HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Cancer. 2016 October ; 122(19): 3059–3068. doi:10.1002/cncr.30142.

Benefit of Adjuvant Radiotherapy after Breast Conserving Therapy Among Elderly Women with T1–2N0 Estrogen Receptor Negative Breast Cancer

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Abstract

Background—The purpose of this analysis is to evaluate the impact of RT among women ≥70 with T1-2N0 ER negative breast cancer using Surveillance Epidemiology and End Results (SEER)-Medicare linked data.

Methods—The study included 3,432 women who received (n=2850) and did not receive (n=582) RT after BCS. Outcomes were estimated by the Cummulative Incidence (CI) method and compared with Gray's test. Fine and Gray's subdistribution hazard regression models were used to assess the impact of RT and other variables.

Results—Women who received RT were more commonly <75 years-old (42% vs. 16%), had T1 tumors (78% vs. 65%), ductal carcinoma histology (91% vs. 88%), a comorbidity index of zero (41% vs. 25%), and received chemotherapy (29% vs. 12%). The 5-year CI of mastectomy and breast cancer-specific death for patients who received versus did not receive adjuvant radiation was 4.9% and 8.3% versus 10.8% and 24.1% (p <0.001). On multivariable analysis, the omission of RT was an independent predictor for increased mastectomy risk (HR=2.33; 95% CI 1.56, 3.49). Among women aged ≥ 80 years or with T1N0 tumors, the mastectomy incidence with or without receipt of RT was 3.4% vs. 6.9%, and 5.3% vs 7.7%, respectively.

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Conflicts of Interest: The authors have no conflicts of interest to disclose.

Author Contributions: Bree R. Eaton: Conceptualization, methodology, formal analysis, investigation, resources, writing – original draft, writing – review and editing, and visualization. Renjian Jiang: Methodology, software, validation, formal analysis, data curation, writing – review and editing, and visualization. Mylin A. Torres: Conceptualization, validation, writing – original draft, writing – review and editing, and supervision. Shannon T. Kahn: Writing – original draft, writing – review and editing, and visualization. Karen Godette: Conceptualization, validation, writing – review and editing, and visualization. Timothy L. Lash: Conceptualization, methodology, and writing – review and editing. Kevin C. Ward: Conceptualization, methodology, validation, investigation, data curation, writing – review and editing, visualization, supervision, and project administration.

Conclusions—The use of adjuvant radiation after BCS in older women with T1-2N0 ER negative breast cancer is associated with a reduced incidence of future mastectomy and breast cancer death. The magnitude of benefit may be small for women ≥80 or with T1 tumors.

Keywords

Breast neoplasms; Radiotherapy; Estrogen receptor; Aged; Mastectomy

Introduction

A meta-analysis of seventeen randomized trials testing adjuvant breast radiotherapy (RT) versus observation following breast conserving surgery (BCS) demonstrated a significant improvement in local-regional control, disease free survival, and breast cancer-specific survival with the use of RT [1]. Adjuvant RT following BCS is therefore standard of care for the majority of women with early stage breast cancer. While the improvement in local-regional control with RT is well recognized in nearly all patients, the magnitude of this benefit and the resulting effect on breast cancer-specific survival depends on multiple prognostic factors, defining a patient's individual risk of disease recurrence.

Advanced age is a well-recognized prognostic factor for a decreased risk of tumor recurrence [2-4], which suggests there may be a diminished benefit of adjuvant radiation therapy in elderly patients. The Cancer and Leukemia Group B (CALGB) and PRIME II randomized trials each demonstrated a modest reduction in local recurrence, but no difference in breast-cancer specific survival with the addition of RT in elderly women with stage I estrogen receptor (ER) positive tumors receiving tamoxifen [5]. As a result, the National Comprehensive Cancer Network adopted the omission of RT as a standard of care option for this subset of patients [6]. However, it remains unknown whether RT may also be safely omitted from a population of elderly women with ER negative tumors.

The magnitude of benefit with adjuvant RT for elderly women with early stage ER negative tumors is poorly understood, since this population is highly underrepresented in the literature. Among the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of individual patient data from 17 randomized trials of adjuvant RT after BCS, only 23 women > 70 years old with T1-T2N0 ER negative tumors were included. This group of women comprised <1% of the total population studied [1].

Despite the association between ER negative tumors and an increased risk for tumor recurrence demonstrated in this analysis [1], other data from both prospective and retrospective studies suggest that patients with ER negative tumors may experience a reduced benefit with adjuvant RT when compared with ER positive patients [1, 7]. Thus, the increased risk of tumor recurrence recognized in patients with ER negative tumors may not necessarily equate to a greater benefit from adjuvant RT.

The purpose of this analysis is to evaluate the benefit of adjuvant radiotherapy following BCS among women ≥70 years old with T1-2 N0 ER negative breast cancer using Surveillance Epidemiology and End Results data linked to Medicare claims (SEER-Medicare). The effect of adjuvant RT on mastectomy incidence and breast cancer specific

death has been assessed in relationship to multiple prognostic factors to explore whether RT may also be safely omitted from a population of early stage, elderly women with ER negative tumors.

Materials and Methods

Data Source

SEER-Medicare data link two large population-based data sources within the United States (US). The SEER Program of the National Cancer Institute is the authoritative source of long-term cancer incidence and survival in the US with current coverage of approximately 28% of the population. Medicare is the federally funded insurance program in the US that provides health insurance to individuals over the age of 65. Medicare data include both fee-for-service and managed care plans but only the fee-for-service claims are included with the SEER-Medicare dataset. For this study, the analytic dataset comprised eligible breast cancer cases diagnosed between 1993 and 2007 with follow-up through 2010. Clinical, demographic and cause of death information were derived from SEER, while covered health services from the time of Medicare eligibility until death were derived from Medicare claims. SEER Registries conduct both active and passive follow-up activities to longitudinally trace a patient's vital status from the point of a cancer diagnosis forward. This protocol includes linking with both state vital records and the National Death Index to ascertain date and cause of death when applicable. Institutional review board approval was obtained for this analysis.

Patient Selection

Women ≥70 years old registered in the SEER-Medicare database with a first primary diagnosis of T1-2, lymph node (LN) negative, ER negative invasive breast cancer who were treated with breast conserving surgery during the first 9 months after diagnosis were selected for inclusion. Ninety-seven percent of all women in the study underwent BCS within 3 months of diagnosis. The 9 month period following breast cancer diagnosis was defined as the treatment window for measuring the initiation of all cancer related treatment in accordance with the work from Smith et al[8]. Women were excluded for the following: simultaneous bilateral breast cancer, non-epithelial histology, distant metastasis, initial treatment with a mastectomy, a second cancer diagnosis, death within the treatment window, a diagnosis date of any subsequent primary was not known, no continuous enrollment in Medicare Parts A and B or enrollment in a HMO during the treatment window, missing or unknown information regarding any component of stage, receptor status, month of diagnosis or month of death.

Independent Variables

The Medicare codes used to define BCS, mastectomy, chemotherapy and external beam RT are listed in Table 1. Receipt of BCS or initiation of chemotherapy and RT were defined by having the corresponding Medicare claims filed within the 9-month treatment window. Patients with both BCS and mastectomy claims within this window were considered to have undergone mastectomy and were excluded. Patients with Medicare claims for radiation planning only or for having less than 15 radiation treatments were considered to have had

non-standard or incomplete treatment and were also excluded from analysis. The period for assessing the delivery of radiation treatment was extended beyond the treatment window as long as RT was initiated within the 9-month window. The receipt of radiation for all patients as defined by SEER was confirmed by Medicare claims. The receipt of chemotherapy was defined by the presence of claims with any of the chemotherapy codes listed in Table 1 in conjunction with a corresponding diagnosis code for breast cancer.

Most of the patient and tumor characteristics (e.g. diagnosis, age, race, marital status, region, histology, grade, year of diagnosis, and receptor status) were taken directly from SEER data. Since SEER does not directly collect information on patient socioeconomic status, an area-based measure of poverty was derived from SEER census tract data and was included with the SEER-Medicare dataset. Tumor stage was defined by the AJCC 6th edition TNM stage for all cases. AJCC staging data were directly available in SEER for cases diagnosed between 2004 and 2007 and were derived from SEER EOD 3rd edition codes for cases diagnosed from 1993 to 2003. A measure of comorbidity for each patient was defined according to the Deyo adaptation of the Charlson comorbidity index [9, 10], modified to exclude incident breast cancer diagnosis. This index used Medicare inpatient, carrier, and outpatient claims during the 12 month period before breast cancer diagnosis, excluding the month of diagnosis.

Statistical Analysis

Study follow-up began at month 10 from diagnosis for all individuals. The primary outcome variable, cumulative incidence (CI) of mastectomy, was defined as the occurrence of mastectomy, or was censored at the time of contralateral breast cancer, loss to follow-up, or the end of the designated period for which follow-up was being assessed (e.g. 5 years). The secondary outcome variable, cumulative incidence of breast cancer death, was defined as the incidence of death due to breast cancer. Censored events were similarly defined. The CI of mastectomy and breast cancer death were generated using cumulative incidence function and using death without the event of interest as the competing risk. CI functions were adjusted with other covariates (all the demographic and clinical characteristics listed in table 1,) at average levels. Chi-square and Fisher's exact tests were used to compare patient, tumor and treatment characteristics between groups. The effect of RT and other demographic and clinical characteristics on the outcome variables was assessed through univariate Gray's test and multivariate Fine and Gray's subdistribution hazard regression. Further sub-group analysis was also performed to assess the effect of RT across strata according to age and T stage. Overall survival was analyzed using the Kaplan-Meier method and compared for patients who did and not receive RT using the log-rank test. All statistics were calculated using SAS software version 9.3 (SAS Institute., Inc., Cary, NC, USA) and all statistical tests were two sided using an $\alpha = 0.05$ Type I error rate.

Results

Patient Population

Of the 516,260 women registered within the SEER-Medicare database and diagnosed with breast cancer between 1993 to 2007, 3,432 women met all eligibility criteria for inclusion

(Figure 1). Patient, tumor and treatment characteristics for patients who received (n= 2850) and did not receive (n=582) radiation therapy are presented in Table 1. Patients who received RT were more often younger, of white race, married, and living in areaswith lower poverty rates. Patients who received RT were also more likely to have lower T stage tumors, and a lower comorbidity index, and less likely to have ductal carcinoma histology, and receive chemotherapy. There were no substantial differences in year of diagnosis, demographic region, progesterone receptor status or histologic grade between patients who received and did not receive radiation therapy. Women ≥75 were more likely to have a comorbidity index ≥2 (52% vs. 37%, p<0.001) and less likely to receive chemotherapy (18% vs. 41%, p<0.001) compared with patients age 70–74. There was no substantial difference in the distribution of histological grade among the varying age groups.

Incidence of Mastectomy

The median follow-up period for mastectomy assessment for the patient population is 45 months (IQR 20–81). The 5-year CI of mastectomy for patients who received vs. did not receive adjuvant radiation were 4.9% (95% CI 4.0%, 5.9%) versus 10.8% (95% CI 7.7%, 14.6%), p<.0001.

On multivariate analysis (Table 2), women treated with BCS alone had a significantly higher incidence of future mastectomy at 5 years compared with women treated with BCS and adjuvant RT, with a HR of 2.3; 95% CI 1.6, 3.5. Multivariate analysis for CI of mastectomy is listed in Table 3. Additional variables associated with MFS were tumor stage and urban residence; less substantial associations also existed between MFS and progesterone receptor status, cormorbidity index, and SEER region.

In further exploratory analysis evaluating MSF among subgroups according to patient age and tumor stage (Table 3), RT was associated with a reduced risk of mastectomy among all subcohorts, though the magnitude of benefit was small in women ≥80 or with T1 tumors. Mastectomy incidence with vs. without RT was 3.4% vs. 6.9% (p=0.05) for women ≥80 and 5.3% vs. 7.7% (p=0.01) for women with T1N0 tumors.

Breast Cancer Specific Survival

The 5-year CI of breast cancer death (BCD) for patients who received versus did not receive adjuvant radiation were 8.3% (95% CI 7.2%, 9.5%) versus 24.1% (95% CI 19.7%, 28.7%), p<.0001. On multivariable analysis (Table 4), women treated with BCS alone had a significantly increased risk of BCD at 5 years compared with women treated with BCS and adjuvant RT, with a HR of 2.2 (95% CI 1.6, 2.8). The associations between all patient and tumor characteristics and CI of BCD are listed in Table 4. Additional variables associated with an increased risk of breast cancer specific death were older age, greater T stage, histologic grade and comorbidity index. Cumulative incidence of BCD with and without RT according to T stage and age group are shown in Table 3.

The 5-year observed overall survival for patients who received versus did not receive adjuvant radiation were 79% (95% CI 77%, 80%) versus 42% (95% CI 38%, 47%), p<0.001

Discussion

This study included a large population based cohort of elderly women ≥70 with T1-2N0 ER negative tumors, who are highly underrepresented in prospective phase III clinical trials evaluating the benefit of adjuvant RT following breast conserving surgery. While ER receptor negative status has previously been demonstrated as a negative prognostic factor for MFS in a SEER-Medicare analysis elderly women [11], the mastectomy rates among this population and the magnitude of benefit with adjuvant RT according to other disease variables has not previously been evaluated in this population. The results of this analysis demonstrate the use of adjuvant RT to be associated with a significantly lower incidence of mastectomy among women ≥70 years old with T1–2 ER negative tumors receiving breast conservation therapy.

The question remains whether there is a subpopulation of elderly women with early stage ER negative tumors who may not need adjuvant radiotherapy. Our results show that a reduced risk of mastectomy among all subgroups of patients according to age or T stage after breast conserving surgery with radiation; however, the magnitude of benefit at 5 years is smallest for women ≥ 80 or with T1N0 ER negative tumors. When analyzing patients ≥ 80 years old and with T1 tumors, the difference in mastectomy incidence with and without RT is no longer significant. This finding is consistent with previous data demonstrating that older age [2-4] and earlier T stage tumors [1, 11] are factors independently associated with a reduced risk of local regional recurrence In recent prospective trials evaluating the omission of adjuvant radiotherapy in women with early stage ER positive breast cancer, local regional recurrence at 5 years was approximately 1% with RT and 4% with BCS alone [5, 12]. “Elderly” was defined as greater than 65 or 70 years in these trials. In comparison, our results show a mastectomy rate of approximately 5% with RT and 11% with BCS alone in women ≥70 with ER negative tumors.

It should be noted that the incidence of mastectomy is analyzed as a surrogate for local tumor control, and data regarding the timing and pattern of disease recurrence cannot be recorded directly from SEER-Medicare data. Patients with local tumor failure may not have undergone mastectomy for several reasons, including patient preference for partial mastectomy at the time of recurrence, poor clinical or functional status that may have precluded surgical management, or the presence of simultaneous distant recurrence. Furthermore, it may be that mastectomies were performed for reasons other than disease recurrence. Biases that may have impacted treatment selection cannot be fully accounted for with this retrospective population based data. Additional factors—such as histologic grade, medical comorbidity, poverty level and urban residence—should be taken into account if considering a subpopulation of women to further investigate the effects of omitting adjuvant radiotherapy, as these variables were also associated with MFS. The incidence of mastectomy was lower among patients with T1 tumors and patients with well-differentiated histology, which is consistent with past literature establishing the association of these variables with improved local regional control [11].

Cause specific survival was poorer among women who did not receive adjuvant radiation. A meta-analysis of patient data from 17 randomized trials of adjuvant breast RT demonstrated

a 5% absolute benefit in survival at 15 years with the use of radiotherapy [1]. Thus, the approximate 15% absolute decrement in cumulative incidence of breast cancer specific death among women without adjuvant RT in this analysis is unlikely related to the lack of benefit from local regional RT alone. Other independent predictors of increased risk of breast cancer specific death in this analysis were older age, greater T stage, higher tumor grade, and increased comorbidity.

Our study is limited in that estrogen receptor status was the primary hormonal receptor used to categorize the population. Additional information about HER-2 receptor status and luminal type, which is also recognized to impact local regional recurrence [7, 13, 14] may have been of value, but was not available in this data set. Additional limitations include unknown surgical margin status, unknown use of endocrine therapy, bias in treatment selection that cannot be accounted for, and the lack of sufficient follow-up in this elderly population to adequately analyze outcomes beyond 5 years.

Conclusions

The use of adjuvant radiation is associated with a significant reduced incidence of mastectomy and breast cancer specific death among elderly women ≥70 with T1–2N0 ER negative tumors, though the magnitude of benefit at 5 years is small in the subgroups of women ≥80 or with T1 tumors.. These findings add to the sparse literate evaluating the benefit of RT in elderly women with ER negative receptor status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development, and Information, CMS; Information Management Services, Inc; the Georgia Cancer Registry supported by NCI contract HHSN261201300015I; and the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the creation of the SEER-Medicare database.

Funding: This work is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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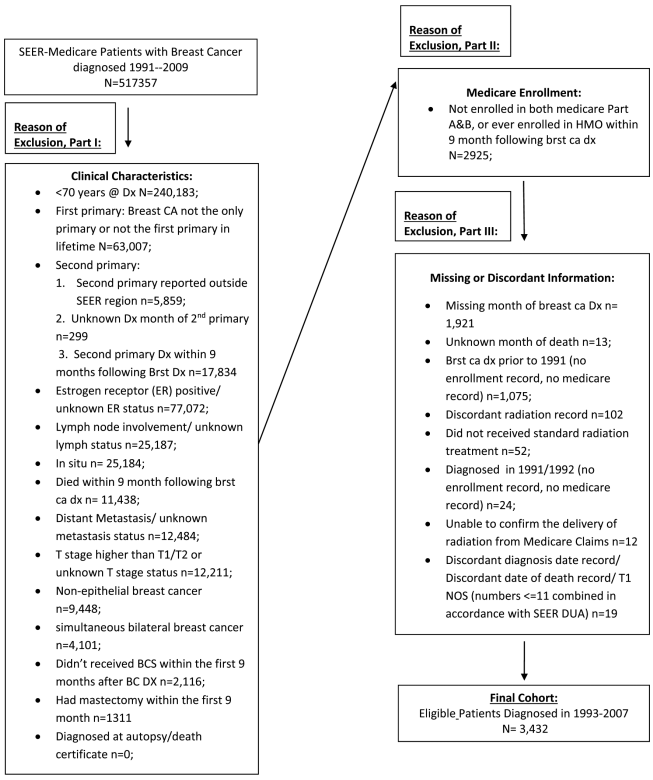

Figure 1.
Exclusion Flow Chart of SEER-Medicare Cases Selected for Analysis

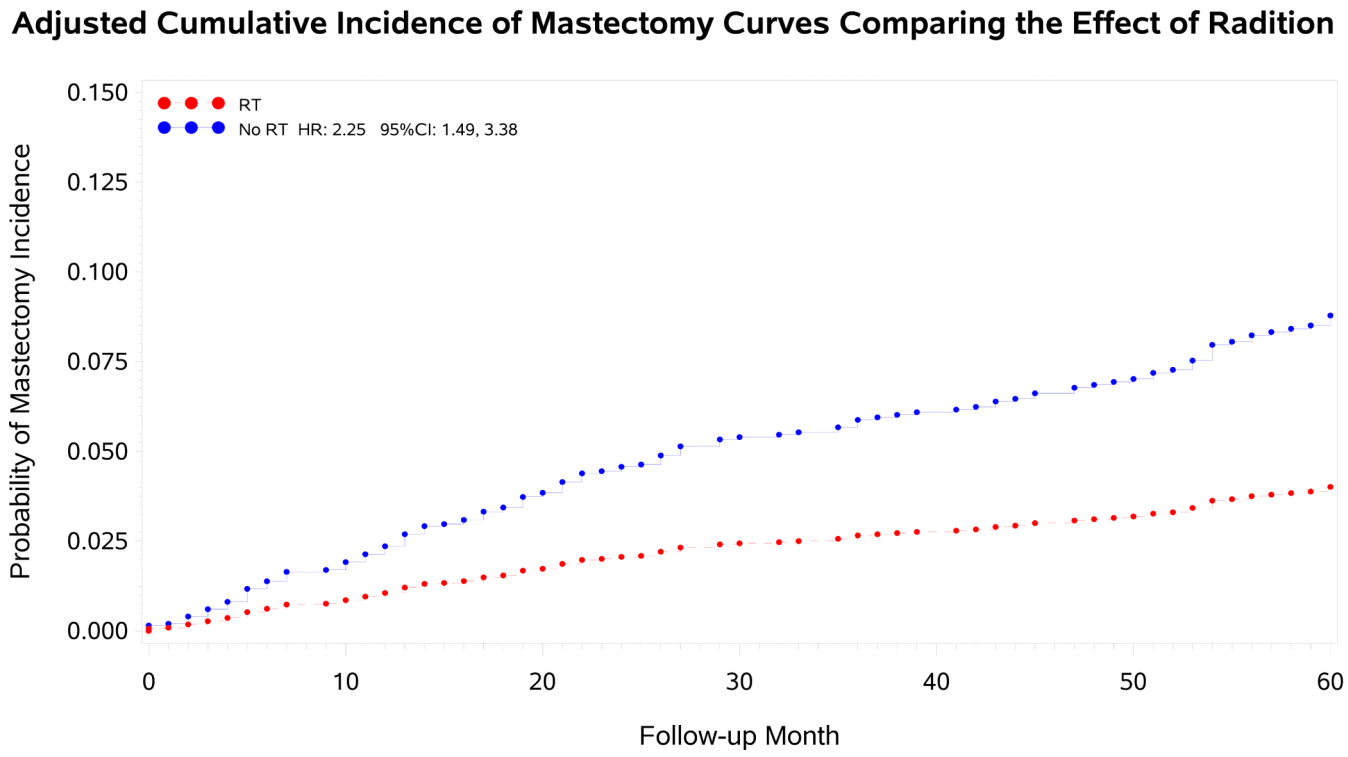

Figure 2.

Adjusted cumulative incidence curves of mastectomy for patients with and without the receipt of adjuvant radiation therapy.

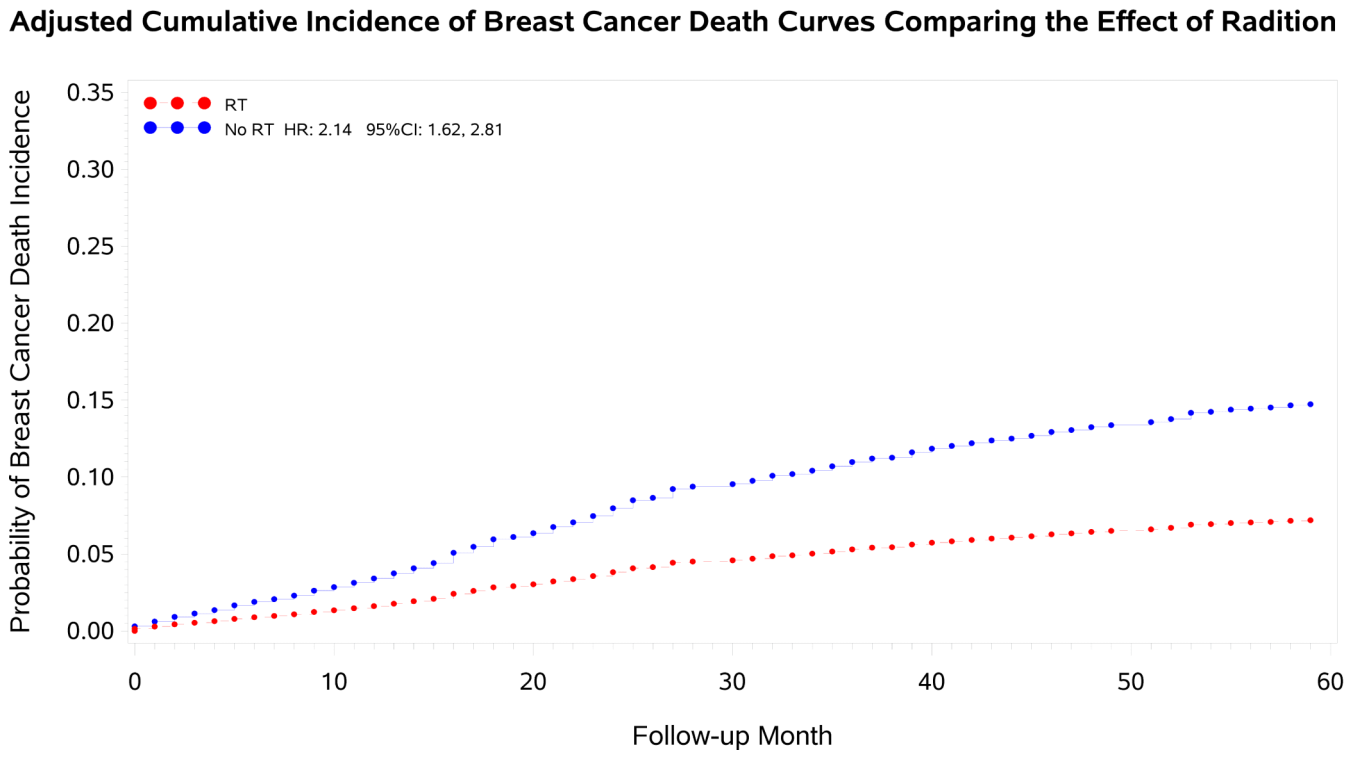

Figure 3.

Adjusted cumulative incidence curves of breast cancer specific death for patients with and without the receipt of adjuvant radiation therapy.

Table 1

Patient, Tumor and Treatment Characteristics

Characteristic	Breast Radiation				P-value[a]
	No		Yes		
	N	%	N	%	
Age					
70–74	93	16%	1204	42%	<0.0001
75–79	116	20%	921	32%	
≥ 80	373	64%	725	25%	
Year of Diagnosis					
1993–1999	135	23%	647	23%	0.54
2000–2004	219	38%	1018	36%	
2005–2009	228	39%	1185	42%	
Derived AJCC T stage					
T1mic+T1a	33	5.7%	270	9.5%	<0.0001
T1b	111	19%	644	23%	
T1c	233	40%	1306	46%	
T2	205	35%	630	22%	
Progesterone receptor status					
Positive	>32	>5.7%	209	7.3%	0.64
Negative	538	92%	2613	92%	
Indeterminate+Not Done+Unknown	<11	<1.9%	28	0.98%	
Tumor Histology					
Ductal Carcinoma	511	88%	2600	91%	0.03
Lobular Carcinoma	24	4.1%	88	3.1%	
Other	47	8.1%	162	5.7%	
Histologic grade					
Well differentiated	41	7.0%	180	6.3%	0.84
Intermediate/moderate	174	30%	823	29%	
Poorly-/Un- differentiated	325	57%	1608	59%	
Not determined	35	6.0%	175	6.1%	
Comorbidity Index[b]					
0	144	25%	1163	41%	<0.0001
1	91	16%	444	16%	
≥ 2	347	60%	1243	43%	
Chemotherapy					
Yes	69	12%	822	29%	<0.0001
No	513	88%	2028	71%	
Race					
White	485	83%	2477	87%	0.02
Black	69	12%	245	8.6%	
Hispanic	<11	<1.9%	33	1.2%	

Characteristic	Breast Radiation				P-value[a]
	No		Yes		
	N	%	N	%	
Asian	<11	<1.9%	44	1.5%	
Other/ Native Amercian[d]	<11	<1.9%	51	1.8%	
Marital status					
Married	142	24%	1320	46%	<0.0001
Unmarried	409	70%	1453	51%	
Unknown	31	5.3%	77	2.7%	
Demographic Region					
West	258	44%	1193	42%	0.63
Midwest	82	14%	412	15%	
South	110	19%	538	19%	
Northeast	133	23%	712	25%	
Urban residence					
Metro	503	86%	2535	89%	0.08
Urban+Rural	79	14%	315	11%	
Census Track Level Poverty[c]					
0.00%–9.99%	345	59%	1921	67%	0.0003
10.00%–19.99%	150	26%	628	22%	
20.00%+	87	15%	301	11%	

[a] P-value is calculated by Chi-square Test except for Race, which is calculated by Fisher's Exact.

[b] 69 patients' Medicare Enrollment in the 12 months prior to Breast Cancer Diagnosis were not continuous, CCI were calculated from all the claims existed in Medicare for these 69 patients.

[c] Zip code poverty level were used for 30 patients with missing census track poverty level

[d] This category also contains a very small number of unknown race subgroup

Table 2

Associations with 5-Year Mastectomy Cumulative Incidence

Characteristic	Gray's Test P-value	Number of Outcomes	Person-Year	HR (95%CI)		P-value
Breast radiation	<.0001					
Yes		97	9793.08	1 (Ref)		
No*		40	1509.5	2.33	(1.56, 3.49)	<.0001
Age	0.93					
70 - 74		53	4558.17	1.41	(0.86, 2.34)	0.18
75 - 79		44	3527.75	1.41	(0.89, 2.24)	0.14
≥ 80		40	3216.67	1 (Ref)		
T Stage	0.01					
T1a + T1mic		13	1004.67	1 (Ref)		
T1b		22	2639.58	0.63	(0.31, 1.28)	0.20
T1c*		57	5257.17	0.75	(0.40, 1.40)	0.36
T2*		45	2401.17	1.01	(0.52, 1.96)	0.97
Progesterone receptor status	0.08					
Positive		5	942.5	1 (Ref)		
Negative		129	10230.5	2.01	(0.82, 4.92)	0.12
Indeterminate		3	129.58	3.43	(0.80, 14.73)	0.10
Tumor Histology	0.89					
Ductal Carcinoma		122	10172.42	1 (Ref)		
Lobular Carcinoma		5	415.33	1.47	(0.60, 3.63)	0.40
Other		10	714.83	1.40	(0.71, 2.74)	0.34
Histologic grade	0.11					
Well differentiated		4	796.83	1 (Ref)		
Intermediate/moderate		35	3386.83	2.21	(0.78, 6.28)	0.14
Poorly differentiated/Undifferentiated		89	6352.25	2.62	(0.95, 7.23)	0.07
Not determined		9	766.67	2.18	(0.66, 7.16)	0.20
Chemotherapy received	0.34					
Yes		40	2885.92	1 (Ref)		
No		97	8416.67	0.90	(0.60, 1.36)	0.62
Comorbidity Index	0.14					
0		41	4299.58	1 (Ref)		
1		26	1823.83	1.47	(0.89, 2.41)	0.13
≥ 2		70	5179.17	1.32	(0.88, 2.00)	0.18
Race	0.45					
White		120	9807.83	1 (Ref)		
Black		9	975.17	0.66	(0.32, 1.36)	0.26
Hispanic		1	155.92	0.52	(0.07, 3.68)	0.52
Other/ Unknown		7	363.67	1.52	(0.67, 3.44)	0.31
Marital Status	0.23					
Married		64	4902.42	1 (Ref)		

Characteristic	Gray's Test P-value	Number of Outcomes	Person-Year	HR (95%CI)		P-value
Unmarried		72	6046.33	0.81	(0.57, 1.16)	0.23
Unknown		1	353.83	0.17	(0.02, 1.22)	0.08
Year of Diagnosis	0.12					
1993-1999		27	3124.92	1 (Ref)		
2000-2004*		68	4935.75	1.58	(1.00, 2.50)	0.05
2005-2009		42	3241.92	1.32	(0.80, 2.18)	0.27
SEER Region	0.07					
West		59	4824.67	1 (Ref)		
Midwest		25	1724.42	1.40	(0.85, 2.31)	0.18
Northeast		22	2777.58	0.69	(0.42, 1.13)	0.14
South		31	1975.92	1.24	(0.78, 1.99)	0.36
Urban Residence	0.03					
Metro		114	10054.08	1 (Ref)		
Urban/ Rural		23	1248.5	1.24	(0.77, 2.02)	0.38
Census Track Level Poverty	0.01					
0.00%-9.99%		80	7612.67	1 (Ref)		
10.00%-19.99%		45	2472.08	1.51	(1.00, 2.30)	0.05
20.00%+		12	1217.83	0.81	(0.43, 1.55)	0.53

Table 3

Stratified 5 Year Cumulative Incidences

		5 Year Cumulative Incidence of Mastectomy CI (95% Confidence Interval)			5 year Cumulative Incidence of Breast cancer death CI (95% Confidence Interval)		
Age Group	**N**	**RT**	**No RT**	**P**	**RT**	**No RT**	**P**
70-74	93	4.0% (2.8%- 5.8%	12.6% (6.6%- 23.9%)	0.002	5.6% (4.0%- 7.7%)	14.8% (9.3%- 23.6%)	0.001
75-79	116	3.8% (2.5%- 5.8%)	10.2% (5.2%- 20.1%)	0.003	7.3% (5.6%- 9.5%)	17.2% (10.6%- 27.6%)	0.001
80+	373	3.4% (2.1%- 5.7%)	6.9% (4.0%- 12.1%)	0.05	9.5% (7.3%- 12.4%)	21.4% (15.9%- 28.9%)	<0.001
T Stage							
T1	377	5.3% (3.1%- 5.2%)	7.7% (5.1%- 11.6%)	0.01	5.3% (4.2%- 6.5%)	12.5% (9.1%- 17.2%)	<0.001
T2	205	4.24% 95% CI: 2.64%-6.81%	9.92% 95% CI: 6.15%-15.98%	0.01	14.2% (11.2%- 18.0%)	28.9% (22.9%- 36.5%)	<0.001

Table 4

Associations with 5-Year Breast Cancer Specific Death Cumulative Incidence

Characteristic	Gray's Test P-value	Number of Outcomes	Person-Year	HR (95%CI)		P-value
Breast radiation	<.0001					
Yes		188	10417.17	1 (Ref)		
No*		97	1636.33	2.15	(1.63, 2.82)	<.0001
Age	<.0001					
70 - 74*		80	4910	0.73	(0.53, 1.01)	0.06
75 - 79		80	3744.67	0.86	(0.63, 1.16)	0.32
≥ 80		125	3398.83	1 (Ref)		
T Stage	<.0001					
T1a + T1mic		10	1078.83	1 (Ref)		
T1b		28	2796.25	1.01	(0.49, 2.08)	0.99
T1c*		113	5574.67	1.85	(0.98, 3.55)	0.07
T2*		134	2603.75	3.77	(2.12, 7.26)	<.0001
Progesterone receptor status	0.07					
Positive		13	986.83	1 (Ref)		
Negative		270	10928.5	1.35	(0.77, 2.35)	0.30
Indeterminate		2	138.17	1.01	(0.23, 4.31)	0.99
Tumor Histology	0.07					
Ductal Carcinoma		267	10834	1 (Ref)		
Lobular Carcinoma		9	437.25	1.11	(0.59, 2.11)	0.75
Other		9	782.25	0.51	(0.27, 1.05)	0.07
Histologic grade	<.0001					
Well differentiated		3	843	1 (Ref)		
Intermediate/moderate		63	3580.92	3.95	(1.24, 12.56)	0.02
Poorly differentiated/Undifferentiated		207	6804.25	5.81	(1.84, 18.35)	0.00
Not determined		12	825.33	3.64	(1.03, 12.90)	0.05
Chemotherapy received	0.58					
Yes		69	3083.17	1 (Ref)		
No		216	8970.33	1.11	(0.81, 1.52)	0.52
Comorbidity Index	0.02					
0		86	4592.17	1 (Ref)		
1		47	1945.67	1.11	(0.77, 1.59)	0.59
≥ 2		152	5515.67	1.10	(0.83, 1.45)	0.51
Race in General	0.96					
White		248	10426.75	1 (Ref)		
Black		24	1070.08	0.91	(0.56, 1.51)	0.73
Hispanic		3	164.08	0.68	(0.22, 2.15)	0.52
Other/ Unknown		10	392.58	1.23	(0.62, 2.45)	0.55
Marital Status	0.13					
Married		107	5243.92	1 (Ref)		

Characteristic	Gray's Test P-value	Number of Outcomes	Person-Year	HR (95%CI)		P-value
Unmarried		167	6441.17	0.95	(0.74, 1.23)	0.69
Unknown		11	368.42	1.07	(0.56, 2.03)	0.85
Year of Diagnosis	0.87					
1993-1999		74	3367.83	1 (Ref)		
2000-2004		124	5223.83	0.94	(0.70, 1.27)	0.68
2005-2009		87	3461.83	0.83	(0.59, 1.15)	0.26
SEER Region	0.09					
West		113	5127.67	1 (Ref)		
Midwest		35	1850.08	0.93	(0.62, 1.40)	0.73
Northeast*		87	2943.58	1.37	(1.01, 1.85)	0.04
South		50	2132.17	1.07	(0.76, 1.52)	0.70
Urban Residence	0.33					
Metro		249	10750.75	1 (Ref)		
Urban/ Rural		36	1302.75	1.21	(0.84, 1.74)	0.32
Census Track Level Poverty	0.81					
0.00%-9.99%		187	8083.58	1 (Ref)		
10.00%-19.99%		68	2673.08	1.05	(0.77, 1.42)	0.77
20.00%+		30	1296.83	0.98	(0.62, 1.55)	0.92