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Better survival after surgery of the primary tumor in stage IV inflammatory breast cancer

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ABSTRACT

Introduction: Information regarding the effects of resection of the primary tumor in stage IV inflammatory breast cancer (IBC) is scarce. We analyzed the impact of resection of the primary tumor on overall survival (OS) in a large stage IV IBC population.

Materials and methods: Patients diagnosed with stage IV IBC between 2005 and 2016 were selected from the Netherlands Cancer Registry, excluding patients without any treatment. To correct for immortal time bias, we performed a landmark analysis including patients alive at least six months after diagnosis. With propensity score matching, patients undergoing surgery of the primary tumor were matched to patients not receiving surgery. Multivariable Cox proportional hazard analyses were performed to determine the association between treatment strategy and OS in the non-matched and matched cohort.

Results: Of the 580 included patients after landmark analysis, 441 patients (76%) received only non-surgical treatments and 139 (24%) underwent surgery (96% mastectomy). Median follow-up was 28.8 and 20.0 months in the surgery and no surgery group, respectively. Surgery in the non-matched cohort was independently associated with better survival (HR0.56[95%CI:0.42–0.75]). In the matched cohort (n = 202), surgically treated patients had improved survival over nonsurgically treated patients ($p < 0.005$). Multivariable analysis of the matched cohort revealed that surgery was still associated with better survival (HR0.62[95%CI:0.44–0.87]).

Conclusion: Although residual confounding and confounding by severity cannot be ruled out, this study suggests that surgery of the primary tumor is associated with improved OS and should be considered as part of the treatment strategy in stage IV IBC.

What's new?

Since the value of surgery of the primary tumor in stage IV IBC is still under debate, this nationwide population-based study in the Netherlands investigated whether surgery of the primary tumor in stage IV IBC is associated with overall survival.

In total, 580 patients who survived at least the first six months after diagnosis were included. Multivariable Cox regression with propensity score matching showed that surgery of the primary tumor in stage IV IBC was associated with improved overall survival. Although confouding by severity and residual confounding cannot be ruled out in observational studies, this study suggests that surgery of the primary tumor should be considered in stage IV IBC.

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1. Introduction

Inflammatory breast cancer (IBC) is a highly aggressive form of breast cancer in which nearly 40% of patients present with synchronously detected distant metastases (stage IV) [1,2].

Current treatment of stage III IBC includes neoadjuvant chemotherapy (NACT), surgery, and adjuvant locoregional radiation therapy (trimodality therapy). Moreover, (neo)adjuvant trastuzumab and adjuvant antihormonal therapy are applied in patients with HER2-positive and/or hormonal receptor (HR) positive tumors, respectively. Incorporation of this treatment regimen has positively influenced the survival of IBC patients in recent years [1].

In metastatic breast cancer in general, the main goals of treatment are improvement or maintenance of quality of life, palliation of symptoms, and prolongation of survival. Literature concerning surgical treatment of the primary tumor in stage IV breast cancer is conflicting. A meta-analysis of retrospective data suggested that primary tumor resection in stage IV breast cancer patients confers a survival benefit [3]. Recently, three prospective trials were conducted evaluating the effect of removal of the primary tumor in stage IV breast cancer, in which two studies could not demonstrate a survival benefit [4,5]. On the other hand, one showed an improved survival after 40 months follow up (initially not showing a survival benefit after 36 months follow up) [6].

With respect to surgery of the primary tumor in stage IV IBC, data is primarily limited to retrospective analyses from single institutions [7,8], or small multicenter cohorts showing that multimodality treatment, including resection of the primary tumor, may result in improved local control and survival [9]. Data from the US National Cancer Database showed that for stage IV IBC patients, negative margin surgery was associated with improved outcome [10].

The purpose of the present Dutch nationwide population study was to investigate the impact of surgery of the primary tumor on OS in stage IV IBC. Since patients treated with surgery have to survive the time until the date of surgery (immortal time bias), we only included patients who survived the first six months after diagnosis (within this time frame almost all patients should have been treated with surgery) to correct for differences in short-term outcome and adequately estimate the effect of surgery [11,12].

2. Materials and methods

2.1. Data source

All newly diagnosed malignancies in the Netherlands are registered in the nationwide population-based Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) is the main source of notification. Trained registrars from the IKNL directly collect data from the patient's medical records. Morphology and differentiation are coded according to the International Classification of Diseases for Oncology (ICD-O), third edition [13]. Staging is coded according to the Tumor, Node and Metastasis (TNM) classification, of which the specific edition depended on the year of incidence [14,15]. However, with respect to IBC, the criteria used in the TNM system have not changed over time. Yearly linkage with the municipal administration was used to verify the patient's vital status and, if applicable, date of death. Follow-up has been completed until December 31st, 2016. The privacy committee of the NCR has approved this study.

2.2. Patients and study variables

All patients diagnosed from 2006 to 2016 with a clinical diagnosis of inflammatory (T4d) breast cancer were selected from the NCR. Patients with cT4dM0 (stage III) breast cancer were excluded as well as patients with missing HR and/or HER2 status (as these are important prognostic factors) and patients not receiving any form of treatment (as including these patients would overestimate the effect of surgery due to inclusion of poor prognosis patients in the no surgery group).

Age and year of diagnosis were evaluated as continuous variables. Histological type, grade and hormone receptor status (ER, PR, and HER2) were assessed in the primary tumor biopsy and/or in postoperative specimens. If data were missing for pretreatment biopsies, this was substituted with data of the postoperative specimen. According to the Dutch guidelines, ER/PR status have been determined with immunohistochemistry (IHC). At least 10% positive tumor nuclei were considered as a positive result. Tumors were considered HER2-positive with an immunohistochemical score of 3 + and/or presence of HER2-amplication.

To analyze the specific sites of distant metastases, we classified patients according to the site of metastasis (bone, lung, liver and other) or in case of multiple organ involvement we classified them as having multiple locations. Metastases diagnosed within three months after the date of diagnosis were considered to be synchronous with the primary tumor and incorporated in initial staging.

Patients who were surgically treated were recorded as having undergone mastectomy or breast-conserving treatment and possible axillary dissection. Chemotherapy, endocrine therapy, locoregional radiation therapy and anti-HER2 therapy were reported as administered or not administered. We analyzed the pathologic complete response (pCR) rate in all patients treated with NACT. pCR was defined as the absence of microscopic residual invasive cancer in the surgically removed specimen after NACT.

2.3. Statistical analysis

Tumor characteristics were compared between the different molecular subgroups using Pearson's chi-squared tests for categorical variables and non-parametric approaches (Mann Whitney-U tests) for continuous variables. Fisher's exact test was used to determine if non-random associations between two categorical variables in case of less than five patients per stratum existed. The p-value was not calculated in case of too little events.

To examine the association of surgery with OS, we performed multivariable Cox proportional hazard regression to estimate hazard ratios (HR) with accompanying 95% confidence intervals (CIs). The assumption of proportional hazards was tested by plotting scaled Schoenfeld residuals over time and judging these for consistency. Since patients treated with surgery have to survive the time until the date of surgery (immortal time bias), we only included patients who survived the first six months after diagnosis a landmark analysis (within this time frame almost all patients should have been treated with surgery). In this way, we corrected for differences in short-term outcome and made the two groups more comparable.

To create even more homogeneous groups, we additionally performed propensity score matching (PSM). The propensity score was calculated based on variables that significantly differed between the treatment groups. Subsequently, patients in the surgery group were 1:1 matched to patients in the non-surgery group based on the propensity score. Balance in baseline characteristics was estimated before and after matching using standardized differences [16]. The standardized difference is the difference of the sample means in the unmatched and matched group as a percentage of the square root of the average of the sample variance in both groups. A standardized difference of $\geq$10% indicates an imbalance in baseline characteristics between the two groups. In both the non-matched as well as the matched cohort a multivariable Cox regression model was applied to determine whether resection of the primary tumor was associated with OS in stage IV IBC patients. Furthermore, interactions between covariates were tested. Follow-up was calculated for every patient from the date of diagnosis to the date of death from any cause, or the date of last observation. All statistical analyses are performed in the software package STATA

version 14.2 (StataCorp LP). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Clinicopathological characteristics

A total of 2235 patients with IBC were diagnosed in the Netherlands between January 2006 and December 2016 of whom 842 patients

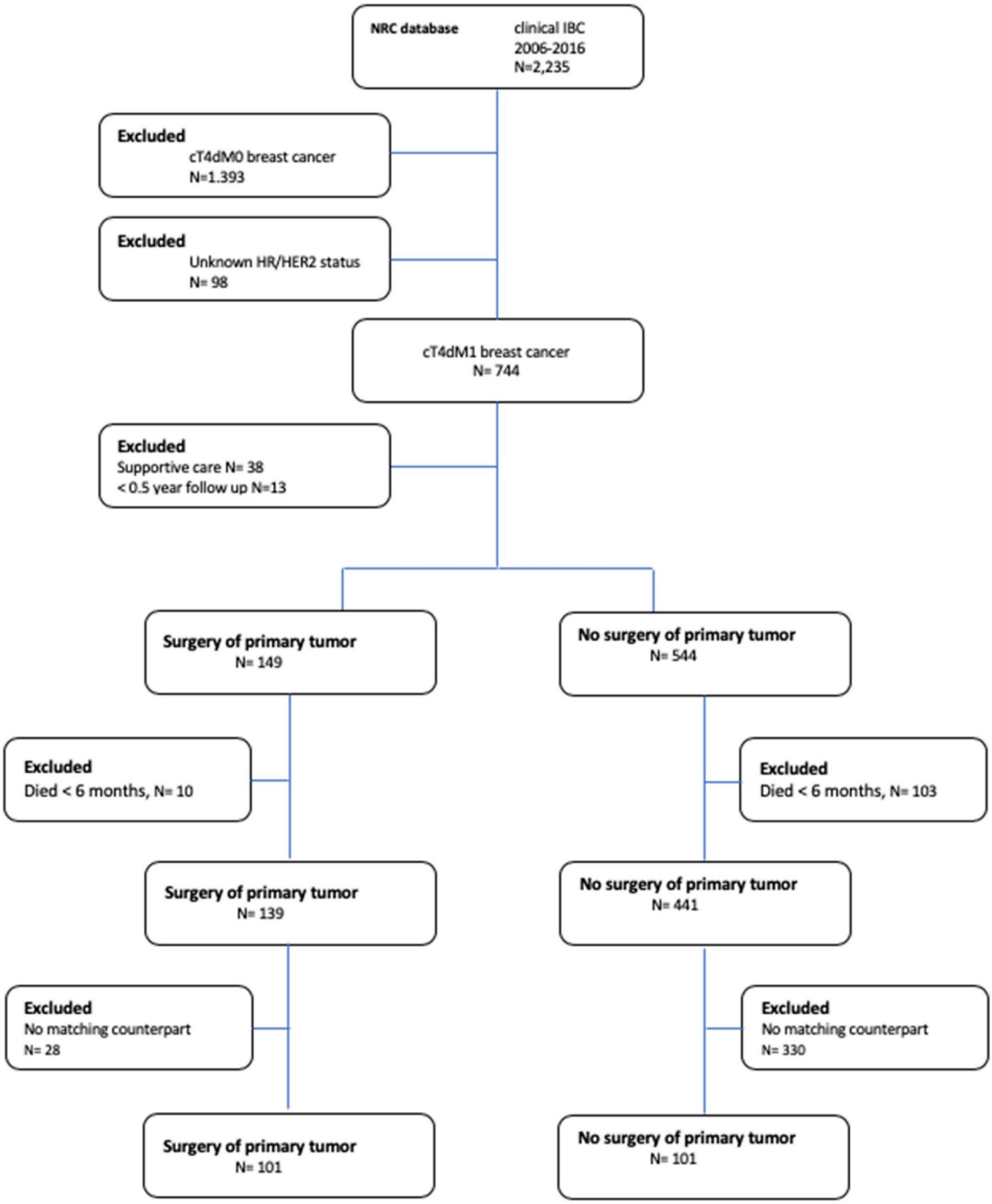

Fig. 1. Flow diagram of patient selection.

presented with stage IV IBC (33.3%) at diagnosis. Due to unknown HR or HER2-status (as these variables are important prognostic factors) 98 patients were excluded.

After exclusion of 123 patients (10 in the surgery group and 113 in the group without surgery) who died within six months after diagnosis, 580 patients were eligible for inclusion in the present study (Fig. 1) with a mean age of 59.0 years (±13.5 years). Table 1 lists the clinicopathological characteristics of the two treatment groups (surgery of the primary tumor, n = 139) and patients receiving other treatment without surgery of the primary tumor (n = 441).

3.2. Treatment

Of the 580 patients, 139 (24.0%) underwent surgery. Surgical procedures included 5 (3.6%) breast conserving surgeries and 133 (95.7%) mastectomies.

Axillary lymph node dissection was performed in 96 patients (69.1%). All patients with surgery underwent some form of accompanying (neo-)adjuvant treatment (Table 2).

In 77 (55.4%) patients who underwent breast surgery, adjuvant locoregional radiation therapy of the primary site was performed. Locoregional radiation therapy of the primary site was performed in 53 patients (11.9%) who did not undergo a surgical procedure. In 9 (2.0%) patients locoregional radiation therapy was combined with chemotherapy.

In the group of patients who underwent breast surgery, 121 patients (87.1%) received NACT, and this was applied most often in the HR-/

Table 1
Patient- and tumor-related characteristics of all patients with stage IV IBC, before and after matching.

	Stage IV IBC prior to matching (n = 580)			Stage IV IBC after matching (n = 202)		
	Surgery of the primary tumor		p-value	Surgery of the primary tumor		p-value
	No (n = 441)	Yes (n = 139)		No (n = 101)	Yes (n = 101)	
	N (%)	N (%)		N (%)	N (%)	
Age, mean (SD)	61.3 (13.6)	55.9 (12.2)	**<0.001**	57.9 (13.5)	58.1 (12.5)	0.618
Breast cancer subtype						
HR+/HER2-	216 (49.0)	56 (40.3)		42 (41.6)	44 (43.6)	
HR+/ HER2+	86 (19.5)	21 (15.1)		16 (15.8)	18 (17.8)	
HR-/HER2+	82 (18.6)	38 (27.3)	**0.043**	26 (25.7)	25 (24.8)	0.925
HR-/HER2-	57 (12.9)	24 (17.3)		17 (16.8)	14 (13.9)	
Clinical node stage						
Node negative	30 (6.8)	11 (7.9)		6 (6.3)	9 (9.0)	
Node positive	328 (86.6)	126 (90.6)		89 (88.1)	91 (90.1)	
Unknown	29 (6.6)	2 (1.4)		6 (6.3)	1 (1.0)	
Metastases*						
Bone	103 (23.4)	54 (38.9)		30 (29.7)	36 (35.6)	
Liver	25 (5.6)	12 (8.6)		10 (9.9)	7 (6.9)	0.838
Lung	27 (6.0)	5 (3.6)	**<0.001**	4 (4.0)	5 (5.0)	
Other	33 (7.6)	32 (23.0)		20 (19.8)	17 (16.8)	
Multiple organs	252 (57.1)	36 (25.9)		37 (36.6)	36 (35.6)	

Numbers are n (%) unless otherwise specified. P-values indicated in bold are considered as statistically significant (p < 0.05). Abbreviations: SD, standard deviation; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Table 2
Treatment characteristics of all patients with stage IV IBC, before and after matching.

	cT4dM1 prior to matching (n = 580)			cT4dM1 after matching (n = 202)		
	Surgery of the primary tumor		p-value	Surgery of the primary tumor		p-value
	No (n = 441)	Yes (n = 139)		No (n = 101)	Yes (n = 101)	
Type of surgery	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
BCT – ALND	NA	1 (0.7)		NA	0 (0.0)	
BCT + ALND	NA	4 (2.9)		NA	2 (2.0)	
MAST – ALND	NA	41 (29.6)	NC	NA	34 (33.7)	NC
MAST + ALND	NA	92 (66.2)		NA	64 (63.4)	
Not further specified	NA	1 (0.7)		NA	1 (1.)	
Chemotherapy	285 (64.6)	126 (90.7)	**<0.001**	79 (78.2)	89 (88.1)	0.060
No Chemotherapy	156 (35.4)	12 (8.6)		22 (21.8)	12 (11.9)	
NACT	NA	112 (80.6)		NA	80 (79.2)	
NACT + adjuvant CT	NA	9 (6.5)	NC	NA	3 (3.0)	NC
Adjuvant CT	NA	6 (4.3)		NA	6 (5.9)	
Locoregional RT (primary site)	53 (11.9)	77 (55.4)	**<0.001**	42 (41.6)	39 (38.6)	0.427
No radiation therapy	388 (88.0)	62 (44.6)		59 (58.4)	62 (61.4)	
In combination with CT$	9 (2.0)	NA	NC	9 (8.9)	NA	
In combination with AT*	7 (1.6)	NA		4 (4.0)	NA	NC
In combination with TT&	0 (0.0)	NA		0 (0.0)	NA	
Antihormonal therapy	233 (52.8)	68 (48.9)	0.421	45 (44.6)	52 (51.4)	0.324
No antihormonal therapy	208 (47.2)	71 (51.1)		56 (55.5)	49 (48.5)	
Neoadjuvant	NA	27 (19.4)		NA	25 (24.8)	
Neoadjuvant + adjuvant	NA	3 (2.2)	NC	NA	3 (3.0)	NC
Adjuvant	NA	38 (27.3)		NA	24 (23.8)	
Anti-HER2 therapy	152 (34.5)	55 (39.6)	0.274	40 (39.6)	39 (38.6)	0.885
No anti-HER2 therapy	289 (65.5)	84 (60.4)		61 (60.4)	62 (61.4)	
Neoadjuvant	NA	35 (25.2)		NA	25 (24.8)	
Neoadjuvant + adjuvant	NA	8 (5.8)	NC	NA	8 (7.9)	NC
Adjuvant	NA	12 (8.6)		NA	6 (5.9)	
Trimodality therapy#						
No	441 (100.0)	96 (69.1)	NC	101 (100.0)	81 (80.2)	NC
Yes	NA	43 (30.9)		NA	20 (19.8)	

Numbers are n (%) unless otherwise specified P-values indicated in bold are considered as statistically significant (p < 0.05). Abbreviations: BCT, breast conserving therapy; MAST, mastectomy; ALND, axillary lymph node dissection; NACT, neoadjuvant chemotherapy; CT, chemotherapy; AT, antihormonal therapy; TT, targeted therapy; HER2, human epidermal growth factor receptor 2; NC, not calculable. NA, not applicable; $ patients treated only with locoregional radiationtherapy and chemotherapy; *patients treated only with locoregional radiationtherapy and antihormonal therapy; & patients treated only with

locoregional radiationtherapy and targeted therapy; # trimodality therapy: neoadjuvant chemotherapy, surgery of the primary breast tumor, adjuvant locoregional radiation therapy of the primary site.

HER2+ subtype: HR+/HER2- (n = 48, 13.5%), HR-/HER2+ (n = 37, 25.0%), HR+/HER2+ (n = 20, 13.7%), HR-/HER2- (n = 21, 12.8%) (Table 2).

Of the 59 patients with HER2-positive (HR-/HER2+ and HR+/HER2+) tumors treated with surgery, 72.9% (n = 42) received neoadjuvant anti-HER2 therapy. In the group without surgery, anti-HER2 therapy was administered in 152 patients (90.5%) with a HER2-positive tumor.

Of the patients operated on, those receiving NACT were younger (53.9 years ± 10.4 years) compared to those receiving neoadjuvant antihormonal therapy (62.4 years ± 11.9 years). The mean age for HER2+ patients receiving neoadjuvant trastuzumab was 53.5 years ± 9.9 years. Patients receiving trimodality therapy were younger (55.0 years ± 10.0 years) compared to patients not receiving it (60.4 years ± 13.6 years). In the surgically treated group, pCR of the breast tumor was achieved in 8 patients (5.6%) in the non-matched cohort and 3 (3.2%) in the matched cohort.

3.3. Overall survival in the non-matched cohort

Median OS of the entire cohort was 16.1 months (interquartile range (IQR):7.1–30.6). In the non-matched cohort, the median OS in the group with surgery was 24.0 months (IQR:9.1–39.4) compared to 15.0 months (IQR:6.7–27.2) for patients without surgery. Surgical patients had improved survival over nonsurgical patients ($p < 0.001$). The Kaplan–Meier survival estimations are presented in Fig. 2A. Multivariable analysis revealed that surgery was independently associated with better survival compared to no surgery (HR 0.56 [95% CI: 0.42–0.75]) (Table 3).

3.4. Overall survival in the matched cohort

PSM was used to create more homogeneous groups using the following variables: year of diagnosis, age, breast cancer subtype, use of targeted therapy, use of radiation therapy and localization of metastases (Table 4). Consequently, 28 patients in the surgery group and 330 patients in the no surgery group were excluded because no matching counterpart was found (Fig. 1 and Tables 1 and 2). A total of 202 patients in the matched analysis remained:101 nonsurgical and 101 surgical. After PSM, baseline characteristics were considered to be balanced as all standardized differences in the matched cohort were <10%, suggesting a well-matched cohort (Table 4).

In the matched cohort, median OS was 22.4 (IQR: 7.3–40.2) and 16.3 months (IQR: 7.1–30.5) for the surgery group and the no surgery group, respectively. Surgical patients had improved survival over nonsurgically treated patients ($p < 0.005$). The Kaplan–Meier survival estimations are presented in Fig. 2B. Multivariable analysis of the matched cohort revealed that surgery was still independently associated with better survival (HR 0.62 [95% CI: 0.44–0.87]). A sensitivity analysis of our results, revealed that the survival benefit was more prononounced in patients receiving adjuvant radiation therapy (HR 0.45 [95% CI: 0.26–0.79]). We also found that the effect of chemotherapy was not significant. We have tested the interaction between HER2-positivity and anti-HER2 treatment and this did not affect our model.

4. Discussion

Surgery of the primary tumor in metastatic breast cancer has been investigated in several studies leading to contradictory conclusions concerning the survival benefit of surgery [4,17,18]. Unfortunately, IBC was an exclusion criterium in all three prospectively conducted studies [4–6]. Therefore, we investigated the impact of surgery of the primary

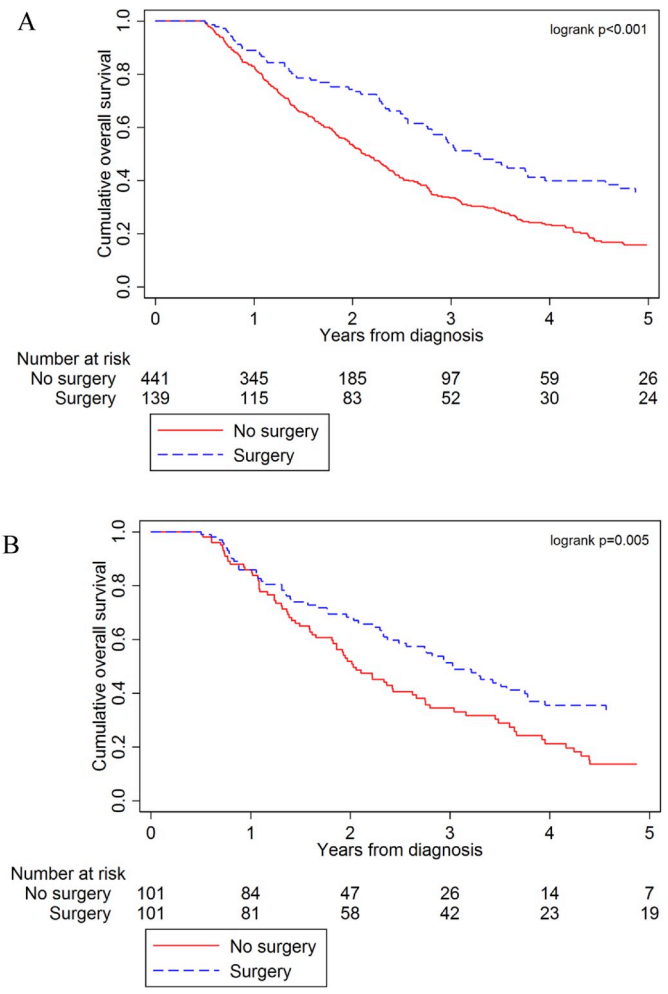

Fig. 2. Kaplan-Meier curves displaying overall survival of all cT4d-patients from 2006 to 2016, before (A) and after (B) matching.

tumor on OS in stage IV IBC in a large nationwide population-based study. Our data suggests that surgery of the primary tumor is associated with improved OS in stage IV IBC. Patients in whom the primary tumor was removed had improved survival over patients not treated surgically. This difference remained after a landmark analysis and performing propensity score matching analysis.

Weiss et al. recently published a similar study from an analysis of SEER data in stage IV IBC [10]. They also performed a propensity scored matched analysis and demonstrated that resection of the primary tumor was associated with improved survival prior to matching. After matching, there only remained a trend for improved survival with surgery. When they only included patients who underwent surgery with negative margins, the results were significantly associated with improved survival, similar as in the present study. However, the survival in our entire cohort was substantially lower than in the patients in the study of Weiss et al. This might partly be attributable to the higher percentage of patients operated on (41% compared to 24.0% in our analyzed cohort). Moreover, the patients who received surgery were younger in the study of Weiss et al. Furthermore, there were more patients with multiple sites of metastases, in whom chemotherapy was administered less often and radiation therapy was less often applied in our cohort. Even though the effect of surgery persisted in a multivariate analysis in our study, adjusting for these potential confounders, there still might be a chance that our study population displayed more negative clinical characteristics and more extensive locoregional and/or distant disease compared to the population analyzed in the study of Weiss et al. Patients with stage IV

Table 3
Multivariable Cox regression analysis predicting overall survival in patients with systemically metastatic inflammatory breast cancer at diagnosis, in the non-matched cohort (n = 580).

		Hazard ratio	(95% CI)	p-value
Surgery of the primary tumor	No	1 (ref)		
	Yes	0.54	0.41–0.70	**<0.001**
Age at diagnosis		1.00	0.99–1.00	0.822
Year of diagnosis		0.93	0.89–0.97	**<0.001**
Molecular subtype	HR+/HER2-	1 (Ref)		
	HR+/ HER2+	1.11	0.79–1.56	0.542
	HR-/HER2+	2.01	1.42–2.86	**<0.001**
	HR-/HER2-	3.43	2.54–4.64	**<0.001**
Systemic metastases				
	Bone	1 (Ref)		
	Liver	0.74	0.47–1.16	0.193
	Lung	1.24	0.79–1.99	0.348
	Other	0.81	0.55–1.19	0.290
	Multiple sites	1.16	0.90–1.49	0.246
Anti-HER2 treatment	Yes	1 (ref)		
	No	1.59	1.16–2.17	**0.003**
RT of the primary site	Yes	1 (ref)		
	No	1.06	0.79–1.41	0.676

p-values indicated in bold are considered as statistically significant ($p < 0.05$). Abbreviations: CI, confidence interval; No., number; RT, radiation therapy.

Table 4
Difference between groups in the propensity matched analysis, before and after matching. Abbreviations: RT, radiation therapy.

	Non-matched cohort (%)	Matched cohort (%)
Year of diagnosis	−1.3	6.0
Age	−41.8	1.1
Molecular subtype	23.4	−7.9
Location of metastases	−47.7	−8.1
RT of primary site	−103.0	7.1
Anti-HER2 therapy	−10.6	2.0

disease who display more detrimental characteristics are less likely to be aggressively treated, which might have led to the observed survival difference between our cohorts [17,19]. An important strength of the present study is the inclusion of a landmark analysis. In this analysis, only patients who survived the first six months after diagnosis were studied to correct for differences in short-term outcome (immortal time bias). This could also be an explanation for the differences found between our study and that of Weiss et al. with regard to the survival benefit of surgery in the matched cohorts. However, we believe that the effect of surgery could be studied even more reliable after the performed land mark analysis. These issues make the results of our study relevant for current daily clinical practice.

The present study has several other strengths compared to previous studies concerning IBC. First of all, this study was based on a nationwide population-based cancer registry including unselected and unbiased data of all hospitals (both academic and non-academic) in the Netherlands, compared to mostly single-center studies [7,8]. Secondly, it contains data of patients treated in more recent years allowing to incorporate breast cancer subtypes. This has not been described in many of the previous studies [7,9]. Thirdly, it contains data of patients treated with current systemic treatments (including trastuzumab), which was not performed in another population based analysis [10].

The primary aim of surgery of the breast in metastatic breast cancer is local control and palliation of symptoms. However, in general, for patients who are asymptomatic at the site of their primary tumor, local treatment is not performed routinely given the conflicting data that it also improves survival [4–6]. Nonetheless, the international consensus on the clinical management of IBC advices to apply the same treatment regimens for both stage III and IV IBC, in which patients with stage IV IBC should always be evaluated for possible surgical management of the primary tumor aiming to control local complications (e.g. bleeding or infection and reduction of local progression in the breast or chest wall) [20,21].

This may be even more important in the era of advances in the systemic treatment approaches for patients with metastatic disease, for example those with HER2-positive disease [22]. Overexpression of HER2 in breast cancer in general is associated with higher recurrence rates and increased mortality, although treatment with trastuzumab improved these results significantly [23]. In the present study, HR-/HER2+ disease showed an increased risk of death. This might especially be due to the fact that not all HER2+ patients were treated with trastuzumab, which may be related to the patient's condition and the trastuzumab-associated side effects. It is important that eligible patients with HER2+ IBC receive trastuzumab, since this currently is the most effective regimen as shown in the NOAH trial in which patients with both non-inflammatory and inflammatory locally advanced breast cancer were included [24].

With expanding availability of targeted treatments, median survival will potentially improve further and this will simultaneously require more attention to local control. It should be noted that even though surgery was independently associated with improved survival, the effect was more pronounced in patients also receiving adjuvant locoregional radiation therapy, suggesting that comprehensive locoregional therapy is important. However, we are not able to draw firm conclusions on this due to small numbers and the fact that residual confounding and confounding by severity cannot be exluded. Furthermore, previously was shown that in patients not willing or able to undergo surgery for stage III, locoregional radiation therapy might be an alternative for local control [26]. This might also apply to stage IV IBC.

We previously showed that for stage III IBC, 78% of patients who underwent surgery also received NACT and adjuvant radiation therapy (trimodality therapy) [25]. Interestingly, only 31% of patients of our entire cohort with synchronous stage IV IBC who underwent surgery, also received this regimen. The exact reason why patients do not receive this trimodality regimen is hard to determine due to the retrospective character of our study. Since patients receiving trimodality therapy were younger compared to patients not receiving it, older age and frailty were most likely important reasons to omit trimodality treatment. Another reason could be due to rapid progression of disease, multi-organ involvement or patients being reluctant to undergo these multimodality treatments in case of stage IV disease.

The mechanisms by which surgery could impact OS are unclear, but might include the subsequent reduction of circulating tumor cells, which is a predictor of outcome in metastatic breast cancer [27].

Since IBC has a higher frequency of clusters of circulating tumor cells (CTC) as compared to non-IBC, the removal of the primary tumor theoretically might have a more pronounced effect in stage IV IBC than in stage IV non-IBC [28].

Several limitations of our study should be acknowledged. First, since this study was based on a retrospective design and the patient assignment was not random, confounding by severity or residual confounding could have influenced our results. Secondly, no information was available concerning clinical or radiological tumor response on neoadjuvant systemic therapies which was a prerequisite in a previously performed randomized trial in non-IBC which showed no survival benefit after surgery of the primary tumor [4]. Data on the clinical response on NACT can be rather observer dependent and also depending on physical examination or imaging techniques and is not registered in the NCR. Pathological response was registered and pathological complete response (pCR) was observed in 5.8% of patients treated with NACT. This is lower than the pCR rates for stage III IBC which we observed in a

previous nationwide study of our group, in which pCR of the breast tumor was achieved in 23.2% in 670 patients who received NACT [25]. Since triple negative tumors are more likely to achieve pCR, a potential contributor to the observed difference might be the higher portion of triple negative patients with stage III compared to the cohort of stage IV IBC. Furthermore, patients with stage IV disease might perhaps have larger tumors or more aggressive disease compared to stage III IBC and have more chance of cessation of neoadjuvant systemic therapy in case of progression of disease. Also, a higher percentage of missing data concerning pCR is present in the current stage IV cohort which might also have influenced these results. Studies in metastatic breast cancer revealed that primary tumor burden, number and location of metastases as well as comorbidity might induce selection bias [17]. In an attempt to correct for these factors, we included both age at diagnosis (to indirectly correct for age-related comorbidities), and the number and location of metastatic sites in the Cox regression analyses. Patients who did not receive surgery were older and more often had multiple metastatic sites. However, the effect of surgery on OS in our population remained after correction for number and type of distant metastases at diagnosis and after 1:1 propensity score matching In addition, by including only those patients who were still alive after six months, we made the two treatment groups more comparable. This was reflected by the exclusion of 123 patients with an extremely poor prognosis in the no surgery group, compared to only 10 in the surgery group.

Thirdly, the NCR does not register cause of death, and therefore breast cancer-specific survival could not be determined. However, since it is estimated that distant metastasis is responsible for about 90% of cancer deaths in stage IV breast cancer, our survival data most likely represent breast cancer-specific survival since we only included stage IV IBC [29].

Finally, decisions concerning treatment strategies, and more importantly, reasons for the waiver of (neo)adjuvant modalities could not be investigated in this database. Potential reasons for waiver might be age, metastatic tumor load and comorbidity. Of the patients operated on, those receiving NACT and neoadjuvant trastuzumab were younger, compared to those receiving neoadjuvant antihormonal therapy. Furthermore, salvage surgery might still have been performed in case of omitted neoadjuvant chemotherapy. This might be responsible for the lack of administered NACT in several patients who underwent surgery.

Treatment recommendations are influenced by the experience of the treating physician and judgment about perceived benefit of the treatment related to the patients' general condition. Moreover, the choice of the patient was not registered. This might have influenced the administration of chemotherapy. However, after matching we analyzed the effect of chemotherapy in the multivariable model which was not significant. This suggests that the correction for other variables such as age and breast cancer subtype in the model largely accounts for the differences between the two groups. However, our results can of course still be influenced by the lack of important variables such as comorbidity and performance status. This makes that we are careful in drawing conclusions.

In the absence of prospective evidence, we present data which suggests a possible benefit of surgery of the primary tumor in stage IV IBC. However, unanswered questions remain throughout the literature such as the complication rate after surgery or the quality of life of patients receiving surgery compared to patients without surgery. Future prospective research should be focused on potential survival advantages after surgery of the primary tumor in IBC in combination with quality of life assessment.

5. Conclusion

Surgery of the primary tumor is associated with improved OS in patients with stage IV IBC at time of diagnosis. While we are careful in drawing conclusions, our data may be used as a foundation for prospective studies regarding the survival benefit of surgery in stage IV IBC with incorporation of performance status, presence of comorbidities, patient's preference and the assessment of quality of life.

Ethics approval and consent to participate

The privacy committee of the NCR has approved this study.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the NCR 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 NCR.

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Authors' contributions

All authors read and approved the final manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

DvU: wrote the main paper.

MvM: contributed to the analysis of the results and to the writing of the manuscript.

PB: discussed the results and implications and commented on the manuscript at all stages.

LS: discussed the results and implications and commented on the manuscript at all stages.

KvdH: discussed the results and implications and commented on the manuscript at all stages.

MS: discussed the results and implications and commented on the manuscript at all stages.

SS: gave technical support and conceptual advice and commented on the manuscript at all stages.

CB: conceived the original idea and commented on the manuscript at all stages.

HdW: supervised the project and commented on the manuscript at all stages.

Declaration of competing interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

D.J.P. van Uden: Writing - original draft. **M.C. van Maaren:** Formal analysis, Writing - original draft. **L.J.A. Strobbe:** Writing - review & editing. **P. Bult:** Writing - review & editing. **M.R. Stam:** Writing - review & editing. **J.J. van der Hoeven:** Writing - review & editing. **S. Siesling:** Conceptualization. **J.H.W. de Wilt:** Project administration. **C.F.J.M. Blanken-Peeters:** Supervision, Writing - review & editing.

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