RESEARCH COMMUNICATION

Survival Analyses of Breast Cancer Patients-the Shaukat Khanum Memorial Experience

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Abstract

Seven hundred subjects with breast cancer malignancies were followed up in time from December 1994 to December 2002 to determine survival distributions between sub-groups of breast cancer patients who had undergone surgical resection of the tumor followed by adjuvant treatment. Tumor size, nodal status, and Estrogen Receptor (ER) status at the time of presentation were ascertained. Tumors were classified according to the TNM system of the American Joint Committee on Cancer (AJCC), sixth edition, and grouped into T1/T2 and T3/T4; lymph nodes were categorized as N0 (node-negative) and N1, N2, and N3 combined (node-positive). The endpoint of interest for disease-free survival was relapse, and for overall survival, it was death. The Wilcoxon statistics for testing the equality of disease-free survival distributions between groups of patients with tumor size greater than 5 versus less than or equal to 5 cm, node-positive versus node-negative, and ER-positive versus ER-negative were found to be statistically significant ($p < 0.05$). For overall survival, substantial differences were found between groups of patients stratified according to tumor diameter and nodal involvement, but none for ER status.

Key Words: Breast cancer - estrogen receptor - nodal status - survival - tumor size

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Introduction

Breast cancer is one of the most common forms of cancers observed in women. However, five times higher rates in Japanese women as compared to those women living in the United States (US) have puzzled researchers over time (Lawson, 1999). At the Shaukat Khanum Memorial Cancer Hospital and Research Center, (SKMCH and RC), in Lahore, Pakistan, breast malignancy is the leading cause of morbidity since the hospital started functioning in December 1994.

Materials and Methods

Population Under Study

This is a sequel to the manuscript written earlier and titled as, "Variables associated with recurrence in breast cancer patients-the Shaukat Khanum Memorial experience," in which, of a total of 2,328 patients, seven hundred patients were selected by following certain criteria. Analyses were conducted on these 700 patients with non-metastatic, invasive breast carcinoma for whom complete information on variables under study was available in the medical records. These patients were registered with the hospital from December 1994 to December 2002 and were treated according to the National Comprehensive Cancer Network (NCCN) guidelines. In a small number of cases, treatment was modified based on physicians' discretion or due to the presence of co-morbidities. However, survival analyses were not stratified by treatment. The study was approved by the Scientific Review Committee at SKMCH and RC.

Variables in the Study

Table 1 summarizes the variables under study along with their distribution. The endpoint of interest for disease-free survival (DFS) analysis was recurrence and for overall survival (OS), it was death. Of the previously selected variables in logistic regression, the ones selected for this study were tumor size, nodal status, and Estrogen Receptor (ER) status. The reason for selection of these predictors was that a sub-group of each showed a significant association with the likelihood of disease recurrence in the multivariate analyses performed earlier.

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Table 1. Distribution of Variables in the Study

Variable	Count (%)
T1/T2	494 (70.6)
T3/T4	206 (29.4)
N0	245 (35.0)
N1/N2/N3	455 (65.0)
ER-negative	454 (64.9)
ER-positive	246 (35.1)

Statistical Analyses

Survival curves were computed by applying the Actuarial (life table) method of analysis. Statistical Package for Social Sciences (SPSS) version 10.0 was used to run all the analyses. Wilcoxon test for measuring significance was performed to investigate the differences in DFS and OS.

Table 2. Distribution of Events and Non-events for Disease-Free Survival According to Variable

Variables	Events (Relapse)	Non-events (Count)
Tumor diameter		
</= 5 cm	80	414
> 5 cm	67	139
Nodal status		
Node-negative	28	217
Node-positive	119	336
ER status		
ER-negative	109	345
ER-positive	38	208

Table 3. Results for Disease-free Survival between Different Levels of Prognostic Factors

Variables	5-year cumulative survival	Mean survival time in months	Wilcoxon stat	DF	*Prob.
Tumor diameter			20.30	1	<.0001
</=5 cm	0.69	68.19			
> 5 cm	0.48	55.60			
Nodal status			18.49	1	<.0001
Node-negative	0.81	74.23			
Node-positive	0.55	59.39			
ER status			10.69	1	0.001
ER-negative	0.58	61.31			
ER-positive	0.71	69.90			

*P is significant at an alpha level of 0.05.

Table 4. Distribution of Events and Non-events for Overall Survival According to Variable

Variables	Events (Death)	Non-events (Count)
Tumor diameter		
</= 5 cm	25	469
> 5 cm	28	178
Nodal status		
Node-negative	08	237
Node-positive	45	410
ER status		
ER-negative	41	413
ER-positive	12	234

Results

For DFS, disease-free interval (DFI) was computed by determining the intervals between the dates of remission and relapse. Tests for significance performed detected appreciable differences in survival curves between sub-groups of all of the variables tested. For overall survival intervals (OSI), dates of diagnosis and death were taken as reference points. In the study of OS, although there were substantial differences in survival distributions within the categories of tumor size and nodal involvement, there were none for ER status. Tables 2-5 display the results for DFS and OS for these selected predictors, whereas, figures 1-6 depict survival curves corresponding to each variable in the analyses.

Table 5. Results for Overall Survival between Different Levels of Prognostic Factors

Variable	5-year cumulative survival	Mean survival time in months	Wilcoxon stat	DF	Prob.
Tumor diameter			14.43	1	0.0001
</= 5 cm	0.86	80.65			
> 5 cm	0.76	75.29			
Nodal status			9.37	1	0.002
Node-negative	0.93	83.35			
Node-positive	0.73	77.42			
ER status			3.47	1	0.06
ER-negative	0.75	73.65			
ER-positive	0.86	83.80			

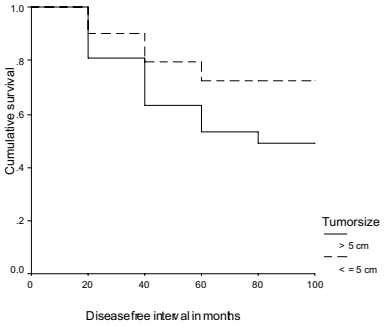

Figure 1

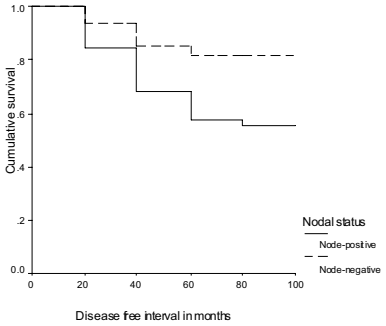

Figure 2

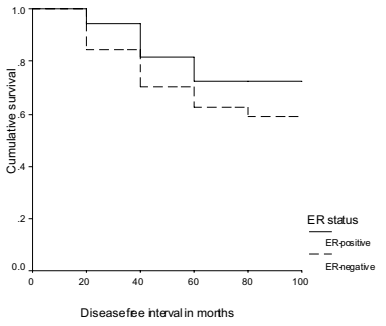

Figure 3

Figures 1-3. Estimated Disease-free survival for Patients with Tumor Size </= 5 cm Versus > 5 cm, Node-negative Versus Node-positive, and ER-positive Versus ER-negative

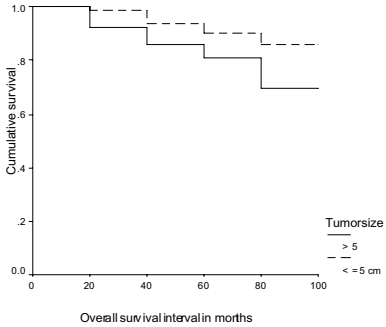

Figure 4

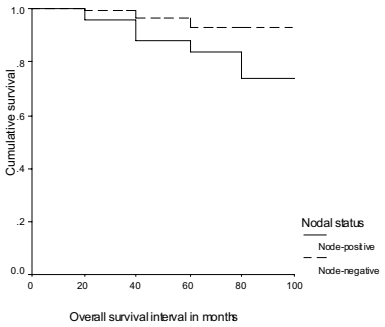

Figure 5

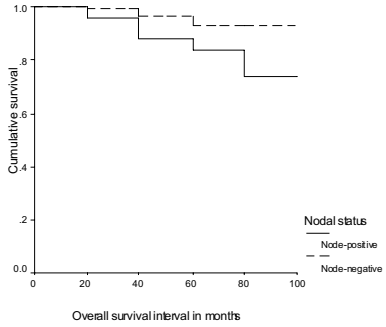

Figure 6

Figures 4-6. Estimated Overall Survival for Patients with Tumor Size </= 5 cm Versus > 5 cm, Node-negative Versus Node-positive, and ER-positive Versus ER-negative

Table 3 summarizes the 5-year cumulative survival rates (5CSR) for predictors under study, with the end point of interest being disease relapse. It also shows that the mean survival time to recurrence ranges from 55.6 to 74.2 months. Figures 1-3 also depict that the 8-year cumulative survival rates (8CSR) for tumor size </= 5 cm, node-negative, and positive ER status, are nearly the same as those after 5 years of start of study.

In table 5, the high 5CSRs also correspond with the high mean survival time to death for each sub-group of the selected tumor characteristic. Moreover, the 8CSR is above 80% for each of these sub-categories, as is clearly seen in figures 4-6.

Discussion

Researchers reporting survival of 24,740 breast cancer patients in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute found an inverse relationship between number of positive lymph nodes and overall survival in tumors grouped into < 2 cm, 2-5 cm, and > 5 cm (Greene et al., 2002). Our study reported decreasing disease-free and overall survivals with increase in tumor diameter and with nodal involvement as is depicted in graphs based on the Actuarial estimates.

Most studies, including one by Carter, have reported increasing tumor size and lymph node involvement to be prognostic factors for breast cancer, decreasing survival independent of one another (Carter et al., 1989). However, one study recently reported lymph node negative status to be most unlikely as a predictor in survival (Moorman et al, 2001). The role and importance of ER have been studied in breast cancer for more than 25 years now (Platet et al., 2004), and it has been demonstrated that the DFS and OS are better in patients with ER-positive status than in negative (Donegan, 1992). Our study has shown substantially improved DFS in those with ER-positive category but for OS the results have remained unremarkable. This may reflect good response to hormonal treatment in those who are positive for ER delaying the onset of recurrence, whereas, later in the course of the disease, confounding by various factors may negatively influence the overall survival interval in each category of ER status.

The survival rates reported in our study, although quite high, do not take into account differences in treatment or a patient's general health; they are only an average of outcomes of patients with the same category. The outlook for any individual patient may differ from these average figures. Despite this, most of the findings in our hospital-based study can be considered consistent with results reported in the developed nations of the world. However, population-based studies undoubtedly remain the cornerstone of prevention and control of cancer, as is seen in many technologically advanced countries of the world.

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