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Are the conclusions of Z11 relevant to community practice?

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Abstract

Background—Findings of the ACOSOG Z11 trial have proven controversial, leaving physicians divided over which patients with positive sentinel lymph nodes (+SLNs) benefit from axillary lymph node dissection (ALND). Our institution reviewed our own experience with Z11-eligible patients who did not undergo ALND and explored factors that predict for +LNs on ALND following 1–2 +SLNs to determine which patients benefit from adjuvant therapy.

Materials and Methods—All breast cancer pathology reports from our institution containing the word “sentinel” between 7/1998 and 12/2001 were reviewed. We obtained follow-up information on patients meeting Z11 eligibility criteria that did not undergo ALND. We also compared pathological characteristics between patients with 1–2 +SLNs and +LNs on ALND to those with no further +LNs.

Results—Of the 432 pathology reports reviewed, 38 were from patients meeting Z11-criteria that did not undergo ALND. At a median follow-up of 11.9yr, these patients had 5yr overall survival (OS) of 93.3% and 10yr OS of 79.3%. No patient had recurrent disease in the axilla. Of the 80 patients with 1–2 +SLNs who underwent ALND, tumors with +LNs on ALND were generally larger, non-ductal histology, more likely to be ER+, and PR+, and less likely to be Her2+.

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Conclusions—Our institution's 5yr OS (93.3%) for Z11-eligible patients closely resembled those from the Z11 trial (92.5%) and our 10yr data provide evidence of what to expect for Z11-enrolled patients on continued follow-up. Larger tumor, non-ductal, ER+, PR+, and Her2- were predictive for further +LNs on ALND which may reflect surgical bias.

Keywords

Breast; Breast-conservation therapy; Z11; sentinel; axillary; lymph node dissection; radiation therapy

Introduction

Patients with breast cancer who have positive nodal metastasis have been shown to have inferior local control and overall survival.¹ Although patients with breast cancer have historically routinely received an axillary lymph node dissection (ALND) at the time of definitive breast surgery,² this procedure can be associated with significant patient morbidity, including seroma, infection, and lymphedema.^{3–5} As a result, sentinel lymph node biopsies have come into favor to determine which patients do not have evidence of any nodal metastasis and can thus avoid a completion ALND.⁶ However, the standard of care until very recently for patients with positive sentinel lymph nodes (+SLNs) was to perform completion ALND.⁷

The recently-reported ACOSOG Z11 randomized trial found that 5 year survival rates were similar in patients with early-stage breast cancer with one or two +SLNs who underwent whole-breast irradiation (WBI) without further ALND compared to those who underwent further ALND and WBI.⁸ The findings of the Z11 trial have proven controversial, leaving physicians divided over which patients with one or two +SLNs may benefit from ALND or axillary-directed radiation.

To date, there have been few reports attempting to study outcomes in the same patient population or otherwise validate the findings of the Z11 trial and the ability to safely omit additional ALND in patients with +SLNs, and no reports exist assessing the generalizability of the Z11 trial in community oncology practices. Our institution sought to review our own experience with Z11-eligible patients who did not undergo ALND to determine their survival and disease control outcomes. We also sought to explore whether radiation therapy for these patients was modified from traditional fields to account for a lack of ALND. We further explored factors that predicted for positive lymph nodes (+LNs) on ALND following one or two +SLNs for the purpose of determining which patients may derive the greatest benefit from adjuvant therapy.

Materials and Methods

Our study group conducted a retrospective analysis assessing characteristics and outcomes for all consecutive patients who underwent breast cancer-related surgery at our institution from July 1998 to December 2001. All pathology reports were reviewed, and those containing the word “sentinel” were further assessed. From these reports, we identified all patients with cT1-T2 tumors with one or two +SLNs and no ALND and obtained follow-up

information on these patients which we compared with the findings of similarly-treated patients who enrolled in the Z11 trial. We also conducted a review of the radiation therapy charts, treatment plans, and imaging of these patients to determine if radiation treatment plans were altered to account for potentially unresected axillary disease.

From these pathology reports, we extracted patient tumor characteristics, including size, histology, grade, receptor status, and results of SLNs and ALND, if performed. We used this data to compare pathological characteristics between all patients with one or two +SLNs with further +LNs on ALND in contrast to those with no further +LNs in an attempt to identify factors which may influence our decision to proceed with further axillary directed treatment.. We also explored the rate of further +LNs on ALND after a negative SLN biopsy.

Two-tailed t-tests were used to determine significance between groups with α for significance set at $p = 0.05$. This study was approved through the Johns Hopkins and Suburban Hospital Institutional Review Boards and ethics committees.

Results

Of the 432 consecutive breast cancer patients reviewed, 134 (31%) were from patients meeting Z11 entry criteria, of which 38 patients did not undergo ALND. At a median follow-up of 11.9 years, these 38 patients had a 5-year overall survival (OS) of 93.3% and 10-year OS of 79.3%. Their 5-year disease free survival (DFS) was 84.8% and 10-year DFS was 79.3%. None of these patients experienced disease recurrence in the axilla. Figure 1 demonstrates survival comparisons between Z11 patients who did not undergo ALND and similarly treated patients at our institution.

All patients who underwent adjuvant radiation therapy at our institution had their radiation plans modified from traditional fields to include more supraclavicular (SCV) lymph nodes, axillary lymph nodes, or both. Seventy-five percent (75%) of these treatment plans included either “high tangents” (fields modified from traditional tangents to include more axillary and supraclavicular lymph nodes) and/or an additional SCV treatment field. Thus, all patients received radiation which specifically included a greater number of axillary and supraclavicular nodes than would be included in traditional tangent fields. Figure 2 demonstrates one example of how radiation fields were modified to treat a greater portion of the levels I and II axillary lymph node regions.

Eighty (80) patients had one or two +SLNs and underwent ALND, of which 19 (23.8%) had further +LNs on ALND (range 1–18). Tumors with further +LNs on ALND were generally larger (2.3cm vs. 1.5cm), less likely to be ductal histology (66 vs. 86%), more likely to be ER+ (100 vs. 83%), and PR+ (88 vs. 66%), and less likely to be Her2+ (0 vs. 14%). However, only ER+ and Her2 status were statistically significant. Table 1 lists tabulated results. Eighty-seven (87) patients with negative SLNs underwent ALND, of which only 4 (4.6%) were found to have further positive LNs.

Discussion

This work was done, in part, to validate our confidence in omitting ALND in breast cancer patients with 1–2 +SLNs. Our rate of +LNs on ALND following one or two +SLN (23.8%) was similar to the rate found in the Z11 study (27.3%), suggesting similar patient populations and the use of similar surgical techniques. Furthermore, our institution's 5 year survival rates for Z11-eligible patients (93.3% OS and 84.8% DFS) closely resembled those from the Z11 trial (92.5% OS and 83.9% DFS), and our 10 year survival data provides some guidance of what to expect on continued follow-up for patients enrolled in the Z11 trial, with 10-year results from that trial pending at this time.

In all cases where patients underwent adjuvant radiation therapy at our facility following one or two +SLNs and no ALND, radiation fields were modified from traditional tangent fields to include supraclavicular lymph nodes, axillary lymph nodes, or both. This is consistent with a recent report of radiation fields from the Z11 clinical trial showing 15% of patients on Z11 were in fact treated to the supraclavicular area and nearly 50% of patients were treated with "high tangents."⁹ In light of the recently presented results of the NCIC-CTG MA20 and Oxford overview¹⁰ suggesting a significant benefit to regional nodal irradiation for patients with 1–3 +LNs, as well as the EORTC 10981–22023 AMAROS trial demonstrating regional nodal RT to be equivalent in control and less morbid than ALND, it is very likely that the modification of radiation therapy fields was responsible for the excellent outcomes seen with omission of ALND in the Z11 study as well as in our patient cohort.

Other questions remain regarding the application of Z11 data to clinical practice. For instance, it is unknown whether patients with 1–2 +SLNs and no ALND who undergo mastectomy would have equivalent outcomes to those undergoing breast-conserving surgery. This is especially important in a setting where these patients would not routinely undergo post-operative radiotherapy, which may have accounted for the equivalent outcomes in patients treated on the Z11 study. Another question regarding the application of Z11 is how to optimally treat patients with micrometastasis (defined on the Z11 trial as tumor deposits ≥ 2.0 mm on hematoxylin-eosin staining). Patients with this amount of nodal disease accounted for a sizable number of patients treated on the Z11 study. It is unclear whether these patients may have derived less benefit from an ALND, masking the benefit of ALND in patients with a greater burden of nodal disease. The recently published IBCSG 23–01 trial, looking specifically at patients with micrometastatic disease in their sentinel lymph nodes, lends support to this theory¹¹. This study concluded that axillary dissection could be avoided in patients with early stage breast cancer and limited sentinel-node involvement without an adverse effect on survival.

It is of clinical interest to identify patients at greater risk of +LNs on ALND after 1–2 +SLNs, as we postulate that patients at risk for un-dissected disease may benefit from additional axillary treatment such as surgical, systemic, or radiation therapies to ensure optimal local control of the axilla. In our study, larger tumor size, non-ductal histology, ER +, PR+, and Her2- status modestly correlated with having further +LNs on ALND, although only ER+ and Her2- status was statistically significant, which may have reflected surgical bias. Patients with these features may derive the greatest benefit from adjuvant therapy,

however randomized trials would need to be performed to confirm the significance of these findings.

Finally, the low rate of axillary nodal metastasis discovered on ALND after negative SLN further increases our confidence in omitting ALND in patients with negative SLNs. This finding validates our reliance on SLN biopsy to rule out further +LNs on ALND and is especially encouraging as we assume SLN techniques have improved over time.

Conclusions

These results show that the findings of the Z11 trial were applicable to our community practice, with acceptable 5 and 10yr outcomes in patients that we preferentially treated with adjuvant axillary-directed radiation.

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Clinical Practice Points

- In a community cancer center, outcomes of patients matching the Z11 trial entry criteria who did not undergo ALND were remarkably similar to those patients treated on the Z11 trial without ALND
- All patients with one or two +SLNs who did not undergo ALND but who received radiation therapy at our cancer center had their radiation therapy fields modified to include more complete coverage of axillary lymph nodes. These findings are consistent with recent studies suggesting radiation therapy may adequately address unresected axillary disease
- Patients who had tumors that were larger in size, non-ductal histology, ER+, PR +, and Her2- were predictive for having further +LNs on ALND after 1–2 +SLNs and may derive the most benefit from adjuvant therapy

Figure 1.
Overall survival (a) and Disease-free survival (b) of Z11-enrolled SLND-Alone Group
Compared with Z11-eligible patients at Suburban Hospital who underwent SLND-Alone.

Figure 2.

An example of how radiation therapy fields were modified to treat a greater portion of the levels I and II axillary lymph node regions: a) axial view of standard tangents, b) axial view of tangents modified to include axillary levels I-II, c) beam's eye view of standard tangents, d) beam's eye view of tangents modified to include axillary levels I-II.

Table 1

Results of ALND by tumor characteristics with 1–2+ SLNs

	ALND+	ALND–	p-value
Overall #	19	61	-----
Overall %	23.8%	76.2%	-----
Median tumor size (cm)	2.3	1.5	0.23
Range tumor size (cm)	0.2–5.0	0.2–8.0	0.23
Ductal (%)	67%	86%	0.19
*ER+	100%	82.8%	0.02
PR+	87.5%	65.5%	0.17
*Her2+	0%	13.8%	0.04
LVI+	85.7%	77.8%	0.70
% Grade 1 or 2 (vs. 3)	50%	56.4%	0.68
% Grade 1 (vs 2–3)	6.25%	10.3%	0.62

* Statistically significant ($p < 0.05$)