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BREAST CANCER IN BABYLON: PROGNOSTIC INDEX AND EVALUATION OF TREATMENT RESULTS

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Summary

Breast cancer is the most common malignancy in females all over the word. It represents about 34% of total malignancies among IRAQI females with high mortality rate representing 1-2% of female mortality &16% of cancer deaths in females in IRAQ. Many prognostic factors which can affect the treatment outcome have been studied to identify patients at high risk of disease relapse who might benefit from post-operative adjuvant therapy. The Aim of this study was evaluation of different prognostic factors to drive a reliable (Prognostic Index) that best fits our breast cancer patients, hoping to give the adjuvant treatment accordingly. This is a study analysis of 566 female patient treated for primary breast cancer between 1992 and 2001 at Oncology Unit, Marjan teaching Hospital. Modified prognostic index (PI.). Was used to identify different prognostic group. We could divide patients into 4 groups : Group 1 with PI <2.5, group 2 with PI > with PI >2.5-3,group 3 with PI>3-3.5 and group 4 with PI>3.5. The 5 year overall survival (OS) and relapse free survival (RFS) were calculated for the whole group and for the different 4 prognostic groups as well as for influence of systemic adjuvant treatment. The 5 year O.S and RES were 75% and 55% respectively for patient with PI< 2.5 and decreased with the increase of the value of PI to reach 50% and 10% respectively in patients with PI> 3.5. The difference in both 5 year O.S, RFS for different prognostic groups was found statistically significant only between patients with PI<3. (Groups 1&2) and those with PI>3. (Groups 3 &4) with P < 0.001. It was shown those patients with PI<3 could benefit from the addition of adjuvant system treatment with better 5 year RFS of 60% in comparison to 40% for patients who did not receive adjuvant systemic treatment (P=0.01). Minimal benefit was obtained in – patients with PI > 3. It was concluded that more intensive adjuvant treatment my be warranted for group 3 and 4 of patients.

Introduction

Breast cancer is the most common malignancy in femlaes all over the world[1-10]. It represents about 34% of total malignancies among Iraqi females with high mortality rate representing 1-2% of females mortality and 16% of cancer deaths in females in Iraq [11-13]. Many prognostic factors that can affect the treatment outcome have been studied to identify patients at high risk of disease

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relapse who might benefit from post-operative adjuvant therapy. The most important factors are tumour size, lymph node status, pathological grade, age of menstrual status and estrogen receptor status[14-17].

A modified prognostic index has been calculated by Todd et al. [(18)] for group of patients with longer follow – up period (minimum 6 year). Also it has been applied prospectively to a further group of 320 patients of 320 patients and shown to be similarly effective in predicting the survival pattern in a group of patients treated by mastectomy.

This prognostic index helped in the selection of patients with excellent prognosis in whom adjuvant therapy was inappropriate and patients with high index score who may benefit from local or systemic adjuvant therapies.

Three prognostic factors were identified by Brown et al.[19] after the study of 1186 patients from 8 centers in York shire Breast Cancer Group, (YBCG). An index had been derived which is a modified of Nottingham PI[20].

YBCGI = 0.1 x Clinical tumor size (cm.) + 0.5 x grade + 0.6 x nodal involvement.

The coding for the various prognostic factors in NPI and YBCGI was as follows:

YBCGI	**N.PI**	
Tumour size	**Clinical (cm.)**	**Pathological (cm.)**
Lymph node involvement	1 = no 3= yes	1= tumour absent 2=tumour present, low axillary 3=tumour present apical, internal mammary
Tumour grade	1=I 2=II+III	1=I 2=II 3=III

Patients in YBCG were divided into 3 groups according to their index score, good (1<1.21), Moderate (1.21 < PI < 1.82) and poor (PI > 1.82). The 10 year O.S. was 65% for the good prognostic patients against 29% for the poor prognostic patients.

The aim of the present study was to evaluate different prognostic factors and to derive a reliable PI that best fits our breast cancer patients, hoping to give the adjuvant treatment accordingly. We also aimed to compare our P.I. with the NPI that was modified by Brown et al. [19].

Patients and Methods

This is a clinical pathological analysis of 566 female patients with breast cancer treated at the Oncology Unit Merjan Teaching Hospital Babylon, in the period between 1992-2001. The patient's files were reviewed for detailed information's about age, menopausal status, stage, histopathological type and grade, lymph node status, clinical and pathological size of the tumours and treatment results.

All patients were treated by radical or modified radical mastectomy followed by comprehensive post-operative radiotherapy. The dose given was 45 Gy/20 fractions over 4 weeks (225 cGy/ fraction) to chest wall and peripheral lymphatics using telecobalt-60 machine, similar to the technique used by Fletcher[9]. Systemic adjuvant chemotherapy was given to 250 patients; 203 patients received CMF combination (Cyclophosphamide, 600 mg/m^2 day 1, Methotrexate 50 mg/m^2 day 1 and 5 Fluorouracil 600 mg/m^2 day) and 47 patients received FAC combination (5 Flourouracil 600 mg/m^2 day 1, A draimycin 40 mg/m^2 day 1 and Cyclophosphamide 600 mg/m^2 day 1). The course was repeated every 21 days for 6 courses.

All patients were followed-up regularly, 3 monthly for 2 years, 4 monthly for 5 more years and annually thereafter. The minimum follow-up period was 2 years and the maximum was 8 years.

Relapse free survival (RFS) and overall

survival (OS) were calculated from the date of mastectomy to the date of relapse or last follow – up.

A trial of application of the prognostic index used by Brown et al. 1993 in the YBCG study was done with some modifications to suit our group of patients.

P1 = 0.1 x pathological tumours size (cm.) + 0.5 x grade + 0.6 * L.N. status. As the majority of our patients had positive axillary lumph nodes and high grade tumours, the coding for the various prognostic factors were modified as follow:

Tumours size	Pathological (cm.)
Lymph nodes	1= No L.N.
	2 = 1-3 + ve L.N.
	3 = 4-7 + ve L.N.
	4 = > 8+ ve L.N.
Grade	1 = I + II

The patients in our study were then divided into groups according to the P1: good (P1 < 1.25) moderate (1.25 ≤ P1 < 1.75) and poor (P1 ≥ 1.75).

We noticed that the majority of our patients were allocated in the poor prognosis group with P1> 1.75. There was only 4 patients with PI, 1.25 and only 6 patients (17%) had PI <1.75. the lowest index detected was 1.20 while the highest was 5.25. These results lead to the search for new cut off values before starting statistical analysis. These new cut off values were 2.5, 3 and 3.5 dividing the sample into 4 groups, each group included approximately one quarter of our sample:

Group	Prognostic index value	Prognosis	No. of patients	%
1	≤2.5	Low	130	23%
2	≥2.5-3	Intermediate low	113	20%
3	>3-3.5	Intermediate high	158	28%
4	>3.5	High	165	29%

Statistical methods

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis using the life test procedure (product limit survival estimates)[21].

Comparisons between groups were performed using the long rank test. AP value 0.05 was considered significant. The analysis was performed for the whole studied groups as well as different prognostic groups after application of PI. The OS and RFS were fperformed in correlation to different tumours size, L.N. status, grade as well as the use of adjuvant systemic treatment.

Results

The characteristics of the 566 patients included in the study are shown in Table I. Their ages ranges between 26 and 75 years with a median age of 43 years, 374 patients (66%) were premenopausal while 192 patients (34%) were post-menopausal.

Patients were staged according to TNM classification (UICC/AJCC). Ten patients (1.7%) had stage I disease, 204 patients (36%) had stage II, and the majority, and I, 351 patients (62%) has stage III disease.

Twenty eight patients (5%) had pathological T1 tumours, 255 patients (45%) had T2 tumours, while T3 was present in 187 patients (33%) and T4 in 96 patients (17%).

As regards axillary lymph nodes, 79 patients (14%) had negative lymph nodes while 487 patients (86%) had positive lymph node. Within the positive lymph node group, 153 patients (27%) had 1-3 positive node, 198 patients (35%) had from 4 to 7 positive nodes and 136 patients (24%) had more than 7 positive nodes.

Median age	43 years	Range 26-75
Menopausal status:		
Premenopausal	374	66%
Postmenopausal	192	34%
Stage:		
I	10	1.7%
II	204	36%
III	351	62%
Tumour size:		
T1<2cm.	28	5%
T2 >2-5cm.	255	45%
T3 >5 cm.	187	33%
T4	96	17%
Lymph node status:		
Negative	79	14%
Positive	487	86%
1-3+ve	153	27%
4-7+ve	198	35%
>7 +ve	136	24%

The majority of patients (90%) had invasive duct carcinoma, 14 patients (2.4%) had grade I tumours, 434 (76.6%) had grade II tumours and 119 patients (21%) had grade III tumours.

The 5 years OS and RFS for all patients were 75% and 55% respectively. Loco-regional relapse occurred in 20 patients (3.5%), distant relapse in 303 patients (53.5%) while 243 patients (43%) had both locoregional and distant relapses. The majority of relapses were observed in the first 2 years postoperatively with gradual decrease in the incidence thereafter. Bone metastasis was the commonest site of distal relapse and was observed in 311 patients (55%) followed by lung metastasis in142 patients (25%). Other sites of distant metastases included liver, brain, pleura, contralateral breast and axilla.

The effect of adjuvant systemic treatment was studied in relation to PI. There has been better 5 year RFS for those patients who received than for those who did not receive adjuvant systemic treatment only in the group of patients with PI≤3.2 (36% and 46% respectively with p=0.017). The 5 year RFS for patients who received adjuvant treatment with PI>3.2 was 16% which is nearly similar to 15% for those who did not receive treatment.

Discussion

In the present study of 566 patients with breast cancer, the median age was 43 years, which is younger than Western series where the median age was reported to be 54 years[22]. The frequency of T1 tumours in the present study was 4% only. This finding differs from that reported in western series as T1 constitute about 30% of cases[22,23]. The majority of our patients presented with T2 tumours (44%) which is similar to western series[21]. T3 and T4 tumours constitute about 35% and 17% of our patients respectively. The frequency is higher than 20% and 5% reported in western series[22].

The majority of patients in the present study had positive axillary lymph nodes (90%). About 64% of patients had 4 or more positive nodes. These figures are different from western series where the incidence of positive lymph nodes was reported to be about 45% with low incidence of 4 or more positive lymph nodes about 17%[19,22,24]. These findings show that our patients presented in more advanced stage than western series. The most frequent pathological type in this study was invasive duct carcinoma (88%), which is similar to most western series[6,15]. Grade I tumour was recorded in 2.5% of our patients. This frequency is considered very low compared to about 30% reported in western series [19,25]. The majority of our patients had grade 2 tumour (74%). Grade III was recorded in 23.5% of our patients, which is similar to most reported series.

Locoregional relapse occurred in 18% of patients, the majority within the 1st 3

years after treatment. Chest wall relapse constituted 85% of locoregional relapse while axillary recurrence was found in 10.4% of patients. The incidence of locoregional recurrence in our study is similar to that reported in Person reported series[26]. Mitchell et al[27] reported 5 years locoregional relapse in 10% of patients.

Distant relapse occurred in 69% of the study group. This high percentage of distant relapses in comparison to western series can be explained by the fact that 90% of our patients had positive axillary lymph node and 52% had T3 and T4 tumours. Kaufann et al[28] showed that only 20-25% of patients with negative lymph node had distant relapse 10 years after treatment while 75% of those patients with positive axillary lymph node had distant relapse.

The 5-year OS for whole group was 75% while 5 year RFS was 55%. The 5 year OS reported to be 80%, in western series[29]. The low value of OS in our study may be explained by the prevalence of more advanced stage that in western series.

Prediction of the patients with breast cancer had been tried by Haybittle et al[20], they introduced the prognostic index concept (NPI) which is a reflection of tumour size, lymph node status and grade. Brown et al[19] modified the NPI to suit best their materials. They divided patients depending on PI (YBCG) into three groups good prognosis (I<1.21), intermediate prognosis (I>1.21 -1.82) and poor group (I≥1.82) with 5-year OS of 84% and 47% respectively.

Reviewing our available materials led us to introduce some modification to suit best our patients. In our modified PI, we used pathological rather than clinical tumour size because we think it is more accurate. Grade was recorded as 1 and 2 versus 3 as the incidence of grade 1 in our patients was very low. As the majority of our patients had positive lymph nodes, nodal status was coded as 1 for negative lymph nodes, 2 for 1-3 positive lymph nodes, 3 for 4-7 positive nodes and 4 for more than 8 positive nodes. Thus new cuts off values (2.5-3-3.5) were testes statistically to separate groups of patients with different survival.

Statistical analysis of patients with PI≤ 3 compared to those >3 showed difference in 5 years OS and RFS which was statistically highly significant ($p \leq 0.001$). Thus, our PI succeeded in dividing the patients into two main groups with different prognosis.

There had been better RFT for patients who received than for those who did not receive adjuvant systemic treatment. This difference was more significant for the patients PI≤ 3($p=0.017$). These results suggest that patient with PI≥ 3 probably need more intensive adjuvant therapy than those with PI≤3. This is in agreement of most reported series who use intensive chemotherapy for those high risk patients[25,30]. Further validation of the PI in a randomised prospective study should be considered for proper evaluation of its value and addition of other prognostic factors.

Conclusion

We may conclude from the present study that our patients with breast cancer present with advanced stage so the results of treatment were inferior to that reported in western series. Using PI we succeeded in dividing patients into two main groups. The prognosis of patients PI> 3 in poorer than those patients with PI≤3. More intensive adjuvant systemic treatment should be considered for patients with PI>3.

References

1. American Cancer Society. Cancer facts and figures 1999.
2. Ferlay J, Bary F, Sankila R, Parkin DM. EUCAN: Cancer incidence. Mortality and Prevalence in the European Union 1995. IARC Cancer Base No. 4 Lyon. IARC press 1999.
3. Chu KC. Tarone RE, Kessler LG, et al. Recenttrends in US breast cancer incidence, survival and mortality rates. J Natl Cancer Inst 1996; 88(21): 1571-9.
4. Garne JP, Aspegren K, Balldin G, Ranstam J. Increasing incidence of and declining mortality from breast carcinoma: Trends in Malmo, Sweden 1961-1992. Cancer 1997; 79: 69-74.
5. Beral V, Hermon C, Reeves G, Peto R. Sudden fall in breast cancer death rates in England and Wales. Lancet 1995; 345: 1642-3.
6. Harris J, Morrow M, Norton L. Malignant tumours of the breast. In: de VT. Hellman S, Rosenberg SA. Editors. Cancer: Principles and practice of oncology. 5th ed. Philadelphia, JB Lippincott. P. 1557-616.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53297 women with breast cancer and 100239 women without breast cancer from 54 epidemiological studies. Lancet 1996; 347(9017): 1713-27.
8. Peto J, Easton DF, Matthews FE, Ford D, Swerdlow AJ. Cancer mortality in relatives of women with breast cancer: the OPCS study. Int J Cancer 1996; 65: 275-83.
9. Fletcher G (ed). Textbook of radiotherapy. In collaboration with Montague ED, Tapley N and Barker JL. Radiotherapy in the management of non disseminated breast cancer. 3rd edition. Lea and Febiger, Philadelphia 1980, p. 27-579.
10. Reynolds T and Ries LAG. Breast cancer deaths in American women ages 40-44. J Natl Cancer Inst 1992; 84: 663.
11. Iraqi Cancer Registry 1999, Results of Iraqi Cancer Reg-istry 1995-1997, Ministry of Health, Baghdad.
12. Al-Alawchi SF, Al-Timimi AH. Study of malignant disease in Babylon province during the period 1990-1999. J Babylon University 2001.
13. Iraqi Cancer Registry 1996. Results of Iraqi Cancer Registry 1992-1994. Ministry of Health, Baghdad.
14. Carter CL, Allen C and Henson DE. Relationship of tumour size, lymph nodes status and survival in 24740 breast cancer cases. Cancer 1989; 63: 181-187.
15. Edward G, Peter MR and Lynn D. Prognostic factors in early breast carcinoma. Cancer 1994; 74: 381-400.
16. Freedman LS, Edward DN, McConnell EM and Dawnham DY. Histological grade and other prognostic factors in relation to survival of patients with breast cancer. Br J of Cancer 1979; 51: 40-44.
17. William L, McCUrie, Atul KT, Craig A, Gary A and Gary M. Prognostic and treatment decisions in patients with breast cancer without axillary node involvement. 1992; 70: 1775-1781.
18. Told JH, Dowle C, Williams MR, Elsto C, Ellis O, Hinton CP, Blameg RW and Haybittle JL. Confirmations of a prognostic index in primary breast cancer. Br J Cancer 1987; 56: 489-492.
19. Brown JM, Benson EA and Jones M. Confirmation of long-term prognostic index in breast cancer. The breast 1993; 3: 144-147.
20. Haybittle JL, Blamey RW, Elston CW, Told JH and Williams MR. A prognostic index in primary. Br Cancer 1982; 45: 361-364.
21. Peto RMC, Armaitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observations of each patients. II analysis and examples. Cancer 1977;35:1-39.
22. Blaslev I, Zxellson CK, Zedeler K, Rasumusern B, Carstensen B and Mouridsen H. The Nottingham prognostic index applied to 9149 patients from the studies of the Danish breast cancer cooperative group (DBCG). Breast cancer research and treatment; 32: 281.
23. Dela Rocheforiere A, Asselian B, Campana F, Scholl SM, Fenton J, Vilcog JR, Durand JC, Paeillart P, Magdelent H and Fourquent A. Age as prognostic factor in premenopausal breast carcinoma. The Lancet 1993; 341: 1039-43.
24. Less AW, Jenkins HJ, May CL, Cherian G, Lan EWH and Hanson J. Risk factors and 10 years breast cancer survival in Northen Alberta. Breast cancer research and treatment 1989; 13: 143-51.
25. Abeloff M, Beveridge RA, Donehower RC and Jakson M. Sixteen week dose chemotherapy in adjuvant treatment of breast cancer. J Natl Cancer Inst 1990; 82: 570-574.
26. Reson PP, Saigo PE, Braun DWJ, et al. Predictors of recurrence in stage II carcinoma. Ann Surg 1981; 194: 526-583.
27. Mitchell AM, CS and Willett W. Cancer of breast. Br J 1993; 53: 428-430.

28.Kaufmann M. Review of known prognostic variables: Anti-cancer drugs 1995; 6: 54-57.
29.Christine L, Carter CL, Allen C and Henson BE. Relation of tumour size 1989; 63: 181-187.
30.Bussoni R, Bbonadonna G, Valagussa P and Veronesi V. Adj chemotherapy with doxorubicin plus cyclophosphamide, methotrexate and fluorouracil in treatment of resectable breast cancer with more than three positive axillary nodes. J Clin Oncol 1991;9:2136-2140.