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Review

Synchronous bilateral breast cancer patients submitted to conservative treatment and brachytherapy – The experience of a service

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ABSTRACT

Introduction: The incidence of breast carcinoma (BC) has increased in the last years. Between 2 and 12% of patients diagnosed with BC will develop bilateral breast carcinoma (BBC). The treatment of these carcinomas is more aggressive than unilateral BC.
Purpose: To perform a retrospective qualitative analysis of BBC patients whose treatment has included brachytherapy (BT) and to present a revised literature on this issue.
Material and methods: The cases of BBC whose treatment included brachytherapy were revised. The literature on this issue was refreshed.
Results: Five women, aged between 54 and 78 at the time of the diagnosis, submitted to conservative surgery followed by external radiotherapy (RT) with boost of BT or exclusive BT (APBI), in the IPO-P BT Service between 2003 and 2016.
Discussion: The patients with BBC have slightly higher rates of local recurrences, mostly in the tumor bed, where there is a higher risk of local recurrence. Patients treated with BT had lower rates of recurrences than those treated with photons and electrons.
Conclusions: BBC represents a complex challenge for doctors, because in some cases there is a tendency to use more aggressive treatments and, at the same time, it is not easy to achieve the timing for the correct treatment.

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1. Introduction

In the developed countries breast carcinoma (BC) is the most frequently detected tumor in women; its incidence has been growing over the years.[1]

The average age at diagnosis is reported to fall between 45 and 65.[2]

About 2–12% of the patients with BC will develop contralateral BC during their lifetime.[3–9]

Between 1970 and 1980, there has been a rise of about 40% in the incidence of synchronous bilateral BC (SBBC), and this figure has remained stable since then. This growth has been explained by the routine bilateral breast screening procedures at the time of the diagnosis.[1]

The annual incidence of bilateral metachronous BC (BMBC) varies between 0.1 and 1.0%[10,11] while the incidence of SBBC varies between 0.3 and 3.0%. This variation is explained by the different definitions of synchronicity.[12,13]

The main risk factors to develop bilateral BC (BBC) are: BC family history, early age at the first breast tumor diagnosis, lobular histology[14] and multicentricity.[6,7,15–22]

The prognosis also varies: the cumulative mortality rates at 10 years are lower for the Unilateral BC (UBC) (33%) and BMBC when the 2 tumors were diagnosed within at least a 10 year gap (34%). For the SBBC, the cumulative mortality rates at 10 years are average, about 45%, and they are higher for BMBC (56%) when both tumors were diagnosed within a 5 year gap.[1]

Although nowadays the therapeutic options for early breast cancer include breast mastectomy or breast conservative surgery followed by RT,[23–25] BBC treatment is usually more aggressive, with a higher number of mastectomies and axillary dissections than UBC.[14]

In our center 5 SBBC cases were treated with conservative surgery followed by RT (3DCRT) to the breast, at a dose of 50 Gy, 2 Gy per fraction, in 25 fractions with photons and *boost* with BT or exclusive BT (APBI), and were subject of a qualitative retrospective analysis.

The need to perform a literature review came from the fact that no specific guidelines for an approach to SBBC had been found.

2. Material and methods

The aim of this study is to characterize the patients with SBBC treated with BT in our institution and to review the literature concerning BBC definition and risk factors, SBCC treatment and prognosis. We included patients with SBBC who had undergone BT treatment at the Instituto Português de Oncologia do Porto (IPO-P) BT Service between 2003 and 2016, and collected demographic data and tumor features, using clinical records. The tumors considered SBBC were those in a 6 month gap or lower.

The criteria for *boost* used were those according to Fourquet.[26]

After surgery, 4 out of 5 patients underwent external beam radiation to the entire breast at a dose of 50 Gy, at 2 Gy per fraction, in 25 fractions with photons, 4 MV energy.

For the brachytherapy treatment, the patients were under anesthesia for the application of hypodermic needles, according to a template, with an interval of 14 mm between needles. The applicator reconstruction is a theoretical one, based on the Paris System modified. The total dose was 15 Gy 85% D. B. and the pulse dose: 0.8 Gy/h with Iridium 192 Pulsed Dose Rate (PDR).

A literature research was taken based on the following key words: bilateral breast carcinoma; bilateral breast carcinoma brachytherapy; bilateral breast carcinoma boost; APBI breast carcinoma brachytherapy.

3. Results

The patients' features and BBC's are displayed in Tables 1–3.

As far as the treatment with BT: patient 1 underwent APBI. 7 hypodermic needles (HN) were applied on the right breast and 9 HN on the left breast with the appropriate template. Total dose: 32 Gy 85% D.B. in 2 fractions/day during four consecutive days with Iridium 192 High Dose Rate (HDR); the remaining patients underwent a brachytherapy boost after RT. The Fig. 1 illustrates treatment planning of patient 3, that received bilateral external radiotherapy, 50 Gy, followed by BT boost, 15 Gy.

4. Discussion

4.1. *Definition of BBC*

Although it is relevant to define the differentiation of the second breast tumor as primary or metastasis,[27] this distinction is not always easy to assume.[28] Some authors suggest that BBC may derive from metastatic cells that migrated to the contralateral breast, or that it can be the result of a hormonal environment that enables the growth of several tumoral focuses.[29] Several genetic studies of BBC cases have shown that these tumors seldom metastasize to the contralateral breast.[30,31]

The molecular methods like "comparative genomic hybridization", used to distinguish a second primary from a metastasis, are very complex, expensive and have not been validated yet.[28] That is why, nowadays, the clinical criteria are most frequently used.

Chaudhary et al. suggested in 1984 four criteria for the breast second primary diagnosis: (i) the presence of carcinoma in situ in the contralateral tumor (absolute evidence); (ii) the second primary should be histologically different from the first tumor; (iii) the degree of the second primary histological differentiation should be higher than the first tumor's; (iv) if there is no histological difference, then there should not be evidence of local, regional or distant metastization of the first tumor.[7]

In our sample, we can confirm that patients 3 and 4 fulfill the 1st criterion (absolute evidence), in which the carcinoma in situ coexists with the invasive carcinoma. In patient 1 the carcinoma in situ was not detected. In patient 2 the component in situ coexisted only in the left breast. In patient 5 we did not have access to the information needed, so we can neither include nor exclude this criterion.

As for the matching of the other criteria, in patient 1 we confirmed that both tumors were histologically different and neither showed evidence of locoregional or distant metastization, fulfilling the 2nd and the 4th criteria. In patient 2,

Table 1 – Characterization of initial treatment.

Patient	1		2		3		4		5	
	R breast	L breast	R breast	L breast	R breast	L breast	R breast	L breast	R breast	L breast
Histology	IDC	MC (ductal and mucinous)	IDC	IDC with lobular areas	IDC	MTC	IDC	IDC	IDC	IDC
DCIS	NO	NO	Not extensive, low grade	Not extensive, low grade	Not extensive, low grade	Not extensive, low grade	Not extensive, medium grade	Not extensive, medium grade	?	?
Size (cm)	1.5	1.8	1.6	0.9	1.6	0.9	1.4	2.4	2.0	1.3
Grade	2	2	1	1	1	1	2	1	1	2
LVI	?	?	NO	Observed, limited	?	?	NO	NO	?	?
ER	75–100%	75–100%	75–100%	75–100%	75–100%	75–100%	75–100%	75–100%	75–100%	75–100%
PR	75–100%	75–100%	50–75%	75–100%	50–75%	75–100%	50–75%	50–75%	75–100%	75–100%
HER 2	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Ki67%	17%	17%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Stage	pT1bN0snM0	pT1cN0snM0	pT1cN0snM0	pT1bN0snM0	pT1cN0snM0	pT1bN0snM0	pT1cN1micM0	pT2N0snM0	pT1cN0snM0	pT1cN0snM0

Legend: R – right; L – left; BC – breast conservation; UIQ – upper inner quadrant; SLND – sentinel lymph node detection; LB – lateral breast; UOQ – upper outer quadrant; AD – Axillary dissection; IB – inner breast; SA – subareolar area; LN – lymph node; SLN – sentinel lymph node; Mic – micrometastases; N/R – not received.

There were 5 patients between the ages of 54 and 79 years. Patients numbered 1, 2 and 4 had bilateral simultaneous surgery. The other two patients had surgeries with a 4-month difference between each breast. Patient 5, being the oldest one, underwent axillary dissection bilaterally, all of which were negative nodes. Patient number 4, with a positive sentinel node, micrometastasis, underwent right axillary dissection.

Table 2 – Characterization of tumors.

Patient	1		2		3		4		5	
Age at the diagnosis	78		54		56		75		79	
	R Breast	**L Breast**	**R Breast**	**L Breast**	**R Breast**	**L Breast**	**R Breast**	**L Breast**	**R Breast**	**L Breast**
Time between surgeries	0		0		4 months (1st L breast)		0		4 months (1st R breast)	
Surgery	BC (UIQ) + SLND	BC (LB) + SLND	BC (UOQ) + SLND 2nd surgery	BC (UOQ) + SLND	BC + SLND	BC (UOQ) + SLND	BC (UOQ) + SLND + AD	BC (UOQ) + SLND	BC (IB) + AD R	BC (SA) + AD L
Excised LNs	0/1 SLN	0/1 SLN	0/3 SLN	0/3 SLN	0/4 SLN + 1 LN	0/2 SLN	1 Mic/1 SLN	0/1 SLN	DU	DU
Axillary Dissection	N/R	N/R	N/R	N/R	N/R	N/R	0/13 LN + 1 SLN	N/R	0/15 LN	0/16 LN
Metastatic LNs	0	0	0	0	0	0	1 Mic	0	0	0

Legend: R – right; L – left; IDC – infiltrating ductal carcinoma; MC – mixed carcinoma; MTC – mixed tubular carcinoma; DCIS – ductal carcinoma in situ; ND – not detected;? – unknown; LVI – limphovascular invasion; ER – estrogen receptors; PR – progesterone receptors; NO – not observed; N/A – not available.
All tumors were infiltrative ductal carcinomas, with the exception of the left breast tumor of patient 1 which was a mixed carcinoma and left breast tumor of patient 3 which was mixed tubular carcinoma.
The size of the tumors ranged from 0.9 to 2.4 cm, they were well differentiated in moderation. All had positive hormone receptors and were Her2 negative. Some of the characteristics of tumors are missing since patients are often drained for the IPO after initial surgical treatment, and there is this description in external examinations.

Table 3 – Adjuvant patients' treatment.

Patient	1		2		3		4		5	
	R breast	L breast	R breast	L breast	R breast	L breast	R breast	L breast	R breast	L breast
RT	N/R	Bilateral breast								
Dose	–	50 Gy								
Gy/fx	–	2								
Fx	–	25								
Energy	–	4 MV								
Skin acute effects	–	Grade 1	Grade 1				Grade 2		Grade 1	
BT	APBI bilateral	Boost	Boost				Boost		Boost	
	7 HN	9 HN	9 HN	7 HN	5 HN	5 HN	5 HN	5 HN	4 HN	6 HN
Dose rate	HDR (superior 12 Gy/h) 8 Gy/day in two fractions.	PDR (0.8 Gy/h) 19 pulses	PDR (0.8 Gy/h) 19 pulses				PDR (0.8 Gy/h) 19 pulses		PDR (0.8 Gy/h) 19 pulses	
Dose	32 Gy	15 Gy	15 Gy				15 Gy		15 Gy	
CT	N/R	4 AC	N/R				Refused		N/R	
HT	Anastrozole	Anastrozole	Anastrozole				Tamoxifen (until 2010) then anastrozole (until 2012)		Tamoxifen	
Follow-up	4 years	3.5 years	11 years				10 years		4.5 years	
Status at last follow-up	Alive, NED	Alive, NED	Alive, NED				Alive, NED		Died 08/07/2012	

Legend: R – right; L – left; RT – external beam radiotherapy; Fx –fractions; BT – brachytherapy; APBI – accelerated partial breast irradiation; HN – hypodermic needles; HDR – high dose rate; PDR – pulse dose rate; CT – chemotherapy; N/R – not received; AC – adriamycin and cyclophosphamide; HT – hormone therapy; NED – no evidence of disease. To characterize the skin acute toxicity we use the "RTOG Acute Radiation Morbidity" table.

All 5 patients had HT. Only patient 2 performed CT and although patient 4 was proposed, she declined.

All of them underwent external beam radiotherapy to both breasts, except the number 1 patient who performed only APBI with BT. They received 50 Gy, at 2 Gy/fraction in 25 fractions with 4 MV energy. The acute skin effects varied between Grade 1 and 2. Subsequently, women who performed external RT received a 15 Gy boost with PDR of 0.8 Gy per hour in 19 pulses. The patient who performed only APBI bilaterally, did 32 Gy with HDR of >12 Gy per hour, 8 Gy each day in two daily fractions.

Follow-up ranged from 3.5 to 11 years. With the exception of patient 5 who died in 2012 with a follow-up of 4.5 years, the other patients are alive and without evidence of disease.

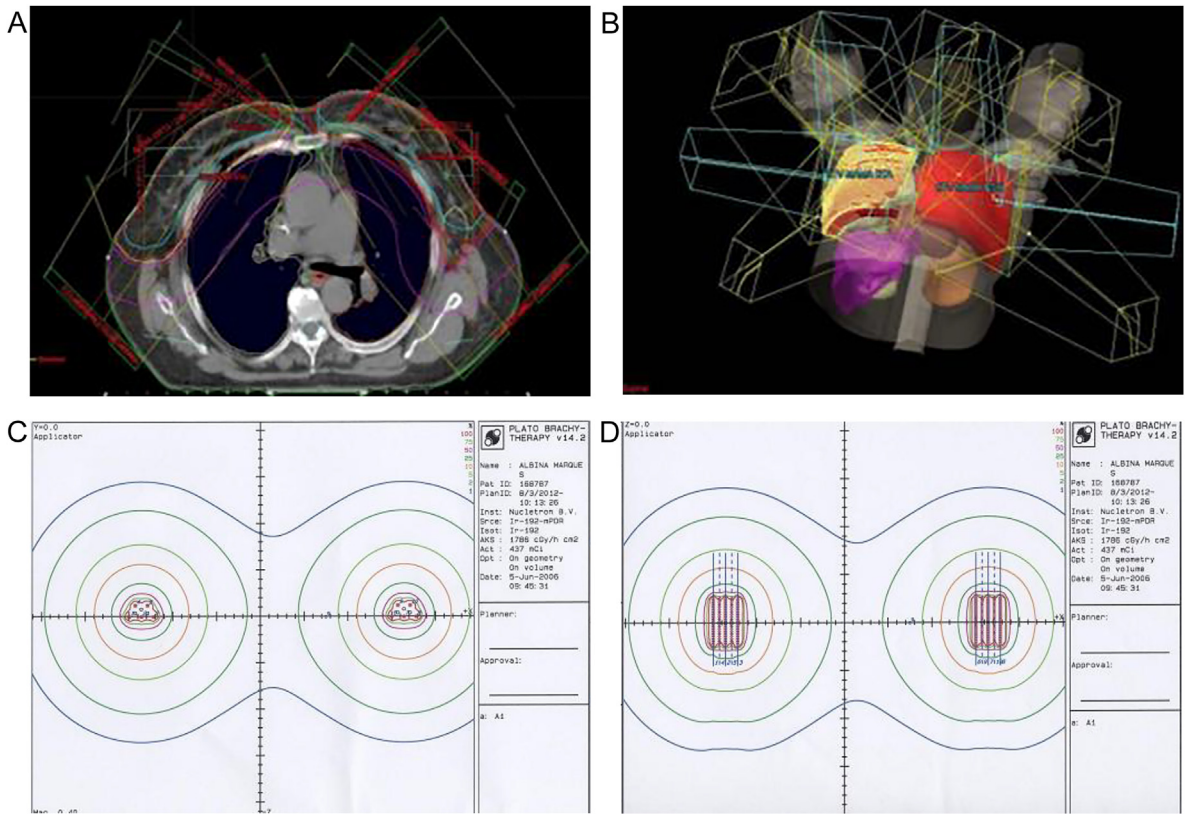

Fig. 1 – Patient 3, treatment planning: A and B – External Radiotherapy; C and D – Brachytherapy boost.

although the tumors are invasive ductal carcinomas, in the left breast the tumor had a lobular area (2nd criterion), a higher histological degree compared to the right breast (GII vs. GI) (3rd criterion), and no metastization (4th criterion). In patient 5 the second tumor histological degree was higher than that of the first tumor. (GII vs. GI), matching the Chaudhary's 3rd criterion.

4.2. *Risk factors*

The main risk factors for BBC referred to in the literature are: BC family history, young age/premenopausal at the first breast tumor diagnosis, lobular histology[14] or multicentricity.[6,7,15–22]

Contrary to the literature, the sample patients had already reached menopause, the nodules were single and although no patients had a pure lobular histology, patient 2 had a lobular component grafted in the left breast invasive ductal carcinoma.

Women with a BC personal history present a 2.6 times increased risk of BC, compared to the general population.

Newman et al., Cook et al. and Broet et al. have shown that there is no connection between radiation (first tumor treatment) and the risk of subsequent contralateral disease.[15]

Chen et al. carried out a retrospective assessment of 161 SBBC cases in an early stage, with prospective validation of potential risk factors, like the presence of "sclerosing adenosis" (HR = 11.8; 95% CI: 5.3–263; $p < 0.001$) and lobular carcinoma component (HR = 2.0; 95% CI: 1.1-3.4; $p < 0.001$). The tumoral microenvironment plays a critical role in the SBBC carcinogenesis.[32]

4.3. *Treatment*

The SBBC treatment is extrapolated from UBC,[29] so the approach must be conducted by the UBC *guidelines*.

4.3.1. *Systemic*

The systemic treatment reduces local recurrences, the risk of BBC and distant metastization.[1]

Patient 2 underwent adjuvant chemotherapy (CT) (4 AC), while patient 4, although instructed to, refused to undergo this treatment. All patients underwent hormonotherapy (HT).

The presence of hormone receptors in the contralateral tumor may be influenced by the use of tamoxifen in the treatment of the first tumor.[28]

4.3.2. *Local*

Whenever we intend to preserve the breast, the standard treatment (Breast Conservative Treatment) implies conservative surgery (CBS) followed by whole breast irradiation (WBI).[23,24,33–39]

Patients with BBC have slightly higher rates of local recurrences. The tumor bed is the area with the highest risk of local recurrences.[40–48] In order to minimize local recurrences in this area, the actual practice consists of administrating an additional dose to the tumor bed after the WBI.[40–42] Normally, this

additional dose is applied to the scarred area and treated with electrons,[30,42] photons or BT.[49–53]

This additional dose with photons or electrons involves the risk of a dose increase to organs at risk and it may represent a late and acute toxicity (e.g. fibrosis and radiation dermatitis, respectively). The study by Terheyden et al. has shown a reduction of the average dose in the lung of patients treated with BT (HDR) compared to patients treated with external RT (average dose of 0.40 Gy vs. 0–79 Gy).[54] The dose rate is also important in the recurrences reduction, because there is an increase in the recurrences number with rates of less than 0.3 Gy dose rates.[55]

Furthermore, patients treated with BT had lower recurrence rates than those treated with photons or electrons. Poortmans et al. confirmed that there was a lower number of local recurrences after 5 years using the boost with BT, instead of electrons or photons.[56] According to Fourquet et al. the boost with BT reduced the breast recurrence risk in 60%.[26]

Using the Boost with BT, we managed to reduce treatment duration in 2 weeks and get a better aesthetic outcome.[57–59]

The study of the APBI, conducted by GEC-ESTRO, compared patients treated with APBI, BT HDR and BT PDR to the conventional fractionation scheme WBI (50 Gy) and a boost with electrons (10 Gy). Thus, the patients treated with APBI experienced a reduced acute toxicity, namely cutaneous toxicity and we also concluded that the use of APBI is safe and well tolerated in selected patients with an early disease, thus proving non-inferiority for WBI.[60,61]

All the patients in the sample underwent BT, 4 patients underwent WBI, while patient 1 underwent bilateral APBI due to her comorbidities. Patients 2, 3, 4 and 5 underwent boost with bilateral BT, 0.8 Gy/h with PDR, in 19 pulses, total dose 15 Gy.

4.4. *Prognosis*

The literature reports contradictory results regarding prognosis.

Some studies state that BBC does not influence survival,[62] but Hartman et al. confirmed that specific cumulative mortality for BC at 10 years is higher in SBBC vs. UBC, with figures of 45% and 33%, respectively[1] Schmid et al. compared 34 cases of SBBC at an early stage to 100 case-controls, confirming the absence of relevant differences in what concerned specific survival by BC (HR 0.932, 95%CI: 0.322–1.07, $p = 0.9$), concluding that prognosis in patients with SBBC is determined by the tumor with the worst prognosis.[63]

Schwentne et al. found a strong association between the adoption of treatment guidelines and the increase of disease free survival and global survival. They also refer that in patients with BBC, the treatment guidelines tend not to be followed, namely in adjuvant RT and CT. These are the areas with a higher influence upon survival.[62]

Our patients follow-up varied between 3.5 and 11 years (patient 2 underwent treatment in 2003 and patient 3 underwent treatment in 2006). Only patient 5 died, completing a follow-up that lasted 4 years and 6 months. The cause of death was not oncological. The remaining patients are alive and show no evidence of a recurrence up to the present date.

5. Conclusion

SBBC represents a complex challenge because the treatment is more aggressive or because it is not easy to achieve the *timing* for the right treatment. In order to achieve results equivalent to those of mastectomy in BC treatment, radiotherapy must follow conservative surgery. Once the BBC have a higher incidence of local recurrences, a boost to the tumor bed must be carried out, preferably with BT, because it provides higher outcomes than the boost carried out with photons or electrons, either in terms of local recurrences or in cosmetic terms, not so much associated to fibrosis.

Conflict of interest

None declared.

Financial disclosure

None declared.

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