CLINICO-PATHOLOGIC ANALYSIS OF 221 CASES OF BREAST CARCINOMA

FRANCISCO SOUSA LÉ, ABÍLIO BRANDÃO, MANUEL A. SOBRINHO-SIMÕES, ARTUR GIESTEIRA DE ALMEIDA.

Serviços de Cirurgia e Anatomia Patológica da Faculdade de Medicina e do Hospital S. João. Porto. Portugal.

SUMMARY

The clinical and pathologic data of the 221 patients with breast carcinoma primarily treated in the Serviço de Cirurgia 3 of Hospital S. João from 1960 to 1979 were reviewed. The 5, 10 and 15-year survival rates of the 215 patients with follow-up information were 63.4 %, 48.2 % and 20.2 %, respectively. Pathologic staging of the axilla was found to be the most important prognostic factor. Tumor size, histologic classification and histologic grading also provided valuable prognostic information and in women without lymph node metastases contributed to define a *high-risk subpopulation*. Postmenopausal women and women less than 35-year-old had in general a more advanced neoplastic disease and a worse outcome than the other women. The survival of patients undergoing modified radical mastectomy was similar to that of patients submitted to Halsted radical mastectomy thus reinforcing the assumption that modified radical mastectomy is a satisfactory alternative to the *standard* radical procedure.

RESUMO

Estudo clínico-Patológico de 221 casos de carcinoma da mama.

Foram revistos os achados clínicos e patológicos relativos a 221 doentes com carcinoma da mama, tratados no Serviço de Cirurgia 3 do Hospital de S. João, de 1960 a 1979. As taxas de sobrevida aos 5, 10 e 15 anos das 215 doentes com *follow-up* foram respectivamente de 63,4 %, 48,2 % e 20,2 %. O estadio patológico dos gânglios axilares revelou-se como o factor prognóstico mais importante. O tamanho do tumor, a classificação histológica e o grau histológico também trouxeram informações importantes para o prognóstico e, nas mulheres sem metástases ganglionares, contribuiram para definir uma subpopulação de alto risco. As doentes no período pós-menopausa e as com menos de 35 anos de idade tinham, em geral, na altura do diagnóstico, uma doença neoplásica mais avançada e vieram a sofrer evolução pior do que as restantes. A sobrevida das doentes submetidas a mastectomia radical modificada foi semelhante à das doentes submetidas à mastectomia radical de Halsted, reforçando a ideia que a mastectomia radical modificada é uma alternativa satisfatória ao procedimento radical *standard*.

INTRODUCTION

The therapeutic approach to mammary carcinoma has been in a state of flux since several authors began challenging Halsted radical mastectomy alone or in combination with radiotherapy as *the* standard procedure.[1]

This has led to multiple clinico-pathological studies which have added an impressive quantity of information but failed to define an undisputable alternative to radical mastectomy.[1, 2] The aforementioned controversy is due, partly at least, to the heterogeneity of most of the series in what concerns both the clinical and the pathological parameters of the cases.[1]

It is also very difficult to compare series from centers specialized in mammary oncology with those from departments of general surgery.

We undertook the present review of all the cases primarily treated in our department from 1960 until 1979 in an attempt to find if some obvious shortcomings at the diagnostic and therapeutic levels had significantly interfered with the survival of the patients. We also intended to verify if it is possible to define, in such conditions, a few reliable parameters which can be used as major prognostic and therapeutic guides.

Received: January 26, 1984

MATERIAL AND METHODS

The hospital charts of the 221 patients with previously untreated, histologically confirmed breast carcinoma admitted to the Serviço de Cirurgia 3 of the Hospital S. João from 1960 to 1979 were reviewed. Two hundred and seventeen patients had unilateral breast cancer while 4 had proven bilateral disease.

Several types of treatment reflecting different clinical situations and different therapeutic policies were used throughout the study period (Tables 1 and 2). Almost all Halsted radical mastectomies were performed in the first years while most modified mastectomies were performed in the second half of the study period.

TABLE 1 **Distribution of patients according to types of treatment**

Treatment	N.° of patients
Surgery	67
Surgery + radiotherapy *	90
Surgery + chemotherapy	4
Surgery + radiotherapy * + chemotherapy	22
Surgery + radiother.* + chemother. + others **	38
Total	221

* Orthovoltage or cobalt source

** Bilateral oophorectomy (31 patients) or hypophysectomy (2 patients) or hormonal treatment (4 patients). One patient was submitted to a bilateral oophorectomy and, afterwards, to a hypophysectomy.

TABLE 2 **Distribution of patients according to types of surgical procedure**

Type of surgery	N.° of patients		Total
	Surgery alone	Surgery + Other therap.	
Radical mastectomy (Halsted)	25	48	73
Modified radical mastectomy (Patey, Madden)	39	92	131
Total (simple) mastectomy	2	1	3
Extended tylectomy	1	6	7
Tylectomy (excision)	—	7	7
Total	67	154	221

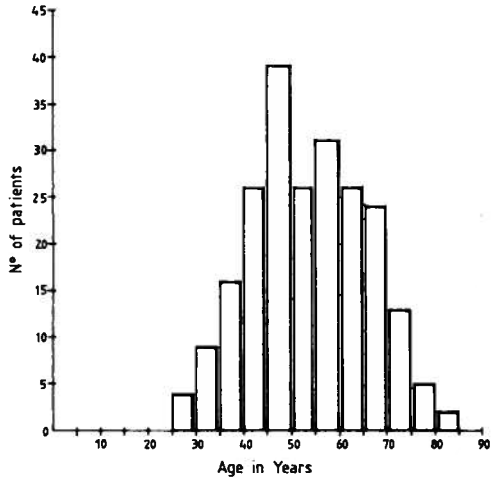

Figure 1: Distribution of 221 patients with breast carcinoma according to age.

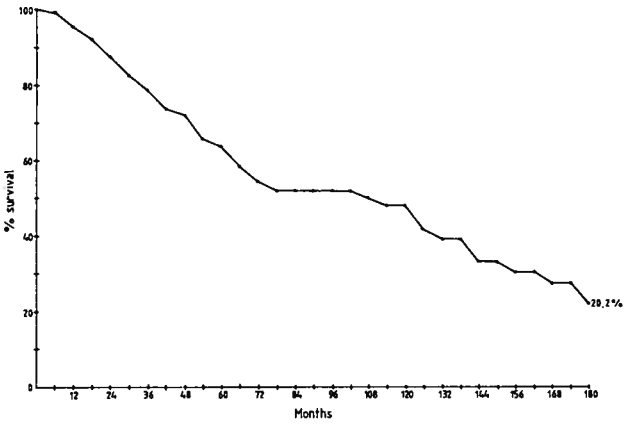

Figure 2: Overall survival curve of 215 patients.

Age of patients at the time of admission was always recorded. Menopausal status was also recorded at the time of admission in 188 women; they were considered as perimenopausal if the last period had occurred whithin the last year and as post-menopausal if the last period had occurred more than one year ago; perimenopausal women were grouped, for statistical purposes, with premenopausal women.[3]

Tumors were classified according to size, as measured in surgical specimens, into three groups: T_1, less than 2 cm (n=78); T_2 between 2 and 5 cm (n=138) and T_3, larger than 5 cm (n=5). Axillary lymph node involvement was pathologically evaluated in all but 16 patients; there were 80 patients without lymph node metastases and 125 with nodal metastases.

The microscopic slides from all cases were reviewed and the histologic classification, as well as the histologic grading of the tumors, were made according to the WHO classification [4] and Bloom and Richardson [5] by an experienced pathologist not aware of the clinical and follow-up data.

Estrogen receptor protein determinations were not made in any patient.

Current follow-up information was obtained in 215 patients (97.3 % of the total). Survival curves were calculated according to Berkson's actuarial method.[6] Results are expressed in percentage or in mean ± standard deviation. Chi-square method and Student's two sided *t* test were used to perform statistical analysis of the results. No statistical mehod was used to compare survival curves.

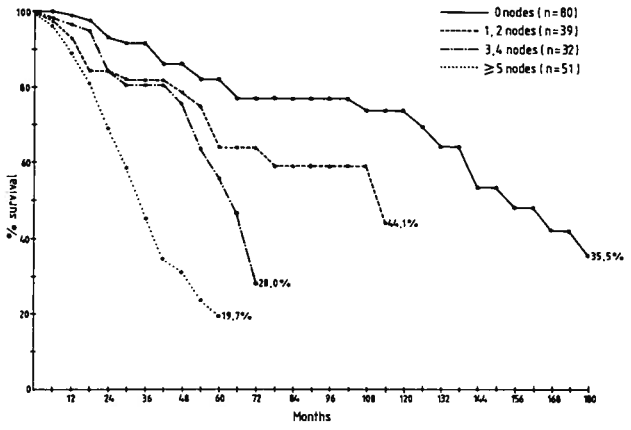

Figure 3: Survival curves of 205 patients according to the presence of lymph node metastases. Sixteen cases were excluded due to lack of information on regional lymph node involvement.

RESULTS

All patients were women with a mean age of 53.1 ± 12.2 years and a range from 25 to 84 years (Fig. 1).

The 5, 10 and 15-year survival rates of the 215 patients with follow-up data are 63.4 %, 48.2 % and 20.2 %, respectively (Fig. 2).

The survival curve of patients without lymph node metastases is much higher than that of patients with pathologically positive axillary nodes (Fig. 3). Within this last group of patients the 5-year survival rate decreases as the number of positive nodes increases (1 or 2 −63.8 %; 3 or 4 −55.9 %; 5 or more −19.8 %).

Patients with T_1 tumors have a better survival curve than patients with T_2 and T_3 tumors (Fig. 4).

The 5-year survival rate of patients with tumors histologically graded as I (93.3 %) is much better than those of patients with tumors which were graded as II (57.4 %) or III (54.9 %).

The analysis of the pathologic parameters of the 16 patients without lymph node metastases who died during the study period is summarized in Table 3 and demonstrates the prognostic importance of the size and histological grading of tumors (all patients had grade II or grade III carcinomas and those dying within eleven years had T_2 tumors). On the other hand, there are 4 women with No, T_2 or T_3, and grade II or grade III tumors who are alive more than six years after the diagnosis (Table 4).

Patients less than 35 years at the time of diagnosis have a worse survival curve than older patient (Fig. 5). Patients ranging from 35 to 55 years have a better survival curve than patients older than 55 years (Fig. 5). Women less than 35 years had a significantly ($p<0.05$) greater percentage of cases with lymph node metastases (90.9 %) than older patients (59.3 %). The percentages of tumors classified as T_1 and grade I were not significantly different is women less than 35 years (41.7 % and 0.0%, respectively) and in older patients (34.9 % and 10.9 %, respectively).

Women that were in postmenopausal status at the time of diagnosis have a worse survival curve than pre and peri-

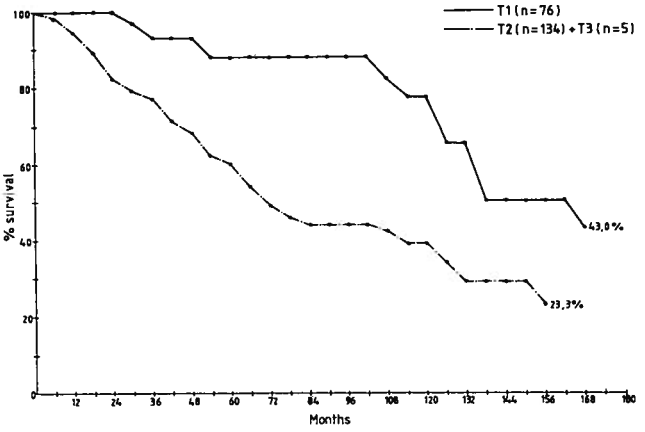

Figure 4: Survival curves of patients according to the size of tumors (T_1 vs T_2/T_3.

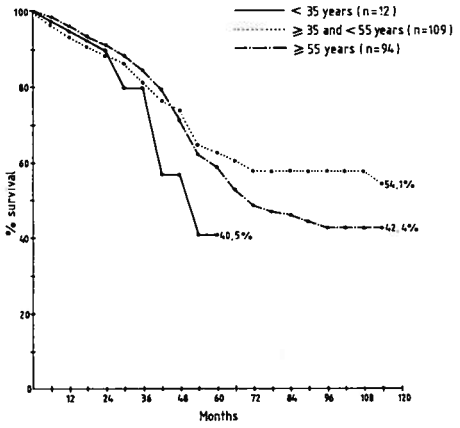

Figure 5: Survival curves of patients according to age at the time of diagnosis.

menopausal women (Fig. 6). Postmenopausal women had a greater, though not significantly, percentage of cases with positive axillary nodes (51.0 %) than pre and perimenopausal women (33.8 %). The percentages of tumors classified as T_2 or T_3 and grade II or III were also greater, though not significantly, in post-menopausal (68.6 % and 90.7 %, respectively) than in the other groups of women (50.1 % and 84.7 %, respectively).

TABLE 3 **Summary of the pathologic parameters of the 16 patients without lymph node metastases (No) who died during the study period**

Age	Survival (months)	Size	Grading Classification
43	10	T_2	II
56	16	T_2	II
48	19	T_2	III
46	22	T_2	II
46	38	T_2	III
62	39	T_2	II
31	41	T_2	II
67	61	T_2	II
68	62	T_2	II
53	126	T_2	II
45	131	T_2	II
46	142	T_1	II
60	142	T_1	II
56	164	T_1	II*
54	178	T_1	II
46	184	T_1	II*

* Ductal invasive carcinomas with predominant intraductal component. All the other tumors were ductal invasive carcinomas.

TABLE 4 **Summary of the pathologic parameters of the 11 patients with No, T_2or T_3, and Grade II or Grade III tumors who did not die during the study period**

Age	Survival (months)	Size	Grading Classification *
58	12	T_3	II
46	19	T_2	III
49	20	T_2	II
54	22	T_2	III
43	20	T_2	II
56	29	T_2	II
37	40	T_2	II
57	80	T_2	II
56	89	T_2	II
62	101	T_2	II
47	112	T_2	II

* All tumors were ductal invasive carcinomas.

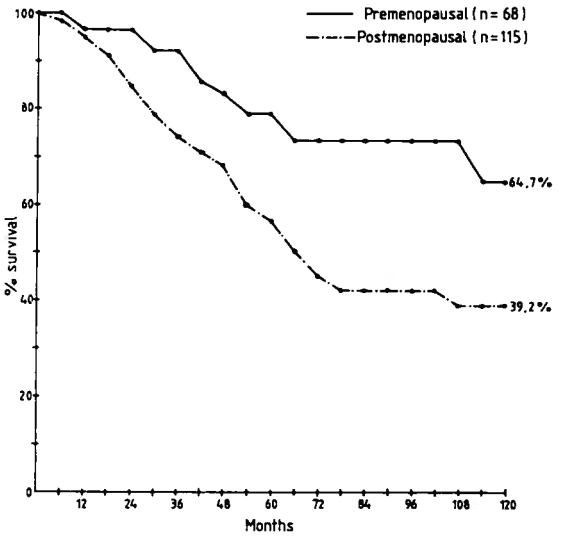

Figure 6: Survival curves of patients according to menopausal status at time of diagnosis. Under the description of premenopausal both pre and perimenopausal women were included.

The survival curve of patients treated by radical mastectomy (alone or in combination with radiotherapy) is similar to that of patients submitted to modified radical mastectomy (alone or in combination with radiotherapy) (Fig. 7). The mean age of women was similar in both groups (56.6 ± 9.8 and 55.7 ± 8.9 years, respectively) which also had similar percentages of cases free of lymph node metastases (48.1 and 50.0 %, respectively) and of T_1 tumors (37.9 % and 42.4 %, respectively).

The survival curve of patients submitted to modified radical mastectomy alone was much better than that of patients undergoing radical mastectomy as the sole type of treatment (Fig. 8). However, these two groups are not comparable, since patients submitted to modified radical mastectomy had a suggestively ($p < 0.1$) greater percentage of cases free of lymph node metastases (100.0 %), as well as a significantly ($p < 0.05$) greater percentage of grade I tumors (23.1 %) than patients treated by radical mastectomy (62.5 % and 4.0 %, respectively).

The survival curve of patients submitted to radical mastectomy as the sole type of treatment is worse than that of patients undergoing this procedure in combination with radiotherapy (Fig. 8) despite the fact that the first group of patients had a significantly ($p \simeq 0.05$) greater percentage of cases free of lymph node metastases (62.5 %) than the second group (36.7 %).

The 10 year-survival rate of patients undergoing radical or modified radical mastectomy as the sole type of treatment (76.6 %) is better than that of patients undergoing surgery plus radiotherapy (52.5 %). However, these two groups of patients are not comparable since patients undergoing surgery alone had a significantly ($p < 0.001$) less percentage of cases with lymph node metastases (15.0 %) than patients undergoing surgery plus radiotherapy (77.0 %).

Chemotherapy was used as the sole adjuvant therapy in 4 patients and in combination with several other therapeutic procedures, almost exclusively after recurrences and in terminal diseases, in 38 patients (Table 1).

Bilateral oophorectomy was the most frequently used endocrine therapy (Table 1). Hypophysectomy was performed in three patients with advanced, terminal disease (Table 5).

DISCUSSION

The overall survival of our patients is similar to that of patients included in the National Surgical Adjuvant Breast Project [7] and worse than most of those reported elsewhere.[2, 8, 9]

Although it is difficult to compare the results obtained in such heterogenous and necessarily different series we think that the poorer outcome of our patients depend mainly upon the high percentage of tumors (about 63 % in our series) which had already extended beyond the limits of the mammary gland at the time of surgery. This assumption is supported by the similarity of the ten-year survival rate of our patients (73.6 %) and of those of other series [7-9] when the comparison is limited to cases without lymph node metastases.

The worse overall survival in our series is also influenced by the worse outcome of patients with lymph node metastases in our series (10-year survival of 27.4 %) than in most of the others in which the 10-year survival rates vary from 24.9 % to 48.3 %.[7-10] This worse outcome probably depends, partly at least, upon the relatively high percentage of cases with 5 or more than 5 histologically *positive* nodes (about 40 % of our cases with nodal metastases) and therefore also reflects the larger extension of the neoplastic disease at the time of surgery.

We have confirmed the major prognostic significance of the pathologic staging of the axilla [9, 11-13] as well as the close relationship between survival and number of metastatic lymph nodes.[7, 10]

We have also confirmed the prognostic value of tumor size and histopathologic evaluation (grading + histologic classification) in patients without lymph node metastases.[14, 15] In fact, most of the women free of regional metastases at the time of surgery and with ductal invasive carcinomas larger than 2 cm and graded as II or III were dead within 10-years after treatment. This finding indicates that these parameters may be used together with skin infiltration [16] to define a so-called *high-risk subpopulation* of patients with no histologic evidence of nodal involvement. It seems that this subpopulation which fairly corresponds to those 25 to 35 per cent of patients with early or limited disease who die within 10 years after mastectomy in almost every series [2, 7] would benefit from an adjuvant therapy but the discussion of this hypothesis is far beyond the scope of the present study.

We have observed in accordance with Goldenberg and colleagues [17] and most other authors [2, 18, 19] that survival is low in women less than 35 years and also decreases from age 55 onward. The worse outcome of young patients was, however, found to be linked to a more advanced extension of the neoplastic disease and therefore, age of patients can not be considered by itself a statistically significant prognostic index like it had already been stressed in several series.[13, 14, 20, 21]

The outcome of postmenopausal women was worse than that of pre and perimenopausal women. This finding fits the previously advanced better prognosis of those women who are menopausal or in the immediate premenopausal interval [3, 7] and also reflects the relatively small number of young premenopausal women in our series.

Since we do not possess any data concerning estrogen receptors, nor precise information about the reasons for most oophorectomies performed in the first years of the study period, we ignore if our results regarding the influence of age and menstrual state on survival can be related with any spe-

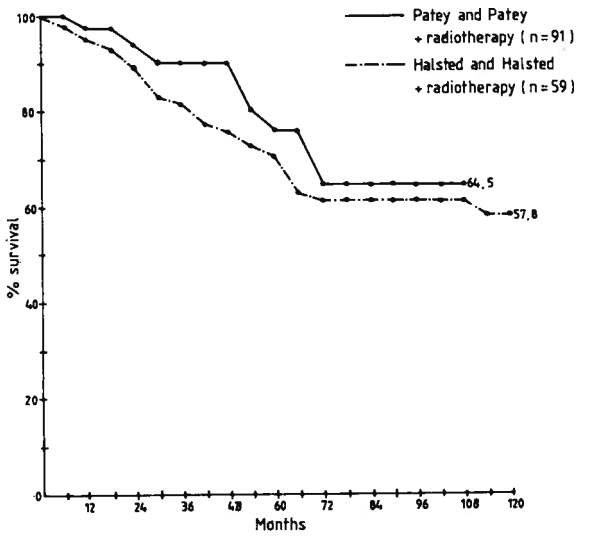

Figure 7: Sulvival curves of patients according to type of treatment.

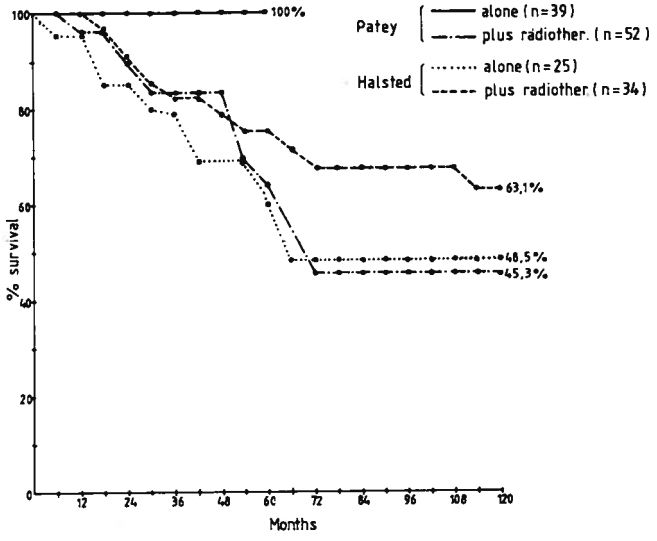

Figure 8: Survival curves of patients according to type of treatment.

TABLE 5 **Summary of data of the three patients submitted to hypophysectomy**

Age, Menopausal status	Pathology	Therapy	Follow-up
53 postmenopausal	T_2; N + > 5 Ductal invasive Grade II	Halsted mastectomy Radioth. (cobalt source) Hypophysectomy	Death (35 months) with distant metastases No autopsy
46 perimenopausal	T_2; N + > 5 Ductal invasive Grade II	Patey mastectomy Radioth. (cobalt source) Bilateral oophorectomy Hypophysectomy	Death (8 months) with distant metastases No autopsy
60 postmenopausal	T_2; N + > 5 Ductal invasive Grade II	Halsted mastectomy Radioth. (cobalt source) Hypophysectomy	Death (13 months) with distant metastases No autopsy

cial features of the tumors, namely in what concerns their hormonal *response*. No conclusions can also be drawn from the exceedingly few cases treated with hypophysectomy or with other forms of endocrine therapy.

The survival of patients undergoing Halsted radical mastectomy was similar to that of patients submitted to Patey or Madden modified radical mastectomies. This result, together with the finding that both groups of patients were comparable regarding the most important prognostic factors, supports the assumption that modified radical mastectomy is a satisfactory alternative to Halsted radical mastectomy adjuvant.[22]

Our results also suggest that adjuvant postoperative radiotherapy increases the survival rate. This is particularly evident when we compare the results obtained using Halsted radical mastectomy in combination with radiotherapy since this second group had worse prognostic indexes than patients undergoing Halsted mastectomy alone. This finding is in keeping with those of Chabazian and colleagues [23] and Wallgren and colleagues [24] but contradicts most of those reported so far in the literature.[1, 2, 25, 26]

We are aware of the fact that our series apart from being too small lacks strict scientific requirements for bias control and therefore does not allow any definite conclusions in such a controversial matter.[1, 2] It must be stressed, however, that all cases submitted to Halsted mastectomy (alone or in combination with radiotherapy) were operated in the first half of the study period and the only bias one can disclose from reviewing the patient charts is that radiotherapy was generally used in those cases in which the clinical and/or pathologic evaluation pointed to a more advanced disease.

No definite conclusions can also be drawn from the use, in the second half of the study period, of limited surgical procedures with or without radiotherapy and/or chemotherapy due to the small size of the sample.

The good results obtained so far with modified radical mastectomy in patients without nodal metastases reinforce the assumption that this procedure should be recognized as the current standard treatment in these cases.[22] The question, now, is to be able to define which of these cases should be considered in *high risk* of developing a systemic disease and therefore treated with adjuvant therapy. As we have previously stressed it is possible that tumor size and histopathologic evaluation (grading + histopathologic classification) may constitute, together with the immunological study of the patients,[27] a good therapeutic guide.

AGRADECIMENTOS

Os autores agradecem à Sr.ª D. Aldina Nascimento a inestimável colaboração técnica.

REFERENCES

1. HENDERSON, I. C.; CANELLOS, G. P.: Cancer of the breast. The past decade (first of two parts). *N. Engl. J. Med.*, 1980; 303: 17-30
2. HAAGENSEN, C. E.: Diseases of the Breast, 2nd ed. Chapters 33, 34 and 35. Philadelphia, WB Saunders, 1971.
3. ALDERSON, M. R.; HAMLIN, I.; STANTON, M. D.: The relative significance of prognostic factors in breast carcinoma. *Br. J. Cancer.*, 1971; 25: 646-656.
4. WHO.: Histological Typing of Breast Tumors, 2nd ed. Geneye, WHO, 1982.
5. BLOOM, H. J. G.; RICHARDSON, W. W.: Histological grading and prognosis in breast cancer. A study of 1409 cases of which 359 have been followed 15 years. *Br. J. Cancer.*, 1957; 11: 359-377.
6. BERKSON, J.; GAGE, R. P.: Calculation of survival rates for cancer. *Mayo. Clin. Proc.*, 1950; 25: 270.
7. FISHER, B.; SLACK, N.; KATRYCH, D.; WOLMARK, N.: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. *Surg. Gynecol. Obstet.*, 1975; 140: 525-534.
8. PAYNE, W. S.; TAYLOR, W. F.; KHONSAN, S.; SNIDER, J. H.; HARRISON, E. G.; Jr., GOLENZER, H.; CLAGETT, O. T.: Surgical treatment of breast cancer. *Arch. Surg.*, 1970; 101; 105-110.
9. SCHOTTENFELD, D.; NASH, A. G.; ROBBINS, G. F.; BEATTIE, E. J.: Ten-year results of the treatment of primary operable breast carcinoma. A summary of 304 patients evaluated by the TNM system. *Cancer.*, 1976; 38: 1001-1007.
10. SMITH, J. A.; GAMEZ-ARAUJO, J. J.; GALLAGER, H. S.; WHITE, E. C.; MCBRIDE, C. M.: Carcinoma of the breast. Analysis of total lymph node involvement versus level of metastasis. *Cancer.*, 1977; 39: 527-532.
11. ROSEN, P. P.; FRACHIA, A. A.; URBAN, J. A.; SCHOTTENFELD, D.; ROBBINS, G. F.: «Residual» mammary carcinoma following simulated partial mastectomy. *Cancer.*, 1975; 35: 739-747.
12. ATKINS, H.; HAYWARD, J. L.; KLUGMAN, D. J.; WAYTE, AB.: Treatment of early breast cancer. A report after ten years of a clinical trial. *Br. Med. J.*, 1972; 2: 423-429.
13. SICHER, K.; WATERHAUSE, J. A. H.: Evaluation of TNM classification of carcinoma of the breast. *Br. J. Cancer.*, 1973; 28: 580-588.
14. HAYBITTLE, J. L.; BLAMEY, R. W.; ELSTON, C. W; JOHNSON, J.; DOYLE, P. J.; CAMPBELL, F. C.; NICHOLSON, R. I.; GRIFFITHS, K.: A prognostic index in primary breast cancer. *Br. J. Cancer.*, 1982; 45: 361-366.
15. SOBRINHO-SIMÕES, M.; SOUSA-LÉ, F.; BRANDÃO, A.; GIESTEIRA ALMEIDA, A.: Prognostic significance of some pathologic factors in breast cancer (in press).
16. SEARS, G. F.; JANUS, C.; NEVY, W.; HOPSON, R.; CREECH, R.; GROTZINGER, P.: Breast cancer without axillary metastases. Are there high-risk biologic subpopulations? *Cancer.*, 1982; 50: 1820-1827.
17. GOLDENBERG, I. S.; BAILAR, J. C. III; HAYES, M. A.; LOWRY, R.: Female breast cancer, re-evaluation. *Ann. Surg.*, 1961; 154: 397-407.
18. SCHWARTZ, G. F.; ZEOK, J. V.: Carcinoma of the breast in young women. *Am. J. Surg.*, 1976; 131: 570-574.
19. BRIGHTMORE, T. G. J.; GREENING, W. P.; HAMLIN, I.: An analysis of clinical and histopathological features in 101 cases of carcinoma of breast in women under 35 years of age. *Br. J. Cancer.*, 1970; 24; 644-699.
20. BIRKS, D. M.; GRAWFORD, G. M.; ELLISON, L. G.; JOHNSTONE, F. R. C.: Carcinoma of the breast in women 30 years of age or less. *Surg. Gynecol. Obstet.*, 1973; 137: 21-25.
21. FREEDMAN, L. S.; EDWARDS, D. N.; MCCONNELL, E. M.; DOWNHAM, D. Y.: Histological grade and other prognostic factors in relation to survival of patients with breast cancer. *Br. J. Cancer.*, 1979; 40: 44-55.
22. Special report: Treatment of primary breast cancer. *N. Engl. J. Med.*, 1979; 301: 340.
23. CHAHBAZIAN, C. M.; DEL REGATO, J. A.; WILSON, J. F.: Postoperative radiation therapy for early carcinoma of the breast. *Cancer.*, 1978; 42: 1125-1128.
24. WALLGREN, A.; ARNER, O.; BERGSTROM, J.; RÄF, L.; KARNSTRÜM, L.; GRANDBERG, P-O.; BLOMSTEDT, B.: Preoperative radiotherapy in operative breast cancer. *Cancer.*, 1979; 42: 1120-1125.
25. LIPWORTH, L.: Survival of cases of surgically treated mammary carcinoma with and without radiation therapy. Cancer registry results. *Lancet.*, 1965; 2: 231-232.
26. NEVIN, J. E.; BAGGERLY, J. T.; LAIRD, T. K.: Radiotherapy as an adjuvant in the treatment of carcinoma of the breast. *Cancer.*, 1982; 49: 1194-1200.
27. MANDEVILLE, R.; LAMGUREUX, G.; LEGAULT-POISSON, S.; POISSON, R.: Biological markers and breast cancer. A multiparametric study II: Depressed immune competence. *Cancer.*, 1982; 50: 1280-1288.

Address for reprints: Sousa Lé
Serviço de Cirurgia 3
Hospital de S. João
4200 Porto. Portugal.