Overview of breast cancerpatients and their prognostic factors treated in Baghdad teaching hospital/ oncology department in the year 2010

Manwar A. Al Naqqash* **DMRT clinical oncology, MSc. pathology.**

Summary:

Background: The breast cancer is the most common non-skin malignancy in women and prognostic factors are important in predicting disease free survival and overall survival.

Objective: To detect prognostic factors of breast cancer patients and study the correlation between these prognostic factors.

Patients and methods: this is a retrospective study which included87 patients with breast cancer receiving chemotherapy in Baghdad teaching hospital/ oncology department in the year 2010. Prognostic factors were registered including: age, histopathological subtype, degree of differentiation, lymph node involvement, ER and PR, Her 2/neu and lymphovascular invasion.

Results: Regarding breast cancer; 55(63.2%) of patients were early breast cancer as compared to32(36.8%)patients with locally advanced breast cancer.Regarding lymph node involvement 31(36.9%) of patients had N0,28(33.3%) had N1, 23(27.4%) had N2 and 2(2.4%) were with N3. Regarding degree of differentiation the most common type was moderately differentiated with 58(66.7%) followed by poorly differentiated with 23 (26.4%) and at last well differentiated tumors with 6(6.9%) patients. Infiltrative ductal carcinoma was the most common subtype other histopathological subtypes as infiltrative lobular carcinoma (13.8%) and medullary carcinoma (2.3%). Intraductal carcinoma were present in 23 cases (25.8%).ER was negative in 33% and PR was negative in 37.5% while the remaining cases shows positivity with different percentage scores.Cross tabulation between different prognostic factors (tumor size, lymph node, degree of differentiation, lymphovascular invasion) were done and results were statistically not significant, regarding ER and PR showed strong significant correlation($p < 0.0005$).between the two markers also significant correlation was found between lymphovascular invasion and lymph nodes involvement.

Conclusion: breast cancer is the most common solid malignancy treated in Baghdad teaching hospital. Early stage breast cancer were more common than advanced breast cancer, ER and PR(good prognostic factors) were statistically correlated to each other so were lymphovascular invasion with lymph nodes involvement(bad prognostic factors).

Keywords: Breast cancer,Estrogen Receptor, Progesterone Receptor, lymphovascular invasion

Fac Med Baghdad 2011; Vol. 53, No.3
Received March. 2011
Accepted Aug. 2011

Introduction:

Carcinoma is the most common malignancy of the breast. In the United States, breast cancer remains the most frequent cancer in women and the second most frequent cause of cancer death(1). A woman who lives to age 90 has a one in eight chance of developing breast cancer. In 2001, almost 240,000 women were diagnosed with breast cancer, and over 40,000 died of the disease (2). In 2007 it accounted for 26% of cancer cases and 15% of cancer deaths, which translates to 176,296 new cases and 40,515 deaths (1). Breast cancer was also the most common form of cancer seen in Europe in 2006, with 429,900 new cases, representing 13.5% of all new cancers(3)
In Iraq according to Ministry Of Health/Iraqi cancer registry, 2004, breast cancer ranks first with 2225 new patients registered and 15.32% of total cancer patients (4). Invasive ductal carcinoma is a term used for all carcinomas that cannot be sub classified into one of the specialized types, the majority (70%-80%) of cancers falls into this group. About 2/3 express ER and PR and about 1/3 overexpress ERBB2(Her2/neu)(2). Lobular carcinomas are more frequently multicentric and bilateral (10%-20%). Almost all of these carcinomas express hormone receptors, but Her 2/neu expression is very rare or absent(2). Medullary carcinoma is a rare subtype of carcinoma comprising about 2% of cases; these carcinomas uniformly lack hormone receptors and do not overexpress Her2/neu (2).
The prognosis of breast cancer is related to a large variety of clinical and pathological factors and the most important prognostic factors includes: patients age, BRCA1 status, early diagnosis, presence or absence of invasion, cytoarchitectural type, tumor size and site, axillary and internal mammary lymph node involvement,microscopic grade, tumor necrosis,stromal reaction,Her/neu, p53 and nm23, bcl2,skin and nipple invasion, lymphatic and vascular invasion, cell proliferation (ki-67), type of therapy and local recurrence and finally gene expression profiling (7).

**Dept. of surgery, College of medicine, University of Baghdad*

Patients &Methods:
Tthis is a retrospective study which included 87patients of breast cancer treated for the first time with chemotherapy in Baghdad teaching hospital/ oncology department in the year 2010.
The data for each patient was collected from their archivesincluding: age, tumor size(T), lymph node (N) and number of lymph node, metastasis (M), histopathological subtype, degree of differentiation, estrogen receptor(ER), progesterone receptor (PR),Her 2/neu, in situ component and lymphatic and vascular invasion.

Results:
Regarding number of patients treated in oncology department; breast cancer was number one with 201 patients (22.33% of all solid cancer patients treated in oncology department as new patients in the year 2010) from which 87 patients were selected to be included in this article.
Prognostic Factors of breast cancer patients. Each breast cancer case was studied individually and various prognostic factors were registered and showed the following results.
Age: Breast cancer is rarely found before the age of 25 years except in certain familial cases. The incidence rises throughout a woman's lifetime. Seventy-seven per cent of cases occur in women over 50 years of age. The average age at diagnosis is 64 years(2). Age of the patients was divided into 6 groups with 10 years interval for each group as seen in figure 1. 56.4% of cases were below the age of 50 years and the model age group was 40-49 years, the youngest patient recorded was 26 years and the oldest was 80 years of age.

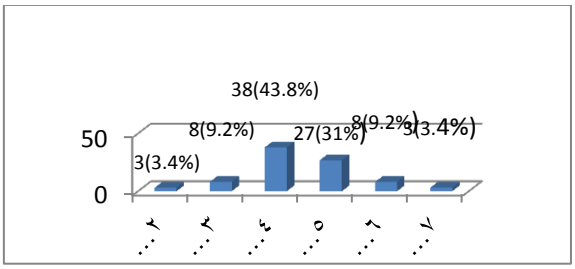
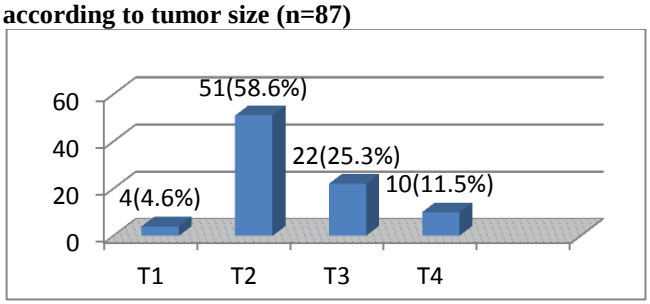


Figure 1: distribution of breast cancer patients according to age groups (n=87)

Tumor size (T): Tumor size was divided According to American Joint Committee on Cancer Staging (5). The diameter of the primary tumor shows a good correlation with the incidence of nodal metastases and with survival rate. As a matter of fact this easily, quickly, and cheaply determined parameter has been found to be one of the strongest predictors of dissemination and rate of relapse in node-negative breast carcinomas (7). Regarding tumor size87 cases were included and showed the following results as shown in figure 2. It was found that 55(63.3%)patients were early breast cancer(T1, T2) as compared with 32 (36.7%) cases only with locally advanced breast cancer(T3,T4).

Figure 2: distribution of breast cancer patients according to tumor size (n=87)



Lymph nodes involvement (N):Lymph nodes involvement was divided According to American Joint Committee of cancer staging (6)
This is one of the most important prognostic parameters. Not only is there a sharp difference in survival rates between patients with positive and negative nodes, but the survival rate also depends on the level of axillary node involved (low, medium, or high), the absolute number (fewer than four versus four and more)(7).
84 cases were with a known lymph node status and the results were shown in figure 3 (3 patients were with unknown lymph nodes status).Also numbers of lymph nodes removed by surgery were registered and showed the following results in table 1 (7 patients histopathological reports did not mention the number of lymph nodes).
The least number of lymph nodes removed were 2 and the largest number removed was 32.

Figure 3: distribution of breast cancer patients according to axillary lymph node involvement (n=84)

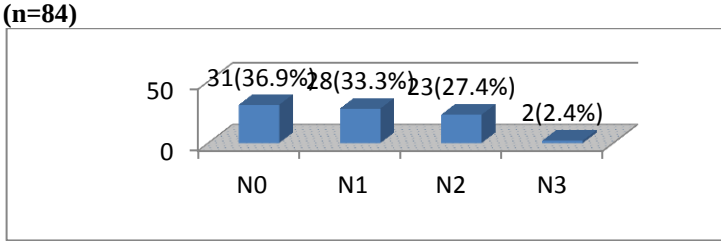


Table 1: showing number of axillary lymph nodes removed by surgery in breast cancer patients

Number of L.N.	Frequency	%
(1-3)	11	14.3
(4-6)	25	32.5
(7-9)	18	23.4
10-	23	29.8
Total	77	100

Degree of differentiation**:** The most common grading system for breast cancer evaluates tubule formation, nuclear grade, and mitotic rate to divide carcinomas into three groups. Well-differentiated carcinomas have a significantly better prognosis as compared with poorly differentiated carcinomas (for patients with the same stage), moderately differentiated carcinomas initially have a better

prognosis, but survival at 20 years approached that of poorly differentiated carcinomas (2).

87 histopathological reports describe the degree of differentiation and the results are shown in figure 4. The most common type was moderately differentiated with 66.7% followed by poorly differentiated with 26.4% and finally well differentiated tumors with 6.9%.

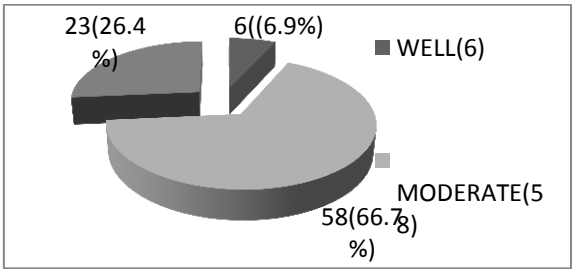


Figure 4: classification of breast cancer cases according to degree of differentiation (n=87)

Histopathological subtype**:**All specialized types of breast carcinoma (tubular,medullary, lobular, papillary, and mucinous) have a somewhat better prognosis than carcinomas of no special type (ductal carcinomas). (2) Although infiltrative ductal carcinoma is the most common subtype other histopathological subtypes as infiltrative lobular carcinoma(13.8%) and medullary carcinoma (2.3%) were present as shown in table 2.

Intraductal carcinoma were present in 23 cases(25.8%). 18 cases associated with infiltrative ductal carcinoma, 5 cases associated with infiltrative lobular carcinoma.

Table 2: classification of breast cancer patients according to histopathological subtypes (n=87).

Histopathological subtype	No.	%
Infiltrative ductal carcinoma	73	83.9
Infiltrative lobular carcinoma	12	13.8
Infiltrative medullary carcinoma	2	2.3
Total	89	100

Estrogen and Progesterone Receptor (ER and PR): ER/PR status has some prognostic value. Patients with ER/PR positive tumors have improved disease-free survival compared to similarly staged patients with ER/PR negative tumors at 5 years, but this difference is less apparent at 10 years (5). Estrogen and progesterone receptor was detected by immunohistochemistry and included only 26 patients and results are illustrated by table Number 6. ER was negative in 33% and PR was negative in 37.5% while the remaining cases shows positivity with different percentage scores. HER 2/neu status: it identifies a subset of patients with poor prognosis. Particularly when lymph node metastases are present (7).

Her/neu was done for 9 cases by immunohistochemistry and shows: 2 cases were negative,1 patient with +1,and 6 cases with +3

Lymphatic and vascular invasion: the presence of tumor emboli in lymphatic vessels within the breast is associated with an increased risk of tumor recurrence while blood vessel emboli shows a high correlation with tumor size, histologic grade, tumor type, lymph node status, development of distant metastases, and poor prognosis (7). 14 histopathological reports referred to lymphatic and vascular invasion and showed:2 patients were negative while 12 cases were positive for lymphatic and vascular invasion. Correlation between prognostic factors**:** in order to study the relation between different prognostic factors, cross tabulation was done and the relations were statistically tested by chi square test There is an obvious correlation between locally advanced breast cancer and lymph node involvement although the results were with equivocal p value (table 3). No correlation was found between degree of differentiation and tumor size or lymph node involvement (the results were not statistically significant). Regarding estrogen and progesterone receptor there was a strong correlation between the two markers also there was a significant correlation between lymphovascular invasion and lymph nodes involvement (table 6).

Table 3: cross tabulation between tumor size and lymph node involvement (n=81)

Tumor size	Lymph node involvement		Total
	N0	N1,2,3	
T1&T2	22	30	52
T3&T4	6	23	29
Total	28	53	81

P= 0.05 (equivocal)

Table 4: cross tabulation between degree of differentiation and lymph node involvement (n=84)

Lymph node involvement	Degree of differentiation			Total
	Well	Moderate	poor	
N0	4	23	5	32
N1,2,3	1	35	16	52
Total	5	58	21	84

P = 0.061

Table 5: cross tabulation between degree of differentiation and tumor size (n=83)

Tumor size	Degree of differentiation			Total
	Well	Moderate	poor	
Early breast cancer (T1&T2)	4	33	15	52
Locally advanced breast cancer (T3&T4)	1	22	8	31
Total	5	55	23	83

P= 0.646

Table 6: cross tabulation between estrogen receptor and progesterone receptor (n= 26)

		PR				Total
		Negative	+	++	+++	
ER	negative	8	0	0	0	8
	+	1	6	0	0	7
	++	0	4	3	1	8
	+++	0	1	0	2	3
Total		9	11	3	3	26

P < 0.0005

Table 7: cross tabulation between lymph nodes involvement and lymphovascular invasion

		Lymph nodes involvement		Total
		Negative	positive	
Lymphovascular invasion	Negative	2	0	2
	positive	2	10	12
		4	10	14

P = 0.016

Discussion:

70% of the cases of breast cancer occurred between the age of 40-60 years and the model age group is 40-49 years, similar results were seen with other Iraqi researchers (9, 10) while Different results were seen in Europe with only 25% of cases < 50 years of age(18).Early breast cancer cases (T1, T2) accounted for 63.3% of non-metastatic cases while locally advanced breast cancer (T3,T4) accounts for 36.7% of non-metastatic cases.Similar results were noticed with previous studies done for Iraqi patients (8,10) with striking predominance of early over locally advanced breast cancer patients.Regarding lymph node involvement only 36.9% had N0 while 63.1% had involved axillary lymph node (N1, N2 or N3). similar results were seen to other Iraqi studies (8,10, and 11) which reflects the fact that although up to 2/3 of breast cancer cases were T1 and T2 still there was a high incident of lymph node involvement which reflect the biological behavior of the tumor and that tumor size is not the only factor that determine liability of tumor to metastasize locally and systematically (7). Moderately differentiated tumors were the most common(66.7%) followed by poorly differentiated tumors (26.4%). In comparison to other studies; most of these studies showed predominance of moderate followed by poorly differentiated tumors with the least percentage for well differentiated tumors (8, 10, 11 and 20). Results show that around 1/3 of cases did not express ER and PR, even these results show compatibility with most pathological and oncological references (2, 5, and 7),some authors believe that repeating the test is of great value (12) because recent guidelines for immunohistochemistry (IHC) testing for ER and PR in breast cancer note that they are inaccurately assessed in up to 20% of tumors(13). Of most concern here is the false-negative rate, which might lead to inappropriate withholding of a minimally toxic and potentially curative hormone therapy(12).And it has been suggested that clinical responses can be seen in women whose tumors express ER in as few as 1% of cells (14). The presence of ER or PR on breast tumors is predictive of a higher likelihood of response to endocrine therapy (15, 16). Patients who have tumors that are both ER and PRpositive will have a 50 to 70% probability of receiving clinical benefit from endocrine therapy. On the other hand, those with ER and PRnegative tumors will have less than a 10% probability of benefiting from endocrine therapy. Patients with either ER or PRpositive tumors will have about a 30 to 33% probability of receiving clinical benefit from endocrine therapy (17). ER-positive PR-negative tumors have more aggressive features than ER^+/PR^+ tumors; they are larger, are more likely to be aneuploid, and proliferate more rapidly. Interestingly, ER^+/PR^- tumors are also associated with a statistically significantly higher frequency of HER-2 overexpression and HER-1 expression than ER^+/PR^+ tumors. Finally, loss of PR in ER positive tumors may be a surrogate marker of aberrant growth factor signaling that could contribute to the tamoxifen resistance, i.e., poorer survival in tamoxifen-treated women (19). Lymphovascular invasion is associated with increased risk of tumor size, histologic grade, tumor type, lymph node status, development of distant metastasis, poor prognosis and tumor recurrence(7) and extensive lymphovascular invasion is one of factors that determine the use of chemotherapy or not in early breast cancer patients(18) and this correlation was seen in this study by the significant correlation between lymphovascular invasion and lymph nodes involvement and this correlation was shown by other authors who regarded lymphovascular invasion as the precursor of lymph nodes involvements (20)

References:

1. American Cancer Society. Breast cancer facts and figures 2005-2006. World Wide Web URL: www.cancer.org.

2. Kumer VI, Cotran RA, Robbins ST (eds.).ROBBINS BASIC PATHOLOGY (7th edition), SAUNDERS, Philadelphia, Pennsylvania 2003:716.

3. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18(3):581.

4. IRAQI CANCER REGISTRY/2004. / Ministry of health/ Iraq P.O.BOX 707 /12112. FAX (+) 9641-4150292 BAGHDAD,IRAQ 2008.

5. DeVita V, Lawrence T, Rosenberg S. De Vita, Hellman and Rosenberg's Cancer:Principles and Practice of oncology, 8th edition cogyright 2008, Lippincott Williams and Wilkins 2008;vol 2:43 1595-1650.

6. Perez C, Brady L, Halperin E, et al. Perez and Brady's, principle and practice of radiation oncology, fifth edition. Copyright 2008 Lippincott Williams and Wilkins 2008;52-54:1162-1315.

7. Rosia J, Desmet V, Brunning R, et al.Rosia and Ackerman's surgical pathology,ninth edition,www.elesvierhealth.com,2004; 9:1763-1877.

8. Al-Anbari S. Correlation of the clinicopathological presentations on Iraqi breast cancer patients with the findings of biofield breast cancer diagnostic system (BDS), HER2andKi-67 immunohistochemicalexpressions.A PhD thesis Baghdad. 2009.

9. AL-JafariWasnaa. Ki-76 immunohistochemistry in breast carcinoma (a pathological and immunohistochemical study) a thesis submitted to the Iraqi Board for Medical Specializations in pathology .2002.

10. Al-Naqqash M. The role of C-myc oncogene as a prognostic marker in breast cancer patients evaluated by immunohistochemistry and in situ hybridization. An M.Sc. thesis Baghdad. 2009.

11. Al-Sanati M. PCR study of BRCA1 BRCA 2 in correlation to immunohistochemical expression of P53, estrogen and progesterone receptors in breast cancer. A PhD thesis Baghdad. 2009.

12. Steffi O., Adrian V. Lee, and Nancy E. Davidson, University of Pittsburgh Cancer Institute, Pittsburgh, PA; Is it time to ReSET the standard for Estrogen Receptor Testing in Breast Cancer ?. Journal of Clinical Oncology: Vol 5,No 6:1-3. 2010

13. Hammond ME, Hayes DF, Dowsett M, et al:American society of clinical oncology. College of American pathologist guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer ,Journal of Clinical Oncology28:2784-2795,2010

14. Harvey JM, Clark GM, Osborne CK, et al: Estrogen receptor status by immunohistochemistry is superior to the ligand binding assay for predicting response to adjuvant endocrine therapy in breast cancer, J ClinOncol 17:1474-1481,1999.

15. Allegra JC, Lippman ME, Thompson EB, et al. Estrogen receptor status: an important variable in predicting response to endocrine therapy in metastatic breast cancer. Eur J Cancer 1980;16:323–331.

16. Allegra JC, Lippman ME. Estrogen receptor status and the disease-free interval in breast cancer. Recent Results Cancer Res 1980;71:20–25.

17. Ravdin PM, Green S, Dorr TM, et al. Prognostic significance of progesterone receptor levels in estrogen receptor–positive patients with metastatic breast cancer treated with tamoxifen: results of a prospective Southwest Oncology Group study. J ClinOncol1992;10:1284–1291.

18. S. Aebi, T. Davidson , G. Gruber & M. Castiglione: primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 21(Supplement 5): v9-v14, 2010.

19. G. Arpino ,H. Weiss, A. V.Lee, et al:Estrogen Receptor–Positive, Progesterone Receptor–Negative Breast Cancer: Association With Growth Factor Receptor Expression and Tamoxifen Resistance;JNCI J Natl Cancer Inst(7 September 2005) 97 (17): 1254-1261.

20. Sebastian F. Schoppmann, MD, Guenther Bayer, MD , et al: Prognostic Value of Lymphangiogenesis and Lymphovascular Invasion in Invasive Breast Cancer ; annals of surgery. 2004 August; 240(2): 306–312.