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Local Recurrence of Breast Cancer after Mastectomy Impact of Residual Tissue on Oncological Follow-Up

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Abstract

Background: Conservative surgery is the standard treatment for breast cancer. However, there are cases in which mastectomy is imperative. There is a risk of developing local recurrence of 2-9.5% according to the literature. The study-aim was to find risk factors of local recurrences after mastectomy and the methods of diagnosis to assess a clinical and radiological follow-up protocol in our hospital.

Methods: A retrospective observational study of breast cancer patients who underwent mastectomy between 2000-2020 was conducted. A total of 809 mastectomies were perfomed, excluding males, distant metastases and losses in follow-up. Local recurrences were observed in 51 patients. We made a comparative analysis using Chi-square and T-student tests, Kaplan Meier and Cox regression comparison of survival with 15-year follow-up.

Results: 772 breast cancer patients were evaluated, of which 6.6% presented local recurrence. 43.1% of these patients died (p<0.001) 17.6% of the recurrences occurred in residual tissue of the same breast and 23.5% in the scar. When we compared the risk factors a significant association was obtained in nodal involvement in the surgical piece (p=0.004), pN stage (p=0.008) positive axillary lymphadenectomy (p=0.012) and triple-negative subtype (p= 0.04), negative progesterone receptors (p=0.04). In the survival analysis we found that 84% of the patients survived at 5 years, and it drops to 63% at 10 years if local recurrence was diagnosed.

Conclusion: Local recurrence is a demonstrated significant factor for mortality after mastectomy. It is of vital importance the detection of risk factors and the creation of a follow-up protocol for its early detection.

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Introduction

Breast cancer is the most common neoplasm among women worldwide. In Spain, 34,088 new cases were diagnosed in 2020 [1]. Despite the increase in the diagnosis of these tumors in early stages and the growing use of conservative surgery, there are still many patients in whom mastectomy is mandatory. Mastectomy is indicated in extensive or multicentric neoplasms, impossibility of achieving negative margins with conservative surgery, patient desire or prevention of cancer development in patients with genetic predisposition [2-4].

Even though all or most of the mammary gland is removed in mastectomy, there is a risk of developing a Local Recurrence (LR) of breast cancer of 2-9.5%, with a mean follow-up of 7 years. Precipitators for this recurrence include lymphatic spread, inoculation metastasis, incomplete removal of the carcinoma, or appearance of a new primary tumor in the residual breast tissue [2,4].

Few studies have addressed the issue of residual breast tissue after mastectomy. They agree that 5-15% of the total amount of breast tissue remains after surgery in 21-76.2% of cases, with the lower outer quadrant being the one with the highest incidence[2]. This residual breast tissue can lead to new breast cancer. Although prophylactic bilateral mastectomy reduces the risk of breast cancer by 90-100% after 3-13 years of follow-up, approximately one in 140 genetically predisposed women will eventually develop a primary breast cancer [5].

Recurrences are diagnosed during follow-up. There are no data to support a particular follow-up protocol; there is a need to balance patient needs and follow-up costs. Patients have clinical follow-up visits every 3 months for the first 3 years, then every 6 months for 2 years, and finally yearly follow-up up to 10 years. Each visit, in addition to the clinical history and a precise physical examination, must include a mammogram +/- breast ultrasound. A breast MRI may be indicated in young patients, especially in cases of dense breast tissue and genetic predisposition [6,7].

This study aims to evaluate the rate of local recurrences after mastectomy and the method by which they have been diagnosed, differentiating recurrences according to the surgical technique performed. This will allow us to assess whether a clinical and radiological follow-up protocol should be established in the case of mastectomy patients in our hospital.

Material and Methods

Sample size and study design

Between January 2000 and December 2020, a total of 929 mastectomies were performed on 876 patients at the Hospital del Mar. Males and patients with distant metastases at the time of diagnosis were excluded from the database. Patients who missed the follow-up were also excluded. In total, 809 tumors from 772 patients were analysed. Follow-up was up to 180 months (15 years). The variables under study were: age [≤50 or >50], laterality [right or left], initial symptom [nodule, microcalcifications, distortion or telorrhage], size (mm), TNM stadium at diagnosis (cTNM), BI-RADS, tumor stage, neoadjuvant therapy [chemotherapy, hormone-therapy and/or radiotherapy], and response [partial, total, stabilization or progression], type of surgery [Simple Mastectomy (SM), SM with sentinel lymph node biopsy (SM+SLNB) or SM with Axillary Lymphadenectomy (SM+AL)], time of reconstruction [immediate or deferred] and type [expander, prothesis or autologous tissue], tumoral type [Ductal Carcinoma In Situ (DCIS), invasive Ductal Carcinoma (IDC), Invasive Lobular Carcinoma (ILC) or other], histological grade [I, II or III], definitive TNM stadium (pTNM), hormone receptors [Estrogen Receptors (ER) and/or progesterone receptors (PR)], proliferation index Ki67 [<14% or ≥14%], Her2/neu [positive, negative or indeterminate], molecular subtype [luminal A, luminal B, triple-negative or HER2], adjuvant therapy [chemotherapy, hormone-therapy and/or radiotherapy], follow-up [disease-free, Local Recurrence (LR), Locoregional Recurrence (LRR) or Distant Metastases (DM)], LR-free interval (0-180 months), exitus and Overall Survival (OS).

Local recurrence was defined as the diagnosis of cancer of the same lineage at the local level during the oncological follow-up of the patient (residual breast tissue, scar, thoracic wall, underarm or cutaneous metastasis), excluding metastases in locoregional nodes. Of this LR were analyzed: Diagnostic method [radiological control (includes contralateral mammography, ultrasound, or nuclear magnetic resonance) or physical examination], laterality [ipsilateral or contralateral], treatment [surgery and/or adjuvant treatment], TNM stadium, tumor type, histological grade, and molecular subtype.

Statistical analysis

All data were collected in a spreadsheet (Excel; Microsoft) and transferred to the statistical programme SPSS® (SPSS 28; IBM) to be analysed. The characteristics of the sample were determined by analysing the percentage of patients who were diagnosed with LR, and the variables observed in them. The characteristics of patients who did not develop an LR were compared with those who did using Chi-Square and T- Student's test. The comparison of LR-free interval between groups according to the involvement of the studied factors was calculated with Kaplan-Meyer statistical analysis. The log-rank test was used to examine the statistical significance of the between-group differences observed. Risk factors for LR were identified using the Cox proportional hazards regression model. Variables that were identified as statistically significant in the univariate analysis were tested in the multivariate analysis. Hazard ratios (HR) adjusted to a 95% Confidence Interval (CI) were reported. Finally, a comparison between the overall survival of patients with LR versus those without LR was carried out with another Kaplan-Meyer statistical analysis and Cox proportional hazards regression model. At all times, a statistically significant difference was considered at a P value of less than 0.05.

Results

Comparative analysis of case characteristics

A total of 809 cases were analysed (Figure 1). The characteristics of the specimens are reflected in Annex 1. 67.5% of the patients were over 50 years old at the time of diagnosis. 51 patients (6.6%) suffered an LR, 22 (2.8%) an LRR and 118 (15.3%) a DM during follow-up. A total of 150 patients (19.4%) died. 54.6% of the specimens were diagnoses at early stages (cT1-T2) in the form of a nodule (73.2%), and 63.8% of the patients had no axillary involvement (cN0). Most of the tumor pieces were IDC (70.6%), histological grade III (40.7%) and had positive hormone receptors (ER: 77.5%; PR: 61.7%). 549 patients (67.9%) underwent SM with AL.

In both groups the age at diagnosis was above 50 years (p=0.172). Of the patient who did not suffer an LR, 17.8% died, while in the group of patients with recurrence, deaths meant

43.1% (P<0,001). More than half of the cancers were diagnosed in early stages (p=0.674), in the form of a nodule (p=0.553) and without axillary involvement (p=0.828) in both groups. There are also no differences in tumor type (p=0.808) or histological grade (p=0.221). The absolute mean difference in tumor size was 0.22 (95% CI -5.004 to 7.306, p=0.991), with larger tumors in the group that did not experience an LR. The differences found in the pN stage of each group are more remarkable (P=0.048). 52.8% of the group without LN did not have positive nodes in the surgical specimen (pN0), while 62.7% of the other group did present them (pN+). Likewise, differences were found in those AL that were positive (P=0.077). In terms of molecular subtypes, most tumors in both groups had positive hormone receptors (ER: P=0.117; PR: p=0.054). The patients who were not diagnosed with LR had mostly luminal A tumors (32.8%), while patients with LR had mainly luminal B tumors (35.3%), this difference was significant (p=0.018). SM with AL was the predominant procedure in both groups, but mostly in the group of patients with LR (80.4%) compared to those without LR (67%) (p=0.024).

Description of the local recurrences' characteristics

Table 1 shows local recurrence's characteristics that were detected during the follow-up of the patients. Most recurrences were in the same breast as the primary tumor (66.7%). 25 (49%) occurred in residual tissue, 17.6% originated in the remaining glandular tissue of the same breast, and 23.5% (12) in the skin scar level. The LR-free interval was 71.47 months on average, 76.57 months median (range 4-176 months). 52.9% of the diagnoses were detected by a palpable mass on physical examination. In 82.4% of the cases cancer was found in early stages (T1-T2), 70.6% with negative lymph nodes (N0) and 72.5% without distant metastases (M0). Most of the tumors were IDC (76.5%) and histological grade III (59.2%). The molecular subtypes detected were generally luminal B (33.3%) and triple-negative (33.3%).

Analysis of risk factors

Follow-up was carried out for 180 months (15 years) to analyse the LR in the group of patients. When comparing the risk factors studied with the appearance of LR, a significant association was obtained with axillary involvement in the definitive surgical piece (p=0.004) (Figure 2A) and, therefore, in the pN staging (P=0.008) (Annex 2A). In contrast, there were no significant differences in axillary disease at diagnosis (p=0.152) (Annex 2B). There was also no association with tumor size at diagnosis (p=0.256) or the size of the definitive tumor piece (p=0.882) (Annex 2C-D). The relationship between the type of surgery performed and the subsequent appearance of LR was notorious (p=0.061) (Annex 2E). And the differences with positive AL were significant (p=0.012) (Figure 2B). There was no difference in tumor type (p=0.834) or histological grade (p=0.355) (Annex 2F-G). Regarding the molecular subtype, a significant difference was observed between the diagnosis of LR and this (p=0.002), with the triple-negative subtype causing a greater and earlier appearance of recurrences, followed by the luminal B subtype (Figure 2C). Negative hormone receptors had a close association with recurrence, being notorious in tumors with ER (P=0.069) (Annex 2H) and significant in those with PR (P=0.043) (Figure 2D). When Ki67 was ≥14% the probability of recurrence was higher (P=0.170) (Annex 2I), but not significantly so. The detection of Her2/Neu also has a notorious, but not significant, relationship with LRs (P=0.082) (Annex 2J). Neoadjuvant therapy and post-intervention treatment show no association with the presence of LR at follow-up.

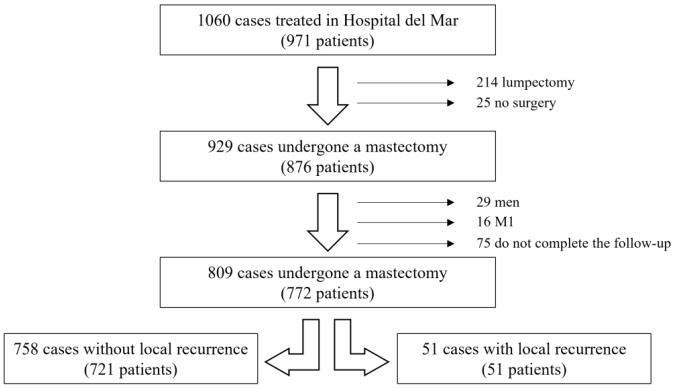

Figure 1: Flow chart of the sample inclusion.

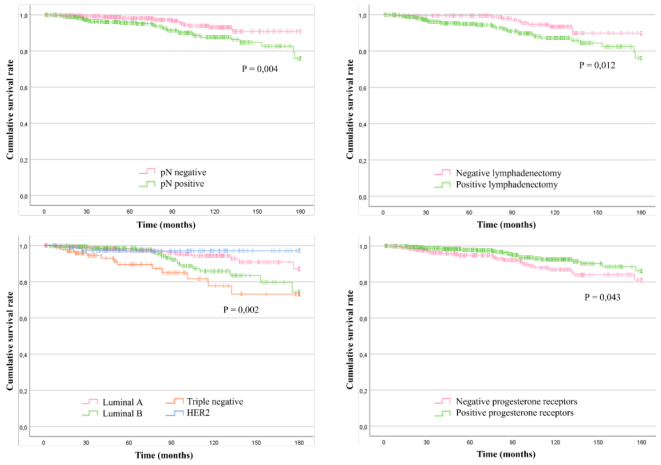

Figure 2

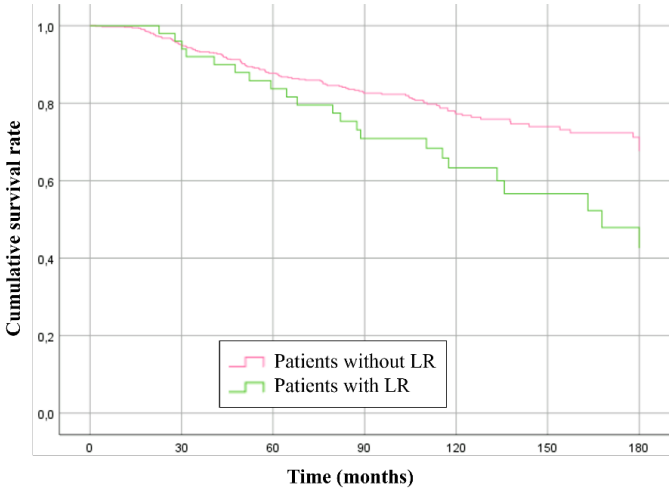

Figure 3

After the univariate Cox regression analysis, it was observed that the risk of suffering an LR in the group of patients studied was increased when obtaining pN+ (HR 2.295; 95% CI 1.274-4.136; p=0.006) and being the AL positive (HR 2.427; 95% CI 1.191-4.945; p=0.015). Regarding molecular subtypes, tumors with the triple-negative subtype were most often associated with the appearance of an LR (HR 2.802; 95% CI 1.488-5.273; p=0.001), while the presence of PR appears to be a protective effect for these recurrences (HR 0.527; 95% CI 0.330-0.990; p=0.046). There was also a protective effect of performing sentinel lymph node biopsy in conjunction with simple mastectomy (HR 0.161, 95% CI 0.034-0.706, p=0.021). Cox multivariate regression again showed a significant relationship between

the presence of positive pathological nodes (HR 2,511; 95% CI 1,386-4,550; p=0.002) and the triple-negative subtype (HR 3.129; 95% CI 1,617- 6,057; p=<0.001). Unlike the univariate analysis, no significant relationship of any kind was shown between SLNB, PR or AL. These results were reflected in Table 2.

Survival analysis

Survival was compared in the group of patients who were diagnosed with LR with those who were not (Figure 3). Survival at 5 years after diagnosis of the primary tumor was 84% among patients with LR versus 88% of patients without LR. At 10 years survival drops to 63% if LR is diagnosed and 78% if not (P=0,008). The presence of LR showed statistically significant differences with breast cancer mortality in univariate Cox analysis (HR 1.839; 95% IC 1,168-2,895; p=0,009).

Table 1: Risk factors for local recurrence using Cox regression analysis and HR.

Factors	Univariate analysis		Multivariate analysis		
Hazard ratio	**95% IC**	**P-value**	**Hazard ratio**	**95% IC**	**P-value**
Age			0.459		
≤ 50			1.000		
> 50		0.810		0.463-1.416	
Laterality					
Left		1.000		0.726	
Right		0.906		0.522-1.572	
Initial lesion			0.576		
Nodule		1.203		0.630-2.298	
MCC/Distortion/Telorrhage			1.000		
cT-stadium			0.258		
cT1-T2		0.716		0.401-1.277	
cT3-T4			1.000		
cN-stadium			0.154		
cN negative			1.000		
cN positive		1.505		0.857-2.642	
Neoadjuvant therapy					
Chemotherapy			0.799		
Yes		0.536		0.150-1.914	
No			1.000		
Hormonotherapy			0.337		
Yes		1.214		0.273-5.407	
No			1.000		
Radiotherapy			0.024		
Yes		10.782		1.360-85.497	
No			1.000		
Type of surgery					
SM			1.000		
SM+SLNB	0.161		0.034-0.706		0.021
SM+AL	0.310		0.075-1.284		0.106
Time of reconstruction			0.645		
Immediate			1.000		
Differed		0.789		0.289-2.159	
Type of reconstruction			0.099		
Expander/Prothesis		0.436		0.162-1.170	
Autologous tissue			1.000		
Tumoral type			0.579		
IDC/ILC		1.335		0.481-3.710	
DCIS			1.000		

Histological grade		0.919		
I		1.035		0.530-2.023
II/III		1.000		
pT-stadium		0.882		
pT1-T2		0.946		0.457-1.959
pT3-T4		1.000		
pN-stadium		0.006		0.002
pN negative		1.000		1.000
pN positive	2.295	1.274-4.136	2.511	1.386-4.550
SLNB		0.428		
Positive		0.390		0.000-119.217
Negative		1.000		
AL		0.015		
Positive		2.427		1.191-4.945
Negative		1.000		
ER		0.072		
Positives		0.581		0.321-1.050
Negatives		1.000		
PR		0.046		
Positives		0.572		0.330-0.990
Negatives		1.000		
Ki67		0.083		
<14%		1.000		
≥14%		1.701		0.789-3.668
HER2		0.095		
Positive		0.370		0.115-1.189
Negative		1.000		
Triple-negative		0.001		<0.001
Yes	2.802	1.488-5.273	3.129	1.617-6.057
No		1.000		1.000
Adjuvant therapy				
Chemotherapy		0.795		
Yes		1.082		0.596-1.967
No		1.000		
Hormonotherapy		0.161		
Yes		0.632		0.333-1.201
No		1.000		
Radiotherapy		0.439		
Yes		1.254		0.707-2.226
No		1.000		

HR: Hazard Ratio; MCC: Macrocalcifications; SM: Simple Mastectomy; AL: Axillary Lymphadenectomy; SLNB: Sentinel Lymph Node Biopsy; IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma; DCIS: Ductal Carcinoma In Situ; ER: Estrogen Receptors; PR: Progesterone Receptors.

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Discussion

Despite the rise of conservative treatment, today mastectomy is still imperative in many cases of breast cancer. However, and despite the radical nature of this, recurrences continue to be diagnosed after surgery in some patients. LR is considered the diagnosis of cancer of the same lineage at the local level and occurs during the oncological follow-up of the patient or after it is finished. Evidence in the literature showed LR rates between 2.8-5.5% [8,9]. In our study, 6.6% of patients evaluated had an LR after mastectomy. LRR was excluded to focus attention on the presence of residual post-mastectomy breast tissue.

These LRs were mostly detected (52.9%) as palpable masses during physical examination. Therefore, this evidence shows the importance of close monitoring of patients, including physical examination in addition to imaging tests such as mammography or ultrasound. 17.6% of the LR diagnosed in our study was

at the expense of residual breast tissue in the same side of the primary tumor, and 23.5% at the skin scar. To date, few studies address the issue of the existence of residual breast tissue after intervention with a mastectomy. Griepsma et al[2] after collecting a total of 7416 biopsy samples from 206 patients, determined that 76.2% of the participants had residual breast tissue in at least one of their samples. The lower outer quadrant of the breast was the place with the highest incidence of the findings. Ustun et al[4] on the other hand, after performing 4 biopsies on 111 patients, detected residual tissue in 10.4% of the participants, with the upper medial quadrant being the most frequent location. Many times, the plane of dissection between the skin and the superficial plane is not always clear, which makes the appearance of residual breast tissue post-mastectomy a proven fact. It is therefore important to be aware of this possibility and act accordingly when planning treatment and follow-up. To do this, it is necessary to be aware of the impact that certain risk factors can have on our patients.

Several studies identify lymph node involvement as a key factor for LR [10-12]. In our study, nodal involvement in the surgical piece showed a significant relationship with the appearance of LR (HR 2.295; 95% CI 1.274-4.136; P=0.006), as did the positive result of the AL (HR 2.427; 95% CI 1.191-4.945; P=0.015). In addition, Fujihara et al [10] identified a significantly increased risk of LR when surgical margins below 2 mm were detected (HR 9.72; 95% CI 1.23-77.13; P=0.047). And Bijker et al [12], opposite to our study, also detected a significant relationship with tumor size in the surgical piece.

Another variable that has been studied as a predictor of local recurrence was breast reconstruction. In their meta-analysis, Zhang et al [13] compared the impact of immediate reconstruction after mastectomy and found significant differences in LR between the two groups (RR 0.92; 95% CI, 0.75-1.13; p=0.41). In our study, however, the differences observed for immediate or deferred reconstruction were not significant for the diagnosis of LR at follow-up (HR 0.436; 95% CI 0.481-3.710; p=0.099).

According to other studies, risk factors for LRR also included certain molecular characteristics such as negative hormone receptor and triple-negative molecular subtype [14]. Despite, as mentioned, our study excluded LRR, significant differences have also been detected with some molecular characteristics of tumors. The presence of PR has a significant protective effect against the appearance of LR (HR 0.527; 95% CI 0.330-0.990; p=0.046), while the triple-negative subtype is a significant risk factor for LR (HR 2.802; 95% CI 1.488-5.273; p=0.001).

Regarding the death of the patients in our study, significant differences were observed between the group of patients who were diagnosed with LR and those who were not. Of the 51 patients with LR, 22 died, with a mortality rate of 43.1% compared to 17.8% in the group of patients who did not have LR. Dent et al [15] analysed 267 women treated for breast cancer between 1987 and 1997 who then developed local recurrence. Of these, 36.3% died within 10 years. Their 5-year survival rate after recurrence was 63%. Considering that the time from diagnosis to recurrence in their study was 5 years on average, we can say that this survival is similar to the 10-year survival of 63% obtained in our study. Despite advances in adjuvant treatment of breast cancer, it is unclear whether the life expectancy of women who experience local recurrence has subsequently increased. Furthermore, the scarce of evidence in the literature for this observation is striking. This finding makes the importance of screening for risk factors that allow the prevention of LR and the reinforcement of post-surgical follow-up protocols even more important, especially nowadays with the growing practice of more conservative interventions.

Limitations

The main limitation of this study was that the sample was limited to patients who underwent mastectomy surgery in our center since 2000 and consequently, there were few cases of local recurrence in which a more novel and conservative surgical technique had been chosen, such as skin-sparing mastectomy, skin and nipple-sparing mastectomy or areola-nipple complex sparing mastectomy. For this reason, no differentiation was made between the different types of mastectomies, so it was not possible to study whether the risk of LR increases with the use of these new techniques, which may be of interest for long-term follow-up at present. In addition, this reduced sample size may have contributed to the appearance of a random error leading to a loss of accuracy in the statistical results. Another potential problem with the study was the lack of information on reconstructions, both immediate and deferred. This deficiency may lead to an underestimation of the impact of reconstruction on patients' prognosis. Reconstruction is a factor that previous evidence had shown to be significant in the occurrence of LR, so it is important to collect more information.

Conclusion

The rate of LR after mastectomy was 6.6%. 17.6% originated in the residual tissue of the same breast and 23.5% in the scar. The detection was mostly given through physical examination in breast pathology consultation, so it is important to reinforce the follow-up protocols to promote the early detection of these. The detection of affected nodes in the surgical piece, the positive AL and the triple-negative molecular subtype were shown to be potential risk factors for LR. On the other hand, positive PR seems to be a protective factor against LR.

The mortality of patients with LR amounts to 43.1%. The overall survival was significantly lower than patients who were not diagnosed with LR. These data reaffirm the vital importance of detecting risk factors to prevent the onset of LR and carrying out follow-up protocols for early detection of LR.

For future studies, it would be interesting to expand the study sample to obtain more precise results in terms of risk factors. Given the current increase in the performance of various mastectomy techniques, it would also be interesting to differentiate the technique performed to be able to know if there is an increasing risk of the appearance of LR when opting for the most conservative. Considering the importance of lymphatic involvement as risk factor for local recurrence, more specific studies should be carried out that consider the number of affected lymph nodes beyond their positivity.

Ethical Statement

Conflict of Interest: All Authors declare that they have no conflict of interest.

The Ethics Committee of the Hospital del Mar gave its approval prior to the start of this retrospective observational study (No. 2021/9953). No written informed consents were required from participating patients. The clinical, demographic, and pathological information of breast cancer patients treated at the Hospital del Mar between 2000 and 2020 was prospectively obtained in a database of the tumor bank.

Informed consent was obtained from all individual participants included in the study.

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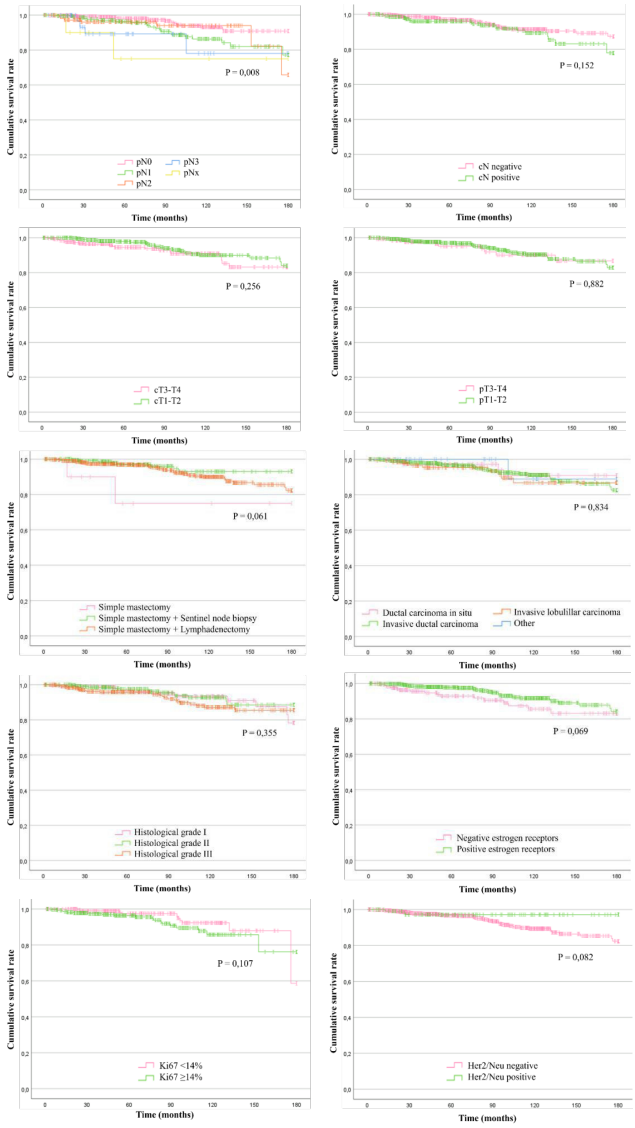
ANNEX 1			Patients and specimens' characteristics	
Characteristics	**Total (N=809)**	**Cases without LR (N=758)**	**Cases with LR (N=51)**	**P-value**
Patients				
Age			0.172	
≤ 50	263 (32.5%)		242 (31.9%)	21 (41.2 %)
> 50	546 (67.5%)		516 (68.1%)	33 (64.7%)
Follow-up				
Disease-free			581/772 (75.3%)	
Local recurrence			51/772 (6.6%)	
Locoregional recurrence			22/772 (2.8%)	
Metastasis			118/772 (15.3%)	
Exitus	150/772 19.4%)	128/721 (17.8%)	22/51 (43.1%)	<0.001
Specimen				
Laterality			1.000	
Right	386 (47.7%)		362 (47.8%)	24 (47.1%)
Left	423 (52.3%)		396 (52.2%)	27 (52.9%)
Initial lesion			0.553	
Nodule	592 (73.2%)		555 (73.2%)	37 (72.5%)
MCC	129 (15.9%)		118 (15.6%)	11 (21.6%)
Distortion	79 (9.8%)		76 (10.0%)	3 (5.9%)
Telorrhage	9 (1.1%)		9 (1.2%)	0 (0.0%)
BI-RADS			0.330	
3	9/515 (1.7%)		8/486 (1.6%)	1/29 (3.4%)
4a	5/515 (1.0%)		4/486 (0.8%)	1/29 (3.4%)
4b	22/515 (4.3%)		22/486 (4.5%)	0/29 (0.0%)
4c	127/515 (24.7%)		122/486 (25.1%)	5/29 (17.2%)
5	352/515 (68.3%)		332/486 (68.3%)	20/29 (69%)
cT-stadium			0.674	
is	94 (11.6%)		90 (11.9%)	4 (7.8%)
1	186 (23.0%)		174 (23.0%)	12 (23.5%)
2	256 (31.6%)		241 (31.8%)	15 (29.4%)
3	163 (20.1%)		149 (19.7%)	14 (27.5%)
4	110 (13.6%)		104 (13.7%)	6 (11.8%)
cN-stadium			0.828	
x	8 (1.0%)		7 (0.9%)	1 (2.0%)
0	516 (63.8%)		487 (64.2%)	29 (56.9%)
1	215 (26.6%)		199 (26.3%)	16 (31.4%)
2	55 (6.8%)		51 (6.7%)	4 (7.8%)
3	15 (1.9%)		14 (1.8%)	1 (2.0%)
Initial stage			0.609	
0	94 (11.6%)		90 (11.9%)	4 (7.8%)
I	143 (17.7%)		137 (18.1%)	6 (11.8%)
IIA	172 (21.3%)		163 (21.5%)	9 (17.6%)
IIB	144 (17.8%)		131 (17.3%)	13 (25.5%)
IIIA	131 (16.2%)		121 (16.0%)	10 (19.6%)
IIIB	82 (10.1%)		76 (10.0%)	6 (11.8%)
IIIC	43 (5.3%)		40 (5.3%)	3 (5.9%)
Type			0.808	
IDC	571 (70.6%)		535 (70.6%)	36 (70.6%)

ILC	125 (15.5%)	115 (15.2%)	10 (19.6%)	
DCIS	83 (10.3%)	79 (10.4%)	4 (7.8%)	
Other	30 (3.7%)	29 (3.8%)	1 (2.0%)	
Histological grade		0.221		
I	152 (18.8%)	141 (18.6%)	11 (21.6%)	
II	311 (38.4%)	296 (39.1%)	15 (29.4%)	
III	329 (40.7%)	305 (40.2%)	24 (47.1%)	
Unknown	17 (2.1%)	16 (2.1%)	1 (2.0%)	
Size, mm, mean (median) range	29.24 (22) 0-150	29.32 (22) 0-150	29.10 (22) 0-110	0.991
pT-stadium		0.971		
x	3 (0.4%)	3 (0.4%)	0 (0.0%)	
0	30 (3.7%)	28 (3.7%)	2 (3.9%)	
is	83 (10.3%)	79 (10.4%)	4 (7.8%)	
1	294 (36.3%)	277 (36.5%)	17 (33.3%)	
2	265 (32.8%)	246 (32.5%)	19 (37.3%)	
3	99 (12.2%)	93 (12.3%)	6 (11.8%)	
4	35 (4.3%)	32 (4.2%)	3 (5.9%)	
pN-stadium		0.048		
x	12 (1.5%)	10 (1.3%)	2 (3.9%)	
0	417 (51.5%)	400 (52.8%)	17 (33.3%)	
1	232 (28.7%)	211 (27.8%)	21 (41.2%)	
2	108 (13.3%)	101 (13.3%)	7 (13.7%)	
3	40 (4.9%)	36 (4.7%)	4 (7.8%)	
Positive sentinel lymph node	41/263 (15.6%)	41/254 (16.1%)	0/9 (0.0%)	0.190
Positive axillary lymphadenectomy	351/552 (63.6%)	319/507 (62.9%)	32/42 (76.2%)	0.077
Receptors				
ER	623/804 (77.5%)	588/753 (78.1%)	35 (68.6%)	0.117
PR	496/804 (61.7%)	471/753 (62.5%)	25 (49%)	0.054
Ki67	295/517 (57.1%)	276/488 (56.6%)	19/29 (65.5%)	0.344
Her2/Neu	143/804 (17.8%)	139/753 (18.5%)	4 (7.8%)	0.158
Molecular subtype		0.018		
Luminal A	262 (32.4%)	249 (32.8%)	13 (25.5%)	
Luminal B	230 (28.4%)	212 (28.0%)	18 (35.3%)	
Triple-negative	109 (13.5%)	96 (12.7%)	13 (25.5%)	
HER2	120 (14.8%)	117 (15.4%)	3 (5.9%)	
Treatment				
Neoadjuvant therapy		0.122		
Chemotherapy	205/248 (82.7%)	190/229 (83%)	15/18 (83.3%)	
Hormonotherapy	40/248 (16.1%)	38/229 (16.6%)	2/18 (11.1%)	
Radiotherapy	3/248 (0.8%)	2/229 (0.9%)	1/18 (5.6%)	
Neoadjuvant response		0.828		
Partial	206/248 (83.4%)	190/229 (83.0%)	16/18 (88.9%)	
Complete	31/248 (12.6%)	29/229 (12.7%)	2/18 (11.1%)	
Stabilization	7/248 (2.8%)	7/229 (3.1%)	0/18 (0.0%)	
Progression	3/248 (1.2%)	3/229 (1.3%)	0/18 (0.0%)	
Type of surgery		0.024		
SM	12 (1.5%)	10 (1.3%)	2 (3.9%)	
SM+SLNB	248 (30.7%)	240 (31.7%)	8 (15.7%)	

SM+AL	549 (67.9%)	508 (67%)	41 (80.4%)
Time of reconstruction		0.356	
Immediate	146/266 (54.9%)	139/250 (55.6%)	9/16 (56.3%)
Differed	120 (45.1%)	111/250 (44.4%)	7/16 (43.8%)
Type of reconstruction		0.116	
Expander	149/266 (56%)	142/250 (56.8%)	7/16 (43.8%)
Prothesis	54/266 (20.3%)	52/250 (20.8%)	2/16 (12.5%)
Autologous tissue	60/266 (22.6%)	53/250 (21.2%)	7/16 (43.8%)
Adjuvant therapy		0.204	
Radiotherapy	372 (46.0%)	347 (45.8%)	25 (49.0%)
Chemotherapy	409 (50.6%)	379 (50.0%)	30 (58.8%)
Hormonotherapy	595 (73.5%)	561 (74.0%)	34 (66.7%)

LR local recurrence, *MCC* macrocalcifications, *SM* simple mastectomy, *AL* axillary lymphadenectomy, *SLNB* sentinel lymph node biopsy, *ER* estrogen receptors, *PR* progesterone receptors, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ



Sup Figure 2: Schematic process of identification, characterization, and future application of herbal plants in cancer therapy [57].