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Omission of Radiotherapy After Breast Conservation Surgery in the Post-Neoadjuvant Setting

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Abstract

Introduction—Breast conservation therapy (BCT) consists of breast conservation surgery (BCS) and radiotherapy (RT). Neoadjuvant chemotherapy (NACT) can downstage tumors, broadening BCS eligibility in patients requiring mastectomy. However, tumor downstaging does not obviate need for RT. This study evaluated factors that predict RT omission after NACT and BCS.

Methods—The National Cancer Database (NCDB) was queried for women with unilateral, clinical stage 2–3 breast cancer, treated with NACT and BCS between 2008–2012. Patients not receiving RT after NACT and BCS were identified. A subgroup analysis was performed eliminating patients for whom RT was recommended but not received.

Results—Among 10,220 patients meeting study eligibility, 974 (9.53%) did not receive RT after BCS. Predictors of RT omission included older age, insurance status, facility type, facility region, more recent year of diagnosis, receptor status unknown, HER2 status positive or unknown, and positive margins. Factors increasing the likelihood of RT receipt included cN3 disease, receptor positivity, and primary downstaging. Race, Hispanicity, education, income, comorbidities, rural versus urban setting, histology, grade, and nodal stage change were not associated with RT omission. When excluding the 314 patients for whom RT was recommended but not received, age, Medicaid insurance, facility type, facility region, receptor status unknown, HER2 status unknown, and positive margins were predictors of RT omission.

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Conclusion—Race, comorbidities, and socioeconomic status were not predictors of RT omission. It remains unclear whether omission of RT in some cases is due to lack of physician knowledge. Further efforts are needed to ensure that physicians and patients recognize that RT is a vital and required part of BCT, even after NACT.

Keywords

Segmental mastectomy; Breast neoplasms; Neoadjuvant therapy; Radiotherapy; Breast/Surgery; Standard of care

Introduction

Breast cancer is one of the most common diseases in women today with an estimated incidence of 252,710 in the United States in 2017.(1) Over the past several decades, breast conserving therapy (BCT) has expanded as the standard of care for treatment for clinical stage I, IIA, IIB or T3N1M0 invasive breast cancer(2) and is increasingly performed for tumors > 5 cm.(3) The American College of Surgeons' National Accreditation Program for Breast Centers (NAPBC) defines this as a standard of care, requiring it to be performed for 50% of all eligible patients with early stage breast cancer.(4)

BCT consists of two distinct modalities: breast conserving surgery (BCS) and radiotherapy (RT). Previous randomized clinical trials comparing total mastectomy, BCS, and BCT have demonstrated that BCS alone produces significantly higher recurrence rates than mastectomy or BCT. While the local rate of recurrence may differ for mastectomy and BCT, the overall survival is equivalent.(5) The Early Breast Cancer Trialists' Collaborative Group showed in over 10,000 women from 17 randomized trials, with over a decade of follow up, that radiotherapy is a critical component of BCT. Furthermore, the group noted that omission of RT increases local recurrence, noting a link between prevention of local recurrence and improved disease-specific survival.(6)

In patients deemed unresectable at diagnosis due to skin or chest wall involvement, neoadjuvant chemotherapy (NACT) has been shown to downstage the primary tumor, allowing for BCS by improving the chances of a resection with negative margins.(7) NACT can also increase the likelihood of successful BCS in patients for whom the primary tumor is initially felt to be too large relative to the breast size, an accepted indication for mastectomy. (8) In addition, NACT provides equivalent survival to adjuvant chemotherapy as shown in two prospective randomized trials.(9) However, NACT is not a substitute for radiotherapy or other adjuvant treatments.

Despite the efficacy of BCT, there may be a subgroup of patients for whom the benefit of RT is small and for whom the omission of RT does not compromise survival. (ie. women over 70 with low risk breast cancers). (10, 11) These patients can be spared the side effects of RT. However, the delivery of NACT should not alter the indications for adjuvant radiation. As proof of this point, the NCCN guidelines recommends that in patients treated with NACT, decisions regarding adjuvant RT and systemic therapy be based on the patient's stage at presentation.(2)

Upon reviewing the patterns of post neoadjuvant RT administration in the National Cancer Database (NCDB), we found that many BCT patients did not receive RT after NACT. This study was performed to determine which factors predicted for the omission of RT as we feel that it is important for surgeons and oncologists to be aware of this phenomenon and to identify which patients are at risk for substandard therapy. Establishment of such risk factors could improve the likelihood that RT is delivered appropriately in patients for whom there is a known benefit.

Methods

Study Design

A retrospective analysis of the NCDB was performed following approval by the institutional review board at Fox Chase Cancer Center and after permission to use the NCDB dataset was obtained from the American College of Surgeons. The NCDB was reviewed for women having unilateral, invasive, non-inflammatory, non-metastatic, clinical stage 2-3 breast cancer, treated with NACT and subsequent BCS between 2008-2012.

In light of prior data of ours(12) noting significant impairment in survival after delays between diagnosis and surgery >90 days, as well as that of others noting significant survival impairment after delays of adjuvant therapy after surgery >90 days(13), the cohort was limited to those starting NACT <90 days after diagnosis but 80-270 days preoperatively allowing for proper chemotherapy administration time. Similarly, only those having RT 0-20 weeks postoperatively were included.(14)

Patients were limited to those having one surgical procedure because of the challenges in differentiating excisional biopsy from lumpectomy in the NCDB, in order to create a more homogeneous cohort, and decrease potential confounding from repeated attempts to address positive margins related to extensive disease. All patients having mastectomy at any point were excluded from the sample. Age and year of diagnosis were analyzed in continuous fashion, while all other variables were treated categorically. Because initial presentation, and clinical tumor (T) and nodal (N) status changes (tumor response) were felt to be most important to the decision to administer radiotherapy, these were included in the models. Pathologic T and N stages would be collinear with these variables and thus were excluded. The NCDB provides data on whether radiotherapy was recommended and/or administered for subgroup analysis. Exclusion criteria and cohort numbers are elaborated in Figure 1 and Table 1, respectively.

Statistical Analysis

We used Pearson Chi-square to determine the relationship between patient, tumor, and treating facility factors and omission of RT. Changes in rates of RT over time were tested using the Cochran-Armitage trend test. We then determined the simultaneous effects of all these factors using multiple logistic regression to model the probability of omission of post-BCS RT.

Our first regression model included all patients who met study inclusion criteria (Table 2). We ran a second model excluding individuals for whom radiation was recommended by the

treating physician, but not received (Table 3). These models used robust standard errors estimated via generalized estimating equations (15) to account for within-hospital clustering.

Results

10,220 patients were identified who fit the study inclusion criteria. In this cohort of patients who received NACT prior to BCS, 974 (9.53%) (Figure 1) did not receive post-operative RT. The majority of these patients (75.19%) were white females with invasive ductal carcinoma who were treated at comprehensive cancer centers or academic research programs.

Many patients undergoing omission of RT after NACT were not low risk patients. There were 22.2% who were clinically T3 or T4 prior to NACT, and 6.7% who were pathologically ypT3 or ypT4 (Table 1). Clinical N2 or N3 status was found in 11.1% prior to NACT, and pathologic N2 or N3 status after NACT was present in 12.6% of patients. Only 29.4% of these patients were intermediate or low grade. Among those patients found to be upstaged on final T or N stage, 15.2% and 8.9% respectively, did not receive radiotherapy.

Factors that predicted the failure of RT receipt included increasing age (OR 1.17 per 10 years of age; 95% CI: 1.09-1.27, $P<0.0001$), insurance status (ORs varied), other specified type of cancer program (e.g. Veterans Affairs or hospital-associated cancer programs); ORs 1.48; 95% CI: 1.02-2.16, $P=0.0404$), facility region (ORs varied), more recent year of diagnosis (OR 1.06; 95% CI: 1.01-1.12, $P=0.0267$), receptor status unknown (OR 1.68; 95% CI: 1.19-2.37, $P=0.003$), HER2 status positive or unknown (ORs varied), and positive margins (ORs 1.67; 95% CI: 1.29-2.16, $P=0.0001$). Factors decreasing the likelihood of RT omission included clinical N3 disease (ORs 0.59; 95% CI: 0.36-0.95, $P=0.0312$), receptor positivity (ORs 0.85; 95% CI: 0.73-0.99, $P=0.0391$), and primary tumor downstaging (ORs 0.84; 95% CI: 0.72-0.98, $P=0.0237$). Factors having no effect on likelihood of RT included race, Hispanicity, education, income, Charlson comorbidity index, urban vs rural setting, histology, clinical T stage, grade, and N stage change (Table 2).

When excluding 314 (32.3%) patients who did not receive RT after it was recommended by the physician, 660 patients remained in this group. The factors that predicted failure of RT receipt in this subset included increasing age (ORs 1.22; 95% CI: 1.11-1.33, $P<0.0001$), Medicaid insurance (ORs 1.38; 95% CI: 1.10-1.73, $P=0.006$), other specified type of cancer program (ORs 2.03; 95% CI: 1.32-3.12, $P=0.0013$), facility region (ORs varied), receptor status unknown (ORs 1.69; 95% CI: 1.13-2.55, $P=0.0115$), HER2 status unknown (ORs 1.33; 95% CI: 1.02-1.74, $P=0.036$), and positive margins (ORs 1.69; 95% CI: 1.26-2.27, $P=0.0005$). The factors that increased likelihood of RT receipt included receptor positivity (ORs 0.83; 95% CI: 0.69-1.00, $P=0.0459$) and N stage downstaging (ORs 0.79; 95% CI: 0.65-0.97, $P=0.0262$). The factors that had no effect on likelihood RT included race, Hispanicity, education, income, Charlson comorbidity index, urban versus rural setting, more recent year of diagnosis, histology, clinical T and N stage, grade, and primary downstaging (Table 3).

Discussion

BCT has been the standard of care for the treatment of invasive breast cancer for decades and is composed of both BCS and RT, irrespective of whether chemotherapy is administered neoadjuvantly or adjuvantly. Surprisingly, our analysis notes that nearly 10% of patients who received NACT in the United States prior to BCS did not receive RT. The presented data demonstrates nine independent predictors of failure of RT receipt in this group of patients. There were a total of 660 patients for whom radiotherapy was not recommended. After removing the 314 (32%) of patients in whom RT was recommended but was declined, we found that most of those independent predictors remained significant.

Although it is not possible to discern from this dataset which specialty or practitioner may have recommended omitting radiotherapy after NACT and BCS, it is the responsibility of all physicians involved to ensure that the requirement for RT after BCS is clearly understood. It is particularly important for surgeons who often see the patients first and decide upon surgical options. This also applies to RT administration in the setting of NACT and BCS. It has previously been demonstrated that patients are more likely to have breast conservation when the physician is the predominant partner in the decision making process(16), and so discussions must emphasize critical nature of radiotherapy as a component of therapy.

In the group of predictors encompassing all patients not receiving RT, we found that for every decade that a patient aged, she was 17% less likely to receive RT following NACT and BCS. This confirms multiple previous studies that have demonstrated deviation of guidelines for elderly patients, compared to their younger counterparts.(17-19) The PRIME II and CALGB 9343 studies found that women who had “low-risk” breast cancer who were older than 65 and 70, respectively, did not require radiotherapy. (10, 11, 20)

It is conceivable that the CALGB study, which garnered significant attention and was first published in 2004, may be reflected in our findings here as suggested by one review of practice patterns related to the trial(21), although the long term follow up data and the PRIME II study were published subsequent to the diagnosis dates of our defined cohort. These trials do suggest an acceptable cohort in whom radiotherapy may potentially be omitted, but the outcome of these trials cannot be extrapolated to the neoadjuvant setting. Neither trial utilized NACT, and both studies were limited to low risk cancers. The PRIME II trial enrolled solely women aged 65 who had lesions that were hormone receptor-positive, axillary node-negative and smaller than 3.0 cm with clear margins. They permitted either lymphovascular invasion or grade 3 tumors, but not both. CALGB 9343 enrolled women 70 having stage I or II initially (then limited to stage I), receptor-positive breast cancers that were clinically node negative with negative margins. Our subjects all received NACT prior to BCT and were frequently high risk breast cancers, as evidenced by the proportion of patients who were of advanced T or N stages, high grade, HER2 positive, margin positive, and receptor negative, strongly suggesting that RT should not have been omitted. Additionally, the clinical T stage made no difference in whether they received RT or not.

The region of the U.S. also remained an independent predictor of failure of RT receipt. Using the Western North Central U.S. as the reference, we found that South Atlantic, East and West South Central, Mountain, and Pacific regions of the U.S. were independent predictors of RT failure. This left New England, Middle Atlantic, and East North Central U.S. regions as having no effect to whether or not RT was received. We hypothesize that this may be due to the higher concentration of academic and cancer programs in New England, Mid Atlantic and East North Central U.S. These regions include only 14 states, yet they contain 39% (27/69) of National Cancer Institute designated cancer centers.(22) We have previously shown that insurance status is associated with disparities in the local management of breast cancer throughout the United States, (23) but physician factors such as lack of knowledge and systemic obstacles may also play a role in this variability.(24) These factors may themselves vary by geographic region, but further studies are required to confirm the true cause of this regional effect.

Our data also suggest that receptor status, HER2 positive or unknown status, and positive tumor margins all independently predict failure of RT receipt. We hypothesize that many physicians alter their treatment plan based on these tumor features because there are other adjuvant therapies. However, there are no data suggesting that systemic therapies are equivalent to fulfilling BCT. Furthermore, a recently released 15-year randomized controlled study was unable to find any tumor characteristics that indicated RT could be omitted.(25) At this time, we believe that it is important that all patients who receive NACT and who undergo BCS complete BCT with RT, or potentially face undertreatment.

The most surprising results of our study stemmed from the factors that had no effect on whether or not RT was received, including race, associated comorbidities, education, and income. Although the last two are socioeconomic indicators, Medicaid insurance, which was associated with lack of RT receipt, can also be a surrogate for socioeconomic status, suggesting that the relationship to this issue may be complex. This is in contrast to multiple other studies that have suggested that these 3 factors are major contributors to medical inequality in the U.S. and associated with reduced RT receipt. (19, 26-29) However, our study suggests that these factors actually do not play a role in whether or not patients receive therapy in this specific setting. Although at first glance one would expect RT omission to increase in likelihood with greater numbers of comorbidities, this was not seen. Candidacy for chemotherapy is more subject to limitations from comorbidities due to its toxicity than radiotherapy. Since all patients in this study were given neoadjuvant chemotherapy, and therefore considered sufficiently robust to withstand the side effects of systemic treatment, it seems logical that concerns about comorbidities and the ability to tolerate RT would be largely resolved after successful systemic therapy administration. If true, a predisposition to omit radiotherapy specifically because of comorbidities may have been selected out by this cohort's NACT administration, explaining this finding.

Our study is limited due to the retrospective nature of our review. Selection bias can occur even in prospectively collected large datasets such as the NCDB, although the large sample size is representative of care given at Commission on Cancer hospitals throughout the United States. We unfortunately cannot discern why the failure of RT recommendation or administration arose, contraindications for RT, and why some patients had finally positive

margins. The NCDB also does not contain practitioner information related to the specialties who saw the patient (such as general surgery vs surgical oncology). This inhibits us from correlating differences in the patterns of specialists seen. Nevertheless, since multidisciplinary care, which is increasing in prevalence(30), requires a unified opinion across practitioners, all specialties should be discussing appropriate management uniformly and are similarly culpable when appropriate treatment recommendations are not conveyed. No dataset, to our knowledge, can discern other reasons for radiotherapy omission, such as the content of discussion with physicians, lack of physician knowledge, patient preference, or other significant factors that could be isolated and combatted as the cause of RT omission in patients.

Conclusion

Despite the clear consensus of the importance of RT following BCS, we have found that nearly 10% of patients who received NACT prior to BCS did not receive the standard of care. In this study we have found multiple factors that may help to predict failure of RT receipt. It is encouraging that race, education and income did not influence the likelihood of RT receipt, (although Medicaid insurance was a predictor). Unfortunately, however, comorbidities which would be the most likely reason, also did not explain the difference in treatment. It remains unclear whether some omission of RT is due to lack of physician knowledge or patient understanding. We believe that the factors we have identified can be used to aid in the identification of patients at higher risk of receiving suboptimal care. Further efforts may be needed to ensure that physicians of all specialties, especially surgeons who frequently introduce the treatment paradigm of BCT and NACT as an option, recognize that RT is a required part of BCT and that this requirement does not change in the face of NACT use(2).

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Figure 1.

Exclusion and inclusion criteria. Numbers represent remaining patients after that set of exclusions. AJCC, American Joint Committee on Cancer; LNs, lymph nodes; N, nodal; NAC, neoadjuvant chemotherapy; RT, radiotherapy; T, tumor.

Table 1
Characteristics of cohort

Characteristic	Patients not receiving RT (n = 974)	Patients receiving RT (n = 9246)	Total
Race			
White	709 (9.33)	6893 (90.67)	7602
Black	212 (10.29)	1849 (89.71)	2061
Other/Unknown	53 (9.52)	504 (90.48)	557
Hispanic			
Yes	108 (14.23)	651 (85.77)	759
No	805 (9.06)	8084 (90.94)	8889
Unknown	61 (10.66)	511 (89.34)	572
Education: Percentage of adults who did not graduate high school			
>21%	212 (12.16)	1531 (87.84)	1743
13%-20.9%	223 (9)	2254 (91)	2477
7%-12.9%	277 (8.62)	2936 (91.38)	3213
<7%	247 (9.33)	2401 (90.67)	2648
Median Income			
< \$38,000	189 (10.43)	1623 (89.57)	1812
\$38,000 - \$47,999	233 (10.51)	1984 (89.49)	2217
\$48,000 - \$62,999	225 (8.42)	2447 (91.58)	2672
> \$63,000	312 (9.24)	3064 (90.76)	3376
Charlson-Deyo Score (Comorbidities)			
0	860 (9.32)	8369 (90.68)	9229
1	100 (11.33)	783 (88.67)	883
2	14 (12.96)	94 (87.04)	108
Insurance Status			
Uninsured	46 (10.02)	413 (89.98)	459
Private insurance and managed care	573 (8.21)	6410 (91.79)	6983
Medicaid	137 (12.09)	996 (87.91)	1133
Medicare	178 (13.01)	1190 (86.99)	1368
Other Government	**	**	120
Unknown	**	**	157
Urban vs. Rural			
Large metropolitan	574 (9.81)	5277 (90.19)	5851
Small metropolitan	261 (9.33)	2536 (90.67)	2797
Suburban	73 (9.28)	714 (90.72)	787
Rural	37 (8.85)	381 (91.15)	418
Unknown	29 (7.9)	338 (92.1)	367
Facility Type			
Community Cancer Program	**	**	804

Characteristic	Patients not receiving RT (n = 974)	Patients receiving RT (n = 9246)	Total
Comprehensive Community Cancer Program	460 (8.36)	5043 (91.64)	5503
Academic or Research Program	434 (11.17)	3453 (88.83)	3887
Other specified type of cancer program	**	**	26
Facility Region *			
New England	29 (5.36)	512 (94.64)	541
Middle Atlantic	121 (8.3)	1337 (91.7)	1458
South Atlantic	236 (9.01)	2383 (90.99)	2619
East North Central	129 (6.7)	1796 (93.3)	1925
East South Central	54 (10.89)	442 (89.11)	496
West North Central	46 (6.45)	667 (93.55)	713
West South Central	157 (18.67)	684 (81.33)	841
Mountain	56 (11.94)	413 (88.06)	469
Pacific	146 (12.61)	1012 (87.39)	1158
Year of Diagnosis			
2003	52 (12.06)	379 (87.94)	431
2004	59 (11.71)	445 (88.29)	504
2005	64 (11.15)	510 (88.85)	574
2006	64 (9.68)	597 (90.32)	661
2007	84 (10.5)	716 (89.5)	800
2008	84 (8.51)	903 (91.49)	987
2009	87 (7.14)	1132 (92.86)	1219
2010	96 (6.44)	1395 (93.56)	1491
2011	139 (7.71)	1664 (92.29)	1803
2012	245 (14)	1505 (86)	1750
Histology			
Ductal	894 (9.44)	8580 (90.56)	9474
Lobular	28 (8.97)	284 (91.03)	312
Other	52 (11.98)	382 (88.02)	434
Clinical T stage (cT)			
0	**	**	27
1	**	**	883
2	660 (9.47)	6313 (90.53)	6973
3	166 (8.75)	1732 (91.25)	1898
4	50 (11.39)	389 (88.61)	439
Pathology T stage (ypT)			
0	227 (9.16)	2251 (90.84)	2478
1	368 (8.33)	4050 (91.67)	4418
2	314 (11.24)	2480 (88.76)	2794
3	50 (12.08)	364 (87.92)	414

Characteristic	Patients not receiving RT (n = 974)	Patients receiving RT (n = 9246)	Total
4	15 (12.93)	101 (87.07)	116
Clinical N stage (cN)			
0	447 (9.53)	4244 (90.47)	4691
1	419 (9.51)	3985 (90.49)	4404
2	88 (10.86)	722 (89.14)	810
3	20 (6.35)	295 (93.65)	315
Pathology N stage (ypN)			
0	605 (9.39)	5839 (90.61)	6444
1	246 (9.13)	2447 (90.87)	2693
2	102 (12.44)	718 (87.56)	820
3	21 (7.98)	242 (92.02)	263
Grade			
1	46 (9.77)	425 (90.23)	471
2	240 (8.17)	2696 (91.83)	2936
3	586 (9.77)	5413 (90.23)	5999
Anaplastic/undifferentiated	**	**	65
Unknown	**	**	749
ER and/or PR Positive			
Negative	423 (9.61)	3979 (90.39)	4402
Positive	452 (8.69)	4748 (91.31)	5200
Unknown	99 (16.02)	519 (83.98)	618
HER2 positive			
Negative	319 (8.76)	3321 (91.24)	3640
Positive	154 (10.47)	1317 (89.53)	1471
Unknown	501 (9.81)	4608 (90.19)	5109
T stage change			
Down	590 (8.62)	6257 (91.38)	6847
None	355 (11.16)	2827 (88.84)	3182
Up	29 (15.18)	162 (84.42)	191
N stage change			
Down	237 (8.67)	2496 (91.33)	2733
None	622 (10.03)	5578 (89.97)	6200
Up	115 (8.94)	1172 (91.06)	1287
Margins			
Negative	885 (9.2)	8735 (90.8)	9620
Positive	74 (15.38)	407 (84.62)	481
Unknown	15 (12.61)	104 (87.39)	119

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**

Cells <11 have been censored to comply with NCDB rules omitting those or any cells that may make such cells calculable.

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Table 2

Multivariable analysis of all patients for whom radiotherapy was omitted.

Factor	OR	CI	P value
Age			
Every 10-year Increase in Age	1.17	1.09 – 1.27	<.0001
Race			
White	Referent		
Black	1.16	0.96 – 1.40	0.1233
Other/Unknown	0.98	0.73 – 1.32	0.8847
Hispanic			
No	Referent		
Yes	1.15	0.87 – 1.50	0.3255
Unknown	1.23	0.89 – 1.69	0.2122
Education: Percentage of adults who did not graduate high school			
>21%	Referent		
13%-20.9%	0.91	0.74 – 1.12	0.3701
7%-12.9%	0.97	0.77 – 1.23	0.8044
<7%	1.17	0.89 – 1.53	0.2748
Median Income			
< \$38,000	Referent		
\$38,000 - \$47,999	1.09	0.89 – 1.33	0.4153
\$48,000 - \$62,999	0.91	0.72 – 1.15	0.4088
> \$63,000	0.99	0.74 – 1.33	0.955
Charlson-Deyo Score (Comorbidities)			
0	Referent		
1	1.16	0.93 – 1.44	0.1804
2	1.24	0.73 – 2.11	0.4309
Insurance Status			
Private insurance and managed care	Referent		
Uninsured	1.06	0.77 – 1.47	0.7068
Medicaid	1.45	1.17 – 1.78	0.0005
Medicare	1.24	1.00 – 1.55	0.05
Other Government	0.92	0.53 – 1.57	0.7523
Unknown	2.17	1.43 – 3.29	0.0003
Urban vs. Rural			
Rural	Referent		
Large metropolitan	1	0.68 – 1.48	0.9901
Small metropolitan	1.05	0.72 – 1.54	0.7982
Suburban	1.11	0.72 – 1.72	0.6257
Unknown	0.81	0.42 – 1.58	0.5387

Factor	OR	CI	P value
Facility Type			
Community Cancer Program	Referent		
Comprehensive Community Cancer Program	0.93	0.69 – 1.26	0.6455
Facility Region *			
West North Central	Referent		
New England	1.05	0.58 – 1.91	0.8761
Middle Atlantic	1.6	1.00 – 2.57	0.0496
South Atlantic	1.89	1.19 – 2.99	0.0065
East North Central	1.13	0.71 – 1.81	0.6081
East South Central	1.96	1.09 – 3.51	0.0242
West South Central	3.59	2.14 – 6.03	<.0001
Mountain	2.70	1.41 – 5.16	0.0027
Pacific	2.51	1.52 – 4.14	0.0003
Year of Diagnosis			
More Recent Year of Diagnosis	1.06	1.01 – 1.12	0.0267
Histology			
Ductal	Referent		
Lobular	0.88	0.60 – 1.31	0.5358
Other	1.19	0.86 – 1.65	0.3014
Clinical T stage (cT)			
0	Referent		
1	0.80	0.28 – 2.31	0.6754
2	0.82	0.29 – 2.32	0.7031
3	0.76	0.27 – 2.16	0.6065
4	0.93	0.31 – 2.76	0.8938
Clinical N stage (cN)			
0	Referent		
1	1.01	0.86 – 1.17	0.928
2	1.10	0.83 – 1.45	0.5027
3	0.59	0.36 – 0.95	0.0312
Grade			
1	Referent		
2	0.83	0.61 – 1.13	0.2316
3	0.99	0.73 – 1.33	0.9463
Anaplastic/undifferentiated	0.65	0.26 – 1.66	0.3707
Unknown	1.36	0.94 – 1.97	0.1003

Factor	OR	CI	P value
ER and/or PR Receptor Status			
Negative	Referent		
Positive	0.85	0.73 – 0.99	0.0391
Unknown	1.68	1.19 – 2.37	0.003
HER2 Status			
Negative	Referent		
Positive	1.34	1.09 – 1.65	0.0063
Unknown	1.37	1.10 – 1.72	0.0049
T stage change			
None	Referent		
Down	0.84	0.72 – 0.98	0.0237
Up	1.35	0.90 – 2.03	0.1438
N stage change			
None	Referent		
Down	0.89	0.74 – 1.08	0.2326
Up	0.89	0.73 – 1.09	0.2644
Margins			
Negative	Referent		
Positive	1.67	1.29 – 2.16	0.0001
Unknown	1.14	0.58 – 2.25	0.7092

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Table 3

Multivariable analysis of all patients for whom radiotherapy was omitted but was recommended.

Factor	OR	CI	P value
Age			
Every 10-year Increase in Age	1.22	1.11 – 1.33	<.0001
Race			
White	Referent		
Black	1.17	0.95 – 1.45	0.1416
Other/Unknown	1.06	0.76 – 1.47	0.7246
Hispanic			
No	Referent		
Yes	1.21	0.89 – 1.66	0.227
Unknown	1.27	0.88 – 1.83	0.2009
Education: Percentage of adults who did not graduate high school			
>21%	Referent		
13%-20.9%	0.96	0.75 – 1.24	0.7712
7%-12.9%	1.02	0.77 – 1.36	0.8784
<7%	1.09	0.78 – 1.52	0.6112
Median Income			
< \$38,000	Referent		
\$38,000 - \$47,999	0.96	0.76 – 1.21	0.715
\$48,000 - \$62,999	0.82	0.62 – 1.09	0.1707
> \$63,000	1.02	0.71 – 1.44	0.9297
Charlson-Deyo Score (Comorbidities)			
0	Referent		
1	1.07	0.82 – 1.39	0.61
2	1.52	0.87 – 2.65	0.1447
Insurance Status			
Private insurance and managed care	Referent		
Uninsured	0.89	0.61 – 1.29	0.5267
Medicaid	1.38	1.10 – 1.73	0.006
Medicare	1.20	0.94 – 1.53	0.1416
Other Government	1.03	0.54 – 1.93	0.938
Unknown	1.63	0.91 – 2.92	0.1
Urban vs. Rural			
Rural	Referent		
Large metropolitan	0.91	0.59 – 1.40	0.664
Small metropolitan	1.00	0.66 – 1.52	0.9828
Suburban	1.22	0.75 – 1.98	0.4203
Unknown	0.85	0.41 – 1.75	0.6505

Factor	OR	CI	P value
Facility Type			
Community Cancer Program	Referent		
Comprehensive Community Cancer	0.96	0.67 – 1.36	0.8023
Academic or Research Program	1.28	0.88 – 1.88	0.2009
Other specified type of cancer program	2.03	1.32 – 3.12	0.0013
Facility Region *			
West North Central	Referent		
New England	0.81	0.39 – 1.70	0.577
Middle Atlantic	1.43	0.82 – 2.50	0.2039
South Atlantic	2.07	1.22 – 3.52	0.0073
East North Central	1.24	0.73 – 2.12	0.4303
East South Central	2.14	1.10 – 4.14	0.0249
West South Central	4.05	2.22 – 7.36	<.0001
Mountain	3.10	1.45 – 6.64	0.0035
Pacific	2.47	1.35 – 4.52	0.0034
Year of Diagnosis			
More Recent Year of Diagnosis	1.05	0.99 – 1.11	0.1263
Histology			
Ductal	Referent		
Lobular	1.03	0.65 – 1.63	0.9704
Other	1.18	0.82 – 1.70	0.3612
Clinical T stage (cT)			
0	Referent		
1	0.52	0.18 – 1.54	0.2362
2	0.49	0.17 – 1.40	0.185
3	0.47	0.16 – 1.34	0.1563
4	0.47	0.16 – 1.43	0.1843
Clinical N stage (cN)			
0	Referent		
1	1.11	0.93 – 1.31	0.2431
2	1.06	0.78 – 1.44	0.6975
3	0.70	0.41 – 1.21	0.2032
Grade			
1	Referent		
2	0.75	0.53 – 1.06	0.1014
3	0.89	0.64 – 1.24	0.4829
Anaplastic/undifferentiated	0.73	0.28 – 1.91	0.5248
Unknown	1.16	0.78 – 1.72	0.4745
ER and/or PR Receptor Status			

Factor	OR	CI	P value
Negative	Referent		
Positive	0.83	0.69 – 1.00	0.0459
Unknown	1.69	1.13 – 2.55	0.0115
HER2 Status			
Negative	Referent		
Positive	1.18	0.91 – 1.53	0.2211
Unknown	1.33	1.02 – 1.74	0.036
T stage change			
None	Referent		
Down	0.92	0.77 – 1.11	0.4027
Up	1.36	0.85 – 2.16	0.1952
N stage change			
None	Referent		
Down	0.79	0.65 – 0.97	0.0262
Up	0.84	0.66 – 1.07	0.1666
Margins			
Negative	Referent		
Positive	1.69	1.26 – 2.27	0.0005
Unknown	1.36	0.68 – 2.71	0.3809

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