Patterns of nodal staging during breast conservation surgery in the medicare patient: will the ACOSOG Z0011 trial change the pattern of care?

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Abstract ACOSOG Z0011 spares axillary dissection (AD) in breast conservation surgery (BCS) patients with T1/T2 tumors and 1–2 positive nodes. Current patterns of care and the impact of Z0011 on AD versus additional surgery rates for Medicare patients undergoing BCS are unknown. SEER data linked to Medicare claims for 1999–2005 were reviewed for women with invasive non-metastatic breast cancer who underwent nodal staging on the same day as BCS. There were 3,280 women with T1/T2 tumors and positive nodes who underwent same-day nodal staging; 2,532 (77.2 %) of these women had 1–2 positive nodes. Assuming 25.7 % have extracapsular extension, 651 women would require AD. However, 1,881 women, or 57.4 % of those with T1/T2 tumors and positive nodes, would be spared AD. Meanwhile, among the 748 women having ≥ 3 positive nodes, 579 underwent same-day AD, but under Z0011, would now wait for permanent section. A total of 160 of these women underwent re-excision or completion mastectomy at a later date anyway, when delayed AD could be performed. The remaining 419

women with ≥ 3 positive nodes would require an additional surgery date for the sole purpose of completion AD. The Z0011 paradigm would consequently necessitate an additional surgery date for 1,070 (651 + 419) women, or 32.6 % of those with T1/T2 tumors and positive nodes. The Z0011 paradigm appears to increase the number of Medicare patients undergoing BCS who require an additional surgery date but decrease the number requiring AD to a greater extent. Future changes in the use of AD or axillary irradiation may yet modify that impact substantially.

Keywords Clinical trials · ACOSOG Z0011 · Lymph node metastases · Sentinel lymphadenectomy · Sentinel node biopsy · Axillary lymphadenectomy · Axillary lymph node dissection · Patterns of care · Surveillance, epidemiology, and end results · Medicare · Medicare claims

Introduction

Since Halsted's radical mastectomy, axillary dissection (AD) followed by pathologic evaluation of nodes has been used to assert regional control over breast cancer and determine treatment and prognosis [1]. However, over the past 20 years, there has been an increasingly minimalist approach to axillary surgery, thereby sparing patients significant morbidity, including infection, seroma, range of motion impairment, paresthesia, and lymphedema [2]. The movement away from axillary surgery began in the 1990s with lymphatic mapping and sentinel lymphadenectomy (LM/SL), which is predictive of the status of the axilla and spares AD in patients with negative sentinel nodes. In 2001, a consensus statement affirmed LM/SL as the standard of care for patients with clinically negative axillae [3].

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More recently, the results of the American College of Surgeons Oncology Group Z0011 trial lent additional momentum to limiting axillary surgery. This prospective, randomized study compared completion AD to no additional axillary surgery in breast conservation surgery (BCS) patients with tumors ≤ 5 cm and 1–2 positive sentinel nodes without extracapsular extension (ECE) treated with whole-breast radiotherapy, nearly all of whom also received adjuvant systemic therapy. Omission of completion AD in these patients did not increase locoregional recurrence or worsen survival [4, 5]. In 2012, these results were incorporated into the National Comprehensive Cancer Network guidelines for the management of breast cancer [6]. Physicians now increasingly await the final pathologic evaluation of the sentinel nodes to determine if ≥ 3 nodes contain metastases or ECE is present before proceeding with completion AD.

The purpose of this study was to determine the impact of the paradigm change brought about by ACOSOG Z0011 on the patterns of care for the United States Medicare patient undergoing breast conservation, by utilizing Surveillance, Epidemiology, and End Results (SEER) data linked to Medicare claims. This dataset provides information that cannot solely be derived from SEER alone, including comorbidities and surgical procedures.

Methods

Data were collected from the SEER–Medicare database which links 3.5 million patients ≥ 65 years in the SEER cancer registry with their Medicare claims data [7]. Most were derived from physician claims, with outpatient and inpatient claims used to complete missing data. The study cohort was composed of female patients diagnosed with invasive breast cancer at age ≥ 65 years who underwent BCS between 1999 and 2005 and were enrolled in Medicare Parts A & B. Patients were excluded if they had stage IV disease or underwent preoperative chemotherapy or radiotherapy. Patients were also excluded if they were enrolled in a health maintenance organization (where claims may be incomplete) or had missing data.

SEER data were reviewed for age, race, tumor size, receptor status, grade, histology, lymph node metastases, and combined stage. Charlson Comorbidity Index was determined from the Medicare diagnosis codes using the method of Klabunde [8, 9]. In order to examine surgery-related variables, billing codes for lumpectomy or local excision, which are often used interchangeably, were grouped. In order to investigate the nodal staging component, billing codes for lymph node excision, blue dye injection, radionuclide injection, and AD were used. A

Table 1 Cohort characteristics

Characteristic	N	%
Median age, years (range)	74 (65–102)	
Race		
White	23,424	90.5
Black	1,372	5.3
Asian	437	1.7
Hispanic	262	1.0
Other	392	1.5
Charlson Comorbidity Index		
0	18,276	70.6
1	5,376	20.8
2	1,514	5.8
≥ 3	721	2.8
Tumor size		
T1 (≤ 2 cm)	20,420	78.9
T2 (2–5 cm)	5,109	19.7
T3 (> 5 cm)	332	1.3
Not stated	26	0.1
Receptor status		
ER positive	19,981	77.2
ER negative	3,103	12.0
ER unknown	2,803	10.8
PR positive	16,637	64.3
PR negative	6,332	24.5
PR unknown	2,918	11.3
Grade		
Well differentiated	6,877	26.6
Moderately differentiated	11,114	42.9
Poorly differentiated	5,880	22.7
Undifferentiated	267	1.0
Not determined/not stated	1,749	6.8
Histology		
Ductal	22,854	88.2
Lobular	2,501	9.7
Other/unknown	532	2.1
LN metastases		
0 positive LN	20,289	78.4
1 positive LN	2,981	11.5
2 positive LNs	1,000	3.9
≥ 3 positive LNs	1,617	6.2
Combined stage ^a		
I	17,066	65.9
II-A	6126	23.7
II-B	2014	7.8
III-A	455	1.8
III-B	119	0.5
III-C	107	0.4

ER estrogen receptor, PR progesterone receptor, LN lymph node

^a The American Joint Committee on Cancer 3rd edition was used to stage tumors between 1999 and 2003 while the 6th edition was used to stage tumors between 2004 and 2005

Fig. 1 Trends over time in breast conservation patients having same-day nodal staging

patient was considered to have had LM/SL attempted or performed if there was a claim for blue dye injection on the date of lumpectomy and/or a claim for radionuclide injection on the date of lumpectomy or up to seven days prior. Of note, ECE is not collected by SEER as a separate variable and cannot be determined from Medicare data. The most comprehensive data on ECE notes a rate of 25.7 % in sentinel nodes [10]. This value was used for calculation.

Trends were evaluated using Cochran–Armitage trend tests and from 1999 to 2005 rates were compared using Chi square tests. Trends in mean number of positive nodes were evaluated using linear regression. Differences in means were evaluated using *t*-tests and differences in medians were evaluated using Wilcoxon rank sum tests to compare distributions. Logistic regression was used to examine trends in positive node status, adjusting for age, tumor size, grade, and receptor status. Statistical significance was set at $p = 0.05$ (two-sided). Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

There were 25,887 women ≥ 65 years with invasive non-metastatic breast cancer who underwent BCS between 1999 and 2005. The majority of women were white, had few comorbidities, and had American Joint Committee on Cancer Stage I ductal carcinomas that were largely estrogen and/or progesterone receptor-positive (Table 1).

Within the entire cohort, 16,882 (65.2 %) underwent nodal staging (LM/SL with or without AD) on the day of their BCS procedure. The rate of same-day LM/SL increased from 22.7 % in 1999 to 83.8 % in 2005 ($p = 0.0003$), while

Fig. 2 Trends over time in for breast conservation patients' sentinel node technique

Fig. 3 Trends over time for nodal positivity

the rate of same-day AD decreased from 66.7 % in 1999 to 42.0 % in 2005 ($p < 0.0001$, Fig. 1).

Compared to the use of radionuclide alone, there were trends toward an increased use of blue dye alone and of both agents together for identification of the sentinel node ($p = 0.0003$). From 1999 to 2005, use of only radionuclide for the procedure declined from 39.2 to 18.6 % of patients. Over the same time period, the use of blue dye alone increased from 28.5 to 37.8 %, while use of both agents increased from 32.3 to 43.6 % of patients (Fig. 2).

Among the 16,674 women having T1/T2 tumors who underwent same-day LM/SL, the percentage with positive nodes decreased slightly from 22.0 % in 1999 to 18.4 % in 2005 ($p < 0.0001$). Over that same time period, the mean number of positive nodes increased from 1.93 in 1999 to 2.56 in 2005 ($p = 0.017$) while the mean number of lymph nodes removed decreased from 8.2 to 4.6 ($p < 0.0001$) (Fig. 3).

Within this same cohort, 3,280 women (19.7 %) had positive nodes, among whom 2,532 had 1–2 positive nodes. Assuming a sentinel node ECE rate of 25.7 %, which would mandate AD for 651 women with 1–2 positive nodes, the Z0011 paradigm would spare AD in 1,881 women, which is 57.4 % ($1,881 \div 3,280$) of those with T1/T2 tumors and positive nodes who undergo BCS [10].

There were 748 women with ≥ 3 positive nodes, 579 (77.4 %) of whom underwent same-day AD. A total of 160 of these women underwent re-excision or completion mastectomy at a later date, when delayed AD could be performed. A total of 419 ($579 - 160$) women with ≥ 3 positive nodes would therefore require an additional surgery date for the sole purpose of completion AD. Thus, the Z0011 paradigm, which requires waiting for the final pathologic evaluation of the sentinel nodes, would necessitate an additional surgery date for 1,070 ($651 + 419$) women, or 32.6 % ($1,070 \div 3,280$) of women with T1/T2 tumors and positive nodes who undergo BCS.

Discussion

Although the ACOSOG Z0011 trial was first published well over 3 years ago, there remains little data [11–13] on its impact on women undergoing BCS. With an increasing emphasis on health care costs and a widening promotion of breast conservation as a quality measure, there is a need to assess the impact of this study on the population of women choosing BCS [14]. As breast cancer is a disease of older age, the Medicare population is an appropriate cohort for evaluation, and has the advantage of consistency in insurance coverage to eliminate this issue as a confounder. The specific nature of the Medicare claims components also have provided a more detailed assessment of nodal staging patterns than would have been possible using SEER data alone. Using this data, we were able to estimate the percentages of patients who would be spared AD versus require additional surgery as a result of the new Z0011 paradigm.

From 1999 to 2005, the rate of same-day LM/SL increased while the rate of same-day AD decreased. These trends parallel the publication of a multitude of studies reporting the safety, feasibility, and accuracy of sentinel node techniques in clinically node-negative patients with breast cancer [15–18]. Our analysis primarily used Medicare claims but found trends that are similar to those analyses using SEER data alone [19, 20].

With respect to sentinel node technique, there was an increasing use of blue dye alone and of both agents when compared with radionuclide alone. In all the years except 1999, the most common technique was to use both agents. We believe the trends seen here are related to two factors.

Firstly, there is data suggesting use of both agents provides the greatest sensitivity and that use of both agents may facilitate learning the technique. Secondly, surgeons may favor blue dye over radionuclide as a single agent given the latter's inconvenience for the patient and greater difficulty in operative scheduling [21]. With imperfect concordance between agents, differences in the number of sentinel nodes identified using one versus two agents will likely affect the future impact of Z0011 [22]. Results from a 2001 survey of 410 Fellows of the American College of Surgeons are consistent with our conclusion that the use of both agents was most common, although this survey noted that 90 % indicated this was their practice, a figure much greater than our finding of 45.0 % in 2001 [23]. It remains unclear whether poor coding practices in our cohort, selection bias from the survey's respondents, or other factors account for the differences in rates.

There was a smaller proportion of node-positive women in 2005 compared to 1999 but a greater number of positive nodes in those having nodal disease despite fewer lymph nodes being removed. These trends may reflect earlier detection of disease, improved sentinel node technique, refined histopathologic analysis, and better prophylaxis of less aggressive disease over time. Meanwhile, among those with positive nodes, the average number increased from 1.93 to 2.56, which exceeds the Z0011 threshold for avoiding AD. Thus, while fewer breast conservation patients were applicable over time to the Z0011 paradigm, greater numbers of node-positive patients would still require AD by virtue of their numbers of positive nodes. The extremes of node-negative disease versus a greater burden of nodal disease in those with positive nodes appear to be increasing, which suggests a narrowing of the population to which Z0011 applies.

These nodal positivity trends in elderly American women differ from those observed in two Danish Breast Cancer Cooperative Group studies which also included younger women. In one of these studies, there was a 40 % increase in the number of node-positive women from 1996 to 2003. The authors believed this trend was due to more meticulous histopathologic analysis during later years [24]. In the other Danish study, the number of positive nodes removed during nodal staging decreased from 2.04 in 1978 to 0.64 in 1994, which was felt to be due to earlier detection of tumors during the later years [25].

We found that the Z0011 paradigm would spare 57.4 % of elderly women undergoing breast conservation with T1/T2 tumors and 1–2 positive nodes from AD. The percentage spared AD in this study is similar to that found when authors from Memorial Sloan-Kettering Cancer Center evaluated the theoretical impact of Z0011 on their clinically node-negative patients undergoing LM/SL from 1997

to 2006. This report found that 48 % of patients would be spared AD [26].

With respect to the impact of Z0011 on the need for additional surgery, we found that 32.6 % of our BCS cohort would require an additional surgery date for the sole purpose of completion AD after permanent section demonstrated ≥ 3 positive nodes or ECE. The tendency to wait for permanent section before proceeding with completion AD is on the rise. Weber et al. [26] found that the use of frozen section to enable completion AD during the same surgery decreased from 100 % in 1997 to 62 % in 2006, even before the Z0011 results were published. We would not expect a reversal in that trend, however, since a decline in the use of intraoperative evaluation is also consistent with the need to wait for permanent section results so that the presence of ECE can be assessed.

The Z0011 trial used ECE as an exclusion criterion for randomization because of the elevated risk of local recurrence that it confers. While a second Memorial study is one of the few to evaluate the impact of Z0011 in practice [11], it found ECE to be present in only 16 of 380 node-positive patients (4 %), far lower than the published estimate in the extensive analysis we have referenced here [10]. It remains uncertain which estimate is the more accurate, as it is possible that either this lower incidence may represent the true incidence in the subset of T1/T2 clinically node-negative breast cancers, or that this low incidence is unique to their patient population. As ECE was an exclusion criterion for entry, the Z0011 publications did not elaborate a denominator of who was excluded from the trial solely for because of ECE. SEER–Medicare data, used here, does not capture national ECE data, and so we utilized the most comprehensive study to date for our estimate [10].

The impact of Z0011 on breast conservation patients demonstrated in our study assumes a 100 % adoption rate for the paradigm, with application of its criteria precisely as defined by the trial. Although it may be reasonable to assume that the advantage of the Z0011 paradigm would persist as time moves forward, axillary surgery indications have been rapidly evolving for years, and data on the efficacy and role of axillary radiotherapy [27] continue to accrue. As the management paradigm of the axilla will likely continue to evolve, we cannot fully predict the impact that ACOSOG Z0011 will have.

There are few studies to date evaluating the impact of Z0011. In one reviewing 2,157 patients with invasive cancer undergoing breast conserving therapy at Memorial Sloan-Kettering Cancer Center, Dengel et al. [11] found that 84 % of breast conservation patients avoided AD and that the criteria for study entry predicted the burden of nonsentinel nodal axillary disease. They did not, however, evaluate the resulting reoperation rate from changes related to the need to use permanent section to assess ECE as we have here. More

recently, published and more consistent with our findings, a population-based study similar to our own [12] found that ADs would be spared in 38 % of patients, but they did not address ECE in their estimates, suggesting that the impact they predicted may be overstated.

All of these changes matter little, however, if the Z0011 results are not being applied, and to our knowledge, only one study to date has assessed the adoption of Z0011 in actual practice. Among surgeons in the Pacific Northwest responding to a survey, a total of 63 % reported performing fewer completion ADs, although nonadherence to the trial criteria was extensive. Fifty-one percent of respondents admitted that they do not perform AD when there were ≥ 3 positive sentinel nodes, and 59 % of respondents omitted AD for 1–2 positive nodes in the mastectomy setting [28].

In this study, Z0011 had a disadvantage of necessitating another surgery date for 33 % ($n = 1,070$) of the total cohort, but this does not take the inaccuracies of intraoperative nodal evaluation into consideration. Many institutions now perform imprint cytology to evaluate sentinel nodes, while using frozen section as a confirmation for equivocal cases. Touch preparations and frozen sections have sensitivities of 63 and 75 %, respectively [29, 30], although the national frequency of use of these techniques individually and together remains unknown. The false negatives occurring with these techniques should increase the reoperation rate of those having intraoperative evaluation and not undergoing Z0011, while decreasing the reoperative disadvantage of waiting for permanent section in patients undergoing the Z0011 paradigm. The magnitude of the effect of such false negatives is impossible to estimate here, however, because SEER–Medicare data does not detail intraoperative pathology and false-negative data. Additionally, even if one were to assume a specific false-negative rate, the amount of overlap between those having ECE or reoperation for other reasons would still be speculative.

Although SEER–Medicare is one of the largest databases in the United States, it does not include data on the uninsured nor those with private insurance, making it unclear whether our findings have implications beyond the Medicare patient. The results are also contingent on accurate coding. Fortunately, the large sample size in the SEER–Medicare linked database likely mitigates this problem. Although SEER data has been found to under-report LM/SL, this does not apply to the Medicare codes on which we based our data [31]. Furthermore, it is unknown whether Z0011 will change the future patterns of care in these breast conservation patients to the degree we estimate that it would have for the period of study between 1999 and 2005. The impact in the coming years will likely be dependent on adoption rates and other factors. Nevertheless, this study demonstrates trends not seen previously.

In conclusion, the data here suggest that Z0011, if applied in the current axillary treatment paradigm, may increase the number of BCS patients requiring additional surgery but decrease the number requiring AD to a greater extent. The implications of sparing these breast conservation patients the morbidity of both additional surgery and AD while also lowering associated costs, anxiety, and complications appear promising, but have yet to be definitively determined.

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