Clinicopathological, immunohistochemical and treatment features of metachronous versus synchronous bilateral breast carcinoma

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ABSTRACT

Objectives. The purpose of this study was to assess and compare the clinicopathological, molecular pathology, treatment and survival characteristics in patients with metachronous bilateral breast cancer (mBBC) and synchronous breast cancer (sBBC)

Materials and methods. A cohort of 658 patients with breast cancer treated at the Coltea Clinical Hospital, Surgery Department, between January 2015 and December 2019 and followed-up until August 2020 was studied. Data pertaining to patients who were diagnosed as having bilateral breast cancer were retrospectively reviewed and collected. A 3-months interval was used to distinguish metachronous from synchronous tumors. Among patients with bilateral breast cancer, assessment parameters included patient characteristics, histological and molecular pathology features and the performed treatment that were statistically evaluated comparing the first and second tumor of each group and among groups. Survival analysis was performed comparing mBBC and sBBC patients. SPSS was used for data analysis.

Outcomes. Of the 658 patients with primary breast cancer, 35 (5.3%) patients were diagnosed as having bilateral breast cancer (25 (3.8%) mBBC and 10 (1.5%) sBBC). When clinical and histopathological parameters were statistically evaluated, age, menopausal status, tumor size, number of invaded nodes and anatomic stage were found to be significant between the tumors of the metachronous group and tumor size, pathologic T(tumor) and stage between tumors of the synchronous group. Hormonal receptor (HR) status concordance was higher in the synchronous group (85.7%, $p = 0.010$), with a higher percentage of ER positive (71.4%) and PR positive (71.4%) concordance of the tumors. In terms of survival analysis, there was a difference in overall survival (OS, $p = 0.005$), disease-free survival (DFS, $p = 0.011$) and distant relapse-free survival ($p = 0.003$) between mBBC and sBBC. The mean disease-free survival for patients in whom metachronous tumor occurred within less than 5 years was 63.3 months, for sBBC patients was 39.6 months, whereas for patients with more than 5 years was 437.9 months ($p = 0.012$, Log Rank). Discordant biomarker defined subgroup (ER,HER2) patients were associated with better disease-free survival ($p = 0.047$, Log Rank) and better distant relapse-free survival ($p = 0.015$, Log Rank) in overall patients. In terms of loco-regional relapse-free survival, although mBBC and sBBC patients showed no statistical significant difference earlier in the time course ($p = 0.088$, Breslow; $p = 0.054$ Tarone-Ware), among mBBC patients was observed a better outcome ($p = 0.027$, Log Rank).

Conclusions. Based on survival analysis, patients in whom metachronous tumor developed after more than 5 years, had a better distant relapse-free survival. Patients with synchronous bilateral breast cancer were associated with worse disease outcome based on overall survival analysis and disease free-survival

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rates with more frequent rates of distant metastasis. Outcome of patients in whom metachronous tumor was diagnosed within less than 5 years might be similar to synchronous tumors. Patients with discordant ER,HER2 status showed a better disease outcome. Although concordance in HR status and molecular subtype, did not show statistical significant differences, it is a subject which deserves further clinical observation.

Keywords: bilateral breast cancer, synchronous, metachronous, survival, local-regional relapse, distant relapse

INTRODUCTION

According to International Agency for Research on cancer (IARC), GLOBOCAN 2020 estimates of cancer incidence and mortality, breast cancer has surpassed lung cancer and is the most commonly diagnosed malignancy in women (24.5%) and both males and females (11.7%) (with an estimated number of 2,261,419 new cases) and is the fifth cause of cancer death (6.9%, 684,996 estimated deaths) worldwide (1). In Romania, according to the most recent report of the regional tumor registry and IARC, breast cancer was the most frequent cancer in women with 26.9% of newly diagnosed cancer cases (12,085 estimated new cases, 65.8/100,000 incidence) and also the first in terms of specific mortality with an estimated 3 918 number of deaths in 2020 (17.3%, 17.4/100,000 mortality rate) (2-6).

Based on the interval time between the diagnosis of first and the second tumor, bilateral breast cancer (BBC) can be classified into metachronous (mBBC) and synchronous (sBBC) (5,6). According to the World Health Organization (WHO), BBC is defined as sBBC when contralateral breast carcinoma is diagnosed at the same time as the first tumor or within 3 months. When contralateral tumor is diagnosed three months or more after the first tumor, is defined as mBBC. (5-10). Some authors have defined sBBC as the diagnosis of the second within 12 months (6-8,11).

As a result of constantly increasing incidence of breast cancer, improved diagnosis methods, progress in systemic and loco-regional treatment and longer life expectancy, the incidence of BBC has been increasing (5,12-15). Reported studies frequency of bilateral breast cancer varies from 1.4% to 11.8%. (5,9,12,15-17). The risk of developing a second primary breast cancer in women who have had previous breast cancer is predicted as 2 to 6 times greater than the first breast cancer in the general population (12,18).

Studies results are still controversial regarding the impact of contralateral breast cancer on survival and still remains uncertain (5,6,9,19-22). Some studies have shown that it remains unaffected while on the contrary, others have suggested that the development of cancer in the contralateral breast negatively affects

survival, being associated with worse outcome and reduced survival (12,14,19, 23,24).

Up to this point there is no specific recommendations for the treatment of bilateral breast cancer (5,9,19,21-23). For synchronous breast cancer, systemic treatment is usually guided by the sBBC tumor with the worse prognosis, whereas metachronous breast cancer tend to be treated like unilateral, independent breast cancer (5).

With these means, the present study aimed to assess patients diagnosed as having bilateral breast cancer and to identify differences in clinical, pathological characteristics and type of performed surgery of the first and second tumor and to compare overall survival rates and disease-free periods.

MATERIAL AND METHODS

Data pertaining to patients diagnosed as having bilateral breast cancer, who were treated for at least one tumor from January 2015 to December 2019 and followed-up until August 2020 at the Coltea Clinical Hospital Bucharest, General Surgery Department, were reviewed retrospectively. Data were gathered from the medical files of the institution (Hospital Manager Suite, InfoWorld; pathologic reports).

Based on the time interval of the diagnosis of cancer in the contralateral breast, patients were divided in two groups: synchronous bilateral breast cancer (sBBC) group and metachronous bilateral breast cancer (mBBC) group. According to the WHO classification of bilateral breast cancer, contralateral breast cancers detected within 3 months from the diagnosis of first tumor were defined as synchronous breast cancer. Regarding the sBBC group, the tumor with larger diameter was considered the first tumor and identified as the dominant tumor. Any second tumor diagnosed in contralateral breast after 3 months was considered metachronous breast cancer.

Inclusion criteria were patients diagnosed with bilateral breast cancer, confirmed pathologically with invasive breast cancer and those who underwent surgery. Patients with the one side tumor described from the pathologists as likely being a metastasis from the contralateral breast, were excluded.

Family history of the patients (considered positive when a first or second degree relative had breast cancer), genetic mutations, tobacco smoking, alcohol consumption, age at first and second tumor, the time elapsed between development of two tumors, state of menopause, the type of performed surgery, axillary dissection and systemic treatment were recorded. From the pathology reports were extracted the diameter of the tumor (in mm), number of tumor foci and tumor focality, histological type, histologic grade (Scarff-Bloom-Richardson – SBR grading system, Nottingham modification), associated ductal or lobular carcinoma in situ (DCIS/LCIS), lymphovascular invasion (LVI), perineural invasion (PNI), status of resection margins, lymph node status, anatomical pathological stage (TNM), estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status and Ki-67 proliferation marker index value.

The performed surgical procedures were classified into three categories: breast-conserving surgery, subcutaneous mastectomy and mastectomy with none, partial or radical axillary lymphadenectomy.

Tumors (T) were classified as smaller than or equal to 20 mm (T1), $>20 \leq 50$ mm (T2), larger than 50 mm (T3) and T4 (direct extension to the chest wall and/or to the skin) as described in AJCC (American Joint Committee on Cancer) Staging Manual Eighth Edition, 2018. In terms of histological features, types were classified according to the WHO Classification of Tumors, fifth edition, 2019, as (a) invasive breast carcinoma of no special type (IBC-NST) (respectively invasive ductal carcinoma (IDC), (b) invasive lobular carcinoma (ILC), (c) mixed IBC-NST and special subtypes, (d) IBC-NST with focal specialized subtype and (e) other special subtypes; if the special subtype carcinoma made up 10-90% of the cancer, was used the term „mixed IBC-NST and special subtype carcinoma”, whereas cancers with $< 10\%$ special subtype were classified as „IBC-NST with focal specialized subtype”.

Histological grades were assigned from well differentiated grade (grade 1, G1), moderately differentiated grade (grade 2, G2) to poorly differentiated grade (grade 3, G3).

Axillary node involvement was categorized as negative (N0) or positive N1 (metastase in 1-3 axillary lymph nodes), N2 (4-9 axillary lymph nodes) and N3 (ten or more axillary lymph nodes) (AJCC Cancer Staging Manual, 8th ed).

Estrogen, progesterone and HER2 receptors were evaluated using immunohistochemical methods with in situ hybridization (ISH, chromogenic and or fluorescence in situ hybridization (CISH, FISH)) where appropriate. ER and PR positivity were defined as no less than 1% stained nuclei according to the American Society of Clinical Oncology/College of American Patholo-

gists (ASCO/CAP) Practice Guideline Update recommendations. Invasive cancers with 1-10% ER positivity were reported as ER low positive. HER2 status was considered positive with a 3+ stain intensity expression and negative when absent or with 1+ expression. In situ hybridization classified further HER2 status in positive or negative for equivocal 2+ tumors. Based on measurements of ER, PR, HER2 and Ki-67, invasive breast carcinomas were further classified into the five molecular subtypes, adopted by the 13th St. Gallen International Breast Cancer Conference (2013) Expert Panel: (1) Luminal A, (2) Luminal B-like HER2 negative, (3) Luminal B-like HER2 positive, (4) HER2-positive (non-luminal) and (5) Triple-negative breast cancer (TNBC). A threshold of 14% Ki-67 value was used to discriminate between less aggressive behaviour Luminal A molecular subtype and more aggressive Luminal B subtype. As published in fifth edition of the WHO Classification of Breast Tumors, 2019 (WHO Blue Books), tumors were also divided into the following biomarker defined subtypes: (1) ER-positive, HER2-negative; (2) ER-positive, HER2-positive; (3) ER-negative, HER2-positive; (4) ER-negative, HER2 negative. Based on the hormone receptor (HR) we had the following groups (1) ER+,PR-; (2) ER+,PR+; (3) ER-,PR+; (4) ER-,PR-.

Loco-regional recurrence (breast, axilla or both relapse) and distant metastasis were also recorded. Distant metastases were defined as any lesion located outside the mastectomy scar or restant breast tissue, axillary or regional (supraclavicular) lymph nodes. Metastatic sites were grouped as single or multiple, subsequently into M1 bone/lung, M1 bone+lung/brain/lung+liver/lung+ distant lymph nodes.

Overall survival (OS) (was calculated from the date of diagnosis of the first tumor until the date of death or the last medical assesement), disease-free survival (DFS, calculated until the date of relapse), loco-regional relapse-free survival (RFS) and distant relapse-free survival rates were calculated with censoring for loss of follow-up. All the mentioned variables were compared between groups.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software version 28.0.0.0 (190). The variables were investigated using descriptive statistics (Frequencies and Descriptives) and presented using median, mean and standard deviation for normally distributed variables. Normality tests Kolmogorov-Smirnov and Shapiro-Wilk were used to determine whether variables were normally distributed. Non-parametric categorical variables were investigated using the Mann-Whitney U test, Pearson Chi-square test or Fisher's exact test, after exclusion of missing values. Survival outcomes were estimated using Kaplan-Meier sur-

vival analysis and compared by Log Rank, Breslow and Tarone-Ware tests. For all statistical analyses, a p value of less than or equal to 0.05 was defined as statistically significant.

OUTCOMES

Of the 658 patients who were diagnosed as breast cancer and treated for invasive breast carcinoma between January 2015 and December 2019, a total of 35 (5.3%) patients were identified and diagnosed as having bilateral breast cancer (BBC). Seven of the cases were males and all of them were unilateral. A number of 10 (1.5%) of the 35 bilateral breast cancer cases had synchronous tumor (28.6%). 25 (3.8%) of the 35 BBC had metachronous breast cancer (71.4%) ($p = .011$ Chi Square test). The mean time interval between two tumors was 0 months in sBBC group and 112.80 months (range 16-372 months) in mBBC group (the median time interval was 66 months). The median age of sBBC patients was 59.50 years, while for mBBC group the median age at the diagnose of the first tumor was 58 years and 65 years for the second tumor and 18 (72%) patients were in the postmenopausal period. The mean follow-up time for mBBC patients was 136.92 months (median 93.0, range 17-528 months), 19.60 months (median 14.50, range 1-60 months) for sBBC and 103.40 (median 51 months) for both groups ($p < .001$).

Patient characteristics, the performed surgical treatment and histological features (descriptives, frequencies, statistical values) regarding metachronous and synchronous tumors are summarized individually for each group in Tables 1 and 2. At inclusion, patients did not show any differences between groups except for one case (4%) that harboured BRCA1 genetic mutation, which was found in mBBC group. None of the groups have had family history of breast cancer and only two patients (20%) acknowledged smoking in the sBBC group. With regard to metachronous tumors, there was found a statistically significant difference between first and second tumor in terms of age ($p < 0.001$) and menopausal status ($p < 0.001$), all patients being menopausal by the time the second tumor was diagnosed. Concerning the comparison of metachronous and synchronous tumors, there were no significant differences regarding the age at initial diagnosis ($p = 0.339$) and menopausal status ($p = 0.928$).

The type of performed surgery did not differ among groups ($p = 0.255$, 0.174) or between first and second tumors ($p = 0.531$, 0.684). Mastectomy was the most common surgical intervention performed to both breasts. Radical axillary lymphadenectomy was performed in all patients in the synchronous group, al-

though no statistically significant difference between groups or tumors ($p = 0.733$).

Regarding tumor pathology features, no statistically significant difference was observed between the histological types of the first and second tumors for mBBC and sBBC ($p = 0.631$). In both groups, the most common histologic type was invasive ductal carcinoma-NOS ($p = 0.313$). Histological type concordance was 28.6% ($p = 0.109$) for mBBC group and 50% ($p = 1.000$) for sBBC group. Histological grade concordance was 27.3% ($p = 0.132$) for mBBC patients and 37.5% ($p = 0.480$) for sBBC patients. Regarding histological type and grade between the two groups, the difference was not significant ($p = 0.286$, $p = 0.637$).

For metachronous group, the mean tumor diameter was 43.85mm in the first tumor and 21mm in the second tumor ($p = 0.004$). Concerning synchronous tumors the mean tumor size in the 1st was 33.40mm and 17.40mm in the 2nd ($p = 0.011$). Second tumors for both mBBC and sBBC were more often of small size (<20 mm) ($p = 0.023$, mBBC; $p = 0.035$ sBBC). The mean tumor diameter was therefore significantly greater in the dominant breast, with no statistically significant difference between groups ($p = 0.784$). No differences were observed in terms of focality, histological grade, intraductal component, lymphovascular or perineural invasion. In synchronous group, pathologic T1 was more often encountered, in 70% of the cases, with no T4 in both tumors of the group ($p = 0.035$). In terms of lymph node metastases, in the metachronous group, the second tumor was in 72% of the cases diagnosed with no regional lymph node invasion ($p = 0.026$). Regarding anatomic pathologic stage TNM, in both metachronous and synchronous groups, when comparing the first tumor to the second, was found that stage IA had the highest incidence among second tumors, 56% in mBBC group ($p = 0.005$) and 40% in sBBC ($p = 0.007$).

Features of the molecular pathology report are shown in Table 3. There was no statistically significant difference between the two tumors of the groups in terms of estrogen, progesterone and HER2 receptors. Estrogen receptor was negative in 48% of the cases ($p = 0.370$), in the first tumor of mBBC group, and, considering all combinations of estrogen and progesterone receptor expression and molecular subtype, ER-, PR- type (48%, $p = 0.387$), ER-,HER2- (44%, $p = 0.217$) and TNBC (44%, $p = 0.111$) were more often observed compared to the second tumor.

When comparing the first tumor of metachronous group with the dominant tumor of synchronous group, the distribution of the molecular subtypes differed among groups, in the mBBC group TNBC was more often diagnosed (44%), whereas in the sBBC was Luminal B-like (HER2-negative) (50%) ($p = 0.035$).

Concordance of biomarkers and intrinsic molecular subtypes between the first tumor and second tumor

TABLE 1. Patient characteristics, surgical treatment and tumor histological features in metachronous tumors

Metachronous tumors, n = 25 (100) Characteristics	First tumor n (%)	Second tumor n(%)	p value
Median age, years (min-max), mean	58 (35-76), 55.56	65 (51-78), 65.40	< 0.001
≤ 40	3 (12)	0 (0)	
41-50	4 (16)	0 (0)	
51-60	12 (48)	7 (28)	
> 60	6 (24)	18 (72)	
Menopausal status			< 0.001
Premenopausal	7 (28)	0 (0)	
Postmenopausal	18 (72)	25 (100)	
BRCA1	1 (4)		
Breast surgery, type			0.531
Breast conserving surgery	1 (4)	2 (8)	
Subcutaneous mastectomy	0 (0)	0 (0)	
Mastectomy	24 (96)	22 (88)	
Unknown	x	1 (4)	
Axillary surgery			0.944
Partial axillar lymphadenectomy	2 (8)	3 (12)	
Radical axillar lymphadenectomy	23 (92)	20 (80)	
None	0 (0)	1 (4)	
Unknown	x	1 (4)	
Tumor size (mm), mean value ± SD; median; min-max	43.85 ±34.5;30; 15-130	21 ± 12.84;15; 6-60	0.004
Tumor size (mm) groups			0.023
≤ 20 mm	4 (16)	16 (64)	
> 20 ≤ 50 mm	10 (40)	7 (28)	
> 50 mm	2 (8)	1 (4)	
Unknown	9 (36)	1 (4)	
Tumor focality			0.917
Unifocal	12 (48)	21 (84)	
Multifocal	1 (4)	2 (8)	
Multicentric	1 (4)	1 (4)	
Unknown	11 (44)	1 (4)	
Number of tumori foci			0.940
Single focus	12 (48)	21 (84)	
More than one focus	2 (8)	3 (12)	
Unknown	11 (44)	1 (4)	
Histological type			0.627
1.IBC-NST, ILC special subtype			
IDC	7 (28)	15 (60)	
ILC	2 (8)	5 (20)	
mixed IDC + ILC	x	1 (4)	
2.mixed IBC-NST and special subtypes			
IDC + acinic cell carcinoma	1 (4)	x	
IDC + metaplastic carcinoma (mixed, epithelial + mesenchymal)	x	1 (4)	
3.IBC-NST with focal specialized subtype			
IDC + invasive papillary carcinoma	1 (4)	1 (4)	
IDC + carcinoma with apocrine differentiation	x	x	

Metachronous tumors, n = 25 (100) Characteristics	First tumor n (%)	Second tumor n(%)	p value
4.Other special subtypes			
Invasive papillary carcinoma	1 (4)	x	
Cribriiform carcinoma	1 (4)	x	
Mucinous carcinoma with focal carcinoma with signet- ring cell differentiation	x	1 (4)	
Metaplastic carcinoma (with squamous differentiation) with focal IDC	x	1 (4)	
Unknown	12 (48)	x	
Nottingham grade			0.296
Grade 1	6 (24)	5 (20)	
Grade 2	5 (20)	14 (56)	
Grade 3	3 (8)	4 (16)	
Unknown	12 (48)	2 (8)	
Associated DCIS/LCIS			0.410
Low nuclear grade DCIS	x	1 (4)	
Intermediate nuclear grade DCIS	1 (4)	6 (24)	
High nuclear grade DCIS	3 (12)	3 (12)	
LCIS	1 (4)	1 (4)	
DCIS+LCIS	x	1 (4)	
None	9 (36)	12 (48)	
Unknown	11 (44)	1 (4)	
Lymphovascular invasion			0.940
Positive	2 (8)	3 (12)	
Negative	12 (48)	21 (84)	
Unknown	11 (44)	1 (4)	
Perineural invasion			0.560
Positive	3 (12)	8 (32)	
Negative	11 (44)	16 (64)	
Unknown	11 (44)	1 (4)	
Margins			0.327
R0	24 (96)	24 (96)	
R1	1 (4)	0 (0)	
Unknown	x	1 (4)	
Pathologic T			0.132
pT1	4 (16)	15 (60)	
pT2	8 (32)	5 (20)	
pT3	2 (8)	1 (4)	
pT4	2 (8)	4 (16)	
Unknown	9 (36)	x	
Invaded lymph nodes, mean (min-max), SD	6.94(0-45), 13.08	1.48(0-25), 5.24	0.026
Nodal status (pN)			0.051
pNx	x	1 (4)	
pN0	6 (24)	18 (72)	
pN1	5 (20)	3 (12)	
pN2	1 (4)	1 (4)	
pN3	4 (16)	1 (4)	
Unknown	9 (36)	1 (4)	
Anatomic stage (TNM)			0.005
Stage IA	1 (4)	14 (56)	
Stage IB	x	x	
Stage IIA	7 (28)	3 (12)	
Stage IIB	2 (8)	x	
Stage IIIA	1 (4)	2 (8)	

Metachronous tumors, n = 25 (100) Characteristics	First tumor n (%)	Second tumor n (%)	p value
Stage IIIB	1 (4)	1 (4)	
Stage IIIC	3 (12)	1 (4)	
Stage V	1 (4)	2 (8)	
Unknown	9 (36)	2 (8)	
Median time of metachronous cancer occurrence, months (min-max), mean	66 (16-372), 112.80		

SD – standard deviation; IBC-NST – invasive breast carcinoma of no special type; IDC – invasive ductal carcinoma; ILC – invasive lobular carcinoma; DCIS – ductal carcinoma in situ; LCIS – lobular carcinoma in situ; R0 – negative surgical margins; R1 – positive surgical margins

TABLE 2. Patient characteristics, surgical treatment and tumor histological features in synchronous tumors

Synchronous tumors, n = 10 (100) Characteristics	Dominant tumor n (%)	Contralateral tumor n (%)	p value
Median age, years (min-max), mean	59.50 (39-81), 60.30	59.50 (39-81), 60.30	> 0.05
≤ 40	1 (10)	1 (10)	
41-50	2 (20)	2 (20)	
51-60	2 (20)	2 (20)	
> 60	5 (50)	5 (50)	
Menopausal status			> 0.05
Premenopausal	3 (30)	3 (30)	
Postmenopausal	7 (70)	7 (70)	
Breast surgery			0.684
Breast conserving surgery	2 (20)	3 (30)	
Subcutaneous mastectomy (TSSM)	1 (10)	1 (10)	
Mastectomy	7 (70)	6 (60)	
Axillary surgery			> 0.05
Partial axillar lymphadenectomy	0 (0)	0 (0)	
Radical axillar lymphadenectomy	10 (100)	10 (100)	
Tumor size (mm), mean value ± SD; median; min-max	33.40 ± 15.96; 27.5; 15-60	17.40 ± 10.76; 16.5; 2-35	0.011
Tumor size (mm) groups			0.035
≤ 20 mm	2 (20)	7 (70)	
> 20 ≤ 50 mm	6 (60)	3 (30)	
> 50 mm	2 (20)	x	
Tumor focality			0.315
Unifocal	6 (60)	9 (90)	
Multifocal	2 (20)	x	
Multicentric	2 (20)	1 (10)	
Number of tumori foci			0.280
Single focus	6 (60)	9 (90)	
More than one focus	4 (40)	1 (10)	
Histological type			0.631
1.IBC-NST, ILC special subtype			
IDC	7 (70)	6 (60)	
ILC	3 (30)	3 (30)	
2.mixed IBC-NST and special subtypes	x	x	
3.IBC-NST with focal specialized subtype			
IDC + carcinoma with apocrine differentiation	x	1 (10)	
4.Other special subtypes	x	x	
Nottingham grade			0.743
Grade 1	3 (30)	3 (30)	

Synchronous tumors, n = 10 (100) Characteristics	Dominant tumor n (%)	Contralateral tumor n (%)	p value
Grade 2	5 (50)	5 (50)	
Grade 3	x	1 (10)	
Unknown	2 (20)	1 (10)	
Associated DCIS			0.853
Low nuclear grade DCIS	x	1 (10)	
Intermediate nuclear grade DCIS	2 (20)	1 (10)	
High nuclear grade DCIS	1 (10)	x	
None	7 (70)	8 (80)	
Lymphovascular invasion			0.739
Positive	x	1 (10)	
Negative	10 (100)	9 (90)	
Perineural invasion			> 0.05
Positive	2 (20)	2 (20)	
Negative	8 (80)	8 (80)	
Margins			0.739
R0	9 (90)	10 (100)	
R1	1 (10)	0 (0)	
Pathologic T			0.035
pT1	2 (20)	7 (70)	
pT2	6 (60)	3 (30)	
pT3	2 (20)	3 (30)	
pT4	x	x	
Number invaded lymph nodes, mean (min-max), SD	3.40 (0-12), 4.0	1.20 (0-6), 1.98	0.190
Nodal status (pN)			0.143
pN0	3 (30)	6 (60)	
pN1	3 (30)	3 (30)	
pN2	3 (30)	1 (10)	
pN3	1 (10)	x	
Anatomic stage (TNM)			0.007
Stage IA	x	4 (40)	
Stage IB	x	x	
Stage IIA	2 (20)	4 (40)	
Stage IIB	4 (40)	1 (10)	
Stage IIIA	3 (30)	1 (10)	
Stage IIIB	x	x	
Stage IIIC	1 (10)	x	
Stage V	x	x	
Smoker	2 (20)		

SD – standard deviation; IBC-NST – invasive breast carcinoma of no special type; IDC – invasive ductal carcinoma;

ILC – invasive lobular carcinoma; DCIS – ductal carcinoma in situ; R0 – negative surgical margins; R1 – positive surgical margins

TABLE 3. Molecular pathology features in metachronous and synchronous tumors

	Metachronous, n = 25 (100%)			Synchronous, n = 10 (100%)		
	1st tumor	2nd tumor	p value	1st tumor	2nd tumor	p value
ER status			0.370			0.710
Low positive	1 (4)	x		x	x	
Positive	7 (28)	9 (36)		6 (60)	5 (50)	
Negative	12 (48)	7 (28)		1 (10)	2 (20)	
Unknown	4 (16)	9 (36)		3 (30)	3 (30)	
Mixed, ER+, ER-	1 (4)	x		x	x	
PR status			0.254			> 0.05
Positive	5 (20)	7 (28)		5 (50)	5 (50)	
Negative	15 (60)	9 (36)		2 (20)	2 (20)	
Unknown	4 (16)	9 (36)		3 (30)	3 (30)	
Mixed, PR+,PR-	1 (4)	x		x	x	
HER2 status			0.964			> 0.05
Positive	2 (8)	1 (4)		1 (10)	1 (10)	
Negative	18 (72)	15 (60)		6 (60)	6 (60)	
Unknown	4 (16)	9 (36)		3 (30)	3 (30)	
Mixed, HER2-,-	1 (4)	x		x	x	
Positive AR	2 (8)	1 (4)	0.730	x	x	x
HR status			0.387			0.456
ER+,PR-	3 (12)	2 (8)		1 (10)	5 (50)	
ER+,PR+	5 (20)	7 (28)		5 (50)	x	
ER-, PR+	x	x		x	x	
ER-, PR-	12 (48)	7 (28)		1 (10)	2 (20)	
Unknown	4 (16)	9 (36)		3 (30)	3 (30)	
Mixed T ¹	1 (4)	x		x	x	
Biomarker-defined subtypes			0.217			0.620
ER+, HER2-	7 (28)	9 (36)		5 (50)	4 (40)	
ER+, HER2+	1 (4)	x		1 (10)	1 (10)	
ER-, HER2+	1 (4)	1 (4)		x	x	
ER-, HER2-	11 (44)	6 (24)		1 (10)	2 (20)	
Unknown	4 (16)	9 (36)		3 (30)	3 (30)	
Mixed T ²	1 (4)	x		x	x	
Ki-67			0.651			> 0.05
< 14%	4 (16)	3 (12)		1 (10)	1 (10)	
≥ 14%	7 (28)	9 (36)		6 (60)	6 (60)	
Unknown	14 (56)	13 (52)		3 (30)	3 (30)	
Mixed T, ≥14% ³	1 (4)	x		x	x	
Intrinsec subtype			0.111			0.902
Luminal A	x	2 (8)		x	1 (10)	
Luminal B, HER2-	5 (20)	6 (24)		5 (50)	3 (30)	
Luminal B, HER2+	1 (4)	x		1 (10)	1 (10)	
HER2+	1 (4)	1 (4)		x	x	
TNBC	11 (44)	6 (24)		1 (10)	2 (20)	
Unknown	6 (24)	10 (40)		3 (30)	3 (30)	
Mixed T ⁴	1 (4)	x		x	x	

ER – estrogen receptor; PR – progesteron receptor; HER2 – human epidermal growth factor receptor type2; Ki-67 – marker of proliferation; TNBC – triple negative breast cancer; Mixed T¹ – mixed tumor subtypes ER+,PR+ and ER-,PR-; Mixed T² – mixed tumor subtypes ER+, HER2- and ER-,HER2-; Mixed T, ≥14%³ – mixed tumor molecular subtypes, both having Ki-67 ≥14%; Mixed T⁴ – mixed tumor with mixed molecular subtypes Luminal B (HER2-) and TNBC.

were further analyzed and compared between mBBC and sBBC (Table 4).

Regarding ER receptor status, a higher percentage of ER-discordant tumors (57.1% vs. 14.3%) in the mBBC group than the sBBC group, however without statistical significance between groups ($p = 0.118$). There was a higher percentage of PR-discordant tumors (71.4%, $p = 0.008$) in metachronous group than the synchronous, where was found no discordance and a higher percentage of positive concordant (71.4%) tumors ($p = 0.257$), with a overall statistical significant difference between groups ($p < 0.001$). In the synchronous group was also found a higher rate of ER positive concordance of 71.4% ($p = 0.102$) compared to the metachronous group (28.6%) ($p = 0.118$, overall statistical significance). Concerning HER2 status, in both groups, were more often encountered negative concordant values (92.9%, 85.7%, $p = 0.219$), however the only significant statistical difference was observed in the mBBC group ($p = 0.001$). Compared to mBBC group sBBC group was more likely to have concordant HR status (85.7% vs. 28.6%, $p = 0.010$), concordant ER,HER2 status (85.7% vs. 35.7%, $p = 0.024$), with statistical significance, and

concordant molecular subtype (71.4% vs. 33.3%, $p = 0.105$), though without significant statistical difference.

With regard to systemic therapy, no statistically significant differences were observed between the first and second tumor in metachronous and synchronous groups or among groups. In the mBBC group, 76% of the patients received adjuvant chemotherapy for the first tumor and 52% patients for the second ($p = 0.639$) and 40% of the patients in the synchronous group ($p = 0.208$, mBBC vs. sBBC patients). Adjuvant hormone-therapy was less prevalent in the metachronous group (36%) than in synchronous patients (60%) ($p = 0.101$). HER2-directed treatment received one patient (10%) in sBBC group, 2 patients (8%) for their first tumor in metachronous group and 1 patient (4%) for the second tumor ($p = 0.876$). Adjuvant radiotherapy was also likewise observed among groups ($p = 0.876$; mBBC, 76% index tumor, 48% second tumor; sBBC, 60% patients).

In terms of local recurrence and distant metastasis, there was no statistically significant difference between the two groups. It was encountered one case of primary metastatic disease (4%) in the metachronous group. Loco-regional recurrence was observed in each group,

TABLE 4. Concordance of molecular pathology characteristics between first tumor and second tumor in bilateral breast cancer, within and between groups

	MBBC (n = 25, valid %)	p value	SBBC (n = 10, valid %)	p value	p value
ER status		0.135		0.102	0.118
Both positive	4(28.6)		5(71.4)		
Both negative	2(14.3)		1(14.3)		
Discordant	8(57.1)		1(14.3)		
PR status		0.008		0.257	<0.001
Both positive	1(7.1)		5(71.4)		
Both negative	3(21.4)		2(28.6)		
Discordant	10(71.4)		0(0)		
HER2-status		0.001		0.059	0.219
Both positive	0(0)		1(14.3)		
Both negative	13(92.9)		6(85.7)		
Discordant	1(7.1)		0(0)		
HR status		0.109		0.059	0.010
Concordant	4(28.6)		6(85.7)		
Discordant	10(71.4)		1(14.3)		
ER, HER2 status		0.285		0.059	0.024
Concordant	5(35.7)		6(85.7)		
Discordant	9(64.3)		1(14.3)		
Ki-67		0.197		0.257	0.517
Both <14%	1(12.5)		0(0)		
Both ≥14%	5(62.5)		5(71.4)		
Discordant	2(25)		2(28.6)		
Molecular type		0.248		0.257	0.105
Concordant	4(33.3)		5(71.4)		
Discordant	8(66.7)		2(28.6)		

mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer; ER – estrogen receptor; PR – progesteron receptor; HER2 – human epidermal growth factor receptor type2; Ki-67 – marker of proliferation

2 cases in mBBC and 2 cases in sBBC, respectively. In the metachronous group, both cases of loco-regional relapse occurred in the breast and in the sBBC, one case in the breast and one in the axilla ($p = 0.577$). Distant relapse occurred in 16% metachronous patients and 30% synchronous ($p = 0.154$). For both groups prevailed multiple metastatic sites (12% mBBC; 20% sBBC; $p = 0.137$). In the metachronous group were found 4 cases (16%) of distant recurrence, corresponding to one case that relapsed in the bone only (M1 bone) associated with concordant luminal B (HER2-negative) subtype, 1 case of relapse (M1) in the bone, lung and lymph node associated with discordant luminal B (HER2 negative) and TNBC subtypes and 2 cases related to concordant TNBC subtype which relapsed (M1) in bone and lung, respectively M1 bone and brain. In the synchronous group were observed 3 cases (30%) of distant recurrence, representing one case of M1 lung related to a concordant luminal B (HER2 positive) subtype, another of M1 bone, lung and liver related to concordant luminal B (HER2 negative) and one case with M1 bone and lung relapse associated with discordant luminal B (HER2 negativ) and luminal A. None of the relapsed cases had positive resection margins (R1). Both patients in mBBC group had loco-regional recurrence of the index tumor before developing carcinoma in the contralateral breast.

Concerning survival analysis, the metachronous and synchronous groups were compared in terms of overall survival, disease-free survival, loco-regional-recurrence free survival and distant-recurrence-free survival.

The follow-up period for mBBC group had a mean of 136.92 months (range 17 - 528 months) and for sBBC a mean of 19.60 months (range 1-60 months). Regarding both groups, after a mean follow-up of 103.4 (range 1-528; median 51) months, there was observed one case of breast cancer related death, which occurred in the synchronous group, after 20 months; due to the fact that all cases from the mBBC group were censored, no statistics could be computed for overall survival (means and medians). On the other hand, the statistical comparisons for OS were found to be statistically significant between groups, at all compared factor levels ($p = 0.005$, Log Rank, Breslow and Tarone-Ware).

Disease-free survival was 391.13 months estimated mean for metachronous tumors and 39.6 months for synchronous tumors and the difference between these groups was statistically significant at all compared levels ($p = 0.011$, Log Rank; $p = 0.044$ Breslow; $p = 0.024$ Tarone-Ware).

Loco-regional relapse-free survival was statistically significant later in the time course ($p = 0.027$, Log Rank) with no differences in the earlier and middle time course ($p = 0.088$, Breslow, $p = 0.054$ Tarone-Ware). The estimated mean for metachronous was 486.31 months and for synchronous was 48.0 months.

Distant relapse-free survival estimated mean was found as 409.39 months for mBBC and 40.20 months for sBBC with a difference between groups of statistically significant value ($p = 0.003$, Log Rank; $p = 0.015$ Breslow; $p = 0.007$ Tarone-Ware).

FIGURE 1.A. Overall survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 1.B. Disease-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 1.C. Loco-regional relapse-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

When comparing the patients from the metachronous group by means of time elapsed until diagnosis of the second tumor, that is <5 years versus >5 years, it was observed that the time interval between mBBC tu-

mors was no predictive of DFS ($p = 0.104$, Log Rank) or loco-regional RFS ($p = 0.904$, Log Rank), however it was statistically significant in terms of distant relapse-free survival (the mean distant relapse-free survival for pa-

FIGURE 1.D. Distant relapse-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 2.A. Overall survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 2.B. Disease-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 2.C. Loco-regional relapse-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

FIGURE 2.D. Distant relapse-free survival. mBBC – metachronous bilateral breast cancer; sBBC – synchronous bilateral breast cancer

tients with less than 5 years was 62.89 months, whereas it was 472.83 months for those with more than 5 years; $p = 0.011$, Log Rank; $p = 0.024$, Breslow; $p = 0.017$, Tarone Ware). Statistics and test of equality for overall survival could not be computed because all cases were censored.

We questioned if there was a difference in terms of survival analysis among the mBBC subgroups (time of diagnosis <5 years, >5 years) and sBBC. It was observed a statistical overall survival difference among groups ($p = 0.018$). We found that sBBC patients had the worst prognosis based on disease-free survival rates and that mBBC patients diagnosed < 5 years might be similar to sBBC (the mean disease-free survival for patients < 5 years was 63.3 months and for sBBC it was 39.6 months, whereas for patients with more than 5 years was 437.9 months, $p = 0.012$, Log Rank). There no statistical difference in terms of loco-regional relapse-free survival ($p = 0.081$ Log Rank; $p = 0.224$, Breslow; $p = 0.148$ Tarone-Ware), although sBBC showed more frequent rates of loco-regional relapse and earlier in the time course. More frequent rates of distant metastasis were in the sBBC and <5 years mBBC with a statistically significant difference (< 5 years mBBC, mean 62.89 months; >5 years mBBC, 472.83 months; sBBC, 40.2 months; $p = 0.001$, Log Rank; $p = 0.010$, Breslow, $p = 0.004$ Tarone-Ware).

It was also analyzed the association of HR concordance, within tumor pairs, biomarker defined subtype (ER,HER2) concordance and molecular subtype concordance and disease-free survival. There was no sta-

tistically significant difference between concordant HR group and discordant HR group in overall patients ($p = 0.280$, Log Rank), mBBC group ($p = 0.846$) or sBBC group ($p = 0.445$). Discordant biomarker defined subgroup patients were associated with better disease-free survival in overall patients ($p = 0.047$, Log Rank) with no differences neither among patients in mBBC group ($p = 0.222$, Log Rank) nor sBBC ($p = 0.445$, Log Rank); in overall patients, distant relapse-free survival was also found to be significant, $p = 0.015$, discordant ER,HER2 subgroups showed a better distant relapse-free survival, no statistical significance in terms of loco-regional relapse-free survival ($p = 0.199$). Concordance in molecular subtype was associated with no statistically significant difference among groups ($p = 0.221$) or with groups (mBBC, $p = 0.263$; sBBC, $p = 0.592$).

DISCUSSION

Women with previous breast carcinoma are at increased risk for developing second primary breast cancer in the contralateral breast, Soerjomataram et al. reported a relative risk of 3.5% (7,28).

By Gollamudi et al., synchronous breast tumors were defined as development of cancer within 1 month of initial diagnosis, by Hartman et al. within 3 months and by Ibrahim, Chen et al. within 12 months of initial diagnosis (12,20,29-33). In this study, was used the interval time of 3 months.

In the present study, out of the 658 evaluated breast carcinoma cases, 35 cases were diagnosed with bilater-

al breast cancer. Several studies had reported the incidence of primary breast cancer development in the contralateral breast cancer as ranging from 1.4% to 11.8%. (5,12,15-17,25-26). In our study, BBC incidence accounted for 5.3% of all cases. According to the existing literature, the incidence rate of metachronous breast cancer ranges from 0.3% to 1%, whereas in this study was found a rate of 3.8% (12,27). The incidence rate of synchronous breast cancer was reported to be less than 2% (10,12). In this study, the incidence rate for synchronous was found to be 1.5%. Studies report that most mBBC cases occur 5 years after the initial diagnosis; the median time in our study was 5.5 years, however in accordance with the literature (12,27).

In the present study there was no statistical significant difference between metachronous and synchronous groups in terms of age at the initial diagnosis ($p = 0.339$). Among the patients with metachronous breast cancer, the median age at the time of initial diagnosis was 58 years, finding surpassing reports from the existing literature, i.e. the median age at initial diagnosis was found as 52 years by Ozturk et al, as 51 years by Diaz et al. and 46 years by Liang et al. (12,31,34).

Tumor characteristic showed no differences between the mBBC and sBBC groups, conversely there were statistical differences within the groups in terms of tumor diameters between the first and second tumors ($p = 0.004$, respectively $p = 0.011$); the second tumor in both metachronous and synchronous groups showed smaller diameters compared to the first malignancy. Kheirleiseid et al. calculated the median first tumor diameter as 20 mm (range, 1-100) and the median second tumor diameter as 15 mm (range, 1-82) in metachronous tumors and the median dominant and contralateral tumor diameters were reported as 24 mm (range, 1-130) respectively 12 mm (range, 1-140); they found a statistically significant difference in the synchronous group (12,32). Ozturk et al. reported the mean tumor diameter in the metachronous group, as 22.3 ± 13 mm for the first tumor and 14.3 ± 11.5 mm for the second tumor; in the synchronous group the mean tumor diameter was calculated as 21.5 ± 13.3 mm in the dominant tumor and 12 ± 8.3 mm in the contralateral tumor; they also detected a significant statistical difference in terms of first and second tumor diameters within groups ($p = 0.008$, $p < 0.001$, respectively (12).

The median time for occurrence of the second tumor differed among previous publications. By Kheirleiseid et al. was reported as 46.8 months, by Liang et al. as 67 months (range, 14-432) and by Ozturk et al as 96 months (range, 12-191) (12,32,34). In this study, the median time of metachronous cancer occurrence was found as 66 months (range, 16-372).

In terms of histological type, some previous publications reported higher prevalence of invasive lobular

carcinoma in sBBC patients and others found invasive ductal carcinoma as the most common type of tumor (5,6,12,20,35,36). In this study, in both groups, the invasive ductal carcinoma-NOS (IBC-NST) type, whether in combination (mixed or focal) with other special subtype carcinomas or not, was the most frequent histological type encountered.

Previously published studies, reported a particularly high level of concordance among sBBC tumors compared to mBBC (5,31,37,38). Huber et al. confirmed a 90.7% level of concordance for HR and suggested that this observation reflects the common environment where sBBC tumors developed in contrast to mBBC tumors, that show a non-significant level of HR-concordance because of intercurrent factors, i.e. adverse effects of treatments for the index tumor, such as chemotherapy, anti-hormone treatment or menopausal status (5). The present study is in accordance with the literature, it was found a 85.7% level of concordance for HR status in sBBC patients and 28.6% in mBBC patients, with statistical significant difference between groups ($p = 0.010$).

In the study of Chen et al. the rates for bilateral mastectomy and breast conserving surgery, reconstruction and combined surgery were 81.1%, 4.4%, 3.0% and 11.5% for patients with mBBC and 86.2%, 6.4%, 3.7% and 3.7%, respectively for patients with sBBC (33). In the study of O'Brien et al. lumpectomy vs. mastectomy was performed to 57% vs. 43% of dominant and 48% vs. 51% of contralateral breast in mBBC patients, respectively 34% vs. 66% of dominant breast and 33% vs. 67% to contralateral breast in the synchronous group; axillary lymph node dissection in 46% vs. 29% in mBBC group and 37% vs. 33% in sBBC group (39). In our study, in the metachronous groups, mastectomy was performed to 96% of dominant breast and to 88% of contralateral, whereas breast conserving surgery to 4% of dominant, respectively to 8% of contralateral; radical axillar lymphadenectomy accounted for the majority of axillar surgery for mBBC tumors. In the sBBC breast conserving surgery was performed at a higher rate, to 20% of patients in the dominant breast and 30% to contralateral, conservative mastectomy accounted for 10% in the first tumor and also in the second, however, non-conservative mastectomy was performed in most cases (70% first tumor; 60% second tumor); radical axillar lymphadenectomy was performed in all cases, both dominant and contralateral breast.

There is no consensus in the literature regarding the outcome of bilateral breast cancer, most studies showing a survival difference between mBBC and sBBC (5,9,36). The study performed by Huber et al. revealed no difference between metachronous and synchro-

nous patients in terms of overall or relapse-free survival, instead it was observed a higher rate of loco-regional recurrence in the mBBC patients (5). In Ozturk et al. series, there was no statistically significant difference between the metachronous and synchronous group in terms of overall survival, local recurrence-free survival and distant metastasis-free survival, however metachronous group displayed better prognosis in terms of disease-free survival ($p = 0.041$) (12). In the present study, the statistical analysis showed a survival difference between the two groups. The study by Ozturk et al. also revealed that the median survival was poorer among patients in whom metachronous tumor occurred within less than 5 years ($p = 0.001$) (12). In this study was found that the time interval between mBBC tumors was statistically significant only terms of distant relapse-free survival ($p = 0.011$). When the two metachronous subgroups were compared with synchronous group, was observed a statistical significance in terms of overall survival, disease-free survival and distant relapse-free survival.

CONCLUSIONS

Bilateral breast cancer represents a reality with a frequency that ranges between 1.4% and 11.8% as reported in the existing literature. In the present study, the most frequent histological type encountered was invasive ductal carcinoma, the finding was consistent with many previous reports. In terms of survival analysis, patients with synchronous tumors showed a worse disease outcome and distant relapse-free survival might be similar among synchronous patients and patients in whom metachronous tumor was diagnosed within less than 5 years. Patients from the sBBC group showed a higher rate of HR concordance with positive concordant ER and PR receptor. Survival analysis showed no significant statistical difference in terms of hormonal receptor concordance or molecular subtype concordance. On the other hand, patients with ER,HER2 discordant tumors, compared to those with concordant ER,HER2 tumors, had a better disease outcome. Consequently, analysing disease outcomes of breast cancer patients at a molecular level deserves further clinical observation.

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