OXFORD

BRIEF COMMUNICATION

Long-Term Outcomes of Sentinel Lymph Node Biopsy for Ductal Carcinoma in Situ

Peiyin Hung (iD) , Shi-Yi Wang, Brigid K. Killelea, Sarah S. Mougalian, Suzanne B. Evans, Tannaz Sedghi, Cary P. Gross

See the Notes section for the full list of authors' affiliations.
Correspondence to: Shi-Yi Wang, MD, PhD, Department of Chronic Disease Epidemiology, Yale School of Public Health, 60 College St, P.O. Box 208034, New Haven, CT 06520 (e-mail: shiyi.wang@yale.edu).

Abstract

The use of sentinel lymph node biopsy (SLNB) for ductal carcinoma in situ (DCIS) is controversial. Using population-cohort data, we examined whether SLNB improves long-term outcomes among patients with DCIS who underwent breast-conserving surgery. We identified 12 776 women aged 67–94 years diagnosed during 2001–2013 with DCIS who underwent breast-conserving surgery from the US Surveillance, Epidemiology, and End Results-Medicare dataset, 1992 (15.6%) of whom underwent SLNB (median follow-up: 69 months). Tests of statistical significance are two-sided. Patients with and without SLNB did not differ statistically significantly regarding treated recurrence (3.9% vs 3.7%; $P = .62$), ipsilateral invasive occurrence (1.4% vs 1.7%, $P = .33$), or breast cancer mortality (1.0% vs 0.9%, $P = .86$). With Mahalanobis-matching and competing-risks survival analyses, SLNB was not statistically significantly associated with treated recurrence, ipsilateral invasive occurrence, or breast cancer mortality ($P \geq .27$). Our findings do not support the routine performance of SLNB for older patients with DCIS amenable to breast conservation.

The role of sentinel lymph node biopsy (SLNB) in the management of ductal carcinoma in situ (DCIS) is controversial and merits scrutiny (1–3). Ongoing campaigns challenge the use of SLNB for patients with small breast cancer, raising doubt for its use in patients with DCIS, whereas proponents of SLNB cite concerns that occult disease may not be detected histologically (4,5). An Agency for Healthcare Research and Quality–funded systematic review documented evidence gaps regarding the benefits and harms of SLNB in the management of DCIS (6). Research after this review indicated that SLNB was not associated with breast cancer mortality (7), a positive sentinel lymph node in the setting of DCIS did not affect survival (8), and short-term side effects were increased with SLNB (9). However, these studies were limited in scope and methodology, underpowered (7), examined an SLNB cohort from a single institution (8), and did not examine long-term impacts (9). Given that SLNB use has increased from 7.2% to 39.4% among patients with DCIS who undergo breast-conserving surgery (BCS) (10), it is critical to determine the associations between long-term outcomes and SLNB use for this population.

This retrospective cohort study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to identify women (aged 67–94 years) diagnosed with DCIS between 2001 and 2013 who received BCS in the first 6 months after diagnosis and did not undergo mastectomy within 9 months postdiagnosis (Supplementary Appendix Figure 1, available online) (11). SLNB was identified using Healthcare Common Procedure Coding System codes 38500, 38525, 38790, 38792, 38900, 78195, A9520, and G8878 (9,12–16). Primary outcomes, suggested by patient and professional advisory committees, included treated recurrence (subsequent mastectomy after 9 months of DCIS diagnosis for the same DCIS primary) (17), incident ipsilateral invasive breast cancer (IBC) occurrence (IBC diagnosis in the same breast), and breast cancer-specific mortality. Treated recurrence and breast cancer-specific mortality were followed through December 2014 and ipsilateral IBC occurrence through December 2013.

Of 12 776 women with DCIS, 1992 (15.6%) underwent SLNB (median follow-up, 69 months). Women who underwent SLNB tended to be younger, white ($P = .007$), diagnosed in recent

Table 1. Unadjusted study outcomes by use of SLNB

	Before matching			After matching		
Outcomes	No SLNB (N = 10 784) No. (%)	SLNB (N = 1992) No. (%)	χ^2 P*	No SLNB (N = 3965) No. (%)	SLNB (N = 1992) No. (%)	χ^2 P*
Mastectomy†	403 (3.7%)	78 (3.9%)	.700	145 (3.7%)	78 (3.9%)	.620
Ipsilateral‡	216 (2.0%)	27 (1.4%)	.052	67 (1.7%)	27 (1.4%)	.329
Breast cancer mortality	116 (1.1%)	19 (1.0%)	.625	36 (0.9%)	19 (1.0%)	861

*P values were calculated by Pearson χ^2 tests for differences in the proportion of patients with a given outcome between patients with and without use of SLNB. DCIS = ductal carcinoma in situ; SEER = Surveillance, Epidemiology, and End Results; SLNB = sentinel lymph node biopsy; N = number of study cohorts with a corresponding outcome in a group.
†Defined by the receipt of mastectomy after 9 months of a DCIS diagnosis.
‡Ipsilateral invasive breast cancer occurrence after 9 months of a DCIS diagnosis, per SEER reports.

Table 2. Unadjusted and adjusted hazard ratios (99% confidence interval) for the associations of SLNB and study outcomes

Outcomes	Unadjusted HR (99% CI)	P	Adjusted* HR (99% CI)	P
Mastectomy†	1.10 (0.77 to 1.57)	.509	1.17 (0.81 to 1.69)	.265
Ipsilateral‡	0.84 (0.54 to 1.31)	.436	0.91 (0.50 to 1.65)	.673
Breast cancer mortality	1.08 (0.52 to 2.22)	.795	1.13 (0.54 to 2.35)	.674

*Estimates were derived from competing risk Cox regression models among 5957 matched female patients with DCIS breast cancer from Mahalanobis matching (Table 1). Models were also adjusted for the following variables: presence of physician visits, any hospitalization 3–24 months before DCIS diagnosis, use of preoperative breast magnetic resonance imaging, surgeon's operation volume, and receipt of radiation therapy. CI = confidence interval; DCIS = ductal carcinoma in situ; HR = hazard ratio; SEER = Surveillance, Epidemiology, and End Results; SLNB = sentinel lymph node biopsy.
†Defined by receipt of mastectomy after 9 months of a DCIS diagnosis. Ipsilateral breast tumor recurrence after 9 months of a DCIS diagnosis, per SEER reports.

years, and estrogen receptor positive and have comedonecrosis or higher-grade, larger (>2 cm) tumors (P<.001, unless specified) (Supplementary Appendix Table 1, available online). To account for potential treatment selection bias, a 1:2 Mahalanobis matching approach was used by selecting the two best non-SLNB patient matches for each SLNB patient (18–20). Matching variables included age, tumor grade, tumor size, hormone receptor status, year of diagnosis, SEER registry site, and geographic region. Missing values of each variable were categorized. All 1992 women who underwent SLNB were successfully matched with 3965 non-SLNB controls (1973 women had two controls, 19 women had one). Baseline characteristics between patients with and without SLNB were well balanced, with standardized differences less than 10 (Supplementary Appendix Table 2, available online) (21).

Cox proportional hazard models were applied to the Mahalanobis-matched cohort to estimate the associations between SLNB and outcomes, controlling for physician visits, hospitalizations, preoperative breast magnetic resonance imaging, surgeon volume, and receipt of radiation therapy. The proportional hazard assumption was tested and satisfied using the Therneau and Grambsch method. Acknowledging that patients who undergo SLNB might be healthier than those who do not, a competing-risk model using death by other causes was employed. Statistical significance was defined as P less than .01, two-sided, using χ^2 tests or log-rank tests.

After Mahalanobis matching, patients with and without SLNB did not differ statistically significantly regarding treated recurrence (3.9% vs 3.7%, P = .62), ipsilateral invasive occurrence (1.4% vs 1.7%, P = .33), or breast cancer mortality (1.0% vs 0.9%, P = .86) (Table 1). Competing-risk Cox proportional hazard models confirmed that SLNB use was not associated with a decrease in treated recurrence (adjusted hazard ratio [AHR] = 1.17, 99% CI = 0.81 to 1.69, P = .27), ipsilateral IBC occurrence (AHR = 0.91, 99% CI = 0.50 to 1.65, P = .67), or breast cancer mortality (AHR = 1.13, 99% CI = 0.54 to 2.35, P = .67) (Table 2).

This study was limited to patients aged 67–94 years and may not be generalizable to a younger population. Although the sample comprises beneficiaries enrolled in Medicare fee-for-service programs, it would be surprising if the outcomes attributed to SLNB differed among Medicare Part C beneficiaries. Further analysis on the benefits of SLNB in DCIS with high-risk features is needed. The primary outcomes neither single out axillary recurrence nor include distant relapse, which merit investigation. Additionally, ipsilateral IBC occurrence was derived from the SEER database and may be underreported for patients with a prior DCIS diagnosis, although it is unlikely that reporting would differ because of SLNB. Although we applied Mahalanobis matching and competing-risk models to reduce bias, this observational study could not establish a strong causal inference. We acknowledge that we were unable to control for unobserved confounding factors, such as obesity, endocrine therapy status, postsurgical margin status, presence of a mass lesion, and provider's treatment preference.

Because our cohort was limited to patients who had a final diagnosis of DCIS, patients who were initially diagnosed with DCIS but were later upstaged to node-positive cancer due to SLNB were excluded in the SLNB group. In contrast, the non-SLNB group may have had undetected IBC; thus, this group (compared with the SLNB group) would have a higher risk of ipsilateral IBC occurrence. Although our study design favors the SLNB group in our cohort, we still found that rates of IBC were similar in both arms, suggesting that SLNB could be safely omitted.

SLNB has become the preferred method of axillary staging for patients with IBC; the proportion of patients who undergo SLNB is a quality metric for early-stage IBC care (22,23). The inclusion of this quality measure in the Centers for Medicare & Medicaid Services' Merit-based Incentive Payment System has financially motivated providers to perform SLNB (24). This increasing trend is a vivid example of "indication creep," promoting the use of an intervention outside the approved indication or target population (25). Patients and surgeons may prefer SLNB if it does not reduce breast cancer mortality but could decrease local or regional recurrences, which could be indications for subsequent undesirable treatments. Therefore, organizations that promote quality for breast cancer care should emphasize the differences between invasive cancer and DCIS, referring to the two distinct SLNB quality measures simultaneously. With increased diagnoses of DCIS, determining the optimal clinical approach to treatment while minimizing side effects is important. Our study adds to the supporting evidence of current treatment guidelines that surgeons should avoid SLNB for women age 67–94 years with DCIS who undergo BCS as their initial treatment.

Funding

Notes

Affiliations of authors: Department of Health Services Policy and Management, Arnold School of Public Health, University of South Carolina, Columbia, SC (PH); Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale Cancer Center, New Haven, CT (SYW, BKK, SSM, SBE, TS, CPG); Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT (PH, SYW); Department of Surgery (BKK) and Section of Medical Oncology, Department of Internal Medicine (SSM) and Department of Therapeutic Radiology (SBE) and Section of General Internal Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT (CPG).

References

1. Prendeville S, Ryan C, Feeley L, et al. Sentinel lymph node biopsy is not warranted following a core needle biopsy diagnosis of ductal carcinoma in situ (DCIS) of the breast. *Breast*. 2015;24(3):197–200.
2. Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? *Am Surg*. 2001;67(6):513–519.
3. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? *Ann Surg Oncol*. 2000;7(9):636–642.
4. European Institute of Oncology. European Institute of Oncology Sentinel Node vs Observation after Axillary Ultra-Sound (SOUND). ClinicalTrials.gov Identifier: NCT02167490; 2017. https://clinicaltrials.gov/ct2/show/NCT02167490. Accessed February 25, 2019.
5. Schmale I, Liu S, Rayhanabad J, Russell CA, Sener SF. Ductal carcinoma in situ (DCIS) of the breast: perspectives on biology and controversies in current management. *J Surg Oncol*. 2012;105(2):212–220.
6. Virnig B. A, Shamliyan T, Tuttle TM, Kane RL, Wilt TJ. Diagnosis and management of ductal carcinoma in situ (DCIS). *Evid Rep Technol Assess (Full Rep)*. 2009;185(185):1–549.
7. Francis AM, Haugen CE, Grimes LM, et al. Is sentinel lymph node dissection warranted for patients with a diagnosis of ductal carcinoma in situ? *Ann Surg Oncol*. 2015;22(13):4270–4279.
8. Wadsten C, Garmo H, Fredriksson I, Sund M, Wärnberg F. Risk of death from breast cancer after treatment for ductal carcinoma in situ. *Br J Surg*. 2017;104(11):1506–1513.
9. Killelea BK, Long JB, Dang W, et al. Associations between sentinel lymph node biopsy and complications for patients with ductal carcinoma in situ. *Ann Surg Oncol*. 2018;25(6):1521–1529.
10. Mitchell KB, Lin H, Shen Y, et al. DCIS and axillary nodal evaluation: compliance with national guidelines. *BMC Surg*. 2017;17(1):12.
11. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(suppl 8):IV-3–IV-18.
12. Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on clinical management of the Axilla in older breast cancer patients: a SEER-Medicare analysis. *Ann Surg Oncol*. 2013;20(13):4145–4152.
13. Davis GB, Peric M, Chan LS, Wong AK, Sener SF. Identifying risk factors for surgical site infections in mastectomy patients using the National Surgical Quality Improvement Program database. *Am J Surg*. 2013;205(2):194–199.
14. Meyer A-M, Reeder-Hayes KE, Liu H, et al. Differential receipt of sentinel lymph node biopsy within practice-based research networks. *Med Care*. 2013;51(9):812–818.
15. Schmocker RK, Caretta-Weyer H, Weiss JM, et al. Determining breast cancer axillary surgery within the surveillance epidemiology and end results-Medicare database. *J Surg Oncol*. 2014;109(8):756–759.
16. Yen TWF, Laud PW, Sparapani RA, Nattinger AB. Surgeon specialization and use of sentinel lymph node biopsy for breast cancer. *JAMA Surg*. 2014;149(2):185.
17. Smith BD, Haffty BG, Buchholz TA, et al. Effectiveness of radiation therapy in older women with ductal carcinoma in situ. *J Natl Cancer Inst*. 2006;98(18):1302–1310.
18. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265–2281.
19. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*. 2013;105(1):25–32.
20. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172(9):1092–1097.
21. Normand S-L, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly. *J Clin Epidemiol*. 2001;54(4):387–398.
22. The American Society of Breast Surgeons. *Measure #264: Sentinel Lymph Node Biopsy for Invasive Breast Cancer – National Quality Strategy Domain: Effective Clinical Care*. Columbia, MD; 2017. https://mdinteractive.com/files/uploaded/264_2012_PhysQualRptg_MeasureSpecificationsManual_122311.pdf. Accessed October 2, 2018.
23. American Society of Breast Surgeons. *Performance and Practice Guidelines for Sentinel Lymph Node Biopsy in Breast Cancer Patients*. Columbia, MD; 201AD. https://www.breastsurgeons.org/statements/guidelines/PerformancePracticeGuidelines_SLN.pdf. Accessed October 2, 2018.
24. Centers for Medicare & Medicaid Services. Medicare program; CY 2018 updates to the quality payment program. *Fed Regist*. 2017;82(220):53568–54229.
25. Djulbegovic B, Paul A. From efficacy to effectiveness in the face of uncertainty: indication creep and prevention creep. *JAMA*. 2011;305(19):2005–2006.