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EPIDEMIOLOGY

Surgery of the primary tumor in patients with *de novo* metastatic breast cancer: a nationwide population-based retrospective cohort study in Belgium

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Abstract

Purpose We aimed to assess the impact of surgery of primary tumor in overall survival (OS) of women with *de novo* metastatic breast cancer.

Methods Nationwide, population-based retrospective cohort study of women diagnosed with *de novo* metastatic breast cancer in Belgium, between Jan/2010-Dec/2014. Data was obtained from the Belgian Cancer Registry and administrative databases. "Surgery" group was defined by surgery of primary tumor up to nine months after diagnosis. We excluded women who did not receive systemic treatment or did not complete nine months follow-up after diagnosis. All the subsequent analyses reporting on overall survival and the stratified outcome analyses were performed based on this nine-month landmark cohort. OS was estimated using Kaplan-Meier method and compared using adjusted Cox proportional hazards models controlling for confounders with 95% confidence intervals (CI). We performed a stratified analysis according to surgery timing and a propensity score matching analysis.

Results 1985 patients, 534 (26.9%) in the "Surgery" and 1451 (73.1%) in the "No Surgery" group. Patients undergoing surgery were younger ($p < 0.001$), had better performance status (PS) ($p < 0.001$), and higher proportion of HER2-positive and triple-negative breast cancer ($p = 0.012$). Median follow-up was 86.0 months (82.6–88.5). Median OS was 60.1 months (57.1–68.2) in the "Surgery" vs. 41.9 months (39.8–44.2) in the "No Surgery" group (adjusted HR 0.56; 0.49–0.64). OS was similar when surgery was performed upfront or after systemic treatment. Propensity score matching analysis confirmed the same findings.

Conclusion Among patients receiving systemic treatment for *de novo* metastatic breast cancer and surviving nine months or more, those who received surgery of the primary tumor within nine months of diagnosis have longer subsequent survival than those who did not.

Keywords Breast neoplasms · Surgery · Survival analysis · Registries

Abbreviations

CI	Confidence interval
HER2	Human Epidermal growth factor Receptor type 2
HR	Hazard ratio
ER	Estrogen receptor
ECOG	Eastern Cooperative Oncology Group
OS	Overall survival
PS	Performance status
TNBC	Triple-negative breast cancer

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Introduction

In Western countries, about 5–10% of patients with breast cancer present with distant metastases at diagnosis [1, 2]. *De novo* metastatic breast cancer is considered an incurable disease and patients are usually treated with systemic therapy aiming to prolong survival and maintain quality of life (QoL). The role of surgery of the primary tumor remains highly debatable in this setting [3].

Historically, surgical resection of the primary tumor in women with metastatic breast cancer has been reserved to relieve symptoms such as pain, bleeding, or infection of the primary tumor. Although there are multiple retrospective cohort studies suggesting a survival benefit from this intervention among women with *de novo* metastatic breast cancer, prospective trials did not confirm this survival benefit. Three meta-analyses of retrospective studies have been performed, pooling data published until 2016, and all of them suggest a survival benefit from surgery of primary breast cancer [4–6]. Some subgroups of patients might have more benefit from this intervention, such as those exposed to systemic therapies and/or radiotherapy [4], or those with smaller tumors, less comorbidities, and/or lower metastatic disease burden [5]. These meta-analyses also suggest that patients with estrogen receptor (ER)-positive tumors derive less benefit from this surgery [4, 6]. Since 2005, five randomized clinical trials were performed to investigate the role of surgery of the primary tumor in patients with *de novo* metastatic breast cancer [7–11], but only the one with longer follow-up (10 years) confirmed overall survival (OS) benefit [12]. Three meta-analyses pooling data from prospective studies failed to demonstrate a benefit of this intervention [6, 13, 14].

International consensus guidelines suggest considering locoregional treatments only in highly selected patients with low disease burden, aiming to improve QoL, and always taking into account patient's preferences [15]. New endocrine therapies and agents targeting human epidermal growth factor receptor type 2 (HER2) for advanced breast cancer led to an improvement in OS of patients with *de novo* metastatic breast cancer [16]. In this context, whether it is beneficial or not to locally treat the primary tumor becomes a current and sensitive topic with a rising number of large case series published during the last years [17–25].

Considering all the real-world data limitations, cancer registries are instrumental to address such questions. The Belgian Cancer Registry contains population-based data from all patients with cancer, diagnosed and treated in all Belgian hospitals. Using this database, we aimed to estimate OS of patients with *de novo* metastatic breast cancer who underwent surgery of the primary tumor within the first nine months after diagnosis compared to those who did not.

Methods

Study design and setting

This is a nationwide, population-based retrospective cohort study of women diagnosed with *de novo* metastatic breast cancer in Belgium. The manuscript was prepared according to the RECORD reporting guidelines [26].

Participants

We included women diagnosed with *de novo* metastatic breast cancer in Belgium, between January/2010-December/2014. We defined a nine-month landmark method to control immortal time bias [27, 28], excluding all patients who did not receive systemic treatment and those who died or were lost to follow-up less than nine months after the diagnosis. All the subsequent analyses reporting on overall survival and the stratified outcome analyses were performed based on this nine-month landmark cohort. Women were categorized in two groups according to their surgery status at the landmark time point: "Surgery" group, including those who underwent surgery of the primary tumor within one month before and up to nine months after the date of diagnosis of *de novo* metastatic breast cancer, and "No Surgery" group, for those who did not undergo surgery of the primary tumor within the same period. The definition of this timeframe for the surgical procedure of the primary tumor with curative intent was based on expert opinion as well as data driven as previously reported [29]. Nine months were considered as the time needed for evaluation of disease response to systemic treatment followed by subsequent planning and conduction of a surgical intervention. It also allows to minimize misclassification bias with surgical interventions aiming to relieve symptoms of progressing primary tumors, typically occurring later in disease course.

Study outcome

OS was defined as the time from diagnosis of *de novo* metastatic breast cancer to death from any cause. This definition is applicable to all the survival analyses performed.

Data sources

Participants were identified from the Belgian Cancer Registry database, which covers the entire country from 2004 onwards. Data on baseline characteristics, received treatment, and survival were obtained from the Belgian Cancer Registry database, insurances databases via the Intermutualistic Agency, and the Crossroads Bank for Social Security. The patient's unique national number was used to link

the databases, as approved by the former Belgian Privacy Commission [30, 31]. Data regarding breast cancer immunohistochemistry was available only for patients diagnosed in 2014. We used surrogate treatment data to classify the patients diagnosed between 2010 and 2013 into the following immunohistochemistry subtypes: (i) ER-positive/HER2-negative: patients who received endocrine therapy (e.g. tamoxifen or aromatase inhibitors) within two years from diagnosis and no trastuzumab; (ii) HER2-positive: women who received trastuzumab within two years from diagnosis, regardless of the ER status; (iii) triple-negative (TNBC): patients who did not receive either endocrine therapy or trastuzumab within 2 years from diagnosis, but received chemotherapy.

Statistical analysis

Baseline characteristics were compared between patients excluded vs. included in the landmark analysis, and among those included between "Surgery" vs. "No Surgery" groups, using Fischer exact and Chi-square tests for categorical variables. All the survival analyses were performed with data from patients included in the landmark analysis. OS was estimated using the Kaplan-Meier method and we used Cox proportional hazards models to compute adjusted hazard ratio (HR) with 95% confidence intervals (CI). Multivariate analyses included potential confounders identified on univariate analyses (age and ECOG performance status [PS] at diagnosis, tumor immunohistochemistry subtype, clinical T-category, and histological grade). For survival analyses, patients without reported death were censored on the date of their last follow-up examination or at the cut-off date (1/April/2020).

A stratified analysis according to the timing of the surgery as upfront treatment, before any systemic therapy ("Upfront Surgery"), or after receiving systemic therapy ("Late Surgery") vs. the "No Surgery" group was performed. Additionally, we conducted a propensity score matching analysis to account for potential treatment selection bias at the nine-month landmark. The propensity score was built with the available variables identified as clinically relevant determinants of surgical decision (age and ECOG PS at diagnosis, tumor immunohistochemistry subtype, histological grade, and clinical nodal status) with optimal matching method and a caliper of 0.20. All tests were two-sided and p-values < 0.05 were considered statistically significant. Analyses were carried out in SAS version 7.1.

Results

Patient characteristics

We identified 2627 women diagnosed with *de novo* metastatic breast cancer between 2010 and 2014, of which 228 did not receive systemic therapy (Fig. 1). Untreated patients were older and had worse ECOG PS at diagnosis ($p < 0.0001$) (Supplementary Table 1). Among patients receiving systemic therapy, 414 (17%) died or were lost to follow-up less than nine months after diagnosis. These women were older, had worse ECOG PS, and presented more frequently with TNBC ($p < 0.0001$) (Supplementary Table 2).

We included a total of 1985 patients in the nine-month landmark analysis, 534 (26.9%) in the "Surgery" and 1451 (73.1%) in the "No Surgery" group. Patients undergoing surgery were younger (median age: 61 vs. 67 years-old, $p < 0.001$), had better ECOG PS (PS 0: 39.4% vs. 25.6%, $p < 0.001$), with higher proportion of HER2-positive and TNBC subtypes ($p = 0.012$). The "Surgery" group had higher likelihood of receiving chemotherapy (+/- trastuzumab) as first-line systemic therapy (61.4% vs. 39.2%, $p < 0.001$) and any type of radiotherapy (65.7% vs. 29.6%, $p < 0.001$) throughout their clinical course. The patterns of treatment were different across regions, with higher proportion of patients treated in Brussels and Wallonia in the "Surgery" group ($p < 0.001$). There was a decrease in the proportion of patients undergoing surgery over time ($p = 0.008$) (Table 1).

Overall survival analysis

The median follow-up of patients alive at the date of censoring was 86.0 months (95% CI, 82.6–88.5). Median OS was 60.1 months (95% CI, 57.1–68.2) in the "Surgery" group vs. 41.9 months (95% CI, 39.8–44.2) in the "No Surgery" group (adjusted HR 0.56; 95% CI 0.49–0.64). Overall five-year survival rate was 50.1% (95% CI, 45.9-54.4%) in the "Surgery" group vs. 32.4% (95% CI, 30.0-34.8%) in the "No Surgery" group (Fig. 2a).

Absolute survival differences were larger in patients with ECOG PS 0 (73.7 vs. 47.5 months; HR 0.58, 95% CI 0.45–0.74) (data not shown), ER-positive/HER2-negative (62.4 vs. 42.6 months; HR 0.58, 95% CI 0.49–0.76) or HER2-positive (72.4 vs. 51.4 months; HR 0.69, 95% CI 0.50–0.95) breast cancer subtypes (Fig. 2b and c). Despite smaller absolute difference, the relative survival superiority in the "Surgery" group was larger in patients with TNBC (21.6 vs. 18.5 months; HR 0.37, 95% CI 0.23–0.60) (Fig. 2d). Surgery was associated with statistically significant OS improvement across almost all subgroups (Fig. 3).

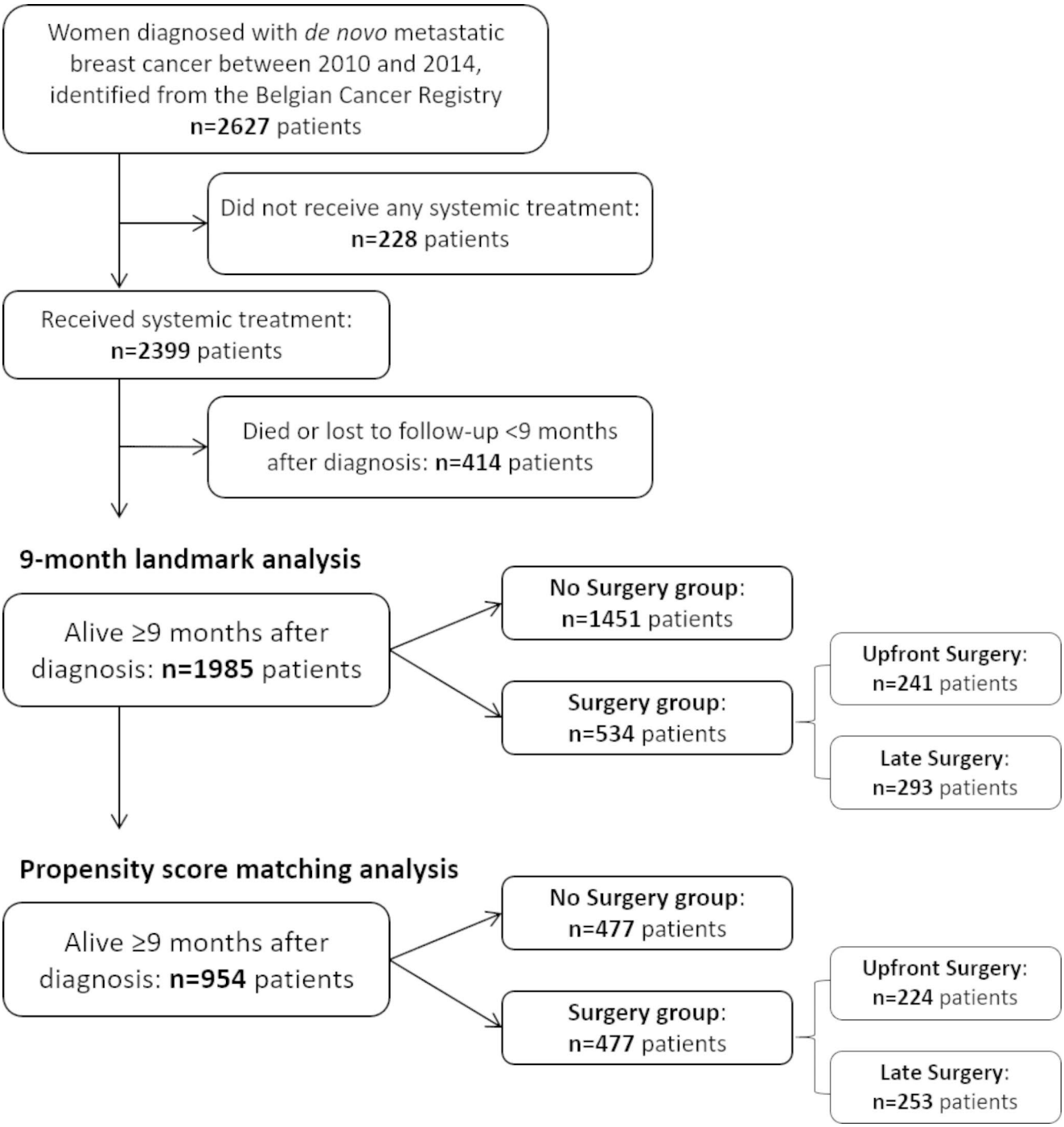

Fig. 1 Patient Flowchart

Stratified analysis

Within women undergoing surgery of the primary tumor (n = 534), 241 (45.1%) received it as upfront therapy, while 293 (54.9%) were operated after receiving systemic therapy. There were no differences in terms of age, distribution of immunohistochemistry and histological subtypes, or type of first-line systemic therapy received between patients in "Upfront Surgery" vs. "No Surgery" groups (Supplementary Table 3). On the other hand, women from "Late Surgery" group were younger ($p < 0.0001$), with higher proportion of HER2-positive and TNBC subtypes ($p < 0.0001$), of ductal histology ($p = 0.0072$), and received more often chemotherapy as first-line treatment ($p < 0.0001$). Women in both surgery groups had better ECOG PS, lower locoregional staging, and higher histological grade compared to

Table 1 Baseline clinicopathological and treatment characteristics of patients in the "No Surgery" vs. "Surgery" groups (nine-month landmark cohort, N = 1985)

	No Surgery (n = 1451), n (%)	Surgery (n = 534), n (%)	p value
Age at diagnosis (in years)			
<50	219 (15.1)	119 (22.3)	**< 0.001**
50–59	248 (17.1)	121 (22.7)	
60–69	328 (22.6)	126 (23.6)	
≥70	656 (45.2)	168 (31.5)	
Clinical T category			
T0	1 (0.1)	0	0.245
T1	170 (13.2)	73 (13.9)	
T2	474 (36.7)	199 (37.9)	
T3	186 (14.4)	91 (17.3)	
T4	462 (35.7)	162 (30.9)	
Missing	*158*	*9*	
Clinical N category			
N0	308 (25.1)	144 (28.2)	**0.047**
N1	623 (50.8)	253 (49.5)	
N2	143 (11.7)	71 (13.9)	
N3	152 (12.4)	43 (8.4)	
Missing	*225*	*23*	
Histological grade			
Grade 1	90 (7.4)	21 (4.2)	**< 0.001**
Grade 2	634 (52.2)	213 (42.6)	
Grade 3	491 (40.4)	266 (53.2)	
Missing	*236*	*34*	
ECOG PS at diagnosis			
0	345 (25.6)	197 (39.4)	**< 0.001**
1	877 (65.0)	272 (54.4)	
2	91 (6.8)	24 (4.8)	
3	25 (1.9)	6 (1.2)	
4	11 (0.8)	1 (0.2)	
Missing	*102*	*34*	
Tumor immunohistochemistry subtype			
ER-positive/HER2-negative	1066 (73.5)	357 (66.9)	**0.012**
HER2-positive	289 (19.9)	128 (24.0)	
TNBC	96 (6.6)	49 (9.2)	
Histology			
Ductal	1076 (74.2)	417 (78.1)	0.152
Lobular	242 (16.7)	71 (13.3)	
Others[1]	133 (9.2)	46 (8.6)	
Region of treatment			
Brussels	115 (7.9)	111 (20.8)	**< 0.001**
Flanders	1022 (70.4)	259 (48.5)	
Wallonia	314 (21.6)	164 (30.7)	
Year of diagnosis			
2010	256 (17.6)	118 (22.1)	**0.008**
2011	290 (20.0)	124 (23.2)	
2012	293 (20.2)	112 (21.0)	
2013	296 (20.4)	93 (17.4)	
2014	316 (21.8)	87 (16.3)	
Type of breast cancer center			
< 125 new cases/year	284 (19.6)	106 (19.9)	0.890
≥ 125 new cases/year	1167 (80.4)	428 (80.2)	
Type of systemic first-line therapy			
Chemotherapy	342 (23.6)	237 (44.4)	**< 0.001**

Table 1 (continued)

	No Surgery (n = 1451), n (%)	Surgery (n = 534), n (%)	p value
Chemotherapy + trastuzumab	226 (15.6)	91 (17.0)	
Endocrine therapy	835 (57.6)	198 (37.1)	
Endocrine therapy + trastuzumab	46 (3.2)	8 (1.5)	
Trastuzumab only	2 (0.1)	0	
Systemic therapy received (ever)			
Chemotherapy – yes	866 (59.7)	401 (75.1)	**< 0.001**
Trastuzumab – yes	274 (18.9)	124 (23.2)	**0.032**
Endocrine therapy – yes	1224 (84.4)	443 (83.0)	0.452
Radiotherapy (any site) – yes	430 (29.6)	351 (65.7)	**< 0.001**
Type of surgery			
Breast conservative surgery	NA	157 (29.4)	NA
Mastectomy	NA	377 (70.6)	
Timing of breast surgery (days after diagnosis)			
<90	NA	252 (47.2)	NA
90–179	NA	123 (23.0)	
≥180	NA	159 (29.8)	

[1] Other histological subtypes include apocrine, clear cell, epithelial, metaplastic, micropapillary, mixed ductal/lobular, mixed ductal/other types, mucinous, Paget's disease, papillary and small cell breast carcinoma

ER: estrogen receptor; NA: not applicable; PS: performance status; TNBC: triple-negative breast cancer

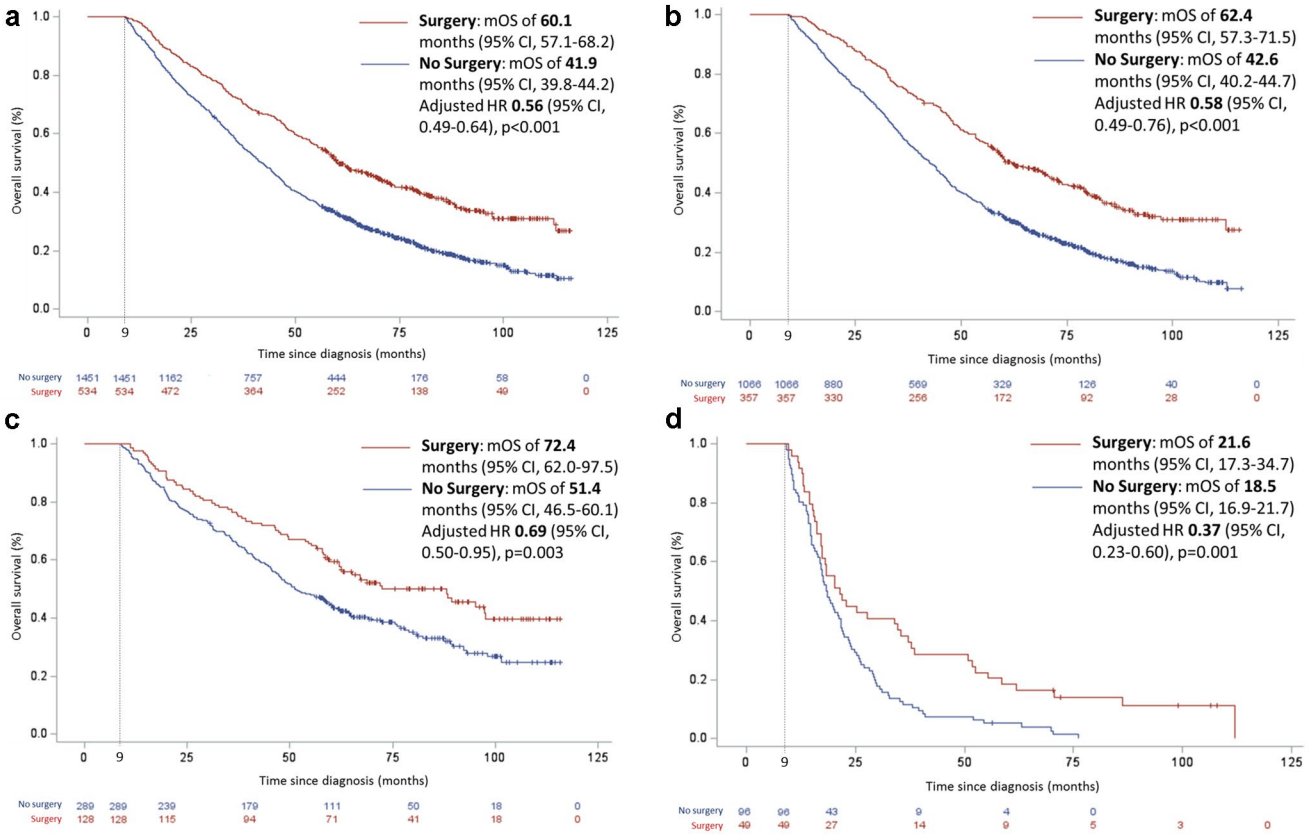

Fig. 2 Kaplan-Meier curves for overall survival in (**A**) all patients, (**B**) patients with estrogen receptor (ER)-positive/HER2-negative subtypes, (**C**) HER2-positive subtype and (**D**) triple-negative subtype (TNBC); CI: confidence interval; HR: hazard ratio – adjusted for age, performance status at diagnosis, tumor immunohistochemistry subtype, clinical T-category and histological grade (nine-month landmark cohort, N = 1985)

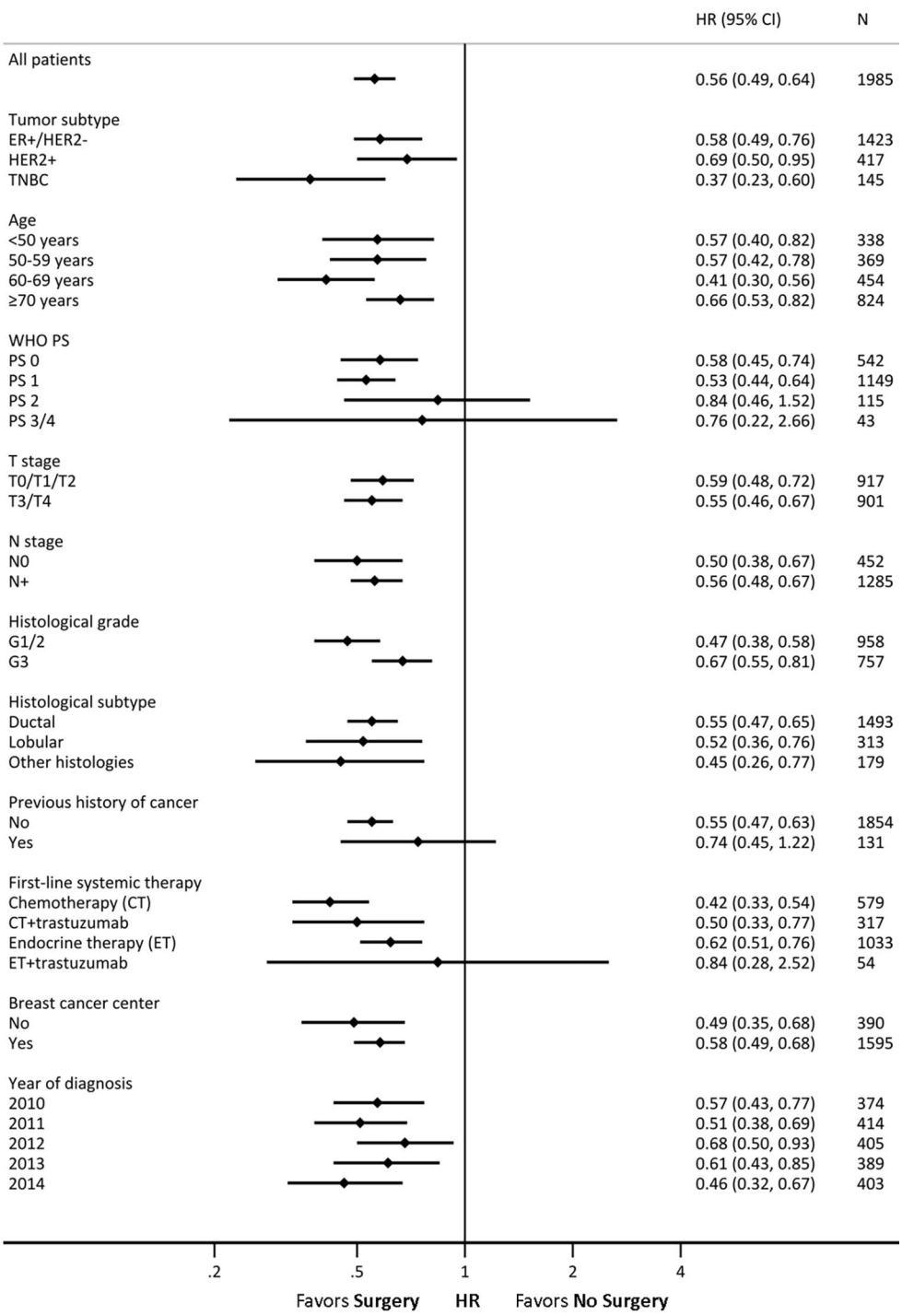

Fig. 3 Multivariable analysis of overall survival according to "Surgery" vs. "No Surgery" within each subgroup of patients; all models included the variables: age, performance status (PS) at diagnosis, tumor immunohistochemistry subtype, clinical T-category and histological grade; CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; TNBC: triple-negative breast cancer (nine-month landmark cohort, N = 1985)

"No Surgery" group. OS was similar in "Upfront Surgery" and "Late Surgery" groups, with a median of 62.6 (95% CI, 56.3–72.8) and 59.5 (95% CI, 53.4–70.0) months, respectively. Both "Upfront" (HR 0.55, 95% CI 0.45–0.66) and "Late Surgery" (HR 0.56, 95% CI, 0.47–0.67) were associated with longer OS than "No Surgery" group (Fig. 4). This was not statistically significant for "Upfront Surgery" in HER2-positive breast cancer. The absolute median survival difference was larger for women with HER2-positive tumors treated with "Late Surgery" (88.5 vs. 42.6 months; HR 0.63, 95% CI, 0.42–0.93) vs. "Upfront Surgery" (72.4 vs. 42.6 months; HR 0.82, 95% CI, 0.51–1.31) (Supplementary Table 4).

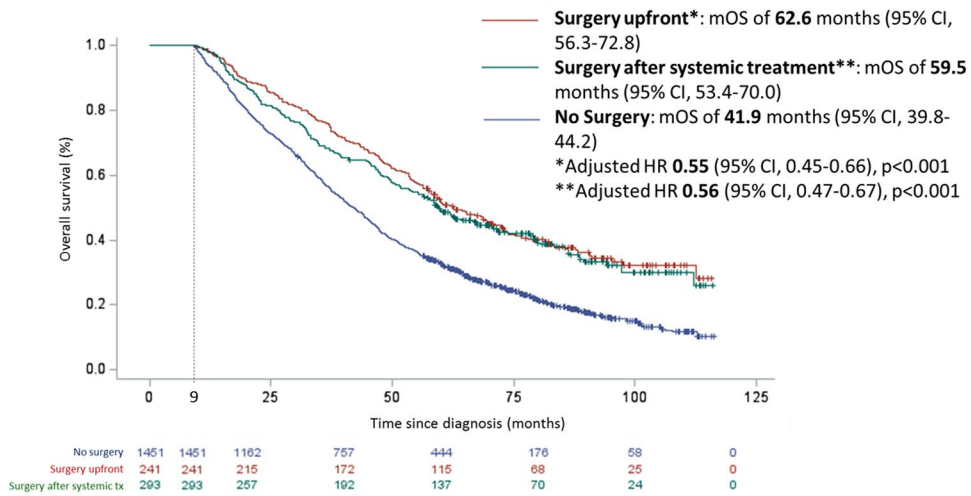

Fig. 4 Kaplan-Meier curves for overall survival according to "Upfront Surgery" vs. "Late Surgery" vs. "No Surgery"; all models included the variables: age, performance status (PS) at diagnosis, tumor immunohistochemistry subtype, clinical T-category and histological grade; CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; TNBC: triple-negative breast cancer (nine-month landmark cohort, N = 1985)

Propensity score matching analysis

A total of 954 women (477 in "Surgery" group vs. 477 in "No Surgery" group) were included in the propensity score matching analysis. Median OS was 62.1 months (95% CI, 57.6–71.5) in the "Surgery" group vs. 42.3 months (95% CI, 37.8–46.5) in the "No Surgery" group (HR 0.60; 95% CI, 0.52–0.70) (Supplementary Fig. 1). Stratifying by surgery timing, 224 (47.0%) received "Upfront Surgery", while 253 (53.0%) were in the "Late Surgery" group. No differences in OS were found between the "Upfront Surgery" and "Late Surgery" groups, with a median of 60.3 (95% CI, 54.2–73.2) and 62.4 (95% CI, 56.3–79.0) months, respectively. Both "Upfront" (HR 0.62, 95% CI, 0.51–0.74) and "Late Surgery" (HR 0.59; 95% CI, 0.49–0.71) were associated with a longer OS than "No Surgery" group (Supplementary Fig. 2).

Discussion

Our study suggests that among patients who are alive at nine months after the diagnosis of *de novo* metastatic breast cancer, those who were selected to undergo surgery of the primary tumor within the first nine months after diagnosis have a statistically significant and clinically relevant longer survival. The absolute survival difference was estimated in about 18 months based on a 44% risk reduction as compared to those who did not undergo surgery. Despite relative survival superiority across almost all subgroups, including in patients with TNBC, the absolute survival difference was larger in women with better ECOG PS, and with ER-positive/HER2-negative or HER2-positive breast cancer subtypes, reaching 20 months difference in these two last subgroups. Women with HER2-positive breast cancer seem to have longer survival when receiving systemic treatment prior to surgery of the primary tumor.

A study conducted by Badwe et al. in India was the first clinical trial randomizing patients with *de novo* metastatic breast cancer to receive locoregional treatment or not [10]. Between 2005 and 2013, 350 patients aged ≤ 65 years were randomized to receive locoregional treatment or not in addition to standard of care. Randomization was stratified by site and number of distant metastases, and by ER status. With a median follow-up of 23 months, the trial failed to show an OS benefit of locoregional treatment [10]. As opposed to our study, the majority of the patients with HER2-positive breast cancer in this trial did not receive anti-HER2 therapy. In fact, none of the patients with HER2-positive disease in the interventional arm received anti-HER2 therapy, compared to 15% in the control arm, which may slightly contribute to better survival outcomes in the control arm. However, nearly all patients evaluated in this trial were responders to first line chemotherapy before randomization, while in our study we have no information about the extent of response to first line systemic therapy. Considering the real-word setting, it is likely that the "No Surgery" group had a higher proportion of non-responders, overestimating the survival difference to the "Late Surgery" group.

The Turkish MF07-01 trial recruited patients with *de novo* metastatic breast cancer between 2007 and 2012, to be randomized for upfront locoregional therapy followed by systemic treatment vs. systemic treatment alone. The 10 years follow-up data of 265 patients were recently reported, demonstrating a significantly prolonged median OS for patients in the interventional arm (46 vs. 35 months, HR 0.71; 95% CI 0.59–0.86) [12]. Patients with ER-positive (HR 0.63; 95% CI 0.44–0.89) and patients with HER2-negative (HR 0.64; 95% CI 0.45–0.91) disease were those benefiting from surgery. As opposed to the Indian study, all the patients treated with locoregional resection were

naïve for systemic therapy, which mimics the scenario of our study comparing "Upfront Surgery" and "No Surgery" groups. However, all the patients included in the MF07-01 trial were amenable to surgical resection of the primary tumor and 45% had bone-only disease, while due to the retrospective nature of our study, we were not able to control for these aspects. This means that there is a considerable risk that patients with visceral disease or unresectable and more advanced locoregional disease were more represented in the "No Surgery" group, overestimating the observed survival difference. Additionally, it is important to highlight the imbalanced randomization in the Turkish trial, with more ER-positive patients in the intervention arm, and more TNBC patients in the control arm, leading to an better prognosis in the locoregional treatment arm [32].

Two other clinical trials that recruited patients between 2011 and 2015, found no benefit of surgical resection of the primary tumor [8, 9]. The Austrian POSYTIVE trial, with a similar design to the MF07-01, was stopped early due to poor recruitment. Therefore, only 90 patients were randomized, which limits the power of the study and potentiates the imbalance between arms [8]. ECOG2108, was conducted in the USA with a similar study design to the Indian trial, but including also patients with stable disease after a maximum of 32 weeks of systemic therapy. Despite higher access to anti-HER2 therapy, reflected in longer survival in both groups when compared to the Indian trial, the ECOG2108 trial randomized 256 patients to locoregional treatment or not, but no benefit of the intervention was found in OS, at a median follow-up of 53 months [9]. As in the Indian trial, randomization was stratified by disease burden and by ER status, which might explain the negative results when compared to MF07-01 where no stratified randomization for these baseline prognostic factors was performed. More recently, the SUBMIT trial [33] was terminated due to low accrual rate, while the Japanese trial JCOG1017 has completed recruitment and the results have been recently presented [11]. This latter trial has a study design similar to ECOG2108 and the Indian trials, and despite the numerically higher median OS in the intervention arm, it also failed to demonstrate a statistically significant OS improvement (75 vs. 69 months, HR 0.86; 95% CI 0.69–1.07). The trial has important weaknesses like the fact that in the intervention arm, no patients received "adjuvant" radiotherapy, 13% had positive margin with no further re-excision, and 13% did not receive systemic therapy. In the subgroup analyses of the Japanese trial [11], there was a signal for benefit from the intervention in pre-menopausal women, similar to age-stratified analyses from MF07-01 and ECOG2108 [9, 12]. The benefit of this intervention in younger patients require further investigation and may explain in part our findings, given the younger age in the "Surgery" group.

However, large population-based real-world studies, such as cohorts from the American College of Surgeons National Cancer Database [17, 34, 35], and Surveillance, Epidemiology, and End Results databases [23, 36] with over 40% of *de novo* metastatic breast cancer patients undergoing surgery of the primary tumor, have been consistently demonstrating survival superiority for surgery of the primary tumor in patients with *de novo* metastatic breast cancer. As our study, despite their population-based nature and the strategies applied to mitigate bias and confounding, these studies frequently lack relevant prognostic variables such as metastatic disease burden. The higher external validity of the locoregional surgical approach of these studies contrasts with the lower internal validity when compared with prospective clinical trials, particularly for those trials that applied stratified randomization for key baseline prognostic factors.

Also aligned with our data, a recently published large population-based cohort study of 928 women with HER2-positive *de novo* metastatic disease, who received first-line treatment with anti-HER2 therapy, reported a survival superiority of patients treated with locoregional therapy in this subgroup [25]. These findings suggest that a higher absolute survival difference might be observed in subgroups with intrinsic better prognosis and/or for which highly effective treatments are available. This is also supported by the underlying biological rationale that the removal of the primary tumor could reduce the tumor burden and minimize the selection of drug resistant clones [37].

Despite the retrospective nature of our study, this is a nationwide analysis with a long median follow-up of more than 7 years (86.0 months), as compared to 23–53 months of the above-mentioned negative trials [8–10]. When compared to other nationwide analyses led in healthcare systems with more heterogeneous access to treatments [17, 21–24], a strength of our study lies on the fact that data is derived from a universal healthcare coverage system, where all patients had access to standard-of-care systemic therapy. Moreover, as opposed to analyses restricted to academic or high-volume centers [18, 19], the population-based nature of our study increases the representativeness of the real-world *de novo* metastatic breast cancer population. As we used treatment data as a surrogate to classify the tumor subtype for a majority of cases, we have tested this approach on the patients diagnosed in 2014 (where immunohistochemistry results were available) and the concordance was found to be very high (data not shown). Still, we acknowledge that some cases of ER-low or more aggressive ER-positive/HER2-negative disease could have been misclassified in the TNBC subtype group. We identify three main sources of selection bias that may contribute to an overestimation of the OS differences. The first is the exclusion of patients who did not

receive systemic therapy, which were older and presented worse ECOG PS at diagnosis. We may argue that in any case these patients are usually offered best supportive care aiming QoL improvement and less focused on survival endpoints. For an accurate identification of these patients, multidisciplinary geriatric and frailty assessments are key. The second source of bias is the exclusion of patients who died or were lost to follow-up less than nine months after diagnosis, who were older and with worse ECOG PS at diagnosis, as well. In these cases, there is a higher likelihood of having a more aggressive disease as we found a higher proportion of TNBC, which, if included, would have probably limited the difference observed in the group of surgical intervention. Although the median OS of the two groups in our study are similar to other retrospective cohort studies [17, 18, 20, 23], these two abovementioned biases might explain a longer survival of the "Surgery" group than the one reported in the randomized clinical trials [8–10, 12]. Therefore, it is important to consider that the findings of our study are only applicable to patients with *de novo* metastatic breast cancer who are candidates to systemic therapy with an estimated prognosis higher than nine months. This landmark approach controlled the risk of immortal time bias related with the classification of surgery group. The third source of bias is the selection for surgery of patients with better prognosis or better response to systemic therapy, as previously described by Poggio et al. [38]. Although we applied robust strategies of multivariate and propensity score matching analyses in line with other studies previously reported [20, 21, 23, 36], controlling for potential confounders, our model does not include other important prognostic variables, such as comorbidities, proportion of oligometastatic disease at diagnosis, or proportion of patients with visceral, central nervous system, bone-only metastatic disease, or laboratory findings of imminent organ failure. Patients with bone-only metastatic disease have been suggested to derive more pronounced benefit from this intervention [4, 5, 39], and some authors refer to the relatively higher proportion of this subgroup in the Turkish trial (47%), as compared to other trials (28–38%), as a potential explanation for the positive impact of primary surgery in OS obtained in this trial [8]. Despite all the adopted strategies to mitigate bias, the retrospective nature of the study, all these unmeasured confounders, and the identified bias of younger and fitter patients in the "Surgery" group, are strong limitations to the validity of our findings. As an example, in our study, we observed a higher likelihood of receiving first-line chemotherapy in the "Surgery" group. This finding might be derived from the younger age and better ECOG PS at diagnosis, and higher proportion of HER2-positive and TNBC subtypes in this group, but also due to a potential unmeasured higher proportion of oligometastatic disease. Those aspects might contribute for a longer median OS in the patients selected for surgical resection of the primary tumor. Despite the controversy about their impact in survival [40, 41], in our study we also do not have specific information on radiotherapy or surgical resection of metastatic lesions that could have been used in selected cases of oligometastatic disease. Ultimately, we do not have data to allow distinction of radiotherapy to primary vs. distant sites, which hinder us to analyze the potential impact of post-operative radiation. Response to first-line systemic treatment might have been an important decision factor for those who received "Late Surgery", which might explain the higher magnitude of survival difference in the HER2-positive subgroup that underwent surgery after prior systemic therapy.

Our cohort operated between 2010 and 2014, which may not reflect a contemporary setting, therefore we should also put our data in the current context of the drugs approved in the most recent years with impact in survival, mainly CDK4/6 inhibitors in ER-positive/HER2-negative disease [42], and pertuzumab [43] and T-DM1 [44] for HER2-positive disease. Additionally, trastuzumab-deruxtecan in HER2-positive [45] and HER2-low disease [46], sacituzumab govitecan in HER2-negative disease [47, 48], and immunotherapy in TNBC [49] might change survival in a near future. Longer follow-up updates of the above mentioned randomized clinical trials will provide more data in the coming future. Molecular platforms such as AURORA [50] will also bring more insight into the biology of *de novo* disease, helping to optimize the design of future trials prospectively assessing surgical interventions in metastatic breast cancer.

Conclusion

Among patients with *de novo* metastatic breast cancer eligible for systemic treatment and surviving nine months or more after diagnosis, those undergoing surgery of the primary tumor had longer OS compared to those who did not undergo surgery within the first nine months after diagnosis. Survival differences were more pronounced among patients with good ECOG PS at diagnosis and with ER-positive/HER2-negative or HER2-positive breast cancer. The findings of this study should be regarded with caution due to its retrospective nature, but they may contribute to informed multidisciplinary clinical discussions about surgery of the primary tumor as a potential therapeutic intervention for selected patients with *de novo* metastatic breast cancer.

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Data Availability The data that support the findings of this study are available from the Belgian Cancer Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Belgian Cancer Registry.

Declarations

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Ethics approval Approval of the Ethical committee was not necessary based on the fact that this retrospective study does not fall under the Belgian Law of 7 May 2004 regarding experiments on human persons (art. 3,§ 2).

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