Factors Associated With Local-Regional Recurrence After a Negative Sentinel Node Dissection

Results of the ACOSOG Z0010 Trial

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Objective: To determine factors important in local-regional recurrence (LRR) in patients with negative sentinel lymph nodes (SLNs) by hematoxylin and eosin (H&E) staining.

Background: Z0010 was a prospective multicenter trial initiated in 1999 by the American College of Surgeons Oncology Group to evaluate occult disease in SLNs and bone marrow of early-stage breast cancer patients. Participants included women with biopsy-proven T1–2 breast cancer with clinically negative nodes, planned for lumpectomy and whole breast irradiation.

Methods: Women with clinical T1–2,N0,M0 disease underwent lumpectomy and SLN dissection. There was no axillary-specific treatment for H&E-negative SLNs, and clinicians were blinded to immunohistochemistry results. Systemic therapy was based on primary tumor factors. Univariable and multivariable analyses were performed to determine clinicopathologic factors associated with LRR.

Results: Of 5119 patients, 3904 (76.3%) had H&E-negative SLNs. Median age was 57 years (range 23–95). At median follow-up of 8.4 years, there were 127 local, 20 regional, and 134 distant recurrences. Factors associated with local-regional recurrence were hormone receptor–negative disease ($P = 0.0004$) and younger age ($P = 0.047$). In competing risk-regression models, hormone receptor–positive disease and use of chemotherapy were associated with reduction in local-regional recurrence. When local recurrence was included in the model as a time-dependent variable, older age, T2 disease, high tumor grade, and local recurrence were associated with reduced overall survival.

Conclusions: Local-regional recurrences are rare in early-stage breast cancer patients with H&E-negative SLNs. Younger age and hormone receptor–negative disease are associated with higher event rates, and local recurrence is associated with reduced overall survival.

Keywords: breast cancer, local-regional recurrence, sentinel lymph node biopsy

(*Ann Surg* 2012;256: 428–436)

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Disclosure: This study has been supported by a grant from the National Cancer Institute (U10-CA76001-15).

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ISSN: 0003-4932/12/25603-0428
DOI: 10.1097/SLA.0b013e3182654494

Sentinel lymph node (SLN) dissection has replaced axillary lymph node dissection (ALND) for staging of the regional lymph nodes in women presenting with clinically node-negative, early-stage breast cancer. Several studies have documented the decreased morbidity of SLN dissection compared with ALND and the increased detection of small volume metastases attributable to more detailed pathologic assessment of the SLNs.[1, 2] Multicenter trials have reported false-negative rates ranging from 5% to as high as 17%, yet SLN dissection was rapidly incorporated into clinical practice before any long-term follow-up data documenting safety in terms of local-regional recurrence and survival[3, 4]. Local-regional recurrence has traditionally been considered a problem of excess tumor burden, but an increasing body of evidence suggests that tumor biology and the effectiveness of systemic therapy have a major impact on local-regional control.

Published studies from single institutions have demonstrated low axillary recurrence rates (0%–4%) after a negative SLN dissection; however, only a few have reported follow-up times beyond 36 months[5, 6]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 investigators recently published low local and regional recurrence rates in patients undergoing SLN dissection with ALND compared with those undergoing SLN dissection alone[7]. The authors have not yet reported on factors associated with local or regional recurrences in patients undergoing SLN dissection alone or in those undergoing complete ALND. Investigators from the Sentinella trial reported a higher rate of local-regional recurrences in patients randomized to the sentinel node only arm of that study and a difference of 2.3% in 5-year disease-free survival compared with patients undergoing ALND, but this did not reach statistical significance[8].

The American College of Surgeons Oncology Group (ACOSOG) Z0010 trial was a prospective evaluation of occult metastases in the SLNs and bone marrow of patients with T1–2 clinically node-negative breast cancer planned for breast conserving surgery and whole breast irradiation. Patients with H&E-negative SLNs did not receive any axillary specific treatment. The overall and disease-free survival results were recently reported and found to be similar in patients with H&E-negative SLNs and those with H&E-negative nodes found to have occult metastases on immunohistochemical (IHC) evaluation[9]. In the current study, we evaluated local and regional recurrence events in Z0010 patients with H&E-negative SLNs and sought to determine clinical and pathologic factors predicting for these events.

METHODS

Patients and Treatments

Z0010 was a prospective study of patients undergoing breast conserving surgery and SLN dissection, approved by the National Cancer Institute Cancer Therapy Evaluation Program and Central Institutional Review Board and the local Institutional Review Board of participating sites. Women with clinical T1-T2,N0,M0 invasive

breast carcinoma planned for breast conserving surgery with whole breast irradiation were eligible. Patients were not eligible if they had neoadjuvant therapy, pre-pectoral breast implants, concurrent bilateral malignancies, multifocal or multicentric disease not amenable to a single lumpectomy, or previous axillary surgery. Informed consent was obtained before registration. Whole breast irradiation was specified in the protocol and excluded treatment with a third supraclavicular field. The dose to the breast was 45 to 50 Gy administered in tangential fields with a coplanar posterior border. Adjuvant systemic therapy decisions were based on primary tumor factors as assessed by treating clinicians.

Sentinel Lymph Node Dissection and Pathologic Assessment

Participating surgeons were required to perform 20 SLN procedures with completion ALND with identification and accuracy rates 85% and higher or provide documentation of training in SLN dissection through a postgraduate surgery training program. The technical results of SLN identification rates and factors influencing the failure to identify a SLN have been previously published[10]. SLNs were formalin-fixed and paraffin-embedded as per institutional protocols. Paraffin blocks were cut into 5-μm sections and assessed for metastases with standard H&E staining. For patients with H&E-negative SLNs, unstained slides were submitted to a central laboratory for IHC to cytokeratin. The results of IHC staining of the SLNs were not made available to patients or their treating clinicians. The incidence of occult metastases in patients with H&E-negative SLNs was 10.3%. There was no difference in overall survival or disease-free survival among patients with H&E-negative and IHC-negative SLNs compared with patients with H&E-negative and IHC-positive SLNs[9].

Women were followed for breast cancer recurrence and death. With respect to breast cancer recurrence, patients were followed until the first local, regional, or distant recurrence. The events of interest for this study were local recurrence, regional recurrence, and distant recurrence. The time to a recurrence was measured from date of study enrollment until the event. Survival was measured from the date of study enrollment until death.

Statistical Analysis

Univariable and multivariable Cox regression models were used to analyze the association between an event (local, local-regional and distant recurrences, and death) and the baseline patient or tumor characteristics. In the models, regional recurrence was not used by itself because there were very few events and it was combined into a local-regional event (ie, the patient had a local recurrence or a regional recurrence). Multivariable models were adjusted for treatments the women received. In the Cox models, patients were censored at last follow-up, a competing recurrence of breast cancer, or death, if the breast cancer recurrence type of interest was not observed. In the multivariable model for overall survival, the local recurrence variable was treated as a time-dependent variable where a woman was in the not-at-risk group until the point at which she had a local recurrence and then was switched to the at-risk group[11].

Because women were only followed for their first breast cancer recurrence, they were censored at the time of the event for analyses that involved a different breast cancer recurrence. For example, if a woman had a local recurrence, she was censored at that time in the analysis of distant breast cancer recurrence. This serves to overestimate the incidence of the different types of breast cancer recurrences. To obtain a better estimate of the breast cancer incidences, cumulative incidence competing risk-regression models were used[12]. These models determined the association between the patient and tumor characteristics and the event of interest in the same manner as the Cox models. The multivariable models adjusted for the treatments patients received. These are the models that were used to estimate the incidence of local, regional, and distant breast cancer recurrence.

All tests were 2-sided, and $P < 0.05$ were considered significant. Statistical analyses were done using the SAS software package (version 9.1.3, SAS Institute, Cary, NC).

RESULTS

Patient and Tumor Characteristics

ACOSOG Z0010 opened May 10, 1999, and completed accrual May 30, 2003, with 5539 patients enrolled from 126 participating sites. Of the 5119 eligible patients who had a SLN identified at surgery, 3904 (76.3%) had H&E-negative SLNs. A CONSORT diagram of the 3904 patients included in the current study is shown in Figure 1. Clinical and pathologic characteristics of the patients with H&E-negative SLNs are listed in Table 1. The median age was 57 years (range 23–95 years) and median follow-up of surviving patients was 8.4 years (range 0–12.4 years). The majority of the patients had invasive ductal histology (79.4%) with clinical T1 (87.6%) tumors that were hormone receptor-positive [estrogen receptor (ER) or progesterone receptor (PR) positive, 83.8%]. Lymphovascular space invasion was reported in 396 (11.6%) patients.

Surgical and Adjuvant Treatments

A summary of the surgical and adjuvant treatments received by the 3904 patients are listed in Table 2. All patients were planned for breast conserving surgery with SLN dissection followed by whole breast irradiation. There were 78 (2.0%) patients who underwent mastectomy as the final surgical procedure due to inability to obtain negative margins with breast conservation. There were 106 (2.7%) patients with H&E-negative SLNs who underwent ALND. Radiation treatment records were incomplete on 657 patients. Of the remaining patients, 2993 (92.2%) completed whole breast irradiation. There were 1432 (43.5%) patients who received adjuvant systemic chemotherapy and 2227 (67.7%) who received adjuvant hormonal therapy.

Local, Regional, and Distant Recurrences

At a median follow-up time of 8.4 years (range 0–12.4 years), there were 127 local, 20 regional, and 134 distant recurrences reported (Table 3). There were 317 deaths reported. We did not find a difference in local, regional, or distant recurrences in the patients with H&E-negative, IHC-negative SLNs compared with those who had H&E-negative, IHC-positive SLNs. The remaining analyses report on local–regional recurrence, distant recurrence, and overall survival for the entire population of patients with H&E-negative SLNs irrespective of IHC results. Clinical and pathologic factors were as-

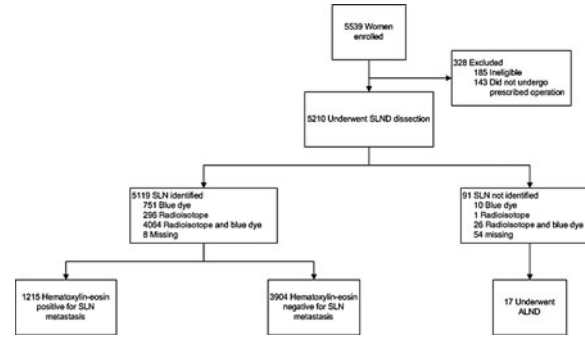

FIGURE 1. CONSORT diagram of study participants.

TABLE 1. Patient and Tumor Characteristics (N = 3904 Women)

Characteristic	
Age, yrs	
Median (min, max)	57 (23, 95)
≤50, n (%)	1030 (26.4)
>50, n (%)	2874 (73.6)
Tumor histology, n (%)	
Ductal	3094 (79.4)
Lobular	319 (8.2)
Both	97 (2.5)
Other	389 (10.0)
Missing, n	5
LVI, n (%)	
Absent	3024 (88.4)
Present	396 (11.6)
Missing, n	484
Tumor size, cm	
Median (min, max)	1.4 (0.0, 19.0)
≤1.0, n (%)	1597 (43.6)
1.1–2.0, n (%)	1609 (44.0)
>2.0, n (%)	455 (12.4)
Missing, n	243
Hormone receptor status, n (%)	
ER or PR positive	3084 (83.8)
Both negative	596 (16.2)
Missing, n	224
Clinical stage, n (%)	
T1	3206 (87.6)
T2	447 (12.2)
T3	8 (0.2)
Missing, n	243
Tumor grade, n (%)	
I	1225 (33.8)
II	1479 (40.8)
III	918 (25.4)
Missing, n	282

ER indicates estrogen receptor; PR, progesterone receptor; LVI, lymphovascular invasion.

TABLE 2. Summary of Treatments Patients Received (N = 3904 Women)

Treatment	
Surgery, n (%)	
BCT	3784 (98.0)
Mastectomy	78 (2.0)
Other surgery	1 (0.02)
Missing, n	41
Chemotherapy, n (%)	
Yes	1432 (43.5)
No	1857 (56.5)
Missing, n	615
Hormonal therapy, n (%)	
Yes	2227 (67.7)
No	1062 (32.3)
Missing, n	615
Radiation therapy, n (%)	
Yes	2993 (92.2)
No	254 (7.8)
Missing, n	657

BCT indicates breast conserving therapy.

TABLE 3. Summary of Patient Outcomes*

Outcome	No. Women	3-yr Cumulative Incidence	5-yr Cumulative Incidence
Local recurrence	127	0.013	0.024
Regional recurrence	20	0.003	0.005
Distant recurrence	134	0.017	0.028

*Median follow-up for patients who are alive is 8.4 years.

sessed in univariable and multivariable Cox models to predict local, local-regional, and distant recurrences and overall survival (Table 4). Although several factors were associated with local recurrence on univariable analysis, only older age [hazard ratio (HR) 0.98, 95% CI 0.96–1.00, $P = 0.018$] and positive hormone receptor status (HR 0.34, 95% CI 0.20–0.58), $P < 0.0001$) predicted for reduced local failure on multivariable analysis. Factors predicting for reduced local-regional recurrence events on multivariable analysis were older age (HR 0.98, 95% CI 0.96–1.00, $P = 0.047$) and positive hormone receptor status (HR 0.39, 95% CI 0.23–0.66, $P = 0.0004$). The presence of lymphovascular invasion (LVI) (HR 2.00, 95% CI 1.20–3.31, $P = 0.008$) and grade II (HR 2.44, 95% CI 1.31–4.56, $P = 0.005$) and grade III disease (HR 3.65, 95% CI 1.82–7.34, $P = 0003$) predicted for distant recurrences. There were 317 deaths in this patient group. Factors predicting for reduced overall survival on multivariable analysis were older age (HR 1.07, 95% CI 1.06–1.08, $P < 0.0001$), increasing tumor size (HR 1.18, 95% CI 1.07–1.31, $P = 0.0013$), and grade III disease (HR 2.65, 95% CI 1.77–3.96, $P < 0.0001$).

Clinical Outcomes Using Competing Risk-Regression Models

Because patients were followed for breast cancer recurrence only until the first recurrence and because patients may die before having a breast cancer recurrence, competing risk models are more appropriate for ascertaining the incidence of the different types of breast cancer recurrence before death. Univariable and multivariable competing risk models are presented in Table 5 and the curves are presented in Figure 2. The competing risk models identified the same risk factors for local recurrence, local-regional recurrence, and distant recurrence as did the Cox time-to-event models, which did not account for competing risks. In addition, the competing risk-regression models revealed that use of chemotherapy predicted for reduced local (HR 0.58, 95% CI 0.35–0.95, $P = 0.030$) and local-regional (HR 0.60, 95% CI 0.37–0.97, $P = 0.0039$) recurrences. The 5-year incidence rates for local recurrence, regional recurrence, and distant recurrence were 2.4%, 0.5%, and 2.8%, respectively.

DISCUSSION

The use of SLN dissection in early-stage breast cancer patients has allowed hundreds of thousands of women to avoid the morbidity of ALND while still providing the anatomic staging information that has traditionally been important in determining prognosis and guiding treatment decisions. However, data from prospective registries and randomized trials have demonstrated that there is a false-negative rate with SLN dissection, even in experienced hands, ranging from 5% to as high as 10%. Several studies have reported low axillary failure rates after a negative SLN dissection, but the follow-up times have been relatively short. In the current study, we evaluated local-regional recurrence rates in women participating in the ACOSOG Z0010 trial that completed accrual in 2003. Of 3904 patients with H&E negative SLNs, only 127 local, 20 regional, and 134 distant recurrences were reported at a median follow-up time of 8.4 years. Clinicopathologic factors associated with local-regional recurrences

TABLE 4. Univariable and Multivariable Cox Models

	Univariable		Multivariable	
Local Recurrence	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age, yrs	0.97 (0.95–0.98)	<0.0001	0.98 (0.96–1.00)	0.018
Tumor size	1.13 (1.00–1.27)	0.042	1.03 (0.84–1.26)	0.79
Clinical stage				
T1	1.00 (ref)			—
T2	1.75 (1.13–2.72)	0.012	—	
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	1.62 (0.99–2.64)	0.056	1.47 (0.85–2.55)	0.17
Tumor grade				
I	1.00 (ref)			
II	1.41 (0.90–2.20)	0.14	1.11 (0.65–1.87)	0.71
III	2.69 (1.66–4.05)	<0.0001	1.31 (0.69–2.47)	0.41
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.32 (0.22–0.46)	<0.0001	0.34 (0.20–0.58)	<0.0001
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.42 (0.99–2.05)	0.056	0.64 (0.39–1.03)	0.068
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.45 (0.31–0.65)	<0.0001		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.89 (0.45–1.76)	0.74	0.83 (0.40–1.72)	0.62
Local-regional recurrence				
Age, yrs	0.97 (0.95–0.98)	<0.0001	0.98 (0.96–1.00)	0.047
Tumor size	1.14 (1.02–1.27)	0.017	1.04 (0.86–1.26)	0.66
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.90 (1.27–2.86)	0.002		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	1.82 (1.16–2.86)	0.010	1.62 (0.88–2.71)	0.062
Tumor grade				
I	1.00 (ref)			
II	1.37 (0.89–2.12)	0.15	1.03 (0.62–1.70)	0.91
III	2.68 (1.75–4.09)	<0.0001	1.42 (0.78–2.59)	0.26
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.33 (0.23–0.48)	<0.0001	0.39 (0.23–0.66)	0.0004
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.41 (1.00–2.00)	0.051	0.66 (0.42–1.05)	0.080
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.45 (0.32–0.64)	<0.0001		
Radiation therapy				
No	1.00 (ref)	0.67	1.00 (ref)	0.78
Yes	0.87 (0.46–1.66)		0.90 (0.44–1.86)	
Distant recurrence	**HR**	***P***	**HR**	***P***
Age, yrs	0.99 (0.97–1.00)	0.099	1.00 (0.98–1.02)	0.76
Tumor size	1.19 (1.09–1.30)	<0.0001	1.16 (1.00–1.35)	0.054
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.80 (1.17–2.76)	0.008		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	2.25 (1.46–3.49)	0.0003	2.00 (1.20–3.31)	0.008
Tumor Grade				
I	1.00 (ref)			
II	1.73 (1.10–2.74)	0.019	2.44 (1.31–4.56)	0.005
III	3.42 (2.18–5.36)	<0.0001	3.65 (1.82–7.34)	0.0003

(*continued*)

TABLE 4. (*Continued*)

Distant Recurrence	HR (95% CI)	*P*	HR (95% CI)	*P*
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.51 (0.34–0.76)	0.0009	1.11 (0.62–2.00)	0.73
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.69 (1.16–2.45)	0.006	1.02 (0.62–1.66)	0.95
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.72 (0.49–1.05)	0.08		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.54 (0.30–0.94)	0.029	0.57 (0.29–1.10)	0.094
Survival				
Age, yrs	1.06 (1.05–1.07)	<0.0001	1.07 (1.06–1.08)	<0.0001
Tumor size	1.14 (1.06–1.22)	0.0004	1.18 (1.07–1.31)	0.0013
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.78 (1.36–2.33)	<0.0001		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	1.60 (1.17–2.18)	0.003	1.27 (0.85–1.88)	0.24
Tumor Grade				
I	1.00 (ref)			
II	1.32 (1.00–1.74)	0.052	1.21 (0.85–1.73)	0.30
III	2.39 (1.81–3.15)	<0.0001	2.65 (1.77–3.96)	<0.0001
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.59 (0.45–0.77)	0.0001	0.96 (0.64–1.44)	0.86
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.86 (0.67–1.11)	0.24	0.91 (0.66–1.26)	0.56
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.64 (0.50–0.82)	0.0005		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.96 (0.60–1.53)	0.86	1.00 (0.56–1.72)	0.99
Local recurrence (time dependent)				
No	1.00 (ref)		1.00 (ref)	
Yes	4.90 (3.27–7.36)	<0.0001	6.73 (4.26–10.63)	<0.0001

HR indicates hazard ratio; LVI, lymphovascular invasion.

in patients with H&E-negative SLNs were hormone receptor-negative disease and younger age. When local recurrence was included in the model as a time-dependent variable, older age, T2 disease, high tumor grade, and local recurrence were associated with reduced overall survival. In addition, in competing risk-regression models, use of chemotherapy was associated with a reduction in local and local-regional recurrences.

Axillary failure rates have generally been reported in the range of 1% to 2% in patients with early-stage breast cancer treated with ALND. Similarly, the incidence of axillary recurrences following a negative SLN dissection have been low, typically less than 1%, although the median follow-up times have been shorter, on the order of 24 to 36 months. One exception is a Japanese study from Imoto et al,[13] where they found a 3.6% axillary recurrence rate at a median follow-up time of 52 months. Thirty years ago, Fisher et al observed in NSABP B-04 that the axillary first failure rate in patients randomized to no axillary dissection was only 50% of what would have been expected based on the incidence of nodal metastases in those randomized to axillary dissection, even in the absence of systemic therapy or radiotherapy[14]. More recently, data from the NSABP B-32 trial revealed no differences in regional failure rates at a mean follow-up time of 95.6 months between patients randomized to SLN dissection alone compared with those who underwent SLN dissection followed by completion ALND (0.7% vs 0.4%)[7]. These data would suggest that not all patients who have disease left behind in the axilla due to a false-negative SLN will manifest clinically relevant disease in terms of axillary nodal recurrence or death due to breast cancer. This is congruent with the recent findings from the ACOSOG Z0011 trial, where there was no difference in regional recurrences or disease-free or overall survival outcomes in patients with 1 or 2 positive SLNs whether they were randomized to undergo completion ALND or SLN dissection alone.[15,16] It is likely that some of the residual nodal disease in the axilla is eradicated by systemic adjuvant therapy or by treatment of the nodes through the tangential breast irradiation fields, and in some cases the disease may remain clinically dormant and not warrant aggressive therapies.

It has become increasingly clear that biologic factors other than tumor size and nodal status are important in prognosis and treatment decisions for breast cancer patients. Gene expression profiling has been shown to separate patients with similar anatomic stages

TABLE 5. Univariable and Multivariable Competing Risk Models

	Univariable		Multivariable	
Local Recurrence	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, yrs	0.96 (0.95–0.98)	<0.0001	0.98 (0.96–0.99)	0.020
Tumor size	1.13 (1.00–1.27)	0.045	0.99 (0.78–1.25)	0.93
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.68 (1.05–2.69)	0.031		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	1.60 (0.98–2.62)	0.062	1.33 (0.74–2.38)	0.34
Tumor grade				
I	1.00 (ref)		1.00 (ref)	
II	1.77 (1.06–2.94)	0.028	1.24 (0.70–2.16)	0.45
III	3.25 (1.96–5.39)	<0.0001	1.59 (0.81–3.12)	0.18
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.32 (0.22–0.46)	<0.0001	0.35 (0.20–0.62)	0.0003
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.43 (0.99–2.05)	0.054	0.58 (0.35–0.95)	0.030
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.45 (0.31–0.65)	<0.0001		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.89 (0.45–1.75)	0.73	0.78 (0.38–1.62)	0.51
Local-regional recurrence				
Age, yrs	0.97 (0.95–0.98)	<0.0001	0.98 (0.96–1.00)	0.049
Tumor size	1.14 (1.02–1.27)	0.019	1.01 (0.82–1.25)	0.91
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.87 (1.29–2.88)	0.005		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	1.80 (1.14–2.83)	0.011	1.49 (0.87–2.55)	0.14
Tumor grade				
I	1.00 (ref)		1.00 (ref)	
II	1.66 (1.02–2.69)	0.040	1.12 (0.66–1.91)	0.68
III	3.21 (1.99–5.16)	<0.0001	1.66 (0.88–3.13)	0.11
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.33 (0.23–0.48)	<0.0001	0.42 (0.24–0.71)	0.0014
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.42 (1.00–2.01)	0.049	0.60 (0.37–0.97)	0.0039
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.45 (0.32–0.64)	<0.0001		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.87 (0.45–1.65)	0.66	0.85 (0.41–1.76)	0.67
Distant recurrence	**HR**	***P***	**HR**	***P***
Age, yrs	0.99 (0.97–1.00)	0.083	0.99 (0.98–1.01)	0.57
Tumor size	1.19 (1.09–1.30)	<0.0001	1.16 (0.99–1.35)	0.064
Clinical stage				
T1	1.00 (ref)		—	—
T2	1.90 (1.22–2.97)	0.005		
LVI				
Absent	1.00 (ref)		1.00 (ref)	
Present	2.23 (1.44–3.45)	0.0003	2.03 (1.22–3.37)	0.0064
Tumor grade				
I	1.00 (ref)		1.00 (ref)	
II	2.00 (1.20–3.34)	0.0078	2.33 (1.22–4.42)	0.0099
III	3.92 (2.37–6.48)	<0.0001	3.43 (1.67–7.04)	0.0008

(*continued*)

TABLE 5. (*Continued*)

Distant Recurrence	HR (95% CI)	*P*	HR (95% CI)	*P*
Hormone receptor status				
Negative	1.00 (ref)		1.00 (ref)	
Positive	0.51 (0.35–0.76)	0.001	1.08 (0.60–1.96)	0.79
Chemotherapy				
No	1.00 (ref)		1.00 (ref)	
Yes	1.69 (1.16–2.46)	0.006	0.97 (0.59–1.59)	0.91
Hormonal therapy				
No	1.00 (ref)		—	—
Yes	0.72 (0.49–1.05)	0.087		
Radiation therapy				
No	1.00 (ref)		1.00 (ref)	
Yes	0.53 (0.30–0.93)	0.028	0.56 (0.29–1.08)	0.083

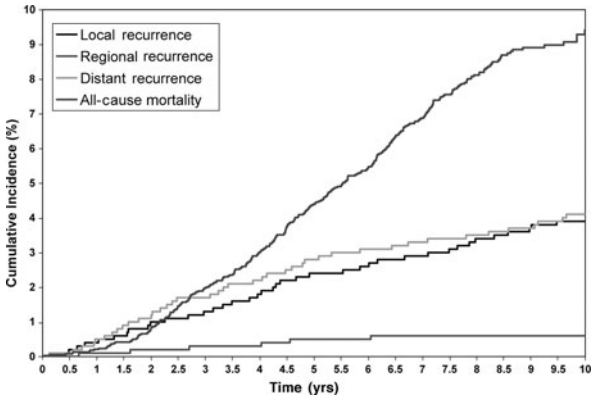

FIGURE 2. Cumulative incidence curves: local recurrence, local-regional recurrence, distant recurrence, and death.

and histologies into distinct subtypes that demonstrate differences in survival outcomes[17]. The molecular subtypes of breast cancer can be approximated through IHC staining for ER, PR, and human epidermal growth factor receptor 2 (HER-2). Nguyen and colleagues[18] have shown that these approximated subtypes are associated with differences in both local and distant recurrence after breast conserving therapy. Voduc et al[19] used an IHC panel to stain tissue microarrays and reported that the HER-2–enriched and triple receptor negative subtypes had an increased risk for local and regional recurrences in patients treated with breast conservation. However, a similar analysis of patients participating in the Danish Breast Cancer Group randomized trials of postmastectomy radiotherapy also showed an increased risk of chest wall recurrence in the triple-negative and HER2 overexpressing subgroups, and 2 recent retrospective comparisons of local recurrence rates in triple-negative breast cancers treated by mastectomy or breast conserving therapy demonstrated no differences between groups.[20–22] In aggregate, these findings indicate that negative ER status is a marker of biologically aggressive tumors, but not a selection factor for mastectomy.

The ACOSOG Z0010 trial was initiated in 1999 before routine HER-2 testing on all clinical breast cancer samples, and, therefore, we cannot approximate the molecular subtypes in this patient population. However, we did find that negative hormone receptor status was associated with higher local, regional, and distant recurrence rates and reduced overall survival. The triple receptor negative subtype has a higher recurrence rate than other subtypes, but it is also associated with a slightly lower nodal positivity rate overall[19]. This suggests that improved systemic therapies, as opposed to more aggressive use of ALND or mastectomy, would have a greater impact on survival outcomes.

The negative impact of higher tumor grade and LVI was evident in the Z0010 cohort in predicting for increased distant recurrence events, and grade III disease was associated with reduced overall survival. Rakha et al[23] recently showed that LVI was an independent predictor of breast cancer–specific survival and distant metastasis-free survival in their population of patients across all stage groupings and approximated molecular subtypes. Although the presence of LVI predicts for a higher rate of recurrences, it is not clear whether any specific local-regional or systemic treatment strategies are able to reduce this risk. Rakha and colleagues[24, 25] also found that grade was a strong predictor of outcome in patients and suggested that it be incorporated in a breast cancer staging system. Tumor grade is currently part of staging systems for prostate cancer, soft tissue sarcomas, and some bone tumors, and Wasif et al[26] recently made a case for incorporating grade into the AJCC (American Joint Committee on Cancer) staging system for pancreas cancer. Several groups have suggested that biologic factors such as ER status, tumor grade, and LVI be added to the AJCC staging system for breast cancer to provide improved prognostic information over what is currently available using anatomic staging with tumor size and nodal status[23, 27].

Although the 5-year local recurrence rate was only 2.4% in the Z0010 cohort, local recurrence was associated with reduced survival. The factors predicting for reduced local recurrence were older age and positive hormone receptor status. Use of adjuvant chemotherapy was not associated with a reduction in local recurrences in the standard Cox models but was statistically significant in the competing risk-regression models. There are now data from multiple studies demonstrating that systemic chemotherapy and hormonal therapy reduce local recurrences in women with breast cancer. We did not have complete radiation therapy records on all of the patients and therefore cannot be certain that omission of radiation in the adjuvant setting did not have an impact on local recurrence rates. The meta-analysis from the Early Breast Cancer Trialists' Collaborative Group has demonstrated that the addition of radiation therapy to the conserved breast reduces the in-breast recurrence rate by half, which in turn reduces deaths due to breast cancer by about one-sixth.[28]

We examined the 3904 patients with H&E-negative SLNs from the ACOSOG Z0010 trial to determine factors important in local-regional recurrence. These patients were intended for breast conserving surgery and whole breast irradiation with no axillary specific treatment. We found that regional nodal recurrences were rare and that hormone receptor–negative disease and younger age predicted for higher rates of local-regional recurrence. Older age, larger tumor size, grade III disease, and local recurrence were associated with

reduced overall survival. SLN dissection alone is safe and avoids the morbidity of ALND in early-stage breast cancer patients with H&E-negative SLNs.

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DISCUSSANT

DR. BARBARA BASS (Houston, TX): In breast cancer surgery, if the NSABP gave us the therapeutic innovation for the breast mound, the gift of the ACOSOG trials, to date, at least, as exemplified in this study and its counterpart Z0011, which we heard about last year, is to inform us about the axilla. This study reassures anyone practicing in this field, including me, that those early clinical judgments that we all made, which drove early adoption of sentinel lymph node axillary staging and early, occasionally angst ridden decisions to forego axillary dissection in patients with early stage breast cancer and minimal axillary nodal disease, those with immunohistochemistry-positive nodes and in transit cells, were correct. Before these data, we hoped to avoid axillary dissection because we knew the very real morbidity of that procedure for many patients. The importance of this study is that it confirms that those decisions for early adoption were spot on.

Regional recurrence is an exceedingly rare event in these sentinel lymph node patients; 0.5% at a median follow-up of 8.4 years in this study for women with negative sentinel lymph nodes. It practically suggests that the axilla, our current bedrock of decision making for staging, is, in fact, a hostile soil for tumor cells, compared to the breast and distant sites. Regional recurrence in this study cohort was so rare that only bundling local and regional recurrence events allowed multivariate analysis to identify two adverse prognostic indicators for local regional recurrence, lymphovascular invasion and hormone receptor negative disease; features that are obviously those of the primary tumor.

Can you tell us why you think that the axilla was practically immune from recurrence? Is this a feature of the tumor, the lymph node as a metastatic site, the metastatic process, or some other factor?

Clearly, those lymph nodes in that space are still there, but the tumor does go or grow there. Even local breast recurrences, or metastatic disease, occur ten times more frequently and are obviously subject to the same adjuvant modalities as the axilla. Why was the axilla spared?

The study also reveals that even in the pre-HER2/neu and pre-triple negative era, as this study was performed in, multidisciplinary adjuvant therapy provides excellent longevity and local regional recurrence for patients with early stage breast cancer undergoing breast conserving therapy.

One must conclude that it is those adjuvant therapies, radiation, systemic hormonal or chemotherapy, that are leading to these improved outcomes, not simply surgical removal of all tumor cells, for we know that we are leaving some behind. That leads me to my second question.

Given that our adjuvant treatment decisions for early breast cancer are now largely governed by the features of the primary tumor, multigene assessments, tumor markers, et cetera, how long will we need to surgically stage the clinically negative axilla, or the ultrasound-negative axilla, in patients with early stage breast cancer who are being treated with breast conserving therapy?

Do the results of this study, which further confirm that the axilla is not a high risk zone for occurrence, coupled to the Z0011 results that tells us that a little bit of nodal disease is A-OK, allow us to forego even sentinel lymph node staging of the axilla for some patients, and I do not just mean elderly women?

Do we have the equipoise to develop a trial to investigate that possibility? When, and for which patients, will we first give up surgical staging of the axilla?

CLOSING DISCUSSANT

DR. KELLY HUNT: In response to your first question, why is the axilla such an infrequent site of recurrence? I think partly we can look back at the NSABP B-04 trial that was done over 30 years ago. In patients with clinically negative nodes, they were randomized to undergo immediate axillary dissection, versus radiation of the axilla, versus no specific axillary treatment. While 40% of the patients who received immediate node dissection had positive nodes, only about 20% of patients who received no specific axillary treatment eventually developed clinically evident disease in the axilla requiring delayed dissection. So, 40% would have been expected to have positive nodes at presentation but only about 20% of patients who did not get any axillary treatment eventually required node dissection.

That was before the standard use of adjuvant therapy, suggesting that some of that nodal disease that we find is not clinically relevant, and does not require any treatment. But with sentinel lymph node surgery, the more we look, the more we find, and when we find these micrometastases, the bias is to treat them.

Certainly, now with improved adjuvant therapies, chemotherapy, endocrine therapy, and radiation therapy, we are eradicating disease with those methods of treatment, and we know this from neoadjuvant trials as well. So, some of the studies that we have done at MD Anderson, where patients received fine needle aspiration biopsy to prove the presence of disease in the regional nodes before chemotherapy, after chemotherapy, about 25% of those patients will have complete eradication of all disease in the nodes.

We know that the chemotherapy is more effective, and now that we understand more about the subtypes, we have seen than in HER2-positive disease, we are eradicating about 75% of the disease in the regional nodes. Our systemic treatments are better, but also, I think there are some nodal metastases that are not clinically or biologically relevant.

In answer to your second question, how long do we continue to stage the axilla, and that is a great question, Armando Giuliano and others, as part of the new Alliance for Clinical Trials in Oncology, have now proposed a trial to randomize patients with early-stage breast cancer to sentinel lymph node surgery versus no treatment of the axilla.

This is based on the fact that we know that different biologic subtypes have very different local and regional recurrence patterns, which some of the data from Z0010 shows as well. So, when we see patients with triple-receptor-negative breast cancer or HER2-positive breast cancer, we already know how we will treat them with systemic therapy; performing the staging of the axilla with sentinel lymph node surgery probably has no impact on their outcomes. We are actually in the process of developing that trial now.

DISCUSSANT

DR. COURTNEY M. TOWNSEND (Galveston, TX): In the patients with local recurrence who subsequently died of metastatic disease, were the local recurrences just the first appearance of systemic disease, or were they truly isolated local recurrences?

CLOSING DISCUSSANT

DR. KELLY HUNT: It is a little bit difficult to assess whether these are isolated occurrences or not, because, typically, for patients who are assessed in follow-up, once they developed a local recurrence, they were no longer followed for subsequent recurrences, either regional or distant. The same is true if they experienced a distant recurrence first, or if they experienced a local and distant recurrence at the same time.

Overall, what we can see from this patient population of clinical T1 and T2 breast cancers, even in the setting of micrometastases identified on IHC, is that the local failure rate was only 2.4% at five years, which is exceedingly small. I think our efforts at breast-conserving surgery are much improved from when I first started practice, where we would tell our patients there was a local recurrence rate in the breast of somewhere between 8% and 10%. It is now actually very rare to see a local recurrence, and we know that endocrine therapy and systemic chemotherapy both decrease local failure rates as well.