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Radiation Use and Long-Term Survival in Breast Cancer Patients with T1,T2 Primary Tumors and 1–3 Positive Axillary Lymph Nodes

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Abstract

Background—For patients with stage II breast cancer with 1–3 positive lymph nodes, controversy exists as to whether radiation as a component of treatment provides a survival benefit.

Methods—We analyzed the data from breast cancer patients with stage II breast cancer with 1–3 positive lymph nodes diagnosed between 1988–2002 in the Surveillance, Epidemiology, and End Results registry and compared the outcome of the 12,693 patients treated with breast conservation therapy with radiation (BCT + XRT) to the 18,902 patients treated with mastectomy without radiation (MRM w/o XRT).

Results—Patients treated with BCT + XRT were younger, were more likely to be treated in recent years of the study period, more commonly had T1 primary tumors, and had fewer involved nodes compared to those treated with MRM w/o XRT ($p < 0.001$ for all differences). The 15-year breast cancer specific survival for the BCT + RT group was 80% vs. 72% for the MRM w/o RT group ($p < 0.001$). Cox regression analysis showed that MRM w/o XRT was associated with a hazard ratio for breast cancer death of 1.19 ($p < 0.001$) and for overall death of 1.25 ($p < 0.001$). The survival benefit in BCT + RT group was not limited to subgroups with high-risk disease features.

Conclusions—Radiation use was independently associated with an improved survival for patients with stage II breast cancer with 1–3 positive lymph nodes. As multivariate analyses of

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retrospective data cannot account for all potential biases, these data require confirmation by randomized clinical trials.

Keywords

mastectomy; radiation; breast cancer; stage II

INTRODUCTION

Radiation therapy plays an important role in the multidisciplinary management of breast cancer. The most recently published meta-analysis by the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) indicated that radiation reduced the probability of local-regional recurrence and improved overall survival when used as a component of breast conservative therapy and, for patients with positive lymph nodes, when used after mastectomy and axillary clearance. {Group, 2005 #1}

The indications for when to use radiation after mastectomy remain unclear despite over 50 years of study. Results from the EBCTCG meta-analysis and the most recent randomized trials that investigated the benefits of postmastectomy radiation suggest that all patients with lymph node-positive disease benefit from this adjuvant treatment. {Group, 2005 #1; Nielsen, 2006 #3; Ragaz, 2005 #2} However, other large studies investigating local-regional failure patterns after mastectomy and systemic treatments have identified subpopulations of patients with lymph node-positive breast cancer for whom the risk of local-regional recurrence is low. In the United States, most patients with lymph node-positive disease who are treated with mastectomy have a standard axillary level I-II lymph node dissection and receive systemic therapy. For patients with stage II breast cancer with 1–3 positive lymph nodes who are treated with this approach, studies have reported that the 10-year local-regional recurrence risk is less than 15%. {Katz A, 2000 #5; Recht A, 1999 #4; Taghian A, 2004 #6} In contrast, randomized trials from Europe and Canada, in which less extensive axillary surgery was performed, reported a local-regional recurrence of 30% or greater for patients with this 1–3 positive nodes. {Nielsen, 2006 #3; Ragaz, 2005 #2} With the lower absolute risk for persistent local-regional disease in the United States series, the local-regional benefits of radiation would be predicted to be much less than that reported from the European and Canadian trials. Consequently, whether adjuvant radiation would favorably affect survival for this cohort of patients treated in the United States is unknown.

The question of whether adjuvant radiation provides a therapeutic advantage for patients with stage II disease and 1–3 positive lymph nodes treated with a modified radical mastectomy and standard systemic therapies would be best addressed through a prospective randomized trial. The potential benefits associated with radiation for this cohort would be predicted to be modest, and as such, a relatively large sample size would be needed. Unfortunately, such a trial was initiated in the United States but failed to meet accrual goals.

An alternative method to study this question is to retrospectively investigate the data within a large United States database. This method was used by Smith et al., who analyzed the benefits of postmastectomy radiation in the Surveillance, Epidemiology, and End Results (SEER) dataset by comparing the outcome of patients treated with mastectomy to those

treated with mastectomy and radiation. {Smith, 2005 #7} This study found radiation use to be associated with an improved survival in patients with more advanced nodal disease, but did not find radiation use to be independently associated with an improved survival in those patients with 1–3 positive lymph nodes. However, it is likely that hidden biases affected these results, as the decision to use radiation after mastectomy was not randomized. Herein, we use an alternative comparison to study the benefits of radiation for patients with stage II disease with 1–3 positive lymph nodes using SEER data. We compared patients with this stage disease treated with breast conservation therapy with radiation to those patients treated with mastectomy without radiation. Our rationale for this approach was that radiation is indicated for all cases treated with breast conservation. Therefore, unlike its use after mastectomy, fewer disease-related biases would affect radiation use patterns in patients treated with breast conservation.

METHODS

We queried the SEER registry of breast cancer patients diagnosed between 1988–2002 using the selection criteria of women with malignant breast cancer, diagnosis year 1988–2002, American Joint Cancer Commission defined stage II disease, 1–3 positive lymph nodes, and age at diagnosis between 25–85. Women who had bilateral breast cancer or another primary cancer were excluded from this study. Finally, the 2,976 patients who were treated with mastectomy and received radiation as a component of their primary treatment (13.6% of the mastectomy population) and the 3,854 patients who were treated with breast conservation but who did not receive radiation (23.3%) were excluded.

The SEER network of cancer registries was established in 1973 and the data for the treatment years of this study included the states of Connecticut, Iowa, Hawaii, New Mexico, Utah, the metropolitan areas of San Francisco-Oakland and Detroit, and registries in Seattle-Puget Sound and Atlanta. In 1992, registries from Los Angeles, San Jose-Monterey, and the Alaska Native Tumor registry were added. The case ascertainment rate from the SEER registries has been reported to be 97.5%. {Zippin, 1995 #8} The ascertainment of inpatient treatment is also high, with a sensitivity of 95% for mastectomy or lumpectomy, but the ascertainment for outpatient treatments such as radiation may be somewhat lower. {Malin, 2002 #9} Despite this limitation, the SEER database remains the authoritative source of population-based information on cancer incidence and survival in the United States.

The resulting study population consisted of 12,693 patients who were treated with breast conservation with radiation (BCT + XRT) and 18,902 patients who were treated with mastectomy without radiation (MRM w/o XRT). All patients included had stage II breast cancer with 1–3 positive lymph nodes. Differences between the two populations were tested using the chi-squared test for categorical variables and t-test for continuous variables. Breast cancer-specific survival and overall survival rates were calculated using the Kaplan Meier method, with differences between the two groups tested with the log rank test. For the purpose of breast cancer-specific survival, deaths from breast cancer were determined using the International Classification of Disease (ICD) 9 code of 1749 or ICD-10 code of C509 ascertained from death certificates. A multivariable analysis was performed using the Cox

regression model. Statistical analyses were performed using SAS software (Version 8.02, SAS Institute, Cary, NC).

RESULTS

Table 1 shows the disease and demographic characteristics of the two comparative populations of this study. As indicated, there were a number of statistical differences between the two groups. Specifically, the BCT+XRT population was younger, was treated during the more recent years of the study, had a lower percentage of African-American patients, had different geographic regions of treatment, had smaller tumor sizes and lower number of positive lymph nodes, had lower grade disease, and had a greater percentage of estrogen receptor-positive and/or progesterone receptor-positive disease.

Figure 1 shows the Kaplan-Meier breast cancer-specific survival curves for the two groups. The 10-year rates were 84.2% for the BCT+XRT group versus 78.2% for the MRM w/o XRT group ($p<0.001$). The 10-year overall survival rates were also significantly different (74.3% vs. 63.1%, $p<0.001$). The results of a multivariable Cox regression analysis for the endpoint of breast cancer-specific survival are shown in Table 2. Treatment with MRM w/o XRT was independently associated with a worse breast cancer-specific survival with a hazard ratio (HR) of 1.19 ($p<0.001$). The HR for treatment with MRM w/o XRT for the endpoint of overall survival was 1.25 ($p<0.001$).

Figure 2 shows breast cancer-specific survival curves for the two groups of patients stratified according to T stage. In both patients with T1 disease with 1–3 positive lymph nodes and in patients with T2 disease with 1–3 positive lymph nodes radiation use was associated with an improved survival. A similar finding was noted when patients were divided according to whether they had 1, 2, or 3 positive lymph nodes (Figure 3). As shown in these curves, and in the data from the Cox multivariable analysis provided in Table 2, BCT + XRT was associated with an improved outcome in each subgroup. We also evaluated the data according to grade and age and found that the survival advantages associated with BCT + XRT treatment were not limited to patients with high grade versus intermediate/low grade disease or to younger aged patients (data not shown).

DISCUSSION

The data from this paper suggest that radiation use may offer a therapeutic advantage for patients with stage II disease with 1–3 positive lymph nodes. This advantage was seen both in patients with T1 disease and in patients with T2 disease, and across all numbers of positive lymph nodes. Using the SEER database to investigate the benefits of radiation use for patients with stage II disease and 1–3 positive lymph nodes has some advantages and disadvantages. The primary advantage of this methodology is that it provides a large sample size that will permit detection of small absolute differences in outcome. Furthermore, it represents standards of United State practice patterns, which may provide more clinically relevant data for patients in the United States compared with randomized studies performed in Europe and Canada. The primary disadvantage of using SEER to investigate this question is that it provides retrospective data. Therefore, decisions concerning the choice of

mastectomy versus breast conserving surgery or the use of radiation treatment for the patients included in this study were made by treating physicians and patients, which introduces biases.

There are many sources of bias that should be considered when interpreting the data in this study. For example, we excluded the 13.6% of mastectomy patients with stage II disease with 1–3 positive lymph nodes who received postmastectomy radiation. It is likely that some of these patients were given radiation because of aggressive disease features, such as lymphovascular space invasion or positive surgical margins, which are variables not captured within SEER. By excluding these patients, the remaining cohort who did not receive postmastectomy radiation becomes a more favorable subset. Similarly, by excluding the 23.3% of breast conservation patients who were not treated with radiation, the study BCT + XRT cohort may have been biased towards having less favorable disease. In contrast, biases likely also exist in the opposite direction. As indicated in table 1, there were clearly differences in the populations that resulted from selection criteria used for the type of surgical therapy. For example, patients with smaller tumors and fewer positive nodes were more often treated with breast conservation. We performed a multivariate analysis to attempt to account for some of these differences but it is likely that additional unrecognized biases also influenced our results. For example, given the more recent years of treatment in the BCT+XRT group, it is likely that a higher percentage of patients in this cohort were treated with a more prolonged course of chemotherapy that included a taxane. It is also possible that BCT+XRT may be more commonly offered in centers with a greater levels of expertise in breast cancer than those centers that more commonly treat stage II breast cancer with mastectomy.

Similar biases need to be considered when interpreting the previously reported study of Smith et al. These authors investigated the question of postmastectomy radiation benefit using the SEER database by comparing the population of patients treated with mastectomy alone versus those treated with mastectomy and radiation. {Smith, 2005 #7} These authors appropriately performed a multivariate analysis and found no statistical survival advantage with the use of postmastectomy radiation for patients with stage II disease and 1–3 positive lymph nodes. However, as previously indicated, important patient and pathological variables that can affect recurrence rates and radiation use patterns are not accounted for in SEER analyses. In addition, our results and the results of previous SEER data concerning this topic may have been affected by possible under-ascertainment of adjuvant radiotherapy by SEER. {Du, 1999 #10} SEER also does not provide details on radiation dose, treatment fields, or whether treatment is completed and no data is available concerning adjuvant systemic therapies. Accordingly, because the Smith et al. results and our results differ, the true benefits of radiation for this cohort of patients on the basis of the data available within SEER are unknown.

The methodology we used to investigate the benefits of radiation for patients with stage II disease with 1–3 positive lymph nodes and the results we found are similar to a previously published meta-analysis. This meta-analysis investigated the outcome of patients who participated in randomized clinical trials and compared breast conservation treatment with radiation versus treatment with a modified radical mastectomy. This study found that for

patients with positive lymph nodes, treatment with breast conservation with radiation was associated with a lower risk of death (hazard ratio – 0.69, $p=0.03$) than treated with mastectomy without radiation {Morris, 1997 #11}. In contrast, the outcomes were equivalent in the trials that allowed postmastectomy radiation to be used.

The most recent randomized trials demonstrating the value of radiation for patients with stage II disease with 1–3 positive lymph nodes are the Danish Cooperative Breast Cancer Group 82b trial and 82c trials and the Vancouver British Columbia trial. All three of these trials randomized patients treated with mastectomy and systemic treatments to the use or omission of postmastectomy radiation. In the Danish trials, 62% of the enrolled patients had 1–3 positive lymph nodes. {Nielsen, 2006 #3} In the Vancouver BC trial, 58% of the study participants had 1–3 positive lymph nodes. {Ragaz, 2005 #2} In both of these studies, radiation use led to a survival advantage. However, as previously noted, the local-regional recurrence risk for patients with stage II disease with 1–3 positive lymph nodes who participated in these trials was significantly higher than the risk seen in United States cohort with similar stage disease. {Katz A, 2000 #5; Recht A, 1999 #4; Taghian A, 2004 #6; Truong, 2007 #12} To further investigate this, the investigators of the Danish trials recently published updated data from their studies and evaluated the outcome of only those patients with 1–3 positive lymph nodes who had 8 or more lymph nodes recovered. Even with a more complete axillary dissection, the patients who received postmastectomy radiation had a significantly lower risk of local-regional recurrence at 15 years (4% vs. 27%, $p<0.001$), and a statistically significant improvement in survival (57% vs. 48%, $p<0.001$). {Overgaard, 2007 #13}

Additional randomized trial data concerning the benefits of radiation for patients with 1–3 positive lymph nodes will not be available for some time. The United States trial designed to investigate this question closed due to poor accrual and a new European trial has been initiated but will require an additional 5–10 years before mature results become available. Therefore, there continues to be uncertainty over whether all patients with 1–3 positive lymph nodes should be recommended to receive radiation.

In conclusion, we found that radiation use, as a component of breast conservation therapy, is associated with a survival advantage compared to treatment with mastectomy without radiation for patients with stage II disease with 1–3 positive lymph nodes. As multivariate analyses of retrospective data cannot account for all potential biases, these data require confirmation by randomized clinical trials.

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Freedom From Breast Cancer Death

Figure 1.

Figure 1 displays freedom from breast cancer death curves for patients treated with breast conservative therapy with radiation (BCT + RT, dark line) versus those treated with mastectomy without radiation (MRM w/o RT, lighter line). The BCT + XRT had an improved breast cancer survival with a Cox adjusted hazard ratio (H.R.) of 1.19.

Freedom From Breast Cancer Death

Figure 2.

Figure 2a and 2b display freedom from breast cancer death curves for patients treated with BCT + XRT versus those treated with mastectomy without radiation according to primary disease stage. The BCT + XRT had an improved breast cancer survival in both subsets of patients.

Freedom From Breast Cancer Death

Figure 3.

Figure 3a, 3b, and 3c display freedom from breast cancer death curves for patients treated with BCT + XRT versus those treated with mastectomy without radiation according to number of positive lymph nodes. The BCT + XRT had an improved breast cancer survival in all three subsets of patients.

Table 1

Demographic and Disease Characteristics of the Study Populations

		BCT+RT, %	MRM w/o RT, %	P*
		(N= 12,693)	(N=18,902)	
Diagnosis year	1988	2.22	6.62	<.0001
	1989	2.26	6.25	
	1990	2.49	5.86	
	1991	3.14	5.91	
	1992	5.14	7.89	
	1993	5.46	7.28	
	1994	5.59	6.88	
	1995	6.33	7.02	
	1996	7.13	6.70	
	1997	7.72	5.88	
	1998	10.34	6.43	
	1999	10.14	6.80	
	2000	10.52	6.59	
	2001	10.46	7.29	
	2002	11.05	6.59	
Age group	25–44	19.22	17.47	<.0001
	45–54	30.21	23.37	
	55–64	24.31	21.76	
	65–74	18.35	22.06	
	75+	7.92	15.35	
Race	White Non-Hispanic	76.70	75.11	0.0027
	Black	8.13	9.18	
	Hispanic	7.03	7.09	
	Other	8.14	8.61	
SEER registry	San Francisco-Oakland	15.65	12.44	<.0001
	Connecticut	9.77	10.79	
	Detroit	10.12	14.24	
	Hawaii	3.66	2.97	
	Iowa	7.49	13.17	
	New Mexico	4.47	4.60	
	Seattle	15.93	10.83	
	Utah	0.06	0.03	
	Atlanta	6.85	7.85	
	Alaska	0.09	0.23	
	San Jose	5.61	5.29	
	Los Angeles	20.19	17.22	

		BCT+RT, %	MRM w/o RT, %	P*
		(N= 12,693)	(N=18,902)	
	Rural Georgia	0.10	0.34	
Tumor size	0–2.0cm	66.23	50.97	<.0001
	2.1–5.0cm	33.77	49.03	
Positive Nodes	1	62.37	54.61	<.0001
	2	25.30	29.09	
	3	12.33	16.31	
Grade	1	13.40	8.34	<.0001
	2	40.31	34.27	
	3	35.77	36.87	
	unknown	10.52	20.52	
Estrogen Receptor Status	Positive	67.96	57.34	<.0001
	Negative	17.92	16.44	
	unknown	14.13	26.22	
Progesterone Receptor Status	Positive	58.73	49.18	<.0001
	Negative	24.59	22.44	
	unknown	16.68	28.38	

* Chi square test

Abbreviations: BCT +RT – breast conservative therapy with radiation, MRM w/o RT – modified radical mastectomy without radiation, SEER - Surveillance, Epidemiology, and End Results

Table 2

Cox Multivariable Regression Analysis for Breast Cancer Deaths

Variable	P Value	Hazard Ratio	95% Hazard Ratio	Confidence Limits
MRM w/o RT vs. BCT+RT	<.0001	1.187	1.099	1.282
1989 vs. 1988	0.8018	0.982	0.849	1.135
1990	0.7195	1.032	0.871	1.222
1991	0.2147	0.895	0.750	1.067
1992	0.1494	0.885	0.750	1.045
1993	0.2101	0.897	0.757	1.063
1994	0.2503	0.903	0.758	1.075
1995	0.0507	0.838	0.701	1.001
1996	0.0058	0.768	0.637	0.927
1997	0.0002	0.677	0.551	0.831
1998	<.0001	0.652	0.528	0.805
1999	<.0001	0.557	0.437	0.710
2000	0.0060	0.679	0.515	0.895
2001	0.1171	0.722	0.481	1.085
2002	0.8853	1.070	0.429	2.667
Age 45–54 vs. 25–44	0.1208	0.929	0.846	1.020
55–64	0.7487	0.984	0.891	1.086
65–74	0.7522	1.016	0.920	1.122
75–84	0.0005	1.229	1.093	1.380
African American vs. White	<.0001	1.394	1.263	1.537
Hispanic	0.4519	1.051	0.923	1.197
Other	0.0149	0.844	0.736	0.967
Tumor size (continuous variable)	<.0001	1.332	1.293	1.373
2 vs. 1 positive nodes	<.0001	1.186	1.100	1.278
3	<.0001	1.476	1.355	1.607
Grade 2 vs. Grade 1	<.0001	2.311	1.832	2.915
Grade 3	<.0001	3.636	2.891	4.573
Unknown grade	<.0001	2.439	1.927	3.087
ER-negative vs. ER-positive	<.0001	1.523	1.368	1.696
ER-unknown	0.1865	1.144	0.937	1.397
PR-negative vs. PR-positive	<.0001	1.505	1.355	1.672
PR-unknown	0.0436	1.220	1.006	1.480

Abbreviations: MRM w/o RT – modified radical mastectomy without radiation, BCT +RT – breast conservative therapy with radiation,