohort		Sensitivity cohort
	Multivariate analysis at baseline (n = 3769)	Multivariate analysis at 1-year landmark (n = 1995)	Multivariate analysis at 1-year landmark (n = 1756)
LRT (yes vs. no)	0.76 (0.64–0.89); 0.001	0.65 (0.55–0.76); 0.001	0.65 (0.54–0.78); < 0.001
Age at diagnosis, years			
< 50	1	1	1
50–70	1.38 (1.23–1.56); < 0.001	1.42 (1.15–1.74); 0.001	1.44 (1.16–1.79); 0.001
> 70	2.05 (1.80–2.35); < 0.001	2.08 (1.66–2.60); < 0.001	2.02 (1.58–2.57); < 0.001
IHC subtype			
TN	1	1	1
HR+/HER2−	0.36 (0.32–0.41); < 0.001	0.51 (0.39–0.68); < 0.001	0.55 (0.40–0.75); < 0.001
HER2+	0.29 (0.25–0.34); < 0.001	0.38 (0.28–0.52); < 0.001	0.41 (0.29–0.58); < 0.001
No. of metastatic sites			
(> 2 vs. ≤ 2)	1.58 (1.40–1.78); < 0.001	1.41 (1.14–1.75); 0.002	1.42 (1.13–1.77); 0.002
Type of metastatic sites			
CNS	1	1	1
Visceral non-CNS	0.54 (0.44–0.65); < 0.001	0.59 (0.38–0.94); 0.026	0.61 (0.38–0.96); 0.034
Non-visceral	0.40 (0.32–0.50); < 0.001	0.50 (0.31–0.80); 0.004	0.50 (0.31–0.82); 0.006

Data are expressed as HR (95% CI); p value

CI confidence interval, *CNS* central nervous system, *HER2* human epidermal growth factor receptor 2, *HR* hazard ratio, *HR+* hormone receptor-positive, *IHC* immunohistochemical, *LRT* locoregional treatment, *n* number of patients, *TN* triple negative

LRT. In all sensitivity analyses, including propensity score matching, women who received LRT were still 35% less likely to die than women who did not (hazard ratio 0.60–0.65, p < 0.001).

Previous large population-based studies found a significant association between LRT and improved OS (hazard ratio 0.46–0.63).[3,15,17,20,21,25] However, most studies were conducted before the use of new systemic treatments and missed critical information on IHC subtype, which is currently a major part of the treatment decision. One recent population-based study showed that survival benefits of local surgery were not affected by IHC, but the median follow-up was only 13 months.[25] The recently published prospective study demonstrated, in unplanned subgroup analyses, that patients with HR+or HER2− primary tumor had a significant survival benefit with initial LRT; however, TN patients did not experience any improvement in survival with LRT (17.5 vs. 18 months).[29]

The strengths of our study were the availability of the IHC tumor subtype, associated with the pattern of metastatic dissemination and metastatic burden. Patients in the FCCCs received modern systemic treatment, adapted to the IHC profile of each tumor. Regarding the IHC characteristics, LRT was not associated with better OS in TN tumor at both baseline (p = 0.54) and the 1-year landmark (p = 0.38). In relation to metastatic burden, baseline analysis showed that there was no survival benefit associated with LRT in patients with more than two metastatic sites involved (p = 0.15), whereas it became significant in those who had a controlled disease with more than 1-year survival (p = 0.006). Furthermore, the difference associated with LRT increased in patients with only one site involved (p < 0.001). This highlights the fact that only patients with controlled systemic disease derived benefit from LRT.

In our series, as expected,[32] patients with HER2+ or TN tumors presented more visceral involvement and polymetastatic disease, whereas HR+/HER2− tumors presented more bone-only metastases. Some authors previously found a benefit of LRT in women with bone-only metastases, a subset that can have a more indolent course.[16] Our analysis demonstrated that LRT was not only associated with OS benefit exclusively in patients with isolated bone metastases (62 vs. 70.4 months, p < 0.001), but also in patients with visceral lesions (52.7 vs. 83 months, p < 0.001).

There were several limitations in our study. First, retrospective, large database studies can lead to errors in recording data and failure to collect some information. We did not have details regarding surgical margins and radiotherapy modalities (doses and fields). Patients treated with radiotherapy alone may have received a suboptimal LRT; however, the optimal LRT for metastatic disease is unknown, and the use of RT alone for the primary site demonstrated a similar magnitude of survival benefit in

TABLE 3 Subgroup univariate analysis in the overall and sensitivity cohorts to assess the LRT effect on OS

Subgroup	Overall cohort (n = 4276)		Sensitivity cohort (n = 3811)
	At baseline	1-year landmark	1-year landmark
IHC subtypes			
TN	19 vs. 18.6; 0.540	33.7 vs. 48.7; 0.382	33.7 vs. 44.4; 0.301
HR+/HER2−	45.9 vs. 61.6; < 0.001	52.9 vs. 76.1; < 0.001	52.9 vs. 76.1; < 0.001
HER2+	52.6 vs. 77.2; 0.008	56.3 vs. NR; < 0.001	56.3 vs. 87.4; 0.001
No. of metastatic sites			
1	55.7 vs. 61.7; 0.087	61.3 vs. 92; < 0.001	61.3 vs. 81.9; < 0.001
> 2	30.4 vs. 32.6; 0.150	43.9 vs. 63; 0.006	43.9 vs. 59.9; 0.023
Type of metastatic site			
Non-visceral	53.7 vs. 70.2; 0.005	61.2 vs. 76.1; < 0.001	61.2 vs. 76.1; < 0.001
Visceral non-CNS	38.4 vs. 47.2; 0.003	52.7 vs. 83; < 0.001	52.7 vs. 83; < 0.001
Bone-only metastases			
Yes	56.5 vs. 75.8; 0.002	62 vs. 76.3; < 0.001	62 vs. 70.4; < 0.001
No	39.1 vs. 48.2; 0.004	50.4 vs. 79.7; < 0.001	50.4 vs. 83; < 0.001

Data are expressed as no-LRT vs. LRT median OS (months); p value

CNS central nervous system, *HER2* human epidermal growth factor receptor 2, *HR+* hormone receptor-positive, *IHC* immunohistochemical, *LRT* locoregional treatment, *OS* overall survival, *TN* triple negative

retrospective studies.[22,33] Moreover, available data did not include PS, a key factor for OS. Thus, the observed differences in OS between groups might just reflect a higher PS and a lower level of comorbidity in the LRT group. Second, the average duration of first-line systemic treatment was two times higher in the LRT group (16.4 vs. 7.8 months), thus we cannot exclude the bias that only patients who responded well to the first systemic treatment were proposed LRT. Third, we could not separate scenarios on how an MBC patient presented at diagnosis. It could be asymptomatic metastases detected by screening tests, a large neglected primary tumor with symptomatic metastases, or an aggressive locoregional disease with only skin nodules on the chest wall. Median OS was 45.2 months (95% CI 43.3–47.1), which is longer than that mentioned in the latest retrospectives studies of de novo MBC patients,[4,5,25] and could be due to new therapeutic agents such as anti-HER2 monoclonal antibodies and new multidisciplinary strategies. We did not have information on the number of lesions per site, and therefore could not individualize oligometastatic disease. Women with oligometastatic disease had a survival benefit with aggressive multimodal therapy,[34,35] and this prolonged median OS can reflect multimodal therapy practices carried out in the FCCCs.

CONCLUSIONS

Findings from this study show that the number and type of metastatic sites involved should not be considered as restrictive factors in the therapeutic decision for LRT, provided that systemic treatment controls the disease. Indeed, contrary to other subtypes, TN patients have little benefit from new therapeutic advances, and, as demonstrated in this study, no association between better OS and LRT. Only a prospective randomized trial that proposes LRT in a subgroup of patients having controlled metastatic disease during the first-line of systemic treatment could definitely address this question. Results are awaited from two prospective randomized trials (JCOG1017 and ECOG NCT01242800). Patients without progression after induction systemic therapy were randomized to undergo LRT or continue systemic therapy.

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AUTHOR'S CONTRIBUTION TF and AL analyzed the data. All authors (ESME investigators: YK, MC, JG, CM, AM, DP, NM, NF, AC, AG, CJ, TDLMR, NP, BDLL, DMB, JMF, LU, JCE, MAMR, TP, MR, CC, EPT and FD) contributed to the interpretation of the results, helped to revise the manuscript, and approved the final version submitted for publication. CC is the Head of Research and Development, R&D UNICANCER, and MR is the Program Director, Biostatistics Unit, Curie Institute, PSL Research University. EPT and FD drafted the manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST Elvire Pons-Tostivint, Youlia Kirova, Amélie Lusque, Mario Campone, Julien Geffrelot, Chafika Mazouni, Audrey Mailliez, David Pasquier, Nicolas Madranges, Nelly Firmin, Agathe Crouzet, Anthony Gonçalves, Clémentine Jankowski, Thibault De La Motte Rouge, Nicolas Pouget, Brigitte de

La Lande, Delphine Mouttet-Boizat, Jean-Marc Ferrero, Lionel Uwer, Jean-Christophe Eymard, Marie-Ange Mouret-Reynier, Thierry Petit, Mathieu Robain, Thomas Filleron, Christian Cailliot, and Florence Dalenc declare that they have no conflicts of interest to disclose.

ETHICS APPROVAL The present analysis was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est II-2015-79). No formal dedicated informed consent was required but all patients had approved the re-use of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorized by the French data protection authority (authorization no. 1704113).

AVAILABILITY OF DATA AND MATERIALS Source data (ESME MBC data platform, NCT03275311) are held by UNICANCER on behalf of the 18 FCCCs and are not publicly archived. UNICANCER has established a transfer agreement and use licence with the Biostatistic Center, Institut Claudius Regaud, Toulouse, for this study. The study-specific datasets are archived at the Institut Claudius Regaud, Toulouse.

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