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Risk of positive non-sentinel nodes in women with 1–2 positive sentinel nodes related to age and molecular subtype approximated by receptor status

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Abstract

Purpose—We examine risk of positive nonsentinel axillary nodes (NSN) and 4 positive nodes in patients with 1–2 positive sentinel nodes (SN) by age and tumor subtype approximated by ER, PR, and Her2 receptor status.

Materials and methods—Review of two institutional databases demonstrated 284 women undergoing breast conservation between 1997–2008 for T1-2 tumors and 1 (229) or 2 (55) positive SN followed by completion dissection.

Results—The median number of SN and total axillary nodes removed were 2 (range 1–10) and 14 (range 6–37), respectively. The rate of positive NSNs ($p=0.5$) or 4 positive nodes ($p=0.6$) was not associated with age. NSN were positive in 36% of luminal A, 26% of luminal B, 21% of TN and 38% of Her 2+ ($p=0.4$). Four or more nodes were present in 17% of luminal A, 13% luminal of B, 0% of TN and 29% of Her2+ ($p=0.1$). Microscopic extracapsular extension was significantly associated with having NSNs positive (55% vs. 24%, $p<0.0001$) and with having total 4 nodes positive (33% vs. 7%, $p<0.0001$).

Conclusions—In a population that was largely eligible for ACOSOG Z0011, the risk of positive NSN or 4 positive nodes did not vary significantly by age. The TN subgroup had the lowest risk of both positive NSN or 4 positive nodes. Several high risk groups with >15% risk for having 4 positive nodes were identified. Further data is needed to confirm that ACOSOG Z0011 results are equally applicable to all molecular phenotypes.

Keywords

Breast cancer; Sentinel Node Biopsy; Axillary Lymph Nodes; Molecular Subtype; Receptor Status

Introduction

The axillary lymph node dissection has been a part of the standard of care of early stage breast cancer for decades. A level I/II axillary dissection once provided crucial diagnostic information about whether or not the axilla was node positive, and how many lymph nodes were positive. This information would guide decisions about use of systemic therapy or radiation therapy. Specifically for radiation treatment decisions, knowing whether a patient had one positive node or four or more positive nodes could influence choice of radiation fields and whether to cover the supraclavicular and high axillary nodes or the breast alone. In addition, a level I/II axillary dissection was also highly effective in securing regional control against axillary node recurrence.

Sentinel node (SN) biopsy was originally introduced into the management of early stage breast cancer in order to spare node-negative women the more extensive operative procedure and long-term morbidity of a level I/II axillary dissection. If negative, a completion axillary dissection could be avoided with 98% accuracy. If positive, a completion axillary dissection could be done either at the time of sentinel node biopsy or a later completion axillary dissection.

The risk of non-sentinel node (NSN) positivity became of greater interest in the past decade for situations where a patient may have refused, or have had contraindications to, a completion axillary dissection after a positive SN biopsy. In those patients, prediction of a high risk for positive NSN may have been an indication for addition of regional node irradiation. There have been a number of studies that examined the incidence of positive NSN after a completion dissection because of a positive SN biopsy. These demonstrated that the risk of positive NSN was related to a number of factors: the primary tumor size (1–3), SN metastasis size (micrometastasis versus macrometastasis) (1, 2, 4), Method of SN detection (IHC versus H&E)(1, 3), lymphovascular invasion (1–3), extranodal extension (1), number of positive SN (2, 4), and number of negative nonsentinel nodes (4). Using combinations of these and other factors, 9 models have been developed that predict the risk of NSN positivity after a positive SN biopsy (5). The MSKCC nomogram, found to be one of the most accurate by Coutant et al (5), uses primary tumor size, method of SN detection, presence of LVI, histology, grade, multifocality, ER status, use of frozen section, and number of positive SN and number of negative SN (6). Similarly, factors have been studied that are associated with having four or more positive nodes on completion dissection after a positive SN biopsy. These factors have included tumor size (7), no drainage detected with

isotope (8), number of positive SN (7–9), proportion of positive SN (7), LVI (8, 9), size of SN metastases (9), and lobular histology (9).

Breast tumors of different gene expression profiles have been identified that are associated with different clinical behaviors. These different classes of tumors can be roughly distinguished in clinical practice by expression of ER, PR and HER2 receptor testing. Luminal A and B subtypes are associated with positive ER. ER negative tumors are divided into those positive for HER-2, or those of ‘basal-like’ expression associated with low to absent ER, PR and HER2 receptor expression (10). Studies have not agreed upon whether molecular subtype does (11, 12) or does not (13–15) affect regional node positivity, and does (12, 14) or does not (13, 15) affect local-regional control. Out of all of the models for prediction of NSN positivity, or 4 or more positive nodes, none of the models incorporated the use of molecular subtypes. Only the model from the Mayo Clinic incorporated patient age (16). It is therefore unknown whether molecular subtype or patient age should be used in the clinic in order to assess who needs a completion axillary dissection after a positive SN biopsy. This may be particularly important for patients meeting criteria for the ACOSOG Z0011 study that randomized patients to completion dissection after breast-conserving surgery and positive SN biopsy (17, 18). These results are being used routinely now to justify omission of the completion dissection, even in women who have a high risk of positive NSN by the models discussed above. However, the results of the study may not extend to all patients, as higher risk subgroups based on age or unfavorable molecular subtype may have been underrepresented and thus were not separately analyzed.

The purpose of this study was to examine a series of patients from two institutions treated by sentinel node biopsy and completion axillary dissection. We wished to determine the risk of positive NSN and the risk of 4 positive nodes in patients with 1–2 positive sentinel nodes (SN) stratified by age and tumor subtype because of the potential implications to the ACOSOG Z0011 paradigm which did not take phenotype into account.

Study Population and Methods

The study population consisted of 284 women treated for breast cancer at the University of California, San Francisco CA, or the Fox Chase Cancer Center, Philadelphia, PA, between 1997 and 2008. These patients’ data was routinely prospectively collected and then available for retrospective review. The protocol for patient collection, storage and abstracting of data was Institutional Review Board approved at both institutions. All patients underwent breast-conserving surgery and SN biopsy. Inclusion criteria were histologically confirmed T1 or T2 invasive carcinomas of the breast. All patients had 1 (229 patients) or 2 (55 patients) positive sentinel nodes. A positive sentinel node was defined as the presence of carcinoma on H&E staining irrespective of IHC findings; IHC staining alone was not considered positive. Patients were excluded if they had gross extracapsular extension (ECE), neoadjuvant therapy, mastectomy, 3 or more SN positive, SN biopsy that was negative, or a positive SN biopsy but no completion dissection. Patients having microscopic extracapsular extension were included, despite their possible exclusion in Z0011 (see discussion), because of the lack of information regarding phenotype and ECE in the same population.

The primary study endpoints were risk of NSN positivity related to age, molecular subtype, number of positive sentinel nodes, LVI and microscopic ECE. Differences between subgroups were compared using the Chi square test. The patients were divided in to molecular subtypes defined as luminal A (ER+ and/or PR+, Her2-), luminal B (ER+ and/or PR+, Her2+), triple negative (ER, PR and Her2-), and Her-2+ (ER and PR -, Her2+).

Results

The patient characteristics relevant to the study primary endpoints are shown in Table 1. Median age was 55 years (range 25–87). The median number of SN removed and total axillary nodes removed were 2 (range 1–10) and 14 (range 6–37), respectively. The median number of total positive axillary nodes was 1 (range 1–36). 66% of tumors were luminal A (ER+ and/or PR+, Her2-), 13% luminal B (ER+ and/or PR+, Her2+), 7% triple negative (TN), and 5% Her-2+ (ER and PR -, Her2+).

The incidence of positive NSN and 4 nodes positive by decade of age at diagnosis is shown in figure 1. NSN were positive in 29% of patients age 40 years, 37% 41–50, 36% 51–60, and 29% > 60 years ($p=0.5$). Four or more nodes were positive in 12% of patients age 40 years, 16% of those 41–50, 20% of those 51–60, and 12% of those > 60 yrs ($p=0.6$).

The median pathologic tumor size was 1.8 cm for luminal A, 2 cm for luminal B, 1.7 cm for TN and 1.9 cm for Her-2 +, respectively ($p=0.28$). The incidence of positive NSN and 4 nodes positive by molecular subtype is shown in Figure 1. NSN were positive in 36% of luminal A, 26% of luminal B, 21% of TN and 38% of Her 2+ ($p=0.4$). The mean total number of positive axillary nodes by subtype was 2.6 luminal A, 2.2 luminal B, 1.6 TN, 3.1 Her-2+ ($p=0.6$). 4+ nodes were present in 17% luminal A, 13% luminal B, 0% TN and 29% Her2+ ($p=0.1$).

Table 1 shows further subgroup analysis of NSN positivity and 4 nodes positive by molecular subtype. There was no significant difference in either endpoint for patients with 1 positive or 2 positive SN. However, those with triple receptor negative breast cancer had the lowest risk of positive NSN (approximately 20%) and 4 or more positive nodes (0%). In the subgroup analysis stratified by tumor size, the highest prevalence of 4 or more positive nodes was seen in T1 tumors with Her-2 positive subtype (38% compared to 0–11% in the other subtypes; $p=0.03$).

NSN were positive in 42% of patients with LVI compared to 30% without LVI, however, there was no significant variation in LVI between the different molecular subgroups. ECE was significantly associated with having a positive NSN (55% vs. 24%, $p<0.0001$) and with having total 4 nodes positive (33% vs. 7%, $p<0.0001$). Patients with ECE and Her-2 positive disease had an 80% risk of 4 or more positive compared with 56% of luminal B, 29% of luminal A, and 0% of TN ($p=0.02$). Among ECE negative patients, the risk of positive NSNs was 33% for Her-2 and 32% for luminal A, versus 4% for luminal B and 0% for TN ($p=0.01$).

We identified several important subgroups with a high risk of having 4 positive nodes. These included the following patients: Her-2+ with ECE; luminal A with 2+ SN, T2, LVI, or ECE; and luminal B with 2+ SN, T2, or ECE, all of which had >15% risk of 4 positive nodes. In the triple negative subgroup, there were no patients with 4 positive nodes.

Discussion

With the publication of the ACOSOG Z0011, one could question the clinical relevance of the various nomograms or studies predicting the risk of positive NSN after a positive SN biopsy. The Z0011 study was a randomized trial of completion axillary dissection versus SN biopsy only for patients with early stage breast cancer and a positive SN biopsy. Women with T1-2 breast cancers, clinically axillary node negative, treated by breast-conserving surgery, with 1–2 positive SN metastases (hematoxylin-eosin detected) were eligible for this trial (17, 18). Only matted nodes or gross ECE at the time of sentinel node biopsy was excluded according to the published eligibility criteria (17, 18). Since not all patients had frozen section analysis of nodes, the trial assumed that a surgeon was able to detect ECE grossly in the operating room. In the analysis of treatment received, 55% had macrometastasis and it is quite possible that some of these patients had microscopic ECE. Microscopic ECE detected later during pathologic examination did not remove women from that trial so was included in our analysis.

In the Z0011 trial, women randomized to completion axillary dissection (ALND) had a 27% risk of positive NSN and 14% risk of 4 or more positive nodes (17). Local-regional recurrence-free survival was 96.7% without ALND and 95.7% with ALND at 5 years. Regional node recurrences were 0.9% in those randomized to sentinel node biopsy (SNB) only and 0.5% in those randomized to ALND. Based on these results one could argue against ALND or regional node irradiation in these women. Also, the use of nomograms predicting the incidence of positive NSN would seem of little clinical value in light of these results – even with 30% rates of NSN positivity, there was no impact on clinical outcome. However, it should be noted that 64% of the patients in this trial were > 50 years of age, 71% had T1 tumors and 83% were ER (+), and 40% had micrometastases. Systemic therapy was given to > 95% of the patients. Higher risk groups such as young age, hormone receptor negative or TN were underrepresented. The results, therefore, are applicable to a select group of women and might not apply to all women with 1–2 positive sentinel nodes. It is possible that in women with a higher axillary tumor burden, regional nodal recurrences could exceed the low rate seen in the Z0011 trial without affecting mortality. Regional node recurrences can be associated with significant morbidity and be difficult to salvage. Therefore, the use of nomograms to predict patients that have a much higher rate of positive NSN or 4 or more positive nodes than seen in the Z0011 study may still be of clinical value. Further investigation is warranted to define a group of women who are at risk for high regional node tumor burden and may benefit from ALND and/or regional node irradiation either in terms of regional control or breast cancer survival.

Our study is unique in that it examined the rate of positive non-sentinel nodes and the risk of 4 positive nodes in patients with 1–2 positive nodes at sentinel lymphadenectomy. The results were stratified by age and breast cancer subtype. We demonstrated that some

subgroups of these patients have a much higher risk of additional axillary node involvement than the levels seen in ACOSOG Z0011. Patients with luminal A or B, or Her-2 positive breast cancers had a 50% or higher risk of having a positive NSN, and a higher than average chance of having 4 positive nodes, especially when extracapsular extension was present. In contrast, although not statistically significant, we saw a trend that the patients with triple receptor negative breast cancer have the lowest risk of positive NSN and lowest risk of having four or more positive axillary nodes. Our findings support the clinical studies published that have not shown a link to triple negative patients and higher risk of regional node positivity (13–15).

Estimating the risk of the residual disease burden in the axilla impacts on decisions for ALND and the design of the radiation treatment fields. Omission of the apical axillary/supraclavicular field in women with 4 positive nodes has been associated with supraclavicular recurrence rates of 15% (19). Haffty et al (20) suggest adding treatment to this region when the risk of 4 positive node exceeds 30%. While radiation has been demonstrated to control microscopic regional node disease, it is less likely to do so in the presence of gross nodal disease (21). It is unknown at the present time as to what volume of residual disease in the axilla is better controlled with ALND as opposed to radiation. Predicting the probability of additional disease in the axilla will become even more important as many of these patients may not receive radiation.

Conclusion

In this population of patients who fulfilled eligibility criteria for ACOSOG Z0011, the risk of positive NSN or the risk of 4 positive nodes did not differ significantly by age. Of note, the triple negative subgroup had the lowest risk of the four subtypes. Molecular subtype when combined with additional pathologic factors predicted a >15% risk for having 4 positive nodes in patients with Her-2+; other high risk groups included those with T2 luminal A or B tumors with ECE. Further data are needed to confirm that the conclusions of the ACOSOG Z0011 are equally applicable to all molecular subtypes of breast cancer, and omission of completion ALND should be considered with caution in these high risk subgroups.

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References

1. Turner RR, Chu KU, Qi K, et al. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. *Cancer*. 2000; 89:574–581. [PubMed: 10931456]
2. Sachdev U, Murphy K, Derzie A, et al. Predictors of nonsentinel lymph node metastasis in breast cancer patients. *American Journal of Surgery*. 2002; 183:213–217. [PubMed: 11943113]
3. Houvenaeghel G, Nos C, Mignotte H, et al. Micrometastases in sentinel lymph node in a multicentric study: predictive factors of nonsentinel lymph node involvement--Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. *J Clin Oncol*. 2006; 24:1814–1822. [PubMed: 16567771]

4. Sanjuan A, Escaramis G, Vidal-Sicart S, et al. Predicting non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement: evaluation of two scoring systems. *Breast J*. 2010; 16:134–140. [PubMed: 20136644]
5. Coutant C, Olivier C, Lambaudie E, et al. Comparison of models to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a prospective multicenter study. *J Clin Oncol*. 2009; 27:2800–2808. [PubMed: 19349546]
6. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol*. 2003; 10:1140–1151. [PubMed: 14654469]
7. Chagpar AB, Scoggins CR, Martin RC 2nd, et al. Predicting patients at low probability of requiring postmastectomy radiation therapy. *Ann Surg Oncol*. 2007; 14:670–677. [PubMed: 17096055]
8. Shahar KH, Hunt KK, Thames HD, et al. Factors predictive of having four or more positive axillary lymph nodes in patients with positive sentinel lymph nodes: implications for selection of radiation fields. *Int J Radiat Oncol Biol Phys*. 2004; 59:1074–1079. [PubMed: 15234041]
9. Katz A, Niemierko A, Gage I, et al. Factors associated with involvement of four or more axillary nodes for sentinel lymph node-positive patients. *Int J Radiat Oncol Biol Phys*. 2006; 65:40–44. [PubMed: 16488555]
10. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and Clinical Characterization of the Basal-Like Subtype of Invasive Breast Carcinoma. *Clin Cancer Res*. 2004; 10:5367–5374. [PubMed: 15328174]
11. Kyndi M, Sørensen FB, Knudsen H, et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group. *J Clin Oncol*. 2008; 26:1419–1426. [PubMed: 18285604]
12. Hattangadi-Gluth JA, Wo JY, Nguyen PL, et al. Basal subtype of invasive breast cancer is associated with a higher risk of true recurrence after conventional breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. 2012; 82:1185–1191. [PubMed: 21601377]
13. Haffty BG, Yang Q, Reiss M, et al. Locoregional Relapse and Distant Metastasis in Conservatively Managed Triple Negative Early-Stage Breast Cancer. *J Clin Oncol*. 2006; 24:5652–5657. [PubMed: 17116942]
14. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol*. 2008; 26:2373–2378. [PubMed: 18413639]
15. Freedman GM, Anderson PR, Li T, et al. Locoregional recurrence of triple-negative breast cancer after breast-conserving surgery and radiation. *Cancer*. 2009; 115:946–951. [PubMed: 19156929]
16. Degnim AC, Reynolds C, Pantvaitya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. *American Journal of Surgery*. 2005; 190:543–550. [PubMed: 16164917]
17. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011; 305:569–575.
18. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010; 252:426–432. discussion 432–423. [PubMed: 20739842]
19. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005; 63:1508–1513. [PubMed: 16169678]
20. Haffty BG, Hunt KK, Harris JR, et al. Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. *J Clin Oncol*. 2011; 29:4479–4481. [PubMed: 22042942]
21. Fisher B, Montague E, Redmond C, et al. Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. *Cancer*. 1980; 46:1–13. [PubMed: 6992972]

Short Summary

Patients with 1 or 2 positive sentinel nodes and completion dissection from two institutions were examined for incidence of non-sentinel nodes (NSN) and 4 positive nodes. Factors associated with a higher risk of 4 positive nodes were Her-2+, 2 positive sentinel nodes, T2 size, and microscopic extranodal extension but not age. More data is needed to determine whether the ACOSOG Z0011 results will apply in these higher risk subgroups.

FIGURE 1.
Percent of patients with NSN + or ≥ 4 nodes + by age and molecular subtype

Table 1

Characteristics of study patients (n=284).

Number of Patients	(n)	%
Age (years)		
Median	55	
Range	25 – 87	
40	17	6
41 – 50	86	30
51 – 60	79	28
> 60	102	36
Tumor size		
T1	166	59
T2	92	32
Unknown	26	9
Sentinel nodes positive		
1	229	81
2	55	19
Sentinel nodes removed		
Median	2	
Range	1 – 10	
Total axillary nodes positive		
Median	1	
Range	1 – 36	
Total axillary nodes removed		
Median	14	
Range	6 – 37	
Subtype		
Luminal A = ER + or PR + and HER2 –	187	66
Luminal B = ER + or PR + and HER2 +	38	13
Triple – = ER – and PR – and HER2 –	19	7
HER2 + = ER – and PR – and HER2 +	14	5
Unknown	26	9
Extranodal Extension		
Positive	88	31
Negative	116	41
Unknown	80	28
Lymphovascular Invasion		
Positive	96	34

Number of Patients	(n)	%
Negative	133	47
Unknown	55	19

Table 2

Percent of patients with NSN + / total 4 nodes +, by number of positive SN, tumor size, lymphovascular invasion (LVI), and extracapsular extension (ECE) (n=284).

	LUM A	LUM B	TN	Her2+	p
1+SN	N=149	N=34	N=14	N=10	
%NSN+	31	24	21	40	0.7
%>=4+ nodes	10	12	0	30	0.2
2+SN	N=38	N=5	N=5	N=3	
%NSN+	58	40	20	33	0.4
%>=4+ nodes	42	20	0	33	0.3
T1	N=123	N=21	N=14	N=8	
%NSN+	29	19	14	38	0.46
%>=4+ nodes	11	5	0	38	0.03
T2	N=64	N=17	N=5	N=6	
%NSN+	50	35	40	33	0.65
%>=4+ nodes	28	24	0	17	0.52
LVI+	N=63	N=16	N=5	N=4	
%NSN+	51	19	20	25	0.07
%>=4+ nodes	24	13	0	25	0.05
LVI-	N=90	N=20	N=7	N=3	
%NSN+	30	30	14	67	0.7
%>=4+ nodes	14	15	0	33	0.7
ECE+	N=58	N=9	N=5	N=5	
%NSN+	48	78	60	80	0.24
%>=4+ nodes	29	56	0	80	0.02
ECE-	N=75	N=23	N=11	N=3	
%NSN+	32	4	0	33	0.01
%>=4+ nodes	9	0	0	0	0.29