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Five Year Survival Analysis of Patients with Clinical Stages I and IIA Breast Cancer who Received Initial Treatment at North Carolina Hospitals

by

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ABSTRACT

This study examines the impact of the three major breast cancer treatment types, age, and stage at diagnosis on the survival rates of breast cancer patients. Research indicates that the survival rates for patients treated with Breast Conserving Surgery (BCS) and radiation (when given together, these two treatments are known as Breast Conservation Treatment or BCT) are comparable to those undergoing mastectomy. In North Carolina, this finding has not been examined on a population level. North Carolina Cancer Registry data for all 3,059 stage I and IIA (earliest invasive) breast cancer cases treated at North Carolina hospitals in 1995 were used in this study. Of the 3,059 patients, 1,721 (59%) underwent mastectomy. The total numbers of patients who underwent BCT and BCS were 750 and 431, respectively. Five-year survival was evaluated using the Cox proportional hazards method. Although multivariate analyses demonstrated that the 5-year overall survival rates of patients treated with BCT was not significantly different from those who underwent mastectomy, the survival rate of BCT patients was significantly higher than that for BCS patients (P-value = 0.046). Survival differences between stages I and IIA were statistically significant (P-value = 0.0001). No significant survival difference was found according to age group. These data indicate that in a large population of breast cancer patients, survival rates are comparable among three standard treatments. There is also some evidence to indicate that Breast Conservation Treatment for stages I and IIA breast cancer patients is a safe alternative to mastectomy and preferable to BCS alone.

NORTH CAROLINA DEPARTMENT OF HEALTH AND HUMAN SERVICES

Introduction

Breast cancer is a disease that occurs almost exclusively in women. Each year, more than 180,000 women in the United States learn they have breast cancer. In 1998 there were 1,168 deaths from breast cancer among North Carolinians. With breast cancer as the second major cause of cancer death among women, this accounted for 7.6 percent of the state's cancer deaths and 1.7 percent of all deaths.[1]

The risk of breast cancer increases gradually as a woman gets older. Most breast cancers occur in women over the age of 50, and the risk is especially high for women over age 60. Research has shown that certain conditions place a woman at increased risk for breast cancer. Women who have had breast cancer face an increased risk of getting breast cancer again. Changes in certain genes make women more susceptible to breast cancer. In families in which many women have had the disease, gene testing can show whether a woman has specific genetic changes known to increase the susceptibility to breast cancer. A woman's risk for developing breast cancer increases if her mother, sister, daughter, or two or more other close relatives, such as cousins, have a history of breast cancer, especially at a young age. Women who had their first child after the age of 30 have a greater chance of developing breast cancer than women who had their children at a younger age. Also at a somewhat increased risk for developing breast cancer are women who started menstruating at an early age (before age 12), experienced menopause late (after age 55), never had children, or took hormone replacement therapy or birth control pills for long periods of time. Each of these factors increases the amount of time a woman's body is exposed to estrogen. The longer this exposure, the more likely she is to develop breast cancer.[2]

Detection of breast cancer at an early stage, when the disease is less severe, provides a greater chance of survival. In addition to serving as a predictor for the probability of survival, disease severity is also of critical importance in determining an individual's breast cancer treatment.[3] The most important predictor of treatment outcome for breast cancer patients is disease severity at the time of treatment.

Stage is one indicator of disease severity. The American Joint Committee for Cancer Staging and End Results Reporting uses the TNM (tumor, nodes, metastasis) classification, in which the stage evaluation includes the size of the primary tumor and its involvement of the skin.[4] Physicians often define the stage of an individual's breast cancer according to the TNM staging system, which is known to be more reliable than just the clinical assessment of tumor size and lymph nodes.[4]

Stage I and IIA (earliest invasive) cancer cases are used for this study. According to the TNM coding system, stage I cancer is defined based on a tumor smaller than 2 cm and no positive movable axillary nodes or with no known distant metastasis. Stage IIA is defined based on a tumor 2-5 cm with no positive axillary nodes or with no known distant metastasis.

Patients with stages I and IIA breast cancer may have three surgical options: 1) Breast Conserving Surgery (BCS), also referred to as a lumpectomy, which can be preformed either with or without an axillary lymph node dissection; 2) Breast Conserving Treatment (BCT), a lumpectomy and radiation therapy; or 3) a mastectomy (subcutaneous, simple, or modified radical). A subcutaneous mastectomy is the surgical removal of the breast glands and fat only, leaving intact the skin, nipple, and lymph nodes. Simple mastectomy is removal of the entire breast, the axillary tail, and the pectoral fascia. Surgical removal of the entire breast as well as the lymph nodes in the underarm region is called a modified radical mastectomy. Breast Conserving Surgery (BCS) is another option for women who have small tumors. This surgery saves as much of the breast tissue as possible and is generally performed on women with smaller tumors. If radiation to the tumor site follows surgery then the treatment

is called Breast Conserving Therapy (BCT). Determining the most appropriate treatment plan for patients with stages I or IIA breast cancer must be individualized by considering the patient's age, lifestyle, and medical needs. There are recommended guidelines for early breast cancer treatment.[5] The National Institute of Health Consensus Panel concluded that a majority of stage I and IIA breast cancer patients are eligible for BCT and that conservative methods are preferable to mastectomy because they allow the patient to preserve the breast. [6]

The results of a randomized study showed that there is no difference in survival between the three treatment groups at a median follow-up of 12.5 years.[7] However, omission of radiation after BCS increases the risk of local recurrence significantly.[8] Combining BCS with radiation can increase the likelihood of destroying any undetected cancer cells remaining after the surgery. Studies indicate that a woman who receives BCT (BCS plus radiation) will have the same overall survival as if she received mastectomy alone.[7,9-16]

Most prospective studies are inclusive of TNM stages I and II (Stage II consists of IIA and IIB). In this study we evaluated the effectiveness of BCT in operable breast cancer with the specific aim of looking at the results of BCT (lumpectomy plus radiation) versus mastectomy or BCS alone (lumpectomy) in patients with TNM stages I and IIA. Another prognostic factor to consider is age. Survival rates for breast cancer increase with age at diagnosis. Women who develop breast cancer when they are younger than 50 have a lower survival rate than older women. Young women with breast cancer, on the basis of age alone, are high risk patients.[17] Researchers speculate that younger women have lower survival rates because their tumors may be more aggressive and less responsive to therapies.[18] It is for these reasons that age at diagnosis was included in the database for this analysis.

Methods

The data was obtained from the computerized breast cancer file from the North Carolina Central Cancer Registry for the year 1995. Information extracted included the following: type of treatment (BCS, BCT, mastectomy), TNM stage (I, IIA), and age at diagnosis. There were two main justifications for selecting only TNM stage I and IIA patients: 1) no known distant metastasis in these two stages, resulting in higher survival rates; and 2) a smaller-primary tumor size which would increase the feasibility of being able to use Breast Conserving Surgery and radiation therapy with minimal distortion of the breast contour. This study included 3,059 patients diagnosed with breast cancer in 1995 for whom stages I and IIA information was available. In order to determine the vital status of the patients diagnosed with breast cancer in 1995, the records were matched with the North Carolina death files from 1995 through 1999. A passive patient survival status (dead or alive) technique was employed and patients were followed until December 31, 1999. The 1995 breast cancer incidence records were matched to the 1995-1999 mortality records (ICD-9=174 and ICD-10=C50) using a SAS program.[19] Each breast cancer incidence record was compared with every death record for agreement on social security number, last and first name, birth date, and race.

The three treatment categories included BCT, BCS, and mastectomy. Mastectomy was the most common course of treatment (1,721), with the modified radical type being the overwhelming choice (1,613), followed by simple (98) and subcutaneous (10). Considering the other types of treatment, 750 received BCT, 431 received BCS, while 157 received an unknown treatment. The survival time in months for each patient was calculated from the date of diagnosis to the date of death. One hundred fifty-one of these patients were reported dead due to breast cancer. A value of 61 months was assigned to those patients who did not die or died of causes other than

breast cancer. These values were considered as "censored" in the analysis. [20-21] The major purpose of the analysis was to determine five-year survival rates from breast cancer. The model included the terms for treatment type, TNM staging, and age group at diagnosis. The data were analyzed with the SAS software.[19] Multivariate survival analyses were conducted using a proportional hazards method proposed by Cox.[22]
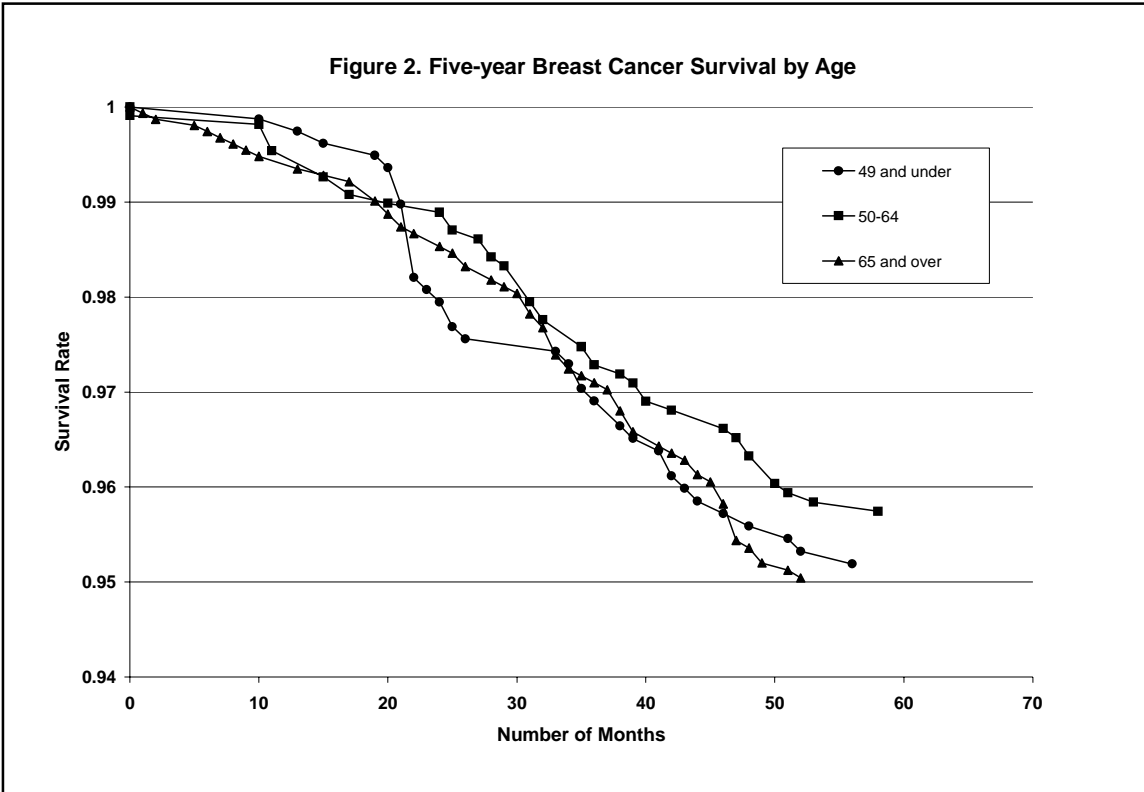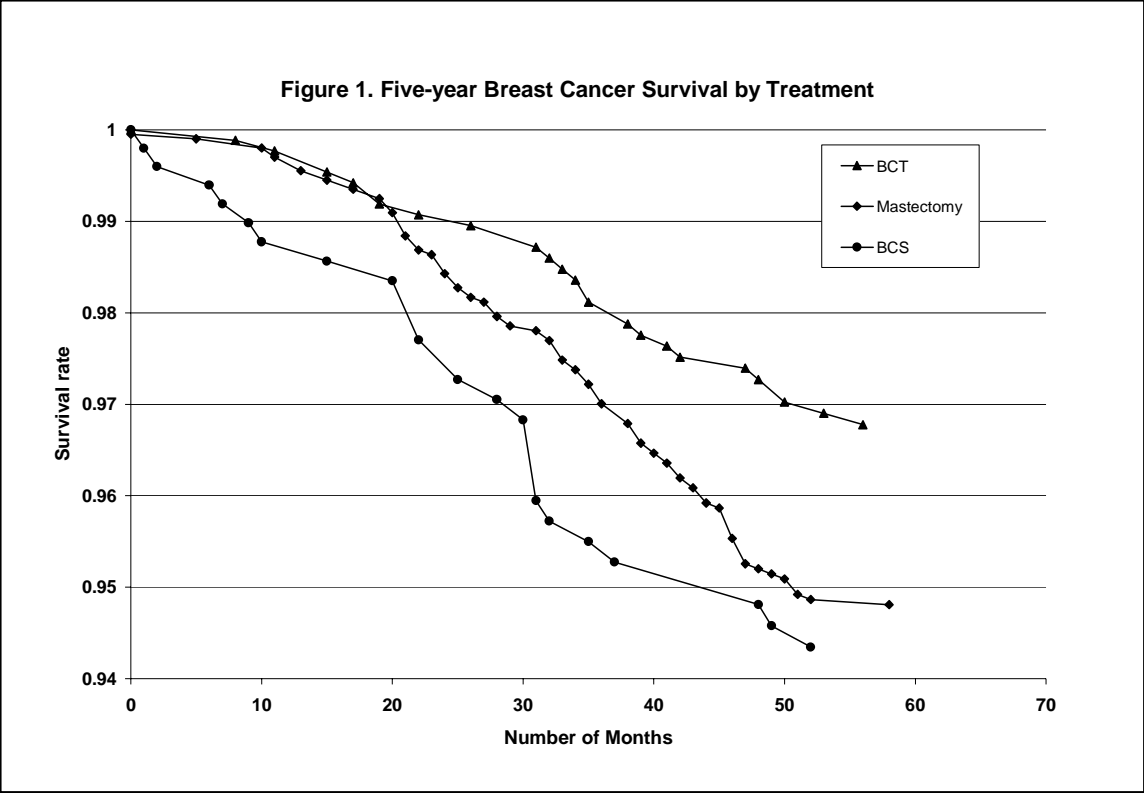
Results

During the study period 1995 to 1999, 151 female breast cancer deaths identified from the Center for Health Informatics and Statistics mortality database met the selection criteria and were included in the survival analysis. The distribution of the study population is presented in Table 1. Among the 3,059 patients, 685 (22%) were less than 50 years of age, 974 (32%) were 50 to 64 and 1,400 (46%) were 65 or older. The women ranged in age from 21 to 97 years, with a median age of 62 years.

Almost two-thirds of the identified cases were classified with Stage I disease; 1,983 or 65 percent were in this group compared to 1,076 or 35 percent who the had more severe stage IIA disease. The distribution by treatment illustrates that the majority of patients were treated with mastectomy (1,721) followed by BCT (750) and BCS (431). Table 1 also presents the number of patients who were alive as of December 31, 1999 (five-year survival) and the results of the five year survival analysis. There was a significant difference in the death rates of patients treated with BCS versus BCT (P-value = 0.046). The BCS patients were 1.73 times as likely to die as patients treated with BCT. The mastectomy patients were 1.33 times as likely to die as patients who received BCT; however, there was no statistically significant difference in survival (P-value = 0.195). Overall survival (refers to survival with or without recurrence of disease) curves for the three treatment types are plotted in Figure 1. There were no statistically significant differences in survival among the three age groups, in this group of women with early-stage breast cancer. Figure 2 illustrates the survival patterns by age group.

			Adjusted		
	Breast	Breast	Survival	Risk of	
	Cancer	Cancer	Rate	Death Ratio	
Prognostic Factors	Cases	Survivors	(Percent)	(95% CI)	P-Value
Age at Diagnosis (yrs)					
49 and under	685	648	95.1	0.88(0.59,1.31)	0.5239
50-64	974	925	95.7	0.96(0.79,1.16)	0.6422
65 and over	1,400	1,321	95.0	1.00	
Stage (TNM)					
Stage I	1,983	1,921	96.8	0.32 (0.23, 0.45)	0.0001
Stage IIA	1,076	981	90.1	1.00	
Treatment Type					
BCS	431	405	94.3	1.73(1.01,2.98)	0.0461
Mastectomy	1,721	1,627	94.8	1.33(0.86,2.05)	0.1953
BCT	750	724	96.7	1.00	
Unknown Treatment	157				

Table 1: Multivariate survival analysis of 1995 patients with breast cancer 5-year follow-up, 1995-1999

Figure 1. Five-year Breast Cancer Survival by Treatment

Figure 2. Five-year Breast Cancer Survival by Age

Twenty-seven of the total patients with unknown treatment were in the under 50 age group, 49 of them were in the 50-64 age group, and the majority of the unknowns were for patients in the 65 and over age group. Fifty-eight percent of the 157 patients with unknown treatment were among the stage I breast cancer patients.

Analysis by Stage of Disease

Stage also had a significant impact on survival rates. The 5-year survival rate among women diagnosed at stage I (96.8%) was significantly higher ($p<.001$) than the survival rate for those diagnosed at stage IIA (90.1%) (Figure 3). The stage I breast cancer patients were 0.32 times as likely to die as patients diagnosed with stage IIA breast cancer (Table 1).

Table 2 describes the number of patients in each treatment group by stage of disease and indicates a greater proportion of mastectomy patients were stage IIA (41%) than for either of the other groups (about 25%). Therefore, there is some potential for bias in the survival comparisons of mastectomy

Table 2: Distribution of treatment according to stage			
Treatment	Stage I	Stage IIA	Total
BCT			
Number of Cases	561	189	750
Percent	75	25	100
BCS			
Number of Cases	312	119	431
Percent	72	28	100
Mastectomy			
Number of Cases	1,019	702	1,721
Percent	59	41	100

with each of the breast conserving therapies. The comparisons between BCT and BCS are less susceptible to selection bias because of the similarity of the patients in terms of disease severity.

Because of this pattern, the initial survival analyses included stage by treatment interaction terms in the model. The p-values for the interaction terms indicated that there was no stage by treatment interaction (p-value > 0.05). From this, we concluded that

Figure 3. Five-year Breast Cancer Survival by Stage at Diagnosis
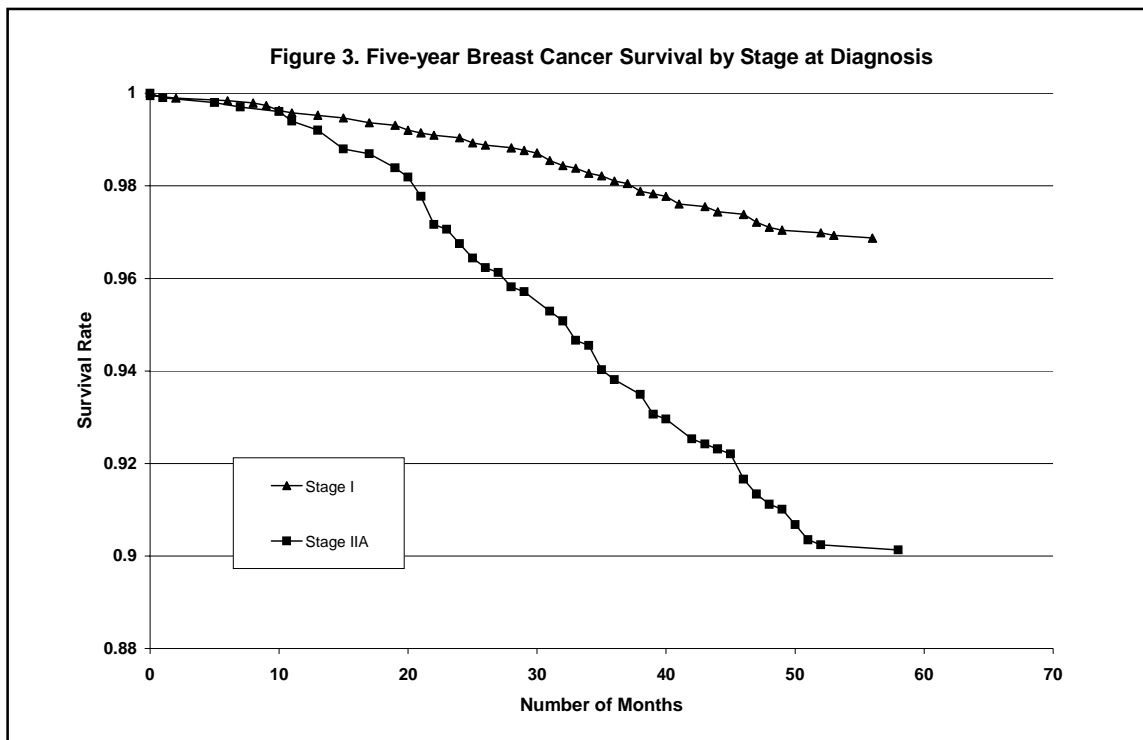
the patterns of survival by treatment do not vary significantly from Stage I to Stage IIA. Since the stage by treatment interaction terms were not significant these terms were dropped from the model.

Discussion

This study provides treatment-specific survival rates for stage I and stage IIA breast cancer patients based on records available from the North Carolina Central Cancer Registry. It also adopts standard survival analysis methods used worldwide.

The overall findings of this study show that a breast cancer patient's chance of surviving is almost the same with either mastectomy or breast conserving surgery combined with radiation (BCT) but significantly lower with breast conserving surgery without radiation (BCS).

The survival difference between BCT and mastectomy for breast cancer has been studied for more than 20 years. However, no previous studies have compared breast mastectomy with breast conserving surgery with and without radiation for stage I and IIA breast cancer patients. This study found that the 5-year survival for Stage I and IIA women treated with BCT was as good as those who received mastectomy. BCS along with radiation did improve survival of these patients. The survival rate was significantly worse for patients who received BCS without any radiation treatment.

One implication of these findings is that BCT could be offered more frequently as a safe alternative to mastectomy for patients with Stage I and IIA breast cancer. Further analysis (not shown here) controlling for stage of disease, indicated that this benefit may be most pronounced among stage I cases, since BCT had a more favorable outcome than either of the other treatment modalities in this group. For stage IIA cases the three treatments yielded equivalent survival rates.

It must be noted that this analysis by stage only partially adjusts for severity of disease, which cannot be completely controlled for due to the observational nature of the study. Clearly, disease severity has some direct impact on both the choice of treatment and on the outcome of treatment. Another consideration in reviewing these findings is that, in this study, approximately 5 percent of breast cancer patients were excluded because treatment information was not recorded in the North Carolina Central Cancer Registry databases. This will not affect the results much unless the characteristics of this group for which treatment information is unavailable differ substantially from the group for which treatment information is available.

To confirm these findings and eliminate potential biases due to study design, a randomized control trial should be conducted. However, in the interim, this analysis suggests benefits of breast conserving surgery combined with radiation (BCT) as a treatment option for women with Stage I or IIA breast cancer.

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