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EPIDEMIOLOGY

Evolution in practice patterns of axillary management following mastectomy in patients with 1–2 positive sentinel nodes

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Abstract

Purpose The optimal management of breast cancer patients with a positive sentinel lymph node (SLN) who undergo mastectomy remains controversial. This study aimed to describe treatment patterns of patients with positive SLNs who undergo mastectomy using a large population-based database.

Methods The NCDB was queried for cT1–2N0 breast cancer patients treated with mastectomy between 2006 and 2014 who had 1-2 positive SLNs. Patients receiving neoadjuvant chemotherapy were excluded. Axillary management included SLN dissection (SLND) alone, axillary lymph node dissection (ALND), post-mastectomy radiation (PMRT) alone, and ALND + PMRT. Trends of axillary management and patient characteristics were examined.

Results Among 12,190 patients who met study criteria, the use of ALND dropped with a corresponding increase in other approaches. In 2006, 34% of patients had SLND alone, 47% ALND, 8% PMRT and 11% ALND + PMRT. By 2014, 37% had SLND, 23% ALND, 27% PMRT and 13% ALND + PMRT. Patients who underwent SLND alone were older (mean 60.6 years) with more comorbidities (Charlson–Deyo score > 2), smaller primary tumors (mean 2.1 cm), well-differentiated histology, hormone receptor-positive, HER2-negative tumors, without lymphovascular invasion (all P values < 0.01). Treatment with SLND alone was more likely if patients had only one positive SLN ($P < 0.001$) or micrometastatic disease ($P < 0.001$), and were treated at community centers compared with academic centers ($P < 0.001$).

Conclusions The management of breast cancer patients undergoing mastectomy with positive SLNs has evolved over time with decreased use of ALND and increased use of radiation. Some patient subsets are underrepresented in recent clinical trials, and therefore, future trials should focus on these patients.

Keywords Axillary management after mastectomy · PMRT rates · ALND rates · Pathologic positive nodal disease after mastectomy · AMAROS

Introduction

Sentinel node dissection was introduced to replace axillary dissection for staging of the axilla. The American College of Surgeons (ACOSOG) Z0011 trial enrolled patients with clinical T1–2 breast cancers and 1–2 positive sentinel lymph nodes (SLNs), who underwent breast conserving surgery and whole breast radiation to assess the need for axillary lymph node dissection (ALND) in patients with positive SLNs [1, 2]. Long-term recurrence and survival data have since shown that patients with 1–2 positive SLNs undergoing breast conservation may safely omit axillary dissection [3–7].

Patients undergoing mastectomy who also have positive SLNs were not eligible for the Z0011 trial but were

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included in the International Breast Cancer Study Group (IBCSG) 23-01 trial and the European Organization for Research and Treatment of Cancer (EORTC) 10981-22023 trial [8] (AMAROS trial) [9]. The IBCSG 23-01 trial limited enrollment to patients with micrometastasis in the SLNs and approximately 9% of the 933 patients were treated with mastectomy. In the AMAROS trial, patients with micrometastasis and macrometastasis were included and approximately 17% were treated with mastectomy. The results of Z0011 were published first and its findings were extended to other patient subsets such as patients undergoing mastectomy [10], neoadjuvant chemotherapy, or those omitting radiation [6]. The publication of AMAROS and IBCSG 23-01 may have influenced this trend as well.

It has been previously reported that for select patients treated with mastectomy with 1–2 positive SLNs, omission of ALND was not shown to impact recurrence or survival [11–14] but these are all small single institution retrospective cohorts. Contemporary axillary management has been examined in a larger population-based study using the National Cancer Database (NCDB) [15]. Although oncologic data regarding the omission of ALND are not available in this database, this study reported that surgeons are omitting ALND in one-third of early-stage mastectomy patients with positive SLNs. Since this study only included patients treated over a 2-year period, it was not able to examine the trends in axillary management since just 2 years were examined.

The primary goal of our study was to describe the axillary treatment patterns over a 9-year period for patients with 1–2 positive SLNs who undergo mastectomy using the NCDB. Secondary goals of this study were to characterize the patients who underwent each type of treatment and to identify areas where data are lacking for some subsets that could be the focus of future clinical trials.

Methods

The NCDB is a nationwide hospital registry and clinical oncology database which captures 70% of new cancer patients in the U.S. treated at Commission on Cancer accredited institutions [16]. The NCDB was queried for patients with clinical T category 1–2 breast cancer undergoing mastectomy, who were clinically node negative but pathologically node positive, with 1–2 positive SLNs. Over the time period 2006–2014, we examined a contemporary set of patients treated during the era of clinical trials addressing management of the axilla [1, 2, 8, 9]. We excluded patients who had neoadjuvant chemotherapy, prior cancers, more than two positive SLNs, unknown tumor size, unknown radiation site or sequence, unknown status regarding distant metastasis, or N0(i+), N1b, or N1c pathologic nodal status (Figure S1). Since NCDB did not explicitly distinguish between SLND and ALND until recently, we defined these procedures based on the number of lymph nodes removed, as published previously [6]. SLND was defined as 6 or fewer lymph nodes removed and ALND was defined as 10 or more lymph nodes removed. We excluded patients who had an unknown type of axillary surgery or 7–9 lymph nodes removed.

Patients with 1–2 positive SLNs only were included to be as representative as possible with regards to the several practice changing axillary management studies published in the last 10 years [2, 8, 9]. Patients with pathologic nodal category of N1b and N1c were excluded to omit patients with internal mammary nodal disease. Axillary management options were classified as SLND alone (no additional axillary treatment), ALND, post-mastectomy radiation (PMRT) and ALND + PMRT. We analyzed the pattern of these treatments over time, clinicopathologic factors and hospital-level factors. In addition, we compared patient characteristics between 2006 and 2014 to determine whether these factors correlated with a change in treatment approach. Beginning in 2010, lymphovascular invasion (LVI) and HER2 status were recorded in NCDB, so differences in patient characteristics between 2011 (first full year to include HER2 and LVI data) and 2014 were also compared.

To estimate the risk of whether a patient with a positive SLN would have additional positive non-SLNs, we used a published nomogram [17] that includes the following factors: histology, tumor size, number of lymph nodes removed, number of positive lymph nodes, micrometastasis versus macrometastasis, lymphovascular invasion, and extranodal extension (ENE) [18]. We included only patients with N1a (assumed macrometastatic) or N1mi (micrometastatic) disease and excluded those with N1 designation for whom nodal metastasis size is unclear. The analysis included only patients diagnosed after 2010 when LVI was available in NCDB. ENE is a variable in the nomogram but not available in NCDB, and therefore, we calculated the estimated risk of additional positive non-sentinel lymph node (NSLN) assuming either the presence or absence of ENE. We restricted the analysis to patients who had SLNB only or PMRT only because the nomogram is not applicable to patients who had ALND.

Chi square test or Fisher exact test was used to test differences of categorical variables and Wilcoxon rank-sum test or Kruskal–Wallis test was used to detect differences for continuous variables between groups [19]. SAS version 9.4 and S-Plus version 8.04 are used to carry out the computations for all analyses. A two-sided P value less than 0.05 was considered statistically significant.

Results

Overall clinical and pathologic characteristics

The study population included 12,190 patients, with clinical T1–2 tumors and 1–2 positive sentinel nodes, who underwent mastectomy (Table 1). For the overall population, the mean age was 57 years and the patients were of predominantly white race with few comorbidities (83% with a Charlson–Deyo score of zero). Mean tumor size was 2.4 cm; 84% of patients had ductal histology, and 29% of patients had micrometastatic disease in the lymph nodes (Table 1). SLND-alone and PMRT groups both had a median of three lymph nodes examined.

Clinicopathologic characteristics were compared among the four treatment groups: SLND alone ($N=4301$), ALND ($N=4068$), PMRT alone ($N=2096$) and ALND + PMRT ($N=1725$). Among the four treatment groups, patients receiving SLND alone were older (mean 60.6 years, $P<0.001$), with more medical comorbidities (Charlson–Deyo score > 2, $P<0.001$) and smaller primary tumors (mean 2.1 cm, $P<0.001$) with well-differentiated histology (20.9%, $P<0.001$) and no lymphovascular invasion (66.8%, $P<0.001$). In the SLND alone group, tumors were usually hormone receptor-positive (89.1%, $P<0.001$), HER2-negative (89.7%, $P=0.003$), and with only one positive SLN (87.9%, $P<0.001$) and micrometastatic disease (47.3%, $P<0.001$) (Table 1).

Trends in axillary management

Between 2006 and 2014, the use of ALND decreased with a corresponding increase in other approaches. In 2006, 34% of patients had SLND alone, 47% ALND, 8% PMRT and 11% ALND + PMRT. By 2014, 37% had SLND alone, 23% underwent ALND, 27% PMRT and 13% ALND + PMRT (Fig. 1). The use of ALND decreased by 50% from 2006 to 2014 (47%-23%), while the use of PMRT increased three-fold (8–27%). The most striking change in treatment patterns appeared to occur after 2010, which corresponds to the publication of results from the ACOSOG Z0011 trial [1]. In 2010, 41.6% of patients underwent ALND, whereas only 29.4% underwent ALND in 2011. In those same 2 years, SLND alone increased from 31.8% of patients to 37.6%, and PMRT increased from 10.9% of patients to 18.6%. In summary, although the use of SLND alone changed minimally from 2006 to 2014, the overall treatment pattern shifted away from ALND and more towards PMRT with or without ALND.

We also evaluated the distribution of treatment patterns based on nodal burden. In patients with micrometastases, the most common treatment was SLND alone with no further axillary treatment in 58% of patients. Of the N1a patients (macrometastases) with two positive lymph nodes (maximal nodal burden in this study), SLND alone represents the smallest proportion (14%) (Table 2).

Hospital characteristics

SLND alone was more likely to be performed at community centers than academic centers (37–38%, versus 32%, $P<0.001$; Fig. 2A). The Northeast had the lowest rate of utilization of SLND alone (30.2%) and the highest rate of patients receiving ALND + PMRT (16.5%), versus the Midwest with 35.9% SLND alone and 14.5% receiving ALND + PMRT, the West with 37.8% SLND alone and 11.7% ALND + PMRT, and the South with 38.8% SLND alone and 11.9% ALND + PMRT ($P<0.001$). Patients with public insurance were more likely to have SLND alone ($P<0.001$). Patient income, high school diploma rate, and hospital setting (urban versus rural) did not appear to have any significant impact on axillary treatment (Table S1).

Trends in patients undergoing SLND alone

Given the changes in the patterns of axillary management during the study period, we investigated whether the clinicopathologic characteristics of patients who underwent SLND alone changed over time. We compared the SLND-alone groups from 2006 to 2014 and we compared an entirely contemporary cohort of patients treated in 2011 with those from 2014 (Table 3). Patients treated in 2014 had slightly larger tumors than those in 2006 (2.3 vs. 2 cm, $P=0.019$), and they were more likely to have hormone receptor-positive disease (91.9 vs. 81.4%, $P<0.001$), and micrometastatic disease (50.6% vs. 31.5% in 2011, $P<0.001$). We did not identify any significant differences in age, sex, race, comorbidities, tumor histology or grade between 2006 and 2014. There were also no differences in the median number of lymph nodes removed over time [3 (range 1–6) in 2006, 2011, and 2014]. When comparing the 2011 patients to those treated in 2014, we saw similar trends with larger tumors (2.3 vs. 2.1 cm, $P=0.021$), more hormone receptor-positive disease (91.9% vs. 88.4%, $P=0.027$), more micrometastatic disease (50.6 versus 47%, $P<0.001$) and more well-differentiated tumors (22.4% versus 20.2%, $P=0.018$).

Overall patients who underwent SLND alone received less adjuvant chemotherapy (52.0% versus 73.7% among ALND patients, 75.0% among PMRT alone patients, and 89.9% among ALND + PMRT patients, $P<0.001$). Among SLND-alone patients, adjuvant chemotherapy was used less frequently as time progressed (63.1% in 2006 compared to 47.3% in 2014, $P<0.001$; and 53.7% in 2011 compared to 47.3% in 2014, $P=0.017$). The use of endocrine therapy

Table 1 General demographics and clinicopathologic variables of the total cohort, compared across different treatment groups

Variable (*N*, %)	*N* overall (12,190, 100%)	SLND alone (no further axillary treatment) (4301, 35%)	ALND (4068, 33%)	PMRT-alone (2096, 17%)	ALND + PMRT (1725, 14%)	*P* value
Age						
Mean, years (SD)	57.3 (13.3)	60.6 (14.1)	56.5 (12.7)	56.3 (12.7)	52.3 (11.3)	**< 0.001**
Sex						
Male	295 (2.4)	102 (2.4)	96 (2.4)	65 (3.1)	32 (1.9)	0.875
Female	11895 (97.6)	4199 (97.6)	3972 (97.6)	2031 (96.9)	1693 (98.1)	
Race						
White	10403 (85.3)	3733 (87.5)	3446 (85.4)	1796 (86.3)	1428 (83.5)	**0.001**
Black	1070 (8.8)	341 (8)	372 (9.2)	168 (8.1)	189 (11.1)	
Other	617 (5.1)	192 (4.5)	216 (5.4)	116 (5.6)	93 (5.4)	
Missing	100 (0.8)					
Charlson-Deyo						
0	10149 (83.3)	3478 (80.9)	3419 (84)	1765 (84.2)	1487 (86.2)	**< 0.001**
1	1656 (13.6)	653 (15.2)	528 (13)	272 (13)	203 (11.8)	
2	385 (3.2)	170 (4)	121 (3)	59 (2.8)	35 (2)	
Tumor size						
Mean, cm (SD)	2.4 (1.7)	2.1 (1.1)	2.2 (1.2)	2.9 (2.2)	3 (2.5)	**< 0.001**
Clinical T stage						
1	7036 (57.7)	2672 (62.1)	2426 (59.6)	1071 (51.5)	867 (50.3)	**< 0.001**
2	5154 (42.3)	1629 (37.9)	1642 (40.4)	1025 (48.9)	858 (49.7)	
Histology						
Ductal	10241 (84)	3618 (84.1)	3539 (87)	1652 (78.8)	1432 (83)	**< 0.001**
Lobular	1739 (14.3)	603 (14)	460 (11.3)	411 (19.6)	265 (15.4)	
Favorable	210 (1.7)	80 (1.9)	69 (1.7)	33 (1.6)	28 (1.6)	
Grade						
Well differentiated	2088 (17.1)	865 (20.9)	657 (16.8)	351 (17.6)	215 (13.1)	**< 0.001**
Moderately	5863 (48.1)	2104 (50.9)	1944 (49.8)	1017 (50.9)	798 (48.5)	
Poorly	3689 (30.3)	1153 (27.9)	1287 (33)	620 (31)	629 (38.3)	
Undifferentiated	34 (0.3)	8 (0.2)	15 (0.4)	9 (0.5)	2 (0.1)	
Missing	516 (4.2)					
Hormone receptor						
Positive	10643 (87.3)	3810 (89.1)	3495 (86.6)	1864 (89.2)	1474 (85.5)	**< 0.001**
Negative	1484 (12.2)	466 (10.9)	543 (13.4)	226 (10.8)	249 (14.5)	
Missing	63 (0.5)					
HER2 status[a]						
Positive	981 (8.1)	339 (10.3)	315 (12.3)	168 (9.2)	159 (12.3)	**0.003**
Negative	8003 (65.7)	2964 (89.7)	2252 (87.7)	1650 (90.8)	1137 (87.7)	
Missing	3206 (26.3)					
Triple negative[a]						
Yes	744 (6.1)	247 (7.5)	227 (8.8)	143 (7.9)	127 (9.8)	**0.04**
No	8237 (67.6)	3045 (92.5)	2339 (91.2)	1675 (92.1)	1169 (90.2)	
Missing	3209 (26.3)					
LVI*						
Yes	3161 (25.9)	959 (33.2)	894 (40.2)	735 (46.3)	573 (51.2)	**< 0.001**
No	4657 (38.2)	1927 (66.8)	1332 (59.8)	852 (53.7)	546 (48.8)	
Missing	4372 (35.9)					
No. of nodes removed, median (range)	6 (1-60)	3 (1-6)	15 (10-60)	3 (1–6)	15 (10–45)	**< 0.001**

Table 1 (continued)

Variable (*N*, %)	*N* overall (12,190, 100%)	SLND alone (no further axillary treatment) (4301, 35%)	ALND (4068, 33%)	PMRT-alone (2096, 17%)	ALND + PMRT (1725, 14%)	*P* value
No. of patients with positive nodes						
1	9249 (75.9)	3782 (87.9)	2966 (72.9)	1597 (76.2)	904 (52.4)	**< 0.001**
2	2941 (24.1)	519 (12.1)	1102 (27.1)	499 (23.8)	821 (47.6)	
Nodal metastasis						
N1mi	3524 (28.9)	2034 (47.3)	730 (17.9)	635 (30.3)	125 (7.2)	**< 0.001**
N1a	6332 (51.9)	1520 (35.3)	2458 (60.4)	1107 (52.8)	1247 (72.3)	
N1	2334 (19.2)	747 (17.4)	880 (21.6)	354 (16.9)	353 (20.5)	
Chemotherapy						
Yes	8358 (68.6)	2236 (52.0)	2998 (73.7)	1573 (75.0)	155 (89.9)	**< 0.001**
No	3832 (31.4)	2065 (48.0)	1070 (26.3)	523 (25.0)	174 (10.1)	
Endocrine therapy						
Yes	9552 (78.4)	3295 (77.9)	3066 (77.1)	1769 (85.7)	1422 (83.2)	**< 0.001**
No	2432 (20.0)	936 (22.1)	913 (22.9)	296 (14.3)	287 (16.8)	
Unknown	206 (1.7)					

Bolded numbers are statistically significant *P* values

SD, standard deviation. LVI, lymphovascular invasion

[a]Data for HER2 status and LVI are only available in NCDB after 2010

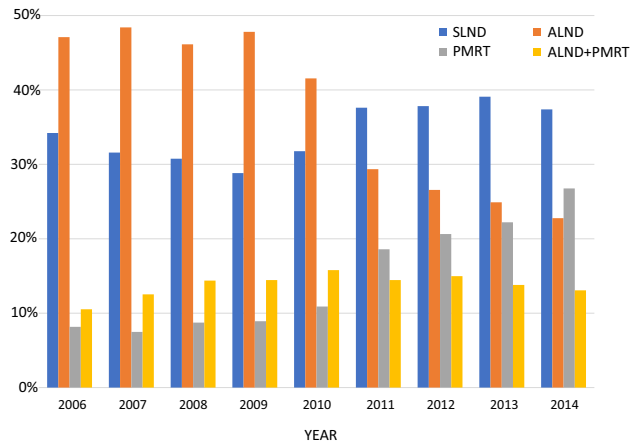

Fig. 1 Trends of performance of sentinel lymph node dissection, axillary lymph node dissection, and post-mastectomy radiation therapy over time, presented as the frequency of procedures performed (percent of 100)

increased from 2006 to 2014 (64.1% versus 76.2% in 2014, $P < 0.001$); its use was not significantly different from 2011 to 2014.

Estimation of additional positive non-SLN

The clinicopathologic profile of patients among the four treatment groups shown in Table 1 suggests that SLND alone was being performed for patients with low-risk disease. To further confirm our findings, we used a nomogram previously published by our group and externally validated to estimate the risk of having additional positive NSLN [17]. Since NCDB does not include data on ENE, which is a factor in the nomogram, we calculated the estimated risk with either presence or absence of ENE. In the absence of ENE, patients who underwent SLND alone would be estimated to have a 17% risk of additional positive NSLN (SD 13%), whereas patients who underwent PMRT would have a 25%

Table 2 Distribution of axillary management by nodal disease burden

N (%)	All N1 *N* = 12,190	N1 *N* = 2334	N1mi *N* = 3524	N1a		
				All N1a *N* = 6332	1 + LN *N* = 4291	2 + LN *N* = 2041
Treatment received						
SLND only	4301 (35.3)	747 (32)	2034 (57.7)	1520 (24)	1239 (28.9)	281 (13.8)
PMRT	2096 (17.2)	354 (15.2)	635 (18)	1107 (17.5)	767 (17.9)	340 (16.7)
ALND	4068 (33.4)	880 (37.7)	730 (20.7)	2458 (38.8)	1682 (39.2)	776 (38)
ALND + PMRT	1725 (14.2)	353 (15.1)	125 (3.5)	1247 (19.7)	603 (14.1)	644 (31.6)

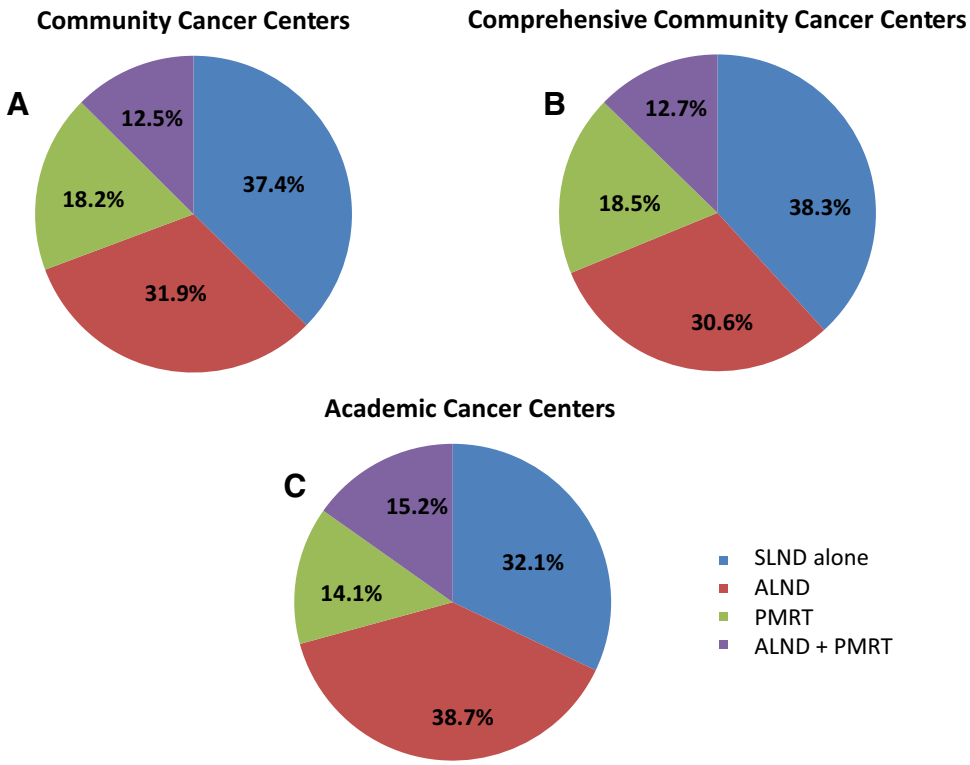

Fig. 2 The distribution of treatments given at each of the following: A) Community Cancer Centers, B) Comprehensive Community Cancer Centers, and C) Academic Cancer Centers

risk (SD 17%) (Table S2). In the presence of ENE, the risk of additional NSLN is 29% for SLND only (SD 17%) and 39% for PMRT (SD 20%). These results suggest that, given the large standard deviations in these calculations, no further axillary treatment was performed for patients with a wide range of estimated additional nodal burden. PMRT was given to patients with a higher risk of additional nodal burden.

Discussion

In this study, we found that practice patterns have changed over the last decade with respect to axillary management in breast cancer patients who undergo mastectomy and have 1–2 positive sentinel nodes. SLND was the treatment of choice for about 37% of patients, and the utilization of ALND dramatically declined. According to this data, the rate of ALND performance dropped significantly after 2011 when ACOSOG Z0011 was published; [1, 2] however, as early as 2006 and throughout the entire study period SLND alone was the most common axillary management strategy for patients with 1-2 positive SLNs. In a single institution study, Kenny et al. observed a similar decrease in the utilization of ALND for mastectomy patients with positive nodes from 82% to 36% before and after publication of Z0011 ($P = 0.001$) [20]. This trend is concerning as ACOSOG Z0011 applied stringent criteria including breast conservation patients only. Furthermore, our dataset largely predates the publication of IBCSG 23-01 [8] and AMAROS [9] as well. While it is reassuring that this study shows patients treated with SLND alone had higher rates of nodal micrometastases than the other axillary treatment groups, IBCSG 23-01 included only 86 mastectomy patients, representing 9% of the study cohort, and was published in 2013 which should have affected only the last 2 years of the current trial's findings. Similarly, only 17% of the AMAROS study patients underwent mastectomy, and it was published in 2014. In the current trial, ALND was being omitted in node-positive mastectomy patients and treatment shifted towards PMRT well before evidence supported the practice.

We were further surprised to find that the estimated risk of additional positive non-SLNs for SLND and PMRT-alone groups was widely variable. Our data indicates that the management of patients with a positive SLN undergoing mastectomy is not uniform in the United States with variability in patient selection as it pertains to the risk of additional nodal burden. Although the retrospective nature of large administrative datasets limits our ability to explain the decision-making process around axillary management strategies, a selection bias does become evident. For example, patients undergoing SLND alone tend to have lower risk disease with smaller and well-differentiated tumors, without LVI and fewer positive SLNs. Our group has previously found that low-risk patients undergoing mastectomy with a positive SLN had similar outcomes with or without completion

Table 3 Comparison of patient characteristics by time who received SLND alone

Variable (*N*, %)	2006 (*N* = 130)	2014 (*N* = 729)	*P* value	2011 (*N* = 674)	2014 (*N* = 729)	*P* value
Age (mean in years, SD)	60 (15.7)	59.8 (13.9)	0.815	60.1 (14.2)	59.8 (13.9)	0.587
Sex						
Male	1 (0.8)	15 (2.1)	0.49	21 (3.1)	15 (2.1)	0.21
Female	129 (99.2)	714 (97.9)		653 (96.9)	714 (97.9)	
Race						
White	114 (89.1)	621 (86.1)	0.102	586 (87.5)	621 (86.1)	0.759
Black	12 (9.4)	58 (8)		48 (7.2)	58 (8)	
Other	2 (1.6)	42 (5.8)		36 (5.4)	42 (5.8)	
Charlson-Deyo						
0	105 (80.8)	586 (80.4)	0.445	545 (80.9)	586 (80.4)	0.478
1	19 (14.6)	123 (16.9)		104 (15.4)	123 (16.9)	
2	6 (4.6)	20 (2.7)		25 (3.7)	20 (2.7)	
Tumor size (mean, cm, SD)	2 (1.1)	2.3 (1.2)	**0.019**	2.1 (1.1)	2.3 (1.2)	**0.021**
Clinical T stage						
1	82 (63.1)	443 (60.8)	0.619	427 (63.4)	443 (60.8)	0.319
2	48 (36.9)	286 (39.2)		247 (36.6)	286 (39.2)	
Pathologic T stage						
0			0.529	1 (0.1)		0.123
1	74 (57.4)	373 (51.3)		370 (55.1)	373 (51.3)	
2	53 (41.1)	326 (44.8)		288 (42.9)	326 (44.8)	
3	2 (1.6)	23 (3.2)		11 (1.6)	23 (3.2)	
4	0 (0)	5 (0.7)		2 (0.3)	5 (0.7)	
Histology						
Ductal	101 (77.7)	609 (83.5)	0.209	576 (85.5)	609 (83.5)	0.582
Lobular	25 (19.2)	101 (13.9)		84 (12.5)	101 (13.9)	
Favorable	4 (3.1)	19 (2.6)		14 (2.1)	19 (2.6)	
Grade						
Well differentiated	22 (18)	158 (22.4)	0.274	133 (20.2)	158 (22.4)	**0.018**
Moderately	65 (53.3)	372 (52.8)		316 (47.9)	372 (52.8)	
Poorly	34 (27.9)	173 (24.6)		210 (31.8)	173 (24.6)	
Undifferentiated	1 (0.8)	1 (0.1)		1 (0.2)	1 (0.1)	
Hormone receptor						
Positive	105 (81.4)	668 (91.9)	**< 0.001**	592 (88.4)	668 (91.9)	**0.027**
Negative	24 (18.6)	59 (8.1)		78 (11.6)	59 (8.1)	
HER2 status[a]						
Positive	–	46 (6.4)	–	91 (13.8)	46 (6.4)	**< 0.001**
Negative	–	674 (93.6)		568 (86.2)	674 (93.6)	
Triple negative[a]						
Yes	–	47 (6.5)	–	52 (7.9)	47 (6.5)	0.327
No	–	673 (93.5)		607 (92.1)	673 (93.5)	
LVI						
Yes	–	231 (36.6)	–	192 (32.7)	232 (36.6)	0.154
No		402 (63.4)		395 (67.3)	402 (63.4)	
No. nodes removed, median (range)	3(1-6)	3 (1-6)	0.234	3 (1–6)	3 (1–6)	0.209
No. of patients with positive nodes						
1	111 (85.4)	652 (89.4)	0.177	582 (86.4)	652 (89.4%)	0.076
2	19 (14.6)	77 (10.6)		92 (13.6)	77 (10.6%)	
Nodal metastasis						
N1mi	41 (31.5)	369 (50.6)	**< 0.001**	317 (47)	369 (50.6)	**< 0.001**
N1a	44 (33.8)	294 (40.3)		236 (35)	294 (40.3)	

Table 3 (continued)

Variable (*N*, %)	2006 (*N* = 130)	2014 (*N* = 729)	*P* value	2011 (*N* = 674)	2014 (*N* = 729)	*P* value
N1	45 (34.6)	66 (9.1)		121 (18)	66 (9.1)	
Chemotherapy						
Yes	82 (63.1)	345 (47.3)	**< 0.001**	362 (53.7)	345 (47.3)	**0.017**
No	48 (36.9)	384 (52.7)		312 (46.3)	384 (52.7)	
Endocrine therapy						
Yes	82 (64.1)	536 (76.2)	**< 0.001**	538 (80.1)	536 (76.2)	0.087
No	46 (35.9)	167 (23.8)		134 (19.9)	167 (23.8)	
Risk prediction for additional positive nodes	–	–	–	17–29% (SD 12, 17)	18–30% (SD 13, 18)	0.136

Patients were compared between 2006 and 2014 to represent the beginning and end of the study period

Patients were also compared between 2011 and 2014 because HER2 status and lymphovascular invasion recording started mid-2010

Bolded numbers are statistically significant *P* values

SD standard deviation, *LVI* lymphovascular invasion

[a]Data available in NCDB after 2010

ALND [14]. Other groups have also examined the outcomes of ALND versus SLND alone in mastectomy patients with early-stage disease with positive SLNs [11, 12, 21]. Milgrom et al. found that early-stage breast cancer patients with a positive SLN who underwent total mastectomy without ALND experienced similarly low rates of locoregional and distant failure at 4 years compared to those who underwent breast conserving surgery (1.7% local, 1.2% regional, and 0.7% distant mastectomy patients; 1.4%, 1.0% and 3.7% breast conserving surgery patients) [12]. Similarly, a retrospective review of a community-based health system cancer registry found that there was no difference in recurrence-free survival for patients with positive SLNs undergoing mastectomy without ALND [22]. A small series by Fu et al. found that completion ALND could be safely omitted for SLN-positive patients only when they received PMRT [11]. These studies support the practice of omitting ALND for select groups of patients with a positive SLN. However, PMRT may not be indicated for all SLN-positive patients. Mamtani et al. reported from a single institution database that the presence of axillary micrometastases and isolated tumor cells are not indications for post-mastectomy radiation therapy [23]. A recent joint statement from the American Society of Clinical Oncology, the American Society for Radiation Oncology and Society of Surgical Oncology recommended that patients with a positive SLN for whom ALND is omitted should only receive PMRT if there is information to justify its use without needing to know whether additional axillary nodes are involved [24]. The safety of omitting any further axillary treatment for higher risk patients remains unclear.

There are several limitations to using NCDB for these analyses. The NCDB does not record all the details of nodal metastases such as specific volume or ENE. Thus, the designation of micro- and macrometastases is approximated by N1mi and N1a in this study, and the nomogram risk prediction may be inaccurate. Similarly, detailed axillary surgery information is not available before 2012; SLNB and ALND were defined by the number of lymph nodes removed similar to the methodology in other studies, so the axillary surgery designations may not match the surgeons' intentions. Additionally, NCDB does not report details of regional nodal irradiation fields [10, 25], which are valuable to evaluate the impact of radiation on outcomes. Finally, NCDB lacks data on recurrence and disease-specific survival data, also making meaningful treatment outcomes comparisons difficult [26].

This study illustrates that diverse treatment patterns exist nationally for patients with a positive SLN who undergo mastectomy. The safety of omitting ALND for patients with a higher risk of additional positive non-SLNs is unclear and a prospective trial would be best to address this issue; however, we acknowledge a randomized trial may not be feasible given the difficulty of randomizing patients to a surgical procedure and low event rates [12, 14]. The need for surgical staging of the axilla is also in question with the availability of genomic assays to predict outcome and response to therapy. The Oncotype DX 21-gene recurrence score (RS) has been shown to predict the risk of locoregional recurrence in both node-negative and node-positive patients with hormone receptor-positive disease [27, 28]. Recently, the TAILORx study found that the RS was useful for guiding adjuvant chemotherapy recommendations for hormone receptor-positive, node-negative patients [29]. In this study, decreasing rates of ALND and potential under-estimation of nodal disease burden did not result in more aggressive systemic therapy. In fact, SLND-alone patients received significantly less chemotherapy over the time course of this study. As such, axillary surgery de-escalation has taken place concurrently with systemic therapy de-escalation, but the safety of this universal de-escalation is unknown. Though the RS is

largely used for adjuvant systemic therapy decisions, it may also have a role in guiding locoregional treatment decisions [30] and more work should be done to determine the best multi-disciplinary approach for these patients.

In conclusion, the management of breast cancer patients with positive sentinel nodes undergoing mastectomy has evolved over time with decreased use of ALND and increased use of PMRT. Many patients with 1–2 positive nodes after mastectomy undergo SLND alone. Some patient subsets are not represented in recent clinical trials, and therefore, future trials should focus on these patients.

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Data Availability The data that support the findings of this study are available from the National Cancer DataBase but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the National Cancer DataBase.

Compliance with ethical standards

Conflict of interest The authors have no relevant financial conflicts to disclose.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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