Review

Which sentinel lymph-node (SLN) positive breast cancer patient needs an axillary lymph-node dissection (ALND) – ACOSOG Z0011 results and beyond

Wolfgang Gatzemeier a,*, G. Bruce Mann b

a Humanitas Clinical Institute, Breast Unit, Via Manzoni 56, Milan, Italy
b The Breast Service, The Royal Melbourne and Royal Women’s Hospital, Victoria, Australia

A B S T R A C T

Axillary management has evolved from routine axillary lymph node dissection (ALND) for most patients to a selective approach based on the assessment of the sentinel node (SN). Validation of this approach for staging the axilla is based on observational studies and multiple randomized trials with near general consensus that in case of negative SN completion ALND is not required and if the SN contained metastatic disease, a completion ALND is recommended.

Multiple observations have challenged the need for routine completion ALND and growing evidence from institutional series have indicated that selective omission of ALND in patients with positive SN was safe. Unfortunately, the main randomized study addressing the question of the need for a completion axillary dissection closed early having failed to meet its accrual targets. The presentation and publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 study has provoked controversy around the world regarding the extent to which this is a practice-changing study. The aim of this review was to critically re-appraise Z0011 results and assess available evidence which should be used to support the decision of which SN positive breast cancer patient needs an ALND.

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Introduction

The management of patients with early breast cancer has changed dramatically over recent decades, guided by a fundamental shift in the perception of the biology of the disease and the development of more targeted interventions. Surgical procedures have become more personalized, with recognition that oncological outcomes in many situations are not compromised with less invasive interventions.

Confirmation that breast conservative treatment (BCT) was safe occurred with results of randomized trials in the 1980’s,1–3 and consequently the majority of patients with early breast cancer are now offered this option.

The first reports of the use of lymphatic mapping and sentinel node biopsy (SNB) in breast cancer appeared in the early 1990’s.4–7 Since then, axillary management has evolved from routine axillary lymph node dissection (ALND) for most patients to a selective approach based on the assessment of the sentinel node (SN). Validation of this approach for staging the axilla is based on observational studies8 and multiple randomized trials9–13 that demonstrated a high level of accuracy, a low – but not negligible – false negative rate of around 7%, equivalent oncological outcomes in terms of distant disease-free and overall survival, and a surprisingly low regional recurrence rate of less than 1%.14,15

While some uncertainty remains regarding the validity of SNB in large and/or multifocal cancers, there is general consensus that these randomized trials demonstrated that in case of negative SN completion ALND is not required.9–13

In light of the importance of regional lymph nodes in breast cancer as a source of prognostic information which may guide treatment choices and potential implications for local control in leaving nodal metastatic disease undissected (which might be linked with survival) the SN technique was introduced with caution, with the vast majority of individuals with any amount of disease in the SN being recommended a completion ALND. This is reflected in various consensus statements and published guidelines.16–18

Multiple observations have challenged the need for routine completion ALND. Validation that axillary metastasis are limited to the SN in 60–70% of patients overall, and in 90% for low volume involvement (micrometastasis/ITC detected by immunohistochemical staining only), respectively,19 raised the possibility of selective completion dissection. The infrequency of axillary recurrence in patients having SNB alone, compared to the number of patients with presumed undissected disease based on the known
false negative rate, indicated that a substantial proportion did not progress to clinically relevant disease. Series of cases emerged where patients with involved SN either chose, or were recommended, to omit the completion ALND, with no apparent detriment to their oncological outcomes. Numerous nomograms were developed to guide clinicians and patients assess the likelihood of their being residual disease in the non-sentinel axillary nodes based on characteristics of the primary cancer and the disease in the SN.

Despite the growing evidence from institutional series that selective omission of completion nodal dissection was safe, there was no high-level evidence, and the main randomized study addressing the question of the need for a completion axillary dissection closed early having failed to meet its accrual targets. The presentation and publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 study has provoked controversy around the world regarding the extent to which this is a practice-changing study.

The aim of this review was to critically re-appraise Z0011 results and assess available evidence which should be used to support the decision of which SN positive breast cancer patient needs an ALND.

American College of Surgeons Oncology Group (ACOSOG)-Z0011 axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis

Design and rationale of the study

ACOSOG Z0011 was designed as a phase III non-inferiority trial that sought to determine whether completion ALND for breast cancer patients with SN metastasis, undergoing breast conservation surgery (BCS) and adjuvant whole breast irradiation (WBI), affects overall survival. It recruited patients from May 1999 through December 2004 in 115 sites.

Eligibility criteria included patients older than 18 years, T1-2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 SN metastasis without extranodal extension detected by frozen section, touch preparation or haematoyxlin–eosin (HE) staining on permanent section. Clinically node positive disease, more than 2 positive sentinel nodes, matted nodes, gross extranodal disease, pre-operative systemic treatments, and isolated tumour cells (ITC) in the SN identified on immunohistochemistry (IHC) only, were exclusion criteria. Stratification was with respect to age (younger or older than 50 years), ER status, and tumour size (<1 cm, 1–2 cm, >2 cm).

All patients underwent BCS and SNB. For all patients histologically negative margins of the lumpectomy specimen were mandatory. Patients with SN metastasis in 1 or 2 nodes were randomly assigned to undergo ALND or no further axillary treatment. In those assigned to ALND a dissection of at least 10 lymph nodes was required. WBI was to be administered after surgery via two tangential fields, without third field. Systemic adjuvant therapy was according to the institutional policies or at the discretion of the treating physician.

The main outcome measure was overall survival, defined as the time from randomization until death from any cause. A secondary outcome measure was disease-free survival, defined as the time from randomization to death or first documented recurrence of breast cancer.

The Z0011 trial was developed as a noninferiority trial and noninferiority was defined as the SNB-only group having a 5-year survival rate of not less than 75% of that observed in the ALND group. Targeted enrolment was 1900 women with a final analysis after 500 deaths.

Implementation, performance, results and conclusion of the study

The trial was closed early with 891 patients enrolled on the recommendation of the independent data safety monitoring committee in December 2004 due to lower than expected accrual and event rates. Participants entered the study through 2 pathways, the most common of which was randomization post-SNB when the final pathohistologic results of examination of the SN were known. However, some patients were preregistered before SNB and then randomly assigned to a treatment arm intraoperatively by an interactive automated telephone system when frozen section or touch preparation analysis documented a tumour-involved SN. Although some of these patients were subsequently found to have 3 or more tumour-involved SNs, they were included in the analyses. Clinical and tumour characteristics were comparable between 445 patients randomized to ALND and 446 randomized to SN biopsy alone. 35 patients (25 on the ALND arm and 10 on the SNB arm) were excluded because they withdrew consent from the study.

The median age in the ALND arm was 56 years and 54 in the SNB arm, resulting in a patient population older than 50 years of 67.4% and 62.6% respectively. The majority of tumours were ER- positive (82.2% and 82.8%), T1 (67.1% and 70.5%), and of infiltrating ductal (IDC) histology (81.2% and 84%), respectively. Statistical analyses were performed on an intent-to-treat basis with 420 patients in the ALND arm and 436 in the SNB arm (intent-to-treat sample). Forty-three patients failed to undergo their assigned treatment for the 420 patients assigned to the ALND arm, 32 (7.6%) did not undergo ALND and, of the patients who were assigned to the SNB arm, 11 (2.5%) had ALND. The number of patients who finally were treated in the study (Treatment received sample) was 388 in the ALND and 425 in the SNB arm.

The primary analyses were performed on the intent-to-treat sample, and all were repeated for the treatment received sample. Both analyses yielded similar results with no significant change in outcomes. Within the intent-to-treat sample, there were 103 ineligible patients: 47 on the ALND arm and 56 on the SNB arm. Reasons for ineligibility were incorrect number of positive SNs (16 ALND arm and 32 SNB arm), SNs positive by IHC only (4 ALND arm and 4 SLND arm), positive lumpectomy margins (6 ALND arm and 7 SBN arm), gross extracapsular extension in the SNs (8 ALND arm and 7 SBN arm), and other (13 ALND arm and 6 SNB arm). In both the intent-to-treat and treatment received samples, the 2 treatment arms were well balanced in terms of baseline patient and tumour characteristics.

The median number of nodes removed was 17 with ALND and 2 with SLND alone. The median number of positive nodes in both groups was 1. 41% of SN were found to contain micrometastases (up to 2 mm in size) only with an imbalance between the two groups 37.5% in the ALND and 44.8% in the SNB arm. Additional axillary metastases were identified in 27% of patients who underwent ALND. Additional disease was found in 10% of those who presented micrometastatic disease only in the SN.

Approximately 96% of patients received some systemic therapy, and this was well balanced between both groups. About 46.5% received hormonal treatment, 58% chemotherapy and therefore nearly 8% received both chemo and hormonal therapy. This pattern is remarkable in that almost 83% of the patients were ER and/or PR positive. Not all patients underwent WBI as required. In the ALND group 88.9% and in the SN group 89.6% received adjuvant irradiation.

At a median follow-up of 6.3 years, 5-year overall survival was 91.8% (95% confidence interval, 89.1%–94.5%) with ALND and 92.5% (95% CI, 90.0%–95.1%) with SNB alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%–86.3%) with ALND and 83.9% (95% CI, 80.2%–87.3%) with SNB alone. Axillary tumour recurrence was 0.5% in the ALND arm and 0.9% in the SNB arm, in-breast recurrence 3.6% and 1.9%, respectively. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56–1.11) without adjustment and 0.87 (90% CI, 0.62–1.23) after adjusting for age and adjuvant therapy.
The investigators concluded from these results: “Among patients with limited SN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SNB alone compared with ALND did not result in inferior survival.”

Reaction

The results provoked much interest, and also much controversy, around the world. As avoiding the potential adverse side effects and morbidity of an unnecessary ALND is a priority, a trial supporting a major change in practice is welcomed. Nonetheless, limitations of the ACOSOG Z0011 trial have led many to consider that caution is required prior to implementing large-scale practice change.

Potential problems with the trial encompass statistical design and interpretation, enrolment of patients, imbalances between the treatment groups and missing data.

The planned target accrual for the ACOSOG Z0011 trial was 1900 patients calculated using a prediction of an overall survival rate of 80% at 5 years for women with optimally treated node-positive breast cancer.36–38 The study had a slow accrual19 (115 sites over 4 years leading to <900 patients – some centres entered less than 3 patients which is not many per site), was unable to complete enrolment of all patients, therefore closed early with less than 50% of the targeted accrual and with lower-than-expected event rates. There was a significant amount of missing data in these reports. This included 98 cases (11%) where the number of lymph node metastases was missing, 217 cases (32%) where tumour grade was missing, 20 cases (2%) where tumour size was missing and 81 cases (9%) where receptor status was missing. The size of the SN metastasis was unknown in 125 cases (15%), while 33 cases (4%) had no lymph node metastases, and 15 cases in the SN arm had more than 2 nodes involved.

27% of the patients in the ALND arm were found to have further positive nodes. Thus 27% of the 388 patients in the SNB arm may have had undissected disease. Macrometastases in the SN were found in 62.5% of patients in the ALND group and in 55.2% of patients in the SNB group. This statistically significant imbalance between the groups raises the question whether the SNB group had less tumour burden in their nodes and, consequently, a more favourable prognosis. Notably, the axillary recurrence rate, even if low, was double in the SNB group. (0.9% vs. 0.5%)

The most critical issue relates to the generalizability of trial results. The eligibility criteria included patients over 18 years old with tumours up to 5 cm with macrometastases in 2 sentinel nodes; however the patients recruited to the study were generally low risk cancers.

The majority of patients had small (T1), ER positive invasive ductal carcinomas, and were over 50 years old, raising the question related to applicability to many patients with cancers that would have met the eligibility criteria but were not represented in the cohort of patients in the trial.

Another concern is regarding the high proportion of patients who were lost to follow-up. (21% in the ALND and 17% in the SN group) A Lost to follow-up rate exceeding 10% is considered to be critical and the validity of the conclusions may be compromised.

An important question concerns the radiation techniques in this trial. According to the study protocol all patients had to undergo WBI with opposing standard tangential fields. No third field irradiation was allowed. This recognizes the fact that radiotherapy can sterilize nodal disease, and the fact that the trial was restricted to patients due to receive radiotherapy implies that this therapeutic effect of radiotherapy was expected to reduce the rate of regional recurrence. However, information regarding dosing, frequency, radiation field description and radiotherapy quality assurance are not captured for patients enrolled in the trial, and it is possible that the fields were not uniform between the randomization arms, as the radiation oncologists were not blinded to the surgical treatment received.

Other reports supporting omission of ALND

There are many published trials and series that provide information regarding the impact of leaving nodal disease undissected. In randomized trials of sentinel node biopsy (SNB) vs. axillary dissection in clinically node-negative patients, the false negative rate of 4–9%39–42 far exceeds the rate of axillary recurrence, suggesting that the majority of occult axillary metastases do not result in regional recurrence, and nor do they affect the oncological outcome. After 8 and 10 year follow up respectively, NSABP B-3215 and Veronesi et al.14 demonstrated axillary recurrence rates of just 0.7% and 0.8% and overall survival rates of 90.3% and 93.5% in those with a negative SNB suggesting that even with a false negative rate of up to 10%, the consequences of a missed positive sentinel node were unlikely to influence survival. This supports the hypothesis that undissected non-sentinel axillary nodes would have little or no clinical impact.

The IBCSG B2331 study addressed a similar question, although its inclusion criteria were limited to patients with micrometastatic disease in the SN. This was a low risk group of patients. 67% of patients had T1 tumours, 74% were grade 1 or 2, 89% ER positive and 67% had micrometastases <1.0 mm. 75% had conservative surgery and 25% mastectomy. 89% had adjuvant radiotherapy. When presented at the San Antonio conference in 2011 the five-year disease-free and overall survival rates for women who did not undergo axillary dissection were reported to be very similar, and any slight differences between the two groups shows axillary dissection does not impact survival. These results have not been published, and may assist in the management of low-risk patients.

Bilimoria et al.30 analysed data from the National Cancer Data Base in 2009 and reported on outcomes of clinically node-negative patients, found to have nodal metastasis on SNB, treated with SNB alone or SNB and ALND. Those treated with SNB alone had smaller tumours that were lower grade and were more likely to have micrometastases. Those with SNB alone had no increased risk of regional recurrence compared to those receiving ALND, whereas for those with macroscopic disease, the axillary recurrence rate was not significantly different in those having and not having axillary clearance even after adjusting for differences in pathology and other treatment.

The authors’ conclusion was that, compared with SLNB alone, completion ALND does not appear to improve outcomes for breast cancer patients with microscopic nodal metastases; however, there was a nonsignificant trend towards better outcomes with completion ALND for those with macroscopic disease.

Other series provide evidence that suggests caution should be used when extending the group of node positive patients for whom ALND is omitted. The group at MSKCC published their long experience of selective ALND in 2007.32 Of 1960 SN positive patients between 1996 and 2004, 1673 (85%) had a completion axillary dissection, and 287 (15%) did not. Those having completion dissection were younger, more likely to have mastectomy, had larger tumours, with fewer low grade cancers, more LV and more multifocality. Of note, 57% of the “no ALND” group had 4 or more nodes excised, and 15% had at least 10 nodes excised. The MSKCC nomogram was used to analyse the groups, and found the median nomogram score in the patients not undergoing ALND was 9 (range 1–89) and that of the group having ALND was 37 (range 2–97). The regional recurrence rates were 6/287 (2%) and 6/1673 (0.4%) respectively. Interestingly, in those patients with positive SN on routine H&E (presumably the macrometastases), the axillary recurrence rate was 5% (3/59).

The MIRROR study was published in 2009.40,41 This was a nationwide study from the Netherlands of patients undergoing SNB.
between 1997 and 2005 identified from the Netherlands Cancer Registry. It included cancers <1 cm, and cancers 1–3 cm that were grade 1 or 2. Patients with ITCs or micrometastases were identified, and analysed according to what further axillary treatment (none, completion ALND or axillary radiation) was received. The amount of adjuvant systemic therapy used was much lower than in other series, with 75% of those with ITCs and 52% with micrometastases in the SN and no axillary treatment receiving no systemic therapy, and 34% in both groups receiving radiotherapy.

Patients in the axillary dissection group had worse prognosis disease at baseline, and were more likely to undergo mastectomy with no radiotherapy and to receive systemic treatment. The former 2 factors would be expected to increase axillary recurrence rates and the last factor to reduce axillary recurrence. Analyses were adjusted for these and other risk factors.

A more recent trial from the Netherlands studied the impact of axillary treatment on 5-years regional recurrence rates in patients with ITCs or micrometastases to the SN.\(^4,2\) The regional recurrence rate was reported and found to be 5.6% at 5 years for those with micrometastases not receiving further axillary treatment, 1% in those receiving ALND, and 0 in those receiving axillary RT. A doubling in tumour size, high grade and negative hormone receptor status were strongly and significantly associated with increased regional recurrence rate, although there large confidence intervals around these factors.

**Discussion**

The surgical management of the axillary lymph nodes has considerably evolved over the last 20 years. The algorithm once was simple — the vast majority of patients with invasive breast cancer were advised to have an axillary clearance for local control and staging purposes, except perhaps elderly patients in whom it was sometimes omitted. The introduction of sentinel node posed challenges initially in the determination of which clinically node negative patients were suitable for sentinel node biopsy. This question had been answered, based on findings of at least 5 randomized trial and numerous observational studies,\(^8\)\(^–\)\(^13\) resulting in a near consensus that all clinically node negative patients were to be offered SNB, and if the SN contained metastatic disease, a completion ALND was recommended.

This algorithm led to the logical introduction of various methods of intraoperative assessment of the SN, to reduce the incidence of a patient requiring a second operation for a positive SN\(^4,3,4\) and to refinement of pre-operative axillary ultrasound (AUS) examination and fine needle aspiration cytology to identify patients with nodal disease who could proceed directly to ALND.\(^4,5,6\)

Nomograms were introduced to identify those SN positive patients with a sufficiently low likelihood of non-SN involvement to make the expected oncological benefit of ALND be less than the likely morbidity of the surgery, and series of cases were reported suggesting that this strategy was reasonable.\(^2\)\(^1\)\(^–\)\(^2\)\(^9\)

In these developments, it has been assumed that removal of cancer-containing non sentinel nodes was of some benefit to the patient. The presentation and publication of the ACOSOG Z11 study has posed challenges to those treating breast cancers and to patients with the disease. The suggestion that there is no oncological benefit to the ALND in the presumed 28% of patients in the no-dissection arm of the study who had residual disease was counter-intuitive to most, and has challenged many entrenched beliefs about the disease and its treatment. While many major institutions, especially in the USA, have significantly changed their practice for patients meeting the inclusion criteria of the study, clinicians in many parts of the world have not embraced these findings and interpretations.

Should ACOSOG Z0011 results move the question from “Which SN positive patient does not require ALND?” to “Which SN positive patients, if any, require ALND?”? We believe that this conclusion is premature.

The findings of ACOSOG Z0011 are impressive. It is true and unfortunate that the study failed to accrue its planned 1900 patients. Statistical analysis suggests however that it is highly unlikely that a study twice the size would have led to a different conclusion in this study population. The imbalances in the two groups that would favour the SN alone arm, the surprisingly large amount of missing data and the large number of patients for whom there was no follow-up do leave some room for doubt, but we conclude that, in the studied population treated with adjuvant whole breast radiotherapy and systemic therapy, ALND offers minimal or no oncological benefit in terms of locoregional control or overall survival.

It is unclear what aspects of the therapy were responsible for the excellent outcomes reported. This is vital information, as many developments are occurring in the various aspects of breast cancer treatment. The fact that the trial was limited to patients who would receive WBI implies that the authors believed that the therapeutic effect of radiation therapy (RT) was important. A key question is to what extent the adjuvant WBI was responsible for the extremely low regional recurrence rate, or in other words whether the axilla truly remained untreated. Some of the potentially involved non-dissected nodes receive considerable treatment already within standard radiation fields, and the possibility that some radiation oncologists may have modified fields via high tangents to achieve a larger coverage of the axilla in those patients who did not have an ALND needs to be clarified.

Reznik and colleagues\(^47\) verified in their investigation that with the standard tangential irradiation fields, the average dose delivered to Levels I, II, III, and is 66%, 44%, and 31% of the prescribed dose, respectively. The axillary coverage increases to 86%, 71%, and 73% of the prescribed dose, respectively, for Levels I, II, III when the high tangential irradiation fields are used. Thus 51% of Level I, 26% of Level II, and 15% of Level III receive 95% of the prescribed dose with normal tangents, whereas the volume increases to 79%, 51%, and 49% of Levels I, II, and III, respectively, with high tangents.

Questions exist about the applicability of the results to patients having mastectomy without RT, to those have partial breast irradiation (PBI), or to those undergoing RT in the prone position, which is likely to include less axillary tissue in the treatment fields.

The above mentioned limitations regarding data collection of the radiation treatment and concerns that unconventionally high tangential fields may have been used to improve axillary coverage in patients assigned to SNB only, have generated uncertainty related to the validity of study result.

The population recruited to the Z0011 trial was a low risk group, and not representative of the spectrum of patients who meet the inclusion criteria. Caution must therefore be used before applying these results to all patients who would have been eligible, rather than restricting it to those patients who were actually included in the study. The ‘average’ patient entered in ACOSOG Z0011 had a 1.7 cm, ER positive, Grade 2 IDC, without lympho-vascular-invasion (LVI), and with 1 of 2 sentinel nodes involved. Using the MSKCC nomogram, the likelihood of additional nodal metastasis for such a patient is 22%, not dissimilar to the 28% of patients in the axillary dissection arm found to have additional disease.

Using the nomogram further, a patient with a 4.9 cm, Grade 3 cancer with LVI and 2/2 sentinel nodes involved has an 84% risk of additional nodal metastases yet still fits the ACOSOG-Z11 eligibility criteria, and many patients who would have been eligible have a much higher predicted risk of additional disease than 28%.

The fact that both the Dutch MIRROR study and Park et al’s institutional series from Memorial showed a 5% regional recurrence
rate in patients with macrometastases receiving no additional axillary treatment is cause for concern. Evidence from randomized trials of SN suggests that around 1 in 6 cases of undissected disease lead to a regional recurrence. This is also the calculated rate given the nomogram scores of the undissected group in Park et al. Thus, should the results of Z0011 be extrapolated to a group of patients with a 50% likelihood of residual disease, it is possible that we might see an 8% RR rate.

Selective dissection for patients with positive sentinel nodes calls into question the rationale for AUS and also for intraoperative assessment of the sentinel node. Both AUS and intraoperative assessment were introduced on the basis that confirmation of sentinel node involvement would allow a single axillary operation for node positive patients. In the era of selective ALND, this can have the impact of leading to ‘unnecessary’ completion dissections, as it is not uncommon for there to be a single node involved after these procedures, and many of these patients would fit the Z0011 inclusion criteria.

Responses to this dilemma include a view that AUS/intraoperative assessment has little if any role. Alternatively, it could be that AUS remains useful, but information on the number of abnormal axillary nodes should be sought, so that those with a significant nodal burden can still be identified and spared a second surgery. A third possibility is that AUS may be able to move the question beyond the issue of the positive SN, and address the question of whether any nodal surgery is required in some patients. Veronesi and colleagues in Milan report a trial in progress — SOUND: Sentinel node vs. Observation after axillary UltraSOUND — that is asking this very question.46

Both the randomized trials and the institutional series demonstrate that not all patients with involved sentinel nodes require an ALND. We are not yet able to accurately define the groups who do. These decisions may not be able to be made in isolation from other practice patterns. If adjuvant systemic therapy is used more selectively, or if radiation therapy is tailored to the disease, the implication of leaving axillary disease undissected may vary.

The status of the axillary nodes has been a guiding factor in the selection of adjuvant systemic therapy for many years, and many medical oncologists are reluctant to lose this information when making treatment recommendations. This is particularly the case for ER positive/Her2 negative cases, where the appropriate use of chemotherapy is often unclear. Many medical oncologists are comfortable in recommending against the addition of chemotherapy to endocrine therapy in patients with smaller, non-high grade cancer, so long as there is limited axillary disease. The very patients who were entered in the ACOSOG-Z0011 trial fit this group, where the presence of additional disease may lead to a change in treatment recommendation. Codv49 argues that this is not the case, as chemotherapy is usually given where this any likelihood of its value, and further, the recent emergence of genomic assays such as Oncotype Dx or MammaPrint60–65 can provide sufficient additional information to make these decisions. The RxSponder trial66 of LN positive patients randomized to chemotherapy vs. none on the basis of a Recurrence Score up to 25 may clarify whether this Genomic assay can be relied upon in these circumstances. Until then, this is likely to remain an area of contention.

The recent presentation of the MA20 study of Regional Nodal Irradiation (RNI) in higher risk early breast cancer is a further complicating factor. It appears that some patients with higher risk early breast cancer benefit from the addition of RNI. The status of non sentinel axillary nodes may influence these treatment recommendations. If changes in axillary surgical management are introduced, then other methods of identifying those patients who would benefit from RNI will need to be developed.

Further trials are clearly needed. It would be dangerous to introduce a large-scale change in surgical management of the entire ACOSOG Z0011-eligible population of early breast cancer patients on the basis of a single, moderate sized trial in a highly selected group of patients treated with extensive adjuvant therapy. There are simply too many unknowns and potential variables for this to be safe. Further, caution is required before the findings are extrapolated beyond the trial population to patients having less than standard WBI.

A confirmatory study — POSNOC (Positive Sentinel Node — Observation or Clearance) — has been proposed in the UK for patients in a similar group.15,30 Unfortunately we are aware of no current or planned large trials that will incorporate the current understanding of the multiple breast cancer subtypes, which may warrant tailored axillary surgical treatment according to the particular subtype.

Conclusion

The results of the ACOSOG Z0011 trial are impressive and informative for the axillary management of patients with a positive SN, a low risk of nonSN involvement who will receive adjuvant systemic therapy and WBI. They are provocative but by no means conclusive for patients with a higher risk of nonSN involvement who would have been eligible, but not informative for those not treated in this manner. It would be unwise to conclude that regional recurrences will not occur, or that they do not matter, without substantially more evidence than is currently available.

Conflict of interest statement

The authors have no conflict of interest to declare.

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