# Comparative Effectiveness of Sentinel Lymph Node Biopsy for Ductal Carcinoma In Situ

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## Study Protocol and Statistical Analysis Plan

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## Rationale and background

Ductal carcinoma in situ (DCIS) of the breast is a condition in which a spectrum of abnormal cells accumulates within the lumen of mammary duct but has not invaded the surrounding breast tissue.[1] Because of the increased use of screening mammography, the incidence of DCIS has increased dramatically, accounting for approximately 25% of all new breast cancer diagnosed in the United States.[2,3] As a result of the non-invasive nature of DCIS, patients treated with available therapies have excellent outcomes and very low rates of breast cancer mortality. Considerable debate exists as to how the DCIS lesion should be treated,[4,5] although there is a movement towards less intensive intervention by the identification of patient subsets with favorable prognoses. Some prospective studies have found that the rate of ipsilateral invasive cancer occurrence is still high after receiving breast conserving surgery (BCS) alone, even among patients with favorable pathologic characteristics. Such findings argue against active surveillance for DCIS treatment. However, evidence exists that older DCIS patients have a lower rate of ipsilateral recurrence because DCIS among older patients tends to be indolent. Identifying suitable subgroups among this lower risk group who may be safe to receive a less aggressive treatment could change the current practice pattern of aggressive treatment.

Even when DCIS patients opt to receive a less intensive treatment such as BCS without radiation therapy, they and their providers need to decide whether to undergo sentinel lymph node biopsy (SLNB). The role of SLNB for DCIS management is controversial in general and needs further scrutiny in particular if patients received BCS without radiation therapy. Significant debates continue about whether SLNB should be performed,[6-8] with some experts advocating for its use.[9,10] Proponents of SLNB cite concerns that occult microinvasive disease within the DCIS may not be detected histologically, with an estimated prevalence of 1.4% to 12%.[11] However, among DCIS patients who receive radiation therapy the likelihood of local recurrence with axillary involvement is low,[12] and routine SLNB is not recommended.[13] Of note, radiation therapy has also been shown to control micrometastasis if present.[14] On the other hand, if we plan to empower DCIS patients to choose less intensive management options, such as BCS without radiation therapy, understanding the role of SLNB will be crucial.

A systematic literature review has shown that evidence gaps exist regarding the benefits of SLNB for DCIS.[15] As far as we know, no study has yet examined SLNB among DCIS patients who received BCS. Because of the current call for less intensive treatment, it is imperative to understand the benefits or harms for DCIS patients who received BCS. A large randomized controlled trial would be providing the best evidence to guide treatment recommendations, but the results would not be available for at least 10 years. Our project will use existing data to swiftly provide comprehensive information about comparative effectiveness across the DCIS care continuum in an observational study setting.

## Study objectives

Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data, our project's overarching aims are:

Among older women with DCIS who have received BCS as their first surgery, to compare the outcomes of receiving SLNB vs. not receiving SLNB within 6 months of DCIS diagnosis:

Aim 1: We will determine associations between SLNB and acute/subacute side effects, including lymphedema, pain, and limitation of movement of upper extremity from the first BCS to 9 months post-diagnosis.
Aim 2: We will determine associations between SLNB and long-term outcomes, including breast cancer specific mortality, ipsilateral invasive breast cancer diagnosis, subsequent mastectomy as treated recurrence, and lasting side effects, from >9 months post-diagnosis to death or the end of this study period.

## Study design

We will conduct a retrospective cohort study. Using the most up-to-date SEER-Medicare database, we will examine the impact of SLNB on clinical outcomes of women with newly diagnosed DCIS among the Medicare population. The nature of SEER-Medicare linking Medicare claims records to tumor registries participating in the NCI's SEER program allows us to select study population based on precise demographic and clinical characteristics of the patients. In our study, the population is DCIS patients older than 67 years (hereafter referred to as older women) who were enrolled in a fee-for-service Medicare program and resided in the SEER areas from 1998 to 2011 (1998-2013 for Aim 2) and who were followed up to 2012 (2015 for Aim 2).

## Methodology

Our study population are generated within the SEER-Medicare linked database. To identify patients with DCIS, we will use histology and behavior codes, which are converted from the ICD-O-3 codes that tumor registries are required to report to SEER for all cases.[16] Specifically, we will identify breast "cancer" patients with in situ tumor behavior (behavior code = 2). DCIS patients will be further limited to those with ICD-O-3 codes consistent with epithelial origin. We select age 67 as a cut-off value because we plan to use two years of claims data to identify patient comorbidities and to control for them in our statistical models, and data is first available at age 65.
Our Aim 1 cohort will include DCIS patients who received BCS as their first surgery (i.e. excluding patients who received mastectomy first). We expect that patients who received BCS with SLNB (compared with those who received BCS without SLNB) would be more likely to end up with mastectomy, and thus would be more likely to have side effects. Findings of the associations between SLNB and mastectomy as the final treatment for DCIS would be informative. We intend to include these patients in Aim 1 so that we can provide a comprehensive picture regarding side effects of SLNB in the context of less intensive managements.
Our Aim 2 will examine the long-term outcomes between patients who received BCS without SLNB and patients who received BCS with SLNB. Patients who received BCS in the beginning yet ended up with mastectomy for their primary DCIS will be excluded. For patients who received BCS plus RT, SLNB will not likely provide any benefits since RT is able to control small lesions. However, we plan to determine the effects of SLNB among patients who received BCS without RT, which will have important clinical implications.
The time period for defining the cohort for the Aim 1 will be between January 1998 and December 2011. Using medical claims for this cohort, we will identify any side effects within a

9-month window (from DCIS diagnosis to 9 months post-diagnosis). The time period for defining the cohort for the Aim 2 will be from January 1998 to December 2012, and patients will be followed from 9 months after DCIS diagnosis through the latest date to which data is available in SEER-Medicare. For instance, the next SEER-Medicare linked dataset will have overall mortality through December 2015, breast cancer specific mortality through December 2013, and claims data (to identify treated recurrence) through December 2014.

We identify interventions and comparators in our study using specific international classification of Diseases, Ninth Revision, (ICD-9) codes, CPT codes and HCPCS codes. We will limit our sample to DCIS patients who received BCS as their first surgery; that is, we exclude patients whose first surgery is mastectomy, because we are only interested in patients who receive less intensive treatment and their outcomes. Because SLNB is performed by a surgeon, we identify it within a window consistent with those used in prior literature to identify breast cancer surgery, that is, between the date of the first BCS and 6 months after DCIS diagnosis. We are aware that patients may receive BCS first and mastectomy later for their primary DCIS. Furthermore, we realize that SLNB may affect whether or not patients receive mastectomy.

Based on the input of our patient and professional advisory committee members, we propose the following outcomes of interest in this project. In Aim 1 we focus on acute/sub-acute side effects. Secondary outcomes include treatment received. In Aim 2, our primary outcomes include breast cancer specific mortality, incident ipsilateral invasive breast cancer occurrence (based on ipsilateral invasive breast cancer from SEER) and treated recurrence (based on follow-up mastectomy). Secondary outcomes include overall survival and lasting side effects. Overall survival, expected to be similar, would be used as a benchmark outcome to check performance of our model.

In addition to the key exposures (interventions and comparators) and endpoints (outcomes of interest), we will further select covariates, including patient demographics, comorbidities, tumor characteristics and prior healthcare utilization, based on prior literature and our experience. We plan to include the following covariates to control for confounding. For patient demographics, we will include patient's age, sex, ethnicity, marital status and years of diagnosis. For geographical and social-economical characteristics, we will include income, education and metropolitan residence. For patient's comorbidities, we plan to include Elixhauser comorbidity index, disability index and prior hospitalization. For DCIS characters, we will include grade, size, comedonecrosis and hormone receptor status. For health care system utilization, we will consider prior influenza vaccination, physician visit, MRI use and surgeon's volume. Last, to control for other treatment patients have received, we will adjust for mastectomy and radiation therapy.

**Data management and statistical analysis**

We plan to create a dataset for this project. Each patient in the SEER-Medicare dataset has a unique patient identification number. Using this information, we will be able to collect patient demographics and DCIS characteristics from the SEER registry as well as claims data from Medicare on what treatment patients have received or what side effects they have experienced. We will manage the dataset in a suitable manner that fully complies with the SEER-Medicare data use rules and confidentiality.

As a secondary data analysis, we will be unable to prevent missing data from the original dataset. We do, however, set a priori exclusion and inclusion criteria for the creation of our cohort. We

will include only DCIS patients who have available claims data (i.e. are enrolled in fee-for-service coverage) during the period between cancer diagnosis and the end of the follow-up (Aim 1: 9 months after DCIS diagnosis; Aim 2: either death or the last date of claims released by SEER-Medicare). Statistically, we plan to create an "unknown" category to capture those patients who had a missing value. Additionally, we will conduct sensitivity analyses regarding whether or not excluding these patients would change our findings.

To compare baseline characteristics between intervention and control groups, we will conduct standard descriptive statistics using $\chi^2$ tests for categorical variables and t-tests for continuous variables. We will tabulate the frequencies of outcomes of interests by the intervention vs. control group. We will use multivariable analyses to test our hypotheses while controlling for unbalanced covariates, as described below.

We plan to control for selection bias using propensity score matching methodology.[17] Specifically, the propensity score matching will be based on the Mahalanobis distance[18] calculated using age, race, residence in a metropolitan county, comorbidity, prior influenza vaccination or prior visit to a primary care physician (both as proxies for access to care), income, preoperative MRI use, and tumor characteristics. Tumor characteristics include size, grade, comedonecrosis, and estrogen receptor status. By incorporating these factors in matching, we expect to substantially decrease bias and balance the risk for outcomes of interest between the SLNB and non-SLNB groups. We will use 2: 1 matching, as prior literature indicated that this approach results in improved precision without a commensurate increase in bias.[19] To ensure robust and comprehensive matching, matches will be assigned by choosing the two best non-SLNB patient matches for each SLNB patient; when two or more SLNB patients match the same control (that is, have Mahalanobis distances minimized by the same control), one will be randomly selected as a match, and this process reiterates until all SLNB patients have two matched controls. We will assess the validity of the matching by comparing risk factors between the SLNB and non-SLNB groups using $\chi 2$ tests. The difference in outcomes between the control and intervention groups will be estimated in a Kaplan-Meier curve. We will estimate the relative risk in the propensity score matched sample using the standard method for matched-pair data.[20] We will use the Cox proportional hazards models to investigate the association between various factors (grade, tumor size, and estrogen receptor status) and outcomes.[21]

For multivariable analyses, we will use conditional logistic regression models for acute/subacute side effects (primary outcomes) and treatment received (mastectomy or radiation therapy; secondary outcomes) in Aim 1, with conditioning on the matched variable. For primary outcomes, we will run 2 models, with or without controlling for treatment received. We will report adjusted odds ratios of SLNB on these outcomes. In Aim 2, we will apply time-to-event models to test whether the intervention is associated with better outcomes, including primary and secondary outcomes. We will report adjusted hazard ratios of SLNB on these outcomes. The proportional hazards assumption will be evaluated for each model using a variety of methods (evaluation of Kaplan-Meier and log(-log) survival plots, Shoenfield residuals, and covariate x time interactions). If the proportional hazards assumption is violated, we will instead use parametric survival models, using AIC and BIC to determine the best parameterization (exponential, Weibull, generalized gamma, Gompertz, lognormal, or loglog). All time-to-event models will incorporate a shared frailty term for the matching group, and will include covariates that are not balanced by matching. These models will allows us to test for association between various factors (grade, tumor size, and estrogen receptor status) and outcomes.

In order to identify suitable patient subgroups that may be able to forego SLNB, we plan to explore the following stratification schemes in Aim 2 analysis: 1. Stratify patients by receipt of radiation therapy; 2. Stratify patients by key DCIS characteristics, including grade, comedonecrosis and tumor size; 3. Stratify patients by their predicted life expectancy, given their age, sex and comorbidities.

## Expected outcomes of the study

According to our specific aims, we propose different outcomes of interest. For Aim 1, our primary outcome is the side effect occurrence within 9 months post-DCIS-diagnosis. The side effects include lymphedema, pain and limitation of movement of extremities. Our secondary outcome for Aim 1 is treatment received. We will examine the relationship between SLNB and subsequent treatment received, including mastectomy within 6 months after DCIS diagnosis and radiation therapy within 9 months after DCIS diagnosis. For Aim 2, we propose several primary outcomes. We will measure the breast cancer specific survival with the timeframe from 9 months post-diagnosis to death or end of study period. We will also assess the ipsilateral invasive breast cancer occurrence and treated recurrence, including mastectomy, within the same timeframe. For Aim 2, our secondary outcomes include overall survival (a benchmark outcome to check the performance of analytic models) and lasting side effects.
As for detailed outcome measurements, we expect to have these estimates by the end of the project: 1. the difference in baseline characteristics between the intervention and control groups and $\chi 2$ statistics that suggests difference significance; 2. the propensity score matching results, including matched cohort and the standardized difference that indicates the balance of matching; 3. the estimate in the main analysis, for example odds ratio, rate ratio or hazard ratio, that could represent the association of intervention and outcome; 4. the estimate in the stratified analysis that could describe the association of intervention and outcome in each clinical subgroup.

## Duration of the project

We are anticipating the project to be completed within 18 months of time.

## Ethical concerns

As a result of the nature of our observational design, we do not anticipate any ethical concerns as we are analyzing existing data. We expect this project will be exempt from full review. However, we will make sure that no member in the project would violate the rules and confidentiality required when analyzing SEER-Medicare database.

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