HHS Public Access

Author manuscript

Clin Breast Cancer. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Clin Breast Cancer. 2018 August ; 18(4): e477–e493. doi:10.1016/j.clbc.2017.09.001.

The State of Surgical Axillary Management and Adjuvant Radiotherapy for Early Stage Invasive Breast Cancer in the Modern Era

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Abstract

Background—For clinical T1-2N0 breast cancer, sentinel lymph node biopsy (SLNB) has been shown in ACOSOG Z0011 to be sufficient for women with 1–2 positive sentinel lymph nodes with no added benefit for completion axillary lymph node dissection (ALND). Z0011 specified whole breast radiotherapy using standard tangential fields; however, later analysis showed variation in field design. We assessed nationwide practice patterns and examined factors associated with patients undergoing completion ALND and subsequent radiation field design.

Methods—Women with clinical T1-2N0 breast cancer who underwent breast-conserving surgery, axillary staging, and whole breast radiotherapy in 2012–2013 were identified in the National Cancer Database (NCDB). Multivariable logistic regression modeling was used to examine axillary management and radiotherapy adjusting for demographic and clinicopathologic factors.

Results—Among 83,555 patients meeting criteria, 9.3% underwent upfront ALND, 75.8% underwent SLNB only, and 14.9% underwent SLNB with completion ALND. From 2012–2013, upfront SLNB increased from 90.1% to 91.4% (OR=1.14, P<0.001). Among 9,474 patients that underwent SLNB with 1 to 2 positive sentinel nodes, 31.2% received completion ALND. Among patients with 1–2 positive sentinel nodes, SLNB increased from 65.8 to 72.1% from 2012 to 2013 (P<0.001). For patients with 1–2 positive lymph nodes that underwent SLNB only, 63.4% underwent breast RT, whereas 36.6% received breast and nodal radiotherapy.

Conclusions—Nationwide practice patterns of axillary management vary. Despite an increasing rate of SLNB, many patients still receive upfront and completion ALND. Furthermore, there is significant variation in radiotherapy field design and modern treatment guidelines are warranted for this patient population.

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An earlier form of the abstract for this manuscript was presented at the 58th annual meeting of the American Society of Radiation Oncology (ASTRO) on September 25th, 2016.

Conflict of interest: The authors have no conflicts to disclose.

Keywords

axillary lymph node dissection; sentinel lymph node dissection; breast radiotherapy; axillary radiotherapy; NCDB; National Cancer Database

Introduction

The surgical management of breast cancer has long been an area of great debate, heavily focused on the extent of surgical resection deemed acceptable. The proposal that less radical surgery may be equally efficacious led to the randomized B-04 clinical trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP), which compared radical mastectomy, total mastectomy, and total mastectomy with whole breast radiotherapy (RT). The study showed no survival benefit with more radical surgery. For patients with positive lymph nodes, the lack of a survival or locoregional recurrence benefit with the Halsted radical mastectomy versus total mastectomy with RT suggested a lack of therapeutic benefit of axillary lymph node dissection.[1] This has guided the evolution from the Halsted radical mastectomy to breast conservation therapy.

Similarly, sentinel lymph node biopsy (SLNB) has supplanted axillary lymph node dissection (ALND) for clinically node-negative breast cancer patients. Axillary staging and management were previously accomplished through the use of ALND, which carries a 10–20% risk of lymphedema.[2] The results of the NSABP B-32 trial demonstrated equivalence of SLNB followed by immediate conventional ALND compared to SLNB alone if sentinel lymph nodes (SLNs) were negative. Overall survival, disease-free survival, and regional control were equivalent between groups, demonstrating the feasibility of no further axillary dissection following a negative SLNB.[3] This less invasive technique has shown decreased morbidity and improved sensitivity in detecting occult nodal disease.[4]

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial investigated the need for further axillary dissection among patients with 1–2 positive SLNs undergoing segmental mastectomy. ACOSOG Z0011 was a phase 3 noninferiority trial in patients with clinical T1-T2N0 breast cancer who underwent SLNB and had 1 to 2 positive SLNs. Patients were randomized to no additional axillary surgery or completion ALND.[5] Over 90% of patients received adjuvant systemic therapy with no differences between groups. Per protocol, patients were to undergo whole-breast radiotherapy following breast conservation surgery (BCS) with opposing tangential-fields. Initial results were published in February 2011 with a median follow-up of 6.3 years, showing no significant difference in overall survival, disease-free survival and local or regional recurrence among women with 1–2 positive SLNs undergoing completion ALND versus SLNB only. This landmark trial altered the treatment paradigm for axillary management and led to the recommendation by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) to recommend no additional axillary surgery beyond SLNB for women meeting ACOSOG Z0011 inclusion criteria planning on receiving RT.[6,7] This practice-changing study counters the argument that completion ALND is needed in patients with 1–2 positive SLNs following segmental mastectomy.

The ACOSOG Z0011 protocol specified that patients receive whole-breast radiotherapy using standard tangential fields and specifically prohibited a supraclavicular field of directed nodal radiation; however, there was no blinding of radiation oncologists, who had discretion over treatment field design.[4] A study analyzing the field design in Z0011 showed that there were differences in radiation delivery noted upon review of 228 detailed radiotherapy records.[8] Within the radiation oncology community, there has been a question as to the optimal RT field design in patients with low-volume axillary disease, who do not receive a completion ALND, thus failing to provide important pathological information that has traditionally been available to the radiation oncologist to aid in guiding treatment.[9]

Given the above, we sought to investigate practice patterns including surgical management and radiation field design for clinically node-negative breast cancer patients undergoing breast-conserving therapy with 1–2 positive SLNs, using the National Cancer Database (NCDB). Notably, data on scope of regional lymph node surgery have been found to under-report SLNB procedures either alone or with ALND, and reviews by the Commission on Cancer (CoC), the Centers for Disease Control and Prevention's National Program of Cancer Registries (CDC/NPCR), and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (NCI SEER), all confirmed miscoding of this data element. Revised coding rules were recently employed for cases diagnosed in 2012 and later providing crucial sentinel node data for the desired study population in the period following the publication and dissemination of results from ACOSOG Z0011, making this study possible.[10]

Methods

Data Source

The National Cancer Database (NCDB) is a joint project of the American College of Surgeons and the American Cancer Society that draws data from more than 1500 accredited cancer programs accounting for 70% of all newly diagnosed cancer cases in the United States. It includes a modern cohort of patients treated from 2012 to 2013 and thus were treated following the publication of the results of ACOSOG Z0011. Advantages of the NCDB over the SEER database include data for younger patients, pathologic factors, chemotherapy use, radiotherapy volumes, and medical comorbidities, which were included in our analysis. Another advantage of using the NCDB is the inclusion of many patients treated in varying settings including academic and community settings.

Patient Selection

Women with clinical T1-T2N0M0 invasive breast cancer with 1–2 positive SLNs who underwent breast conservation surgery, axillary management, and adjuvant radiotherapy from 2012–2013 were included in this analysis. Axillary management included SLNB alone, SLNB followed by ALND, or ALND. All patients were required to have received surgery at a Commission on Cancer (COC) facility and adjuvant external beam radiotherapy. Radiotherapy volumes included whole breast RT or whole breast plus regional lymph node RT. Interrogation of the NCDB yielded a total of 83,555 patients who met the search parameters.

Definition of Variables

Patient and treatment characteristics included facility type, age, ethnicity, insurance status, median income, education**,** geographic location, Charlson-Deyo comorbidity score, year of diagnosis, breast cancer laterality, grade, clinical and pathologic tumor size, number of nodes positive (1 or 2), clinical and pathologic stage, presence of lymphovascular invasion (LVI), hormone receptor subtype, surgical margin negativity, radiation technique (3D or intensity-modulated radiotherapy), receipt of adjuvant chemotherapy, and receipt of endocrine therapy. Patient exclusion criteria were similar to ACOSOG Z0011 criteria - women with 3 or more positive SLNs, mastectomy, matted nodes, gross extranodal disease, or if they received neoadjuvant systemic therapy.

Statistical Analysis

We calculated summary statistics using frequencies and proportions for categorical variables. We compared patient demographic, prognostic, and facility characteristics between treatment groups using the chi-square test. Univariate and multivariable logistic regression analyses were employed to determine the factors independently associated with receipt of each treatment (i.e., separate models for each treatment of interest). Factors of interest included facility type, facility location, age, race/ethnicity, insurance status, income, education, urban/rural status, Charlson-Deyo comorbidity score, year of diagnosis, laterality, grade, tumor size, number of regional lymph nodes examined, number of positive lymph nodes, clinical T stage, pathologic T stage, pathological N stage, analytic stage, lymphovascular invasion, hormone receptor subtype, Bloom-Richardson grade, surgical margins status, chemotherapy, and hormone therapy. Factors that were significant ($P<0.05$) in the univariate analyses were included in the multivariable models. Three separate multivariable logistic regression models were constructed in patient subgroups of interest including: factors associated with patients undergoing sentinel lymph node dissection with or without axillary lymph node dissection compared to upfront axillary lymph node dissection; factors associated with patients undergoing completion axillary lymph node dissection after 1–2 positive sentinel nodes; and factors associated with patients with 1–2 positive sentinel nodes who undergo SLNB only, who then go on to receive adjuvant radiotherapy to the breast and regional lymph nodes compared to breast radiotherapy alone. Patients with missing covariate data were excluded from the multivariable regression models. Co-linearity between covariates in the models was evaluated prior to the formulation of the final multivariable models. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) were reported. C-statistics were calculated to evaluate the discriminative capacity of each multivariable model. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Institutional IRB approval was waived for this study.

Results

Independent factors associated with patients undergoing sentinel lymph node dissection with or without axillary lymph node dissection compared to upfront axillary lymph node dissection

Of the 83,555 patients in the cohort, a total of 9.3% (N=7738) underwent upfront ALND, 75.8% (N=63346) underwent SLNB only, and 14.9% (N=12471) underwent SLNB followed by completion ALND. On multivariable logistic regression, statistically significant factors associated with patients undergoing sentinel lymph node dissection with or without axillary lymph node dissection compared to upfront axillary lymph node dissection were facility type and location, age, race, insurance status, income, education level, population density, year of diagnosis, clinical T-stage and hormone receptor subtype (Table 1). Patients with triple negative disease were not more likely to undergo upfront ALND. The rate of upfront SLNB +/− ALND in patients showed an absolute increase over 2012 to 2013 from 90.1% to 91.4% (OR=1.14, P<0.001). The rate of patients undergoing SLNB +/− ALND, rather than upfront ALND, was greater in patients with clinical T1 disease (91.3% versus 89.3%, respectively, OR=1.12, P=0.01).

Independent factors associated with patients undergoing completion axillary lymph node dissection after 1–2 positive sentinel nodes

Factors associated with completion ALND in patients who had 1 to 2 positive sentinel lymph nodes at the time of SLNB were determined. Out of 63,346 patients who underwent sentinel lymph node biopsy, there were 9,474 with 1–2 positive SLNs (15.0%). Among these patients, a total of 68.8% (N=6520) underwent no further axillary dissection (SLNB only) and 31.2% (N=2954) received SLNB followed by completion axillary dissection (SLNB + ALND). On multivariable logistic regression, statistically significant factors associated with patients with 1–2 positive sentinel nodes undergoing completion ALND compared to sentinel lymph node biopsy only were facility type and location, age, race, year of diagnosis, and the number of positive sentinel nodes (Table 2). The rate of sentinel lymph node biopsy only with no completion dissection for patients with 1–2 positive SLNs increased from 65.8% to 72.1% from 2012–2013. Patients with two positive sentinel lymph nodes at the time of SLNB had a significantly increased rate of completion ALND, compared to patients with only one positive SLN (OR=2.31, P<0.001).

Independent factors associated with patients with 1–2 positive sentinel nodes who undergo SLNB only, who then go on to receive adjuvant radiotherapy to the breast and regional lymph nodes compared to breast radiotherapy alone

Among patients who had 1–2 positive sentinel nodes at the time of SLNB, and no completion axillary dissection, we investigated the radiotherapy volumes, whole breast RT versus whole breast plus regional nodal RT. Among these patients, 63.4% (N=4136) underwent whole breast RT and 36.6% (N=2384) received whole breast and regional nodal RT. On multivariable logistic regression, statistically significant factors associated with patients receiving whole breast and regional nodal RT compared to breast RT alone were facility type and location, race, insurance status and median income, and the number of positive sentinel nodes (Table 3). Regarding the number of positive sentinel nodes, patients

with two positive SLNs had a greater likelihood of receiving RT to the breast and regional lymphatics compared to the breast alone (OR=1.96, P<0.001). Community cancer programs have a greater rate of treating the breast and regional lymphatics (OR=1.35, P=0.002). The treatment year that patients received radiotherapy was not significant.

Discussion

The present study reports the influence of the dissemination of ACOSOG Z0011 utilizing a prospective nationwide database analyzing the surgical and radiotherapy management of patients with early-stage clinically node-negative breast cancer with low-volume axillary disease. These results show an absolute increase in the rate of upfront SLNB of 1.3% (OR=1.14, P<0.001). Despite the reduction in upfront ALND, almost 9% of patients meeting the Z0011 entry criteria underwent ALND upfront, rather than SLNB.

The NSABP B-32 trial is a large phase 3 trial showing equivalence in disease outcomes between upfront ALND alone versus upfront SLNB with completion dissection for positive SLNs found at the time of SLNB. With regards to reliability, SLNB demonstrated a 97.2% technical success rate of sentinel lymph node removal with a 9.8% false negative rate.[11] Morbidity data from the B-32 trial at 3 years showed reduced residual shoulder abduction deficits, arm volume differences, arm numbness, and arm tingling in the SLNB arm.[12] These results are concordant with other studies also evaluating SLNB versus ALND, including the ALMANAC trial, which demonstrated reduced morbidity with SLNB rather than ALND.[13] Despite this, ur findings show that nearly 10% of all patients with clinically node-negative breast cancer still receive upfront ALND.

One of the criticisms of ACOSOG Z0011 was that the initial report had a median follow-up of only 6.3 years, which was arguably insufficient to assure non-inferiority, as differences in overall survival may only show up with longer term follow-up.[14] The recent publication of the long-term outcomes now with a median follow-up of 9.25 years continues to show no significant difference in cumulative incidence of local, regional, or locoregional recurrences, maintaining the original conclusion that SLNB without completion ALND offers excellent regional control for select patients with low-volume axillary disease who receive breast conservation therapy followed by whole breast radiotherapy.[15]

Since the publication of ACOSOG Z0011's results in 2011, various institutional reports have shared their axillary management practice patterns. Analysis of the ALND rate following SLNB in three tertiary referral care centers showed a significantly reduced number completion ALNDs performed in SLN-positive patients in the post-Z0011 period (71.4 %) compared to the pre-Z011 period (93.7 %, P=0.0022), indicating adoption of this new practice in a high-volume center.[16] A review of 658 patients with T1–2 tumors planned for breast conservation treated at MD Anderson showed that prior to the publication of Z0011, 85 % (53/62) of SLN positive patients underwent completion ALND versus 24 % (10/42) after the publication of Z0011 (P<0.001).[17] Additionally, a study from the Mayo Clinic also showed a reduction in the rate of completion ALND in patients with positive SLNs following Z0011's publication (83% to 62%; P<0.01), and showed no difference in the number of sentinel nodes harvested before and after publication of Z0011.[18]

A national survey sent to members of the American Society of Breast Surgeons in 2011 showed that 56.9% of respondents would not routinely perform ALND in patients with 1 or 2 positive SLNs planned to receive whole breast RT. Among respondents, 36% would consider omitting completion ALND in patients going on to receive accelerated partial breast radiation and 26.6% would omit ALND in patients not receiving any radiation.[19] A prior NCDB study analyzing patients treated from 1998–2011 meeting Z0011 eligibility criteria, showed an increase in sentinel lymph node biopsy alone from 6.1% in 1998 to 23.0% in 2009 and to 56.0% in 2011 ($p<0.001$).[20] It should be noted that this study utilized data from before 2012, which has been shown to under-report SLNB procedures either alone or with ALND.[10] Despite this noted issue with the data reporting at that time, this upward trend is concordant with our data that shows a sentinel lymph node biopsy alone rate of 65.8% in 2012 and 72.1% in 2013.

While there is increasing evidence that the results of Z0011 are being incorporated by the medical community, there has yet to be a large investigation into the wide scale adoption of Z0011 results until now. The primary aim of this study was to determine practice patterns of axillary management using the National Cancer Database after the publication of Z0011 and any significant social, economic, or clinicopathologic factors that may influence these practices. National practice patterns of axillary management have adjusted in accordance with the results of ACOSOG Z0011. Our data shows an absolute reduction in the rate of completion ALND following SLNB among patients meeting Z0011 criteria from 2012–2013 from 34.2% to 27.9%. Nevertheless, 27.6% and 47.4% of patients with 1 and 2 positive sentinel nodes found on biopsy, respectively, undergo completion ALND, despite data showing no difference in outcomes.[15] Interestingly, clinical T-stage was not associated with patients undergoing completion axillary dissection after positive SLNB. Given the demonstrated safety of avoiding an ALND for women with fewer than three positive sentinel lymph nodes, who receive adjuvant whole breast RT, the updated practice guidelines recommending no completion dissection should be further encouraged.

While the results of ACOSOG Z0011 provide valuable information regarding surgical management for this patient population, the issue of optimal radiation volumes remains an area for future investigation. Our data also shows the impact of facility type and location, race, insurance status and median income, and the number of positive sentinel nodes in patients who received RT to the breast and regional nodes. While the Z0011 specified standard tangent radiation fields, many patients received high tangents, which traditionally encompass levels 1 and 2 of the axilla.[21] Review of radiation field design in a subset of patients in ACOSOG Z0011 showed that half received high tangents, 17–21% had supraclavicular RT, and 6–10% had a posterior axillary boost, however, these protocol violations were evenly distributed between both arms of the study. Additionally, the highest rates of deliberate nodal treatment were seen in those with multiple nodes.[8] The variation in radiation fields in ACOSOG Z0011 and our study may be due to the lack of pathologic nodal data formerly provided by a completion axillary dissection. There did not seem to be any impact of treatment year (2012 versus 2013) in our analysis, but practice appears to vary significantly depending on type of center patients are treated at, with significantly greater amounts of patients in community practices receiving axillary nodal coverage as part of the radiotherapy course. There are no official guidelines by the American Society for Radiation

Oncology (ASTRO) regarding radiation treatment volumes for patients with low-volume axillary disease. Given the wide variation in radiation treatment volumes seen in the ACOSOG Z0011 trial, further efforts are needed to determine the optimal design of treatment fields.

The present analysis has several important limitations, the most important being that it is retrospective and non-randomized, subject to selection bias or influenced by variables that cannot be controlled for in the NCDB. Due to the inherent design of the NCDB, it is not possible to confirm treatment use coding data with individual patient data as data is only reported in the aggregate. Data representative of institutional treatment, but not an individual surgeon or radiation oncologist treating breast cancer is used. Furthermore, the NCDB definition of radiation to the breast and lymph nodes implies a deliberate attempt to include regional lymph nodes in the treatment of the breast but does not specify whether high tangents or a supraclavicular field are used, therefore either treatment field technique could have been utilized to include regional nodal volumes.

Conclusion

Despite the proven safety and efficacy of sentinel lymph node biopsy, almost 10% of clinical T1-2N0 breast cancer patients are undergoing upfront axillary lymph node dissection suggesting that the adoption of NSABP B-32 remains ongoing. For patients meeting ACOSOG Z0011 criteria, nearly one-third of patients received a completion axillary dissection, despite the low risk of axillary recurrence and lack of clinical benefit. Finally, due to large variations in radiation field design, further research and consensus guidelines are warranted in this post-Z0011 era.

Acknowledgments

Funding sources: This was supported through grant UL1 TR000457-06 from the National Center for Advancing Translational Sciences, National Institutes of Health.

Dr. Christos and Ms. Wu are supported in part by the CTSC funded through grant UL1 TR000457-06 from the National Center for Advancing Translational Sciences, National Institutes of Health. The authors wish to sincerely thank John Ng, M.D. and Onyinye Balogun, M.D. for reviewing this manuscript.

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Clinical Practice Points

The seminal ACOSOG Z0011 trial published in 2011 led to the recommendation for no additional axillary surgery beyond SLNB for women with clinical T1-T2N0 breast cancer who undergo SLNB and have 1 to 2 positive SLNs going on to undergo whole-breast radiotherapy following breast conservation surgery (BCS). Results from the National Cancer Database show that from 2012–2013, the rate of upfront SLNB has increased by 1.3%, while the rate of completion ALND for patients with 1–2 positive sentinel lymph nodes decreased 6.2%. For patients who receive SLNB only with 1–2 positive nodes who go on to receive adjuvant radiotherapy (RT), 63.4% receive whole breast RT and 36.6% receive whole breast and nodal RT. Nationwide practice patterns continue to evolve, however many patients still receive axillary dissection. There remains significant variation in radiation field design in the adjuvant setting, warranting further research in this area.

Table 1

Multivariable analysis for independent factors associated with patients undergoing sentinel lymph node dissection with or without axillary lymph node dissection compared to upfront axillary lymph node dissection

Outcome Event = SLNB +/− ALND		**N=75,360**		
Facility Type	**Percent (%)**	**OR**	**95% CI**	***p*-Value**
Academic/research program	30.25	reference	reference	reference
Community cancer program	11.54	0.78	0.72–0.85	<0.001
Comprehensive community cancer program	49.01	1.14	1.07–1.21	<0.001
Other	9.20	1.38	1.23–1.55	<0.001
Facility location				
New England	7.29	reference	reference	reference
Middle Atlantic region	16.80	1.33	1.19–1.48	<0.001
South Atlantic region	20.48	138	1.24–1.53	<0.001
East North Central region	18.68	1.18	1.06–1.31	0.002
East South Central region	4.81	0.9	0.78–1.02	0.11
West North Central region	7.40	1.62	1.41–1.85	<0.001
West South Central region	5.55	0.9	0.79–1.02	0.11
Mountain region	4.67	2.01	1.70–2.38	<0.001
Pacific region	12.43	1.49	1.33–1.68	<0.001
Age at diagnosis (years)				
40–49	14.36	reference	reference	reference
50–59	28.05	1.03	0.95–1.12	0.45
60–69	34.70	0.97	0.89–1.06	0.47
70–79	18.57	0.88	0.79–0.98	0.02
≥80	4.31	0.81	0.70–0.94	0.004
Race				
White	78.21	reference	reference	reference
Black	9.73	0.95	0.87–1.03	0.23
Hispanic	4.78	0.8	0.71–0.91	<0.001

Outcome Event = SLNB +/− ALND		**N=75,360**		
	Percent (%)	**OR**	**95% CI**	***p*-Value**
Asian/Pacific	3.33	0.99	0.85–1.15	0.87
Other or Unknown	3.96	0.68	0.61–0.76	<0.001
Insurance status				
Not insured	1.68	reference	reference	reference
Private insurance	55.08	1.36	1.14–1.61	<0.001
Medicaid	5.64	1.16	0.95–1.41	0.14
Medicare	35.37	1.41	1.17–1.68	<0.001
Other Government	2.23	0.88	0.70–1.10	0.27
Median Income				
<$38,000	13.20	reference	reference	reference
$38,000–$47,999	20.45	0.96	0.88–1.05	0.36
$48,000–$62,999	26.93	1.05	0.95–1.15	0.33
$63,000 +	39.41	1.13	1.02–1.26	0.02
Education (% of regional population with no high school degree)				
≥ 21%	12.98	0.77	0.69–0.86	<0.001
13–20%	22.53	0.91	0.83–1.00	0.04
7.0–12.9%	34.00	0.88	0.82–0.95	<0.001
<7%	30.37	reference	reference	reference
Population density of patient residence				
Metro counties	84.39	0.99	0.80–1.23	0.93
Urban counties	11.80	0.84	0.68–1.05	0.13
Rural counties	1.34	reference	reference	reference
Unknown	2.47	0.97	0.74–1.27	0.83
Year of diagnosis				
2012	50.92	reference	reference	reference
2013	49.08	1.15	1.09–1.21	<0.001
Clinical T-stage				

Outcome Event = SLNB +/− ALND		**N=75,360**		
	Percent (%)	**OR**	**95% CI**	***p*-Value**
Clinical T1, T1A, T1B, T1C and T1mi	83.62	1.12	1.02–1.22	0.01
Clinical T2	16.38	reference	reference	reference
Hormone receptor subtype				
Hormone receptor positive and HER2−	80.65	reference	reference	reference
Hormone receptor positive and HER2+	5.48	0.9	0.81–1.01	0.07
Hormone receptor positive and HER2 borderline	1.52	0.68	0.57–0.81	0.07
Hormone receptor negative	0.29	0.4	0.27–0.58	<0.001
HER2+	2.26	0.89	0.75–1.05	0.15
Hormone receptor negative and HER2 borderline	0.16	0.53	0.32–0.88	0.01
Triple negative	9.27	1.02	0.93–1.12	0.7
Unknown	0.37	0.6	0.42–0.87	0.007

Table 2

Multivariable analysis for independent factors associated with patients who undergo completion axillary lymph node dissection after 1–2 positive sentinel lymph nodes

Outcome event = SLNB + ALND		**N=9157**		
	Percent (%)	**OR**	**95% CI**	***p*-Value**
Facility Type				
Academic/research program	30.27	reference	reference	reference
Community cancer program	10.60	1.67	1.43–1.96	<0.001
Comprehensive community cancer program	49.06	1.31	1.17–1.46	<0.001
Other	10.07	1.17	0.97–1.41	0.11
Facility location				
New England	6.81	reference	reference	reference
Middle Atlantic region	16.07	1.44	1.16–1.79	<0.001
South Atlantic region	21.69	1.25	1.02–1.54	0.04
East North Central region	19.27	1.53	1.24–1.88	<0.001
East South Central region	4.63	1.21	0.92–1.60	0.18
West North Central region	7.79	1.39	1.09–1.77	0.009
West South Central region	5.02	1.44	1.10–1.88	0.008
Mountain region	5.57	1.07	0.81–1.40	0.64
Pacific region	13.15	0.91	0.72–1.14	0.4
Age at diagnosis (years)				
40–49	17.27	reference	reference	reference
50–59	29.77	0.87	0.76–0.99	0.04
60–69	31.73	0.91	0.79–1.04	0.15
70–79	16.59	0.86	0.73–1.00	0.05
≥80	4.64	0.57	0.44–0.73	<0.001
Race				
White	77.89	reference	reference	reference
Black	9.92	1.25	1.07–1.46	0.004
Hispanic	5.55	1.23	1.00–1.51	0.05
Asian/Pacific	3.20	0.83	0.62–1.10	0.2
Other or Unknown	3.44	0.88	0.68–1.14	0.33
Year of diagnosis				
2012	52.08	reference	reference	reference
2013	47.92	0.75	0.69–0.82	<0.001
Number of positive nodes				
1	82.07	reference	reference	reference
2	17.93	2.31	2.06–2.58	<0.001

Table 3

Multivariable analysis for independent factors associated with regional nodal radiotherapy compared to whole breast radiotherapy only in patients with 1–2 positive nodes who undergo SLNB only

Outcome event = Radiotherapy directed at the breast and regional lymph nodes		**N=6336**		
	Percent (%)	**OR**	**95% CI**	***p*-Value**
Facility Type				
Academic/research program	32.47	reference	reference	reference
Community cancer program	9.77	1.35	1.12–1.64	0.002
Comprehensive community cancer program	49.80	1	0.88–1.13	0.97
Other	7.97	0.71	0.57–0.88	0.002
Facility location				
New England	7.32	reference	reference	reference
Middle Atlantic region	15.85	0.65	0.52–0.83	<0.001
South Atlantic region	21.50	1.02	0.81–1.27	0.88
East North Central region	18.30	1	0.80–1.25	0.99
East South Central region	4.67	0.97	0.71–1.32	0.86
West North Central region	7.65	0.91	0.69–1.18	0.46
West South Central region	4.70	0.71	0.52–0.97	0.03
Mountain region	5.79	1.09	0.81–1.45	0.58
Pacific region	14.23	0.82	0.65–1.04	0.11
Race				
White	78.40	reference	reference	reference
Black	9.25	1.05	0.86–1.27	0.64
Hispanic	5.35	0.78	0.60–1.01	0.06
Asian/Pacific	3.42	0.71	0.52–0.97	0.03
Other or Unknown	3.57	0.83	0.62–1.10	0.19
Median Income				
<$38,000	13.54	reference	reference	reference
$38,000–$47,999	19.60	1.13	0.94–1.37	0.17
$48,000–$62,999	27.19	1.19	0.99–1.43	0.04
$63,000 +	39.51	1.01	0.85–1.21	0.71
Number of positive nodes	0.15			
1	86.30	reference	reference	reference
2	13.70	1.97	1.70–2.28	<0.001

Table 4

Baseline characteristics for patients undergoing sentinel lymph node dissection with or without axillary lymph node dissection compared to upfront axillary lymph node dissection

Demographic or Clinical Characteristics Univariate Analysis (N = 83555)	**ALND only (N=7738, 9.26%)**		**SLNB +/− ALND (N=75817, 90.74%)**		
	No.	**%**	**No.**	**%**	***p* Value**
Facility Type					<0.0001
Community cancer program	1232	12.78	8411	87.22	
Comprehensive community cancer program	3522	8.60	37429	91.40	
Academic/research program	2385	9.44	22891	90.56	
Other	599	7.79	7086	92.21	
Facility location					<0.0001
New England	625	10.26	5464	89.74	
Middle Atlantic region	1299	9.25	12739	90.75	
South Atlantic region	1456	8.51	15652	91.49	
East North Central region	1539	9.86	14069	90.14	
East South Central region	523	13.03	3492	86.97	
West North Central region	452	7.31	5730	92.69	
West South Central region	660	14.24	3976	85.76	
Mountain region	222	5.69	3677	94.31	
Pacific region	786	7.57	9602	92.43	
Unknown region	176	11.06	1416	88.94	
Age at diagnosis (years)					0.0031
<40	176	11.06	1416	88.94	
40–49	1092	9.28	10681	90.72	
50–59	2063	8.97	20930	91.03	
60–69	2583	9.08	25859	90.92	
70–79	1451	9.53	13771	90.47	
≥80	373	10.56	3160	89.44	
Race					<0.0001
White	5722	8.76	59627	91.24	

Demographic or Clinical Characteristics Univariate Analysis (N = 83555)	ALND only (N=7738, 9.26%)		SLNB +/− ALND (N=75817, 90.74%)		
	No.	%	No.	%	*p* Value
Black	874	10.76	7252	89.24	
Hispanic	499	12.50	3494	87.50	
Asian/Pacific	218	7.84	2564	92.16	
Other or Unknown	425	12.86	2880	87.14	
Insurance status					<.0001
Not insured	191	13.57	1216	86.43	
Private insurance	3989	8.67	42031	91.33	
Medicaid	566	12.02	4143	87.98	
Medicare	2730	9.24	26823	90.76	
Other	262	14.04	1604	85.96	
Median Income					<.0001
<$38,000	1286	11.68	9728	88.32	
$38,000–$47,999	1801	10.55	15263	89.45	
$48,000–$62,999	2058	9.16	20411	90.84	
$63,000 +	2579	7.84	30297	92.16	
Unknown	14	10.61	118	89.39	
Education (% of regional population with no high school degree)					<.0001
≥21%	1348	12.43	9494	87.57	
13–20%	1874	9.96	16949	90.04	
7.0–12.9%	2696	9.20	25711	90.80	
<7%	1896	7.45	23566	92.55	
Unknown	14	12.61	97	87.39	
Population density of patient residence					<0.0001
Metro counties	6302	8.94	64213	91.06	
Urban counties	1142	11.59	8715	88.41	
Rural counties	113	10.09	1007	89.91	
Charlson-Deyo Comorbidity Score					0.47
0	484	10.57	4096	89.43	

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Demographic or Clinical Characteristics Univariate Analysis (N = 83555)	ALND only (N=7738, 9.26%)		SLNB +/− ALND (N=75817, 90.74%)		
	No.	%	No.	%	*p* Value
1	6007	8.91	61383	91.09	
2	173	13.67	1093	86.33	
Year of diagnosis					<0.0001
2012	4220	9.92	38327	90.08	
2013	3518	8.58	37490	91.42	
Laterality					0.37
Right	3868	9.30	37624	90.70	
Left	3870	9.20	38177	90.80	
Grade					<.0001
Well differentiated	1869	8.17	21008	91.83	
Moderately differentiated	3266	9.23	32115	90.77	
Poorly differentiated	1926	10.45	16511	89.55	
Tumor Size					<.0001
1–5 mm	707	8.22	7898	91.78	
6–10 mm	1757	8.27	19493	91.73	
11–20 mm	3360	9.26	32924	90.74	
21–50 mm	1725	10.87	14145	89.13	
Regional Nodes Positive					<.0001
All nodes examined are negative	6001	8.45	65017	91.55	
1	886	10.23	7775	89.77	
2	338	16.59	1699	83.41	
Clinical T-Stage					<.0001
T1	5573	8.67	58724	91.33	
T2	1343	10.66	11253	89.34	
Pathologic T-Stage					<.0001
T1	1041	8.75	8528	91.25	
T2	1757	10.97	14255	89.03	
Lymphovascular Invasion					<.0001

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Demographic or Clinical Characteristics Univariate Analysis (N = 83555)	ALND only (N=7738, 9.26%)		SLNB +/− ALND (N=75817, 90.74%)		
	No.	%	No.	%	*p* Value
Absent	5648	8.85	58204	91.15	
Present	1041	10.88	8528	89.12	
Hormone receptor subtype					<0.0001
Hormone receptor positive and HER2+	484	10.57	4096	89.43	
Hormone receptor positive and HER2−	6007	8.91	61383	91.09	
Hormone receptor positive and HER2 borderline	173	13.67	1093	86.33	
Hormone receptor negative	43	17.92	197	82.08	
HER2+	206	10.89	1686	89.11	
Hormone receptor negative and HER2 borderline	22	16.92	108	83.08	
Triple negative	760	9.81	6988	90.19	
Surgical Margins					<.0001
Negative	7378	9.13	73403	90.87	
Positive	293	11.81	2188	88.19	
Radiation Technique					0.0076
Conformal or 3-D Therapy	591	7.96	6833	92.04	
IMRT	286	9.57	2704	90.43	
Receipt of Chemotherapy					<.0001
None	4893	8.48	52826	91.52	
Chemotherapy given	2695	11.04	21714	88.96	
Receipt of Endocrine Therapy					<0.001
None	1788	10.68	14961	89.32	
Endocrine therapy given	5765	8.88	59187	91.12	

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Table 5

Baseline characteristics for patients who undergo completion axillary lymph node dissection after 1–2 positive sentinel lymph nodes

Demographic or Clinical Characteristics Univariate Analysis (N = 9474)	**SLNB only (N = 6520, 68.82%)**		**SLNB and ALND (N = 2954, 31.18%)**		
	No.	**%**	**No.**	**%**	***p* Value**
Facility Type					<.0001
Community cancer program	623	62.00	381	38.00	
Comprehensive community cancer program	3175	68.30	1473	31.70	
Academic/research program	2070	72.20	798	27.80	
Other	652	68.30	302	31.70	
Facility location					<.0001
New England	464	74.00	163	26.00	
Middle Atlantic region	1005	68.00	474	32.00	
South Atlantic region	1363	68.30	634	31.70	
East North Central region	1160	65.40	614	34.60	
East South Central region	296	69.50	130	30.50	
West North Central region	485	67.60	232	32.40	
West South Central region	298	64.50	164	35.50	
Mountain region	367	71.50	146	28.50	
Pacific region	908	75.00	302	25.00	
Unknown region	174	64.70	95	35.30	
Age at diagnosis (years)					0.0031
<40	176	11.06	1416	88.94	
40–49	1092	9.28	10681	90.72	
50–59	2063	8.97	20930	91.03	
60–69	2583	9.08	25859	90.92	
70–79	1451	9.53	13771	90.47	
≥80	373	10.56	3160	89.44	
Race					0.0008
White	5112	69.30	2267	30.70	
Black	603	64.20	337	35.80	

Demographic or Clinical Characteristics Univariate Analysis (N = 9474)	SLNB only (N = 6520, 68.82%)		SLNB and ALND (N = 2954, 31.18%)		
	No.	%	No.	%	*p* Value
Hispanic	349	66.40	177	33.60	
Asian/Pacific	223	73.60	80	26.40	
Other or Unknown	233	71.50	93	28.50	
Insurance status					0.042
Not insured	129	68.25	60	31.75	
Private insurance	3642	68.91	1643	31.09	
Medicaid	402	63.41	232	36.59	
Medicare	2198	69.69	956	30.31	
Other	70	67.31	34	32.69	
Median Income					0.1321
<$38,000	883	67.98	416	32.02	
$38,000–$47,999	1278	66.60	641	33.40	
$48,000–$62,999	1773	69.78	768	30.22	
$63,000 +	2576	69.62	1124	30.38	
Unknown	10	66.67	5	33.33	
Education (% of regional population with no high school degree)					0.0721
≥21%	821	66.97	405	33.03	
13–20%	1518	67.95	716	32.05	
7.0–12.9%	2158	68.33	1000	31.67	
<7%	2015	70.85	829	29.15	
Unknown	8	66.67	4	33.33	
Population density of patient residence					0.0823
Metro counties	5568	69.22	2476	30.78	
Urban counties	720	67.16	352	32.84	
Rural counties	77	61.60	48	38.40	
Charlson-Deyo Comorbidity Score					0.47
0	5490	68.76	2494	31.24	
1	871	69.85	376	30.15	

Demographic or Clinical Characteristics Univariate Analysis (N = 9474)	SLNB only (N = 6520, 68.82%)		SLNB and ALND (N = 2954, 31.18%)		
	No.	%	No.	%	*p* Value
2	159	65.43	84	34.57	
Year of diagnosis					<.0001
2012	3248	65.80	1686	34.20	
2013	3272	72.10	1268	27.90	
Laterality					0.5301
Right	3264	68.53	1499	31.47	
Left	3254	69.10	1455	30.90	
Grade					<.0001
Well differentiated	1495	71.88	585	28.12	
Moderately differentiated	3146	69.79	1362	30.21	
Poorly differentiated	1423	63.50	818	36.50	
Tumor Size					<.0001
1–5 mm	160	74.42	55	25.58	
6–10 mm	948	72.87	353	27.13	
11–20 mm	3370	69.18	1501	30.82	
21–50 mm	2000	66.05	1028	33.95	
Regional Nodes Positive					<.0001
1	5627	72.37	2148	27.63	
2	893	52.56	806	47.44	
Clinical T-Stage					0.0052
T1	4609	69.90	1985	30.10	
T2	1480	66.73	738	33.27	
Pathologic T-Stage					<.0001
T1	4373	70.33	1849	29.67	
T2	2028	65.93	1048	34.07	
Lymphovascular Invasion					0.0002
Absent	3649	70.42	1533	29.58	
Present	2023	66.50	1019	33.50	

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Demographic or Clinical Characteristics Univariate Analysis (N = 9474)	SLNB only (N = 6520, 68.82%)		SLNB and ALND (N = 2954, 31.18%)		
	No.	%	No.	%	*p* Value
Hormone receptor subtype					<0.0001
Hormone receptor positive and HER2+	306	64.56	168	35.44	
Hormone receptor positive and HER2−	5592	69.85	2414	30.15	
Hormone receptor positive and HER2 borderline	92	67.65	44	32.35	
Hormone receptor negative	4	50.00	4	50.00	
HER2+	127	66.49	64	33.51	
Hormone receptor negative and HER2 borderline	5	62.50	3	37.50	
Triple negative	380	60.41	249	39.59	
Surgical Margins					0.578
Negative	6242	68.87	2821	31.13	
Positive	260	67.53	125	32.47	
Radiation Technique					0.6913
Conformal or 3-D Therapy	671	70.41	282	29.59	
IMRT	255	69.29	113	30.71	
Receipt of Chemotherapy					<.0001
None	3035	73.88	1073	26.12	
Chemotherapy given	3401	64.82	1846	35.18	
Receipt of Endocrine Therapy					<0.001
None	783	62.99	460	37.01	
Endocrine therapy given	5623	69.69	2446	30.31	

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Table 6

Baseline characteristics for patients receiving regional nodal radiotherapy compared to whole breast radiotherapy only in patients with 1–2 positive nodes who undergo SLNB only

Demographic or Clinical Characteristics Univariate Analysis (N = 6520)	**Whole breast RT (N = 4136, 63.44%)**		**Breast and nodal RT (N = 2384, 36.56%)**		
	No.	**%**	**No.**	**%**	**p Value**
Facility Type					0.0003
Community cancer program	349	56.00	274	44.00	
Comprehensive community cancer program	2008	63.20	1167	36.80	
Academic/research program	1334	64.40	736	35.60	
Other	445	68.30	63	31.70	
Facility location					<0.0001
New England	278	59.90	186	40.10	
Middle Atlantic region	706	70.20	299	29.80	
South Atlantic region	829	60.80	534	39.20	
East North Central region	703	60.60	457	39.40	
East South Central region	182	61.50	114	38.50	
West North Central region	303	62.50	182	37.50	
West South Central region	203	68.10	95	31.90	
Mountain region	219	59.70	148	40.30	
Pacific region	599	66.00	303	34.00	
Unknown region	114	65.50	60	34.50	
Age at diagnosis (years)					0.3651
<40	114	65.52	60	34.48	
40–49	665	63.09	389	36.91	
50–59	1174	61.99	720	38.01	
60–69	1303	65.28	693	34.72	
70–79	670	62.50	402	37.50	
≥80	210	63.64	120	36.36	
Race					0.0029
White	3203	62.70	1909	37.30	

Demographic or Clinical Characteristics Univariate Analysis (N = 6520)	Whole breast RT (N = 4136, 63.44%)		Breast and nodal RT (N = 2384, 36.56%)		
	No.	%	No.	%	p Value
Black	369	61.20	234	38.80	
Hispanic	245	70.20	104	29.80	
Asian/Pacific	158	70.80	65	29.20	
Other or Unknown	161	69.10	72	30.90	
Insurance status					0.4771
Not insured	84	65.12	45	34.88	
Private insurance	2280	62.60	1362	37.40	
Medicaid	256	63.68	146	36.32	
Medicare	1408	64.06	790	35.94	
Other	50	71.43	20	28.57	
Median Income					0.0107
<$38,000	568	70.00	3	30.00	
$38,000–$47,999	783	64.33	315	35.67	
$48,000–$62,999	1084	61.27	495	38.73	
$63,000 +	1694	61.14	689	38.86	
Unknown	7	70.00	3	30.00	
Percent with High School degree					0.079
≥21%	533	64.92	288	35.08	
13–20%	935	61.59	583	38.41	
7.0–12.9%	1342	62.19	816	37.81	
<7%	1321	65.56	694	34.44	
Unknown	5	62.50	3	37.50	
Population density					0.0123
Metro counties	3570	64.12	1998	35.88	
Urban counties	421	58.47	299	41.53	
Rural counties	48	62.34	29	37.66	
Charlson-Deyo Comorbidity Score					0.3379
0	3464	63.10	2026	36.90	

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Demographic or Clinical Characteristics Univariate Analysis (N = 6520)	Whole breast RT (N = 4136, 63.44%)		Breast and nodal RT (N = 2384, 36.56%)		
	No.	%	No.	%	p Value
1	572	65.67	299	34.33	
2	100	62.89	59	37.11	
Year of diagnosis					0.5852
2012	2071	63.76	1177	36.24	
2013	2065	63.11	1207	36.89	
Laterality					0.5027
Right	2061	63.14	1203	36.86	
Left	2073	63.71	1181	36.29	
Grade					0.0014
Well differentiated	984	65.82	511	34.18	
Moderately differentiated	2025	64.37	1121	35.63	
Poorly differentiated	850	59.73	573	40.27	
Tumor Size					<.0001
1–5 mm	112	70.00	48	30.00	
6–10 mm	662	69.83	286	30.17	
11–20 mm	2151	63.83	1219	36.17	
21–50 mm	1189	59.45	811	40.55	
Regional Nodes Positive					<.0001
1	3701	65.77	1926	34.23	
2	435	48.71	458	51.29	
Clinical T-Stage					<.0001
T1	2999	65.07	1610	34.93	
T2	870	58.78	610	41.22	
Pathologic T-Stage					<.0001
T1	2844	65.04	1529	34.96	
T2	1209	59.62	819	40.38	
Lymphovascular Invasion					0.0797
Absent	2333	63.94	1316	36.06	

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Demographic or Clinical Characteristics Univariate Analysis (N = 6520)	Whole breast RT (N = 4136, 63.44%)		Breast and nodal RT (N = 2384, 36.56%)		
	No.	%	No.	%	p Value
Present	1246	61.59	777	38.41	
Hormone receptor subtype					0.078
Hormone receptor positive and HER2+	182	59.48	124	40.52	
Hormone receptor positive and HER2−	3582	64.06	2010	35.94	
Hormone receptor positive and HER2 borderline	61	66.30	31	33.70	
Hormone receptor negative	3	75.00	1	25.00	
HER2+	79	62.20	48	37.80	
Hormone receptor negative and HER2 borderline	3	60.00	2	40.00	
Triple negative	215	56.58	165	43.42	
Surgical Margins					0.7915
Negative	3959	63.43	2283	6.57	
Positive	167	64.23	93	35.77	
Radiation Technique					0.1031
Conformal or 3-D Therapy	376	56.04	295	43.96	
IMRT	158	61.96	97	38.04	
Receipt of Chemotherapy					<.0001
None	2011	66.26	1024	33.74	
Chemotherapy given	2067	60.78	1334	39.22	
Receipt of Endocrine Therapy					0.0386
None	470	60.03	313	39.97	
Endocrine therapy given	3589	63.83	2034	36.17	

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