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GRADO EN MEDICINA

TRABAJO DE FIN DE GRADO

**Análisis de los factores relacionados con la
afectación de los márgenes quirúrgicos en la
cirugía conservadora oncoplástica del cáncer de
mama**

**Analysis of factors related to affected surgical
margins in oncoplastic breast-conserving
surgery**

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1. ABSTRACT

BACKGROUND. Breast conserving surgery (BCS) with oncoplastic approach (OCBS) is the gold standard for the treatment of early breast cancer. The main objective is to achieve complete tumor excision with no involved surgical margins. It was defined the use of “no ink on tumor” as the standard for an adequate negative margin in invasive breast cancer.

OBJECTIVE. Analyze the rate of affected margins and describe which clinic-pathologic factors are significantly related to positive margins after BCS. Study its use in counseling surgery and potentially, in reducing the number of recurrences and re-excisions.

PATIENTS AND METHODS. Between 2013 and 2016, 152 patients with breast cancer were operated undergoing BCS with oncoplastic techniques at the Breast Unit (HUMV, Santander). A multivariate analysis was used to test for association between clinic-pathologic variables and positive surgical margins.

RESULTS. The rate of affected margins was 13.2% and 11.2% patients underwent re-interventions. The unique variable that was significantly associated with increased risk of positive margin was multifocality.

CONCLUSION. Multifocality can be assessed preoperatively, so this provides the opportunity to optimize preoperative counseling for each patient and enables the adjustment of surgical method.

Key Words: *Multifocality, Oncoplastic breast conserving surgery, Surgical margin*

2. RESUMEN

INTRODUCCIÓN. La cirugía conservadora con técnicas oncoplásticas es el gold estándar en el tratamiento del cáncer de mama en estadios tempranos. Su principal objetivo es la escisión completa del tumor sin márgenes afectados. El término “no tinta en el tumor” es el gold standard para alcanzar un margen negativo adecuado.

OBJETIVO. Analizar la tasa de márgenes afectados y describir cuales son los factores clínico-patológicos que están relacionados significativamente con un margen positivo después de una cirugía conservadora de mama. Estudiar su utilización en el asesoramiento de la cirugía y potencialmente, en la reducción del número de recurrencias y re-escisiones.

PACIENTES Y MÉTODOS. Entre 2013 y 2016, 152 pacientes fueron operadas mediante cirugía conservadora con técnicas oncoplásticas en la Unidad de Mama (HUMV, Santander). Se realizó un análisis multivariante para comprobar la asociación entre variables clínico-patológicas y márgenes de cirugía positivos.

RESULTADOS. La tasa de márgenes afectados fue 13,2% y un 11,2% de los pacientes fueron reintervenidos. La única variable significativamente asociada con un riesgo aumentado de márgenes positivos fue la multifocalidad.

CONCLUSIÓN. La multifocalidad puede ser evaluada preoperatoriamente, lo que brinda la oportunidad de optimizar el asesoramiento preoperatorio para cada paciente y posiblemente el ajuste del método quirúrgico.

Palabras clave: Cirugía conservadora oncoplástica de mama, Márgenes quirúrgicos, Multifocalidad.

3. INTRODUCCION

3.1 Importance of breast cancer

Breast cancer is the most frequent malignant tumor of Spanish women, which means 29% of all malignant tumors; in 2015, 27.747 new breast cancers were diagnosed in Spain.

The overall mean survival of breast cancer after five years is high around 89.2% but, it depends on the stage in which the cancer has been diagnosed; for example, breast cancer in stage I (tumor with less than 2 cm and without positive lymph nodes) has a survival rate higher than 98% but in more advanced stages such as stage III (with extensive lymph node involve) drops to 24%.

Although mortality has decreased during the lasts decades due to screening programs spreading and treatment amelioration, it follows being the first cause of women's death in Spain with 6,705 deaths in 2012.¹ The same year in Europe, breast cancer incidence was 458,718 with a mortality of 131,347.²

In our county, the register of Cantabria (General Direction of Public Health) shows a stable incidence during 2012 -2013 of 238 new cases each year³ and 80 women death for this reason, which means a mortality rate of 33 per 100,000 inhabitants.

3.2 Advances in treatment of breast cancer.

Nowadays, breast cancer is treated by multidisciplinary approach involving surgical oncology, radiation and medical oncology which has been associated with a reduction in breast cancer mortality⁴.

The surgical treatment of breast cancer has made substantial changes from radical procedures such as Halsted mastectomy, which were followed by important sequelae and health quality of life deterioration, moving towards those which achieve complete tumor resection preserving most of the breast tissue with a low morbidity. Currently, breast conserving therapy (BCT) is the gold standard for the treatment of early breast cancer.

BCT is defined as a breast conserving surgery (BCS), which means a surgical excision of the tumor within a margin of surrounding normal tissue, followed by whole-breast irradiation (WBRT) ⁶. This combined treatment results in long-term survival rates greater than 95% for women with DCIS.⁷⁻⁹ This is due to the addition of WBRT does not improve survival, but it reduces rates of ipsilateral breast tumor recurrence (IBTR) even in smaller non-high-grade DCISs.^{7,10} This approach is oncologically safe, with equivalent survival rates when compared with mastectomy.⁵

In the last two decades, a new surgical approach named oncoplastic breast conserving surgery (OBCS) has emerged to allow a complete resection of tumor preserving normal parenchyma tissue and the use of local or regional tissue for immediate breast reconstruction at the time of partial mastectomy. It has numerous benefits including better aesthetic outcomes, better tumor margins and high patient satisfaction and the ability to extend the option of breast conservation.¹¹

The reconstructive options available are primarily determined by the size of the breast and the tumor to breast ratio. For example, in smaller breasted woman are more likely to need regionally-based flaps, while patients with macromastia have more options available for reconstruction, whether it is local tissue rearrangement, local or regional flaps, or reduction mammoplasty/mastopexy.¹²

Following OBS, many women desire symmetry-achieving surgery because contralateral breast appearance is important in the overall aesthetic outcome.¹³

2.3 Consensus of clear margins

The main BCT objective is to achieve complete tumor excision with no involved surgical margins. Despite the commonly use of BCT for more than 30 years, there used to have disagreement between physicians about what constitutes an optimal margin width. Some examples of different surgical resection criteria found in literature were more than 5mm of negative surgical margin in Cancer Institute Hospital of the Japanese Foundation for Cancer Research ¹⁴ or 10 mm in Nottingham City Hospital.¹⁵

Consequence of that, one each three women treated by BCT for DCIS undergo secondary re-excision to attain wider margins¹⁶. It's supposes added discomfort, surgical complications, and higher economic, psychological and cosmetic costs to the patient. Additionally, re-excisions have been associated with conversion to mastectomy.¹⁷

This lack of consensus was the reason why the Society of Surgical Oncology (SSO), American Society of Radiation Oncology (ASTRO) and American Society of Clinical Oncology (ASCO) used a meta-analysis to evaluate IBTR in relation to margin width for DCIS and other for invasive breast cancer (stages I and II).

In February 2014, the SSO/ASTRO published the guideline addressed to patients with invasive breast cancer who have undergone WBRT. It was defined the use of “no ink on tumor” as the standard for an adequate negative margin in invasive breast cancer. This means no cancer cells adjacent to any inked edge/surface of specimen and it is associated with low rates of IBTR, and potentially decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.¹⁸

The guideline scope did not encompass patients with noninvasive breast cancer, patients treated with partial-breast irradiation, and/or patients treated with systemic therapy before surgery.

Subsequently, in November of 2015 was approved a guideline with standards for BCT for DCIS in order to assist physicians and patients to take clinical decisions based on the best available evidence. The mainly conclusions of this multidisciplinary consensus were:

- (1) Patients with positive margin, defined as ink on DCIS, have significant increased IBTR (24%) compared with negative margins (12%). It implies an incomplete resection of DCIS and this higher risk is not nullified using WBRT.²⁰
- (2) The narrower negative margin width is 2 mm, which associate reduced risk of IBTR for DCIS in patients receiving WBRT. Negative margins wider than 2 mm is not supported by the evidence.
- (3) Treatment with excision alone, in spite of margin width, is associated with higher rates of IBTR than combined excision with WBRT, even in low risk patients.
- (4) IBTR are reduced with endocrine therapy in patients with positive margins but there was no evidence to suggest an association between negative margin width and benefit of endocrine therapy.⁶

There are two diagnoses for which there is overlap between DCIS margin guideline and the SSO-ASTRO invasive cancer margin guideline.¹⁹ The first one, DCIS with microinvasion (DCIS-M), defined as extension of cancer cells beyond the basement membrane with no focus larger than 1mm in greatest dimension²⁰. Studies have suggested that IBTR is similar to those with pure DCIS (because majority of the lesion is composed of DCIS), so it should be consider DCIS when determining the optimal margin width.

Secondly, in case of invasive cancer with a DCIS component, regardless of extent, should be treated as invasive cancer guideline recommends because lesions are more similar to those of invasive cancer, even when the close margin contains DCIS.

The two guidelines, both for DCIS and also for early invasive breast cancer, apply only to patients treated with WBRT. Furthermore, there were considered clinical circumstances that might affect the relationship with an optimal margin, which are cases with increased risk of IBTR in young patients (<40 years), patients not receiving adjuvant systemic therapy, unfavorable biologic subtypes (as triple-negative breast cancers) and invasive lobular cancer, and there is no evidence suggesting the need of margins wider than no ink on tumor.²¹ So, margin widths should not be influenced by patient and tumor features.

This increased risk in IBTR is not nullified by delivery of a boost, delivery of systemic therapy (endocrine, chemotherapy, biologic therapy) or favorable biology, so the choice of WBRT delivery technique, fraction, and boost dose should not be dependent on the margin width.

Therefore, the antique routine practice of obtaining negative margin widths wider than 2mm is not supported by evidence to decrease IBTR significantly. Although there are an evidence that the 2 mm margin optimized local control, clinical judgment must be used in determining whether patients with smaller negative margin widths require re-excision. Some factors known to be important to consider include: assessment of IBTR risk (residual calcifications on postexcision mammography, extent of DCIS in proximity to margin and which margin is close), cosmetic impact of re-excision, and overall life expectancy.⁶

3.4 Factors influencing BCS margin

There are clinicopathologic factors that could contribute in the variation of re-excision rates as age at diagnosis, tumor size, grade, nodal status or ER, PR, or HER2 status. Lobular tumors have been known to lead to a higher rate of re-excision and mastectomy and the patterns of growth in tumors of mixed ductal and lobular histology are similar to those of lobular histology and also may have higher re-excision rates. ²²⁻²⁵

Another factor that may affect re-excision rates is the surgical technique. Intraoperative imprint cytology and frozen section analysis have shown results of lower rates.^{26,27} Intraoperative ultrasound is a non-invasive adjunct in surgery that reduces the incidence of positive margins, but DCIS cannot be evaluated with this approach. In a recently published randomized trial, the procedure of cavity shave margins, which removes an additional piece of breast tissue at each margin of the tumor cavity after the tumor has been excised, results in reduced re-excision rates too.²⁸

Several studies reported on predictive factors for surgical margin status in BCS. Due to tumor-positive resection margins are regarded as a strong predictor for local recurrence, preoperative prediction of the likelihood of positive resection margins could result in improved counseling regarding surgery and potentially a reduction in the number of re-excisions.

A retrospective, population- based, cohort study done by Erasmus MC Cancer Institute of Rotterdam²⁹ have identified patient and tumor characteristics that are associated with a high risk of tumor positive margins after breast-conserving surgery (BCS). By univariate analysis were significantly associated with involved margins factors as age<60 years, multifocality, lobular subtype, tumor size >2 cm, intermediate and high grade, positive ER status, positive Her2 status, angio-invasion and presence/extent of DCIS component. The strongest associations with involved margins in multivariate analysis were multifocality, lobular subtype, large tumor size>2 cm, and the presence of DCIS.

Because these features can be assessed preoperatively by imaging and needle biopsy, this provides the opportunity to optimize preoperative counseling regarding optimal surgery and reduce the number of positive margins in those with a substantial risk by adjustment of local therapy.

4. OBJECTIVE

The purpose of this study is a statistical analysis of the variables collected in the database of the Breast Unit of General Surgery Service at HUMV since 2013 to 2016, of patients with breast cancer undergoing conserving surgery with oncoplastic techniques, describing which clinic-pathologic factors are significantly related to positive margins.

5. PATIENTS AND METHODS

This is a retrospective observational study carried out during the 6th year of degree in Medicine held at the University of Cantabria and the Hospital Universitario Marqués de Valdecilla.

The database used for the study was obtained from nine databases previously provided by the HUMV breast unit with a total number of 530 patients diagnosed of breast cancer treated in the unit. Once duplications were eliminated, we had 250 clinical history numbers that were reviewed one by one in order to complete the 30 variables required in the database. The information was obtained from the reports of multiple disciplines: radio-diagnostic, pathological anatomy and general surgery dedicated to breast unit.

All patients treated with conserving surgery were included to obtain the refined database. Patients treated initially by mastectomy were excluded, but those who attempted BCS but ultimately required mastectomy due to inadequate margins were included as “conserving- mastectomy cases”.

Finally, our database for the study included 152 patients who had operable breast cancer treated with OBCS from 4 June 2013 to 15 November 2016. Most of the patients from the screening program for breast cancer of Cantabria and others were diagnosed by other ways.

The variables entered in database for analysis were as follows:

1. Number of medical history
2. Date of birth
3. Date of histological diagnosis
4. Menstrual stage: pre/ postmenopausal
5. Affected breast: right / left breast or bilateral
6. Location of the tumor through the breast: four quadrants, four intersections, central position and inframammary fold
7. Multifocal: several tumor foci in the same quadrant or less than 4-5 cm between them (Yes/No)
8. Multicentric: several tumor foci in different quadrants or more than 4-5 cm between them (Yes/No)
9. Radiological tumor size (mm)
10. Radiological measure: echography, mammography or magnetic resonance.
11. Infiltration: in situ/ infiltrating
12. Histological type: ductal, lobular, mixed, papilar, medular, solid, other, tubular
13. ER status
14. PR status
15. HER2 status
16. Ki67
17. Date of surgery
18. Sentinel lymph node biopsy: yes, no, unknown
19. Lymphadenectomy: yes, no, unknown
20. Number of studied nodes
21. Number of affected nodes
22. Type of surgery: tumorectomy, partial mastectomy, total mastectomy
23. Incision pattern: lateral or raquet, omega or batwing, round block or donut, Wise, diamond, fusiform or I and other.
24. Radioguided: No /Yes, unknown
25. Number of wires

26. Pathological size (mm)
27. Margin status: affected, reach, free, wide, unknown
28. Histology of affected margin: infiltrating, in situ, both
29. Re-intervention (Yes/No)
30. Conserving surgery: BCS, BCS-mastectomy, mastectomy.

The mean time between the date of pathological diagnosis of the breast cancer to the date of the surgery is 38. Prior to surgery all patients were discussed at the multidisciplinary meeting comprising of surgeon, radiologist, pathologist and oncologist.

In those patients with impalpable breast lesion it was used needle-wired localization named “bracketing”. At the Radiological Department, surgeon and radiologist decide how many wires and where they should be inserted to accurate a complete resection with free radiological margins, inserting them at 1 cm distant to radiological limits.³⁰ In all cases, specimen is marked with stitches and intraoperative specimen mammography is immediately performed to confirm that calcification and tumor shadows had been appropriately excised.

Pathologic slides of patients informed as not free margins in the breast tissue which was removed were revised by a pathologist applying the consensus guideline on margins for BCS “no ink on tumor as the standard for an adequate margin in invasive cancer” published on March 2014, because some cases were evaluated before this criteria. A clear superior, inferior, lateral and medial pathological margin based on no ink on tumor is considered as free margin.

The variable age at diagnose was calculated, and five variables were transformed: age (in two groups <50 years or ≥ 50 years), histologic subtype (in lobular, non-lobular and mixed), intrinsic subtype (luminal A, luminal B, HER2, triple negative, luminal-herb2), positive nodes (none, 1 or more) and margin status (free, affected).

5.1 Statistical analysis

Analysis was carried out using SPSS Statistics® software from IBM® (v22.0).

First, we described the distribution of clinical and pathological variables in the series of patients. The quantitative variables have been expressed as mean and standard deviation (SD) and qualitative variables such as number (N) and percentage (%). Table 1.

Second, we compared the distribution of categorical variables between two groups, patients with free margins and those with involved margins.

Last of all, Univariate and multivariate logistic regression analyses with the method enter were performed to test for association between clinic-pathologic variables and positive resection margins in 152 patients with invasive non bilateral breast cancer. Table2.

A p value (<0.05) was consider statistically significant. We excluding those variables that cannot reliably be assessed preoperatively.

6. RESULTS

✓ **Patients**

Overall, we included 152 cases of breast cancer reported from June 2013 to November 2016. The median age of our cohort was 60.2 years old (Range 40-80), due to mostly of our patients came from the screening program and were menopausal (90.8%). All the patients underwent BCS. Neo adjuvant chemotherapy was not administered in any of the patients.

The mean long-axis length of the tumors on radiological image was 15.90mm (9.8 DS) which had a high correspondence with pathological one, 15.92 mm (12.02 DS).

Demographic characteristics of the patients are described in Table 1.

TABLE 1. Patients and tumor characteristics of 152 patients.

Variable	Number or mean	Percentage or standard deviation
Age at diagnosis	60.2 (range 40-80)	SD 6.425
Menstrual stage		
• Premenstrual	14	(9.2 %)
• Postmenstrual	138	(90.8 %)
Affected breast		
• Right	75	(49.3 %)
• Left	75	(49.3 %)
• Bilateral	2	(1.3 %)
Location of the tumor		
1. Upper outer quadrant	54	(35.5%)
2. Upper inner quadrant	8	(5.3 %)
3. Lower inner quadrant	9	(5.9 %)
4. Lower outer quadrant	3	(2.0 %)
5. Central	11	(7.2 %)
6. Upper intersection	27	(17.8 %)
7. Inner intersection	2	(1.3 %)
8. Lower intersection	5	(3.3 %)
9. Outer intersection	33	(21.7 %)
10. Mammary fold	0	
Multifocal		
• Yes	133	(87.5 %)
• No	19	(12.5 %)
Multicentric		
• Yes	3	(2.0 %)
• No	149	(98.0 %)
Infiltration		
• In situ	13	(8.6 %)
• Infiltrating	139	(91.4 %)
Histology		
• No-lobular	128	(84.2 %)
• Lobular	14	(9.2 %)
• Mixed	10	(6.6 %)
Intrinsic subtype (only invasive)		
• Luminal A	69	(45 %)
• Luminal B	41	(27.0 %)
• HER2 +	6	(3.9 %)
• triple negative	11	(7.2 %)
• luminal-herb2	12	(7.9 %)
Missing	13	
Sentinel lymph node biopsy		
• Yes	144	(94.7 %)
• No	8	(5.3 %)
Lymphadenectomy		
• Yes	14	(9.2 %)
• No	138	(90.8 %)

Positive lymph nodes (axillary)		
• 0	119	(78.3%)
• >=1	33	(21.7 %)
Type of surgery		
• Tumorectomy	128	(84.2 %)
• Partial mastectomy	24	(15.8 %)
Incision pattern		
• Lateral or raquet	27	(17.8 %)
• Omega or batwing	4	(2.6 %)
• Round block or donut	20	(13.2 %)
• Wise	55	(36.2 %)
• Diamond	21	(13.8 %)
• fusiform or I	1	(0.7%)
• other	23	(15.1 %)
Missing	1	
Radioguided		
• Yes	148	(97.4 %)
• No	4	(2.6 %)
Number of wires		
• 0	4	(2.6 %)
• 1	52	(34.2 %)
• 2	88	(57.9 %)
• 3	7	(4.6 %)
• 4	1	(0.7 %)
Conserving surgery:		
• BCS	143	(94.1 %)
• BCS-mastectomy	9	(5.9 %)
Margin status:		
• Free	132	(86.8 %)
• Affected	20	(13.2 %)
Histology of affected margin		
• Infiltrating	7	(4.6 %)
• In situ	11	(7.2 %)
• Both	2	(1.3 %)
Re-intervention		
• Yes	17	(11.2 %)
• No	135	(88.8 %)
Radiological tumor size (mm)	15.90	9.824 (SD)
Pathological size (mm)	15.92	12.024
Studied nodes	2.95	3.867
Affected nodes	0.36	0.952

✓ **Resection margin status**

Resection margin status was reported for all the patients undergoing BCS.

Overall, 20 patients had involved surgical margins (13.2%), 7 of them with invasive cancer (4.3%), 11 with ductal carcinoma in situ component (7.2%) and 2 with both (1.3%).

Re-operation was required in 17 patients (11.2%). A women was operated for a haemorrhage as a surgical complication and 16 for oncological reason: 12 with affected margins, 2 of them within also positive sentinel lymph node, and 4 for positive sentinel lymph node.

The type of reintervention was variable, 3 by re-excisions (1.9%) (one with lymphadenectomy associated), 9 mastectomies (5.9%), one of them combined with lymphadenectomy, and 4 just for lymphadenectomies. The final rate of BCS was 94.1%. After this 16 re-interventions, residual cancer was found in 7 (46%) of them (4 re-operated by mastectomy, 1 by re-excision and 2 lymphadenectomies). Re-interventions are shown in Table 2.

Once performed logistic regression analysis, the unique variable that was significantly associated with increased risk of positive margin in univariate analysis was multifocality (strong effect $OR > 5$), which is the same variable significantly associated with positive margins by multivariate analysis. Respect from other variables, the numbers were too small to show statistical significance. Results presents in Table 3.

TABLE 2. Reinterventions.

Histologic type	Cause of reintervention	Type of reintervention	Residual cancer	Type of residual cancer
Invasive lobular carcinoma	Affected margins	Mastectomy	YES	Invasive lobular carcinoma
Invasive Lobular carcinoma	Affected margins	Mastectomy	YES	In situ lobular pleomorphic carcinoma
Invasive ductal carcinoma	Affected margins	Mastectomy	NO	
Invasive mixed ductal and lobular carcinoma	Affected margins	Mastectomy	NO	
Invasive and in situ ductal carcinoma	Affected margins	Mastectomy	NO	
Invasive glucogenic carcinoma	Affected margins	Mastectomy	NO	
Invasive lobular carcinoma	Affected margins	Mastectomy	NO	
In situ ductal carcinoma	Affected margins	Mastectomy	YES	In situ ductal carcinoma
Invasive and in situ ductal carcinoma	Affected margins	Re excision	NO	
Invasive and in situ ductal carcinoma	Affected margins	Re excision	YES	In situ ductal carcinoma
Invasive lobular carcinoma	Affected margins Positive sentinel lymph node (4)	Re-excision	YES	2 positive lymph nodes of 18 removed
		Lymphadenectomy		
Invasive ductal carcinoma	Affected margins Positive sentinel lymph node (1)	Mastectomy	YES	Invasive and in situ ductal carcinoma
		Lymphadenectomy		
Invasive ductal carcinoma	Positive sentinel lymph node (1)	Lymphadenectomy	NO	0 affected lymph nodes of 14 removed

Invasive ductal carcinoma	Positive sentinel lymph node (2)	Lymphadenectomy	NO	
Invasive ductal carcinoma	Positive sentinel lymph node (3)	Lymphadenectomy	YES	1 affected lymph nodes of 11 removed
Invasive ductal carcinoma	Positive sentinel lymph node (1)	Lymphadenectomy	NO	
In situ ductal carcinoma	Haematoma	Drainage	NO	

TABLE 3. Statistical analysis of 152 patients with no bilateral invasive cancer.

Variable	Total	Free margins	Positive margins*	p	Univariate OR	CI 95%	p	Multivariate OR	CI 95%
Age (years)									
<50	10 (6.6)	9 (6.8)	1(5.0)	0.761	0.719	0.08-6.003	0.999		
≥50 (reference)	142 (93.4)	123 (93.2)	19(95.0)						
Multifocality									
Yes	19 (12.5)	12 (9.1)	7(35.0)	0.003	5.385	1.80- 16.07	0.001	8.472	2.27-31.49
No (reference)	133 (87.5)	120 (90.9)	13 (65.0)						
Multicentric									
Yes	3 (2.0)	3 (2.3)	0 (0.0)	0.999			0.999		
No	149 (98.0)	129(97.7)	20(100)						
Lobular histologic subtype									
No (reference)	128(84.2)	113 (85.6)	15 (75.0)	0.488			0.534		
Yes	14 (9.2)	11(8.3)	3 (15.0)	0.308	2.055	0.51- 8.21	0.463	2.028	0.30- 13.40
Mixed	10 (6.6)	8 (9.1)	2 (10.0)	0.449	1.883	0.36- 9.71	0.346	2.674	0.34- 20.66
Infiltration									
In situ	13 (8.6)	11 (8.3)	2(10.0)	0.804	0.818	0.16-3.99			
Infiltrating	139 (91.4)	121 (91.7)	18 (90.0)						
Radiological tumor Size (mm)									
<20 mm (reference)	110 (73.3)	98 (74.8)	12 (63.2)	0.784	1.007	0.961-1.055	0.906	0.996	0.93-1.05
≥20 mm	40 (26.7)	33 (25.2)	7 (36.8)						
Intrinsic subtype									
Luminal A (reference)	69 (49.6)	62 (51.2)	7 (38.9)	0.595			0.626		
Luminal B	41(29.5)	33 (27.3)	8 (44.4)	0.173	2.147	0.716-6.443	0.139	2.723	0.72- 10.25
HerB2	6 (4.3)	6 (5.0)	0 (0.0)	0.999			0.999		
Triple-negative	11 (7.9)	11 (9.1)	0 (0.0)	0.999			0.999		
Luminal_Her2+	12 (8.6)	9 (7.4)	3 (16.7)	0.163	2.952	0.64-13.53	0.248	2.960	0.46- 18.68
Positive axillary Lymph nodes									
Yes	33 (21.7)	28 (21.2)	5 (25.0)	0.702	1.2338	0.41-3.70	0.702	1.29	0.34-4.78
No (reference)	119 (78.3)	104 (78.8)	15 (75.0)						

* Positive margins definition as no ink on tumor. OR (odds ratio). CI (confidence interval)

Percentage in brackets. P<0.05 statistic significant

7. DISCUSSION

Patients with early invasive breast cancer who undergo BCS followed by radiotherapy have a survival that is similar to patients who undergo a mastectomy.^{31,32} The main goal of BCS is to achieve totally tumor-free resection margin in order to minimize the rate of positive margins and re-excision.

We obtained 13.2 % rate of positive margins which is lower than others recently published which analyzed large series of patients from population registers and similar to others OBCS series.

Laws A et al³³ reported an overall positive margin rate of 20.8% while studying 1165 patients undergoing wire-localized BCS for invasive cancer in Alberta, Canada. Langhans L.³⁴ communicated a positive margins and reoperation rate of 17.6% after wire-guided BCS in a large series of 4118 women (data from Danish National Patient Registry from 2010 to 2013). Reoperations were 593 re-excisions (14.4%) and 132 mastectomies (3.2%). After that, positive margins were still present in 97 patients (16.7%) and this risk was significantly higher to patients with DCIS, so they conclude that DCIS increases the risk of affected margins and reoperation three times over invasive cancer. In our study, residual cancer was founded in 7 cases and DCIS was present in four of them.

Haloua MH et al.³⁵ reported an 16. 4% rate of involved surgical margins after BCS for invasive carcinoma and in situ carcinoma combined and 10.2 % rate for invasive carcinoma alone. This study collected data from a Netherland nation-wide network during 2012-2013 analysing 9276 pathology excerpts.

That results may also be compared with articles focus on OBCS as Carter SA et al,³⁶ who published that the rate of positive or close margins was lower for oncoplastic techniques (5.8%) than conventional ones (8.3%) based on 10,697 operations in which 75% of the patients had early cancer stage (I or II). They also report that during the period of the study, from 2007 to 2014, the use of oncoplastic breast conserving surgery fourfold increase in the percentage of all breast cancer surgeries as sample of the commonly spread of the oncoplastic approach.

The mainly advantage is that OBCS allows carrying out a wide resection of a large tumor size with a small alteration of breast cosmetic outcome and achieve low positive margin rates, so this confirms that oncoplastic techniques help reduce the risk of positive margins compared with standard BCS.^{37,38}

At the Paris Breast Center, Clouhrg KB⁵ reported a rate of 11.9% of positive margins in 272 patients who undergone level II oncoplastic techniques based on mammoplasties, involving resection of between 20-50% of breast volume. They identified by multivariate analysis that patients with invasive lobular carcinoma had a significantly higher risk of positive margins. Their final BCS rate was 91%, a bit lower than in our study (94.1%).

In a recent population-based cohort study with nation-wide data from The Dutch Pathology Registry, van Deurzen CHM²⁹ reported a 16.9% rate of affected surgical margins from a high number of patients with invasive breast cancer (25,315) treated by BCS between 2009 and 2015. The multivariate logistic regression analysis found that the presence of DCIS, lobular subtype, multifocal location, large tumor size and were strongest associated with involved margins (OR>2).

As we mention before, this supposes the opportunity to optimize preoperative counseling regarding optimal surgery by imaging and needle biopsy, although it could have some limitations. One one hand, histologic grade may be underestimated on a biopsy specimen³⁹. Obviously, the needle biopsy only represents a part of the tumor, usually the invasive central component, whereas DCIS could be surroding it. So, this factors can be absent on the biopsy and still be present in the excision specimen, limiting the value of these factor preoperatively²⁸. On the other hand, imaging breast modalities are suboptimal for preoperative size estimation of the DCIS component. Although MRI is the most sensitive method for estimating the extent of DCIS, it is not routinely preformed for all patients undergoing BCS.^{40,41}

In our work, only multifocality is significantly associated to the increment of involved margins (OR>5). It is the clinical-pathologic variable most commonly mentioned in articles, so our result is according with the literature. This variable,

described in our data base as “several tumor foci in the same quadrant or less than 4-5 mm between them” can reliably be determined by imaging preoperatively.

However, the present study has some limitations. Our findings is about single-center retrospective study, relatively small. Imaging diagnosis, surgical procedures, specimen handling, and pathological diagnosis can vary greatly across centers and physicians. Although considering that present study was performed with unified criteria at a single center, the limited data might be more accurate and consistent than data from a multicentre study. We analysing our data according to the SSO/ASTRO guideline, which defines an adequate margin of BCS as the absence of tumor reaching the ink, in order to compare our results with other European and North American countries. Finally, a substantial proportion of data (9.9%) were missing by the statistical analysis program.

Our study has demonstrated that in our daily clinical practice, multifocality is a prognostic factor for positive margin. Once we know multifocality increases significantly the risk of positive margins in our patients, this may be used by the surgeon to be aware of the excisions of tumors with that characteristic in order to guarantee a negative margin wide.

8. CONCLUSIONS

In our study, we obtained an approvable rate of positive margins which is settled in the lower band of published range and high final rate of BCS.

We identified that the factor multifocality of the tumor is significantly associated with involved resection margins after OBCS for breast cancer. Because this feature can be assessed preoperatively, this provides the opportunity for an optimal preoperative risk prediction of each patient and possibly adjustment of surgical method.

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