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Original Article

Impact of Adjuvant Systemic Therapy and Differences in Synchronous and Metachronous Bilateral Early Breast Cancer in Long-Term Outcome

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Abstract

Aims: The aim of this study was twofold: to analyse the 20-year outcomes and differences of invasive synchronous bilateral breast cancer (SBBC) and invasive metachronous bilateral breast cancer (MBBC) and to determine the impact on outcomes of the increased use of adjuvant systemic therapy (AST).
Material and methods: Data were obtained from our prospective population-based cohort study that included women, diagnosed with early breast cancer (BC) between 1984 and 2015. Bilateral breast cancer (BBC) was defined as SBBC (≤3 months of the first primary) or MBBC (>3 months after the first primary).
Results: The incidence of SBBC was 1.2% and that of MBBC 9.5%. MBBC status was an independent significant predictor of local failure (hazard ratio [HR]: 1.7; 95% confidence interval [CI]: 1.4–2.2). SBBC status was an independent predictor of distant metastases (HR: 2.3; 95% CI: 1.4–3.7) and showed a worse disease-specific survival (DSS) (HR: 2.4; 95% CI: 1.5–4.0) than unilateral breast cancer (UBC). The use of AST nearly doubled between 1984 and 1998 and 1999 and 2015. The 20-year MBBC-free survival was better for those with AST with an HR of 0.5 (95% CI: 0.4–0.6) than for those without AST. This increased use of AST had a positive effect on DSS for SBBC, MBBC, and UBC.
Conclusion: The increased use of AST over time had a positive effect on incidence of MBBC and on survival for SBBC, MBBC, and UBC. Women suffering from SBBC have almost a three times higher BC mortality rate than women suffering from UBC. Patients with MBBC demonstrated a worse local relapse-free survival than those with unilateral breast cancer (UBC) for both periods.

Key words: Adjuvant systemic therapy; bilateral breast cancer; incidence; metachronous; outcome; synchronous

Introduction

Worldwide, breast cancer (BC) is the most frequently diagnosed female malignancy [1]. Increasing BC incidence rates, improved treatment strategies, and growing life expectancy have led to the increasing incidence of developing bilateral breast cancer (BBC) [2]. BBC accounts for about 2–11% of all BCs [2–5].

Whether the development of BBC compromises prognosis remains controversial. Studies have reported that the prognosis of BBC patients was similar or worse than that for women with unilateral breast cancer (UBC) [6–9].

According to the interval time between the diagnosis of the first and second tumours, BBC can be divided into two groups: synchronous bilateral breast cancer (SBBC) and metachronous bilateral breast cancer (MBBC). This interval time varies between studies, and SBBC has been defined as two cancers diagnosed with an interval of 1–12 months after diagnosis of the first BC, resulting in conflicting predictions of survival [10,11].

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In this study, we used our prospective longitudinal single-centre cohort study to analyse the outcome of SBBC and MBBC versus UBC on outcomes and more specifically looked at the impact of the use of adjuvant systemic therapy (AST) over time.

Patients and Methods

We selected all early-stage BC women, who had been treated with breast-conserving therapy (BCT) from our cohort study, diagnosed between 1984 and 2015.

Patient data, including demographics, histology, staging, treatment, and outcome, were recorded initially and regularly updated. All histological examinations were carried out at the laboratory of pathology. Tumours were classified according to the tumor, nodal and metastases involvement classification (TNM-classification) of the International Union Against Cancer (UICC), 7th edition 2009, resulting in 61.7% stage I, 36.0% stage II, and 2.3% unknown early BCs.

We defined SBBC as BC diagnosed in both breasts simultaneously or as a second BC diagnosed within 3 months of diagnosis of the first tumour and as assumed this to be true SBBC. MBBC was defined as BC diagnosed in the contralateral breast at 3 months after diagnosis of the tumour in the first breast.

For the purposes of this study, the cut-off date for analysis was October 2025.

Treatment

Historically, BCT initially involved lumpectomy with axillary lymph node dissection (ALND), followed by whole breast irradiation (WBI) and a subsequent boost directed to the lumpectomy area. However, after 2001, axillary staging was mainly carried out by sentinel lymph node biopsy (SNB) and followed by ALND in cases of histologically proven axillary lymph node metastases or if sentinel node biopsy had failed. Moreover, since 2010, patients with micrometastases in axillary lymph nodes would often receive irradiation of the axilla rather than ALND [11]. Initially, WBI was delivered at a total dose of 50 Gy in 2-Gy fractions, followed by a boost dose of 14 Gy, irrespective of margin status. Since 2004, the indication to administer a boost dose was determined by age, lymph node status, and margin status. Patients with no lymph node metastases, tumour-free resection margins, and a tumour size $\leq$1.0 cm for age $>$60 years, as well as those with a tumour size $\leq$2.0 cm and age $>$70 years no longer received a boost dose. Since 2010, a hypofractionation schedule of 42.56-Gy WBI with a fraction dose of 2.66 Gy was administered, eventually followed by a boost of 13.3 Gy. Patients over 50 years of age with a tumour-free margin of $>$2 mm for invasive cancer and/or $>$5 mm for ductal carcinoma *in situ* no longer received a boost.

AST and regional radiotherapy were given in line with existing treatment guidelines. Regional radiotherapy was administered in patients suffering from either four or more axillary lymph node metastases or if extranodal disease was detected or in cases of a positive axillary apex node.

In the late 1980s, AST was administered to patients with histologically proven axillary lymph node metastasis. From 1992 onwards, premenopausal patients with histologically proven axillary lymph node metastases received adjuvant chemotherapy. For postmenopausal patients, adjuvant hormonal therapy was given in cases of tumour-positive axillary lymph nodes and bearing an oestrogen receptor (ER)−positive primary BC. Since 1998/1999, the indications for AST were also determined by the mitotic activity index (MAI), histological grade, and tumour size. Premenopausal women received both chemotherapy and hormonal therapy if the ER was positive. Eventually, from 2000 onwards, postmenopausal women also received adjuvant chemotherapy in addition to hormonal therapy, though this was only indicated, in conformance with the guidelines, for patients aged $<$70 years.

In late 2004, treatment with Human Epidermal growth factor Receptor 2 (HER2)-directed therapy in combination with adjuvant chemotherapy was introduced for HER2-positive cases.

Statistical Methods

Time to recurrence and length of follow-up were calculated from the start of BCT. To test for between-group differences in categorical data, chi-squared tests were used.

The local regional relapse-free survival (LRFS) is defined as survival without ipsilateral breast recurrences. Survival statistics were acquired in relation to the number of patients and calculated by the method proposed by Kaplan and Meier. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated for the number of patients. This means that patients who died of other causes were censored at the date of death. Distant metastasis−free survival (DMFS) is defined as survival without distant metastasis in the patient.

For comparison of survival distributions, the log-rank test was used.

The Cox proportional hazards model was used to test for the independent effect of timing of radiotherapy (RT) after adjusting for known prognostic factors and hazard ratios (HRs) estimated at 95% confidence interval (CI) limits are presented. We performed a 20-year multivariate Cox regression stepwise survival analysis that took into account those variables that had been found to be significant during the univariate analysis. All analyses were done on the primary BC.

We used STATA 14.2 (Stata Corp, College Station, TX) software for all the statistical analysis.

Results

The selected data include 5.126 BCT cases in 4.929 women. Considering the 5.126 cases, 197 women had a second BCT in the contralateral breast and 51 women underwent mastectomy of the contralateral breast before

these were recorded in the database. For the analysis, both were excluded, leaving 4.878 BCT cases in 4.878 women. For the analysis, we used for MBBC the primary tumour characteristic and for SBBC, at random one of the tumours.

In this cohort of 4.878 women, 10.7% (521/4.878) had been diagnosed with invasive BBC. In 1.2% of those (59/4.878), SBBC had been diagnosed and MBBC in 9.5% (462/4.878).

The follow-up of the whole cohort took place 3–493 months with a median of 171 months. According to the presence of BBC, those women with SBBC, MBBC, and UBC had median follow-up at 132, 224.5, and 166 months, respectively.

Table 1 shows the characteristics for SBBC, MBBC, and UBC at the time of the BCT. Women with MBBC tended to be younger, showed more frequently carcinoma *in situ* in the lumpectomy specimen, received a boost dose more frequently, and received less AST.

During the period 1984–2015, the use of AST increased due to an increase in adjuvant treatment indications. In the period 1984–1998 (n = 1.494), the average use of AST was 26.8% versus 49.1% in the period 1999–2015 (n = 3.384). A separate analysis will be performed over these two time periods.

The incidence of SBBC and MBBC for the two periods were 1.5% (23/1.494) and 12.7% (190/1.494) for the first period, respectively, and 1.1% (36/3.384) and 8.0% (272/3.384) for the second period, respectively.

The interval between the primary diagnosis and the occurrence of MBBC ranged from 6 to 431 months with a median of 145 months during the first period, and from 4 to 285 months, with a median of 96.5 months, during the second period. Figure 1 shows the impact of AST over the two periods for MBBC. As a consequence of the small number of SBBC, we restricted this analysis to MBBC. In the first period, we had registered 190 MBBCs, of which 75.3% had not received AST compared to 24.7% who did. The 20-year MBBC-free survival for those with AST showed an HR of 1.0 (95% CI: 0.7–1.4) compared to that of those without AST. In the second period, we had registered 272 women who developed MBBCs, of which 66.2% did not receive AST versus 33.8% who did. The 20-year MBBC-free survival was better for those with AST with an HR of 0.5 (95% CI 0.4–0.6) than for those without AST.

Local Relapse-Free Survival

During follow-up, 9.5% of women (465/4.878) developed a local recurrence; the incidence was 5.1% (3/59) in women with SBBC, 22.5% (104/462) in MBBC, and 8.2% (358/4.357) in UBC (Table 2). Of those 22.5% local recurrences with MBBC, 10.8% had been diagnosed with MBBC before the appearance of a local recurrence, 3.9% at the same time, and 7.8% after the local recurrence.

The 20-year LRFS for the whole cohort was 87.1%, and according to the three groups, 80.2% for SBBC, 77.2% for MBBC, and 88.6% for UBC.

A 20-year multivariate Cox regression analysis was performed, followed by a stepwise regression. MBBC was an independent predictor of local failure with an HR of 1.7 (95% CI: 1.4–2.2) compared to UBC (Table 3).

Separate multivariate analyses over the two periods showed for both periods a worse LRFS for MBBC than for UBC but not for SBBC.

Figure 2 shows the 20-year smoothed hazard estimates of the local failures over the two periods for UBC, SBBC, and MBBC. For the first period, we noted a late high peak at about 192 months for SBBC and two small peaks for MBBC at about 126 and 198 months. For the second period, we noticed for MBBC a late high peak starting at about 174 months. The numbers of local recurrences over the two periods are shown in Table 2, showing none for SBBC in the second period but which might be due to the small number of SBBCs.

Distant Metastases–Free Survival

During follow-up, 18.2% of women (886/4.878) developed distant metastases, with 30.5% for SBBC, 26.0% for MBBC, and 17.2% for UBC (Table 2).

The 20-year DMFS for the whole cohort was 79.0%, and according to the groups, 61.7% for SBBC, 75.5% for MBBC, and 79.9% for UBC. According to the two periods, we noted 41.8% DMFS for SBBC in the first period compared to 87.8% in the second period with an HR of 0.2 (95% CI: 0.07–0.7). For MBBC, we noted DMFS values of 73.7% and 76.6% with an HR of 0.8 (95% CI 0.5–1.2) and for UBC, 70.3% and 84.2% with an HR of 0.4 (95% CI: 0.4–0.5) in the first and second periods, respectively.

In the 20-year multivariate Cox regression stepwise analysis, SBBC was an independent predictor of worse DMFS with an HR of 2.3 (95% CI: 1.4–3.7) (Table 2). The outcome for MBBC was not related to a worse or better DMFS than UBC.

Table 3 shows the multivariate analyses over the two periods. For the first period, SBBC had a worse DMFS than UBC, while for the second period, there was no significant worse or better DMFS for SBBC and MBBC. Figure 3 shows the hazard estimates over the two periods for UBC, SBBC, and MBBC. In the first period, SBBS showed a high peak at about 72 months, while for MBBC, we noticed a slight increase with a peak at about 135 months. The second period showed no peak for SBBC and a late peak at about 189 months for MBBC. Table 2 shows the incidence rate of distant metastases for the various types of BBC.

Disease-specific survival

During follow-up, the number of BC tumour deaths among the three groups was 30.5% for SBBC, 22.9% for MBBC, and 15.6% for UBC (Table 2).

The 20-year DSS for the whole cohort was 80.8% and according to the groups, 56.9% for SBBC, 79.5% for MBBC, and 81.6% for UBC. For the two periods, we noted for SBBC 38.9% in the first and 86.6% in the second period with an HR of 0.2 (95% CI: 0.08–0.8) compared to the first period. For MBBC, we noted 75.2% and 83.1% with an HR of 0.6 (95% CI: 0.4–1.0) and for UBC, 72.6% and 85.5% with an HR of 0.4

Table 1
Clinical, histological, and treatment characteristics of the primary tumour at diagnosis for 4.878 breast-conserving treatments in 4.878 women with breast cancers, according to unilateral breast cancer (UBC), synchronous bilateral breast cancer (SBBC), and metachronous bilateral breast cancer (MBBC)

Characteristics	UBC n=4.357 (%)	SBBC* n=59 (%)	MBBC** n=462 (%)	*P* value
Age category				
≤ 40 years	222 (5.1)	3 (5.1)	34 (7.5)	
41–50 years	877 (20.1)	4 (6.8)	119 (25.9)	**<0.001**
>50 years	3258 (74.8)	52 (88.1)	309 (66.7)	
First-degree relative				
None	3324 (76.3)	41 (69.5)	317 (68.6)	
One	833 (19.1)	12 (20.3)	117 (25.3)	**0.002**
≥ 2	200 (4.6)	6 (10.2)	28 (6.1)	
Localisation primary				
Lateral	2915 (66.9)	36 (61.0)	315 (68.2)	
Medial	1258 (28.8)	22 (37.3)	130 (28.1)	0.540
Central	184 (4.2)	1 (1.7)	17 (3.7)	
Histology				
Ductal carcinoma	3582 (82.2)	43 (72.9)	357 (77.1)	
Lobular carcinoma	407 (9.3)	7 (11.9)	61 (13.3)	
Medullar carcinoma	51 (1.2)	1 (1.7)	6 (1.3)	0.081
Tubular carcinoma	185 (4.2)	6 (10.2)	24 (5.2)	
Others	132 (3.0)	2 (3.4)	14 (3.1)	
Hormone receptor status				
ERPR-positive	2890 (66.3)	40 (67.8)	304 (66.0)	
ERPR-negative	598 (13.8)	4 (6.8)	61 (13.1)	
ER-pos + PR-neg	574 (13.2)	8 (13.6)	65 (13.9)	0.500
ER-neg + PR-pos	67 (1.5)	2 (3.4)	11 (2.4)	
Unknown	228 (5.2)	5 (8.5)	21 (4.6)	
Malignancy grade				
Grade 1	1170 (26.8)	16 (27.1)	127 (27.4)	
Grade 2	1693 (38.9)	19 (32.2)	174 (37.7)	0.942
Grade 3	940 (21.6)	12 (20.3)	93 (20.0)	
Unknown	554 (12.7)	12 (20.3)	68 (14.9)	
Mitotic activity index				
≤ 12 p. mm^2	2519 (57.8)	33 (55.9)	265 (57.3)	
> 12 p. mm^2	977 (22.5)	12 (20.3)	100 (21.6)	0.959
Unknown	861 (19.7)	14 (23.7)	97 (21.1)	
Lymph vascular space invasion				
Yes	462 (10.6)	5 (8.5)	44 (9.6)	
None	3838 (88.1)	53 (89.8)	417 (90.2)	0.670
Unknown	57 (1.3)	1 (1.7)	1 (0.2)	
Presence of CIS				
DCIS	1210 (27.8)	15 (25.4)	145 (31.6)	
LCIS	175 (4.0)	5 (8.5)	44 (9.6)	**<0.001**
None	2972 (68.2)	39 (66.1)	273 (58.8)	
IHC profile				
Luminal A	1703 (39.1)	28 (47.5)	135 (29.2)	
Luminal B	110 (2.5)	1 (1.7)	6 (1.3)	
Triple negative	327 (7.5)	4 (6.8)	30 (6.3)	0.766
Nonluminal HER2 positive	74 (1.7)	0	7 (1.5)	
Unknown	2143 (49.2)	26 (44.1)	284 (61.7)	
HER2				
Negative	2324 (53.4)	37 (62.7)	197 (42.3)	
Positive	231 (5.3)	1 (1.7)	18 (3.9)	0.372
Unknown	1802 (41.3)	21 (35.6)	247 (53.8)	
Margin status				
Negative	3886 (89.2)	51 (86.4)	409 (88.5)	
Positive IC	279 (6.4)	6 (10.2)	25 (5.5)	**0.039**
Positive DCIS	156 (3.6)	1 (1.7)	17 (3.7)	
Positive IC + DCIS	36 (0.8)	1 (1.7)	11 (2.4)	

Table 1 (*continued*)

Characteristics	UBC n=4.357 (%)	SBBC* n=59 (%)	MBBC** n=462 (%)	*P* value
Tumour size				
≤1 cm	1113 (25.5)	22 (37.9)	133 (28.5)	
1.1–2 cm	2227 (51.1)	24 (40.7)	228 (49.9)	0.213
2.1–5 cm	986 (22.6)	13 (22.0)	99 (21.6)	
Rest	31 (0.7)	0	0	
Lymph node status				
Negative	3172 (72.8)	44 (74.6)	347 (74.9)	
Positive	1107 (25.4)	12 (20.3)	107 (23.3)	0.436
Unknown	78 (1.8)	3 (5.1)	8 (1.4)	
Adjuvant radiotherapy				
Breast only	3681 (84.5)	52 (88.1)	396 (85.6)	
Breast + regional	676 (15.5)	7 (11.9)	66 (14.4)	0.593
Adjuvant systemic therapy				
None	2469 (56.7)	24 (40.7)	323 (69.9)	
Hormonal	963 (22.1)	21 (35.6)	56 (12.2)	
Chemotherapy	337 (7.8)	3 (5.1)	46 (9.8)	**<0.001**
Chemo + hormonal therapy	481 (11.0)	9 (15.2)	33 (7.2)	
Chemo + immunotherapy	107 (2.4)	2 (3.4)	4 (0.9)	

The *P* value has been calculated on the known components of the variables. CIS: carcinoma *in situ*; DCIS: ductal carcinoma *in situ*; ER, oestrogen receptor; IC, invasive carcinoma; IHC, Immunohistochemical; LCIS, lobular carcinoma *in situ*; PR, progesterone receptor. SBBC*: these are the characteristics of one of the tumour, determined at random; MBBC**: these are the characteristics of the primary tumour.

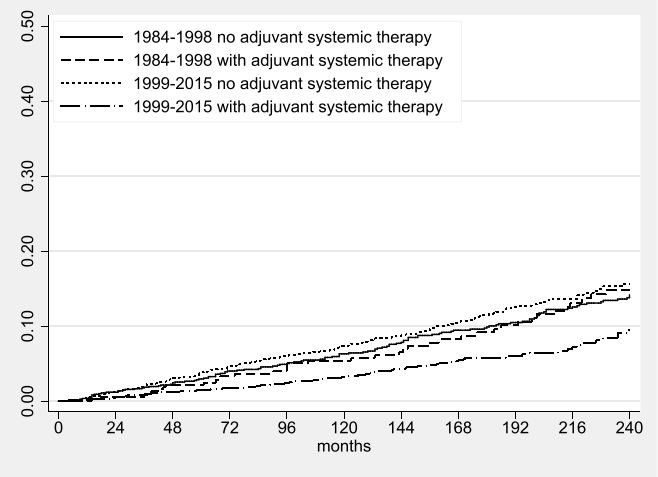

Fig 1. The impact of adjuvant systemic therapy on the incidence of metachronous bilateral breast cancer (MBBC) after the diagnosis of the primary breast cancer over 20-years for the two periods 1984–1998 (n = 1.494 and 26.8% adjuvant systemic therapy) and 1999–2015 (n = 3.384 and 49.1% adjuvant systemic therapy).

(95% CI: 0.4–0.5), respectively. Figure 4 shows the 20-year DSS for MBBC and UBC over the periods.

In the 20-year multivariate Cox regression stepwise analysis, SBBC was associated with a worse DSS with an HR of 2.4 (95% CI: 1.5–4.0) than UBC. MBBC was not associated with a worse or better DSS than UBC (Table 3).

The results of the separate multivariate analyses over the two periods are shown in Table 3.

The number of events over the two periods was 60.9% (14/23) for SBBC over 1984–1998 and 11.1% (4/36) over 1999–2015 (Table 2). This was 34.2% (65/190) for MBBC and 15.1% (41/270) over the two periods.

Discussion

This study with long-term follow-up has demonstrated that the increased use of AST resulted in less MBBC and a better DSS for MBBC, which was also seen in women with SBBC. We demonstrated clear differences between SBBC and MBBC outcomes. Women with SBBC had a worse DMFS and DSS than women with UBC, while women with MBBC showed a worse LRFS.

The 20-year cumulative incidence of 6.6% of BBC is comparable with the literature [12].

The incidence of SBBC, as reported in the literature, is low at between 1 and 3% of all of BC cases, which is comparable with our study [3,15]. This low incidence of SBBC means that results should always be assessed with some caution.

Looking at the characteristics, we noted that women with MBBC were younger, often had a family history of a first-degree relative with BC, and received less AST compared to women with UBC. On the other hand, SBBC was diagnosed more often in older women. We did not find significant differences between UBC, MBBC, and SBBC with respect to malignancy grading, MAI, hormone receptor status, or positive lymph nodes. The latter implies that the phenotypes, expressing more or less aggressive disease, did

Table 2
The cause of death of 4.878 women with breast cancer for unilateral breast cancer (UBC), metachronous bilateral breast cancer (MBBC) and synchronous bilateral breast cancer (SBBC) overall and during the periods 1984–1998 and 1999–2015, including the use of adjuvant systemic therapy and the presence of distant metastases and local recurrences for the two periods

Characteristics	UBC n=4357 (%)	MBBC n=462 (%)	SBBC n=59 (%)	*P* value
Causes of death	**Overall 1984–2015** (n=4878)			
Alive	2.239 (51.4)	223 (48.3)	24 (40.7)	
Tumour dead	679 (15.6)	106 (22.9)	18 (30.5)	**<0.001**
Other causes	1.439 (33.0)	133 (28.8)	17 (28.8)	
Distant metastases				
None	3609 (82.8)	342 (74.0)	41 (69.5)	
Yes	748 (17.2)	120 (26.0)	18 (30.5)	**<0.001**
Local recurrences				
None	3999 (91.8)	358 (77.5)	56 (94.9)	
Yes	358 (8.2)	104 (22.5)	3 (5.1)	**<0.001**
	1984–1998 (n=1.494)			
	n=1281 (85.7%)	n=190 (12.7%)	n=23 (1.5%)	
Cause of death				
Alive	307 (24.0)	54 (28.4)	2 (8.7)	
Tumour dead	357 (27.9)	65 (34.2)	14 (60.9)	**0.001**
Other causes	617 (48.1)	71 (37.4)	7 (30.4)	
Adjuvant systemic therapy				
None	939 (73.3)	143 (75.3)	12 (52.2)	
Yes	342 (26.7)	47 (24.7)	11 (47.8)	0.061
Distant metastases				
None	907 (70.8)	122 (64.2)	9 (39.1)	
Yes	374 (29.2)	68 (35.8)	14 (60.9)	**0.001**
Local recurrences				
None	1.098 (85.8)	134 (70.5)	20 (87.0)	
Yes	183 (14.2)	56 (29.5)	3 (13.0)	**<0.001**
	1999–2015 (n=3.384)			
	n=3076 (91.0%)	n=272 (8.0%)	n=36 (1.1%)	
Causes of death				
Alive	1932 (62.8)	169 (62.1)	22 (61.1)	
Tumour dead	322 (10.5)	41 (15.1)	4 (11.1)	0.342
Other causes	822 (26.7)	62 (22.8)	10 (27.8)	
Adjuvant systemic therapy				
None	1530 (49.7)	180 (66.2)	12 (33.3)	
Yes	1546 (50.3)	92 (33.8)	24 (66.7)	**<0.001**
Distant metastases				
None	2.702 (87.8)	220 (80.9)	32 (88.9)	
Yes	374 (12.2)	52 (19.1)	4 (11.1)	**0.004**
Local recurrences				
None	2.901 (94.3)	224 (82.3)	36 (100.0)	
Yes	175 (5.7)	48 (17.7)	0	**<0.001**

not differ between the three groups. This is not in line with the study of Qui *et al.*, which reported substantial differences between SBBC and MBBC [11].

In 2015, we published our first study on BBC showing a higher local failure rate for MBBC and a higher distant metastasis rate for SBBC both compared to UBC. In the present study, we hoped to confirm those results with more data and longer follow-up times, which gave us the opportunity to present 20-year results and even to look at the value of the increased use of AST over recent decades. During the study period 1984–2015, the use of AST nearly doubled from 26.8% in the first time period to 49.1% in the second period.

The incidence for MBBC across the two periods was 12.7% in the first and 8.0% in the second period, which is in line with a large study by Rasmussen *et al.* that showed a decreasing incidence of MBBC over a 30-year period and attributed this to being most likely an increase in the use of AST [14]. We demonstrated that the decrease was mainly due to the use of adjuvant hormone therapy which is in line with the literature [15]. The numbers of SBBC were too small to look for any impact of the two periods.

Table 3
The 20-year multivariate outcomes of local relapse-free survival (LRFS), distant metastasis–free survival (DMFS), and disease-specific survival (DSS) of 4.878 women with breast cancer according to the presence (MBBC or SBBC) or absence (UBC) of bilateral breast cancer.

Characteristics	LRFS HR (95% confidence interval)	DMFS HR (95% confidence interval)	DSS HR (95% confidence interval)
Overall 1984–2015			
UBC	1	1	1
SBBC	1.1 (0.4–3.6)	**2.3 (1.4–3.7)**	**2.4 (1.5–4.0)**
MBBC	**1.7 (1.4–2.2)**	1.0 (0.8–1.2)	0.9 (0.7–1.1)
1984-1998 with 26.8% adjuvant systemic therapy (n=1494)			
UBC	1	1	1
SBBC	0.7 (0.2–2.4)	**2.5 (1.4–4.5)**	**2.2 (1.2–4.0)**
MBBC	**1.8 (1.2–2.7)**	0.7 (0.6–1.0)	0.7 (0.5–1.0)
1999-2015 with 49.1% adjuvant systemic therapy (n=3384)			
UBC	1	1	1
SBBC	n.a.	1.6 (0.6–4.4)	2.0 (0.7–5.5)
MBBC	**1.9 (1.4–2.7)**	1.2 (0.9–1.7)	1.0 (0.7–1.4)

Significant values are in bold; HR, hazard ratio; MBBC, metachronous bilateral breast cancer; n.a., not available; SBBC, synchronous bilateral breast cancer; UBC, unilateral breast cancer.
Data are presented for the overall time period and over the two time periods.

For the entire cohort, the LRFS, DMFS, and DSS significantly improved in the second period compared to the first period. For the three groups, UBC demonstrated an improvement for all outcomes, while SBBC led to an improvement for DMFS and DSS, and MBBC led to a marginal improvement for DSS only, all over the whole period.

Considering LRFS, we noted for MBBC a significant increase over both periods, namely before and after 1999, compared to UBC. The absolute numbers of local failures decreased from 29.5% to 17.4% in the second period. On the other hand, UBC demonstrated a significant improvement over the two periods, while for SBBC, no local failures were seen during the second period which can be regarded as an improvement, although the numbers are small. Looking at the incidence of MBBC over the two periods, the increased use of AST appears to lead to a postponement of local recurrences. The use of better imaging techniques over time might have had any impact on the diagnosis of MBBC, but this was not evaluable for us as imaging data are not available.

With the high rate of local recurrences in MBBC, the question is raised of whether the first is triggered by the second or vice versa. Since in only 22.5% of all 462 MBBCs were a local recurrence diagnosed, of which 48.1% occurred before, 34.6% after, and 17.3% at the same time of the local recurrence, this question is impossible to answer. On the other hand, we still see a high local recurrence rate in MBBC of 29.5% in the first period and 17.6% in the second. In a time in which personalised follow-up is increasingly common, this observation should make professionals

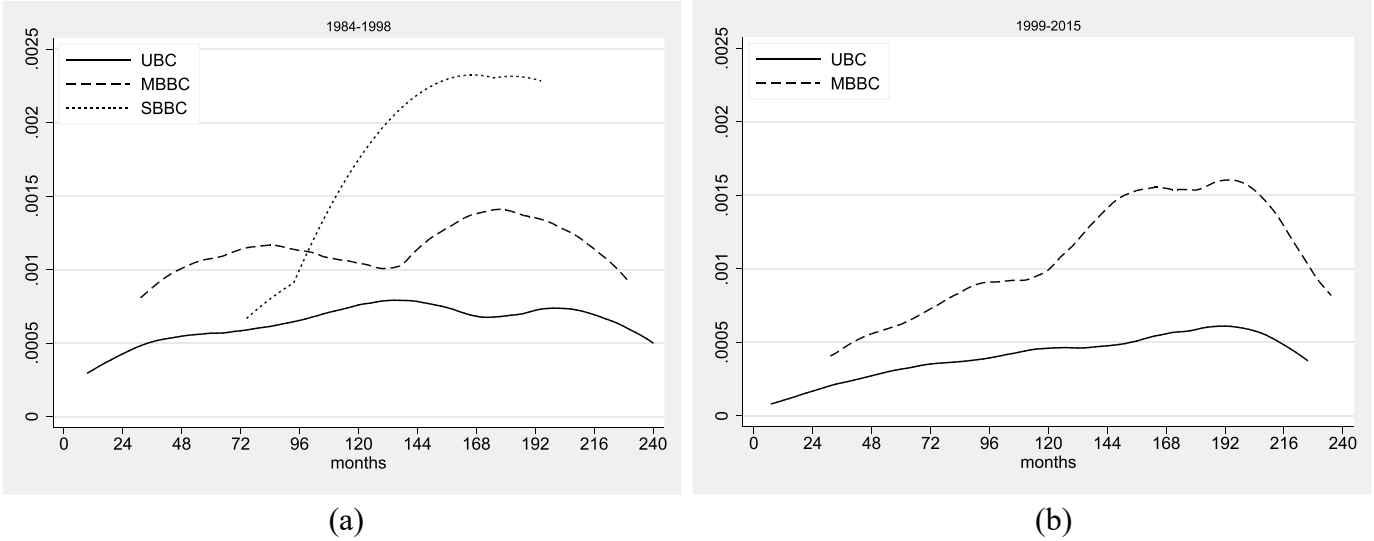

Fig 2. The 20-year hazard estimates for local recurrences over the two periods 1984–1998 (**a**) (n = 1.494 and 26.8% adjuvant systemic therapy) and 1999–2015 (**b**) (n = 3.384 and 49.1% adjuvant systemic therapy) in women with breast cancer according to the presence of unilateral breast cancer (UBC), metachronous and synchronous bilateral breast cancer (MBBC, SBBC).

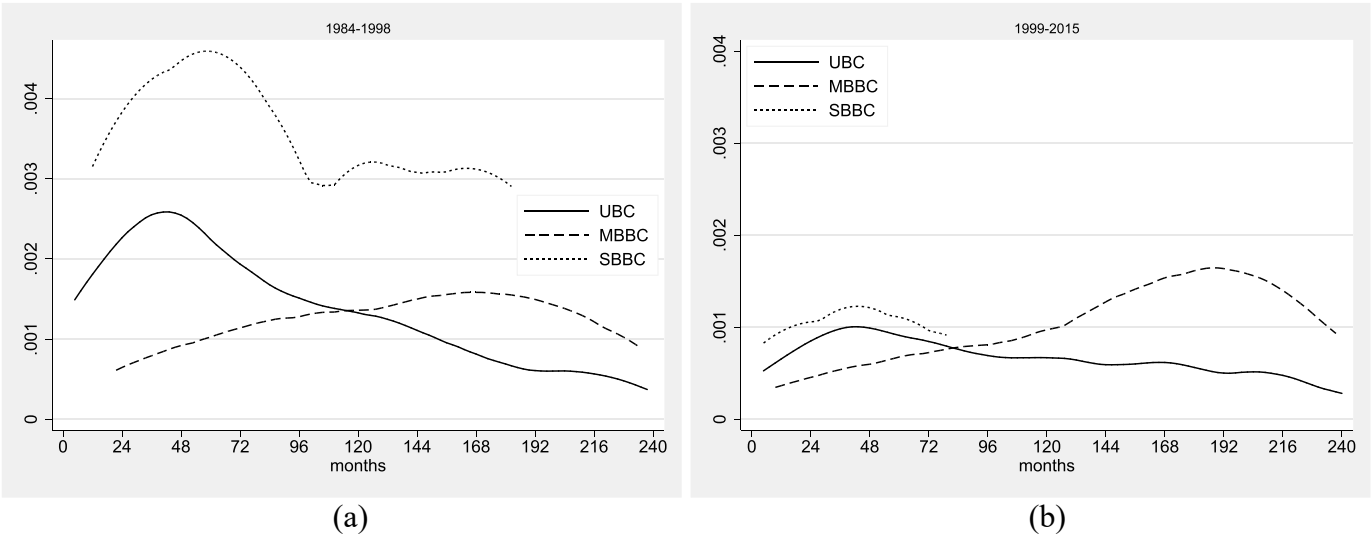

Fig 3. The 20-year hazard estimates for distant metastases over the two periods 1984–1998 (**a**) (n = 1.494) and 1999–2015 (**b**) (n = 3.384) in women with breast cancer according to the presence of unilateral breast cancer (UBC), metachronous bilateral breast cancer (MBBC) and synchronous bilateral breast cancer (SBBC).

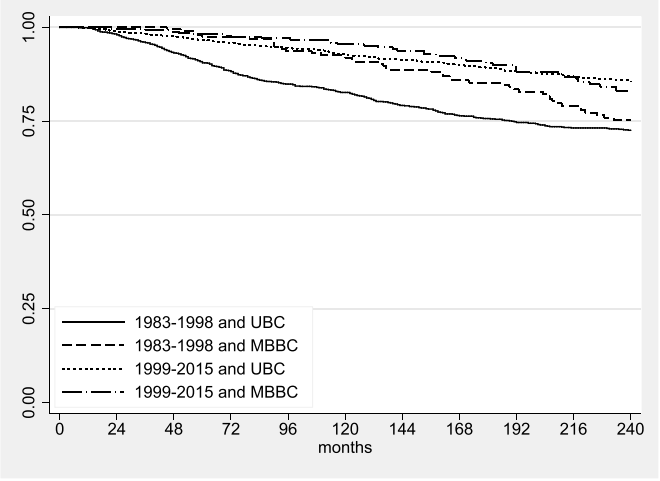

Fig 4. The 20-year disease-specific survival over the two periods 1984–1998 (n = 1.494 with 26.8% adjuvant systemic therapy) and 1999–2015 (n = 3.384 with 49.1% adjuvant systemic therapy) in women with breast cancer according to the presence of unilateral breast cancer (UBC) and metachronous bilateral breast cancer (MBBC).

consider more regular local follow-up (examination or mammography) in case of MBBC.

When we consider the DMFS, the outcome for SBBC almost doubled from 41.8% in the first period to 87.8% in the second. This could be the result of the increased use of AST, although we have to consider the small numbers of SBBC. In the multivariate analyses, an increased HR was noted over both periods for SBBC compared to UBC. This study suggests that the use of AST in SBBC might have a positive effect on DMFS and therefore should be considered as an indication for AST.

The hazard estimates for distant metastases showed for SBBC an absolute decrease in the second period compared to the first, while the decrease for UBC was mainly due to a decrease during the first 10 years; see Figure 3. For MBBC, no improvement was seen; only the time interval of distant metastases appears to have shifted to a later time when we compared the first and second periods. This could be the result of the increased use of AST in the latter period.

With respect to the DSS, SBBS demonstrated, both overall and over the two periods, a worse outcome than UBC, while for MBBC, outcomes were comparable.

Comparing the outcomes of SBBC and MBBC with those reported in the literature is difficult due to use of varying time intervals to divide BBC into SBBC or MBBC. Overall, SBBC is regarded as having a worse survival rate than UBC [10,11,13].

The relevance of this study is that it demonstrates that the occurrence of SBBC is associated with higher rates of distant metastases and impaired DSS. This was demonstrated both overall and over the two time periods. Nowadays, the most common approach when determining if AST is indicated for SBBC is to look at the known parameters, such as histological grade, age, and hormone receptor status. However, this study suggests that SBBC should be used as a separate indicator for AST use. The latter has also been suggested by Holm *et al.* in a meta-analysis and review of SBBC [13]. However, opponents of that view can argue that our study is not a phase III study. We have to bear in mind that performing a randomised phase III trial is not feasible, given the low incidence rates of SBBC of 1–3% of all BCs.

Also, both overall and between the two periods separately, no differences of DMFS and DSS were seen, which

might suggest that there is no effect of the increased use of AST on the outcome for MBBC. Looking at the occurrence of MBBC over a long range of 4–431 months, indicating that MBBC occurs in long-term UBC survivors, one can expect a good survival rate that is comparable to UBC.

The strengths of our study include (1) a large population-based cohort; (2) its completeness, the long follow-up, and the small proportion of patients lost to follow-up (2.0%); (3) all women were treated for their radiotherapy in the same centre; and (4) only one pathology laboratory was involved.

Conclusions

The increased use of AST over time had a positive effect on incidence of MBBC and on survival for SBBC, MBBC, and UBC. Women suffering from SBBC have almost three times the BC mortality rate compared to women suffering from UBC. Women with MBBC demonstrated a worse local relapse-free survival than those with UBC for both periods.

Informed consent

Informed consent was obtained from all individual participants included in this study.

Author contribution

Conception and design: J.J. Jobsen.

Data collection: J.J. Jobsen,

Analysis and interpretation: J.J. Jobsen, H. Struikmans, and J. van der Palen.

Writing of manuscript: J.J Jobsen, H. Struikmans, J van der Palen, and E. Siemerink.

Approval of the final article: J.J Jobsen, H. Struikmans, J. van der Palen, and E. Siemerink.

All authors have read and approved the final manuscript.

Data availability

All data generated or analysed during this study are included in this published article.

Ethics

All procedures performed in studies involving human participants were followed in accordance with the ethical standards of the institution.

The Twente Medical Ethical Committee approved the analysis on the data.

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Conflict of Interest

The authors declare no conflict of interest.

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