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Successful Completion of the Pilot Phase of a Randomized Controlled Trial Comparing Sentinel Lymph Node Biopsy to No Further Axillary Staging in Patients with Clinical T1-T2 N0 Breast Cancer and Normal Axillary Ultrasound

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Abstract

Background—Axillary surgery is not considered therapeutic in patients with clinical T1-T2 N0 breast cancer. The importance of axillary staging is eroding in an era where tumor biology, as defined by biomarker and gene expression profile, is increasingly important in medical decision making. We hypothesize that axillary ultrasound (AUS) is a noninvasive alternative to sentinel lymph node biopsy (SLNB), and AUS could replace SLNB without compromising patient care.

Study Design—Patients with clinical T1-T2 N0 breast cancer and normal AUS were eligible for enrollment. Subjects were randomized to no further axillary staging (Arm 1) versus SLNB (Arm 2). Descriptive statistics were used to describe the results of the pilot phase of the randomized controlled trial.

Results—68 subjects were enrolled in the pilot phase of the trial (34 subjects in Arm 1, no further staging; 32 subjects in Arm 2, SLNB, and 2 subjects voluntarily withdrew from the trial). The median age was 61 years (range 40-80) in Arm 1 and 59 years (range 31-81) in Arm 2, and

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there were no significant clinical or pathologic differences between the arms. Median follow-up was 17 months (range 1-32). The negative predictive value (NPV) of AUS for identification of clinically significant axillary disease (> 2.0 mm) was 96.9%. No axillary recurrences have been observed in either arm.

Conclusions—Successful completion of the pilot phase of the randomized controlled trial confirms the feasibility of the study design, and provides prospective evidence supporting the ability of AUS to exclude clinically significant disease in the axilla. The results provide strong support for a phase 2 randomized controlled trial.

INTRODUCTION

The current standard of care for patients with a new diagnosis of clinical T1-T2 N0 breast cancer is to perform a sentinel lymph node biopsy (SLNB). SLNB is an invasive surgical procedure based on the hypothesis that the pathologic status of the “sentinel” lymph node(s) predict the pathologic status of the corresponding lymph node basin. In current practice, radiolabeled sulfur colloid and/or blue dye are injected into the breast near the primary breast cancer and travel via lymphatics to the sentinel lymph node(s) (SLN), which are surgically removed through an incision in the axilla. If the SLN are free of metastases, it is unlikely that any other lymph nodes will have metastases. Thus, SLNB provides important staging information that can be used to tailor adjuvant therapies to individual patients.

Despite this elegant hypothesis, we believe that SLNB is already an outdated procedure, and an invasive procedure may no longer be required for staging the axilla in early stage breast cancer patients. There are several important reasons to consider a noninvasive alternative to SLNB. First, SLNB is an invasive surgical procedure. Although SLNB has fewer and less severe complications compared to axillary lymph node dissection (ALND) [1-4], it is not a risk-free procedure. Large prospective trials such as ACOSOG Z0010, NSABP B-32, and the ALMANAC trial have documented SLNB complications including allergic reactions to isosulfan blue dye (0.1-1.0%), wound infection (1.0-10%), seroma (7.1%), paresthesias (8.6-11%), lymphedema (6.9%), and hematoma (1.4%) [2, 5-7]. For many breast cancer patients, SLNB is more morbid than partial mastectomy. Second, axillary surgery is not considered therapeutic in early stage breast cancer. Level 1 evidence supports the hypothesis that axillary surgery is not therapeutic in patients with early stage, clinically node-negative disease. The ACOSOG Z0011 trial randomized women with clinical T1-T2 N0 breast cancer and a positive SLNB to no further axillary surgery or to completion ALND. The Z0011 trial demonstrated no local control or survival advantage with completion ALND, even in the setting of known axillary disease [8, 9]. Similarly, the International Breast Cancer Study Group (IBSCG) 23-01 trial randomized women with micrometastatic disease in the SLN to no further axillary surgery or to completion ALND. This trial also demonstrated no local control or survival advantage associated with ALND [10]. Retrospective studies also support the concept that axillary surgery is not therapeutic in early stage breast cancer [11-17]. Third, the importance of axillary staging information provided by SLNB is decreasing in importance. Decisions regarding adjuvant systemic therapy are complex, and integrate a significant amount of clinical and pathologic information such as patient age, medical history, menopausal status, tumor size, biomarker profile, gene expression profile, and

axillary lymph node status. Although axillary staging remains important, it is of decreasing importance as a driver of medical oncology decision making. For instance, chemotherapy is now recommended in most patients with triple-negative breast cancer (TNBC), including patients with node-negative disease. The importance of axillary staging may be further eroded in the future, as gene expression profiles, such as Oncotype DX, are increasingly used to not only better define a patient's risk of distant recurrence, but also to predict response to specific therapies, such as chemotherapy [18-26].

AUS is a noninvasive alternative to SLNB for staging of the axilla in early stage breast cancer. AUS can identify disease in axillary lymph nodes (ALN) based on the size and morphologic features of the lymph nodes [27, 28]. Several reports have documented the accuracy of AUS with or without fine needle aspiration biopsy (FNA) [29-34], and a 2011 meta-analysis by Houssami et al. reported a 79.6% sensitivity, 98.3% specificity, and 97.1% positive predictive value for AUS with FNA or core-needle biopsy (CNB) [35]. However, following publication of the ACOSOG Z0011 trial results, the role of AUS in axillary staging has become less clear [36, 37]. We recently completed a retrospective study specifically focused on the ability of AUS to accurately exclude clinically significant disease in the axilla [38]. AUS had a sensitivity of 76% and a negative predictive value (NPV) of 89% for the detection of clinically significant disease (> 2.0 mm). On multivariate analysis, no patient or tumor characteristics significantly impacted the sensitivity, specificity, or NPV of AUS detection of metastatic breast cancer to the axilla, and the median size of a "missed" ALN metastasis was 2.0 mm (range 0.1-21 mm, mean 3.7 mm).

Taken together, the fact that axillary surgery is not therapeutic, the limited impact of axillary staging in the modern era of breast cancer treatment, and the excellent performance characteristics of AUS for the detection of clinically significant disease, strongly support prospective investigations of AUS for axillary staging in breast cancer. We recently completed the pilot phase of a randomized controlled trial focused on the role of AUS in axillary staging to assess the feasibility of such a trial, and obtain prospective information about the performance characteristics of AUS for detection of clinically significant axillary disease.

METHODS

Randomized controlled trial

Institutional Review Board approval was obtained prior to initiation of the randomized controlled trial (NCT01821768). Subjects were recruited from the Siteman Cancer Center at Washington University School of Medicine (WUSM). Eligible participants included women aged 18 and over with newly diagnosed clinical T1-2 N0 M0 breast cancer who were candidates for breast conservation therapy and a normal AUS. AUS was considered abnormal based on consensus criteria (hypoechoic nodes, loss of the fatty hilum, and/or focal cortical thickening or bulge ≥ 4.0 mm). AUS was performed by radiologists specializing in breast imaging prior to initiation of any therapy. Patients were enrolled by Siteman Cancer Center research support staff. After enrollment, subjects were randomized in a 1:1 ratio to no further axillary staging (Arm 1), or SLNB (Arm 2) (Figure 1). Randomization was assigned using SAS PROC PLAN and was performed in small blocks of

4-6 patients using the WUSM RedCap website. In addition to definitive surgery, subjects received adjuvant systemic and/or radiation therapy as clinically indicated. Subjects in Arm 1 (no further axillary staging) were considered pathologically node-negative for the purposes of adjuvant systemic therapy decisions and radiation treatment planning. Axillary radiation was prohibited. Subjects were followed as per National Comprehensive Cancer Network (NCCN) guidelines with at least semi-annual clinical examination, annual mammography for patients with intact breasts, and additional imaging as indicated by symptoms or examination. Data recorded included patient age; tumor size, histology, grade, and receptor status; presence and type of postoperative complications; adjuvant therapy received; use and type of neoadjuvant systemic therapy; presence and location of disease recurrence; and patient death due to breast cancer or any cause. For patients in Arm 2 (SLNB), the number of sentinel nodes removed and pathologic status of the lymph nodes was recorded.

The primary objective of the pilot phase of the randomized controlled trial was to demonstrate feasibility of the trial design, and obtain prospective evidence supporting the ability of AUS to exclude clinically significant disease in the axilla. The primary objective of the phase 2 randomized controlled trial is to determine if axillary recurrence rates for patients randomized to Arm 1 (no SLNB) are equivalent to axillary recurrence rates for patients randomized to Arm 2 (SLNB).

Data analysis

The distribution of demographic and clinical characteristics in each arm was summarized using descriptive statistics and compared by two-sample t-test, Mann-Whitney rank-sum test, or Fisher's exact test as appropriate. All analyses were two-sided and significance was set at a p value of 0.05. For subjects in Arm 2, the negative predictive value (NPV) of AUS was calculated. Statistical analyses were performed using SAS (SAS Institutes, Cary, NC).

RESULTS

To evaluate the role of AUS as a noninvasive alternative to SLNB for staging of the axilla in breast cancer, we initiated a randomized controlled trial. Patients with clinical T1-T2 N0 breast cancer and normal AUS were eligible for enrollment. Subjects were randomized to no further axillary staging (Arm 1) versus SLNB (Arm 2) (Figure 1). Subject accrual began in April, 2013, and the pilot phase of the study was completed in December, 2015. 68 subjects were enrolled in the pilot phase of the trial. 34 subjects were randomized to Arm 1, 34 subjects were randomized to Arm 2, and 2 subjects randomized to Arm 2 withdrew from the trial. 34 patients from Arm 1, and 32 patients from Arm 2 completed the study interventions and are included in the analysis. The median age in Arm 1 was 61 (range 40-80 years) and the median age in Arm 2 was 59 (range 31-81). Median follow-up is 17 months (range 1-32 months). Subject demographic and tumor characteristics are summarized in Table 1. The two arms are well-matched in terms of patient age, tumor histology, tumor size, biomarker profile and length of follow-up.

There were no unexpected adverse events in either arm. In Arm 2 (SLNB), there 2 cases of grade 1 lymphedema, one case of grade 1 infection, two cases of grade 2 seroma, one case of grade 1 paresthesia, and one wound hematoma requiring operative intervention. There

have been no in-breast, axillary, or distant recurrences in either arm. Of the 32 subjects randomized to Arm 2 (SLNB), three were found to have axillary disease (Figure 2). One subject was a 47 year old with a T2, grade 2 invasive ductal carcinoma, ER⁺, PR⁺, and HER2⁻. There was a 1 mm micrometastasis in the SLN, and at ALND one of 15 nodes was found to have a focus of disease < 2.0 mm. The second subject was a 66 year old with a T1b, grade 2 invasive ductal carcinoma, ER⁺, PR⁺, and HER2⁻. One SLN was removed and had a single focus of disease < 2.0 mm. No axillary dissection was performed. The third subject was a 55 year old with a T2, grade 3 invasive ductal carcinoma, ER⁺, PR⁺, and HER2⁻. Her SLNB procedure failed to identify a SLN, and on ALND, two of 13 lymph nodes were positive, with the largest metastasis measuring 7 mm. The NPV of AUS for identification of any axillary disease was 90.6%, and the NPV for identification of clinically significant disease > 2.0 mm was 96.9%.

DISCUSSION

Axillary staging impacts all the major stakeholders in breast cancer care, including patients, surgeons, medical oncologists, and radiation oncologists. Adoption of AUS for axillary staging represents a major paradigm shift, and AUS will not replace SLNB until a phase 3 randomized controlled trial documents the noninferiority of AUS. We have successfully completed the pilot phase of a randomized controlled trial comparing no further axillary staging to SLNB in patients with clinical T1-T2 N0 breast cancer and a negative AUS. Successful completion of the pilot phase of the trial confirms the feasibility of the study design. Feasibility is a critical issue as two recent randomized controlled trials evaluating the role of axillary surgery in clinical T1-T2 N0 breast cancer (ACOSOG Z0011 and IBCSG 23-01) were closed to enrollment without meeting accrual goals. These studies had poor accrual as patients and physicians had strong preconceptions about the potential therapeutic benefit of axillary surgery, making randomization problematic. Specifically, many patients and physicians were unwilling to consider less aggressive surgical management of the axilla. There is now strong evidence that axillary surgery is not therapeutic in patients with clinical T1-T2 N0 breast cancer, and the current goal of SLNB is limited to axillary staging. Demonstrating the feasibility of the randomized controlled trial design represents an important first step in evaluating AUS as a noninvasive alternative to SLNB.

The pilot phase of the randomized controlled trial also provides important prospective evidence confirming the performance characteristics of AUS for the exclusion of clinically significant disease. In Arm 2, the NPV of AUS for identification of any axillary disease was 90.6%, and the NPV for identification of clinically significant disease > 2.0 mm was 96.9%. These findings confirm the results of our retrospective study demonstrating the ability of AUS to accurately exclude clinically significant disease in the axilla [38]. In the pilot phase of the randomized controlled trial, the median size of a missed axillary metastasis was < 2.0 mm. This is consistent with our retrospective study and others demonstrating that patients with a false negative AUS typically have minimal disease in the axilla [38, 39]. Of note, micrometastatic disease in the axilla (disease < 2.0 mm) has almost no impact on prognosis and medical decision making [40-45]. Numerous studies have demonstrated that additional sections, immunohistochemistry (IHC), or molecular analysis of “negative” SLN will identify “occult” micrometastatic disease in a significant proportion of cases, and occult

disease has minimal impact on clinical outcome. For example, a retrospective analysis of specimens obtained from NSABP B-32 identified occult metastases in 15.9% of cases when additional sections and IHC were performed [40]. Although the presence of occult metastases was associated with decreased overall survival, the difference was small (94.6% vs. 95.8%), and was not considered to be clinically significant. Given that micrometastatic disease is not considered clinically relevant, current guidelines for the pathologic analysis of SLN are focused on identification of disease > 2.0 mm [46]. In this context, the relative inability of AUS to detect micrometastatic disease has questionable clinical significance.

In the pilot phase of the randomized controlled trial, there were 3 false negative AUS studies in Arm 2. Critical review of the adjuvant treatment recommendations in these patients suggests that the SLNB results did not alter medical decision making. Despite axillary disease identified by SLNB, these patients all had further evaluation with Oncotype DX testing at the request of the medical oncologist, and all were treated with endocrine therapy but not chemotherapy. These results highlight an important evolution in medical decision making. In the past, axillary staging was a key contributor to medical decision making. Presently, tumor biology as defined by biomarker profile (and gene expression profile in select cases) are increasingly used to not only better define a patient's risk of distant recurrence, but also to predict response to specific therapies, such as chemotherapy. Several large retrospective studies have used clinical specimens from randomized controlled trials to evaluate the utility of Oncotype DX in patients with node-negative and node-positive disease. Patients with ER⁺, node-negative disease and a low Oncotype DX recurrence score have a low risk of distant recurrence and receive little benefit from the addition of chemotherapy, whereas patients with a high recurrence score are significantly more likely to experience distant recurrence, and benefit from the addition of adjuvant chemotherapy [23, 24]. Similar results have been obtained in patients with ER⁺, node-positive disease [22]. These results have now been confirmed in prospective randomized controlled trials. The TAILORx trial enrolled ER⁺, node-negative breast cancer patients and randomized them to either endocrine therapy alone, or chemotherapy and endocrine therapy based on gene expression profile [21]. The results were recently published in the *New England Journal of Medicine*, dramatically confirming the value of Oncotype DX for medical decision making in node-negative patients [20]. Similar prospective studies are ongoing in node-positive disease, including the MINDACT and RxPONDER breast cancer trials [18, 19]. Although these prospective randomized controlled trials are ongoing, gene expression profiles are already being used to make adjuvant therapy recommendations, highlighting the decreasing importance of axillary staging. (Please note that current ASCO guidelines currently recommend against genomic testing in patients with node-positive breast cancer).

Radiation treatment planning may be influenced by the presence, absence, and/or extent of axillary disease. Specifically, the number of involved nodes may influence the selection of radiation fields. Patients who undergo BCT are typically treated with breast radiotherapy, which includes the lower portion of the axilla in many individuals. Axillary radiotherapy is typically directed at the axilla and the medial part of the supraclavicular fossa. Some radiation oncologists have proposed that radiation therapy may impact axillary recurrence rates in patients with low volume axillary disease [47]. In general, patients with four or more positive lymph nodes and selected patients with 1-3 positive nodes are treated with axillary

and supraclavicular fields [48, 49]. However, in the post-ACOSOG Z0011 era, the exact extent of disease may not be available, as patients who have a positive SLNB may not undergo completion ALND. Further confusing this issue, the ACOSOG Z0011 study results suggest that axillary radiotherapy is not required for patients with low volume disease, although there is some concern about the validity of the ACOSOG Z0011 trial results, as the incidental coverage of level I and II axillary nodes seen with whole breast radiation may have contributed to the low axillary recurrence rate in the SLNB only arm (0.9%) [8, 9]. Jagsi et al. analyzed the Z0011 radiation fields to assess the extent of incidental axillary radiation received to determine if radiation treatment differed between the SLNB and completion ALND arms. Most patients did not receive axillary radiation, as outlined in the study protocol. Patients who had more lymph node disease were more likely to receive axillary radiation, but there was no significant difference in the use of prohibited nodal radiation fields between the two treatment groups [50]. Jagsi et al. concluded that patients with known SLN disease who do not undergo completion ALND should receive standard tangential radiation therapy but they were unable to make any definitive recommendations regarding axillary or supraclavicular-specific fields. Of note, the potential impact of a FN AUS on radiation oncology decision making has never been studied.

The performance characteristics of AUS vary widely in the literature [35, 51-56], and criteria for classifying ALN as positive or negative have not been clearly defined. Proposed criteria include cortical thickness, eccentric or focal cortical enlargement, lymph node shape, size, and echogenicity, and the presence or absence of a hyperechoic hilum. Bedi et al. demonstrated that focal cortical lobulation and/or hypoechoic appearance with absent hilum had the highest positive predictive value for the identification of metastatic disease [57]. We have adopted these criteria at our institution. Other studies have confirmed that criteria based on lymph node morphology improve the sensitivity and specificity of AUS compared to criteria based on size alone [34]. One limitation of the randomized controlled trial reported here is that radiologists at WUSM are specialized in breast imaging and have a particular interest in axillary staging; the sensitivity of AUS may be lower at other institutions or in the community setting.

Despite the success of our pilot trial we acknowledge that SLNB is currently considered an elegant, minimally invasive, and accurate procedure for axillary staging. In addition, the results of AUS are operator-dependent, and the excellent results that have been reported at select institutions with a specific interest in AUS may not be reproducible at all institutions. We believe that a phase 2 randomized controlled trial at select institutions with a special interest in the use of AUS for staging of the axilla in breast cancer is the most feasible and expeditious path forward at the present time. If the phase 2 trial confirms the performance characteristics of AUS and demonstrates the noninferiority of no further staging compared to SLNB, this will provide strong rationale for a larger, phase 3 trial in the context of an NCI cooperative group.

Conclusions

In summary, SLNB is an invasive surgical procedure, and represents an enormous investment in health care resources. Given that axillary surgery is not considered therapeutic

in patients with clinical T1-T2 N0 breast cancer, and axillary staging information provided by SLNB is decreasing in importance, we believe that noninvasive alternatives to SLNB should be considered. AUS is relatively inexpensive, widely available, and demonstrates excellent performance characteristics for the exclusion of clinically significant disease. We have demonstrated the feasibility of a randomized controlled trial comparing no further axillary staging to SLNB in patients with clinical T1-T2 N0 breast cancer and negative AUS. Preliminary results provide prospective evidence confirming the performance characteristics of AUS. Taken together, the results provide strong rationale for a larger randomized controlled trial to rigorously evaluate the role of AUS in axillary staging.

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Figure 1.

Study schema. AUS, axillary ultrasound; SLNB, sentinel lymph node biopsy; XRT, radiation therapy; NCCN, National Comprehensive Cancer Center Network.

Figure 2.

Pilot study results. The negative predictive value of axillary ultrasound was 90.6% for the detection of any disease in the axilla, and 96.9% for the detection of clinically significant (> 2.0 mm) disease in the axilla. AUS, axillary ultrasound.

Table 1

Demographics, Tumor Characteristics, and Follow-Up for 66 Patients with Normal Axillary Ultrasound Randomized to No Surgical Axillary Staging (Arm 1) vs Sentinel Lymph Node Biopsy (Arm 2)

Characteristic	Total n = 66	Arm 1 n = 34	Arm 2 n = 32	p Value
Patient demographic				0.106
Median age, y, (range)	60 (31-81)	61 (40-80)	59 (31-81)	
Median follow-up, months, (range)	17 (1-32)	17 (2-32)	18 (1-32)	
Tumor histology, n (%)				0.143
Invasive ductal carcinoma	58 (88)	32 (94)	26 (81)	
Invasive lobular carcinoma	7 (11)	1 (3)	6 (19)	
Other histology	1 (2)	1 (3)	0 (0)	
Tumor size, n (%)				0.256
T1a/mi	5 (8)	4 (12)	1 (3)	
T1b	22 (33)	10 (29)	12 (38)	
T1c	27 (41)	16 (47)	11 (34)	
T2	12 (18)	4 (12)	8 (25)	
Tumor grade, n (%)				0.595
Tumor grade I	25 (38)	14 (41)	11 (34)	
Tumor grade II	28 (42)	12 (35)	16 (50)	
Tumor grade III	12 (18)	7 (21)	5 (16)	
Tumor grade unknown	1 (2)	1 (3)	0 (0)	
ER status, n (%)				0.668
ER ⁺	61 (92)	32 (94)	29 (91)	
ER ⁻	5 (8)	2 (6)	3 (9)	
PR status, n (%)				0.428
PR ⁺	59 (89)	29 (85)	30 (94)	
PR ⁻	7 (11)	5 (15)	2 (6)	
HER2 status, n (%)				0.140
HER2 ⁺	5 (8)	3 (9)	2 (6)	
HER2 ⁻	57 (86)	27 (80)	30 (94)	
HER2 unknown or equivocal	4 (6)	4 (12)	0 (0)	

ER, estrogen receptor; PR, progesterone receptor; HER2, Human epidermal receptor 2