Breast Cancer Res Treat (2015) 153:277–283
DOI 10.1007/s10549-015-3538-5

PRECLINICAL STUDY

Bilateral breast cancer, synchronous and metachronous; differences and outcome

J. J. Jobsen[1] · J. van der Palen[2] · F. Ong[1] · S. Riemersma[3] · H. Struikmans[4]

Received: 1 March 2015 / Accepted: 10 August 2015 / Published online: 13 August 2015

Abstract The aims of this study were twofold: to analyze the incidence of patients having synchronous or metachronous bilateral invasive breast cancer (SBBC and MBBC) and to assess the characteristics and outcome compared to those having unilateral breast cancer (UBC). The used data were obtained from our prospective population-based cohort study which had been started in 1983. Bilateral breast cancer (BBC) was categorized as SBBC (≤3 months of the first primary) or MBBC (>3 months after the first primary). The incidence of SBBC was 1 % and that of MBBC 7.0 %. Patients with UBC showed more ductal carcinoma compared to patients with BBC. MBBC status was an independent significant predictor of local failure (HR 1.9; 95 % CI 1.3–2.7). SBBC status was an independent predictor of distant metastases (HR 2.6; 95 % CI 1.4–4.5). Overall survival (OS) was better for MBBC (HR 0.6; 95 % CI 0.4–0.8) and worse for SBBC (HR 2.3; 95 % CI 1.5–3.6) compared to UBC. We noted: (1) MBBC showed a significant higher local failure compared to UBC, (2) SBBC, compared to MBBC and UBC had a significant higher distant metastases rate, (3) disease-specific survival and OS were significantly worse for SBBC compared to UBC and MBBC, and (4) that the OS for MBBC compared to UBC, was significantly better.

Keywords Synchronous · Metachronous · Bilateral breast cancer · Incidence · Prognosis

Introduction

Overall increasing breast cancer incidence rates, improving diagnosis and management modalities, and better life expectancy have resulted in an increasing number of women at risk for bilateral primary breast cancer.

The most common second malignancy in patients with breast cancer is cancer of the contralateral breast [1, 2]. The incidence rate of bilateral breast cancer (BBC) in the literature ranges from 2 to 11 % [3–5]. Women diagnosed with breast cancer are at a two- to six-fold increased risk for contralateral breast cancer compared to the general population of women developing a first primary cancer [1–3].

Most cases bear metachronous tumors and were diagnosed during long-term follow-up. Synchronous tumors are less frequent although their incidence may be increasing with more modern imaging techniques.

There has been conflicting evidence on the impact of BBC on management and outcome. Patients are often treated with bilateral mastectomy rather than breast-conserving therapy, although there was no evidence sustaining such a choice. The potential benefit of prophylactic mastectomy in reducing the rate of contralateral breast cancer and improving survival is controversial [6, 7].

Optimal surveillance and management of women having one or two primary breast cancers is a challenge. Only

✉ J. J. Jobsen
jjjobsen@hetnet.nl; J.Jobsen@mst.nl

[1] Department of Radiation Oncology, Medisch Spectrum Twente, Haaksbergerstraat 55, 7513 ER Enschede, The Netherlands

[2] Department of Research Methodology, Measurement, and Data Analysis, Faculty of Behavioural Science, University of Twente, Enschede, The Netherlands

[3] Laboratorium Pathologie Oost Nederland, Hengelo, The Netherlands

[4] Department of Radiation Oncology, Leiden University Medical Centre, Leiden, The Netherlands

limited data on incidence and management of BBC are available. Moreover, results are conflicting and little is known about the prognostic impact of BBC.

The objectives of this study were to analyze the incidence of synchronous and metachronous bilateral breast cancer (SBBC and MBBC) and to assess the characteristics and outcome of patients with either SBBC or MBBC when compared to those of unilateral breast cancer (UBC).

Patients and methods

From the start of breast-conserving treatment (BCT) in our region in 1983, all patients with breast cancer receiving BCT were registered, and entered into a cohort study at the department of Radiation Oncology of the Medisch Spectrum Twente. Pathological examination was carried out in the Laboratory of Pathology Oost Nederland. From 1983 through to 2011 a total of 4211 BCT in 4065 women was registered. Those patients with BBC and a second BCT were included for primary breast cancer only, leaving 4065 BCT/patients.

We defined SBBC as breast cancer diagnosed in both breasts simultaneously or a second breast cancer developed within 3 months of diagnosis of the first tumor and regard this as true SBBC. MBBC was defined as breast cancer occurring in the contralateral breast over 3 months after diagnosis of the tumor in the first breast that was affected. Forty women presenting with a previous history of breast cancer in the contralateral breast, all of whom treated with mastectomy, were excluded from analyses. Analyses were based on 4025 patients.

To arrive at the most reliable family history (FH), we only recorded the history of the first-degree relatives (FDR) (mother, sister, and daughter). This was recorded as none versus one or more ($\geq$1).

As it is often difficult on morphological grounds to differentiate between a local recurrence and a new primary tumor in the treated breast, all recurrences, invasive carcinoma (IC), and/or DCIS, found in the ipsilateral breast during follow-up were classified as ipsilateral breast tumor recurrence (IBTR).

Patient data, including demographics, histology, staging information, treatment, and outcome were recorded prospectively and updated regularly, resulting in a loss to follow-up of only 0.9 %.

Patients were classified according to the TNM classification, 7th edition 2009.

For the purposes of this study, the cut-off date for analysis was June 2015.

Treatment

BCT initially consisted of lumpectomy with axillary clearance of levels I–III, followed by whole breast radiotherapy followed by a subsequent boost aimed at the lumpectomy cavity. After 2001, axillary staging was primarily performed by sentinel lymph node procedures, only followed by complete axillary dissection in cases with proven axillary lymph node metastases or when sentinel node biopsy had failed. Radiotherapy consisted of 50 Gy in 2 Gy fractions, administered to the whole breast, followed by a subsequent boost of 14 Gy to the lumpectomy cavity, irrespective of margin status. In 16 % of all patients slightly altered fractionation schedules for the boost were used. Since 2004 the indication to administer a boost dose has been dependent on age, lymph node status, and margin status: patients without any lymph node metastases, negative margins, and tumor size $\leq$1.0 cm for age $>$60 years and $\leq$2.0 cm for age $>$70 years did not receive a boost. Adjuvant systemic and regional radiotherapy was given according to existing treatment guidelines. Regional radiotherapy was indicated for patients with 4 or more axillary lymph node metastases or for patients in whom extra-nodal disease was present.

In the late eighties, adjuvant systemic therapy was given to patients with histological proven axillary lymph node metastasis. From 1992 onward, all premenopausal patients with histological proven axillary lymph node metastasis received chemotherapy. Adjuvant hormonal therapy was given to postmenopausal patients if they had tumor-positive axillary lymph nodes. Since 1999 the indications for adjuvant systemic therapy had not only just been dependent on lymph node status but also on the mitotic activity index (MAI), histological grade and tumor size. Premenopausal women received chemotherapy and hormonal therapy if the estrogen receptor status was positive.

In late 2004, treatment with trastuzumab in combination with adjuvant chemotherapy was introduced into our region for Her2-positive cases.

Statistical methods

Time to recurrence and length of follow-up was calculated from the start of the treatment. To test between-group differences for categorical data Chi-square tests were used. The analyses for BBC with regard to local and regional recurrences were performed in relation to *the number of BCT*. The local recurrence-free survival (LRFS) is defined as survival without local recurrent disease, ipsilateral breast tumor recurrence (IBTR).

Distant metastases (DM) and survival statistics were carried out in relation to *the number of patients* and calculated by log rank and the Kaplan–Meier method. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated in relation to the number of patients. This means that data on patients who died of other causes were regarded as censored data. For comparison of survival distributions the log rank test was used.

Multivariate survival analysis was carried out using Cox regression analysis.

Analyses were performed using STATA 12.1 (Stata Corp, College Station, TX).

Results

In the cohort of 4025 women with breast cancer who had all been treated with BCT, 323 (8.0 %) developed a contralateral primary breast cancer. Of those women who had BBC, 41 (1.0 %) showed SBBC and 282 (7.0 %) showed MBBC. The interval between the first primary diagnosis and the development of MBBC ranged from 6 to 330 months with a median of 80.5 months. Figure 1 shows the hazard estimates for the 282 patients with MBBC, in whom a constant increase with a peak at about 254 months had been observed.

Figure 2 shows the incidence of SBBC during the study period.

At the time of diagnosis of the initial tumor, the median age for women with SBBC was 61 years, versus 55 years for those with MBBC, and 58 years for women with UBC.

Table 1 shows the characteristics for SBBC, MBC, and UBC at the time of diagnosis of the primary tumor. The histological patterns showed significant differences with UBC showing more ductal carcinomas, and BBC showing more different types such as lobular, medullar, and tubular carcinoma. Women with BBC tend to be younger. Looking at the adjuvant therapy after diagnosis of the primary tumor, those with MBBC (73.8 %) were significantly less frequently treated with adjuvant systemic therapy.

The follow-up period ranged from 3 to 360 months with a median of 111 months for all 4025 women; those with an MBBC and a SBBC had a median follow-up of 160 and 86 months, respectively.

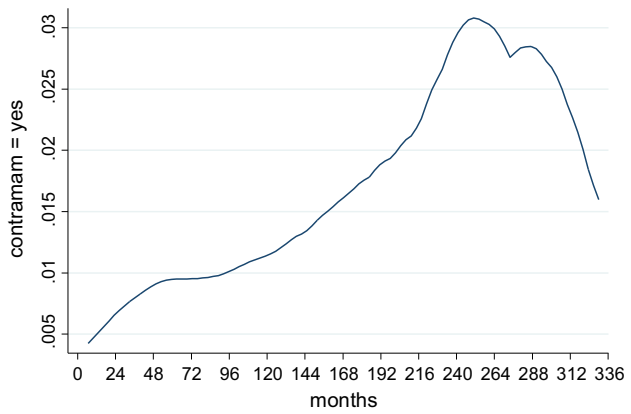

Fig. 1 The smoothed hazard estimates for the occurrence of 282 metachronous bilateral breast cancer cases during follow-up time of the primary breast cancer

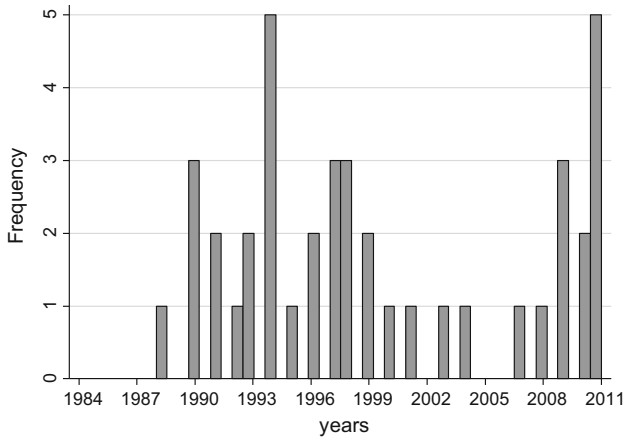

Fig. 2 The incidence of synchronous bilateral breast cancer over a nearly 30-year study period

Local recurrence-free survival (LRFS)

The 15-year LRFS for all women was 89.6 %. Women with UBC had a 15-year LRFS of 90.4 %. For women with MBBC the 15-year LRFS was 82.2 % (HR 2.0; 95 % CI 1.4–2.8; $p < 0.001$) and for SBBC 85.0 % (HR 1.2; 95 % CI 0.3–4.7; $p = 0.834$) compared to UBC.

In multivariate Cox regression analyses, where variables significant in univariate analyses were taken into account, MBBC status was an independent predictor of local failure (HR 1.9; 95 % CI 1.3–2.7; $p < 0.001$).

Figure 3 shows the smoothed hazard estimates of the IBTR rate according to BBC. The curves show significant differences ($p < 0.001$). In patients with UBC a steady increase with a peak at approximately 109 months was seen, whereas in patients with MBBC two peaks at approximately 46 and 126 months were noted.

Separate analyses for MBBC in relation to IBTR showed that 51 (18.1 %) of the 282 with IBTR had both, IBTR and MBBC. Out of those 51 patients, 19 (37.2 %) had their IBTR before having MBBC, 26 (51.0 %) after having MMBC, and 6 (11.8 %) at the same time as having MBBC.

Distant metastases-free survival (DMFS)

The 15-year DMFS for all women was 80.1 %. Women with UBC had a 15-year DMFS of 80.6 %. For women with MBBC the 15-year DMFS was 79.8 % (HR 0.9; 95 % CI 0.7–1.2; $p = 0.637$) and for SBBC 54.4 % (HR 2.7; 95 % CI 1.6–4.7; $p < 0.001$) compared to UBC.

Table 1 Clinical, histological, and treatment characteristics of the primary tumor diagnosis for 4025 women according to unilateral (UBC), metachronous (MBBC), and synchronous (SBBC) bilateral breast cancer

	UBC $n = 3702$ (%)	MBBC $n = 282$ (%)	SBBC $n = 41$(%)	*P* value
Age category				
≤40 years	203 (5.5)	26 (9.2)	3 (7.3)	
41–50 years	797 (21.5)	71 (25.2)	4 (9.8)	0.009
>50 years	2702 (73.0)	185 (65.6)	34 (82.9)	
Family history				
≥1 FDR	885 (23.9)	86 (30.5)	12 (29.3)	
None	2807 (75.8)	194 (68.8)	29 (70.7)	0.032
Unknown	10 (0.3)	2 (0.7)	0	
Histology				
Ductal carcinoma	3020 (81.6)	213 (75.5)	29 (61.7)	
Lobular carcinoma	369 (10.0)	40 (14.2)	5 (10.6)	
Tubular carcinoma	174 (4.7)	16 (5.7)	8 (17)	0.019
Medullar carcinoma	44 (1.2)	6 (2.2)	3 (6.4)	
Others	95 (2.6)	7 (2.6)	2 (4.3)	
Hormone receptor status				
ERPR-positive	2421 (65.4)	176 (62.4)	24 (58.5)	
ERPR-negative	498 (13.4)	43 (15.3)	4 (9.8)	
ER-pos + PR-neg	488 (13.2)	38 (13.5)	6 (14.6)	ns
ER-neg + PR-pos	66 (83.5)	11 (3.9)	2 (4.9)	
Unknown	229 (6.2)	14 (5.0)	5 (12.2)	
Malignancy grade				
Grade 1	911 (24.6)	63 (22.5)	7 (17.1)	
Grade 2	1425 (38.5)	102 (36.2)	12 (29.3)	ns
Grade 3	823 (22.1)	60 (21.8)	11 (26.8)	
Unknown	543 (14.7)	57 (20.7)	11 (26.8)	
Mitotic activity index				
$\leq$ 12 p. mm^2	1991 (53.8)	144 (51.1)	15 (36.6)	
$>$ 12 p. mm^2	885 (23.9)	60 (21.3)	12 (23.3)	ns
Unknown	826 (22.3)	78 (28.4)	14 (34.1)	
Lymph vascular space invasion				
Yes	350 (9.4)	34 (12.0)	5 (12.2)	
None	3324 (89.8)	248 (88.0)	36 (87.8)	ns
Unknown	28 (0.7)	0	0	
Margin status				
Negative	3254 (87.9)	253 (89.7)	35 (85.4)	
Positive IC	272 (7.4)	11 (3.9)	5 (12.2)	0.003
Positive DCIS	141 (3.8)	9 (3.2)	0	
Positive IC + DCIS	35 (1.0)	9 (3.2)	1 (2.4)	
Tumor size				
pT1	2819 (76.2)	220 (78.0)	32 (78.1)	
pT2	872 (23.5)	61 (21.6)	9 (21.9)	ns
Rest	11 (0.3)	1 (0.4)	0	
Lymph node status				
pN0	2648 (71.5)	217 (76.9)	28 (68.3)	
pN1-2	990 (26.7)	60 (21.3)	10 (24.4)	ns
Unknown	64 (1.7)	5 (1.8)	3 (7.3)	
Adjuvant radiotherapy				
Yes	560 (15.1)	51 (18.1)	7 (17.1)	
None	3142 (84.9)	231 (81.9)	34 (82.9)	ns

Table 1 continued

	UBC $n = 3702$ (%)	MBBC $n = 282$ (%)	SBBC $n = 41$(%)	*P* value
Adjuvant systemic therapy				
Yes	1561 (42.2)	74 (26.2)	25 (61.0)	
None	2141 (57.8)	208 (73.8)	16 (39.0)	<0.001

P value has been calculated on the known components of the variables

FDR first-degree relative; *ns* not significant

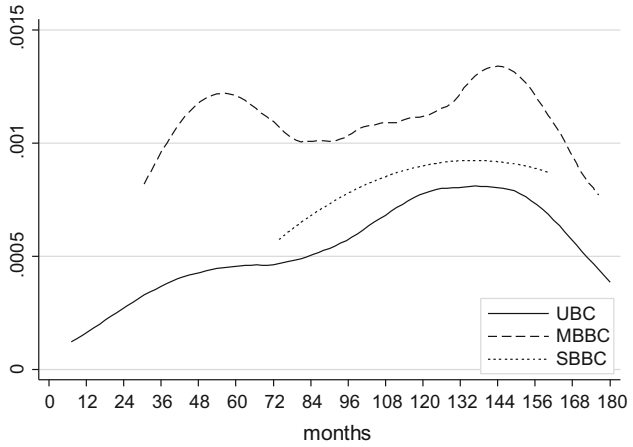

Fig. 3 The hazard estimates for local failure of 4.025 breast-conserving treatments according to bilateral breast cancer, metachronous bilateral breast cancer (MBBC), synchronous bilateral breast cancer (SBBC), and unilateral breast cancer (UBC)

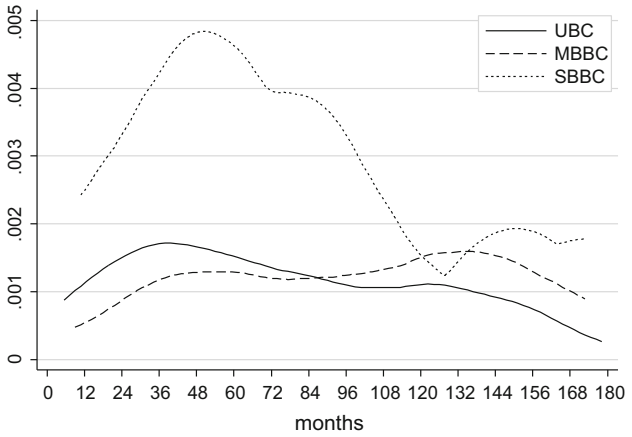

Fig. 4 The Hazard Estimates for distant metastases of 4.025 women with breast cancer, treated with breast-conserving therapy, according to the presence (MBBC or SBBC) or absence (UBC) of bilateral breast cancer

In multivariate Cox regression analyses, where variables significant in univariate analyses were taken into account, SBBC status was an independent predictor of worse DMFS (HR 2.6; 95 % CI 1.4–4.5; $p = 0.001$) compared to UBC.

Figure 4 shows the smoothed hazard estimates of the distant metastases rate according to BBC, which differs significantly ($p < 0.001$). Women with SBBC show a significant high, early peak at about 27 months, in comparison to a low, comparable slope with two small peaks for UBC and MBBC.

Disease-specific survival (DSS)

The 15-year DSS for all women was 82.2 %. Women with UBC had a 15-year DSS of 82.3 %. For women with MBBC the 15-year DSS was 85.0 % (HR 0.8; 95 % CI 0.5–1.1; $p = 0.218$) and for SBBC 51.8 % (HR 3.0; 95 % CI 1.7–5.3; $p < 0.001$) compared to UBC.

In multivariate Cox regression analyses, where variables significant in univariate analyses were taken into account, SBBC status was an independent predictor of worse DSS (HR 2.8; 95 % CI 1.6–5.2; $p = 0.001$), compared to UBC. The MBBC status showed a borderline significantly better DSS (HR 0.7; 95 % CI 0.5–1.0; $p = 0.055$) compared to UBC.

Overall survival (OS)

The 15-year OS for all women was 64.9 %. Women with UBC had a 15-year OS of 64.3 %. For women with MBBC the 15-year OS was 75.0 % (HR 0.6; 95 % CI 0.5–0.8; $p < 0.001$) and for SBBC 31.4 % (HR 2.5; 95 % CI 1.6–3.8; $p < 0.001$) compared to UBC. In multivariate Cox regression analyses, where variables significant in univariate analyses were taken into account, SBBC status was an independent predictor of worse OS (HR 2.3; 95 % CI 1.5–3.6; $p < 0.001$), compared to UBC. The MBBC status was an independent predictor of better OS (HR 0.6; 95 % CI 0.4–0.8; $p < 0.001$) compared to UBC. In analyzing the impact of age we noted that this finding was limited to women aged >50 years.

Figure 5 shows the hazard estimates according to UBC, MBBC, and SBBC. The hazard estimate for SBBC is significantly higher compared to UBC and MBBC ($p < 0.001$).

Due to the long study period we were able to analyze the OS for MBBC for the following three period, 1983–1991, 1992–2003, and 2004–2011. For OS of these periods we noted for MBBC versus UBC the following HR values: 0.5, 0.6, and 0.7, respectively. Except for the latter period, which may be due to a short duration of follow-up, all differ significantly. For SBBC the numbers were too small to perform such analyses.

Discussion

We analyzed the incidence and outcome of BBC and found marked differences between MBBC and SBBC. Firstly, the incidence of BBC is 8.0 % and mainly comprises patients with MBBC. Secondly, the outcome with respect to IBTR and DM differs for MBBC and SBBC. MBBC is related to IBTR and SBBC to DM. Thirdly we noted a positive effect of MBBC on OS, while SBBC had a negative effect on OS.

MBBC was seen more often in younger women while SBBC was more often seen in elderly women.

The incidence rate of 8.0 % is comparable to that described in the literature. Women diagnosed with breast cancer have a two- to six-fold higher risk for contralateral breast cancer compared to women at risk of a first breast cancer in the general population [3]. Improved survival of breast cancer patients, coupled with the increased incidence of the disease, has also played a role in the incidence of contralateral breast cancer [3, 8]. With respect to MBBC we noted an incidence of 7.0 % with a constant increase over the years (Fig. 1). The majority of cases of MBBC occurred after 5 years, with a median time interval of 75 months. The strength of this study is the long time line of data acquisition (1983–2011), providing a good insight

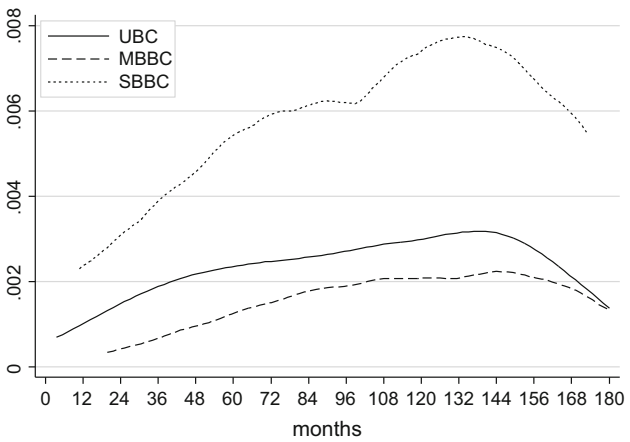

Fig. 5 The hazard estimates for overall survival of 4.025 women with breast cancer, treated with breast-conserving therapy, according to the presence (MBBC or SBBC) or absence (UBC) of bilateral breast cancer

in MBBC development and outcome. Despite the development in treatment and diagnostic tools during the years, in particular adjuvant systemic therapy, the incidence increased over the time mainly due to the long follow-up.

Risk factors for the appearance of BBC in the literature for instance are younger age, lobular histology, and family history [7–10]. In our study the median age for MBBC of 55 years was younger compared to UBC and SBBC. Looking at different age categories we noted significantly younger women with MBBC, and older women for SBBC. With respect to family history we noted a higher rate for MBBC and SBBC compared to UBC, but not significant. With respect to lobular histology, our study showed significantly more lobular histology with MBBC (14.2 %) compared to the other two. This is in contrast to the literature, advocating more lobular type with SBBC [11–13].

We did not find any significant differences between UBC, MBBC, and SBBC with respect to malignancy grading, MAI, hormone receptor status, and positive lymph nodes, meaning that the phenotype, more or less aggressive, between the three did not differ.

In our analyses we noted a significant difference for IBTR. MBBC showed significantly more IBTR's compared to UBC and SBBC. In multivariate analyses, MBBC proved to be an independent prognostic factor for LRFS. The Hazard estimates showed two peaks, an early one and a late one. Despite the higher incidence of IBTR, the OS was significantly better compared to UBC and SBBC. This might indicate that a good treatment of IBTR should have any effect on survival. Few studies confirm the higher IBTR rate in MBBC [7, 14]. Looking at the prognostic value of MBBC in relation to IBTR, it is of interest that out of 282 women with MBBC, just 18.1 % (51/282) had IBTR. From these 49 women, 19 women first had IBTR, 26 first MBBC, and 6 women developed IBTR and MBBC simultaneously. This makes it difficult to conclude which of those two, MBBC or IBTR, had a major impact on the other with respect to prognosis.

Our study showed a low incidence of SBBC compared to the literature, which might be due to the fact that we only included those women with BCT in the cohort [3, 7]. Women diagnosed with SBBC might more often opt for bilateral ablation. This study also demonstrates, that when looking at the incidence of SBBC over time there is no apparent increase, despite the better diagnostic tools nowadays, such as MRI. In meta-analyses of observational studies Holm et al. noted that SBBC had a negative impact on prognosis [15]. Our study showed after Cox regression analyses, incorporating all variables significant in univariate analyses, that SBBC, when compared to UBC, had a negative effect on DMFS, DSS, and OS with HR of 2.6, 3.0, and 2.3, respectively. The reason for a worse prognosis for SBBC compared to UBC might be the larger tumor

burden, or the fact that not just one but two locations, creating a bigger chance on metastases. A study by Kwast et al. found an increased risk of third primary cancers of non-breast origin among women with BBC [16]. This might indicate that SBBC represent a yet undiscovered genetical entity, which might also be of significance in the progression of the cancer. International evidence of the prognostic significance of SBBC is not consistent, although many studies suggest an equivalent or poorer survival compared to UBC [7, 14, 17–22]. Despite the worse prognosis for SBBC, it is not accepted as a predictor for adjuvant systemic therapy. However, the latter should be considered, as we will never have randomized trials or large studies of SBBC, due to the small incidence rate of about 1 %.

Our study showed a significantly better OS for MBBC compared to UBC, irrespective of the time period. This was limited to women older than 50 years at the time of the first primary. With respect to DSS, the MBBC showed borderline significance as a predictor for a better DSS compared to UBC. This might be due to the developments in adjuvant systemic therapy over the years. Women with UBC, when compared to those with MBBC, comprised significantly older women, which might be a reason for the better OS. The latter has not been mentioned before in the literature.

The weakness of this study is the small number of women with SBBC. The strong points of our study include (1) a large population—based cohort, (2) the completeness, the long follow-up and the small number of patients lost to follow-up, (3) all women treated in one center, and (4) one pathology laboratory. The conclusions of this study are (1) MBBC show a significant higher local failure compared to UBC, (2) SBBC show a significant higher DM rate compared to MBBC and UBC, (3) the DMFS, DSS, and OS are significantly worse for SBBC compared to UBC and MBBC, and (4) the OS for MBBC is significantly better compared to UBC. SBBC seems to be a predictive factor for DMFS, DSS, and OS and should be considered in relation to adjuvant therapy.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

References

1. Soerjomataran I et al (2005) Risk of second primary breast and urogenital cancers following female breast cancer in the south of The Netherlands, 1972–2001. Eur J Cancer 41:2331–2337
2. Lu W et al (2009) The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer. Eur J Cancer 45:3000–3007
3. Chen Y, Thompson W, Semenciw R et al (1999) Epidemiology of contralateral breast cancer. Cancer Epidemiol, Biomark Prev 8:855–861
4. Beinart G, Gonzalez-Angulo AM, Broglio K et al (2007) Clinical course of 771 patients with bilateral breast cancer: characteristics associated with overall and recurrence-free survival. Clin Breast Cancer 7:867–874
5. Kheirelseid EAH, Jumustafa H, Miller N et al (2011) Bilateral breast cancer: analysis of incidence, outcome, survival and disease characteristics. Breast Cancer Res Treat 126:131–140
6. Quan G, Pommier SJ, Pommier RF (2008) Incidence and outcome of contralateral breast cancer. Am J Surg 195:645–650
7. Hartmann LC, Schaid DJ, Woods JE et al (1999) Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77–84
8. Bernstein JL, Lapinski RH, Thakore SS et al (2003) The descriptive epidemiology of second primary breast cancer. Epidemiology 14:552–558
9. Li CI, Malone KE, Porter PL et al (2003) Epidemiologic and molecular risk factors for contralateral breast cancer among young women. Br J Cancer 89:513–518
10. Malone KE, Daling JR, Weiss NS et al (1996) Family history and survival of young women with invasive breast carcinoma. Cancer 78:1417–1425
11. Verkooijen HM, Chatelain V, Fioretta G et al (2007) Survival after bilateral breast cancer: results from a population-based study. Breast Cancer Res Treat 105:347–357
12. Senkus E, Szada J, Pieczyriska B et al (2014) Are synchronous and metachronous bilateral breast cancers different? An immunohistochemical analysis aimed at intrinsic tumor phenotype. Int J Clin Exp Pathol 7:353–363
13. Shi YX, Xia Q, Peng RJ et al (2012) Comparison of clinicopathological characteristics and prognoses between bilateral and unilateral breast cancer. J Cancer Res Clin Oncol 138:705–714
14. Beckmann KR, Buckingham J, Craft P et al (2011) Clinical characteristics and outcome of bilateral breast cancer in an Australian cohort. Breast 20:158–164
15. Holm M, Tjonneland A, Balslev E et al (2014) Prognosis of synchronous bilateral breast cancer: a review and meta-analysis of observational studies. Breast Cancer Res Treat 146:461–475
16. Kwast ABG, Liu L, Roukema JA et al (2012) Increased risk of third primary cancers of non-breast origin among women with bilateral breast cancer. Br J Cancer 107:549–555
17. Carmichael AR, Bendall S, Lockerbie L et al (2002) The long-term outcome of synchronous bilateral breast cancer is worse than metachronous of unilateral tumors. Eur J Surg Oncol 28:388–391
18. Heron DE, Komarnicky LT, Hyslop T et al (2000) Bilateral breast carcinoma. Risk factors and outcome for patients with synchronous and metachronous disease. Cancer 88:2739–2750
19. Roder D, De Silva P, Zorbas H et al (2012) Survival from synchronous bilateral breast cancer: the experience of surgeons participating in the Breast audit of the Society of Breast Surgeons of Australia and New Zealand. Asian Pac J Cancer Prev 13:1412–1418
20. Kolias J, Ellis IO, Elston CW et al (2001) Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg 25:1117–1124
21. Jobsen JJ, Van der Palen J, Ong F et al (2003) Synchronous bilateral breast cancer: prognostic value and incidence. The Breast 12:83–88
22. Polednak AP (2003) Bilateral synchronous breast cancer: a population-based study of characteristics, method of detection, and survival. Surgery 133:383–389