

## Scientific Article

# Is completion axillary lymph node dissection necessary in patients who are underrepresented in the ACOSOG Z0011 trial?

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Received 12 October 2017; received in revised form 3 January 2018; accepted 27 March 2018

## Abstract

**Purpose:** The American College of Surgeons Oncology Group trial Z0011 demonstrated that axillary node dissection (ALND) can be omitted in patients managed with breast conserving surgery and 1 to 2 positive sentinel lymph nodes (SLNs) without adverse effects on locoregional recurrence or disease-free survival (DFS). We investigated patients with breast cancer for whom clinicopathologic features were underrepresented in the Z0011 trial and analyzed radiation therapy treatment patterns and clinical outcomes.

**Methods and materials:** We retrospectively reviewed records of patients who underwent a lumpectomy and SLN biopsy with positive SLNs but not an ALND and completed adjuvant radiation therapy. Eligible patients had T3 tumors, >2 positive SLNs, invasive lobular carcinoma, estrogen receptor negative status, extranodal extension, Nottingham Grade 3, or were age <50 years.

**Results:** We identified 105 women treated between July 2011 and July 2016 with a median follow-up time of 48.5 months (Range, 11–83 months). There were 40 women with an extranodal extension (38.9%) and 42 women with grade 3 disease (40.0%). Nineteen patients received whole breast irradiation alone (18.1%) and 86 patients were treated with modified tangent fields including the superior axilla level I/II (81.9%). Thirty-three patients (31.4%) also received a 3<sup>rd</sup> supraclavicular, nodal-directed field. Among the 86 patients who received axillary nodal irradiation, nodal volume contouring was performed in 77 patients (89.5%). Fifty-one patients (48.6%) also received adjuvant chemotherapy. The overall rates of 4-year DFS and locoregional control (LRC) were 94.3% and 98.1%, respectively. Of all patients, 1 patient experienced an internal mammary nodal recurrence, another patient a contralateral breast tumor, and two patients distant metastases. There were no axillary or ipsilateral breast tumor recurrences.

**Conclusions:** This retrospective analysis of women who were underrepresented or excluded from the Z11 trial and underwent a lumpectomy and SLN biopsy with positive SLNs demonstrated comparable rates of LRC and DFS. The high rates of LRC and DFS suggest that completion ALND

Conflicts of interest: There are no conflicts of interest to disclose.

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<https://doi.org/10.1016/j.adro.2018.03.004>

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may be safely omitted in this patient population but larger data sets and longer follow-up times are needed to confirm this finding.

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## Introduction

The American College of Surgeons Oncology Group (ACOSOG) trial Z11 demonstrated that axillary lymph node dissection (ALND) can be omitted in patients with breast cancer who undergo breast conserving surgery after positive sentinel lymph node biopsy (SLNB) without compromising disease outcomes. The results from the trial demonstrated no significant differences in locoregional recurrence (LRR), disease-free survival (DFS), or overall survival (OS) after SLNB alone versus completion ALND in patients with clinical T1 to T2 N0 invasive breast cancer who present with 1 to 2 positive SLNs.<sup>1</sup>

However, translating these results into clinical practice is complicated by the inconsistent use of adjuvant radiation therapy (RT) fields in the study. Fifty percent of patients with available treatment data received high tangent fields that covered the superior level I and II axillary nodes and 15% of patients were treated with a 3<sup>rd</sup> level III and supraclavicular nodal (SCN)-directed field. This complicates the interpretation of the data because the contribution of nodal irradiation to the noninferiority of SLNB alone compared with ALND is not clear.<sup>2</sup> For instance, the After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial demonstrated that regional nodal irradiation (RNI) after positive SLNB can provide similar disease control outcomes as ALND with improved morbidity.<sup>3</sup> Furthermore, the National Cancer Institute of Canada (NCIC) MA.20 and European Organization for Research and Treatment of Cancer (EORTC) 22922 studies showed significant improvements in DFS after RNI in node-positive or high-risk patients.<sup>4,5</sup>

Collectively, these studies suggest that adjuvant RT with fields that are guided by pathologic characteristics after SLNB without completion ALND can offer improvements in morbidity and mortality in select patients with breast cancer. However, the heterogeneity of RT fields among these trials limits the translation into clinical practice. Moreover, the results may not be generalizable to all patients because the majority of subjects in the Z11 trial were negative for extranodal extension (ENE) and presented with hormone receptor positive cancer and 1 to 2 axillary metastases. Furthermore, many patients had a low burden of axillary disease with micrometastases only.

Herein, we report on the RT treatment patterns and clinical outcomes of patients with breast cancer with features that were underrepresented in the Z11 trial. Specifically, we add to the existing literature with data on omission of ALND in patients with one or more of the following fea-

tures: T3 tumors, >2 positive SLNs, hormone receptor negative status, ENE, or Nottingham grade 3 histology.

## Methods and materials

Patient data from the UPMC Hillman Cancer Center (Pittsburgh, PA) were obtained from the ARiA record and Varian database (Varian Medical Systems, Palo Alto, CA). After institutional review board approval, we identified women with clinically node-negative invasive breast cancer who underwent segmental mastectomy and SLNB with positive sentinel nodes and also received adjuvant RT between July 2011 and July 2016. Our inclusion criteria were broad and included patients with T3 tumors, >2 positive SLNs, invasive lobular carcinoma histology, estrogen receptor negative status, any extent of ENE, Nottingham grade 3, and/or age <50 years. We excluded patients who received neoadjuvant chemotherapy or hormonal therapy, underwent completion ALND or mastectomy, did not receive adjuvant RT, or whose radiation treatment plans were unobtainable. The decision to omit ALND was made after a discussion with the patient with regard to the risks of disease recurrence and the potential morbidity of ALND on the basis of the currently available literature.

Individual patients' RT plans were individually reviewed by a single radiation oncologist using the Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA). RT fields were categorized as whole breast irradiation (WBI) alone using standard tangent fields, modified tangent (MT) fields for coverage of the superior level I and II axilla, or MT and the addition of a 3<sup>rd</sup> level III and SCN-directed field.

All data analysis was performed with SPSS Statistics 24 (IBM Corp., Armonk, NY). Binary logistic regression was utilized to test for associations between patient characteristics and delivered RT fields. The Kaplan-Meier method was used to estimate DFS and locoregional control (LRC) rates and the log-rank test was performed to identify potential associations with risk factors.

## Results

### Patient population

The RT fields, treatment outcomes, and pathological factors in 105 patients who met the inclusion criteria were reviewed. The median patient age was 57 years (Range,

35-90 years). Eighty-five patients (81.0%) presented with invasive ductal carcinoma and 103 patients (98.1%) had negative surgical margins. Eighty-four patients (80.0%) presented with macro-metastases (pN1a) and 40 patients (38.1%) had ENE, including 10 patients (9.5%) with >2 mm ENE and 29 patients (27.6%) with ≤2 mm ENE. Ninety-nine patients (94.3%) were human epidermal growth factor receptor 2 negative and 42 patients (40.0%) presented with grade 3 disease. The median number of nodes resected and positive nodes were 3 (Range, 1-7) and 1 (Range, 1-3), respectively. Twenty patients had 2 positive nodes, and 1 patient had 3 positive nodes. Comprehensive treatment and patient characteristics are reported in [Table 1](#).

### Treatment characteristics

The median RT dose in this cohort was 50.4 Gy (Range, 40.0-50.4 Gy) and the median boost dose was 10.0 Gy (Range, 8.0-20.0 Gy). Ninety-two patients (87.6%) were treated with conventionally fractionated schedules and 13 patients (12.4%) underwent hypofractionated RT. Three-dimensional chemoradiation therapy was used for planning in 56 patients (53.3%) compared with tangential beam intensity modulated RT in 49 patients (46.7%). Nineteen patients (18.1%) received WBI alone and 86 patients (81.9%) were treated with MT fields including the superior axilla level I/II. Thirty-three patients (31.4%) also received a 3<sup>rd</sup> SCN-directed field. Among the 86 patients who received axillary nodal irradiation, nodal volume contouring was performed in 77 patients (89.5%). Fifty-one patients (48.6%) also received adjuvant chemotherapy.

### Factors that predict radiation therapy field use

Binary logistic regression demonstrated a trend toward a significant association between modified-tangent axillary coverage and estrogen-receptor negative status ( $P = .094$ ). Binary logistic regression also revealed a trend toward an association between the use of a 3<sup>rd</sup> SCN field and pN1a disease ( $P = .062$ ), positive ENE ( $P = .058$ ), and increased tumor size ( $P = .062$ ).

### Treatment outcomes

The median time to follow-up among living patients was 48.5 months (Range, 11-81 months) and the DFS ([Fig 1](#)) and LRC rates at 4 years were 94.3% and 98.1%, respectively. Univariate analyses demonstrated no association between DFS and treatment of the axilla ( $P = .574$ ), use of a 3<sup>rd</sup> SCN-directed field ( $P = .180$ ), pT stage ( $P = .435$ ), pN stage ( $P = .843$ ), overall stage ( $P = .272$ ), estrogen-receptor negative status ( $P = .0321$ ), progesterone-receptor negative status ( $P = .0905$ ), human epidermal growth factor

**Table 1** Patient and treatment characteristics (n = 105)

Factor	57 (Median) n	35-90 (Range) %
Age (years)	57 (Median) n	35-90 (Range) %
Pathologic tumor stage		
1A	3	2.9
1B	10	9.5
1C	57	54.3
2	34	32.4
3	1	1.0
Pathologic nodal stage		
1mic	21	20.0
1A	84	80.0
Overall stage		
1B	17	16.2
2A	53	50.5
2B	34	32.4
3A	1	1.0
Tumor size (mm)	18 (Median)	4-72 (Range)
Estrogen receptor status		
Positive	98	93.3
Negative	7	6.7
Progesterone receptor status		
Positive	85	81.0
Negative	20	19.0
Her-2 receptor status		
Positive	6	5.7
Negative	99	94.3
Triple negative		
Yes	7	6.7
No	98	93.3
Histology		
Infiltrating ductal carcinoma	85	81.0
Infiltrating lobular carcinoma	20	19.0
Nottingham grade		
1-2	63	60.0
3	42	40.0
Extranodal extension		
Positive	40	38.1
Negative	65	61.9
Extent of extranodal extension		
≤2 mm	29	27.6
>2 mm	10	9.5
Extent not reported	1	1.0
Surgical margin status		
Positive	2	1.9
Negative	103	98.1
Number nodes resected	3 (Median)	1-7 (Range)
Number positive nodes	1 (Median)	1-3 (Range)
Planning		
3-dimensional conformal	56	53.3
IMRT	49	46.7

(continued on next page)

**Table 1** (continued)

Factor	57 (Median) n	35-90 (Range) %
Fractionation		
Conventional	92	87.6
Hypofractionation	13	12.4
Radiation therapy dose (Gy)	50.4 (Median)	40.0-50.4 (Range)
Boost dose (Gy)	10.0 (Median)	8.0-20.0 (Range)
Axillary nodal coverage		
WBI only	19	18.1
Level I/II Axilla	86	81.9
Axillary nodal contouring		
Yes	77	73.3
No	28	26.7
Supraclavicular field		
Yes	33	31.4
No	72	68.6
Adjuvant chemotherapy		
Yes	51	48.6
No	54	51.4

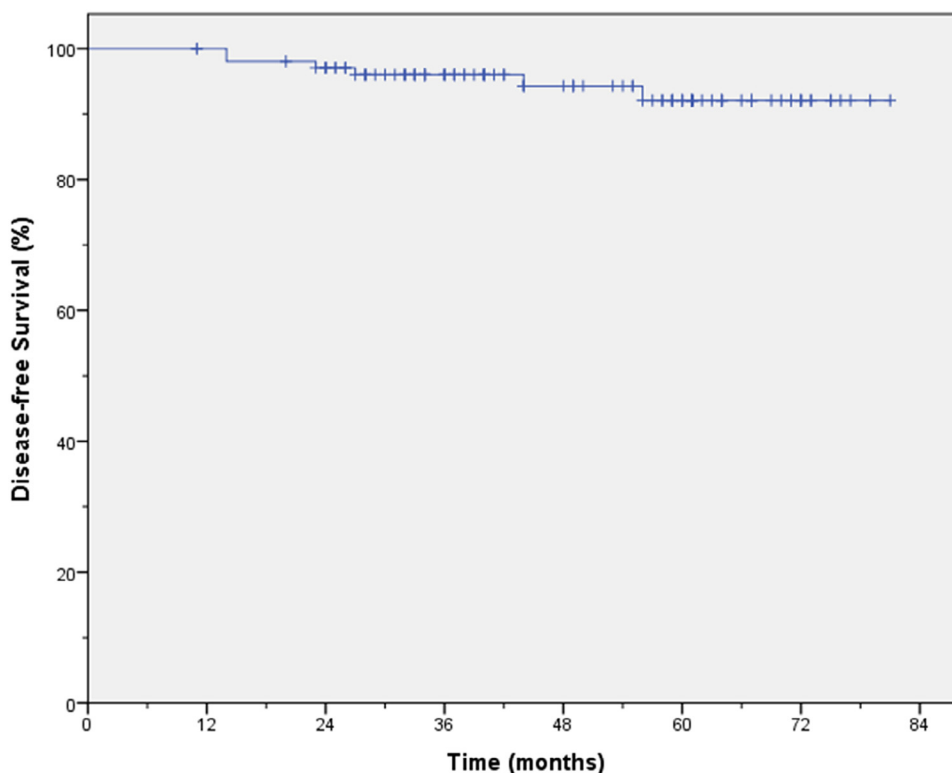
IMRT, intensity modulated radiation therapy; WBI, whole breast irradiation.

receptor 2 positive status ( $P = .0545$ ), invasive ductal vs lobular histology ( $P = .271$ ), Nottingham grade 3 ( $P = .169$ ), positive margins ( $P = .724$ ), or use of adjuvant chemotherapy ( $P = .107$ ). The univariate analysis did demonstrate an association between decreased DFS rates and any extent of ENE ( $P = .025$ ). There was a trend ( $P = .051$ ) toward decreased DFS when ENE was categorized into no ENE,  $\leq 2$  mm ENE, or  $>2$  mm ENE, with 4-year DFS rates of 100%, 89.3%, and 78.8%, respectively (Fig 2).

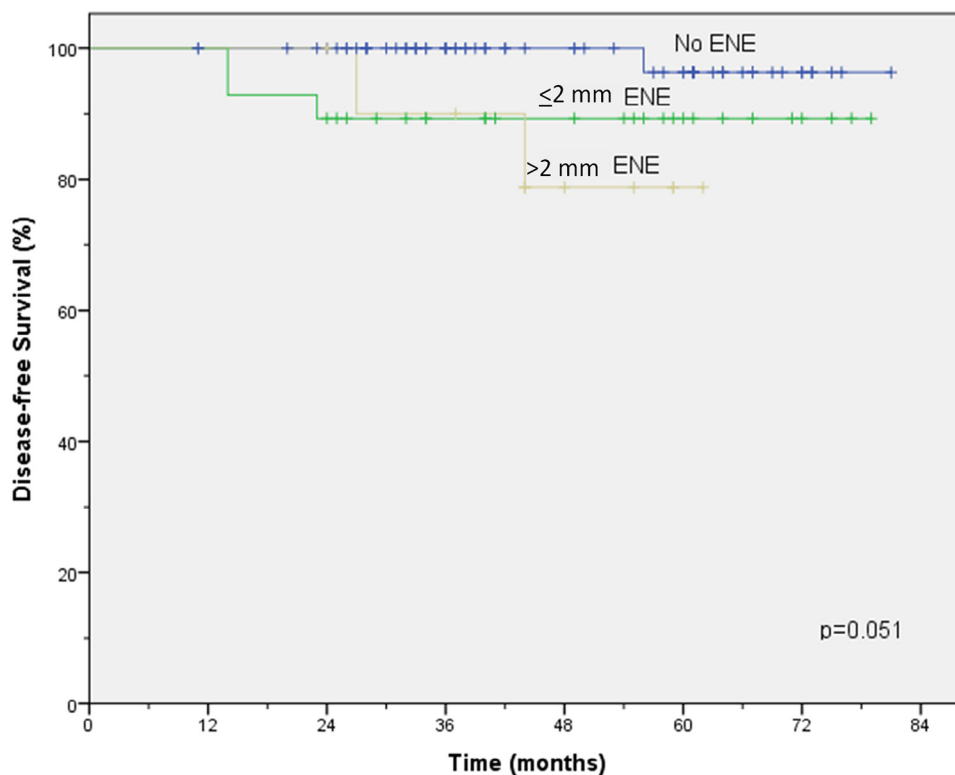
Among the subset of 40 patients with ENE positive, 2 patients (5.0%) developed distant metastases. One patient with  $\leq 2$  mm ENE was diagnosed with osseous, pulmonary, and adrenal metastatic disease at 14 months from diagnosis and remained stable on systemic therapy 26 months later. The 2<sup>nd</sup> patient had  $>2$  mm ENE and was diagnosed with a regional recurrence at an ipsilateral internal mammary node 38 months from the time of diagnosis. She subsequently developed hepatic metastases 6 months later and died of the disease 15 months thereafter.

### Discussion

We report on a retrospective analysis of adjuvant RT outcomes in a population of 105 patients who underwent lumpectomy and SLNB without ALND and were underrepresented in the ACOSOG Z11 trial. Our cohort of patients



**Figure 1** Kaplan-Meier estimate of disease-free survival.



**Figure 2** Kaplan-Meier estimate of disease-free survival by extent of extranodal extension.

with risk factors for disease recurrence including hormone receptor negative tumors, Nottingham grade 3 histology, macro-metastases, and ENE demonstrated favorable outcomes after SLNB and adjuvant RT with the omission of ALND, which suggests that ALND after SLNB can potentially be omitted in this population.

These findings are noteworthy given the recognized morbidities that are associated with ALND including paresthesia, lymphedema, shoulder pain, seroma, and wound infection.<sup>6-8</sup> The Z11 trial found that the addition of ALND to SLNB alone was a significant predictor of wound infections, paresthesia, and axillary seromas (70% in ALND vs 25% in SLNB alone) as well as self-reported lymphedema at 1 year after treatment (28% vs 15%) and beyond.<sup>9</sup>

Notably, a large proportion (39%) of our cohort had pathologic findings of ENE, which is typically an indication for ALND after SLNB.<sup>10</sup> ENE involves the extension of tumor cells beyond the lymph node capsule and parenchyma, which often spreads to the surrounding extranodal fat. The current standard of care for patients with ENE is ALND after SLNB and several studies have suggested that an increased axillary nodal burden is associated with ENE. The current literature reports incidence rates between 58 and 84% for nonsentinel nodal involvement in patients with ENE.<sup>11-13</sup> For comparison, the rate of nonsentinel nodal involvement in patients in the ACOSOG Z11 trial, which excluded patients with ENE, was 27%. Additional studies have reported an association between ENE and the diagnosis of pN2 breast cancer.<sup>14,15</sup>

Among the 40 patients with ENE, 2 patients (5%) developed distant metastatic disease. Both were treated with RNI including level I/II of the axilla and a 3<sup>rd</sup> SCN-directed field. The fact that neither patient experienced failure within the axilla suggests that a completion ALND likely would not have prevented the development of distant metastasis.

As with ENE, Nottingham tumor grade, lymphovascular spread, and hormone receptor negative status also represent validated risk factors for nonsentinel nodal involvement.<sup>16-21</sup> Therefore, patients who present with these characteristics are expected to benefit from additional targeted axillary treatment beyond SLNB.<sup>22</sup> However, our results suggest that a de-escalation from ALND, which is the current standard of care in this cohort, to SLNB plus adjuvant WBI with axillary and with or without SCN RNI in these patients can provide favorable outcomes with the potential to reduce morbidity and particularly from lymphedema.

Even though both RNI and ALND are associated with an increased lymphedema risk compared with WBI alone, current evidence suggests lower toxicity rates with the addition of RNI over ALND. The AMAROS trial demonstrated significant increases in lymphedema at 1 year after treatment and beyond in node-positive patients who were treated with ALND compared with those who received RNI.<sup>4,23</sup> Moreover, patients undergoing ALND may still benefit from RNI. Ninety-six percent of patients in the NCIC MA.20 trial received an ALND and this cohort experienced lower



disease recurrence after RNI. The study authors also postulated that these benefits would still occur in the absence of ALND on the basis of comparable recurrence rates between the ALND and non-ALND arms of the Z11 trial.<sup>4</sup> Therefore, the disease control benefits of adding RNI to WBI appear to be achieved without introducing the unnecessary toxicities of ALND. As such, SLNB followed by adjuvant RNI may represent the optimal balance of disease outcomes and toxicity for this population of patients given the present data examined in the context of the existing literature.

The favorable outcomes in our population may be partially attributed to the use of directed adjuvant RT on the basis of patients' clinicopathologic characteristics, which may reduce the risk of recurrence in patients who met the Z11 criteria.<sup>24</sup> Additional nodal metastases were identified in 27% of the ALND arm in the Z11 trial but <5% developed LRR despite the heterogeneity of the treatment fields.<sup>1</sup> In the AMAROS trial, 33% of the ALND arm had additional nodal metastases and the recurrence rates were similarly low.<sup>3</sup>

The AMAROS trial, in contrast with the Z11 trial, treated the non-ALND arm with comprehensive RNI volumes. Thus, although the efficacy of adjuvant RT in the prevention of LRR is clear, uncertainty remains in the optimal nodal volumes that should be included. The majority of patients (82%) in the present study received, at minimum, coverage of levels I and II of the axilla with modified tangents and nodal volumes were contoured in most patients.

The rate of utilization of a 3<sup>rd</sup> SCN field (32%) was lower, which may be due to the fact that many patients were treated prior to the final publication of the AMAROS, EORTC, and NCIC RNI trials.<sup>3-5</sup> We identified a trend toward the utilization of a 3<sup>rd</sup> SCN field with pN1a disease, positive ENE, and increased tumor size. These women were apparently selected for more intensive treatment due to elevated risk factors for recurrence but despite the fact that they had less favorable baseline disease characteristics, their rates of DFS were not worse than those of the rest of the population.

The MA.20 and EORTC 22922 trials collectively demonstrated a 1% to 2% improvement in regional control with the addition of RNI.<sup>4,5</sup> This translated to an approximate 3% to 5% benefit in overall DFS, which suggests that the impact of RNI extends beyond improving regional control. Regional lymph nodes that harbor subclinical disease are a potential source of distant seeding and comprehensive RNI may thereby reduce the risk of distant metastasis and improve overall outcomes. Notably, RNI fields in the MA.20 and EORTC 22922 trials included elective coverage of the internal mammary nodes (IMNs) but the vast majority of our patients did not receive IMN coverage.

Elective IMN coverage remains controversial due to a lack of benefit shown in prior trials and the potential risk of increasing late cardiac toxicity.<sup>25,26</sup> However, more recent evidence has demonstrated a benefit to IMN radiation; thus, at our institution the threshold for electively covering IMN

in high-risk patients has decreased and particularly in those with right-sided tumors.<sup>27</sup> Notably, 1 patient with >2 mm ENE developed an ipsilateral IMN recurrence and subsequent distant metastasis. This patient was treated with RNI that did not include elective coverage of the IMN chain.

The limitations of this study include the follow-up time and patient numbers. However, with newer data to substantiate RNI, many recent patients are no longer treated according to the Z11 trial. Thus, this study provides valuable data in a patient group that may be difficult to study moving forward. Axillary recurrences have been reported at a median of 15 to 30 months, which is well within our median follow-up time of 48.5 months.<sup>28,29</sup>

Furthermore, while others have validated the Z11 trial outcomes after omitting ALND in women with sentinel node involvement, this is the first study to our knowledge that demonstrates favorable DFS and LRC after ALND omission in women who did not meet the Z11 study criteria.<sup>24</sup> Our results appear promising to reduce potential morbidity in clinical practice because the data demonstrate excellent outcomes with directed adjuvant RT in patients who present with high-risk features such as ENE, Nottingham grade 3 disease, or hormone receptor negative tumors despite the omission of ALND.

A significant limitation of this study is its retrospective nature, which precludes the identification of causal relationships. The low number of events further limits the ability to identify significant associations with patient outcomes. As such, further prospective work needs to be done to validate these findings. Moreover, our cohort contained relatively few patients with Stage 3 disease, estrogen-receptor negative status, and positive surgical margins. Therefore, our analyses may lack the statistical power to generate robust conclusions about the omission of ALND after SLNB among these subgroups. Nonetheless, these favorable results add to the growing body of literature on ALND omission after SLNB and provide an impetus for additional study in underrepresented patient populations.

## Conclusions

This retrospective analysis of women who were underrepresented or excluded from the Z11 trial and underwent a lumpectomy and SLN biopsy with positive SLNs demonstrated comparable rates of LRC and DFS. The high rates of LRC and DFS suggest that completion ALND may be safely omitted in this patient population but larger data sets and longer follow-up times are needed to confirm this finding.

## References

1. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and

- sentinel node metastasis: A randomized clinical trial. *JAMA*. 2011;305:569-575.
2. Jagji R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. *J Clin Oncol*. 2014;32:3600-3606.
  3. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303-1310.
  4. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373:307-316.
  5. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med*. 2015;373:317-327.
  6. Yeoh EK, Denham JW, Davies SA, Spittle MF. Primary breast cancer. Complications of axillary management. *Acta Radiol Oncol*. 1986;25:105-108.
  7. Lotze MT, Duncan MA, Gerber LH, Woltering EA, Rosenberg SA. Early versus delayed shoulder motion following axillary dissection: A randomized prospective study. *Ann Surg*. 1981;193:288-295.
  8. Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. *Br J Cancer*. 1992;66:136-138.
  9. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25:3657-3663.
  10. American Society of Breast Surgeons. Performance and practice guidelines for axillary lymph node dissection in breast cancer patients. Available at: [https://www.breastsurgeons.org/statements/guidelines/PerformancePracticeGuidelines\\_ALND.pdf](https://www.breastsurgeons.org/statements/guidelines/PerformancePracticeGuidelines_ALND.pdf). Accessed December 21, 2017.
  11. Choi AH, Surrusco M, Rodriguez S, et al. Extranodal extension on sentinel lymph node dissection: Why should we treat it differently? *Am Surg*. 2014;80:932-935.
  12. Changsri C, Prakash S, Sandweiss L, Bose S. Prediction of additional axillary metastasis of breast cancer following sentinel lymph node surgery. *Breast J*. 2004;10:392-397.
  13. Abdessalem SF, Zervos EE, Prasad M, et al. Predictors of positive axillary lymph nodes after sentinel lymph node biopsy in breast cancer. *Am J Surg*. 2001;182:316-320.
  14. Gooch J, King TA, Eaton A, et al. The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1-T2 breast cancer. *Ann Surg Oncol*. 2014;21:2897-2903.
  15. Choi AH, Blount S, Perez MN, et al. Size of extranodal extension on sentinel lymph node dissection in the American College of Surgeons Oncology Group Z0011 Trial Era. *JAMA Surg*. 2015;150:1141-1148.
  16. Degnim AC, Reynolds MD, Pantvaia G, et al. Nonsentinel node metastasis in breast cancer patients: Assessment of an existing and a new predictive nomogram. *Am J Surg*. 2005;190:543-550.
  17. Smidt ML, Kuster DM, van der Wilt GJ, Thunnissen FB, Van Zee KJ, Strobbe LJ. Can the Memorial Sloan-Kettering Cancer Center nomogram predict the likelihood of nonsentinel lymph node metastases in breast cancer patients in the Netherlands? *Ann Surg Oncol*. 2005;12:1066-1072.
  18. Kocsis L, Svébis M, Boross G, et al. Use and limitations of a nomogram predicting the likelihood of non-sentinel node involvement after a positive sentinel node biopsy in breast cancer patients. *Am Surg*. 2004;70:1019-1024.
  19. Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br J Surg*. 2008;95:302-309.
  20. Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. *BMC Cancer*. 2008;8:66.
  21. Haffty BG, Hunt KK, Harris JR, Buchholz TA. Positive sentinel nodes without axillary dissection: Implications for the radiation oncologist. *J Clin Oncol*. 2011;29:4479-4481.
  22. Donker M, Rutgers E, van de Velde CJ, et al. Axillary lymph node dissection versus axillary radiotherapy: A detailed analysis of morbidity. Results from the EORTC 10981-22023 AMAROS trial. *Eur J Cancer*. 2013;49:S14.
  23. Rotter T, Kinsman L, James EL, et al. Clinical pathways in hospitals. *Cochrane Database Syst Rev*. 2010;(3):CD006632.
  24. Morrow M, Van Zee KJ, Patil S, et al. Axillary dissection and nodal irradiation can be avoided for most node-positive Z0011-eligible breast cancers: A prospective validation study of 793 patients. *Ann Surg*. 2017;266:457-462.
  25. Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys*. 2013;86:860-866.
  26. Thorsen LBJ, Thomsen MS, Berg M, et al. CT-planned internal mammary node radiotherapy in the DBCG-IMN study: Benefit versus potentially harmful effects. *Acta Oncol*. 2014;53:1027-1034.
  27. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol*. 2016;34:314-320.
  28. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347:567-575.
  29. Greco M, Agresti R, Cascinelli N, et al. Breast cancer patients treated without axillary surgery: Clinical implications and biologic analysis. *Ann Surg*. 2000;232:1-7.