Published in final edited form as:
J Surg Res. 2012 September ; 177(1): e21–e26. doi:10.1016/j.jss.2012.03.015.

Utilization of Lymph Node Assessment in Patients with Ductal Carcinoma In Situ Treated with Lumpectomy

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Abstract

Background—Lymph node assessment (LNA), including sentinel lymph node biopsy (SLNB), is controversial in patients undergoing lumpectomy for ductal carcinoma in situ (DCIS). Our goal was to identify factors influencing LNA in these patients.

Methods—We used the Surveillance Epidemiology and End Results database to identify all female patients treated with lumpectomy for DCIS from 2000–2008. We excluded patients without histologic confirmation, including those diagnosed at autopsy, and those for whom LNA status was unknown. Multivariate logistic regression models predicted use of LNA. Likelihood of undergoing LNA was reported as odds ratios (OR) with 95% confidence intervals (CI.

Results—A total of 62,935 patients met inclusion criteria. Approximately 15% (N = 9726) had regional LNA at the time of lumpectomy, with 12% (N =7294) undergoing SLNB. Factors associated with an increased likelihood of undergoing LNA included treatment in the Southeast (OR 1.25, CI−1.04–1.22), treatment after the year 2000, grade II (OR 2.71, CI 2.48–2.96), III (OR 2.38, CI 2.18–2.59), or IV (OR 2.61, CI 2.37–2.88) tumors, DCIS size 2–5 cm (OR 1.49, CI −1.37–1.62) or > 5 cm (OR 2.16, CI−1.78–2.61), and ER negative (OR 1.29, CI−1.16–1.43) or PR negative (OR 1.22, CI 1.11–1.33) tumors. Factors associated with a decreased likelihood of undergoing regional LNA were age > 60 (OR 0.83, CI −0.79–0.87), and Asian (OR 0.88, CI 0.81–0.96) race. Factors predictive of LNA in general were also predictive of SLNB.

Conclusion—Although LNA is controversial for patients undergoing lumpectomy for DCIS, it is utilized in 15% of cases. Further research establishing for the benefit of LNA in DCIS patients treated with lumpectomy is needed.

Keywords

sentinel lymph node biopsy; ductal carcinoma in situ; SEER; lymph node assessment; lumpectomy

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Presented in part at the Seventh Annual Academic Surgical Congress, Las Vegas, NV, February 14–16, 2012.

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Introduction

Lymph node assessment (LNA), including sentinel lymph node biopsy (SLNB), is controversial among patients undergoing lumpectomy for the treatment of ductal carcinoma *in situ* (DCIS). While opponents argue that DCIS has no potential to metastasize to regional lymph nodes, proponents of LNA counter that sampling error and missed underlying invasion may necessitate additional surgery for lymph node staging; at definitive surgery, DCIS may be upstaged to invasive carcinoma in 10% to 38% of cases(1–5). Even among patients with pure DCIS without evidence of invasion, sentinel node metastases may be found in 1% to 7%, although their oncologic significance is unknown (6, 7).

Recognizing the importance of invasion risk assessment on the use of LNA, the American Society of Clinical Oncology (ASCO) established guidelines for the use of SLNB in cases of DCIS in 2005 (8). The guidelines specifically do not recommend the routine use of SLNB for DCIS patients undergoing lumpectomy, but instead suggest SLNB for DCIS lesions > 5 cm or those associated with suspected or proven microinvasion.

We sought to determine how frequently LNA, particularly SLNB, is used among women undergoing lumpectomy for DCIS and to identify specific patient, tumor, and geographic factors that influence the use of LNA in these patients using a national, population-based database.

Methods

We used the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database to identify all women undergoing lumpectomy for the treatment of DCIS from 2000 to 2008. We identified patients as having undergone LNA if one or more lymph nodes were removed and examined. Patients were only identified as having had a SLNB if it was specifically stated or coded under one of two field categories. We excluded patients without histologic confirmation, including those diagnosed at autopsy, and those for whom the status of nodal assessment was unknown. All size measurements reported represent that of the primary tumor *in situ* component.

We used multivariate logistic regression to evaluate the relationship between tumor- and patient-related factors on the likelihood of undergoing LNA. Covariates evaluated included age (≤ 60, older than 60), race (white, black, Asian, Hispanic, native American, other), year of diagnosis (2000–2008), grade (I, II, III, IV, unknown), size of DCIS (< 2 cm, 2–5 cm,> 5 cm, unknown), estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, borderline, unknown), and regional location (West, Midwest, Northeast, Southeast). Likelihood of undergoing LNA was reported as odds ratios (OR) with 95% confidence intervals (CI).

Since information in the SEER registry contains de-identified patient data, this study was exempt from institutional review board approval.

Results

Table 1 depicts the patient- and tumor-related characteristics of the cohort. Briefly, a total of 62,935 patients met inclusion criteria. The mean age was 60 years, with most of these being white women (75%) residing in areas reporting to Western or Northeastern SEER registries (77%). Approximately 15% (N = 9726) of patients had a regional LNA at the time of lumpectomy, with 75% (N = 7294) of these being a SLNB. Tumor grade was unknown for 19% of patients. Of those patients for whom tumor grade was known, 69% had grade II or III tumors. A majority of patients (59%) did not have complete data on the size of their

DCIS focus. Among patients for whom the size of the DCIS was known, 84% had areas of DCIS less than 2 cm. By contrast, 2% had DCIS greater than 5 cm. Only 4% of all patients who underwent LNA or SLNB had DCIS measuring ≥ 5 cm. In general, DCIS is regarded as being hormone receptor positive. As such, it was not tested and therefore unknown in the majority (58–61%) of patients.

From 2000 to 2008, the rate of LNA and SLNB increased without an associated increase in the use of lumpectomy for DCIS **(see** Figure 1). LNA increased from 10% to 20% of all cases of DCIS treated with lumpectomy from the year 2000 to 2008. Over the same time period, use of SLNB increased from 5% to 16% of all lumpectomy cases.

Tables 2 depicts the results of multivariate logistic regression models assessing the likelihood of undergoing LNA or SLNB. An increased likelihood of undergoing a LNA or SLNB was associated with the following factors: year of diagnosis, advancing or unknown tumor grade, increasing size of DCIS, southeast geography, and negative ER and PR status. Age greater than 60 and Asian race/ethnicity were the only factors associated with a decreased likelihood of undergoing regional LNA and SLNB.

Discussion

Despite a paucity of evidence indicating a benefit, approximately 15% of women in our study underwent LNA at the time of lumpectomy for DCIS. We identified several factors that increase the likelihood of receiving a LNA. Many of these, such as increasing DCIS size, advancing tumor grade, negative hormone receptor status, and younger age reflect risk factors of underlying invasive carcinoma (2, 4, 9, 10). In particular, size of the DCIS component has been identified by the ASCO as a factor that may influence the use of a LNA, particularly SLNB. These guidelines allow for the use of LNA for DCIS foci greater than 5 cm in size. In our current series, however, only 1% of patients satisfied this criterion.

Potential risk factors for occult invasive carcinoma which we did not or could not identify from SEER data include the presence of comedo necrosis (11), microinvasion (2, 12) and palpable disease. Although these factors remain relatively rare, they are not without clinical significance. Schroen et al (13) surveyed and analyzed data from 459 American College of Surgeons members regarding their use of SLNB for DCIS. Overall, 79% of surgeons reported offering SLNB to patients with DCIS. When asked about factors influencing their decision to perform a SLNB for DCIS 84% reported the presence of microinvasion, 55% cited palpable disease, and 38% comedo necrosis.

Interestingly, our study noted age-related, racial, and regional disparities in use of LNA and SLNB. Several studies have documented age-related disparities in all treatment modalities for breast cancer(14, 15), including LNA and SLNB (16), independent of medical co-morbidities. While these previous studies demonstrated age-based disparities in treatment, these were most commonly noted among the most elderly subgroups. By contrast, we observed disparities in patients as young as 60 years old. Lack of access to Medicare insurance in the 60–65 year old subgroup may partially account for these disparities (17). However, Mandelblatt et al. demonstrated that patient-perceived ageism by their physician may also account for these differences (14). Other large epidemiological studies have demonstrated that racial/ethnic minorities, especially blacks, are less likely to undergo SLNB for early stage breast cancer (16–18). In our current study, both blacks and Asians were less likely to undergo SLNB compared to whites. While the scope of our study is limited in its ability to account for such differences, this disparity may be independent of socioeconomic status, and tumor characteristics (16). Regional disparities in treatment may also represent time-related shifting in geographic distributions of underserved, minority women that are less likely to receive standard of care. For example, in 2005, Southern women were less likely to receive SLNB as standard of care for breast cancer than Southern women in 1998 (18). In our study, they were more likely to undergo controversial LNA and SLNB for DCIS .

We also noted an increase in the rate of LNA within the time period of our study, even after publication of the 2005 ASCO guidelines. Despite this, the overall rate of LNA for DCIS appears to have decreased over the last two decades. In a SEER analysis encompassing the years 1988 to 2002, Porembka et al (19) reported LNA rates of 22% in patients undergoing lumpectomy for DCIS. During most of the time period of their study, however, SEER did not specifically code for the use of SLNB. The majority of LNAs in Porembka's study, therefore, were axillary lymph node dissections (ALNDs). In 2002, when SEER was coding for both ALND and SLNB, 67% of LNAs were still ALNDs, but there was a growing trend in use of SLNB. By contrast, 75% of LNAs performed within the time period of our study were done using SLNB. The advent of SLNB has made LNA easier to do and has decreased the rate of complications relative to axillary lymph node dissection (20). This ease and perceived lack of morbidity are likely responsible for its increased use. Approximately 60,000 patients are diagnosed with DCIS each year (21). If we assume that 80% are eligible for breast conservation, then as many as 48,000 patients could receive lumpectomy for DCIS. If SLNB was performed on all of these patients, we would expect 2,304 (20%) to be positive due to previously occult invasive disease and another 1,536 (4%) to be positive in the setting of pure DCIS. Such aggressive use of SLNB would result in 3,360 (7%) patients with lymphedema using ACOSOG Z0010 estimates, as well as additional thousands with other morbidities, such as paresthesias and seromas (22). We would hope and expect that use of LNA and SLNB for patients undergoing lumpectomy for DCIS will decrease over time, with increased recognition of the improving diagnostic accuracy of core needle and vacuum assisted biopsies and the published morbidity rates of SLNB. It is possible, however, that indications for SLNB may change if it's demonstrated that a SLNB is a more sensitive screening test for occult invasive cancer that is missed on routine pathologic examination, but identified on a more thorough evaluation prompted by a positive sentinel lymph node on immunohistochemistry (23).

Our study's results should be interpreted with an understanding of the limitations inherent to studies utilizing population-based data such as SEER. SEER only represents 17 cancer registries nationwide and represents 26% of the total U.S. population. In addition, while, the population reporting to SEER is comparable to the general population of the United States with respect to measures of poverty and education; it over represents minority racial/ethnic groups, foreign-born, and urban populations (Yu (24) et al). Our patient population was also limited because we excluded cases of DCIS prior to 2000. We chose these years because they incorporated years before and after ASCO guidelines for the use of SLNB for DCIS and represented a more modern era of LNA. SEER data provide no information regarding individual patients' past medical or family history that may predispose them to have higher risks of invasive breast cancer. Such patients may have been seen as having a significantly high risk of invasive disease to warrant LNA. Furthermore, we are unable to analyze all patients that received lumpectomy for DCIS. Some of these patients were undoubtedly found to have invasive breast cancer on final pathology, and SEER would code these patients according to their most invasive tumor component without regard for associated DCIS. The current analysis represents only patients that carried a diagnosis of DCIS after definitive surgery, and may represent, by definition, a lower risk group with respect to clinical predictors of invasive disease. Data completeness could have influenced our data. We had a large proportion of patients with unknown DCIS size of DCIS extent. It is possible that these patients were determined to have high-risk disease on the basis of their physical examination or imaging results. We did not exclude these patients from analysis since these predictors may not necessarily be available to all surgeons at the time of surgery for DCIS.

Due to improved breast cancer awareness and mammographic screening, the incidence of DCIS in women has steadily increased since 1970s with 32.5 out of 100,000 women being diagnosed every year (25). As more woman present for treatment for DCIS, further research directed at identifying the subgroup of women who should receive SLNB at time of initial operation as well as research directed at determining the oncologic significance of a positive SLNB will be necessary to minimize costs and morbidity of potential reoperation. We hoped to have helped in this matter by identifying disparities between current consensus guidelines and actual practice as well identifying common risk factors considered to be important in the decision to perform LNA or SLNB.

Acknowledgments

Supported by Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NNCRR or NIH. Information on NCRR is available athttp://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp

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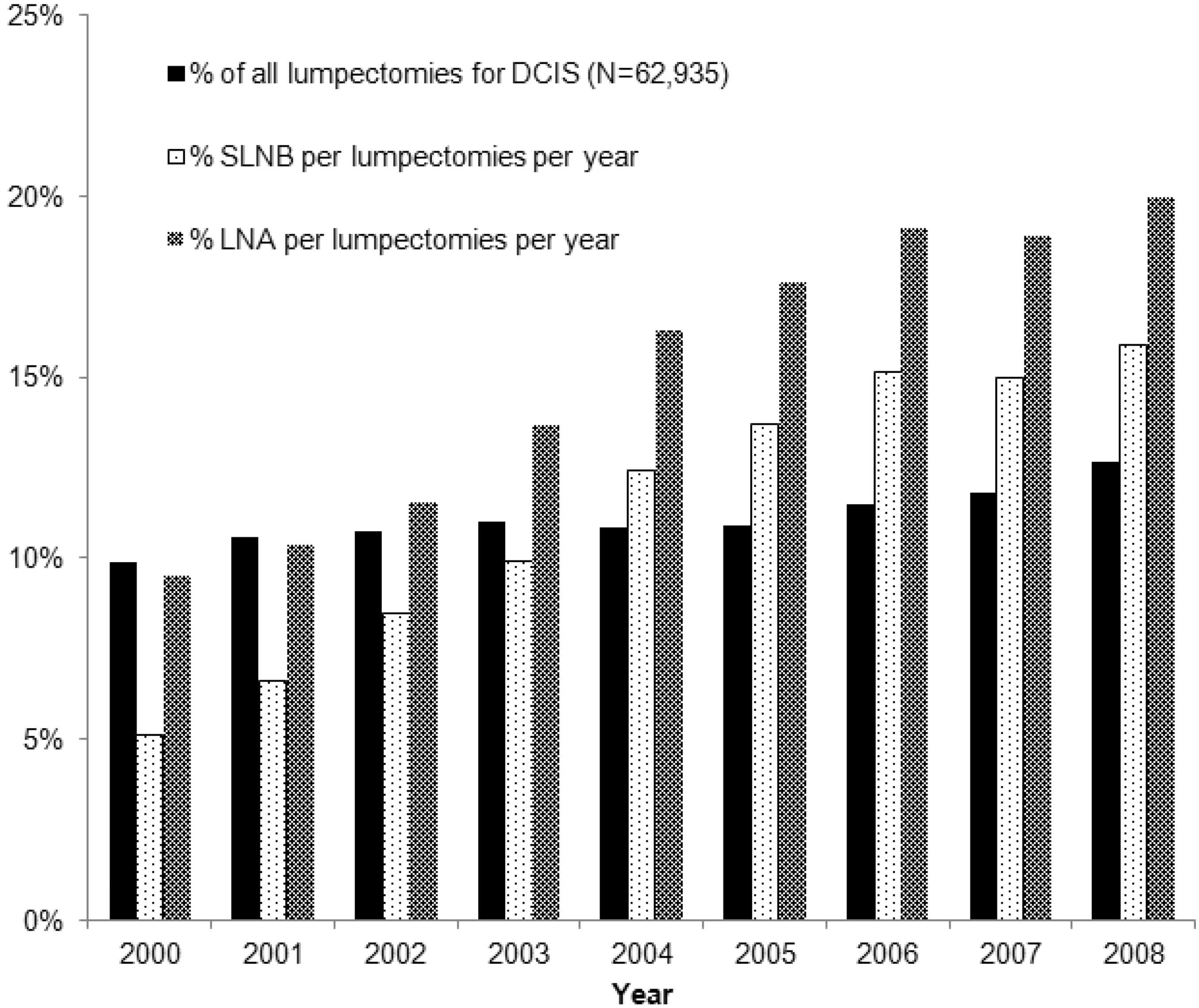

Figure 1.
Trend in LNA and SLNB over time period of study. Percentage of LNA and SLNB represent proportion of each performed per total lumpectomies per given year. Abbreviations: LNA- Lymph node assessment, SLNB - Sentinel lymph node biopsy.

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Table 1

Patient and tumor characteristics

Patient Characteristic	Total, N=62935 (%)	SLNBX, N=7294 (%)	LNA, N=9726 (%)
Age			
≤60 years	33353(53)	4192(57)	5547(57)
>60 years	29582(47)	3102(43)	4179(43)
Race			
White	47101(75)	5520(76)	7276(75)
Asian or Pacific Islander	5467(9)	614(8)	784(8)
Black	5396(9)	551(8)	809(8)
Hispanic	4241(7)	552(8)	774(8)
Native American/Alaskan	228(<1)	17(<1)	28(<1)
Unknown	502(1)	40(<1)	55(<1)
Grade			
I	7858(12)	493(7)	736(8)
II	21542(24)	1982(27)	2685(28)
III	14055(22)	2402(33)	3080(32)
IV	7823(12)	1444(20)	1760(18)
Unknown	11657(19)	973(13)	1465(15)
DCIS Size			
<2cm	21977(35)	3054(42)	3830(39)
2–5cm	3573(6)	771(11)	969(10)
>5cm	517(<1)	142(2)	184(2)
Unknown	36868(59)	3327(46)	4743(49)
SEER Registry			
West	34376(55)	4347(60)	5484(56)
Midwest	6538(10)	633(9)	900(9)
Northeast	14015(22)	1323(18)	1968(20)
Southeast	8006(13)	991(14)	1374(14)
ER			
Positive	22308(35)	3189(44)	4018(41)
Borderline	70(<1)	10(<1)	14(<1)
Negative	3965(6)	986(14)	1196(12)
Unknown	36592(58)	3109(43)	4498(46)
PR			
Positive	18302(29)	2475(34)	3168(33)
Borderline	170(<1)	22(<1)	30(<1)
Negative	6316(10)	1405(19)	1704(18)
Unknown	38147(61)	3392(47)	4824(50)

Abbreviations: SLNB - Sentinel lymph node biopsy; LNA -Lymph node assessment, ER-Estrogen receptor, PR- progesterone receptor, DCIS- ductal carcinoma in situ

Table 2

Patient and tumor factors associated with odds of lymph node assessment and sentinel node biopsy

	SLNB		LNA	
	OR	95%CI	OR	95%CI
Age				
≤60 years	Reference		Reference	
>60 years	0.82	0.78–0.86	0.83	0.79–0.87
Year Diagnosis				
2000	Reference		Reference	
2001	1.33	1.14–1.54	1.11	0.99–1.24
2002	1.72	1.49–1.98	1.24	1.10–1.38
2003	2.18	1.90–2.50	1.61	1.44–1.79
2004	2.12	1.83–2.47	1.58	1.40–1.79
2005	2.43	1.93–2.61	1.67	1.47–1.89
2006	2.54	2.19–2.96	1.85	1.64–2.10
2007	2.53	2.17–2.95	1.84	1.63–2.09
2008	2.73	2.35–3.18	2	1.76–2.26
Race				
White	Reference		Reference	
Asian or PI	0.86	0.78–0.95	0.88	0.81–0.96
Black	0.85	0.77–0.94	0.95	0.87–1.03
Hispanic	1.03	0.94–1.14	1.18	1.08–1.28
Native American/Alaskan	0.63	0.37–1.01	0.84	0.55–1.25
Unknown	0.6	0.40–0.86	0.61	0.43–0.84
Grade				
I	Reference		Reference	
II	2.83	2.55–3.15	2.71	2.48–2.96
III	2.62	2.36–2.91	2.38	2.18–2.59
IV	2.96	2.65–3.31	2.61	2.37–2.88
Unknown	1.51	1.35–1.69	1.49	1.36–1.64
DCIS Size				
<2cm	Reference		Reference	
2–5cm	1.4	1.28–1.54	1.49	1.37–1.62
>5cm	1.89	1.53–2.31	2.16	1.78–2.61
Unknown	0.93	1.35–1.69	0.94	0.88–1.00
SEER Registry				
West	Reference		Reference	
Midwest	0.83	0.76–0.91	0.95	0.87–1.03
Northeast	0.83	0.77–0.89	0.98	0.92–1.04
Southeast	1.13	1.04–1.22	1.25	1.16–1.34

	SLNB		LNA	
	OR	**95%CI**	**OR**	**95%CI**
ER				
Positive	Reference		Reference	
Borderline	1	0.46–2.04	1.16	0.58–2.20
Negative	1.25	1.11–1.39	1.29	1.16–1.43
Unknown	0.69	0.59–0.80	0.8	0.7–0.92
PR				
Positive	Reference		Reference	
Borderline	0.81	0.49–1.28	0.84	0.54–1.28
Negative	1.26	1.14–1.40	1.22	1.11–1.33
Unknown	1.19	1.03–1.37	1.09	0.95–1.24

Abbreviations: OR- Odds ratio, CI- 95% Confidence Interval