

Multidisciplinary Approach to Breast Cancer Management in Kuwait, 1993-1998

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ABSTRACT

Background and Objectives: In Kuwait, breast cancer is the most common form of cancer among women. The present study reviews the clinical features, treatment methods and treatment results of breast cancer patients registered in the Kuwait Cancer Control Center (KCCC) and compares these features with those reported in other Arab countries, Europe and North America.

Material and Methods: The present study examines 823 patients with breast cancer who were registered in the KCCC from 1993 to 1998. Patients were identified through the Kuwait Cancer Registry and their cases were followed for at least five years.

Results: Eleven males accounted for 1.3% of all patients. The average age was one decade younger than that reported in western countries but similar to reports from Egypt and GCC countries. Surgery was applied in 90.4% of patients. Breast conservation (lumpectomy and axillary clearance) was performed in 19.6% of patients, while mastectomy and axillary clearance was adopted in 60.8%. Radiotherapy was applied in 67.7% of patients and chemotherapy in 60.8%. The long-term overall survival and disease-free survival amounted to 76±6.4% and 54±4.6% respectively. Prognostic factors were analyzed using univariate and multivariate analysis. According to multivariate analysis the nodal status, the number of involved nodes and histopathology were independent prognostic factors. Comparable results were achieved after both breast conservation and mastectomy.

Conclusions: Since breast conservation protocols yield results similar to mastectomy, its use should be extended. Search for biological prognostic indicators should continue for their potential use as guides for treatment decisions.

Key Words: Breast cancer - Epidemiology - Multidisciplinary treatment - Kuwait.

INTRODUCTION

Breast cancer is the most frequent malignant tumor in women worldwide. The incidence and mortality rates among females vary among countries but are steadily increasing worldwide [1,23]. Breast cancer is most common in the USA and least prevalent in Japan. It is estimated to affect one out of fourteen women during their lifetime, and one out of every three affected women will die of the disease. The female to male ratio of breast cancer incidence is 50:1 [4].

In Kuwait, breast cancer is the most common form of cancer among women. During 2001, the breast cancer age standardized incidence rate (ASR) amounted to 36 among Kuwaiti females and 39.5 among non-Kuwaiti female residents [1]. The present report analyzes the results of surgery, radiotherapy and chemotherapy in the management of breast cancer patients seen in Kuwait from 1995 to 1998.

MATERIAL AND METHODS

All breast cancer patients registered in The Kuwait Cancer Registry from 1995 to 1998 were included. After patient identification, patients completed a study form and their cases were followed for at least five years.

Treatment Protocols:

The treatment protocol adopted between 1993 and 1998 was an extension of previous

treatment protocols used in the KCCC. The TNM classification of the UICC was adopted. Physicians of different specializations participated in the execution of the treatment protocol including surgeons, radiation oncologists, medical oncologists along with pathologists and diagnostic radiologists.

Radical treatment was adopted for patients without evidence of distant metastases. The type of surgery varied with the tumor size. For tumors less than 3cm with negative or positive nodes (N0 or N1) breast conservative surgery (BCS) with axillary clearance was adopted. On the other hand, patients with 3cm tumors or larger with negative or positive nodes were subjected to mastectomy with axillary clearance. After surgery, the choice of adjuvant treatment was based on the final pathology report. The adjuvant chemotherapy adopted depended on the number of positive nodes [5,6]. For patients having less than three involved nodes, six cycles of CMF (cyclophosphamide, methotrexate and 5 FU) were administered. Six cycles of the FAC combination (5 FU, adriamycin and cyclophosphamide) were administered to patients with more than three positive nodes. The same FAC protocol was adopted for node negative patients having two or more risk factors including tumor size >2cm, tumor grade III, negative hormone receptors and vascular invasion. Adjuvant hormone treatment (20mg Tamoxifen/day for five years) was given to patients having hormone receptor positive tumors [7-9].

The BCS protocol involves excision of the primary tumor with a safety margin and axillary nodal dissection. The adequacy of the surgical margin should be verified by thorough histological examination. This is followed by whole breast irradiation to a dose of 50Gy/five weeks using either telecobalt or 6 MeV linear accelerator [10]. This is followed by a boost dose to the tumor bed with a dose of 14Gy in seven fractions using a 10-12 MeV electron beam.

After mastectomy, post-operative radiotherapy was given according to standard criteria [5,11,12]. Mastectomy patients having a tumor 3cm or more were subjected to chest wall irradiation using a 7-10 MeV electron beam, according to chest wall thickness, with a dose of 50Gy in 25 fractions over five weeks. For patients with central or medial quadrant tumors or patients with heavily infiltrated axillary

nodes, the internal mammary chain was irradiated with a mixed beam (20Gy/10 fractions of photons +30Gy/15 fractions of 12 MeV electrons). These patients were also subjected to supraclavicular irradiation with a dose of 50Gy/25 fractions in five weeks.

Statistical Analysis:

For the statistical analysis, an IBM compatible computer was used along with the STATISTICA 6.0 for Windows XP statistical package. Descriptive statistics were presented as means \pm standard deviations, median values, the 95% confidence interval, along with number and percentage (frequency distributions). The analytical tests used for comparing the two groups included the unpaired student *t*-test (two-sided). Analysis of variance (F-test) was also used to compare more than two groups, while the post hoc test was used for comparing only two groups. Nonparametric testing was also used to confirm significance. The Chi-square test was used for contingency table analysis and the Fisher's exact test for 2x2 tables. Overall survival (OS) and disease free survival (DFS) were estimated according to the Kaplan Rank Test. Multivariate analysis was also performed using the Cox regression model. The significance levels were set at the 0.05 and 0.01 levels [13].

RESULTS

From 1993 to 1998, 823 patients were examined in Kuwaiti hospitals having been diagnosed with primary breast cancer. There were 11 males representing 1.3% of the whole group.

Table (1) gives the demographic and clinical data, while Table (2) gives the pathological and treatment data.

As shown in Table (1), 426 patients (52%) were Kuwaitis while other Arabs represented 31% and non-Arabs 17%. Most patients (58%) were treated in the KCCC and only 14% were treated abroad. Age ranged from 22 to 92 years with a median age of 45 years. Patients older than 70 years represented 3.7% while 3.0% of patients were in the 20 to 30 year-old age group.

The mean tumor size at presentation was 3.8 ± 2.3 cm. Tumors larger than 5cm represented 26% of the group while 55% were node positive (N1 and N2) and distant metastases (M1) were detected in 7.3%.

Table (1): Characteristics of 823 female patients with breast cancer managed at KCCC.

	No	%
<i>Nationality:</i>		
Kuwaiti	426	51.77
Other Arab	255	30.98
Non-Kuwaiti	142	17.25
<i>Diagnosis Hospital:</i>		
KCCC	429	58.21
Other hosp. Kuwait	203	27.54
Abroad	105	14.25
<i>Age groups:</i>		
<20 y	210	25.18
40 y	510	61.15
60+ y	114	13.67
<i>Age: (year)</i>		
Mean \pm SD	46.8 \pm 10.8	
Median	45.0	
Range	22.0:92.0	
95% CI	46.13:47.61	
<i>Menopausal status:</i>		
Pre-menopausal	518	62.9
Post-menopausal	305	37.1
<i>T-stage:</i>		
T1	177	21.9
T2	417	51.61
T3	91	11.25
T4	123	15.24
<i>N-stage:</i>		
N0	365	45.4
N1	335	41.66
N2	104	12.94
Mean N+ve	7.2 \pm 7.9	
Mean examined nodes	20.4 \pm 10.2	
<i>M stage:</i>		
M0	745	92.66
M1	59	7.34

Table (2) illustrate that invasive duct carcinoma was the most prevalent histopathological type (73%). This was followed by ductal carcinoma in situ (12.7%). Stage I disease accounted for 16% only while Stage II was the most prevalent stage (52%). Stages III and IV accounted for 21% and 7.4% respectively. Fifty-five per cent of patients were node positive (N1+N2) at presentation. With regard to the tumor differentiation status, 50% of patients had G2 tumors while poorly differentiated G3 tumors accounted for 35%.

As shown in Table (3), 753 patients (91%) underwent surgery. Mastectomy with axillary clearance was performed in 592 out of these

723 patients, while lumpectomy with axillary clearance (breast conservation) was performed in 161 patients. Of the entire group, 70 (8.5%) did not undergo surgery mostly due to advanced disease or distant metastases. Post-operative radiotherapy was given in 68% of patients. Adjuvant chemotherapy, with or without hormone therapy, was applied in 62% of patients.

Table (2): Pathologic characteristics of 823 female patients with breast cancer managed at KCCC.

	No	%
<i>Tumor size (cm):</i>		
0-	75	16.71
2-	258	57.46
5-	402	22.72
10+	14	3.11
Mean \pm SD	3.8 \pm 2.3	Range 0.3:19.0
<i>Histological diagnosis:</i>		
LCIS	14	1.75
DCIS	101	12.66
IDCa	580	72.68
ILCa	39	4.89
Medullary Ca	34	4.26
Others	30	3.76
<i>Stage:</i>		
I	134	16.28
IIA	233	28.3
IIB	216	26.2
IIIA	78	9.47
IIIB	88	10.7
IV	59	7.17
Unstaged	15	1.8
<i>Nodal status:</i>		
-ve	305	43.7
+ve	386	55.3
Unknown	7	1.0
<i>Tumor differentiation:</i>		
Well	102	15.55
Moderate	326	49.69
Poor	228	34.76

Table (3): Treatment modality of 823 female patients with breast cancer treated in KCCC (1993-1998).

	No	%
<i>Surgery:</i>		
No surgery	70	8.5
Lumpectomy/ax clear	161	19.6
Mastectomy/ax clear	592	72
<i>Treatment adopted:</i>		
S +	753	91.4
RT +	561	68.2
CT +	507	61.6
Hormone +	474	57.6

Tables (4,5) give the treatment results. For the whole group, the overall and disease free survival rates at five years amounted to $76\pm 6.4\%$ and $54\pm 4.6\%$, respectively. Univariate analysis showed that age, tumor size, TNM-categories, nodal status, histological type, tumor differentiation grade, and ER and PR status were significant determinants of both the overall and the disease-free survival rates. Remarkably, no significant differences as regard to overall survival and disease-free survival were noted between patients subjected to either mastectomy plus axillary clearance (OS=79.1%, DFS=56.5%) or lumpectomy +axillary clearance (overall survival=88.6%, DFS=55.4%). This means that breast conservation could attain the same overall survival and disease-free survival levels as mastectomy. Multivariate analysis using the Cox hazard model showed that the independent prognostic factors were limited to nodal status, number of involved nodes and histopathology.

Tables (6,7) give an analysis of the local recurrence and the local recurrence plus distant metastases rates in relation to the different variables. A strong correlation is shown between the local and distant recurrence rates and the TNM parameters, histopathology and ER and PR status.

Table (8) shows an analysis of the recurrence patterns. Of the 161 patients subjected to the breast conservation protocol, there were 12 recurrences (7.5%) within the irradiated breast. A similar incidence rate (7.4%) of chest wall recurrence was noted in the 592 patients subjected to mastectomy. The overall incidence of recurrences in the axillary nodes in both breast conservation and mastectomy groups amounted to 5.8%. Distant metastases developed in 197 patients of both groups. Bones were the most common site of distant metastases (51%), followed by lung (31%), liver (25%) and brain (12.7%).

Table (4): Overall and disease free survival in relation to prognostic factors at 60 months follow-up.

	No (N=823)	OS	<i>p</i> -value	DFS	<i>p</i> -value
Whole group	823	76.0±6.4		54.0±4.6	
<i>Nationality:</i>					
Kuwaiti	426	74.8	0.07	50.9	0.48
Other Arab	255	88.5		51.5	
Non Kuwaiti	142	84.4		61.3	
<i>Age groups:</i>					
<20	210	74.8	0.033	59.0	0.26
40 +	510	84.9		61.5	
60+	114	66.1		61.3	
<i>Menopausal status:</i>					
Pre-menopausal	518	83.7	0.0016**	65.8	0.007**
Post-menopausal	305	73.3		37.6	
<i>T-stage:</i>					
T1	177	89.7	0.001**	61.6	0.0001**
T2	417	83.7		61.8	
T3	91	78.4		39.8	
T4	123	44.03		23.9	
<i>N-stage:</i>					
N0	365	94.03	0.0001**	75.9	0.0001**
N1	335	59.5		42.3	
N2	104	45.7		42.3	
<i>M stage:</i>					
M0	745	72.3	0.0001**	53.8	0.0001**
M1	59	40.15			
<i>Tumor size (cm):</i>					
0-	75	96.2	0.0002**	71.4	0.0007**
2-	258	63.5		70.13	
5+	416	55.3		33.7	

Table (5): Overall and disease free survival in relation to prognostic factors at 60 months follow-up.

	No (N=823)	OS	p-value	DFS	p-value
<i>Histological diagnosis:</i>					
LCIS	14	100.0	0.001*	71.4	0.006**
DCIS	101	94.7			
IDCa	580	60.2			
ILCa	39	100.0			
Medullary Ca	34	100.0			
<i>Stage:</i>					
I	110	95.8	0.0001*	61.7	0.001**
II	451	74.9			
III	165	68.4			
IV	58	40.3			
<i>Nodal status:</i>					
-ve	365	92.6	0.0002**	68.3	0.001**
+ve	439	66.4			
<i>Tumor differentiation:</i>					
Well	102	76.4	0.006*	54.5	0.006**
Moderate	326	85.6			
Poor	228	75.6			
<i>Surgery:</i>					
Lumpectomy/ax clear	161	88.6	0.3	55.4	0.5
Mastectomy/ax clear	592	79.1			
<i>ER and PR:</i>					
+ve	109	67.7	0.01	50.2	0.007**
-ve	362	77.8			

Table (6): Recurrence rate in relation to different prognostic factors.

	LR	%	p-value	LR&DM	%	p-value
<i>Age groups:</i>						
<20	14	6.7	0.38	59	28.1	0.11
40 +	31	6.1				
60+	11	9.7				
<i>Menopausal status:</i>						
Pre-menopausal	30	5.8	0.13	112	21.6	0.043**
Post-menopausal	26	8.5				
<i>Stage:</i>						
I&II	35	7.3	0.37	109	16.34	0.001**
III	16	9.7				
IV	4	6.9				
<i>T-stage:</i>						
T1	16	9.1	0.09	25	14.2	0.001**
T2	20	4.9				
T3	10	10.9				
T4	9	7.4				
<i>N-stage:</i>						
N0	21	5.8	0.49	51	13.75	0.00**
N1	25	7.5				
N2	9	8.7				
<i>M stage:</i>						
M0	52	6.9	0.57	172	22.78	0.01**
M1	3	5.1				
<i>Tumor size (cm):</i>						
<2	11	3.7	0.01	16	21.25	0.07
2-5	13	5.04				
5+	7	11.8				
<i>Tumor differentiation:</i>						
Well	8	7.8	0.18	27	25.47	0.04*
Moderate	18	5.5				
Poor	22	9.7				

Table (7): Recurrence rate in relation to different pathological and treatment factors.

	Local recurrence			Local & distant recurrence		
	No.	%	p-value	No.	%	p-value
<i>Pathology:</i>						
LCIS	0	0.0	0.23	1	7.14	0.004**
DCIS	7	6.9		16	15.53	
IDCa	46	7.9		159	27.04	
ILCa	0	0.0		8	27.51	
Medullary Ca	1	2.9		3	8.82	
<i>Nodal status:</i>						
N-ve	14	5.6	0.09	37	12.1	0.001**
N+ve	33	8.6		124	32.1	
<i>ER and PR status:</i>						
-ve	22	6.08	0.69	77	20.92	0.025*
+ve	9	8.33		34	31.19	
<i>Surgery:</i>						
Lumpectomy/ax.clear	15	9.4	0.23	37	23.1	0.8
Mastectomy/ax clear	39	6.6		141	23.9	

Table (8): Site of recurrence of 197 breast cancer patients after initial treatment.

Site of Recurrence	No	%
Breast	12/161	7.5
Chest wall	44/592	7.43
Regional nodes	41/713	5.75
Bone	100/197	50.8
Liver	51/197	15.4
Lung	60/197	30.5
Brain	25/197	12.7
Soft tissue	2/197	1.02
Lymph node	4/197	2.03
Other	4/197	2.03

DISCUSSION

The clinicopathological features of the present study of breast cancer agree in some aspects and differ in others when compared with other published reports [14]. Males represented 1.3% of the present series, which agrees with the 1% value reported by Donn and Muir, [15] and the 44:1 female: male ratio given for Egyptian patients by El-Bolkaini [16].

In the present study the average age at diagnosis was 45 years, which is one decade younger than that in most Western countries. Giles and Thursfield, for example, reported an average age of 56 years for breast cancer patients in Victoria, Australia [17]. As reported by Bolkaini [16], the median age incidence of Egyptian breast

cancer patients was 46 years, which is close to that of Kuwaitis. A similar age incidence has been reported for patients in all GCC countries by Hamadan [18]. It is interesting to note that in the present report patients older than 70 years represented 3.7% of the whole group while 3.0% were between 20 and 30 years old.

The overall survival of the entire group at 60 months amounted to $76 \pm 6.4\%$ with a disease-free survival of $54.3 \pm 4.5\%$. These results are comparable to those reported in Egypt (five-year disease-free survival of 33-46%) but lower than the results given in western literature (84.0% given in an Australian report [17]). This difference reflects the higher representation of the more advanced stages due to a tendency for late diagnosis. This is shown by a mean tumor size at diagnosis of $3.8 \pm 2.3\text{cm}$, while 26% of the tumors were $>5\text{cm}$. These are larger sizes than those generally reported in the Western literature, for example by Gills and Thursfield [17], where tumors $>5\text{cm}$ represented 3.8% only. In the present series, 55% of patients were node positive (N1+N2) while 7.3% had distant metastases (M1). The tendency for late diagnosis is also reflected as a relatively low representation of stage I (14.0%) while about 38% of patients were in stages III and IV. Furthermore, 44% of patients were node positive. In addition to late diagnosis as an interpretation for the relative prevalence of late advanced stages, there is also the possibility of a relatively more biologically aggressive tumors in Kuwait as suggested by the predominance of the disease (67%) in pre-

menopausal women. Irrespective of the interpretation, this advanced stage pattern urges for the reinforcement of the early detection programs.

Univariate statistical analysis showed a number of prognostic factors including tumor size, TNM stage, histological type, nodal status, number of positive nodes, histological grade and ER and PR status. However, multivariate analysis using the Cox-model showed that the nodal status, number of involved nodes and histopathology were the only independent prognostic factors. These patterns are in general agreement with certain published reports, for example the report of Voogd, et al. [19], where the nodal status is the only independent significant prognostic factor ($p=0.03$) with regard to disease-free survival.

Breast conservation strategy was adopted in 161 patients. This procedure yielded similar treatment results as the group of 592 patients subjected to mastectomy. The only clinical difference between the two groups was related to the size of the primary tumors; breast conservation was limited to patients with tumors less than 3cm. Recent published results in the Western literature showed that breast-conserving therapy could generally yield similar results to mastectomy in Stage I and II breast cancer [19, 20]. The combined EORTC and DBVG report given by Voogd et al., [19] is a typical example.

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