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ORIGINAL ARTICLE – GLOBAL HEALTH SERVICES RESEARCH

The Association Between Surgical Axillary Staging, Adjuvant Treatment Use and Survival in Older Women with Early Stage Breast Cancer: A Population-Based Study

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ABSTRACT

Background. Choosing Wisely guidelines recommend against surgical axillary staging (AS) in women ≥70 years with ER+/HER2– early stage breast cancer (BC). This study examined the impact of AS omission on survival in older patients with BC.

Methods. This was a population-based cohort study using health administrative data in Ontario, Canada. We identified women aged 65–95 years who underwent surgery for Stage I/II BC between 2010 and 2016. Patients were weighted by propensity scores for receipt of AS that included patient and disease characteristics using overlap weights. Association with overall survival (OS) was calculated using weighted Cox models, and breast cancer-specific survival (BCSS) was calculated using weighted Fine and Gray models, adjusting for biomarkers and adjuvant treatments. Adjuvant treatment receipt was modelled with weighted log-binomial models.

Results. Among 17,370 older women, the 1771 (10.2%) who did not undergo AS were older, more comorbid, and less likely to undergo mastectomy. Women who did not undergo AS were less likely to receive adjuvant chemotherapy (RR 0.68, 95% CI 0.57–0.82), endocrine therapy (RR 0.85, 95% CI 0.81–0.89) or radiotherapy (RR 0.69, 95% CI 0.65–0.74). After weighting and adjustment, there was no significant difference in BCSS (sdHR 0.98, 95% CI 0.77–1.25), but women who did not undergo AS had worse OS (HR 1.14, 95% CI 1.04–1.25). The results among 6215 ER+/HER2– women ≥70 years undergoing SLNB vs no AS were similar.

Conclusions. The omission of AS in older women with early stage BC was not associated with adverse BCSS, although OS was worse.

The use of surgical axillary lymph node staging among older women with early stage breast cancer is controversial. Two randomized controlled trials completed between 1993 and 2002 showed no significant difference in survival between women who received axillary lymph node dissection (ALND) and no staging.[1–3] These findings informed clinical guidelines[4] and a recommendation from the Choosing Wisely campaign[5] to omit surgical axillary staging in women ≥ 70 years of age with estrogen receptor (ER)+, human epidermal growth factor receptor (HER)-2(–) early stage breast cancer.

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Despite this evidence, surgeons have expressed concern with the recommendations, citing the low morbidity of modern staging procedures such as sentinel lymph node biopsy (SLNB), and the utility of SLNB in making decisions about adjuvant treatments.[6,7] Indeed, population-based studies have demonstrated that older women who do not undergo axillary staging are approximately half as likely to receive adjuvant chemotherapy or radiotherapy.[8] Surgeons' practice patterns have reflected these concerns–over 80% of older women continue to receive axillary staging, with no appreciable decrease over time.[8–10]

Population-based studies of axillary staging have found that patients without axillary staging tend to be older, with more comorbid illnesses, and more favorable disease characteristics than those who underwent staging, suggesting that surgeons are selective in their omission of the procedure.[8,10,11] Despite this, observational research studies report that older women who do not undergo axillary staging have worse overall survival, even after adjustment for patient and disease characteristics; however, these studies have limitations.[8,10,11] In particular, there has been inconsistent use of competing risks analysis[10] (which considers the competing risks of death from other causes in this elderly population), comorbidity is not available in some data sources,[8] HER2 status is not incorporated in all analyses,[10,11] and information on adjuvant treatments is not comprehensive.[8] It remains unclear to what extent the association between axillary staging and survival is due to unmeasured confounding or underutilization of adjuvant treatments informed by SLNB. We assembled a population-based cohort of women 65 years and older undergoing surgery for early stage breast cancer in Ontario between 2010 and 2016.

The aim of this study was to examine the impact of omitting surgical axillary staging on breast cancer specific and overall survival in older women with early stage breast cancer, addressing limitations of previous work and exploring the role adjuvant treatment use may have in modifying the effect of axillary staging omission.

METHODS

Study Design and Data Source

We performed a population-based cohort study using linked health administrative data in Ontario, Canada. Data were obtained from ICES[12] (formerly known as the Institute for Clinical Evaluative Sciences), an independent, non-profit research institute that maintains health administrative data for more than 14 million Ontarians. These data sets were linked using unique encoded identifiers and analyzed at ICES (Supplementary Material 1). We followed the STROBE statement in the preparation of this manuscript (Supplementary Material 2).[13] The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board.

Patient Population

Using the Ontario Cancer Registry (OCR), we identified Ontario women aged 65–95 years with valid Ontario Health Insurance Plan (OHIP) numbers who underwent surgery for Stage I/II breast cancer diagnosed between January 1, 2010 and December 31, 2016. International Classification of Diseases for Oncology (ICD-O-3) codes were used to select patients with invasive breast neoplasms with histology of interest (Supplementary Material 3).

Exclusion criteria included (a) invalid birth/death date or male sex, (b) non-Ontario resident, (c) not pathologic Stage I/II disease, (d) previous history of breast cancer, (e) invalid records for retrieving tumor information, (f) did not receive breast surgery within 6 months of diagnosis, (g) neoadjuvant chemotherapy, (h) bilateral disease, or (i) neoadjuvant endocrine therapy. Clinical stage was not available in the data sets used and could not be used as an exclusion criterion. This is consistent with limitations of similar studies using the SEER cancer registry, where clinical stage is not additionally available in patients with pathological nodal information.[8,10]

Exposure and Covariates

The primary exposure of interest was omission of axillary staging, compared with receiving axillary staging. Procedure codes representing SLNB and ALND (Supplementary Material 4) were used to identify women who received axillary staging. Women who underwent mastectomy or breast conserving surgery (BCS) without procedural codes indicating SLNB or ALND were defined as not receiving axillary staging. Axillary procedures did not need to occur on the same day as the primary breast surgery to be included. If ALND was performed after an initial SLNB, but within 6 months of the breast cancer diagnosis date, axillary staging was classified as ALND.

Patient characteristics were determined from the Registered Persons Database, disease/tumor characteristics were taken from the OCR, and healthcare interactions/surgeries were assessed using the Canadian Institute for Health Information Discharge Abstract Database. Covariates included age at diagnosis, year of diagnosis, histology, surgery type (mastectomy or BCS), tumor grade, tumor size (< 2 cm or ≥ 2 cm), hormone receptor status and HER2 status, laterality, Charlson comorbidity score (0/missing, 1, 2, and ≥ 3), previous history of non-breast

cancer (< 5 years, ≥ 5 years, no past malignancy), socioeconomic status/rurality, and receipt of adjuvant chemotherapy, radiotherapy, and endocrine therapy. The 7th edition of the American Joint Committee on Cancer (AJCC) guidelines was used for breast cancer stage.

We determined socioeconomic status using income quintiles from Canadian census data, which assign individuals into income strata based on their postal code of residence.[14] Rurality was similarly derived from Canadian census data, with rural status defined as residence in a community ≤ 10,000 individuals in size. Adjuvant chemotherapy was defined as chemotherapy administered within 12 months following diagnosis. Chemotherapy was determined from the Cancer Activity Level Reporting database, New Drug Funding Plan database, and OHIP billing codes. Adjuvant radiotherapy was defined using the same data sources as radiotherapy administered within 12 months following diagnosis, and was categorized as chest wall/breast radiotherapy, axillary radiotherapy, or combination radiotherapy using body region codes. Endocrine therapy was defined as the administration of the following medications, as observed in the Ontario Drug Benefit database, at any point between diagnosis and the last day of follow-up: tamoxifen, anastrozole, letrozole, exemestane, and raloxifene. There was no limitation on administration date as endocrine therapy would be unlikely to be used as the sole treatment for newly metastatic or recurrent disease.

Age was treated as continuous and the remaining covariates were considered categorical. HER2 status was only available in patients diagnosed in 2012 and later and was therefore not included in the main analysis. If HER2 status was missing, and patients received trastuzumab, they were considered to be HER2 positive.

Outcomes

The primary outcomes of interest were overall survival (OS) and breast cancer-specific survival (BCSS). The index date was the date of breast cancer diagnosis. OS was defined as the number of months from index date to death, or until January 31, 2020. Patients were censored at the study cut-off. Deaths for BCSS were classified as death due to breast cancer, or death due to other causes. The final date of follow-up for BCSS was June 30, 2017.

Cause of death was determined from the Ontario Cancer Registry and the Ontario Office of the Registrar General. To be defined as a breast cancer death, a woman must have a death certificate including breast cancer (ICD-10 code C50^^) in addition to evidence of the following: recurrence accompanied by change in treatment (surgery, chemotherapy, radiotherapy, or endocrine therapy) within 60 days, recurrence or change in treatment alone with no evidence of a second primary malignancy, admission to hospital with the primary diagnosis of breast cancer within 60 days of death, or palliative care billing codes with no evidence of a second primary malignancy. Women with breast cancer on their death certificate with no evidence of recurrent or progressive disease underwent independent review of their most recent hospitalization prior to death by two members of the research team (MC and LP) to determine cause of death. Conflicts were resolved by discussion and, if required, a third reviewer (ER) was used for adjudication.

Secondary outcomes included receipt of adjuvant treatments after surgery, including chemotherapy, endocrine therapy, and radiotherapy.

Statistical Analysis

Baseline characteristics stratified by axillary staging status were ascertained and differences between the two groups were assessed using standardized mean differences (SMDs). To address confounding between those who did and those who did not receive axillary staging, we built a propensity score model for axillary staging including age at diagnosis, year of diagnosis, socioeconomic status, tumor size, ER/progesterone receptor (PR) receptor status, grade, Charlson comorbidity score, breast surgery type, histology, and history of cancer. Receipt of adjuvant treatments was not included in the propensity score model as they occur temporally after axillary staging. However, these important potential confounders were included in the final survival models as non-time-varying covariates. Patients were weighted by their propensity scores using overlap weights.[15–17]

We generated weighted and unweighted Kaplan-Meier curves to compare OS between women who did and did not undergo axillary staging. The hazard ratio (HR) and 95% confidence interval (CI) of axillary staging omission was determined using weighted Cox proportional hazards models. A robust sandwich estimator was used to estimate the variance. For BCSS, we accounted for the competing risk of death from non-breast-cancer causes, and the subdistribution hazard ratio (sdHR) and 95% CI were determined from weighted Fine and Gray models.[18] Additional post-weighting adjustment was performed for receipt of adjuvant treatments. We were a priori interested in exploring the impact of adjuvant treatments on omission of axillary staging; thus, models were specified including interaction terms between each of chemotherapy, endocrine therapy, and radiotherapy administration and axillary staging strategy.

For the secondary outcomes, adjuvant treatment receipt was modelled with weighted log-binomial models and risk ratios (RR) with 95% CIs reported. Subgroup analyses were additionally performed by age (65–69 and 70+ years), Charlson score (0/missing and 1+), and lobular histology. We also examined women in whom HER2 status

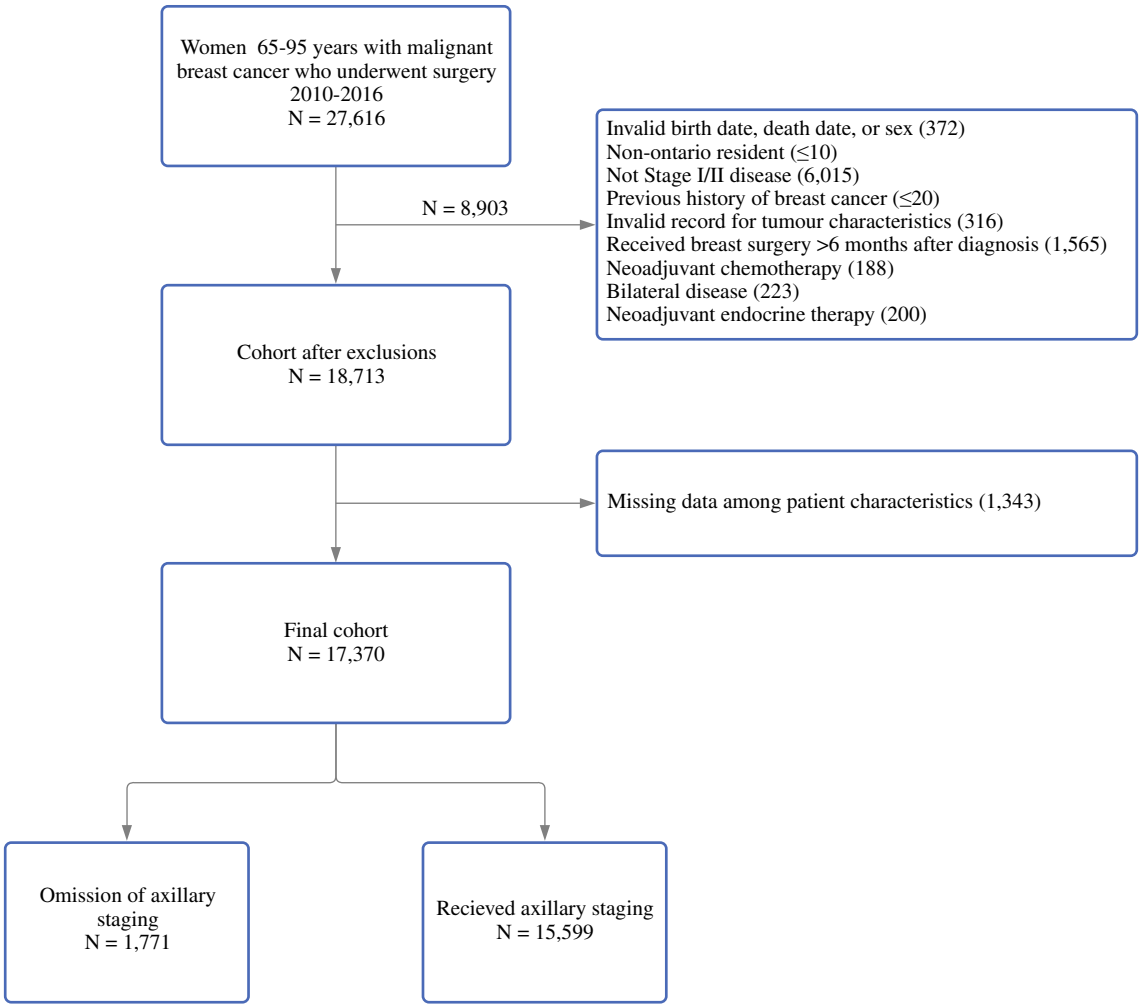

FIG. 1 Development of a cohort of older breast cancer patients. Exclusions were applied sequentially in the order presented

was available (diagnoses after 2012). This cohort was restricted to women age 70+ with ER+, HER2 negative tumors undergoing either SLNB or no axillary staging (the clinical scenario discussed in the Choosing Wisely guidelines[5]).

Patients with missing data for any covariate except HER2 status were excluded. The data analysis for this paper was generated using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

We identified 27,616 women aged 65–95 years undergoing surgery for malignant breast cancer between 2010 and 2016 in the OCR. After application of the exclusion criteria, 17,370 women with Stage I/II breast cancer were included (Fig. 1). Of these, 15,599 (89.8%) underwent axillary surgery and 1771 (10.2%) did not. Baseline patient characteristics are presented in Table 1.

Omission of Axillary Staging Compared with those that underwent axillary staging, those that did not were older (median 82 years vs 72 years; $p < 0.001$, SMD = 0.87). More than 90% of women under the age of 80 underwent axillary staging, while the majority of women between 90 and 95 years did not undergo axillary staging (Fig. 2). Women who did not undergo axillary staging were also more likely to have BCS (77.8 vs. 74.1%; $p < 0.001$, SMD = 0.08), have comorbid illnesses (8.6% Charlson 3+ vs. 3.8%; $p < 0.001$, SMD = 0.20), and larger tumors (49.6% $\geq$ 2 cm vs. 41.2%; $p < 0.001$, SMD = 0.17). Patients who did not have staging were similar in terms of ER positivity and PR positivity compared with those who had staging (ER positive 88.9% vs. 88.7% and PR positive 80.6 vs. 79.6%; $p > 0.05$ for both). After the cohort was weighted

TABLE 1 Patient characteristics before and after overlap propensity score weighting

Characteristic	Value	Cohort (N = 17,370)	Before propensity score weighting				After propensity score weighting		
			Axillary staging (N = 15,599)	No axillary staging (N = 1771)	*p*-value	SMD	Axillary staging (N = 1370.1)*	No axillary staging (N = 1310.1)*	SMD
Age	Mean ± SD	73.79 ± 6.82	73.07 ± 6.27	80.12 ± 8.13	< 0.001	0.97	78.52	78.52	0.000
	Median (IQR)	72 (68-78)	72 (68-77)	82 (73-87)	< 0.001	0.87			
Year of cancer diagnosis	2010	2196 (12.6%)	1915 (12.3%)	281 (15.9%)	< 0.001	0.1	211 (15.4%)	203.5 (14.9%)	0.015
	2011	2388 (13.7%)	2117 (13.6%)	271 (15.3%)		0.05	230.2 (16.8%)	205.5 (15%)	0.049
	2012	2254 (13.0%)	1998 (12.8%)	256 (14.5%)		0.05	191.5 (14%)	201.7 (14.7%)	0.021
	2013	2502 (14.4%)	2232 (14.3%)	270 (15.2%)		0.03	192.1 (14%)	213.9 (15.6%)	0.045
	2014	2601 (15.0%)	2330 (14.9%)	271 (15.3%)		0.01	184.1 (13.4%)	213.6 (15.6%)	0.061
	2015	2657 (15.3%)	2422 (15.5%)	235 (13.3%)		0.06	177.8 (13%)	181.8 (13.3%)	0.008
	2016	2772 (16.0%)	2585 (16.6%)	187 (10.6%)		0.18	183.2 (13.4%)	150.3 (11%)	0.074
Histology	Cystic, mucinous, and serous neoplasms	578 (3.3%)	490 (3.1%)	88 (5.0%)	< 0.001	0.09	61.8 (4.5%)	61.8 (4.5%)	0.000
	Ductal and lobular neoplasms	16,072 (92.5%)	14,459 (92.7%)	1613 (91.1%)		0.06	1253.5 (91.5%)	1253.5 (91.5%)	0.000
	Other	720 (4.1%)	650 (4.2%)	70 (4.0%)		0.01	54.8 (4%)	54.8 (4%)	0.000
Laterality	Left	8922 (51.4%)	8022 (51.4%)	900 (50.8%)	0.628	0.01	702.5 (51.3%)	702.5 (51.3%)	0.000
	Right	8448 (48.6%)	7577 (48.6%)	871 (49.2%)		0.01	667.6 (48.7%)	667.6 (48.7%)	0.000
Tumor Size	<2cm	10,058 (57.9%)	9165 (58.8%)	893 (50.4%)	< 0.001	0.17	725.9 (53%)	725.9 (53%)	0.000
	≥2cm	7312 (42.1%)	6434 (41.2%)	878 (49.6%)		0.17	644.2 (47%)	644.2 (47%)	0.000
Past malignancies	<5 years	578 (3.3%)	503 (3.2%)	75 (4.2%)	< 0.001	0.05	57.7 (4.2%)	57.7 (4.2%)	0.000
	≥5 years	1197 (6.9%)	1041 (6.7%)	156 (8.8%)		0.08	114.5 (8.4%)	114.5 (8.4%)	0.000
	No past malignancy	15,595 (89.8%)	14,055 (90.1%)	1540 (87.0%)		0.1	1197.9 (87.4%)	1197.9 (87.4%)	0.000
Breast surgery	BCS	12,941 (74.5%)	11,564 (74.1%)	1377 (77.8%)	< 0.001	0.08	1043.2 (76.1%)	1043.2 (76.1%)	0.000
	Mastectomy	4429 (25.5%)	4035 (25.9%)	394 (22.2%)		0.08	326.9 (23.9%)	326.9 (23.9%)	0.000
ER status	ER+	15,407 (88.7%)	13,833 (88.7%)	1574 (88.9%)	0.803	0.01	1219.1 (89%)	1219.1 (89%)	0.000
	ER-	1963 (11.3%)	1766 (11.3%)	197 (11.1%)		0.01	151 (11%)	151 (11%)	0.000
PR status	PR+	13,844 (79.7%)	12,416 (79.6%)	1428 (80.6%)	0.304	0.03	1102.4 (80.5%)	1102.4 (80.5%)	0.000
	PR-	3526 (20.3%)	3183 (20.4%)	343 (19.4%)		0.03	267.7 (19.5%)	267.7 (19.5%)	0.000
HER2 status	Negative	11,544 (66.5%)	10,428 (66.9%)	1116 (63.0%)	< 0.001	0.08	846.6 (61.8%)	877.8 (64.1%)	0.047
	Positive	1242 (7.2%)	1139 (7.3%)	103 (5.8%)		0.06	82.5 (6%)	83.3 (6.1%)	0.003
	Pre-2012 diagnosis	4584 (26.4%)	4032 (25.8%)	552 (31.2%)		0.12	441.2 (32.2%)	409 (29.9%)	0.051
Grade	Low	4619 (26.6%)	4130 (26.5%)	489 (27.6%)	0.495	0.03	377.7 (27.6%)	377.7 (27.6%)	0.000
	Medium	8618 (49.6%)	7742 (49.6%)	876 (49.5%)		0	680.1 (49.6%)	680.1 (49.6%)	0.000
	High	4133 (23.8%)	3727 (23.9%)	406 (22.9%)		0.02	312.2 (22.8%)	312.2 (22.8%)	0.000

Table 1 (continued)

Characteristic	Value	Cohort (N = 17,370)	Before propensity score weighting				After propensity score weighting		
			Axillary staging (N = 15,599)	No axillary staging (N = 1771)	*p*-value	SMD	Axillary staging (N = 1370.1)*	No axillary staging (N = 1310.1)*	SMD
Charlson comorbidity score	0/missing	13,981 (80.5%)	12,740 (81.7%)	1241 (70.1%)	< 0.001	0.27	994.4 (72.6%)	994.4 (72.6%)	0.000
	1	1623 (9.3%)	1396 (8.9%)	227 (12.8%)		0.12	166.7 (12.2%)	166.7 (12.2%)	0.000
	2	1016 (5.8%)	866 (5.6%)	150 (8.5%)		0.11	108 (7.9%)	108 (7.9%)	0.000
	≥3	750 (4.3%)	597 (3.8%)	153 (8.6%)		0.2	101.1 (7.4%)	101.1 (7.4%)	0.000
Socioeconomic status	1	2786 (16.0%)	2475 (15.9%)	311 (17.6%)	0.185	0.05	234.2 (17.1%)	234.2 (17.1%)	0.000
	2	3135 (18.0%)	2811 (18.0%)	324 (18.3%)		0.01	249.2 (18.2%)	249.2 (18.2%)	0.000
	3	2998 (17.3%)	2677 (17.2%)	321 (18.1%)		0.03	245.7 (17.9%)	245.7 (17.9%)	0.000
	4	2942 (16.9%)	2669 (17.1%)	273 (15.4%)		0.05	215.7 (15.7%)	215.7 (15.7%)	0.000
	5	3214 (18.5%)	2892 (18.5%)	322 (18.2%)		0.01	252 (18.4%)	252 (18.4%)	0.000
	Rural	2295 (13.2%)	2075 (13.3%)	220 (12.4%)		0.03	173.5 (12.7%)	173.5 (12.7%)	0.000
Adjuvant radiotherapy†	Any axillary radiation	1736 (10.0%)	1659 (10.6%)	77 (4.3%)	< 0.001	0.24	124.7 (9.1%)	65.1 (4.8%)	0.172
	Chest wall/breast only	9232 (53.1%)	8651 (55.5%)	581 (32.8%)		0.47	689.8 (50.4%)	498.2 (36.4%)	0.285
	No radiotherapy	6402 (36.9%)	5289 (33.9%)	1113 (62.8%)		0.61	555.6 (40.6%)	806.9 (58.9%)	0.373
Adjuvant chemotherapy†	No	14,018 (80.7%)	12,359 (79.2%)	1659 (93.7%)	< 0.001	0.43	1217.5 (88.9%)	1266.4 (92.4%)	0.123
	Yes	3352 (19.3%)	3240 (20.8%)	112 (6.3%)		0.43	152.6 (11.1%)	103.7 (7.6%)	0.123
Endocrine therapy†	No	5332 (30.7%)	4474 (28.7%)	858 (48.4%)	< 0.001	0.41	487.1 (35.6%)	622.2 (45.4%)	0.202
	Yes	12,038 (69.3%)	11,125 (71.3%)	913 (51.6%)		0.41	883 (64.5%)	747.9 (54.6%)	0.202

SMD: standardized mean difference, *BCS*: breast conserving surgery, *ER*: estrogen receptor, *PR*: progesterone receptor, *HER2*: human epidermal growth factor receptor 2

Balance between the groups is assessed using SMDs. Larger values indicate a greater difference, with values > 0.1 defined as an important difference

*Sample sizes represent the weighted size of the cohort

†Radiotherapy, chemotherapy, and endocrine therapy were not included in the propensity score model

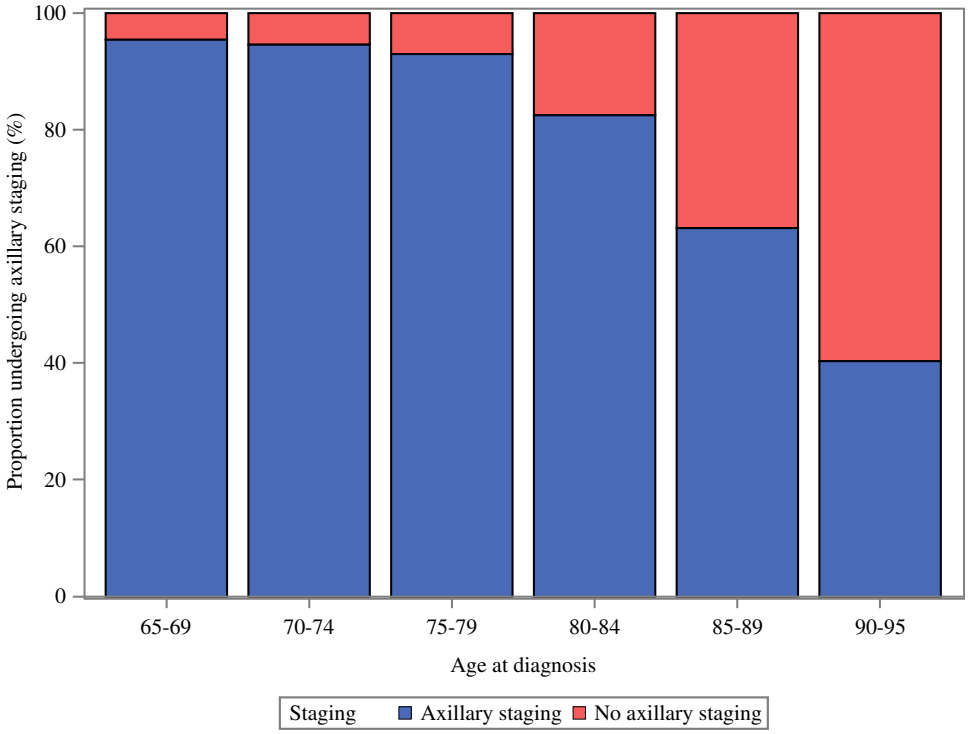

FIG. 2 Proportion of patients receiving axillary staging by age

by the propensity score, important confounders included in the propensity score model were well balanced between the two groups (all SMDs < 0.1; Table 1).

Overall Survival

Over the study period, 3393 women died (19.5%) and median follow-up was 6.3 years (IQR 4.7–8.2 years). Unadjusted 5-year overall survival was lower for women who did not undergo axillary staging (68.0%, 95% CI 65.7–70.2 vs. 87.7%, 95% CI 87.1–88.2; $p < 0.001$). The weighted Kaplan-Meier curve is presented in Fig. 3A. Unadjusted curves are shown in Supplementary Material 5. After propensity score weighting and adjustment accounting for age, year of diagnosis, SES, tumor size, receptor status, tumor grade, comorbidity, surgery type, tumor histology, cancer history, and adjuvant treatments, women who did not undergo axillary staging continued to have worse OS (HR 1.14, 95% CI 1.04–1.25; Table 2). However, there were differences among subgroups. There was no significant difference in OS after weighting and adjustment among women aged 65–69 (HR 1.35, 95% CI 0.95–1.90), and those with no comorbidities (HR 1.09, 95% CI 0.97–1.23). Subgroup analyses in older women (70+ years), patients with lobular histology, and those with Charlson comorbidity scores of 1 or greater had results similar to the main analysis. The results among 6215 ER+/HER2- women ≥ 70 years undergoing SLNB vs no axillary staging were also similar (adjusted HR 1.24, 95% CI 1.07–1.45).

Breast Cancer-Specific Survival

Among the 3393 deaths observed in the cohort, 564 (16.7%) were determined to be breast cancer deaths. Median follow-up was 3.5 years (IQR 1.9–5.3 years). For women who did not undergo axillary staging, there was a higher 5-year incidence of breast cancer deaths (7.6%, 95% CI 6.1–9.2 vs. 4.3%, 95% CI 3.9–4.7; $p < 0.001$; Fig. 3B and Supplementary Material 6). However, after weighting and adjustment for covariates, there was no significant difference between the groups for BCSS (sdHR 0.98, 95% CI 0.77–1.25). Similar results were seen for subgroups including older vs younger women, those with and without comorbidities, patients with lobular carcinoma, and patients meeting the Choosing Wisely criteria (ER+/HER2– women ≥ 70 years undergoing SLNB vs no axillary staging). These results are shown in Table 2.

Receipt of Adjuvant Treatments

At baseline, 20.8% of women who received axillary staging received adjuvant chemotherapy compared with 6.3% of women who did not undergo staging ($p < 0.001$; SMD = 0.43). Similar patterns were seen for radiotherapy and endocrine therapy (Table 1). After propensity score weighting, women who did not undergo axillary staging

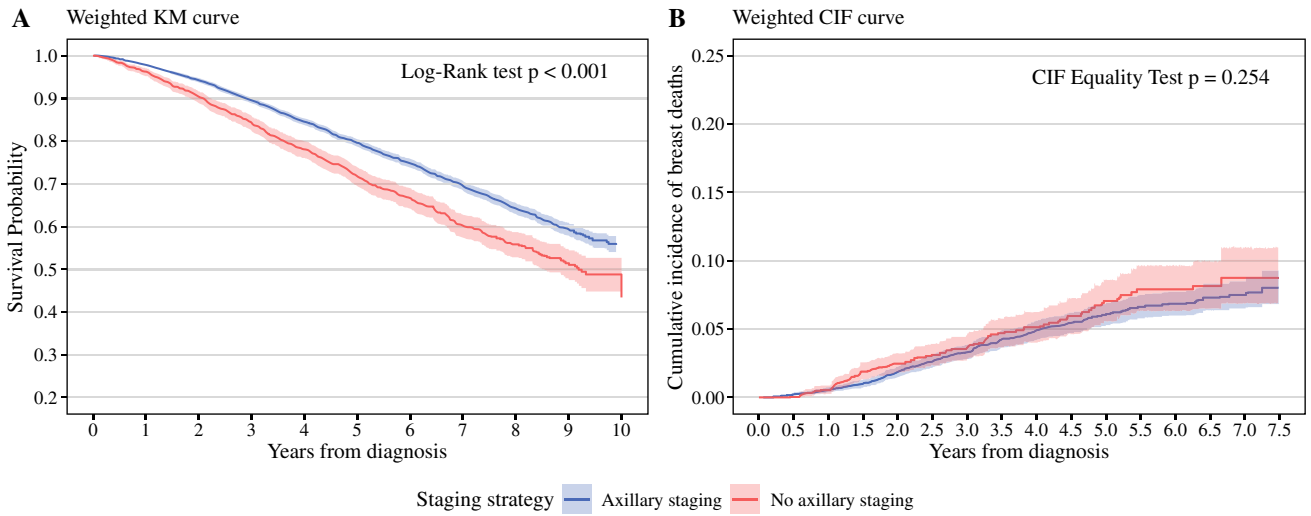

FIG. 3 (**A**) Weighted Kaplan-Meier (KM) curve demonstrating overall survival among women receiving and not receiving axillary staging, and (**B**) weighted cumulative incidence function (CIF) curves demonstrating breast cancer deaths between women receiving and not receiving axillary staging

continued to be less likely to receive adjuvant chemotherapy (risk ratio [RR] 0.68, 95% CI 0.57–0.82), endocrine therapy (RR 0.85, 95% CI 0.81–0.89) or breast/chest wall radiotherapy (RR 0.69, 95% CI 0.65–0.74). However, these patients were also more likely to receive axillary radiotherapy (RR 1.33, 95% CI 1.06–1.66). These results are presented in Table 3.

Differences were seen among subgroups. When restricted to those with comorbidities or lobular histology, there were no significant differences in adjuvant chemotherapy use by axillary staging strategy (Table 3). Patients were less likely to receive endocrine therapy or breast/chest wall radiotherapy in all subgroups examined. The finding that patients not receiving axillary staging were more likely to have axillary radiotherapy was only found among those with no comorbidities (RR 1.40, 95% CI 1.09–1.81) and patients 70 years and older (RR 1.32, 95% CI 1.02–1.70).

Adjuvant Treatments Modified the Effect of Axillary Staging Omission

To assess whether the effect of axillary staging on survival was modified by adjuvant treatment use, adjusted survival models included an interaction term between these factors (Fig. 4). We observed differences in overall survival according to adjuvant treatment use. Women who did not undergo axillary staging and did not receive adjuvant treatments had worse OS compared with women who had axillary staging without adjuvant treatments. This was shown for chemotherapy (HR 1.14, 95% CI 1.04–1.25), endocrine therapy (HR 1.19, 95% CI 1.04–1.35), and radiotherapy (HR 1.23, 95% CI 1.10–1.38). However, among patients who received adjuvant chemotherapy, endocrine therapy, chest wall/breast radiotherapy, or axillary radiotherapy, there were no significant differences in OS by axillary staging strategy (Fig. 4A).

There were no significant differences in BCSS after adjustment between women who did and did not receive axillary staging according to adjuvant treatment use (Fig. 4B).

DISCUSSION

This population-based study of older women with early stage breast cancer in Ontario showed that women who did not undergo staging were older, had more comorbidities, and had larger tumors. These patients were also significantly less likely to receive adjuvant chemotherapy, endocrine therapy, or chest wall/breast radiotherapy. After adjustment for baseline characteristics, omission of axillary staging was associated with worse overall survival, but not breast cancer-specific survival. Results were similar when restricted to women meeting the Choosing Wisely criteria (age 70+ with ER+, HER2 negative tumors undergoing either SLNB or no axillary staging). Importantly, omission of axillary staging was not associated with worse BCSS among women who did not receive further adjuvant treatments.

There is a growing literature demonstrating that the proportion of older breast cancer patients who do not undergo axillary staging is less than 20%, and does not appear to be decreasing over time.[8–10,19] Researchers have highlighted a need to understand factors associated with omission of axillary staging.[9] Consistent with prior research,[8,10,11] women who did not have staging were older

TABLE 2 Overall survival and breast cancer-specific survival, comparing women who did not receive axillary staging with those who did receive staging

Cohort	Sample size	Number of deaths	Number of breast cancer deaths	Overall survival, HR (95% CI)		Breast cancer-specific survival, sdHR (95% CI)	
				Unweighted	Weighted and adjusted	Unweighted	Weighted and adjusted
All ages, 2010 to 2016	17,370	3393	564	2.789 (2.568, 3.029)	1.136 (1.036, 1.246)	1.806 (1.458, 2.237)	0.979 (0.767, 1.249)
Ages 65-69, 2010 to 2016	5831	544	100	1.467 (1.045, 2.06)	1.348 (0.954, 1.904)	0.972 (0.398, 2.379)	1.114 (0.416, 2.987)
Ages 70+, 2010 to 2016	11,539	2849	464	2.516 (2.309, 2.742)	1.118 (1.014, 1.233)	1.647 (1.317, 2.06)	0.985 (0.762, 1.274)
Charlson score 0/Missing, 2010 to 2016	13,981	2210	418	2.563 (2.301, 2.855)	1.09 (0.967, 1.228)	1.71 (1.312, 2.229)	0.98 (0.725, 1.324)
Charlson score 0/Missing, age 75+, 2010 to 2016	5076	1431	250	1.986 (1.763, 2.237)	1.073 (0.938, 1.229)	1.365 (1.012, 1.841)	0.955 (0.678, 1.344)
Charlson score 1+, 2010 to 2016	3389	1183	146	2.553 (2.247, 2.902)	1.284 (1.108, 1.488)	1.794 (1.24, 2.595)	1.013 (0.669, 1.535)
Lobular, 2010 to 2016	2465	471	57	3.485 (2.819, 4.307)	1.437 (1.129, 1.831)	1.996 (1.056, 3.771)	0.764 (0.368, 1.587)
ER+, HER2-, no axillary dissection, 2012 to 2016, age 70+	6215	1072	111	2.949 (2.586, 3.362)	1.243 (1.068, 1.446)	2.414 (1.607, 3.626)	1.083 (0.665, 1.762)

Models were weighted by the overlap propensity score weights, and further adjusted for receipt of adjuvant chemotherapy, radiotherapy, or endocrine therapy. Analyses are presented for the entire study cohort, and for subgroups of interest

HR: hazard ratio, *sdHR*: subdistribution hazard ratio, *CI*: confidence interval, *ER*: estrogen receptor, *HER2*: human epidermal growth factor receptor 2

and had more comorbidities. Although previous studies have shown more favorable disease characteristics for these women, we found these patients were more likely to have larger tumors.[8,10]

This study builds upon previous observational studies in this area, and addresses some important limitations of the literature. In a study of 157,584 older women in the National Cancer Database (NCDB), Chagpar et al.[10] showed omission of axillary staging was associated with worse OS (HR 1.58, 95% CI 1.53–1.63), even after adjustment for patient and disease characteristics. The same authors performed a parallel analysis in the SEER registry (N = 115,059), showing similar results for OS (HR 2.39, 95% CI 2.33–2.45) and BCSS (HR 2.21, 95% CI 2.09–2.34). Our group performed a replication study[8] in the SEER registry (N = 144,329), utilizing more advanced methods of addressing confounding (propensity score overlap weighting) and competing risks analysis for BCSS. Although we also found that omission of axillary staging was associated with worse OS (HR 1.22, 95% CI 1.19–1.25) and BCSS (HR 1.14, 95% CI 1.08–1.21), the effect estimates were more attenuated compared with the early Chagpar et al.[10] study. However, we did not have access to comorbidity data in SEER, and details surrounding adjuvant treatment were limited.

The current study is able to address the limitations of the prior analyses. We have incorporated comorbidity data into the propensity score model and, after weighting, the cohort was well-balanced with respect to this confounder. Using healthcare administrative data sets, we were also able to accurately determine adjuvant chemotherapy, endocrine therapy, and radiotherapy use and incorporate all three factors into our survival models. Our results show a further attenuation of the effect size for omission of axillary staging on OS (HR 1.14, 95% CI 1.04–1.25), with a lower confidence limit near the null. Our results for BCSS show no significant difference between the two staging strategies (HR 0.98, 95% CI 0.77–1.25). These findings suggest that we have addressed unmeasured confounding to a greater degree than previous studies, and omission of axillary staging may not adversely affect BCSS. We have also confirmed these results in a population that meets the Choosing Wisely criteria.

There is a clear relationship between the decision to omit axillary staging and receipt of adjuvant treatments.[20] We have confirmed these findings, showing that women who did not receive axillary staging were less likely to have adjuvant chemotherapy, endocrine therapy, or chest wall or breast radiotherapy. However, our study is the first to examine axillary radiotherapy separately from chest wall or breast radiotherapy, and showed omission of axillary staging was associated with increased likelihood of receiving axillary radiotherapy. This association was

TABLE 3. Receipt of adjuvant treatments, comparing women who did not receive axillary staging with those who did receive staging

Cohort	Sample size	Chemotherapy, RR (95% CI)	Endocrine therapy, RR (95% CI)	Radiotherapy, RR (95% CI)	
				Breast radiotherapy	Axillary radiotherapy
All ages, 2010 to 2016	17,370	0.679 (0.565, 0.816)	0.847 (0.808, 0.887)	0.691 (0.651, 0.735)	1.326 (1.063, 1.655)
Ages 65-69, 2010 to 2016	5831	0.714 (0.556, 0.917)	0.915 (0.846, 0.991)	0.895 (0.823, 0.972)	1.246 (0.798, 1.945)
Ages 70+, 2010 to 2016	11,539	0.624 (0.484, 0.805)	0.839 (0.794, 0.887)	0.647 (0.599, 0.698)	1.316 (1.02, 1.699)
Charlson score 0/Missing, 2010 to 2016	13,981	0.668 (0.542, 0.823)	0.85 (0.806, 0.897)	0.724 (0.677, 0.774)	1.443 (1.111, 1.875)
Charlson score 0/Missing, age 75+, 2010 to 2016	5076	0.368 (0.214, 0.632)	0.841 (0.777, 0.909)	0.604 (0.54, 0.677)	1.284 (0.911, 1.809)
Charlson score 1+, 2010 to 2016	3389	0.71 (0.483, 1.044)	0.837 (0.761, 0.921)	0.597 (0.519, 0.688)	1.041 (0.688, 1.576)
Lobular, 2010 to 2016	2465	0.572 (0.318, 1.029)	0.889 (0.81, 0.976)	0.693 (0.587, 0.817)	1.66 (0.926, 2.973)
ER+, HER2-, no axillary dissection, 2012 to 2016, age 70+	6215	0.511 (0.308, 0.846)	0.837 (0.785, 0.893)	0.656 (0.593, 0.726)	1.246 (0.878, 1.769)

All models were weighted by the overlap propensity score weights. Analyses are presented for the entire study cohort, and for subgroups of interest

RR: relative risk, *CI*: confidence interval, *ER*: estrogen receptor, *HER2*: human epidermal growth factor receptor 2

maintained when the cohort was restricted to women with no comorbidities. This important finding requires further exploration. While it is possible this may represent targeted axillary treatment for worrisome pathology in the primary tumor, we did not find significantly worse BCSS among women who were not staged and who did not receive further adjuvant treatments. This suggests that women who do not have axillary staging are highly selected and the lack of information about the axilla does not result in adverse breast cancer outcomes.

There are limitations to this analysis. The Ontario Cancer Registry does not contain separate information on clinical staging when pathological staging information is available (i.e., from lymph node staging). Therefore, we were unable to confirm whether patients were clinically node negative prior to axillary staging. Similar limitations are present in the SEER registry data and affect other studies in this area.[8,10] However, we excluded T3/T4 tumors, patients with metastatic disease, and those who received neoadjuvant chemotherapy. Although we have access to comorbidity and more granular adjuvant treatment data, and used advanced methods of addressing confounding, there is likely residual confounding. Worse OS with no difference in BCSS among women who did not have axillary staging and did not receive further adjuvant treatments suggests that this group has competing risks of death from non-breast-cancer causes. The Charlson score is calculated based on a weighted index of comorbid diseases and is an adequate representation of medical complexity compared with individual comorbidity adjustment.[21,22] However, the score does not provide insight into patient values and decision-making with respect to pursing aggressive breast cancer treatment in older women. There is a delay in the availability of cause of death in our data sources after a death is registered; therefore, the median follow-up for the BCSS analysis is shorter than the OS analysis. This may have led to an underestimation of breast cancer events and lower power. Finally, our competing risks analysis may be limited by the accuracy of cause of death in the Ontario Cancer Registry. However, we extensively explored the cohort for evidence of disease recurrence and treatment changes among those with breast cancer listed as the cause of death.

The evidence supporting omission of axillary staging in older women with early stage breast cancer is controversial. Unlike the de-escalation of treatment that has occurred more broadly in breast cancer,[19] surgeons continue to offer axillary staging in older women and have expressed uncertainty about the strength of evidence in this area.[7] This population-based study addresses limitations of previous observational work showing worse survival among older women who do not receive staging. Our results suggest women who do not receive staging are highly

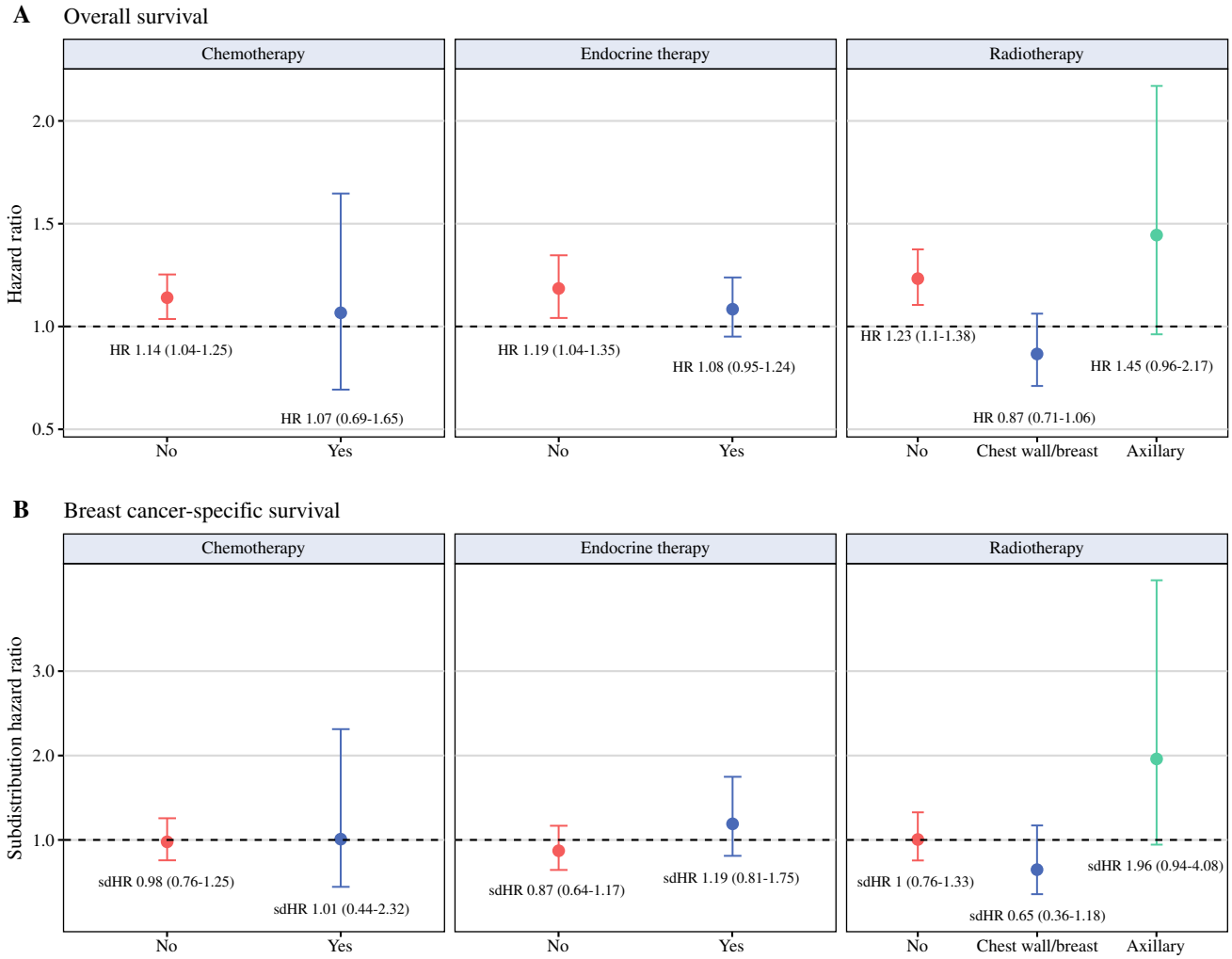

FIG. 4 Interaction terms between receipt of adjuvant treatments and the omission of axillary staging for (**A**) overall survival and (**B**) breast cancer-specific survival. Models are weighted by the overlap propensity score weight, and adjusted for receipt of other adjuvant treatments

selected, but do not experience worse breast cancer-specific mortality as a result, even when they do not have further adjuvant treatments. However, it is still unclear whether omission of axillary staging can be extended to older women with early stage breast cancer more broadly, and careful consideration should be given to the information gained from staging against the morbidity of modern SLNB. Further qualitative or prospective work is needed to understand the complex decision making that is occurring between older breast cancer patients and their surgeons when approaching the role of axillary staging.

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