



ORIGINAL ARTICLE

# Factors predicting local relapse and survival in patients treated with surgery for breast cancer



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Received 2 September 2018; received in revised form 30 October 2018; accepted 12 November 2018

Available online 7 December 2018

## KEYWORDS

Breast cancer;  
Local recurrence;  
Survival;  
Predictive factor

**Summary** *Background:* Assessment of local relapse in patients treated with surgery for breast cancer.

*Materials and methods:* This observational study included 673 patients treated with surgery for breast cancer between 2005 and 2010, who were monitored for a 7-year minimum follow-up period. The study was concluded on 2017 and yielded a total of 31 cases of local relapse.

*Results:* 4.6% of patients presented local relapse, most of them during the first 3 years of follow-up; 45% of patients with local relapse subsequently presented the disease at distant points. The association between the occurrence of local relapse and later onset of the disease at distant points was significant. The Kaplan–Meier survival analysis revealed that negative results for the presence of progesterone receptors, the use of neoadjuvant chemotherapy and the presence of the disease at distant points were factors that significantly influenced patient survival.

*Conclusions:* Almost half of the patients suffering relapse subsequently present the disease at distant points. Certain factors increase the aggressiveness of the disease, predict higher risk of relapse and determine its prognosis.

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<https://doi.org/10.1016/j.asjsur.2018.11.005>

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## 1. Introduction

In breast cancer, certain factors predict higher probability of local relapse and are associated to poorer prognosis and reduced overall survival.<sup>1</sup> Such characteristics should be taken into account when choosing a specific treatment and planning postoperative follow-up.<sup>2,3</sup> In order to identify them, local relapse was analyzed in patients previously treated with surgery for breast cancer, emphasizing those factors that influenced relapse appearance and the relationship with the presence of disease at distant points.

## 2. Materials and method

This observational study was carried out using consecutive sampling on 673 patients treated with surgery for breast cancer between 2005 and 2010. The minimum follow-up period was 7 years. The study was concluded on January 2017. Thirty-one cases of local relapse were evaluated and compared with 31 random control patients, also treated with surgery on the same year, who did not suffer relapse. These controls were selected by a simple random sampling. During the study, whenever a case arose, a random control was selected for the group of patients also treated with surgery for breast cancer on the same month in order to have a similar follow-up period than the observed case.

All patients presenting local-regional recurrence after conservative or radical surgery for breast cancer were included, provided that they fulfilled the following selection criteria: presenting the same location, histological type and histochemical characteristics of the first tumor. Patients presenting a new primary tumor or distant metastasis for the first time were excluded. The following variables were established and studied: age, type of previous surgery, lesion size, histological type, histological grade, axillary involvement, lymphovascular infiltration, multifocality, use of neoadjuvant therapy and immunohistochemical characteristics, as well as margin involvement, surgical technique used in the second intervention and presence of the disease at distant points. Quantitative variables were categorized, in order to make them nominal, with 2 homogeneous groups that could be compared; additionally, this prevented sample dispersion. Patients' disease-free interval and relationship between local relapse and subsequent disease at distant points were defined.

An age cutpoint was established at 50 years because of its association with menopause and consequent hormonal alterations.<sup>4</sup> Tumor size over 2 cm in diameter and histological grade corresponding to moderate or poor differentiation have been associated with increased relapse

rates,<sup>5</sup> thus we chose those parameters as delimitation for a better differentiation between both groups. The following biological factors were defined: estrogen receptors, considered to be positive for values higher than 1%; Ki-67 considered to be positive for values higher than 20%; and HER2, which was defined on the basis of crosses in the immunohistochemical study more than 3 was considered positive, 1 was considered negative and 2, undetermined; in such cases, an additional *in-situ* hybridization assay was carried out, in order to confirm or rule out positivity.<sup>6</sup>

In order to compare nominal variables, 2 × 2 contingency tables were created by using the long-rank test (Mantel–Cox) with  $p < 0.05$  significance level. In determining the variables that were significantly associated with local relapse in an independent way, construction of multiple multivariate-analysis models was initiated, including 4 variables at a time, so that there was one variable maximum per 5 observed events (local relapse), thus building a Kaplan–Meier survival analysis with the IBM® SPSS® Statistics v. 21 software package.

## 3. Results

Up to 4.6% of patients treated with surgery for breast cancer presented local relapse most of them during the first 3 years of follow-up with a mean disease-free interval of 34.5 months (Fig. 1). Radical rescue surgery was used in 94% of cases, while a conservative approach was only adopted in a small percentage of cases; both techniques produced similar outcomes in terms of subsequent appearance of the metastatic disease (Table 1). Age, tumor size, axillary involvement, multifocality, use of neoadjuvant chemotherapy, biological factors and margin involvement were independent variables significantly associated with local relapse (Table 2); 45% of patients with local relapse presented the disease at distant points, whereas metastasis was only observed in 6.4% of patients without relapse. The association between local relapse and disease at distant points was significant (Table 2).

The Kaplan–Meier survival analysis (Table 3) revealed that negative presence of progesterone receptors (Fig. 2A), use of neoadjuvant chemotherapy (Fig. 2B) and presence of the disease at distant points (Fig. 2C) significantly influenced patient survival, with higher relevance than the rest of studied variables.

## 4. Discussion

The risk of local relapse varies between 3 and 15% depending on the type of patient studied,<sup>1,7</sup> and occurs

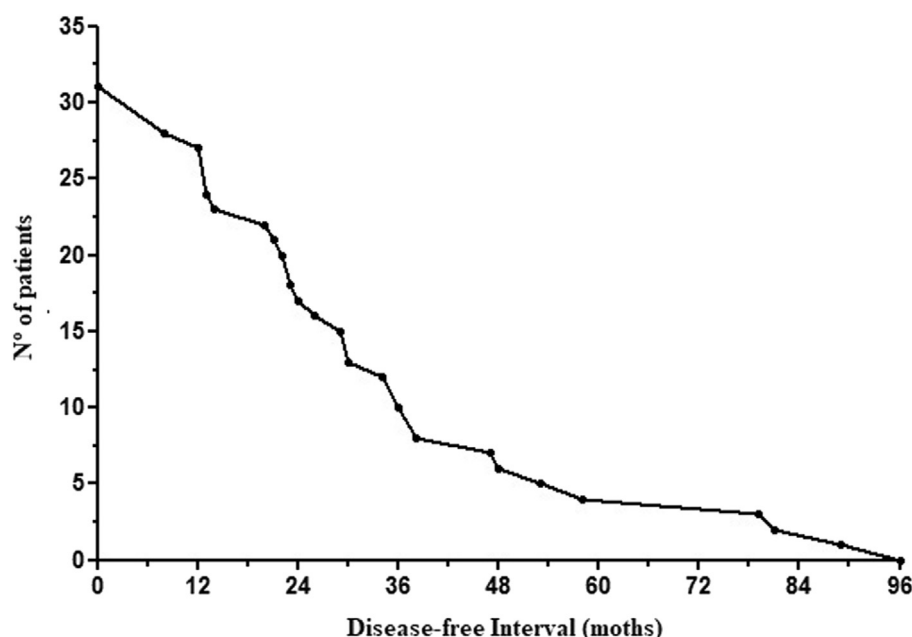


Figure 1 The median disease-free interval of recurrence.

Table 1 Surgical treatment of recurrence (n = 31).

	Metastasis	No Metastasis	p-Value
Breast conserving surgery	1 (50)	1 (50)	0.886
Radical rescue surgery	13 (45)	16 (55)	

The relationship between the chosen surgical treatment for recurrence and the subsequent presence of metastatic disease was not significant ( $p > 0.05$ ).

mostly during the first few years of follow-up, especially in younger and triple-negative patients.<sup>3,4,8</sup> The free-of-disease survival rate at 5 years is higher than 80% and depends on certain factors that should be considered in follow-up.<sup>9</sup> In our study, recurrence rates were acceptable and occurred mainly in the first 3 years.

Tumor location and histopathological characteristics are essential to differentiate relapse from new primary tumors, which have a better prognosis.<sup>10,11</sup> Younger patients present a widely-studied hormonal component, which facilitates tumoral recurrence<sup>12</sup>; additionally, they survive more years, which influenced the observed disease-free interval.<sup>3,4</sup>

If the relapse lesion has an adequate size and oncologic safety of the resection can be guaranteed, a conservative approach may be adopted, since no significant differences were found between relapse treatment through conservative surgery or mastectomy<sup>7,11,13,15</sup>; although the second was chosen in most studies.<sup>7,11,14,15</sup> To make this decision, the type of tumor and the time to recurrence should also be evaluated, because they give information on the aggressivity.<sup>7,11</sup> Furthermore, in patients with local relapse without axillary invasion, the sentinel node must always be examined.<sup>13,15,16</sup> In our center, we prefer mastectomy,

although in certain cases with favorable prognostic factors, a conservative management is possible.

In some published series, the initial tumor size is the most important factor for local relapse, with differences between T3 or 4 and T1 or 2 statistically significant.<sup>5</sup> Axillary involvement increases the rate of local-regional relapse, especially when associated to other unfavorable factors.<sup>17–19</sup> The presence of axillary micro-metastases should also be identified and differentiated; this factor is not significantly associated with increased relapse, especially in patients receiving external axillary radiotherapy.<sup>20</sup> In our study, both factors showed significant differences in relation to the presence of relapse.

Clearly, the closeness of resection margins is a debated issue. In recent years, it has been considered that this factor does not increase the rates of recurrence, because what matters is not the distance, but the occurrence (or not) of contact with the ink.<sup>21,22</sup> Furthermore, recent studies have suggested that a focally involved margin would not increase such figures either, so that re-intervention of the patient would not be necessary.<sup>4</sup> Moreover, margin involvement is not related with recurrence in patients initially mastectomized.<sup>23</sup> In spite of all the above mentioned, it should always be highlighted that the presence of a tumor in contact with the margins of conservative surgery is the only variable that can be controlled by the surgeon and it would undisputedly be an indication for re-intervention.

Multifocality and the presence of intraductal carcinoma may lead to incomplete initial resection, which is associated with more re-interventions necessary to get free margins with the consequent morbidity increase.<sup>12,23,24</sup> A similar situation occurs with lobular carcinoma, since its special characteristics make local control more difficult, as compared with ductal carcinoma.<sup>25–28</sup> Lymphovascular

**Table 2** Characteristics of patients.

	Local recurrence n(%)		p-Value
	Present	Absent	
Cases	31 (50)	31 (50)	
Age (years)			0.058
<50	19 (61)	11 (35)	
≥50	12 (39)	20 (65)	
First surgical treatment			0.611
Breast conserving surgery	26 (84)	24 (77)	
Mastectomy	5 (16)	7 (23)	
Tumor size (mm)			< 0.001
<20	5 (16)	20 (65)	
≥20	26 (84)	11 (35)	
Clinical lymph node status			0.008
Positive	21 (68)	11 (35)	
Negative	10 (32)	20 (65)	
Multifocality			0.004
Yes	26 (84)	14 (45)	
No	5 (16)	17 (55)	
Neoadjuvant chemotherapy			< 0.001
Yes	20 (65)	5 (16)	
No	11 (35)	26 (84)	
Histological type			0.107
Ductal	26 (84)	29 (94)	
Lobular	5 (16)	2 (6)	
Ductal carcinoma <i>in situ</i>			0.317
Yes	17 (55)	21 (68)	
No	14 (45)	10 (32)	
Lymphovascular involvement			0.165
Yes	12 (39)	6 (19)	
No	19 (61)	25 (81)	
Histological grade			0.367
<G2	5 (16)	8 (26)	
≥G2	26 (84)	23 (74)	
Estrogen receptor			< 0.001
Positive	17 (55)	26 (84)	
Negative	14 (45)	5 (16)	
Progesterone receptor			< 0.001
Positive	9 (29)	22 (71)	
Negative	22 (71)	9 (29)	
HER2			0.006
Positive	9 (29)	2 (7)	
Negative	22 (71)	29 (94)	
Positive margins			0.003
Yes	18 (58)	7 (23)	
No	13 (42)	24 (77)	
Metastasis			< 0.001
Yes	14 (45)	2 (6)	
No	17 (55)	29 (94)	

infiltration is related with local-regional relapse but, more importantly, with the dissemination of the disease to the rest of the body, which promotes the appearance of metastatic disease.<sup>18</sup>

A result of negative progesterone receptor is predictive of relapse, even in the presence of positive estrogen

**Table 3** Kaplan–Meier survival analysis.

Independent variables	OR (95%CI)	p-Value
Progesterone receptor negative	1.8 (1.2–2.7)	<b>0.002</b>
Neoadjuvant chemotherapy	1.6 (1.1–2.4)	<b>0.009</b>
Metastasis	1.9 (1.3–2.7)	<b>&lt; 0.001</b>
Positive margins		0.058
Tumor size ≥ 20 mm		0.096
Clinical lymph node positive		0.468
Multifocality		0.471
Estrogen receptor negative		0.968
HER2		0.751

OR: odds ratio; CI: confidence interval.

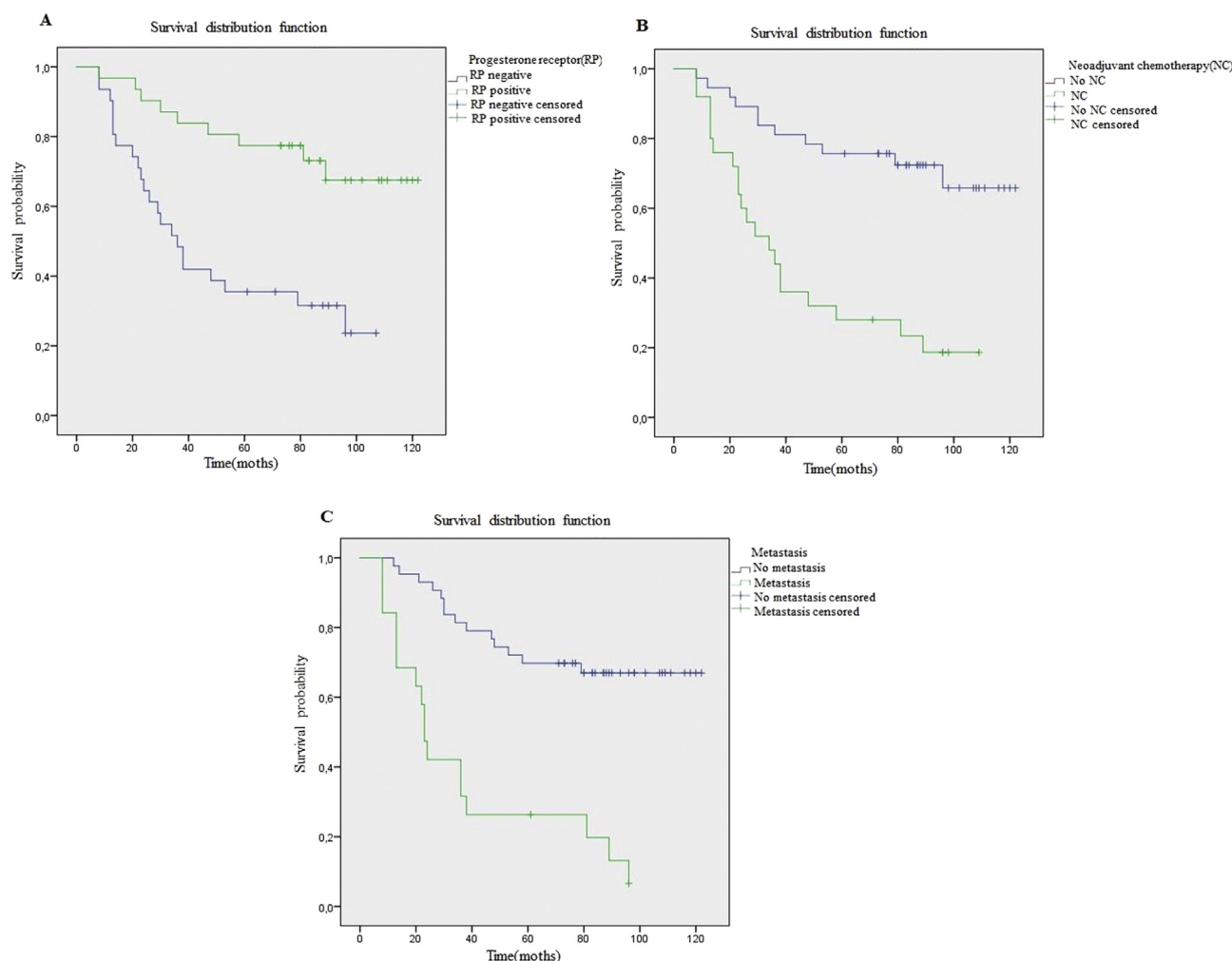
receptor,<sup>29</sup> and is a very important factor in the choice of treatment. Furthermore, not using hormonal therapy for systemic control promotes subsequent development of the disease at distant points, which reduces overall survival.<sup>30</sup> Given that positive HER2 in the immunohistochemical study is treated a specific way, it could be currently considered a good-prognosis factor<sup>31</sup>; however, it was not significant in our study, similarly to Ki-67 a cell proliferation marker usually elevated accordingly to the aggressiveness of the tumor.<sup>6</sup>

From a surgical point of view, the use of neoadjuvant therapy impairs tumor delimitation and might be significantly associated with increased local relapse in these patients.<sup>9</sup> However, these patients usually present large initial tumors, with axillary involvement or unfavorable biological factors (where we include triple-negative ones), all of which could potentially account for unfavorable outcomes rather than the treatment<sup>25,32</sup>. A further issue to take into account is that triple-negative patients do not present higher risk of local relapse, but of disease at distant points, which would effectively influence overall survival.<sup>8</sup>

The relationship between local relapse and subsequent presence of metastatic disease was significant; global survival decreased, in agreement with some published series, which reported rates below 40%.<sup>29,32</sup> Survival was lower depending on the time of onset and the location, with the poorest rates for brain metastases.<sup>24</sup> We observed such a relationship in our study.

In spite of the prolonged follow-up time, these Results should be considered with caution because, from a statistical point of view, this experience corresponded to only one centre and was conducted on a limited amount of patients; however, most of our outcomes were in agreement with those reported in the literature.

Local relapse rates have decreased throughout the time, due to the use of early-diagnosis techniques – based on screening the population at risk – selective surgical approach to small non-palpable tumors and adjuvant treatments that become more and more specific for different types of patient. However, there will always be factors influencing a patient's prognosis and these should be taken into account in planning the follow-up.



**Figure 2** Survival probability curves. A result of negative progesterone receptor (A), the use of neoadjuvant therapy with chemotherapy (B) and the presence of disease at distant points (C) are factors that reduced overall survival ( $p < 0.05$ ).

## 5. Conclusions

Patients treated with surgery for breast cancer should be closely monitored, especially during the first few years post-intervention, since most cases of relapse occur in that period. Conservative management of relapse is possible, provided that suitable margins can be obtained; supporters of this approach remark that this is the most important factor to consider. Almost half of patients suffering recurrence subsequently presented the disease at distant points, which reduced their quality of life and global survival. Certain factors may increase the aggressiveness of the disease, predict higher risk of relapse and determine the prognosis of recurrence; thus, these factors should be evaluated in order to enhance the therapeutic approach and life expectancy.

## Author contributions

Tejera Hernández, Ana Alicia. Surgical intervention and patient follow-up, data search and collection, data processing, statistical analysis, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Vega Benítez, Víctor Manuel. Surgical intervention and patient follow-up, data search and collection, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Rocca Cardenas, Juan Carlos. Data processing, statistical analysis and bibliographic research.

Gutiérrez Giner, María Isabel. Surgical intervention and patient follow-up.

Díaz Chico, Juan Carlos. Data processing and statistical analysis.

Hernández Hernández, Juan Ramón. Surgical intervention and patient follow-up, drafting and preparation of the manuscript, bibliographic research and manuscript review.

## Disclosure

The authors report no proprietary or commercial interests in any product mentioned or concept discussed in this article. The authors report not having a conflict of interest.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.



This article has been approved by the Ethics Committee of our hospital. Does not contain patient data or human experiments.

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