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CLINICAL ARTICLE

Factors predictive of mortality in a cohort of women surgically treated for breast cancer from 1997 to 2014

Antonio García-Fernández [a,*], Israel Barco [a], Manel Fraile [b], José M. Lain [c], Ana Carmona [d], Sonia Gonzalez [e], Antoni Pessarrodona [d], Nuria Giménez [f,g], Marc García-Font [h]

[a] Breast Unit, Department of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Terrassa, Spain
[b] Nuclear Medicine Department, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Terrassa, Spain
[c] Breast Unit, Department of Gynecology, Hospital of Terrassa, Health Consortium of Terrassa, Terrassa, Spain
[d] Department of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Terrassa, Spain
[e] Department of Hemato-Oncology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Terrassa, Spain
[f] Research Unit, Research Foundation Mútua Terrassa, University of Barcelona, Terrassa, Spain
[g] Laboratory of Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain
[h] International University of Catalonia, Barcelona, Spain

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ABSTRACT

Objective: To determine whether previously reported factors predictive of breast cancer mortality are effectively linked with mortality, particularly breast-cancer-specific mortality. *Methods:* In a prospective study, clinical, surgical, and follow-up data were assessed for consecutive patients with breast cancer who underwent surgery between 1997 and 2014 at two centers in Barcelona, Spain. Predictors of mortality were assessed by multivariate analysis. *Results:* Overall, 2134 patients were treated for 2206 breast tumors. Overall mortality was 15.0% (n=319), and breast-cancer-specific mortality was 9.0% (n=191). On multivariate analysis, the most significant factors associated with breast-cancer-specific mortality were clinical stage, inmunohistochemical profile, locoregional relapse, and lymphovascular invasion (all $P<0.001$). Age at onset, participation in the mass-screening program, histologic grade, and multicentricity were not significant. Patients with three or more positive axillary nodes sustained a specific mortality significantly higher than did node-negative patients or those with fewer than three positive nodes. *Conclusion:* Factors predictive of breast cancer mortality were clinical stage, locoregional relapse, molecular classification, lymphovascular invasion, and neoadjuvant chemotherapy. As a single factor, nodal disease becomes relevant only when three or more lymph nodes are involved.

1. Introduction

Breast cancer is the single most prevalent malignancy in women, accounting for up to 25% of all cancer cases [1]. It is also the leading cause of cancer mortality in the female population of high-income countries [2]. In 2012, 1 676 633 new cases of breast cancer were diagnosed worldwide, 25 215 of which were in Spain, which is ranked 25th in Europe, with an annual incidence of 84.9 new cases per 100 000 women [2].

In the past 30 years, the incidence of breast cancer has increased worldwide [3], which is probably linked with the progressive aging of the population, in addition to advances in diagnosis and mass-screening programs. However, there has been a substantial concurrent decrease in mortality due to breast cancer in high-resource countries [3]. Such a decrease in mortality is probably related to both improvements in adjuvant therapy and earlier diagnosis because of the implementation of mass-screening programs.

Factors predictive of breast cancer mortality include age at presentation, tumor size, immunohistochemical profile, histologic type, and hormone-receptor status [4,5]. Such factors seem to correlate well with overall mortality among patients with breast cancer, but the available data are not fully conclusive for breast-cancer-specific mortality [5]. Early diagnosis seems to be of paramount importance, because tumor size is correlated with nodal disease and stage, both of which govern local and distant recurrence [6]. For patients undergoing conservative surgery, local relapse is linked with an increased risk of distant metastases and death [6,7].

The aim of the present study was to determine whether the considered factors (age, clinical stage, histologic type and grade, immunohistochemical profile, distant metastases, and disease-free survival, among others) are effectively linked with mortality, particularly breast-cancer-specific mortality.

* Corresponding author at: Breast Unit, Department of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, C/Sant Antoni, 21, 08221 Terrassa, Spain. Tel.: +34 93 536 50 85; fax: +34 93 736 50 86.
E-mail address: drgarciafdez@hotmail.com (A. García-Fernández).

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Table 1
Baseline characteristics of 2134 patients with breast cancer.[a]

Characteristic	Value
Age, y	58 ± 13 (22–103)
<50	551 (25.8)
50–69	1153 (54.0)
>69	430 (20.1)
Histologic type (n=2206)	
Ductal carcinoma	1802 (81.7)
Lobular carcinoma	161 (7.3)
Intraductal carcinoma	243 (11.0)
Invasive carcinoma	1963 (89.0)
Histologic grade	
Grade 1	599 (30.5)
Grade 2	853 (43.5)
Grade 3	452 (23.0)
Grade not known	59 (3.0)
Tumor size (n=2206)	
Tis	243 (11.0)
T1	1168 (52.9)
T2	665 (30.1)
T3	68 (3.1)
T4	59 (2.7)
Occult breast cancer	3 (0.1)
Axillary tumor burden (invasive carcinoma; n=1963)	
Lymph node positive	750 (38.2)
Lymph node negative	1177 (60.0)
Not known	36 (1.8)
Intraductal carcinoma (n=243)	
Axillary tumor burden	114 (46.9)
Lymph node positive	3 (2.6)
Lymph node negative	111 (97.4)
Not known	129 (53.1)
Immunohistochemical subtype (n=1963)	
Luminal A	862 (43.9)
Luminal B	755 (38.5)
Pure Her2	93 (4.7)
Triple negative	246 (12.5)
Not known	7 (0.4)
Surgery: invasive carcinoma (n=1963)	
Conservative	1279 (65.2)
Radical	684 (34.8)
Sentinel node biopsy	1062 (54.1)
Neoadjuvant chemotherapy	98 (5.0)
Surgery: intraductal carcinoma (n=243)	
Conservative	163 (67.1)
Radical	80 (32.9)
Sentinel node biopsy	102 (42.0)

[a] Values are given as mean ± SD (range) or number (percentage).

2. Materials and methods

In a prospective observational study, consecutive patients with breast cancer referred to the Breast Unit of the University Hospital Mútua Terrassa and Hospital of Terrassa for surgical treatment of either primary or recurrent tumors between January 1, 1997, and December 31, 2014, were included. The study was performed in accordance with the Research Ethics Committee of Mútua Terrassa Hospital. Written informed consent was obtained from the patients for all invasive procedures and surgery, and for the inclusion of their data in the study database.

All patients had been referred either from the regional public healthcare system or from the national breast cancer screening program. Neoadjuvant chemotherapy was the preferred treatment option for suitable patients, mainly those with T4, triple-negative, or human epidermal growth factor receptor-2 (HER2)-positive tumors, and also some patients with locally advanced luminal tumors. Neoadjuvant chemotherapy was used to reduce tumor size and to transform radical into conservative surgery (lumpectomy or quadrantectomy). Patients who were not suitable for neoadjuvant chemotherapy underwent conservative or radical surgical procedures according to disease stage and/or tumor volumetry.

The database included histologic type and grade (differentiation grade and histologic grade), age, tumor size, status of estrogen receptor, status of progesterone receptor, Ki67 (available from 2006 onward), and human epidermal growth receptor-2 factor (HER2/neu; available from 2003 onward), all of which were on the basis of the histopathology of the surgical specimen at diagnosis. Nodal status, distant metastases, disease-free survival, and mortality were also recorded. For patients treated before the test became available, HER2/neu was subsequently analyzed in a retrospective manner.

Follow-up of patients was done by a multidisciplinary breast committee. Patients regularly attended the oncology and gynecology outpatient clinics every 6 months during the first 5 years of follow-up, and yearly afterwards. Staff members from the departments of Medical Oncology and Gynecology at the hospitals updated the study database on a daily basis. An update was also performed twice a year by the general data managers from both hospitals in conjunction with the CatSalut (Catalan Health Service) registry staff. As part of the updates, electronic National Health System patient files were reviewed for possible events. In case of substantial missing data, a telephone interview was conducted. For patients moving to other areas, data were censored at the time of last follow-up.

For the present analysis, breast cancer was classified into four groups according to its immunohistochemical profile (estrogen receptor, progesterone receptor, HER2, histologic grade, and Ki67): luminal A, luminal B, HER2 pure, and triple negative. Other variables considered in the analysis were patient age (<50, 50–69, and >69 years), tumor size (T1, T2, T3, and T4), histologic type (ductal, lobular, and mixed carcinoma), grade (1, 2, and 3), lymphovascular invasion, tumor stage (0, I, IIA, IIB, IIIA, IIIB, and IIIC), number of tumors (unifocal, multifocal, or multicentric), screening program, axillary tumor burden (0, 1, 2, 3, and >3 positive lymph nodes), surgery (radical or conservative),

Table 2
Survival, and overall and specific mortality by year of follow-up among patients with invasive carcinoma (n=1963).

No. of years of follow-up	Total no. of patients	Overall mortality			Specific mortality			Specific survival, %
		No. of women	Annual, %	Accumulated, %	No. of women	Annual, %	Accumulated, %	
1	1905	23	1.2	1.2	15	0.8	0.8	99.2
2	1882	43	2.3	3.5	29	1.5	2.3	97.7
3	1839	40	2.2	5.7	24	1.3	3.6	96.4
4	1799	46	2.6	8.2	35	1.9	5.5	94.5
5	1753	23	1.3	9.5	14	0.8	6.3	93.7
6	1730	28	1.6	11.1	21	1.2	7.5	92.5
7	1702	15	0.9	12.0	8	0.5	8.0	92.0
8	1687	12	0.7	12.7	7	0.4	8.4	91.6
9	1675	22	1.3	14.0	8	0.5	8.9	91.1
10	1653	18	1.1	15.1	11	0.7	9.6	90.4
11	1635	6	0.4	15.5	3	0.2	9.8	90.2
12	1629	7	0.4	15.9	1	0.1	9.9	90.1
13	1622	8	0.5	16.4	5	0.3	10.2	89.9
14	1614	7	0.4	16.8	4	0.2	10.4	89.6
≥15	1607	11	0.7	17.5	6	0.4	10.8	89.2

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