Original Article

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Clinicopathological Characteristics, Treatment and Outcome of 123 Patients with Synchronous or Metachronous Bilateral Breast Cancer in a Swiss Institutional Retrospective Series

Alexandre Huber[1], Stéphanie J. Seidler[2], Daniela E. Huber[2]
[1]Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[2]Gynecology Department, Hôpital du Valais, Sierre, Switzerland

ABSTRACT

Objective: To evaluate the prognosis, the patient and tumor characteristics, and the treatment of bilateral breast cancer (BBC) and to compare synchronous (sBBC) and metachronous BBC (mBBC).

Materials and Methods: For this retrospective study, data from 123 consecutive BBC patients (56 sBBC and 67 mBBC) that were presented at the Sion Hospital tumor board between 2007 and 2018 were collected retrospectively.

Results: Mean follow-up was 85 months. 2nd tumors in both groups were more often diagnosed radiologically. Mean time interval between mBBC was 115 months. A shorter interval was positively correlated with a negative hormonal receptor (HR) status and higher grade for the 2nd tumor. There was no difference in overall survival (OS) and relapse-free survival (RFS) between sBBC and mBBC. OS was longer if both tumors were hormonal receptor (HR) positive. mBBC exhibited a higher local recurrence rate than sBBC (p=0.03).

Conclusion: sBBC and mBBC patients did not show any difference in OS or RFS, although mBBC patients were more prone to local relapses.

Keywords: Bilateral breast cancer, contralateral breast cancer, synchronous, metachronous, survival, local relapse

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Introduction

Breast cancer is the second most frequent cancer in women and the fifth cause of female malignancy-related deaths worldwide (1). In our population, according to the most recent report of the regional tumor registry, breast cancer was the first female cancer (32% of newly diagnosed cancer cases, with a mean range of 249 new cancers/year between 2011 and 2015 and the second in terms of specific mortality (16% of all cancer-related death in women) (2).

Breast cancer survivors are at risk of developing a second primary malignancy, the most common being a second ipsilateral or contralateral breast cancer (3). Reported incidence of bilateral breast cancer (BBC) varies from 1.4% to 11.8% of all breast cancer cases (4, 5). The availability and adhesion to the screening programs, increasing use of modern imaging methods such as digital tomosynthesis, elastography and MRI, progress in systemic and loco-regional treatments and growing life expectancy result in an increasing BBC incidence.

The time interval between the index and the 2nd tumor classifies BBC into synchronous (sBBC) and metachronous (mBBC). According to the World Health Organization (WHO), synchronous tumors are diagnosed at the same time as the index tumor or in the three following months. The contralateral tumor is deemed metachronous if diagnosed three months or more after the index tumor. Some authors extend this cutoff to 6 or even 12 months (6, 7).

Circulating breast cancer cells may be detected in 20 to 25% of patients with localized disease at the time of diagnosis raising the question of the *de novo* vs. metastatic origin of the contralateral 2nd tumor (8, 9). However, genomic analyses indicate that only a small proportion (6%) of contralateral breast cancers are metastasis of the index tumor (10). Controversies persist about the impact of contralateral

Corresponding Author :
Daniela Huber; DanielaEmanuela.Huber@hopitalvs.ch

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breast cancer on survival and how the time interval between the index and the 2nd tumor influences the prognosis of these patients with conflicting reports (11-19). So far, there are no specific recommendations for the treatment of BBC despite the fact that their prognosis seems poorer than unilateral tumors (5, 11, 14, 15, 18-20). Systemic treatments are usually guided by the sBBC tumor with the worse prognosis, while mBBC tumors tend to be treated like independent unilateral breast cancer.

We hereby report the analysis of 123 sBBC and mBBC patients treated and followed-up in our Institution aiming at identifying differences in epidemiological, clinical and pathological characteristics and at comparing outcomes.

Materials and Methods

Information on patients with BBC, who were treated for at least one tumor and followed-up in our Institution, was retrospectively collected by systematically screening tumor board registers between January 1st, 2007 and December 31st, 2018. Data were gathered from the medical files of the institution or general practitioners when follow-up data were incomplete. The study was approved by the local ethics committee (protocol number 2018-02320).

Patients were divided in two groups based on the time interval between the surgical resection of the contralateral breast tumor. Following the WHO classification for BBC, all 2nd contralateral breast cancers detected within 3 months from the diagnosis of first tumor were considered as sBBC. The one with the larger diameter was considered the index tumor. All contralateral breast tumors diagnosed after 3 months were considered mBBC.

The family history of patients was considered positive when a first- or second-degree relative had breast cancer. Age at both first and second cancer diagnosis, tobacco smoking and alcohol consumption, diagnostic tool (clinical examination, mammography, ultrasonography or MRI), histological tumor characteristics and type of surgery and adjuvant/ neoadjuvant treatments were recorded.

Histological type and grade (Elston and Ellis), multicentricity, lymph node status, pathological stage, HR status, Her-2/neu expression were extracted from pathology reports. Tumors were classified according to the International classification of Disease for Oncology as *in situ*, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), mixed IDC/ILC or other type. Tumors (T) were classified as smaller than or equal to 2 cm (T1), T2-3 or T4. The expression of HR and Her-2/neu was evaluated immunohistochemically. Her-2 was considered positive with a 3+ expression and negative when absent or with a 1+ expression. FISH evaluation classified further Her-2/neu status in positive or negative for intermediate 2+ tumors. Axillary node involvement was categorized as negative or positive (N0 or N1-3) and the axillary surgery in sentinel node biopsy and classical lymphadenectomy. Breast surgery was categorized as none, conservative (lumpectomy) or radical (mastectomy). Adjuvant radiotherapy and systemic therapy (chemotherapy or hormonotherapy) were recorded if performed.

The two groups (sBBC and mBBC) were compared for patient and tumor characteristics and the following outcomes: disease-free survival (DFS), overall survival (OS), specific mortality, and locoregional and

Key Points

- No difference in global and recurrence-free survival was observed between sBBC and mBBC patients.
- Metachronous BBC patients had a higher rate of loco-regional relapse than sBBC. Most loco-regional relapses were due to the 2nd tumors in mBBC patients.
- Metachronous BBC were more frequently hormone receptor-negative than sBBC.

Table 1. Patient characteristics

	Synchronous (%)	Metachronous (%)	Total (%)	p
Total	56 (100)	67 (100)	123 (100)	
Age				0.6
Mean (min-max)	63 (28-90)	62 (42-86)	63 (28-90)	
≤40	3 (5)	0 (0)	3 (2)	
41-50	11 (20)	12 (18)	23 (19)	
51-60	7 (13)	14 (21)	21 (17)	
>60	35 (63)	41 (61)	76 (62)	
Family History				0.99
Yes	26 (46)	35 (52)	61 (50)	
No	23 (41)	31 (46)	54 (44)	
Unknown	7 (13)	1 (1)	8 (7)	
Menopause				0.002
Yes	41 (73)	62 (93)	103 (84)	
No	15 (27)	4 (6)	19 (15)	
Man	0 (0)	1 (1)	1 (1)	
Marital status				0.6
Single	4 (7)	3 (4)	7 (6)	
Married	21 (38)	38 (57)	59 (48)	
Divorced	5 (9)	5 (7)	10 (8)	
Widowed	3 (5)	6 (9)	9 (7)	
Unknown	23 (41)	15 (22)	38 (31)	
Alcohol				0.21
Yes	8 (14)	20 (30)	28 (23)	
No	23 (41)	31 (46)	54 (44)	
Unknown	25 (45)	16 (24)	41 (33)	
Smoker				0.65
Yes	11 (20)	19 (28)	30 (24)	
No	25 (45)	35 (52)	60 (49)	
Unknown	20 (36)	13 (19)	33 (27)	
Pregnancies				0.34
Yes	37 (66)	52 (78)	89 (72)	
No	15 (27)	14 (21)	29 (24)	
Unknown	4 (7)	1 (1)	5 (4)	

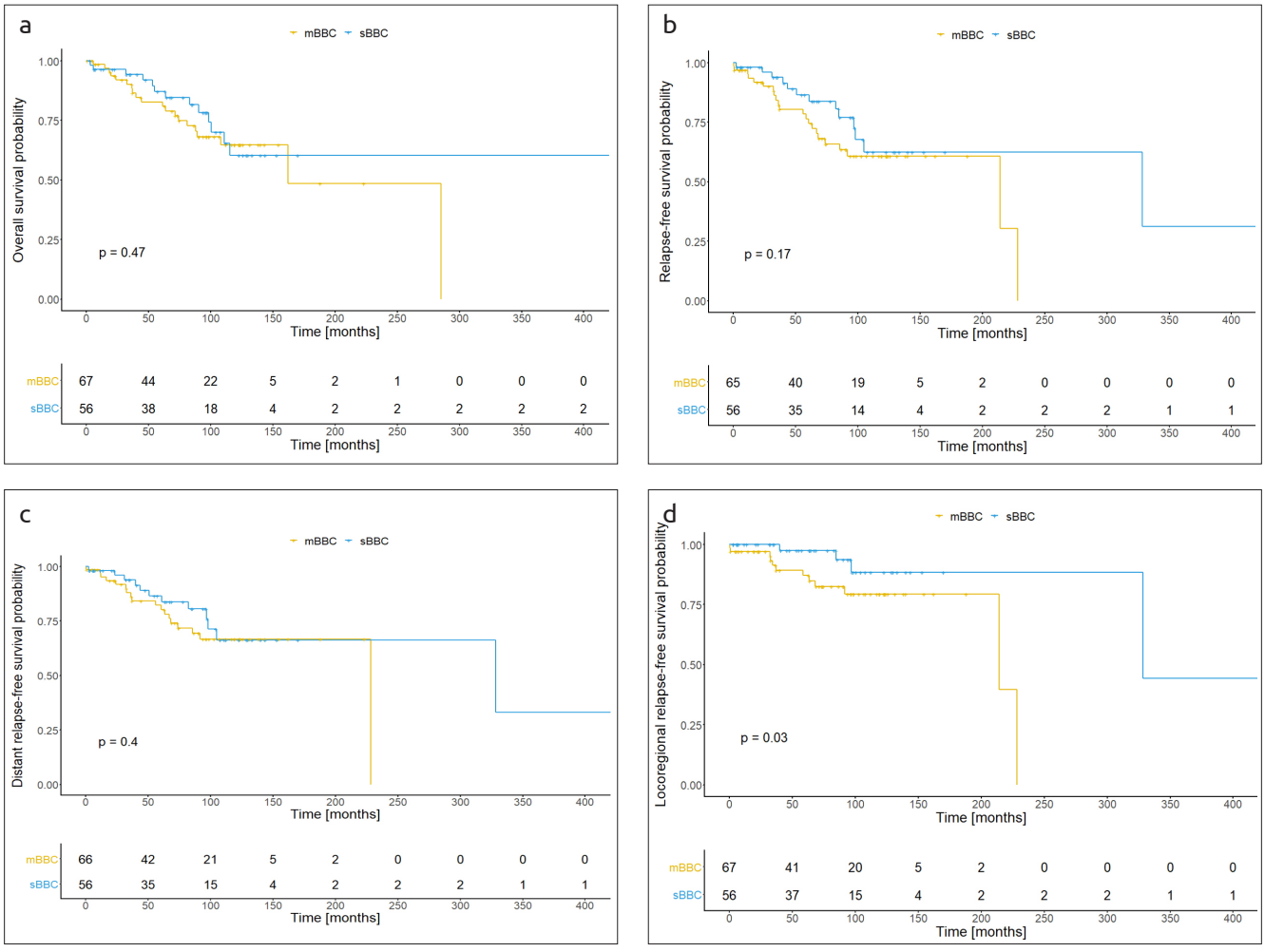

Figure 1. a-d. Survival analyses of sBBC and mBBC patients. (a) Overall survival. (b) Relapse-free survival (c) Distant relapse-free survival. (d) Loco-regional relapse-free survival

distant recurrence-free survival. Survival was calculated from the date of the second intervention (or the first if sBBC) until the date of death (OS) or relapse (DFS) with censoring for loss of follow up.

Statistical analysis

Data were analyzed by R version 3.5.3 (Lucent Technologies, USA), considering p values <0.05 as significant. All continuous variables were described by their mean and range and were analyzed using the Kruskal-Wallis test. Categorial variables were compared using the Chi-square test after exclusion of missing values. Survival curves were computed using the survival R package (version 2.44) by means of the Kaplan-Meier method and compared using the log rank test. Univariate and multivariate survival analyses were performed with Cox proportional hazard models. Agreement between tumor characteristics for each patient were analyzed using Cohen's kappa statistics.

Results

Population description

We identified 123 patients, 122 female and 1 male. Fifty-six (45.5%) were diagnosed with sBBC and 67 (54.5%) with mBBC. The mean time interval between mBBC was 115.5 months (min 13 months, max 288 months, SD 68.8). The median time interval was 111 months. The mean age of sBBC patients was 63, whereas for mBBC the mean age is 53 for the index tumor and 62 for the 2nd tumor. Patient inclusion by date of surgery of the 2nd tumor is plotted in Supplementary Figure S1. The mean follow-up time was 82 months for mBBC patients, 89 months for sBBC and 85 months for the entire cohort.

Patients' characteristics are summarized in Table 1. They did not show any difference at inclusion except for the menopausal status, as mBBC patients were more frequently menopaused compared to the sBBC population (p=0.002). Sixty-one out of 123 patients (49.6%) had a positive family history without significant differences between the groups.

Tumor characteristics

The tumor characteristics are compared in Table 2. No significant difference between the histological types of the 1st and 2nd tumors were observed for sBBC and mBBC. In both groups, most of the tumors were invasive ductal carcinomas. Second tumors of sBBC patients were more frequently well differentiated than mBBC 2nd tumors (p<0.001). Conversely, a higher prevalence of poorly differentiated tumors was observed in mBBC 2nd tumors compared to 2nd sBBC (p<0.001).

Second sBBC tumors were more often diagnosed radiologically than index tumors (p<0.001). Although there was a similar tendency in the mBBC cohort, the difference was not significant (p=0.08). Second sBBC tumors were more often of small size (T1) compared to sBBC index tumors (p=0.002) and to the mBBC 2nd tumors (p=0.04). They

Table 2. Tumor characteristics

	Synchronous (%)		Metachronous (%)		
	Index	2nd tumor	Index	2nd tumor	p (x^2)
Total (%)	56 (100)	67 (100)			
Histology					0.74
In situ only	4 (7.1)	9 (16.1)	3 (4.5)	4 (5.9)	
Invasive ductal	35 (62.5)	33 (58.9)	44 (65.7)	44 (65.7)	
Invasive lobular	9 (16.1)	9 (16.1)	12 (17.9)	13 (19.4)	
Invasive mixt	5 (8.9)	3 (5.3)	4 (5.9)	3 (4.5)	
Other	1 (1.8)	1 (1.8)	2 (3)	3 (4.5)	
Unknown	2 (3.6)	1 (1.8)	2 (3)	0	
Grade					< 0.001
1	16 (28.6)	24 (42.8)	17 (25.4)	7 (10.4)	
2	25 (44.6)	24 (42.8)	26 (38.8)	35 (52.3)	
3	12 (21.4)	4 (7.2)	17 (25.4)	23 (34.3)	
Unknown	3 (5.4)	4 (7.2)	7 (10.4)	2 (3)	
Multifocal					0.24
Yes	18 (32.2)	14 (25)	15 (22.4)	12 (17.9)	
No	35 (62.5)	41 (73.2)	49 (73.1)	55 (82.1)	
Unknown	3 (5.3)	1 (1.8)	3 (4.5)	0	
pT					0.037
T1 (≤2 cm)	34 (60.7)	49 (87.5)	39 (58.2)	49 (73.1)	
T2-3	17 (30.6)	5 (8.9)	22 (32.8)	15 (22.4)	
T4	2 (3.6)	1 (1.8)	3 (4.5)	2 (3)	
Unknown	3 (5.3)	1 (1.8)	3 (4.5)	1 (1.5)	
pN					0.01
N-	33 (58.9)	45 (80.4)	38 (56.7)	42 (62.7)	
N+	20 (35.8)	6 (10.7)	21 (31.3)	20 (29.8)	
Unknown	3 (5.3)	5 (8.9)	8 (12)	5 (7.5)	
Hormonal receptors					0.02
ER+ / PR+	45 (80.4)	43 (76.7)	42 (62.7)	39 (58.2)	
ER- / PR-	6 (10.7)	2 (3.6)	15 (22.4)	18 (26.9)	
ER+ / PR-	3 (5.3)	4 (7.2)	5 (7.5)	9 (13.4)	
ER- / PR+	0	1 (1.8)	1 (1.5)	0	
Unknown	2 (3.6)	6 (10.7)	4 (5.9)	1 (1.5)	
HER-2 status					0.47
Positive	7 (12.5)	4 (7.2)	3 (4.5)	11 (16.4)	
Negative	39 (69.6)	36 (64.3)	19 (28.3)	39 (58.2)	
Unknown	10 (17.9)	16 (28.5)	45 (67.2)	17 (25.4)	

also exhibited a less frequent axillary lymph node invasion compared to sBBC index tumors (p<0.001) and mBBC 2nd tumors (p=0.01). HR-negative tumors were more prevalent in the mBBC cohort than in the sBBC cohort (p<0.001).

Histological type concordance between the index and 2nd tumors was 58.5% (kappa 0.175, p=0.033) for the mBBC group, and 48.1% (kappa 0.095, p=0.249) for the sBBC group. Histological grade concordance was 27.6% (kappa -0.124, p=0.173) for mBBC patients, and

Table 3. Surgical treatments

	Synchronous (%)		Metachronous (%)		
	Index	2nd tumor	Index	2nd tumor	p (x^2)
Total	56 (100)	67 (100)			
Breast surgery					0.13
Conservative	28 (50)	31 (55.3)	47 (70.2)	40 (59.7)	
Mastectomy	28 (50)	25 (44.6)	20 (29.8)	27 (40.3)	
Margins					0.90
R0	46 (82.1)	47 (83.9)	53 (79.1)	55 (82.1)	
R1	10 (17.9)	8 (14.3)	13 (19.4)	11 (16.4)	
Unknown	0	1 (1.8)	1 (1.5)	1 (1.5)	
Second surgery					0.24
No	47 (83.9)	53 (94.6)	60 (89.6)	62 (92.5)	
Yes	9 (16.1)	3 (5.4)	7 (10.4)	5 (7.5)	
Axillary surgery					<0.001
Sentinel node	30 (53.5)	39 (69.6)	11 (16.4)	38 (56.7)	
Axillar lymphadenectomy	23 (41.1)	10 (17.9)	51 (76.1)	25 (37.3)	
None	3 (5.4)	6 (10.7)	4 (6)	4 (6)	
Unknown	0	1 (1.8)	1 (1.5)	0	

Table 4. Radiotherapy and systemic treatments

	Synchronous (%)	Metachronous (%)		
		Index	2nd tumor	p (x^2)
Total	56 (100)	67 (100)		
Radiotherapy				0.13
Yes	43 (76.8)	55 (82.1)	45 (67.2)	
No	13 (23.2)	12 (17.9)	22 (32.8)	
Hormonotherapy				0.047
Yes	49 (87.5)	47 (70.2)	44 (65.7)	
No	7 (12.5)	19 (28.3)	19 (28.3)	
Unknown	0	1 (1.5)	4 (6)	
Chemotherapy				0.008
Yes	17 (30.3)	38 (56.7)	25 (37.3)	
No	39 (69.7)	28 (41.8)	38 (56.7)	
Unknown	0	1 (1.5)	4 (6)	

56.9% (kappa 0.308, p=0.0023) for sBBC patients. Considering all combinations of estrogen and progesterone receptor expression, HR status concordance was 60% (kappa -0.016, p=0.846) for the mBBC cohort, and 90.7% (kappa 0.462, p>0.001) for the sBBC cohort.

Treatment

Types of breast surgery did not differ among groups or between index and 2nd tumors (Table 3). Sentinel lymph node biopsies were less prevalent among mBBC index tumors (p<0.001 vs. sBBC index tumor; p<0.001 vs. mBBC 2nd tumors). Conversely, axillary lymphadenectomy was more often performed for the mBBC index tumor (p=0.01 vs. sBBC index tumor; p=0.002 vs. mBBC second tumor). Axillary lymphadenectomy was also more prevalent for the 2nd tumor among mBBC patients compared to sBBC patients (p=0.0496). No significant difference in adjuvant radiotherapy was observed (Table 4). Adjuvant hormonotherapy was less prevalent in the mBBC cohort than in sBBC (p=0.03). Conversely, mBBC patients received more chemotherapy for their index tumor compared to sBBC patients (p=0.003). They also received significantly more chemotherapy for their index tumor than for their 2nd tumor (p=0.04).

Outcome

5- and 10-year OS were 87.1% and 60.4% respectively in the sBBC cohort; 82.8% and 64.7% in the mBBC cohort (Figure 1a). 5- and 10-year DFS were 86.4% and 62.4% respectively for sBBC patients; 76.8% and 61.5% for mBBC patients (Figure 1b).

Distant RFS did not show any significant difference between the two groups with 5- and 10-year rates of 86.4% and 66.2% respectively for the sBBC cohort and 82.2% and 66.7% for the mBBC cohort (Figure 1c). Loco-regional RFS was significantly higher in the sBBC group with 5- and 10-year rates of 97.6% and 88.5% compared with the mBBC group with 87.1% and 79.4% rates respectively (Figure 1d). mBBC loco-regional relapses were more frequently observed on the side of the 2nd tumor (8/11) vs. the index tumor (2/11); data were missing for 1 loco-regional relapse.

Of all 17 loco-regional relapses, 13 occurred in the breast only, 3 in the axilla, and 1 in both breast and axilla. Among the 4 axil-

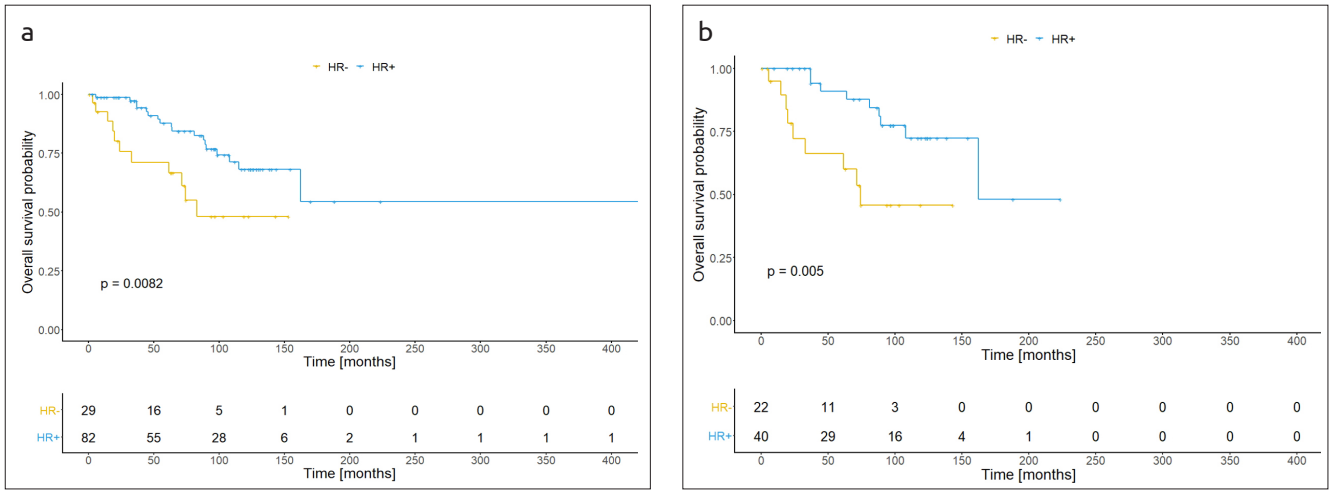

Figure 2. a, b. Survival analyses by HR status (HR-: either or both tumors HR-negative; HR+: both tumors HR-positive). (a) Whole population. (b) mBBC

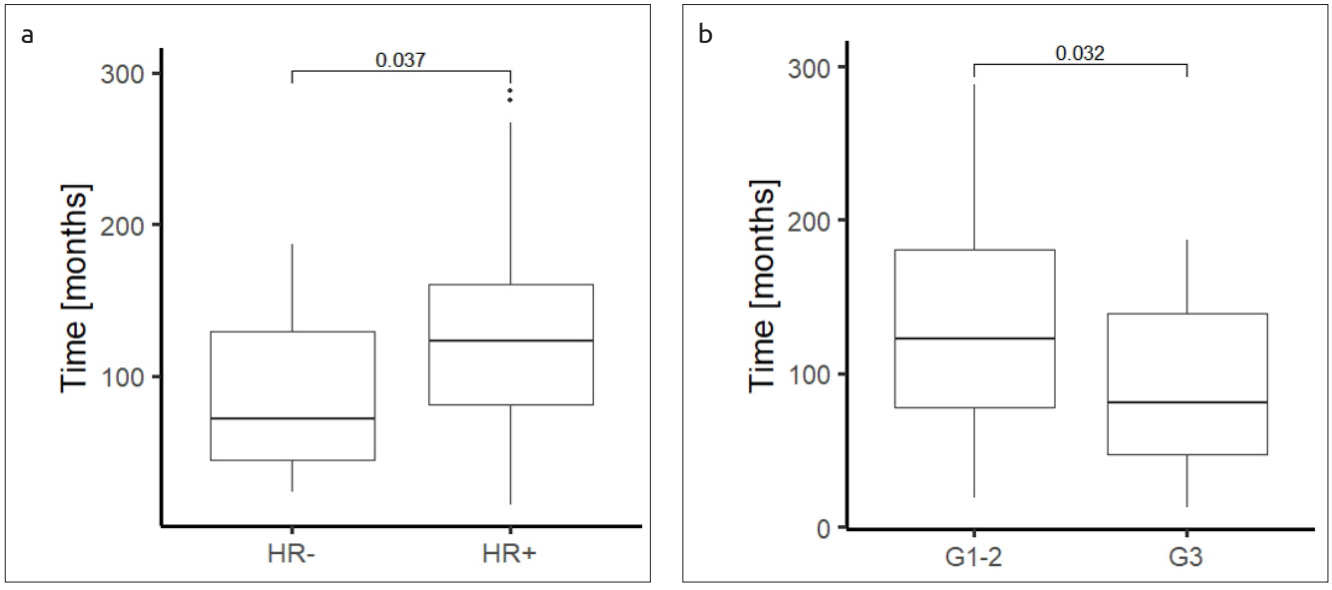

Figure 3. a, b. Correlation of time interval between mBBC tumors with HR status (a) and grade (b) of the 2nd tumor

lary relapses, 3 patients had previously underwent axillary lymphadenectomy and one had no previous axillary surgery. One out of 12 patients with breast relapses and complete pathological data had an R1 status with positive margins ≤1 mm. One patient had a loco-regional relapse of the index tumor before developing the contralateral one.

OS was increased for patients with both tumors being HR-positive compared to those with at least one HR-negative tumor (Figure 2a; Supplementary Figure S2). The same difference was observed for mBBC patients and remained statistically significant (Figure 2b). There were only a few HR-negative tumors within sBBC patients, and no such difference could be detected.

The time interval between mBBC tumors was not predictive of OS (hazard ratio 1.00, p=0.73) or RFS (hazard ratio 1.00, p=0.86) and was independent of nodal status (p=0.339). It was however correlated with the HR status of 2nd tumors, as HR-positive tumors occurred after a significantly longer interval (Figure 3a). A short time interval was associated with 2nd tumors of higher grade (Figure 3b).

Discussion and Conclusion

We analyzed clinical and pathological characteristics of patients with BBC and their outcomes over a 12-year period.

Patients' characteristics were well balanced between the sBBC and mBBC groups except for the menopausal status which was more prevalent among mBBC patients. This observation might be linked to prior systemic treatments (chemotherapy) of the index tumor, rather than age which was similar in both populations.

Standard preoperative assessment of the patients in our series includes mammography and breast ultrasound. Since 2010, breast MRI was widely introduced in the Wallis region, enhancing the diagnosis of subclinical tumors. This advancement partially explains the higher rate of radiological diagnosis for the sBBC contralateral tumors. The high rate of radiological diagnosis among mBBC and the mean interval of nearly 10 years between tumors occurrence underlines the importance of long term follow up in patients with breast cancer.

Tumor characteristics showed differences between the sBBC and mBBC groups. The fact that 2nd sBBC tumors were smaller and more often well differentiated and node-negative compared to mBBC 2nd tumors might be due to the definition of the sBBC index tumor (i.e. larger size). In contrary to previous publications (16, 21, 22), we did not observe any higher prevalence of invasive lobular carcinomas in sBBC patients.

Most patients had HR-positive tumors and underwent adjuvant hormonal therapy. A higher prevalence of HR-negative tumors was observed in the mBBC group compared to sBBC in accordance with prior published series (22, 23). This difference is probably expected for the 2nd tumor as most mBBC patients benefited from prior hormonotherapy. However, mBBC index tumors were also enriched in HR-negative tumors vs. sBBC, possibly reflecting a different biology and a younger age at diagnosis. Also, HR-positive patients benefited from hormonotherapy, which significantly reduces contralateral breast cancer incidence. Indeed, our data showed a shorter time interval between mBBC tumors to be correlated with a higher prevalence of HR-negative tumor and a higher grade. Although there was no correlation between the more aggressive tumor biology and survival in our series, larger studies have shown that a shorter time interval between mBBC tumors carries a worse prognosis and our series may be too small to reflect this difference (14, 24).

The concordance of histological subtypes between index and 2nd tumors was significant only in the mBBC group. Conversely, tumor grade and HR status concordances were only significant for sBBC patients. Our data confirms a particularly high level of concordance (90.7%) for HR status, in line with previously published studies (25-27). As previously suggested, this observation likely reflects the common environment where sBBC tumors developed. In contrast mBBC tumors show a lower and non-significant level of HR status concordance because of multiple intercurrent factors such as anti-hormone treatment, previous chemotherapy, age, menopausal status and possible lifestyle modifications as the result of the prior cancer diagnosis and adverse effects of treatments for the index tumor.

Previous reports showed a more aggressive breast surgery for sBBC compared to mBBC (15, 28-30). In our series, no such difference was observed. Radical lymphadenectomy accounted for the majority of axillar surgery for mBBC index tumors. However, most of these were performed before sentinel node biopsy was progressively introduced in our institution since 2004 and therefore do not reflect a more aggressive therapeutic approach. Axillary surgery for mBBC 2nd tumors was significantly more aggressive than for sBBC 2nd tumors. This observation is in line with the lesser axillary node involvement of sBBC 2nd tumors.

Chemotherapy was used more often for the index tumor of mBBC patients, probably reflecting their younger age and their treatment prior to the de-escalation of systemic therapies with the introduction of predictive molecular tests. Conversely, hormonotherapy was less often prescribed to mBBC patients, reflecting their higher rate of HR-negative tumors compared to sBBC patients.

There was no difference in overall or relapse-free survival between mBBC and sBBC patients in our series. There is no consensus in the literature regarding the outcome of BBC. Most studies showing a survival difference between sBBC and mBBC patients used national registries with a longer follow up (14, 22).

Our data showed a higher rate of loco-regional recurrence in mBBC patients that is consistent with previous reports (15). Most of loco-regional relapses were due to the 2nd tumors, which might be explained by two factors: a higher grade and therefore more aggressive 2nd tumors and a potential selection bias toward a favorable index tumor biology as, by definition, mBBC patients survived until the diagnosis of the contralateral tumor.

The strengths of our study are the nearly complete follow up data, and the homogeneity of patient care and diagnostic procedures given its unicentric design. Its weaknesses include its retrospective nature over a long period of time with evolving treatments and the small number of patients compared to large registry-based series.

In our series, no significant difference of survival between sBBC and mBBC patients was observed, although mBBC patients showed a higher loco-regional relapse rate. In both groups the 2nd tumor was more often diagnosed radiologically highlighting the importance of contralateral breast imaging and the need of a long term radiological follow up of breast cancer patients. Both index and contralateral mBBC tumors were more frequently HR-negative than sBBC, probably reflecting a different biology and the consequences of treatments and lifestyle modifications following the index tumor.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Canton de Vaud (CER-VD; 2018-02320).

Informed Consent: Written informed consent was waived by the Ethics committee for patients until 2017. General informed consent was obtained for all other patients.

Peer-review: Externally peer-reviewed.

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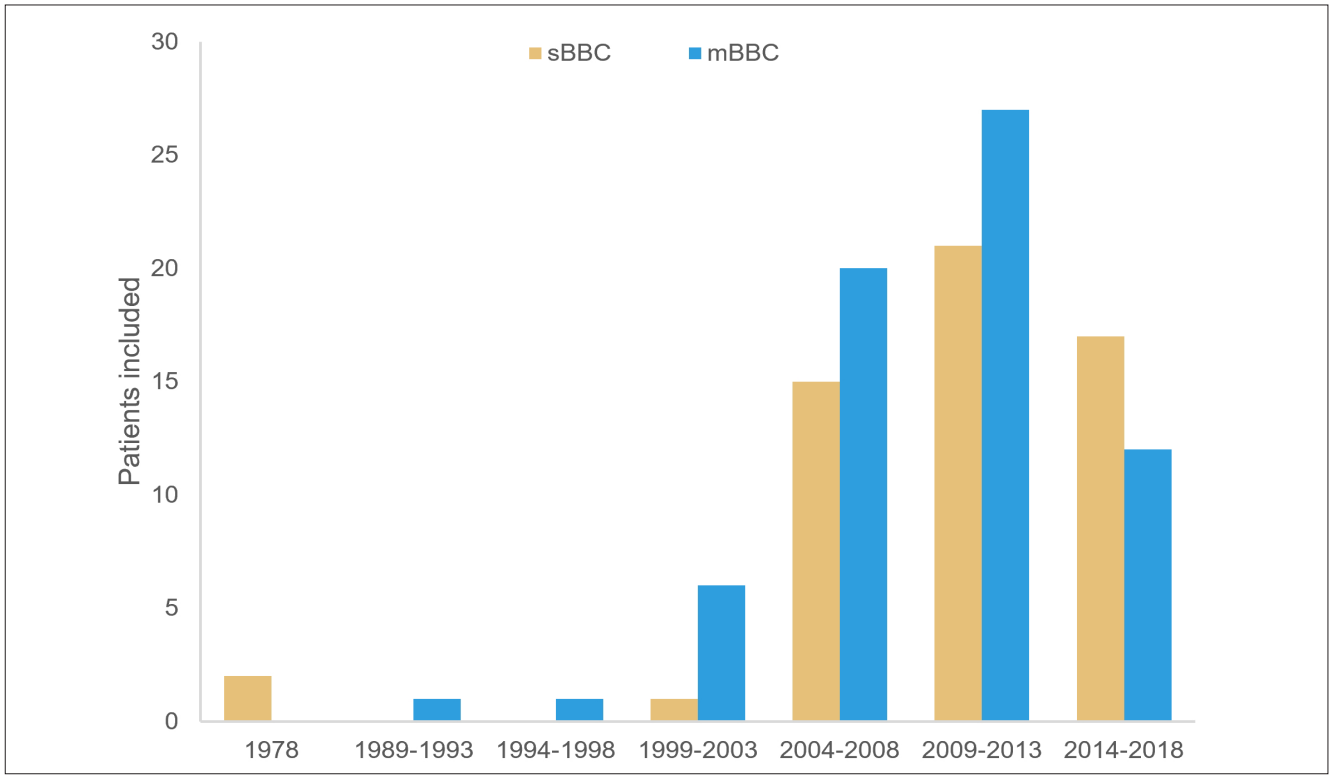

Figure S1. Number of patients by date of 2nd tumor surgery

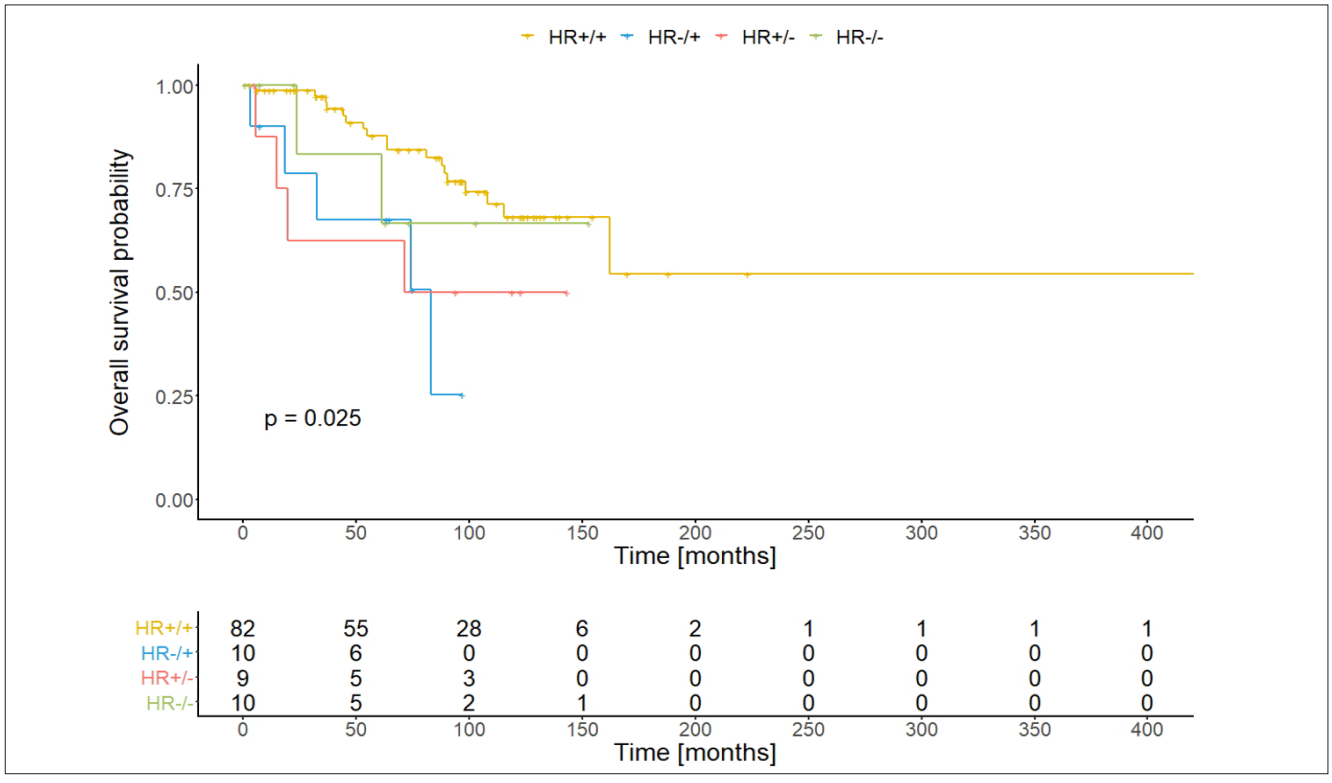

Figure S2. Survival analysis of the whole population by HR status of both tumors (HR status index tumor/2nd tumor)