

Carcinoma *in situ* and early breast carcinoma

Survey of the Portuguese Senology Society on treatment in Portugal and its evolution between 1985 and 2000

C.F. de Oliveira¹, Ph.D.; V. Rodrigues², Ph.D.; H. Gervásio³, M.D.;
J. Moura Pereira³, M.D.; J. Albano³, M.D.; N. Amaral¹, M.D.

¹Department of Gynecology, Hospital da Universidade de Coimbra;

²Department of Epidemiology, Faculdade de Medicina da Universidade de Coimbra

³Centro Regional de Oncologia de Coimbra, Instituto Português de Oncologia, Coimbra (Portugal)

Summary

By means of a questionnaire sent to Portuguese hospitals which diagnose and treat most female patients with breast cancer, it was intended to assess the situation regarding the treatment of carcinoma *in situ* and early breast cancer (T1 or T2, N0 or N1), as well as their evolution between 1985 and 2000.

The hospital participation rate was 65% and a sample of 865 patients was collected, distributed by the years 1985, 1990, 1995 and 2000.

It was observed that, in terms of surgery, there was an increase in conservative surgery, which was over 40% in 2000, as well as an increase in the average of excised axillary lymph nodes. Progress in the surgical approach was similar both in cancer centres and in large and university hospitals, when compared with the other surveyed hospitals. Also, no differences between these two hospital groups in disease-free survival and overall survival were found.

Postoperative radiotherapy was employed in more than 90% of the patients submitted to conservative surgery and adjuvant chemotherapy was used in 39% of all the patients, while tamoxifen as adjuvant treatment was used in 58% of the patients.

Key words: Breast cancer; Early breast cancer; Treatment; Carcinoma "*in situ*"; Survey; Portugal.

Introduction

The age-standardised incidence rate in Portugal in 1995 was 70.4 new cases per 100,000 women [1], which provided an annual diagnosis of more than 3,500 new cases of breast cancer per year.

On the other hand, the mortality caused by breast cancer in 1995 was 24.9 in Portugal and 30.5 per 100,000 women in the European Union [1].

Until the early 90s in Portugal, both diagnosis and treatment of breast cancer were concentrated in the three centres of the Portuguese Cancer Institute and in another additional five or six large and/or university hospitals in Lisbon, Oporto and Coimbra. With the appearance of new medical teams interested in senology, the current number of institutions diagnosing and treating this pathology has significantly increased.

The Portuguese Senology Society was created in 1989. Since then it has become responsible for disseminating guidelines on the diagnosis and treatment of breast cancer. Initially, this was achieved through scientific meetings, and later by organizing national consensus meetings on breast cancer. The first consensus meeting took place in September 1993, followed by three other meetings every three years. The last meeting was in May 2002. The conclusions of the consensus meetings may be found in the Internet page of the Society (www.spsenologia.pt).

In order to assess the situation in Portugal, as was done in other countries [2], a commission appointed by the Portuguese Senology Society developed a questionnaire on the diagnosis and treatment of breast cancer from 1985 to 2000, which was sent to the majority of the Portuguese hospitals with breast units. The results for the treatment are presented here.

Aims

To assess which treatments were employed and what their evolution was in the period between 1985 and 2000 in Portuguese hospitals with a major participation in the diagnosis and treatment of breast cancer. Further, to evaluate overall survival and disease-free survival, as well as to ascertain if there are any differences between the groups of hospitals in this study.

The assessment was conducted by means of a questionnaire, under the responsibility of the Portuguese Senology Society. This questionnaire was designed by an expert commission and sent to a group of doctors in charge of the diagnosis and treatment of breast cancer in 26 Portuguese hospitals and cancer centres.

Material and Methods

An extensive questionnaire on the various treatment methods used in patients with breast cancer treated in 23 Portuguese Hospitals (5 university hospitals and 18 non-university hospitals) and in the three Regional Cancer Centres was developed.

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In each institution, it was requested that a physician be identified to be in charge of collecting and filling in the questionnaire, and the following inclusion criteria were defined:

(a) Female patients with carcinoma *in situ* of the breast or with invasive carcinoma clinically classified as T1N0M0, T1N1M0, T2N0M0 and T2N1M0.

(b) The patient must have been subject to surgical treatment (modified radical mastectomy or conservative surgery).

(c) Sequential inclusion of the patients treated as of January 1 of the years 1985, 1990, 1995 and 2000.

(d) Inclusion of 20 patients per each of the periods mentioned in the previous section (maximum of 80 patients per institution).

(e) The institution had to choose at least two periods (minimum of 40 patients), with the exception of hospitals in the autonomous regions of Azores and Madeira.

(f) Assessment of the patients' condition on December 31, 2000 or at the time of death or loss of control.

Data were filled in during the last three months of 2001, and in 2002 a computer database was developed. The data were validated and statistically analysed through the SPSS programme.

Of the 26 institutions invited to participate in the assessment, 17 answered (65%), including four of the five university hospitals (80%), two of the three cancer centres (67%) and 11 of the remaining 18 hospitals (61%).

Eight hundred and sixty-five patients were included, of which 61 were from 1985 (7.1%), 134 from 1990 (15.5%), 335 from 1995 (38.7%) and 335 from 2000 (38.7%).

The distribution of patients in the institutions showed that three institutions provided data on all four studied periods (1985, 1990, 1995 and 2000), four other institutions provided data on three periods (1990, 1995 and 2000) and the remaining ten institutions provided data on two periods (1995 and 2000). It should be noted that the institutions which provided data on three or four periods (1985, 1990, 1995 and 2000) were those with a larger tradition and experience in diagnosing and treating breast cancer, and which we named "Group A", whereas the institutions which only provided data on two periods (1995 and 2000) were referred to as "Group B".

Average patient age was 57.8 ± 12.9 years, varying between 22 and 91 years. Regarding hormonal status, 31% were premenopausal and 69% were postmenopausal. Variations across the studied periods were not significant.

Clinically, the patients were classified according to the TNM classification, as shown in Table 1. Of these, 6.8% were carcinomas *in situ*, 19% were invasive carcinomas not more than 1 cm, 22.5% were invasive carcinomas more than 1 but not more than 2 cm and 44.5% were invasive carcinomas more than 2 cm. Regarding the axilla, 72.9% had negative axilla (N0) and 23.7% positive axilla (N1).

Table 1. — Clinical classification according to TNM classification.

TNM	865 patients n (%)
Without T information	20 (2.5)
Tis	59 (6.8)
T1a	56 (6.5)
T1b	108 (12.5)
T1c	195 (22.5)
T2	394 (45.5)
Tx	33 (3.8)
Without N information	29 (3.4)
N0	631 (72.9)
N1	205 (23.7)

Results

Surgical treatment

Figure 1 shows the distribution of several forms of surgical treatment. It was found that conservative surgery (tumourectomy or quadrantectomy) was performed in 26.1% of the patients and modified radical mastectomy (MRM) in 70%.

Axillary dissection was not performed in 5.1% of the patients, corresponding to the majority of the carcinomas *in situ* and in 2.3% of the patients the information regarding this surgical procedure was unsatisfactory.

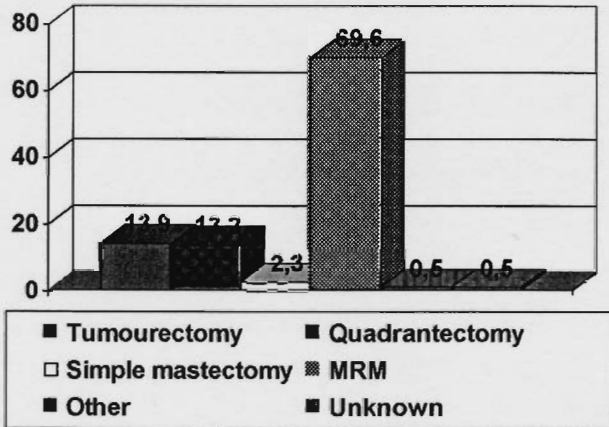


Figure 1. — Modalities of surgical treatment.

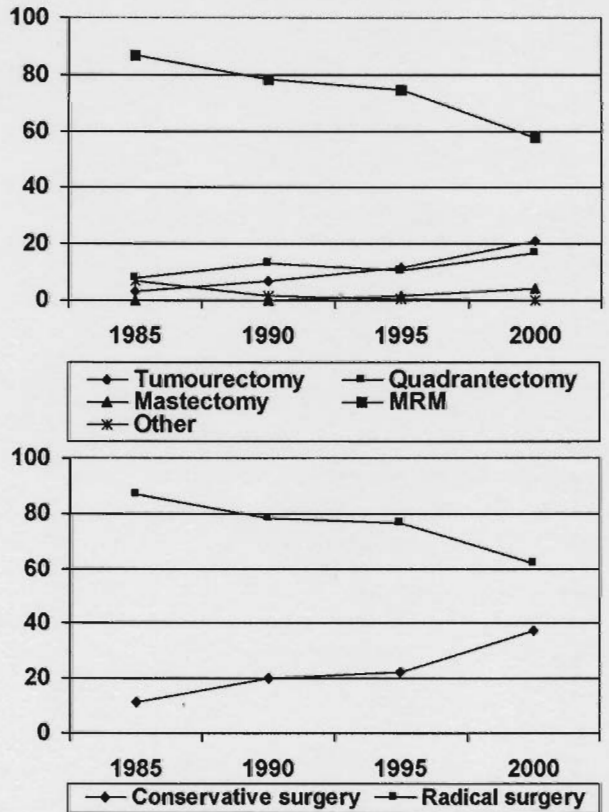


Figure 2. — Percentage evolution of the surgery type in the period between 1985 and 2000.

Figure 2 shows the percentage of evolution of the kind of surgery performed in the period between 1985 and 2000. It is worth highlighting that in 1985 tumorectomies corresponded to 3.3% and in 2000 to 21.2% of the surgeries. In the same period, quadrantectomies rose from 8.2% to 16.7% and modified radical mastectomy decreased from 86.9% in 1985, to 57.9% in 2000. In 2000, when comparing conservative surgery with radical surgery, these values were 37.6% and 62.1%, respectively. If carcinomas *in situ* are not taken into account, conservative surgery in invasive carcinoma increased from 22.4% in 1995 to 37.6% in 2000.

Figure 3 shows the evolution in conservative surgery between 1995 and 2000, according to the type of hospital. The behaviour of the two hospital groups is different in the period between 1995 and 2000: the hospitals with a larger tradition and experience in diagnosing and treating breast cancer (Group A) had an increase in conservative surgery from 30.4% to 41.9%, whereas in the other hospitals (Group B) these percentages increased from 16.4% to 35.5%.

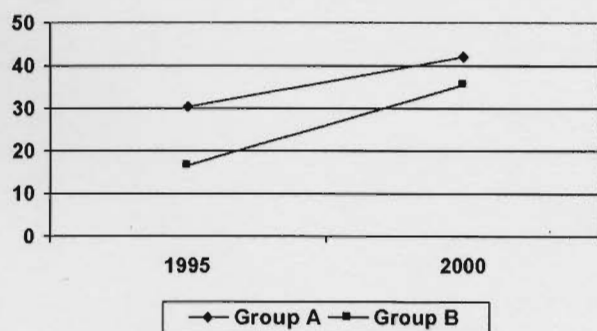


Figure 3. — Percentage evolution of conservative surgery between 1995 and 2000 according to the type of hospital.

The impact of reconstructive plastic surgery after mastectomy, immediate or delayed, varied between 2% and 16%, and was more frequent after 1995: 2% in 1985, 6% in 1990, 16% in 1995 and 10% in 2000.

Pathology

Regarding the 59 carcinomas *in situ*, it was found that 54 (91.5%) were ductal carcinomas *in situ* (DCIS) and five (8.5%) were lobular carcinomas *in situ* (LCIS).

Eighty-seven percent of the invasive carcinomas were ductal, 5.1% were lobular, 6.3% were other kinds and 1.3% were not characterized.

Axillary dissection in invasive carcinomas was frequently surveyed and Figure 4 shows the time evolution, in average of excised lymph nodes and in unsatisfactory dissection (less than 10 identified lymph nodes). The average number of excised lymph nodes increased from 9.3 in 1985 to 14.9 in 2000. On the other hand, the percentage of axillary dissection with less than ten lymph nodes decreased from 65% in 1985 to 21% in 2000.

Figure 5 shows the evolution in the average number of excised lymph nodes in the two hospitals groups. No difference is observed in the period between 1995 and 2000.

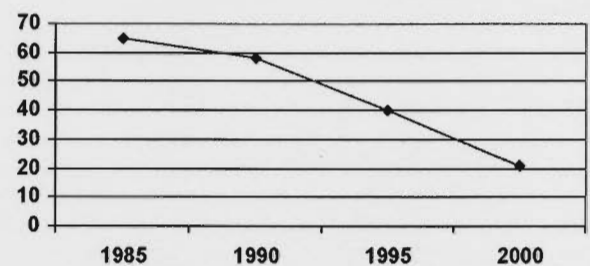
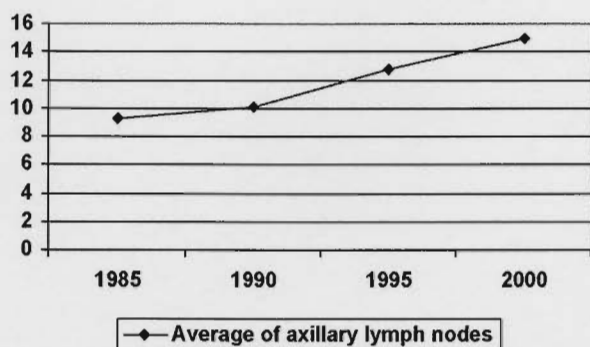


Figure 4. — Time evolution between 1985 and 2000 of the average number of excised lymph nodes and the percentage of axillary dissection with less than 10 lymph nodes.

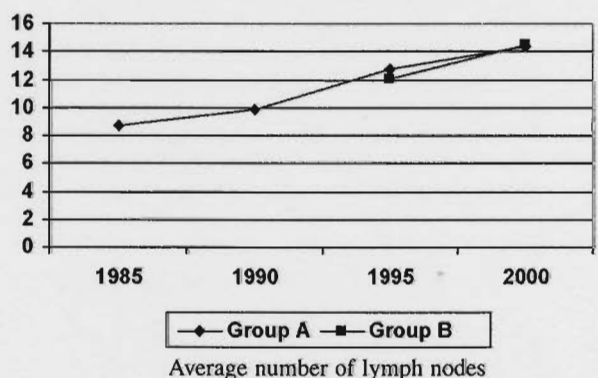
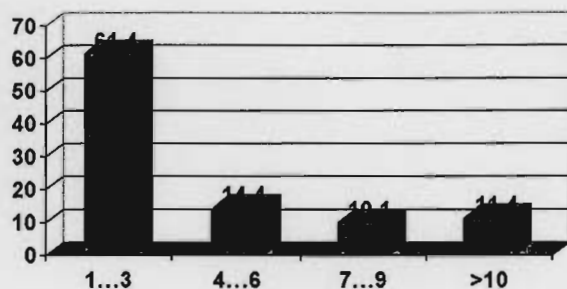


Figure 5. — Evolution of the average number of excised lymph nodes according to the type of hospital.

In invasive carcinomas, axillary lymph nodes were invaded (pN+) in 39.7% of the patients and the axilla was negative (pN0) in 60.3%.

Figure 6 shows the distribution percentage of lymph node invasion in situations of invasive carcinoma with the pN+ axilla; 61.4% of the patients with pN+ had one to three invaded lymph nodes, whereas 35.9% had at least four invaded lymph nodes and 11.4% had at least ten invaded lymph nodes.

Table 2 shows the size of axillary metastasis in the 320 patients with positive axillas (pN+). There is no information on 18.4% of the patients, lymph node metastasis less



■ Percentage of the number of invaded lymph nodes

Figure 6. — Percent distribution of the number of invaded lymph nodes in pN+ invasive carcinomas.

Table 2. — Size of axillary lymph node metastasis.

	No. of patients	Percentage
Without information	59	18.4
Micrometastasis < 2 mm	30	9.4
Metastasis with 2-20 mm in 1-3 N+	117	36.6
Metastasis with 2-20 mm in > 4 N+	77	24.1
Metastasis < 20 mm with capsular involvement	18	5.6
Metastasis > 20 mm	19	5.9

than 2 mm in 9.4% and lymph node metastasis more than 2 mm but not more than 20 mm in one to three lymph nodes in 36.6%.

Regarding invasive cancer, Table 3 points out the size of the tumour reported by the pathologist (pT). In 18% of the cases, the pathologist did not provide any information regarding the size of the tumour, or that pT1 (< 2 cm) tumours accounted for 47.5% or that, despite the fact that tumours clinically larger than 5 cm (T3) had been excluded from the survey, the histopathological study identified 0.9% patients with pT3 (> 5 cm) tumours.

Table 3. — Tumour size in invasive carcinomas.

	No. of patients	Percentage
Without information	145	18.0
Tumour not more than 5 mm	26	3.2
Tumour more than 6 but not more than 10 mm	91	11.3
Tumour more than 11 but not more than 20 mm	266	33.0
Tumour more than 21 but not more than 30 mm	186	23.1
Tumour more than 31 but not more than 50 mm	85	10.5
Tumour more 50 mm	7	0.9

The histological grade was not reported in 256 cases (31.8%). Of the 550 cases where it was reported, 23.7% were well-differentiated tumours (G1), 55.8% moderately differentiated (G2) and 20.9% were poorly differentiated (G3).

In the period between 1995 and 2000, 573 patients with invasive carcinoma were treated. In this group, oestrogen receptors (ER) were unknown in 117 patients (20.4%). Of the 456 patients with known ER, 343 (75.2%) had positive ER (ER+) and 113 (24.8%) had negative ER (ER-). Progesterone receptors (PR) were unknown in 157 patients (27.4%). Of the 416 patients with known PR, 263 (63.2%) had positive PR (PR+) and 153 (36.8%) had negative PR (PR-).

In 2000, in a group of 141 patients (45% of the total for that period), C-erb2 expression was determined, being negative in 46.1%, positive with one "+" in 27.7%, positive with two "++" in 12.7% and positive with three "+++" in 13.5%.

Radiotherapy

Post-surgery radiotherapy was performed in 28 of the 59 patients with carcinoma *in situ*, corresponding to 47.5%, and in 402 out of 806 with invasive carcinoma, i.e., 49.9%. In tumourectomies, post-surgery treatment by radiation was carried out in 91% of the patients, after quadrantectomy in 93% and after modified radical mastectomy in 33% of the patients.

Chemotherapy

Concerning chemotherapy, 315 patients (39%) underwent treatment with cytostatic drugs. Of these, 27 (9%) were submitted to neo-adjuvant chemotherapy, 256 (81%) to adjuvant chemotherapy and 32 (10%) to both neo-adjuvant and adjuvant chemotherapy.

The patients submitted to neo-adjuvant chemotherapy were premenopausal and showed tumours clinically classified as T2 N1 M0. Those who had adjuvant treatment showed axillary invasion and/or other high-risk factors for prognosis.

The regimes of cytostatics employed included 33% without antracyclins, 60% with antracyclins and 7% with taxanes.

Hormonal treatment

Tamoxifen was employed as an adjuvant in 58% of the patients and prophylactic castration was carried out in 11% of the patients (surgical castration in 3.4% and chemical castration with LHRH analogues in 7.6%).

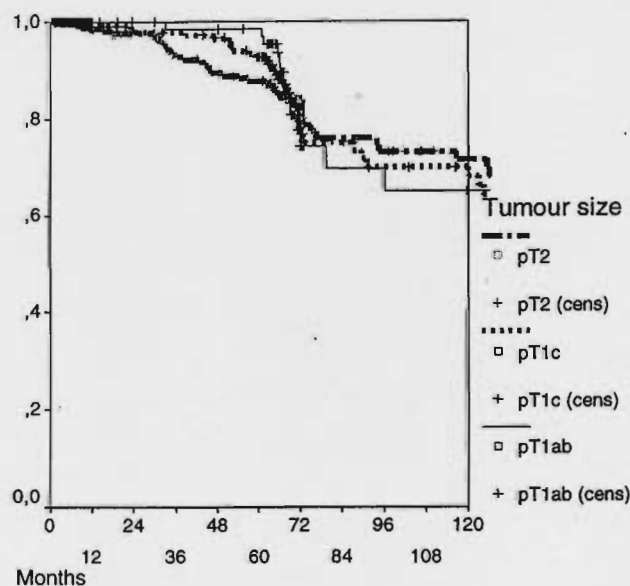


Figure 7. — Invasive carcinoma of the breast – disease-free survival according to tumour size (pT). pT1ab versus pT1c versus pT2: $p = 0.66$.

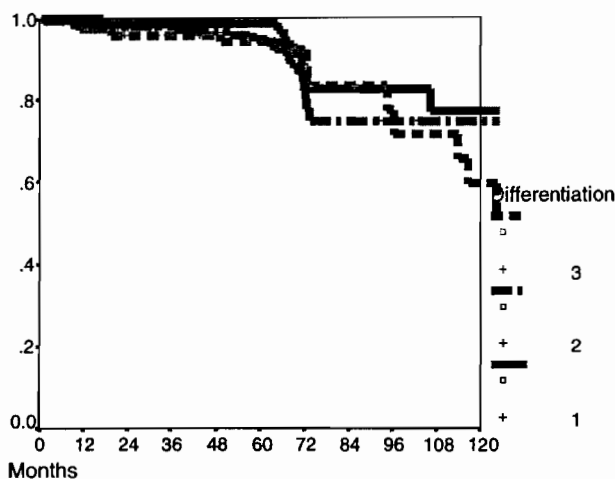


Figure 12. — Invasive carcinoma of the breast: Overall survival according to differentiation grade: $p < 0.72$.

(iv) According to hormonal receptor status

Figures 13 and 14 show the disease-free and overall survival of the patients with invasive carcinoma according to oestrogen receptors (ER).

Independently of the ER being positive or negative, there was no significant difference in the disease-free survival and in the overall survival at ten years.

(v) According to type of hospital

Figures 15 and 16 show the disease-free survival and overall survival of the patients with invasive carcinoma according to the type of hospital.

It can be observed that both in the more differentiated hospitals in Group A, and in the less differentiated hospitals in Group B, disease-free survival and global survival at five years were identical.

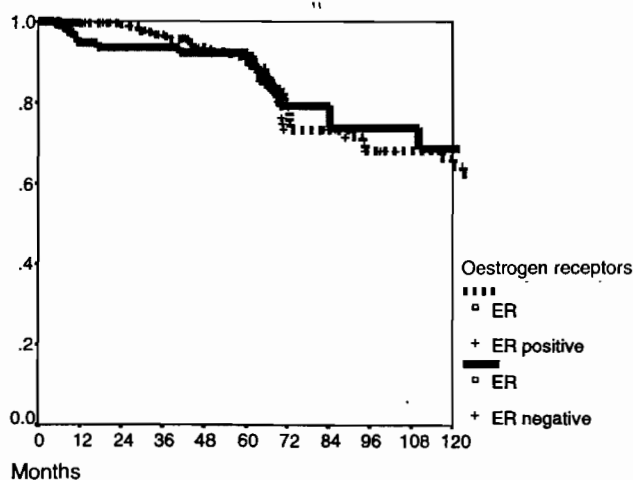


Figure 13. — Invasive carcinoma of the breast – disease-free survival according to oestrogen receptors. ER+ versus ER- : $p < 0.74$.

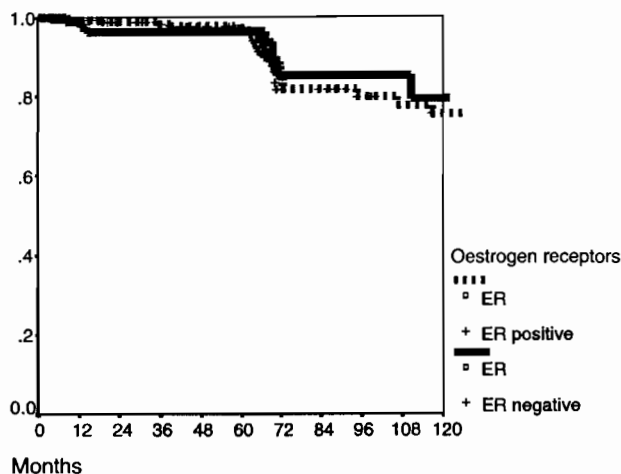


Figure 14. — Invasive carcinoma of the breast: Global survival according to oestrogen receptors. ER+ versus ER-: $p < 0.61$.

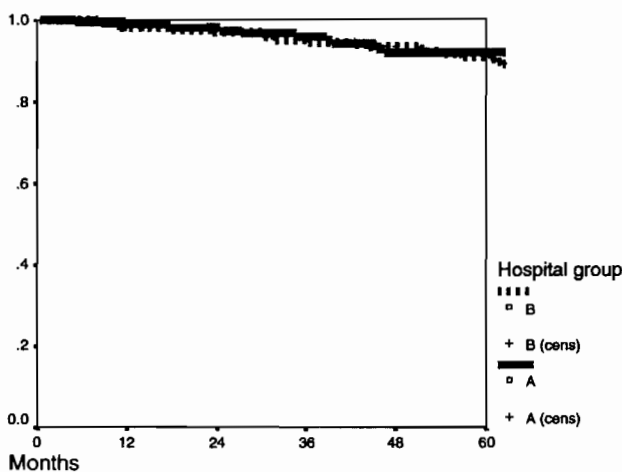


Figure 15. — Invasive carcinoma of the breast: Disease-free survival according to type of hospital: Hospitals in Group A versus Group B: $p < 0.19$.

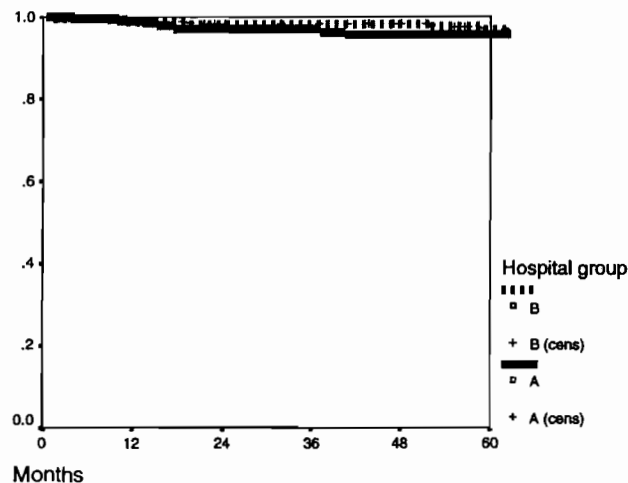


Figure 16. — Invasive carcinoma of the breast: Global survival according to type of hospital. Hospitals in Group A versus Group B: $p < 0.15$.

Disease-free survival and overall survival

(i) According to tumour size

Figures 7 and 8 show the disease-free and overall survival of the patients with invasive carcinoma according to tumour size (pT).

It was found that there are no significant differences during a 10-year follow-up when comparing pT1a,b tumour versus pT1c or pT2.

(ii) According to lymph node status

Figures 9 and 10 show the disease-free and overall survival of the patients with invasive carcinoma according to the condition of the lymph nodes (pN).

In terms of disease-free survival at ten years, there is a significant difference ($p < 0.0001$) between the patients with axillary lymph node invasion (pN+) and without

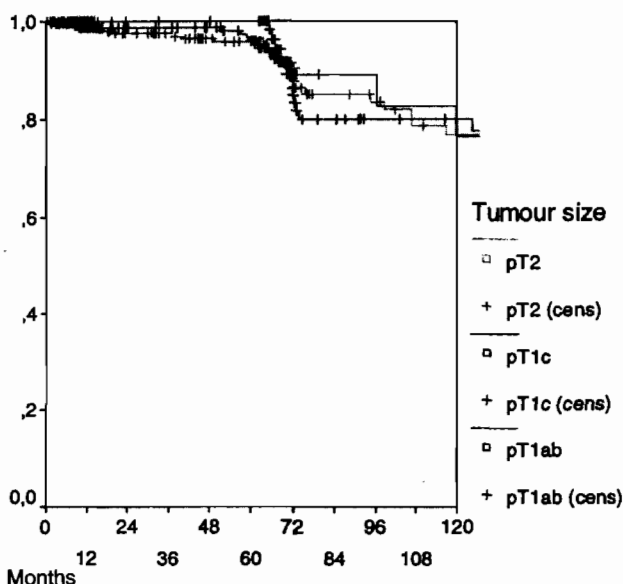


Figure 8. — Invasive carcinoma of the breast – overall survival according to tumour size (pT). pT1ab versus pT1c versus pT2: $p = 0.64$.

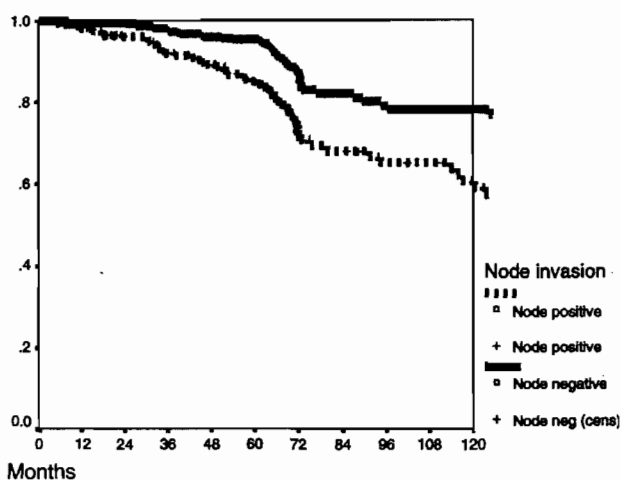


Figure 9. — Invasive carcinoma of the breast – disease-free survival according to lymph node status (pN). Positive lymph nodes versus negative lymph nodes: $p < 0.0001$.

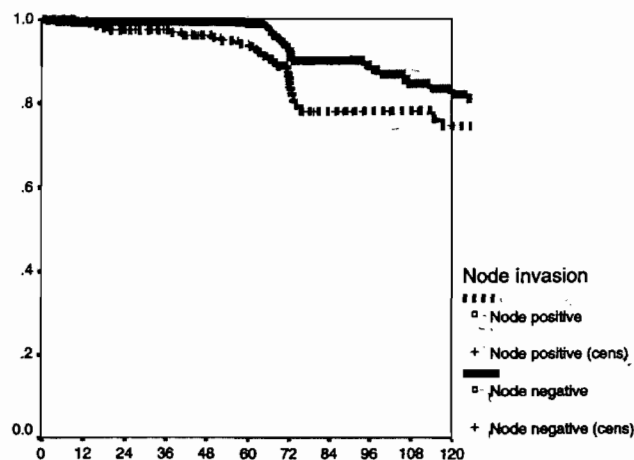


Figure 10. — Invasive carcinoma of the breast – overall survival according to lymph node status (pN). Positive lymph nodes versus negative lymph nodes: $p < 0.08$.

axillary lymph node invasion (pN-). However, the difference in the overall survival at ten years is not statistically significant between groups, but the overall survival is higher in pN- patients.

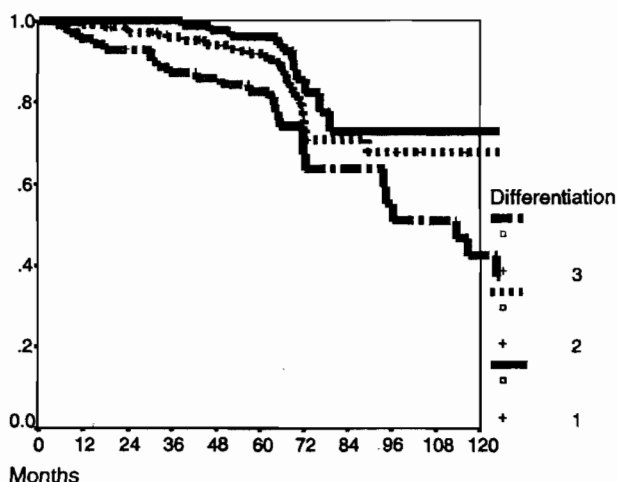


Figure 11. — Invasive carcinoma of the breast – disease-free survival according to differentiation grade: $p < 0.01$.

(iii) According to differentiation grade

Figures 11 and 12 show the disease-free and overall survival of the patients with invasive carcinoma according to differentiation grade (G).

In terms of disease-free survival at ten years, there is a significant difference ($p < 0.01$) between patients with G1 and G3 tumours, with those with better-differentiated tumours (G1) having a better prognosis. Again, no significant difference in the overall survival at ten years was found according to differentiation grade.

Discussion and Conclusions

This assessment, by means of a questionnaire only, was an attempt to collect data on cases with tumours not more than 5 cm in diameter diagnosed and treated in the surveyed hospitals. It should be highlighted that in 1985 most breast cancers were treated in the three IPOFG Cancer Centres and in six or seven large and/or university hospitals in Lisbon, Oporto and Coimbra. In 2000, the number of hospitals that started diagnosing and treating breast cancer tripled. The Portuguese Senology Society identified 26 hospitals which reported having Breast Units.

The conduction of a questionnaire to assess the treatment of *in situ* and early breast carcinoma (T1 and T2, N0 or N1) aimed at evaluating the situation in the 26 Breast Units identified in Portugal, comparing these units and assessing the evolution in the period comprised between 1985 and 2000.

The assessment was conducted using previously defined inclusion criteria by means of an extensive questionnaire. Seventeen hospitals answered the questionnaire (65%). The group of non-participants only comprised one of the three cancer centres and one of the five university hospitals. The remaining seven non-responding hospitals are institutions comprising breast units with very limited experience.

In this study, 865 patients were assessed, of which 6.8% had carcinomas *in situ*, 19% invasive carcinomas not more than 1 cm, 22.5% invasive carcinomas more than 1 but not more than 2 cm and 45.5% invasive carcinomas more than 2 cm but not more than 5 cm.

Assessment of the surgical treatment allowed us to observe that, in general, conservative surgery was performed in 26.1% of the patients and that in 2000 this value was already 37.6%. Conservative surgery was more frequent in more differentiated hospitals (Group A; 41.9%) than in less differentiated hospitals (Group B), although these report 35.5%.

The "1991 National Survey" conducted in the USA, which considered only carcinomas *in situ* and Stage I and II tumours, found that of 32,569 patients conservative surgery was performed in 18.9% of the cases in the years 1983 and 1990 [2]. In Portugal in 1985, conservative surgery was reported in 11.5% of the cases. This value increased to 20.1% in 1990.

The impact of breast reconstruction varied between 2% and 16% during the periods considered in this survey. In the USA in 1990, reconstructions were carried out in 7.2% of the patients submitted to surgery (all stages included) [2], whereas in Portugal in the same period and only in 0, I and II stages, they were performed in 6%.

Adding the percentages for conservative surgery and breast reconstruction in 2000, the value rises to 47.6%, which we considered satisfactory when taking into account the diversity of the assessed hospitals, which have different technical conditions and, sometimes, difficult accessibility to radiotherapy.

Axillary dissection in invasive carcinomas was evaluated in an attempt to control the quality of the performed

surgery. In 1995 the average number of excised lymph nodes was slightly higher in the more differentiated hospitals (Group A) than in the less differentiated ones (Group B) with 12.8 and 12.1, respectively. In 2000 this average was identical: 14.4 and 14.5. On the other hand, in 2000 the percentage of axillary dissection with less than 10 lymph nodes was 21% in both hospital groups. This percentage is considered high, and it may justify some of the results we found for disease-free and overall survival.

Still regarding the axilla pathological status, we underline that 39.7% were positive (in clinical assessment only 23.7% were considered N1), and within this group of invasion of axillary lymph nodes, 11.4% had ten or more invaded lymph nodes.

Concerning the pathology, 34.5% of the tumours were more than 2 cm, 20.9% poorly differentiated (G3) and 24.8% with ER- (the ER status was unknown in 20.4% of the patients).

In terms of adjuvant therapies to surgery, post-surgical radiotherapy was employed in 49.9% of the patients with invasive carcinoma. Of the patients submitted to conservative surgery by tumourectomy and quadrantectomy, respectively, 91% and 93% were submitted to radiotherapy. In the assessment conducted in the USA, radiotherapy following conservative surgery varied between 62% (without previous axillary dissection) and 68.8% (with previous axillary dissection) [2].

Regarding adjuvant systemic therapy, cytotoxic chemotherapy was employed in 39% of the patients and hormonal treatment with tamoxifen in 58%. In 1990, the American survey reported 46.6% for both adjuvant chemotherapy and tamoxifen [2].

In the surveyed Portuguese hospitals, prophylactic castration was carried out in 11% of the patients, two thirds of which with LHRH analogues.

The disease-free survival and the overall survival at ten years were assessed according to tumour size, axillary lymph node status, differentiation grade, hormonal receptors and the type of hospital where the surgery was performed. Significant differences in disease-free survival were found only when comparing tumours with axillary lymph node invasion *versus* without invasion and in poorly differentiated tumours (G3) *versus* well-differentiated (G1). The heterogeneity of the material, the non-review of the pathologies and the multiplicity of the participants may justify the fact that other important prognostic factors, such as tumour size and oestrogen receptor positivity, did not allow us to demonstrate significant differences in survival and disease-free interval. Importantly, we did not find any significant difference in survival when comparing more and less differentiated hospitals, which is in line with the surgical approach to these tumours, which was similar.

The most important conclusion we may draw from this survey is that the participating hospitals show a similar behaviour in approaching breast cancer, demonstrating identical results. Furthermore, there was considerable progress during the considered periods between 1985 and

2000, which was more evident between 1995 and 2000. It is worth highlighting that this happened after the National Consensus Meetings on Breast Cancer, promoted by the Portuguese Senology Society since 1993.

Portuguese Senology Society Collaborators

Invited Consultants: V. Veloso M.D., E. Passos Angelo M.D., C. Lopes Ph.D., H. Pereira M.D., E. Vaz Pereira M.D., J. Leal Faria M.D., C. Abrantes M.D..

Participants: A. Torres Ph.D.; A. Botte M.D.; A. Fráguas M.D.; A. Lagoa M.D.; A. Mendes Araújo M.D.; A. Ramos Jerónimo M.D.; E. Granjo M.D.; F. Jesus Fernandes M.D.; F. Campos M.D.; I. Monteiro Grillo Ph.D.; J. Pires Teixeira M.D.; L. Mestre M.D.; M. Figueiredo Dias Ph.D.; M. Chumbo M.D.; O. Campos M.D.; R. Nabicho M.D.; R. San-Bento M.D..

Data managers: A. P. Parreira; M. Dardenne.

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Address reprint requests to:
C.F. DE OLIVEIRA, Ph.D.
Servico De Ginecologia
Hospitais de Universidade
de Coimbra
Apartado 9015 Huc Praceta
Mota Pinto
Coimbra Codex 3001-301 (Portugal)