FACTORS THAT INFLUENCE TREATMENT DELAY FOR PATIENTS WITH BREAST CANCER

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Competing of interests

The authors declare that they have no competing interests.

ABSTRACT

Introduction

The diagnosis or treatment of breast cancer is sometimes delayed. A lengthy delay may have a negative psychological impact on patients. Our study aim is to evaluate the sociodemographic, clinical and pathological factors associated with delay in the provision of surgical treatment for localised breast cancer, in a prospective cohort of patients.

Method

This observational, prospective, multicentre study was conducted in ten hospitals belonging to the Spanish national public health system, located in four Autonomous Communities (regions). The study included 1236 patients, diagnosed through a screening programme or found to be symptomatic, between April 2013 and May 2015. The study variables analysed included each patient's personal history, care situation, tumour history and data on the surgical intervention, pathological anatomy, hospital admission and follow-up. Treatment delay was defined as more than 30 days elapsed between biopsy and surgery.

Results

Over half of the study population experienced surgical treatment delay. This delay was greater for patients with no formal education and among widows, persons not requiring assistance for usual activities, those experiencing anxiety or depression, those who had a high BMI or an above-average number of comorbidities, those who were symptomatic, who did not receive NMR spectroscopy, who presented a histology other than infiltrating ductal carcinoma or who had poorly-differentiated carcinomas.

Conclusions

Certain sociodemographic and clinical variables are associated with surgical treatment delay. This study identifies factors that influence surgical delays, highlighting the importance of preventing these factors and of raising awareness among the population at risk and among health personnel.

Key words: *Breast cancer, Delay, Prognosis, Tumour biology*

1. Introduction

Breast cancer is the most frequently diagnosed malignant tumour in developed countries. In 2018, its incidence in Europe was 74.4 per 100,000 inhabitants and in Spain it was 74.5 per 100,000. In both geographic areas, breast cancer is the most prevalent form of cancer among women. However, its mortality Europe-wide is 14.9 per 100,000 but in Spain, only 10.6 per 100,000. This difference influences the five-year prevalence, which is 534.7 per 100,000 inhabitants in Europe and 549.6 in Spain. Thanks to significant advances in diagnosis and treatment, mortality figures are low, compared to other tumours, but in consequence, the prevalence is very high (1), which heightens the need for healthcare resources for these patients; for example, the follow-up period is longer, and they require more specialised and individualised care (2).

This pathology is addressed by a wide variety of healthcare professionals, in both primary and hospital care, and so effective coordination is needed to ensure continuity and consistency. This coordination, in turn requires effective management of the processes involved in disease treatment (3)

Many factors must be taken into account in providing healthcare for a patient with breast cancer. Sociodemographic parameters, clinical characteristics and lifestyle habits can all influence the patient's situation and treatment needs. Moreover, comorbidities such as chronic obstructive pulmonary disease, chronic heart failure and diabetes produce a negative impact on the healthcare status of these patients (4,5). Other variables that can influence the care process are age, sex and belief systems (6).

The diagnosis and/or treatment of breast cancer is sometimes delayed. Apart from clinical considerations, either type of delay can be psychologically distressing for patients (7). In the present study, we focus on surgical treatment delay (STD), taking as reference variables the dates of the biopsy and surgery performed. Opinions are divided as to whether STD is associated with shorter survival for breast cancer patients, as other clinical and sociodemographic factors are also involved, such as tumour stage, previous comorbidities and the patient's age (8-11). To enhance our understanding of these questions, this study evaluates the sociodemographic, clinical and pathological factors associated with STD in localised breast cancer, in a prospective cohort of patients.

2. Materials and methods

2.1. Study design

Observational prospective multicentre study, with the participation of ten hospitals belonging to the Spanish National Health System, located in four Autonomous Communities (regions). The study population forms part of the NHS Breast Cancer and Health Services Research Cohort (CAMISS), belonging to the National Health System.

2.2. Inclusion and exclusion criteria

The prospective cohort was composed of 1236 patients, who were diagnosed through a screening programme or who presented symptoms during the period April 2013 to May 2015.

The patients included were all women aged at least 18 years, diagnosed with ductal carcinoma in situ, invasive ductal carcinoma, tubular carcinoma, mucinous carcinoma, papillary carcinoma, cribriform carcinoma or invasive lobular carcinoma.

Patients receiving neoadjuvant treatment, or who had been diagnosed with sarcoma, lymphoma or inflammatory carcinoma, or who suffered a recurrence of breast cancer, or whose disease was terminal or who presented any condition that interfered with their ability to complete the questionnaires were excluded.

2.3. Study variables

Data for the following study variables were compiled: the patient's personal history (age, educational background, employment status, household situation), health care, tumour history prior to the intervention, the surgery performed, pathological anatomy, hospital admission and follow-up. The EQ-5D health-related quality of life (HRQoL) instrument was applied. In this descriptive system, HRQoL is defined in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (12). STD was defined as the elapse of more than 30 days between the date of biopsy and the date of surgery.

2.4. Ethical considerations

Qualified research personnel informed patients of the nature and characteristics of this study, and all gave their signed consent before being included. All the study data were processed in accordance with applicable legislation, and the patient's confidentiality was protected at all times. The Ethics Committee at each

participating hospital approved the study. This study is registered with Clinical Trials.gov (Identifier: NCT02439554).

2.5. Statistical analysis

In the descriptive analysis performed, measures of central tendency, position and dispersion were used for the quantitative variables, and of frequency distribution for the qualitative ones. Taking STD as the segmentation variable (≤ 30 days vs. > 30 days), bivariate analysis was performed using the chi-square test for dichotomous qualitative variables (or the linear test, for ordinal qualitative variables), and Student's t test for independent quantitative variables. The level of statistical significance assumed was $p < 0.05$.

In the multivariate analysis, the outcome variable taken was the presence of STD, and variables were considered by conditional forward and backward stepwise selection. The variables initially included in this analysis were all the independent variables for which $p < 0.01$ according to the bivariate analysis, in addition to the patient's age.

3. Results

The initial study population was composed of 1463 women with breast cancer, of whom 1270 had not received neoadjuvant treatment. After applying the inclusion and exclusion criteria, the final sample contained 1236 patients, of whom 689 experienced STD. The mean age of these patients, both overall and in the STD group, was 57.7 years (SD: 11.7%) ($p = 0.323$) (Table 1). The median surgical delay was 35 and the IQR was 24. The mean BMI for all patients was 26.8 (SD: 5.5%). For those in the non-STD group it was 26.4 (SD: 5.3%) and for the STD group it was 27.2 (SD: 5.6%). The difference was statistically significant ($p = 0.018$).

With respect to the patients' education background, the association with STD was inverse; in other words, patients with a higher level of education were less likely to suffer STD. Specifically, 63.3% of patients with no educational qualifications experienced STD, versus 50.4% of those with university studies ($p < 0.001$).

Differences were also observed with respect to marital status. STD was most likely to affect widowed women (66.2%), while only 46.6% of those who were single experienced delay ($p = 0.016$).

Of the patients who did not require assistance in the home, 376/614 (61.2%) had experienced STD, whereas among those who did require such assistance, 285/540 (52.82%) had been in this situation. The difference was statistically significant ($p=0.005$).

The responses to the EQ-5D HRQoL questionnaire (regarding mobility, self-care, usual activities, pain/discomfort and anxiety/depression) revealed significant differences in the presence or otherwise of anxiety-depression. Thus, 61% of the patients who presented this condition had experienced STD versus 51.3% of those with no such problem ($p=0.002$).

The Charlson index showed that STD was much more likely among patients who presented three or more comorbidities, among whom 65% experienced STD ($p=0.011$). Similarly, symptomatic patients were more subject to STD than those who presented without symptoms ($p=0.029$) (Table 2).

Women with more advanced tumour stages were more likely to suffer STD ($p=0.009$). The delay was longer among patients who had a diagnosis other than infiltrating ductal carcinoma ($p<0.001$) and those with poorly-differentiated tumours ($p=0.025$). Finally, patients who had not undergone NMR spectroscopy were also more likely to experience STD ($p<0.001$).

In the multivariate logistic regression model, among the sociodemographic variables, the presence of STD was independently predicted by educational background (maximum STD among those with “Primary education or less”, OR: 1.54; 95% CI: 1.13-2.08), by BMI (OR: 1.04; 95% CI: 1.01-1.07) and by those who needed assistance in the home (maximum STD among those classed as “Not needed”, OR: 1.41; 95% CI: 1.05- 1.90). The relevant clinical variables were the presence of symptoms (OR: 1.69; 95% CI: 1.25- 2.29) and the non-diagnosis of infiltrating ductal carcinoma (OR: 1.90; 95% CI: 1.37-2.63). The model achieved an acceptable goodness of fit, with a value of $p=0.393$ according to the Hosmer and Lemeshow test (Table 3).

4. Discussion

Treatment delay for patients with breast cancer impacts on health and, probably, on survival (13), and therefore it is of vital importance to understand the factors involved. Moreover, it is important to address the questions of fairness that must be taken into account in the scheduling and administration of treatments. Waiting for treatment is one of the events that produces most stress among patients and delay is one of their most frequent causes of complaint (14). Unlike previous research in this field, the present study

prospectively evaluates a large number of patients diagnosed and treated in different public-sector hospitals (15). Over half of our study sample experienced STD. The impact was most severe among patients with little or no formal education, those who did not require home assistance, those with a high BMI and those whose condition was symptomatic.

In fact, more than half of all patients affected by STD had few educational qualifications. This parameter has been cited in previous studies of treatment delay, for other types of tumours (16). Our work, thus, corroborates previous research, underlining the conclusion that the empowerment of patients is a factor that directly affects the healthcare decisions taken. In short, education background is a powerful factor underlying the patient's involvement in potentially crucial treatment decisions (17-20).

Our study results also show that marital status and the need for assistance in the home are significantly related to the psychosocial support received, which is known to reinforce adherence to treatment and follow-up (21,22). In our study sample, a large proportion of the women who experienced STD were widows, whose isolation at least in part accounts for the greater likelihood of their being affected by treatment delay. A similar reasoning is applicable to the case of patients who do not need assistance in the home. These findings corroborate our hypothesis of a close relationship between STD and the absence of psychosocial support. Patients with greater assistance needs due to a loss of autonomy require continuous care at the social and health levels, which may mean they receive greater attention in disease treatment, due to their more frequent contact with the health system.

An important aspect of the present study is that it is based on the use of a validated measurement instrument, the EQ-5D HRQoL questionnaire, which objectively evaluates patients' experience of healthcare diagnosis and treatment in cases of breast cancer (12). With respect to the quality of life, more than half of the patients who experienced STD presented anxiety and/or depression (23), possibly due to their concerns and lack of optimism about the surgery proposed and the course of their disease (24,25).

High BMI, overweight and obesity are known risk factors for breast cancer (26). Furthermore, although research findings in this respect are scarce, obesity is considered a risk factor for any type of intervention, which might justify delaying surgery. Moreover, obese patients are at greater risk of suffering treatment complications, compared to those with normal BMI (27,28). In this respect, Roy et al. (2019) proposed a risk stratification model for immediate microvascular breast reconstruction in which obesity was

incorporated as an important predictor (29). For these reasons, a high BMI may increase the waiting time for surgery, an association that is confirmed in our study.

The Charlson index for our study results shows there is a positive association between STD and the presence of comorbidities, which confirms a study conducted in the USA by Yancik et al. (2001), who reported that the greater the number of comorbidities, the lower the patient's probability of receiving the recommended treatment (30). This association may be due to the physician having to evaluate various treatment options for patients with multimorbidity, or because they are not candidates for more extensive primary treatment or because they might not be able to withstand it. Any of these considerations might cause a delay in reaching a final surgical decision (31,32).

Treatment delay for symptomatic patients may be motivated by the aggressiveness of the tumours, as suggested by the association observed in our patients between STD and tumour stage and degree of differentiation. In advanced stages of the disease, diagnosis may lead to more complementary tests being conducted, requiring more time before surgery can be performed. However, in a study of patients with breast cancer, Redondo et al. (2009) observed a shorter treatment delay in patients whose disease was at a more advanced stage (13). This conflicting finding might be indicative of the changing nature of treatment for breast cancer, from a period when fewer complementary tests were performed after mammography, such as biopsy and the labelling of suspicious nodules. Furthermore, multidisciplinary committees are now commonly formed to carry out a more comprehensive assessment of the patient's condition, sometimes requiring further diagnostic tests and even second biopsies (3).

Infiltrating ductal carcinoma is one of the most common diagnoses in breast cancer, and is also one of the most common histological types found in advanced stages of the disease (33). As this tumour is highly aggressive, it should come as no surprise that it is associated with lower levels of treatment delay compared with other histological types, as has also been reported in previous studies (13). When a histological type such as lobular carcinoma is identified, it is recommended that the study be extended with a mammary MRI since these tumours are usually multifocal and/or multicentric. In this diagnostic test, suspicious lesions may appear, requiring further biopsies and diagnostic confirmation, thus delaying the first treatment. Furthermore, since the tumours are frequently multicentric, a mastectomy is usually required. This factor, too, could result in treatment being delayed (34). Finally, in this large group of non-IDC tumours there would also be carcinomas in situ, which due to their low risk to life are often treated non- preferentially.

The present study has certain limitations, which should be acknowledged. Ideally, we should have assessed the first treatment received, whether surgery, chemotherapy, radiotherapy or any other approach. However, patients with neoadjuvant treatment had to be excluded from the study sample because in many cases the date of first treatment was unknown. For this reason, we define STD as the period elapsed from biopsy until the surgical intervention, i.e. the first treatment for women who did not receive neoadjuvant treatment. Another consideration is that little previous research has been conducted in this field, which hampers our ability to compare and corroborate our findings, although it also represents a plus point in that the data reported are novel. Furthermore, as a strength of this study, the period of treatment delay considered is comparable to that assumed in earlier papers (11,35,36). Finally, the multicentre nature of our research enhances the representativeness of the data analysed.

In view of the findings obtained in this research, the implementation of measures to reduce the surgical waiting times for patients with breast cancer is recommended.

To conclude, we emphasise that certain risk habits and sociodemographic and clinical variables have a negative impact on STD. Our identification of factors that influence surgical delay highlights the need to raise awareness of their importance among the population at risk and among healthcare personnel. In addition, more attention should be paid to patients with little formal education, in order to enhance the clinical management of their cancer.

5. Conflicts of interest

The authors declare that they have no conflict of interest regarding the present study.

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Variable	Total (n: 1236)		Surgical treatment delay				p	
			≤30 days (n: 547)		>30 days (n: 689)			
	Mean	SD	Mean	SD	Mean	SD		
Age ⁽¹⁾	57.7	11.7	57.4	11.2	58.1	12.1	0.323	
BMI ⁽²⁾	26.8	5.5	26.4	5.3	27.2	5.6	0.018	
	Total (n: 1236)		Surgical treatment delay				p	
			≤30 days (n: 547)		>30 days (n: 689)			
	N	%	n	%	n	%		
Education background ⁽³⁾								
	No formal education	150	13.1	55	36.7	95	63.3	<0.001
	Primary education	463	40.5	179	38.7	284	61.3	<0.001
	Secondary education	269	23.5	121	45.0	148	55.0	
	University education	262	22.9	130	49.6	132	50.4	
Occupationally active ⁽⁴⁾								
	No	615	53.8	251	40.8	364	59.2	0.194
	Yes	529	46.2	237	44.8	292	55.2	
Marital status ⁽⁵⁾								
	Single	118	10.2	63	53.4	55	46.6	0.016
	Married/Cohabiting	768	66.6	326	42.4	442	57.6	
	Separated-Divorced	122	10.6	54	44.3	68	55.7	
	Widowed	145	12.6	49	33.8	96	66.2	
Need home assistance ⁽⁶⁾								
	No	614	53.2	238	38.8	376	61.2	0.005
	Yes	540	46.8	255	47.2	285	52.8	
Receive social assistance ⁽⁷⁾								
	No	997	86.8	426	42.7	571	57.3	0.942
	Yes	152	13.2	66	43.4	86	56.6	
Household situation⁽⁸⁾								
	Living alone	182	15.8	72	39.6	110	60.4	0.403
	Accompanied	967	84.2	418	43.2	549	56.8	
Pregnant ⁽⁹⁾								
	No	958	98.4	396	41.3	562	58.7	0.958
	Yes	16	1.6	6	37.5	10	62.5	
Baseline EQ-5D Mobility ⁽¹⁰⁾								
	No problems	1020	87.9	439	43	581	57	0.511
	Problems	141	12.1	56	39.7	85	60.3	
Baseline EQ-5D Self-care ⁽¹¹⁾								
	No problems	1100	94.9	466	42.4	634	57.6	0.704
	Problems	59	5.1	27	45.8	32	54.2	
Baseline EQ-5D Usual activities ⁽¹²⁾								
	No problems	1012	87.2	428	42.3	584	57.7	0.552
	Problems	148	12.8	67	45.3	81	54.7	
Baseline EQ-5D Pain/Discomfort ⁽¹³⁾								
	No problems	738	63.6	328	44.4	410	55.6	0.113
	Problems	423	36.4	167	39.5	256	60.5	
Baseline EQ-5D Anxiety/Depression ⁽¹⁴⁾								
	No problems	421	36.3	205	48.7	216	51.3	0.002
	Problems	738	63.7	288	39	450	61	

Note: The percentage for total patients is expressed by the column, and percentage by treatment delay, by the row.

Losses: 1=4; 2=319; 3=92; 4=92; 5=83; 6=82; 7=87; 8=87; 9=262; 10=75; 11=77; 12=76; 13=75; 14=77

BMI: Body Mass Index/ EQ-5D: European Quality of Life- 5 dimensions/ SD: Standard deviation

Table 1. Outcomes according to sociodemographic and HRQoL variables

Variable	Total (n: 1236)		Surgical treatment delay				p
			≤30 days (n: 547)		>30 days (n: 689)		
	n	%	n	%	N	%	
Habitual smoker ⁽¹⁾ (n - %)							
	Never	659	267	40.5	392	59.5	0.124
	Current	267	126	47.2	141	52.8	
	Ex-smoker	190	87	45.8	103	54.2	
Habitual alcohol use ⁽²⁾ (n - %)							
	No	1210	533	44.0	677	56.0	0.519
	Yes	9	5	55.6	4	44.4	
Prior neoplasia (n - %)							
	No	1122	498	44.4	624	55.6	0.851
	Yes	114	49	43.0	65	57.0	
Family history of gynaecologic cancer ⁽³⁾ (n - %)							
	No	769	331	43.0	438	57.0	0.919
	Yes	425	185	43.5	240	56.5	
Charlson index (n - %)							
	0	968	449	46.4	519	53.6	0.011
	1	160	58	36.3	102	63.8	
	2	76	29	38.2	47	61.8	
	3 or more	32	11	34.4	21	65.6	
Asymptomatic ⁽⁴⁾ (n - %)							
	No	521	211	40.5	310	59.5	0.029
	Yes	714	335	46.9	379	53.1	
Detected by screening (n - %)							
	No	551	227	41.2	324	58.8	0.06
	Yes	685	320	46.7	365	53.3	
Tumour stage ⁽⁵⁾ (n - %)							
	0	126	50	39.7	76	60.3	0.009
	I	663	319	48.1	344	51.9	
	II	341	141	41.3	200	58.7	
	III-IV	82	26	31.7	56	68.3	
Infiltrating ductal carcinoma ⁽⁶⁾ (n - %)							
	No	469	175	37.3	294	62.7	<0.001
	Yes	763	372	48.8	391	51.2	
Degree of differentiation ⁽⁷⁾ (n - %)							
	I	273	139	50.9	134	49.1	0.025
	II	597	260	43.6	337	56.4	
	III	278	115	41.4	163	58.6	
Expression of ER ⁽⁸⁾ (n - %)							
	Negative	147	68	46.3	79	53.7	0.721
	Positive	1063	471	44.3	592	55.7	
Expression of PR ⁽⁰⁹⁾ (n - %)							
	Negative	272	126	46.3	146	53.7	0.557
	Positive	937	413	44.1	524	55.9	
Expression of HER2 ⁽¹⁰⁾ (n - %)							

MNR⁽¹¹⁾ (n - %)	Negative	1039	472	45.4	567	54.6	0.319
	Positive	110	56	50.9	54	49.1	
	No	476	171	35.9	305	64.1	<0.001
	Yes	758	375	49.5	383	50.5	

Note: The percentage for total patients is expressed by the column, and percentage by treatment delay, by the row.

Losses: 1=120; 2=17; 3=42; 4=1; 5=24; 6=2; 7=4; 8=26; 9=27; 10=87; 11=88

ER: Estrogen Receptor /PR: Progesterone Receptor /HER2: Human Epidermal Growth Factor Type II /MNR: Magnetic Nuclear Resonance

Table 2. Outcomes according to risk habits and clinical variables

Variable		β	p	Odds ratio	95% CI	
					Lower	Upper
Education						
	Secondary-University			1.00		
	None-Primary	0.43	0.01	1.54	1.13	2.08
BMI		0.04	0.01	1.04	1.01	1.07
Need assistance						
	Yes			1.00		
	No	0.34	0.02	1.41	1.05	1.90
Asymptomatic						
	Yes			1.00		
	No	0.53	<0.001	1.69	1.25	2.29
Histologies other than IDC						
	Yes	0.64	<0.001	1.90	1.37	2.63
	No			1.00		
BMI: Body Mass Index / IDC: Infiltrating ductal carcinoma						

Table 3. Multivariate logistic regression model for presence of surgical treatment delay (>30 days)