Male Breast Cancer

A Reappraisal of Clinical and Biologic Indicators of Prognosis

Saudade André, Isabel Fonseca, António E. Pinto, Paula Cardoso, Teresa Pereira and Jorge Soares

From the Departamento de Patologia Morfológica, Instituto Português de Oncologia de Francisco Gentil, Centro de Lisboa, Portugal

Correspondence to: Saudade André, MD, Departamento de Patologia Morfológica, Instituto Português de Oncologia de Francisco Gentil, 1099-023 Lisboa, Portugal. Tel: +351 21 7200 475. Fax: +351 21 722 8925.

Acta Oncologica Vol. 40, No. 4, pp. 472–478, 2001

Between 1970 and 1998, 90 cases of male breast cancer with available pathological material were retrieved. The disease often presented in aged patients (median—66 years) and as advanced stage (stage III/IV—51%). Excluding stage IV disease, the neoplasia were predominantly ductal invasive carcinomas, NOS (not otherwise specified) (92%), grade 1 and grade 2 (94%), positive for estrogen and progesterone receptors (72% and 74%), negative for androgen receptors (100%), p53 negative (95%), c-erbB-2 negative (88%) and DNA aneuploid (73%). Assessment of disease outcome is determined by stage at time of diagnosis, and axillary lymph node status was the only parameter found to have a statistically significant correlation with either disease-free interval or overall survival ($p < 0.001$) by multivariate analysis. Clinically useful information on the probability of relapse can be added by determining c-erbB-2 ($p = 0.02$) and progesterone receptors ($p = 0.04$) in stage III and tumor ploidy ($p = 0.04$) in pN1 subgroups of patients.

Received 28 September 2000
Accepted 23 January 2001

Male breast cancer is a rare disease that predominantly occurs in older men, and in some studies it has been associated with an unfavorable outcome (1, 2). In South Portugal (3), the annual incidence of male breast cancer is 1.1/100000 population, which is similar to data reported for other countries (1, 2). The American Joint Committee on Cancer (AJCC) disease stage (4) and its components, namely the status of axillary lymph nodes, are the most important predictors of disease outcome (2, 5, 6). Male breast cancer is classically described as having a poorer prognosis than female breast carcinoma, but recent studies comparing disease outcome in men and women, stratified according to stage and age, found remarkable similarities (6–10). All histological types have been reported in men, but infiltrating lobular carcinoma is extremely rare (8). Estrogen receptors are more prevalent in male breast cancer than in female breast carcinoma and their presence seems to have therapeutic and prognostic implications (1, 2, 9). The predictive value of biologic markers, namely the clinical value of p53 and c-erbB-2 gene products and nuclear DNA ploidy, has been extensively investigated in female breast cancer (1), but their role in the management of male breast cancer remains undetermined (11, 12).

The purpose of this study of 90 male breast cancer was to describe the clinical, morphologic and biological features and to report the influence on disease outcome of patients' age, tumor dimensions, axillary lymph node status, pathological stage, histological type, grade of differentiation, estrogen and progesterone receptors, p53, c-erbB-2 and DNA ploidy.

MATERIAL AND METHODS

Clinical data

The Instituto Português de Oncologia, Lisboa, serves the population of Southern Portugal. Between 1989 and 1999, a mean of 633 cases, per year, of female breast cancer and 7 cases (1.1%) of male breast cancer were diagnosed. Ninety cases of invasive male breast cancer with available pathological material were retrieved from the files of the Instituto Português de Oncologia, Lisboa, spanning a 29-year period (1970–1998). Data concerning age, family history of breast cancer, clinical characteristics, modalities of treatment and information on disease-free interval (DFS) and overall survival (OS) were obtained from a review of the clinical charts. DFS was defined as the interval between surgical resection and the first local or distant recurrence. Duration of follow-up was calculated as the time elapsed between primary surgery and the last clinical observation, or death.

 ISSN 0284-186X

Pathologic characteristics

Original tumor samples were formalin-fixed and paraffin-embedded. Paraffin blocks were re-cut, stained with hematoxylin and eosin and evaluated by two pathologists (S.A. & J.S.).

Pathological stage and its components (pT and pN) as well as the histopathological type were evaluated according to AJCC definitions (4). Tumor dimensions were obtained from a review of the original pathological reports and axillary lymph node status re-evaluated by new hematoxylin- and eosin-stained sections.

Tumor differentiation was assessed in all cases (with the exception of those treated with neoadjuvant therapy) using the Nottingham grading system (13).

Immunohistochemistry

A representative tissue block of every case was selected for the immunohistochemical study. Two independent observers (S.A. & P.C. or S.A. & T.P.) assessed the immunostaining analysis, scored the slides and discussed discrepant results. The percentage of positive tumor cells was estimated semiquantitatively. The results were recorded as a percentage of positively stained target cells. The threshold considered for positivity was 10% (nuclear staining for hormone receptors and p53 and membrane staining for c-erbB-2) (14, 15).

Hormone receptors. Estrogen, progesterone and androgen receptors (NCL-ER-6F11, NCL-PGR and NCL-AR-2F12 antibodies, respectively; Novocastra Laboratories, Newcastle, UK) were determined by immunocytochemical analysis using the streptavidin-biotin complex peroxidase technique. Pretreatment procedures included endogenous peroxidase blocking with H_2O_2 and antigen retrieval using a pressure cooker with citrate buffer, pH 6.0. The sections were rinsed in TBS, pH7.4–7.6, incubated for 30 min at room temperature with the respective primary monoclonal antibodies at dilution 1 : 10, washed in TBS and incubated with biotinylated rabbit anti-mouse (E413, Dako, Glostrup, Denmark) at 1 : 250 for 30 min. The sections were rinsed again in TBS and StreptABC complex (K377, Dako) at dilution 1 : 100 was applied for 30 min. After washing in TBS, diaminobenzidine was used as chromogen for 8 min. The sections were then washed in distilled water and counterstained with Mayer's hematoxylin. Androgen receptors were negative in all cases in two assessments. Only a few cases showed positive epidermal cells overlying the tumor. A group of 10 female breast carcinomas known to be positive for androgen receptors was used as the control.

p53 and c-erbB-2. Immunoexpression of p53 protein and c-erbB-2 was evaluated in the whole series, using the streptavidin-biotin method previously described, with a polyclonal antiserum (CM1 Novocastra Laboratories, Newcastle, UK and A0485, Dako, Denmark, respectively). CM1 was diluted at 1/2500, after pretreatment of the sections in a microwave oven (15 min at 500 W).

Image and flow cytometry

Nuclear DNA ploidy was assessed by image cytometry (50 cases) and by flow cytometry (47 cases), 29 cases being evaluated concurrently using both methods. For image analysis, 4–5 μm sections from paraffin-embedded material were collected on coated slides and stained according to Feulgen's method (16). Evaluation was performed using an Acas Ahrens System (Germany) and 2 c standard was established in each case using intralesional lymphocytes. A mean of 100 tumor nuclei were assessed in each case and histograms were classified as diploid when more than 90% of the cells had a DNA content between 1.8 c and 2.2 c The remaining cells were classified as aneuploid. Flow cytometric analysis was performed on paraffin-embedded material according to the method of Hedley et al. with slight modifications (17), on an Epics Profile II flow cytometer (Coulter Electronics, Hialeah, FL, USA) equipped with a 488 nm, 15 mW argon-ion laser as light source and a 575 nm band-pass filter for red fluorescence detection. Cell cycle analysis of flow DNA histograms was performed using the Multicycle software program (Phoenix Flow Systems, San Diego, CA, USA), developed by Peter S. Rabinovitch (University of Washington, Seattle), and based upon the mathematical method described by Dean & Jett (18).

Statistical analysis

Patients with stage IV disease were not included in the statistical analysis for the prognostic factors, which was done in the remaining 82 patients. The correlation between pN and the variables age, ploidy and grade of differentiation was assessed using Fisher's exact test. Overall survival (OS) and DFS rates were estimated by the Kaplan–Meier method (19) and a log-rank test (20) was used for comparing the survival curves. Patients who died from causes other than their neoplasms were considered as censored observation for overall survival. The variable duration of follow-up of the cases induced us to consider a maximum 9-years' follow-up period for both DFS and OS. We assessed the prognostic value of the following characteristics: patients' age (≤ 45 vs. 46–64 vs. ≥ 65 years), tumor dimensions (pT1 vs. pT2 vs. pT4), axillary lymph node status (pN0 vs. pN1), pathological stage (stage I vs. stage II vs. stage III), histological type (ductal invasive, NOS (not otherwise specified) vs. other types), grade of differentiation (G1 vs. G2 vs. G3), estrogen (ER) and progesterone (PR) receptors (negative vs. positive), p53 (negative vs. positive), c-erbB-2 (negative vs. positive) and DNA ploidy (diploid vs. aneuploid). We searched for the association between pN and categorical age, grade of differentiation and DNA ploidy. The very different neoadjuvant and

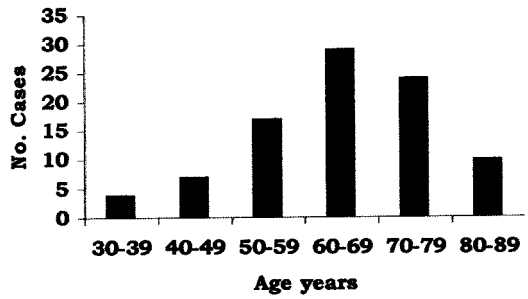

Fig. 1. Age distribution of the 90 patients.

adjuvant therapeutic modalities adopted during this 29-year period did not allow for a study of their relative importance in the survival of the patients. In the subgroups of patients with (pN1) and without (pN0) axillary lymph node metastasis, we studied the prognostic value of pT, histological grade, ploidy, ER, PR, p53 and c-erbB-2 status. In the subgroups of patients with stage II and stage III disease, we evaluated the usefulness of histological grade, ploidy, ER, PR, p53 and c-erbB-2 status. The scarcity of stage I patients and their excellent survival rates did not allow statistical analysis for prognostic factors in this subset.

To determine the relative predictive strength of the prognostic variables, Cox's proportional hazard regression model was used (21). The statistical significance was evaluated using the Wald test, and results were displayed through the relative risk and respective 95% confidence interval for each category. Probability (p) values less than 0.05 were considered statistically significant.

RESULTS

Clinical data

Age, occurrence of non-breast carcinomas and family history. Patients' ages ranged from 38 to 87 years (average 64.5 ± 11.9; median 66), the majority (92%) being aged over 45 years (see Fig. 1). Two tumors recurred in the group of seven patients younger than 45 years but no significant difference was found between the three groups of patients (≤ 45 vs. 46–64 vs. ≥ 65 years) for overall survival ($p = 0.359$). Five (7%) out of 70 patients for whom the family history was recorded had relatives with breast cancer (2 in a first-degree relative—one with an affected sister and one with an affected brother—and 3 in a second-degree relative). One of the patients with a history of breast cancer in a second-degree female relative also developed colon adenocarcinoma 6 years after breast cancer. The data of the patients with a family history are summarized in Table 1.

Treatment. The majority of the patients (75–83%) underwent either radical or modified radical mastectomy as the primary treatment. Tumorectomy or simple mastectomy with the addition of radiotherapy and/or chemotherapy was used in advanced-stage patients, with palliative intent.

Thirteen patients received neoadjuvant treatment (radiotherapy—9 patients; chemotherapy—3 patients; hormone therapy (tamoxifen)—1 patient) and adjuvant therapy was used in 58 patients (radiotherapy—56 patients; hormone therapy—29 patients; chemotherapy—16 patients).

Follow-up

The estimated 5-year DFS and OS rates of all 90 patients were 61% and 69%, respectively. The eight patients with clinical evidence of distant metastases at time of presentation (stage IV) died of disease after a short interval (average 18 months; range 6 to 36).

Follow-up periods of the 82 patients out of stage IV ranged from 12 months to 26 years after surgery (median 132 months). Thirty-six patients (44%) died of disease and 14 (17%) died of other causes within the follow-up period. Local recurrences and/or distant metastases (lung, liver and bone) were reported in 41 patients (50%). The actuarial 5- and 9-year DSF rates were 56% and 49%, respectively, while the actuarial 5- and 9-year OS rates were 72% and 53%, respectively.

Pathological parameters

Pathological stage. More than half of the 90 patients (51%) presented with stage III and stage IV disease. The

Table 1

Characteristics of the patients with a family history[1]

Patient	Age	Stage	H. type	Dif.	RE/RP	Ploidy	P53	c-erb B2	Therapy	Survival
1.	56	2	D. NOS	2	P/N	A	N	N	C+R	d–72 mos
2.	87	4	D. NOS	2	P/N	A	N	N	H	d–24 mos
3.[2]	69	2	D. NOS	2	P/P	D	N	N	C+R+H	a–132 mos
4.	73	2	APO.	2	P/N	D/A[3]	N	P	R	d–60 mos
5.	73	3	D. NOS	2	P/P	A	N	N	R	d′–72 mos

[1]Abbreviations: A = aneuploid; D = diploid; NOS = not otherwise specified; C = chemotherapy; R = radiotherapy; H = hormone therapy.
[2]The patient also developed colon carcinoma.
[3]D/A Image and flow cytometry gave discrepant data; d—dead of disease; a—alive; d′—dead owing to other causes.

Table 2

Data of the tumors correlated with 9-year disease-free survival (DFS) and overall survival (OS)—82 patients (univariate analyses)

Characteristics	DFS (p-value)	OS (p-value)
PT	0.001	<0.001
PN	<0.001	<0.001
Stage	<0.001	<0.001
Histological type	0.819	0.456
Grade	0.509	0.171
ER status	0.653	0.473
PR status	0.814	0.821
p53 status	0.078	0.648
C-erbB-2 status	0.966	0.620
Ploidy	0.345	0.438

distribution per pathological stage of the 82 patients out of clinical stage IV was: stage I—18 cases (22%); stage II—26 cases (32%) and stage III—38 cases (46%). The 9-year survival rates for stages I, II and III were 93%, 59% and 28%, respectively. We found the correlation between disease stage and both DFS and OS ($p < 0.001$) to be statistically significant (Table 2).

Tumor dimensions. Nearly half of the 82 patients (46%) had pT4 tumors, most of them with skin ulceration; 29% had pT1 tumors and 24% had pT2 tumors. The size of the male mammary gland explains the absence of pT3 tumors. Correlation of pathologic tumor size with DFS and with OS was statistically significant in univariate analyses ($p < 0.001$) (Table 2).

Axillary lymph node metastasis. Metastasis of the axillary lymph nodes was found in 39 (55%) of the 71 patients who underwent axillary lymph node dissection. No significant association was found between pN and categorical age ($p = 0.672$), grade of differentiation ($p = 0.862$) and DNA ploidy ($p = 0.745$). The presence of axillary node metastasis was statistically significantly associated with both DFS and OS ($p < 0.001$) in univariate analyses (Table 2). In a multivariate analysis, nodal stage was the only parameter of independent prognostic significance in relation to DFS or OS (pN1—relative risk 7.51 (2.53–22.66); $p < 0.001$).

Histological type. The 82 tumors included 75 (92%) ductal invasive carcinomas, NOS, 2 mucinous carcinomas, 2 apocrine carcinomas, 3 ductal invasive carcinomas with predominant intraductal component and 3 papillary invasive carcinomas. Ductal invasive carcinomas, NOS, did not show any significant differences from all the other subtypes in relation to DFS ($p = 0.819$) and OS ($p = 0.456$) (Table 2).

Histological grade. Excluding the neoplasms with preoperative treatment ($n = 12$), 31 tumors (44%) were classified as grade 1 (G1), 35 (50%) as grade 2 (G2) and the remaining 4 (6%) as grade 3 (G3). The association between histological grade and prognosis did not reach statistical significance with either DFS ($p = 0.509$) or OS ($p = 0.171$) (Table 2).

Hormone receptors

All tumors were negative for androgen receptors. In the group of 59 patients (72%) with positive estrogen receptors, 50% were free of disease and 55% were alive at the 9-year follow-up ($p = 0.653$ and $p = 0.473$, respectively) (Table 2).

In the group of 61 patients (74%) with neoplasms that exhibited positive progesterone receptors, 50% were free of disease and 58% were alive at the 9-year follow-up ($p = 0.814$ and $p = 0.821$, respectively) (Table 2).

Molecular prognostic factors

p53 positivity was found in 4 cases (5%), two patients being alive and without disease, and c-erbB-2 positivity in 10 cases (12%). The correlation between these molecular prognostic factors and DFS and OS was not statistically significant (p53: $p = 0.078$ and $p = 0.648$; c-erbB-2: $p = 0.966$ and $p = 0.620$, respectively) (Table 2).

DNA ploidy

Sixty-six cases were evaluated by flow cytometry and/or by image cytometry. Four cases (6%) of the 29 tumors determined by the two methods gave divergent data. Irrespective of the DNA ploidy evaluation method, and excluding the cases with discrepant results, 48 tumors were aneuploid (73%) and 14 were diploid (27%). The correlation of ploidy with DFS ($p = 0.345$) and OS ($p = 0.438$) was not statistically significant (Table 2).

Prognostic factors in subgroups of patients

pN0 and pN1. In the subgroups of patients with pN0 and pN1 tumors, the parameters pT, histological grade, ER, PR, p53 and c-erbB-2 status did not significantly predict recurrence or overall survival. However, in the subgroup of pN1 cases, the ploidy had a significant correlation with disease-free interval ($p = 0.043$) (Table 3).

Pathological stages II and III. In the subgroups of patients with stages II and III disease, histological grade, ER and p53 status did not significantly predict recurrence or overall survival. Yet, in stage III patients, the positivity of progesterone receptors and of c-erbB-2 seemed to influence prognosis of the disease, particularly the disease-free interval (PR status: $p = 0.041$; c-erbB-2 status: $p = 0.015$) (Table 3).

DISCUSSION

The incidence of male breast cancer in Southern Portugal does not differ significantly from that reported in most countries (1, 2). Male breast carcinoma exhibits epidemiological characteristics of a sporadic disease, with no increase in the incidence or mortality over the past decades (1, 5).

Several studies, including ours, confirmed that men develop breast carcinoma at an older age (1, 2, 5, 12). Mejias

Table 3

Subgroups of pN0, pN1, stage II (EII) and stage III (EIII) tumors—correlation with 9-year disease-free survival (DFS) and overall survival (OS)

Characteristics	DFS (p-value)				*OS (p-value)*			
	pN0	pN1	EII	EIII	pN0	pN1	EII	EIII
PT	0.463	0.427	–	–	0.081	0.431	–	–
Grade	0.787	0.199	0.214	0.296	0.484	0.205	0.572	0.205
ER status	0.327	0.660	0.998	0.685	0.688	0.572	0.367	0.572
PR status	0.438	0.769	0.288	0.041	0.784	0.438	0.059	0.438
P53 status	–	0.919	0.596	0.217	–	0.380	0.934	0.380
C-erbB-2 status	0.994	0.681	0.619	0.015	0.528	0.382	0.097	0.382
Ploidy	0.318	0.043	0.143	0.253	0.367	0.063	0.318	0.063

(22) found that features associated with a poor prognosis were more prevalent in young men (< 45 years). In our study, age was not correlated with overall survival.

Hereditary breast cancer was recognized among male patients and a positive family history was elicited in percentages varying from 5.5% to 27% (1, 9, 23, 24). The presence of a family history seems not to affect the disease outcome (23). We found a relatively low incidence of cases (7.1%) with a history of breast cancer in first- and second-degree relatives, one case being that of an affected brother.

The heterogeneity of therapeutic modalities reported in male breast cancer, as well as in our patients, has implications for selecting optimal treatment and more data from multi-institutional studies are needed to establish a wide consensus on the subject (2, 8, 9).

The assumption that breast cancer affecting men has a poorer outcome than in women is controversial and is not supported by the estimated 5-year and 9-year DFS and OS found in our series. The reported poorer prognosis could be related to the older age of men at the time of diagnosis, a more advanced stage of disease at presentation and higher mortality owing to other causes (6, 7, 9, 22). Guinee et al. (6) studied a series of 335 patients and found that 47% of the 178 deaths were due to causes other than tumor progression, but in our study, this was observed only in 14 out of the 90 cases (15.5%).

In our series, TNM stage of disease has, once more, demonstrated its value in that the prognosis of male breast cancer was significantly more favorable for cases treated at an early stage. Still, our data confirmed that male breast carcinoma is frequently presented at the advanced stage of disease (51% of the patients presented with stage III and stage IV disease). Joshi et al. (12) suggested that tumor growth immediately beneath the nipple skin is responsible for dermal lymphatic spread, early regional dissemination and consequent advanced stage. In support of this view, we found, in a previous study of 44 consecutive male breast carcinomas (25), that skin ulceration and peritumoral lymphatic permeation were present in 27% and 64% of the tumors, respectively, the latter parameter being related to survival.

Salvadori et al. (26), in their study of 170 consecutive male breast cancers using multiple regression analysis, showed that tumor size was a statistically significant prognostic factor. Nevertheless, Stierer et al. (27) (169 cases), similar to us, reported that pT had prognostic significance but only in univariate analyses.

Axillary lymph node involvement was found in a similar proportion of cases compared to that reported in other studies (9, 12), and its independent prognostic value in relation to DFS and OS confirms that axillary status constitutes the most valuable prognostic factor in males as well as in females (1, 2, 5–8, 26).

Invasive ductal carcinomas of no special type (NOS) constitute the majority of male breast cancers, but all the histological types, including lobular carcinoma, were described and reported to occur in less than 15% of cases (1, 2, 8, 12). Papillary carcinoma, constituting 3.4% in our series, has been reported to be more common among men than women (28).

Regarding histological grade, some studies showed a slight predominance of poorly differentiated (G3) versus well-differentiated (G1) tumors (12, 28, 29). In our study, half of the cases were moderately differentiated (G2) and we found a greater predominance of G1 versus G3 tumors. The 5-year survival rate was similar in G1 and G3 tumors and, although divergent at 9-years, did not reach a statistically significant level, which is in accordance with most of the previous studies (12, 28, 29).

It is commonly referred to that the positivity of estrogen and progesterone receptors is higher in male than in female breast carcinoma (1, 7, 9). By using immunocytochemical methods, our data confirmed these findings. Donegan et al. (30), in their study of 217 cases of male breast carcinoma, verified that tumor hormone receptors are associated with a favorable outcome. In our study, ER and PR status did not show an impact on disease prognosis, but PR positivity was associated with favorable behavior in the subgroup of stage III patients.

Pich et al. (31) described androgen receptor immunostaining with a weak intensity in 34% of male breast carcinomas. In our study, using the same clone as a source of antibody, we did not find a single case with androgen

receptor positivity. In the study by Dash et al. (32), a different monoclonal antibody was used and older archival material showed lower immunoreactivity than recent samples, leading those authors to suggest their exclusion in retrospective studies. All positive controls used in this study had less than one month of archival time, which reinforces that antibody sensitivity is archival time dependent.

There is limited information, discrepant data and conflicting results regarding the predictive influence of p53 and c-erbB-2 in male breast cancer (1, 2, 11, 12, 14). Most authors did not find these markers to be of prognostic value in male breast cancer. However, in the series of 38 patients that, in our study, constituted the stage III subgroup, c-erbB-2 positivity was a strong predictor of relapse, and we suggest its clinical utility.

Few studies (11, 14, 28, 29, 33) have approached the subject of the prognostic significance of DNA ploidy in male breast cancer. Nuclear DNA aneuploidy, ranging from 27.3% to 78% in the reported series, was high in our study (72.2%). The combined use of image cytometry and flow cytometry increased our sensitivity to detect DNA aneuploidy, especially by discriminating diploid vs. tetraploid cases, a condition in which flow cytometric interpretation of histograms is known to be difficult. Only Pich et al. (14) (26 cases) found a statistically significant association between ploidy and survival in male breast cancer. In our subgroup of pN1 patients (39 cases), ploidy showed a statistically significant correlation with disease relapse ($p = 0.043$) and a trend toward correlation with disease survival ($p = 0.063$).

In conclusion, the present study corroborates that most male breast cancers present with advanced stage disease, occur in old patients, are aneuploid, have a histological low-grade, high estrogen/progesterone receptor content, and p53 and c-erbB-2 negativity. Our results also confirm that the prognosis relies on disease stage, nodal status being the most reliable marker for the outcome assessment. Useful clinical information can be added by determining c-erbB-2 and PR in stage III and tumor ploidy in pN1 subgroups of patients.

ACKNOWLEDGEMENTS

The project was supported in part by a grant from the Comissão de Fomento de Investigação em Cuidados de Saúde—Ministério da Saúde (projecto 3/97).

REFERENCES

1. Tavassoli FA. Pathology of the breast, 2nd ed. Connecticut: Appleton & Lange, 1999: 837.
2. Ravendi-Kashani F, Hayes TG. Male breast cancer: a review of the literature. Eur J Cancer 1998; 9: 1341–7.
3. Incidência e Mortalidade no Registo Oncológico Regional Sul, Lisboa, 1997: 7.
4. American Joint Committee on Cancer. In: Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds. Manual for staging of cancer. 5th ed. Philadelphia: JB Lippincott, 1997.
5. Gateley CA. Male breast disease. The Breast 1998; 7: 121–7.
6. Guinee VF, Olsson H, Moller T, et al. The prognosis of breast cancer in males. A report of 335 cases. Cancer 1993; 71: 154–61.
7. Vetto J, Jun SY, Padduch D, Eppich H, Shih R. Stages at presentation, prognostic factors, and outcome of breast cancer in males. Am J Surg 1999; 177: 379–83.
8. Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma. A review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. Cancer 1999; 85: 629–39.
9. Cutuli B, Lacroze M, Dilhuydy JM, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995; 31A: 1960–4.
10. Willsher PC, Leach IH, Ellis IO, et al. A comparison outcome of male breast cancer with female breast cancer. Am J Surg 1997; 173: 185–8.
11. Clark JL, Nguyen PL, Jaszcz WB, Jatoi A, Niehans GA. Prognostic variables in male breast cancer. Am Surgeon 2000; 66: 502–11.
12. Joshi GM, Lee AKC, Loda M, et al. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. Cancer 1996; 77: 490–8.
13. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19: 403–10.
14. Pich A, Margaria E, Chiusa L, Ponti R, Geuna M. DNA ploidy and p53 expression correlate with survival and cell proliferative activity in male breast carcinoma. Hum Pathol 1996; 27: 676–82.
15. Colleoni M, Orvieto E, Nolé F, et al. Prediction of response to primary chemotherapy for operable breast cancer. Eur J Cancer 1999; 35: 574–9.
16. Auer G, Askensten U, Ahrens A. Cytophotometry. Hum Pathol 1989; 20: 518–27.
17. Hedley DW, Clark GM, Cornelisse CJ, et al. Consensus review of the clinical utility of DNA cytometry in carcinoma of the breast. Cytometry 1993; 14: 482–5.
18. Dean PN, Jett JH. Mathematical analysis of DNA distributions derived from flow microfluorometry. J Cell Biol 1974; 60: 523–7.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.
20. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chem Rep 1966; 50: 163–70.
21. Cox DR. Regression models and life tables. J R Stat Soc B 1972; 34: 187–220.
22. Mejias A, Sittler S, Mies C. Poor prognosis features are prevalent in young men with breast carcinoma. Mod Pathol 1994; 7: 18A.
23. Hill A, Yagmur Y, Tran KN, et al. Localized male breast carcinoma and family history—an analysis of 142 patients. Cancer 1999; 86: 821–5.
24. Gough DB, Donohue JH, Evans MM, et al. A 50-year experience of male breast cancer: is outcome changing? Surg Oncol 1993; 2: 325–33.
25. Cunha F, André S, Soares J. Morphology of male breast carcinoma in the evaluation of prognosis. Path Res Pract 1990; 186: 745–50.
26. Salvadori B, Saccozzi R, Manzari A, et al. Prognosis of breast cancer in males: an analysis of 170 cases. Eur J Cancer 1994; 39A: 930–5.

27. Stierer M, Rosen H, Weitensfelder W, et al. Male breast cancer: Australian experience. Word J Surg 1995; 19: 687–92.
28. Jonasson JG, Agnarsson BA, Thorlacius S, Eyfjord JE, Tulinius H. Male breast cancer in Iceland. Int J Cancer 1996; 65: 446–9.
29. Gattuso P, Reddy V B, Green L, et al. Prognostic significance of DNA ploidy in male breast carcinoma. Cancer 1992; 70: 777–80.
30. Donegan WL, Redlich PN. Breast cancer in men. Surg Clin North Am 1996; 76: 343–63.
31. Pich A, Margaria E, Chiusa L, Candelaresi G, Dal Canton O. Androgen receptor expression in male carcinoma: lack of clinicopathological association. Br J Cancer 1999; 75: 959–64.
32. Dash RC, Ballo MS, Layfield LJ. Decay of androgen receptor immunoreactivity in archived tissue by using monoclonal antibody F39.4.1. Appl Immunohistochem 1998; 6: 145–9.
33. Hatschek T, Wingren S, Carstensen J, Hultborn R. DNA content and S-phase fraction in male breast carcinomas. Acta Oncol 1994; 33: 609–13.