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Clinical Investigation

Trends in Local Therapy Utilization and Cost for Early-Stage Breast Cancer in Older Women: Implications for Payment and Policy Reform

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Summary

A population-based database of 55,327 older women with early-stage breast cancer treated during 2000 to -2008 was used to determine trends in local therapies and their associated costs. During this interval, the use of mastectomy in the elderly declined

Purpose: Older women with early-stage disease constitute the most rapidly growing breast cancer demographic, yet it is not known which local therapy strategies are most favored by this population in the current era. Understanding utilization trends and cost of local therapy is important for informing the design of bundled payment models as payers migrate away from fee-for-service models. We therefore used the Surveillance, Epidemiology, and End Results Medicare database to determine patterns of care and costs for local therapy among older women with breast cancer.

Methods and Materials: Treatment strategy and covariables were determined in 55,327 women age ≥66 with Tis-T2N0-1M0 breast cancer who underwent local therapy between 2000 and 2008. Trends in local therapy were characterized using Joinpoint. Polychotomous logistic regression determined predictors of local therapy. The

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in favor of breast conserving strategies. Mastectomy with reconstruction was infrequently used. Costs generally grew faster than inflation and varied substantially by chosen local therapy, suggesting that policies encouraging high-value care are needed.

median aggregate cost over the first 24 months after diagnosis was determined from Medicare claims through 2010 and reported in 2014 dollars.

Results: The median age was 75. Local therapy distribution was as follows: 27,896 (50.3%) lumpectomy with external beam radiation, 18,356 (33.1%) mastectomy alone, 6159 (11.1%) lumpectomy alone, 1488 (2.7%) mastectomy with reconstruction, and 1455 (2.6%) lumpectomy with brachytherapy. Mastectomy alone declined from 39.0% in 2000 to 28.2% in 2008, and the use of breast conserving local therapies rose from 58.7% to 68.2%. Mastectomy with reconstruction was more common among the youngest, healthiest patients, whereas mastectomy alone was more common among patients living in rural low-income regions. By 2008, the costs were $36,749 for lumpectomy with brachytherapy, $35,030 for mastectomy with reconstruction, $31,388 for lumpectomy with external beam radiation, $21,993 for mastectomy alone, and $19,287 for lumpectomy alone.

Conclusions: The use of mastectomy alone in older women declined in favor of breast conserving strategies between 2000 and 2008. Using these cost estimates, price points for local therapy bundles can be constructed to incentivize the treatment strategies that confer the highest value.

Introduction

Older women with early breast cancer constitute the most rapidly growing breast cancer demographic, with an estimated 114,000 cases annually and a growth forecast of 57% from 2010 to 2030 (1). Historically, the most common local treatments for such women were lumpectomy followed by approximately 6 weeks of external beam radiation or mastectomy without reconstruction. However, recent literature suggests that many older women may be appropriate candidates for either brachytherapy, which conveniently decreases the radiation treatment course to 1 week, or complete omission of any radiation, which confers even more convenience (2-4). Despite increasing support for these convenient options for breast conservation, recent patterns of care studies have demonstrated an increasing use of mastectomy in the overall breast cancer population, potentially driven by the greater availability and use of breast reconstruction (5-9).

For older women with early breast cancer, it is not known whether the increasing availability of more convenient breast conservation strategies has led overall to an increased use of breast conservation, or whether the increasing availability of breast reconstruction has led to an increased use of mastectomy. Understanding utilization and cost trends in this large and growing population of older women with early breast cancer is critically important for promoting value, defined as the quality of outcomes achieved per dollar spent, as payers migrate away from fee-for-service reimbursement toward bundled care payment models (10-12). We therefore used the Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort to characterize population trends in the use of local therapy and to characterize the predictors and cost of local therapy for older women with early breast cancer who are Medicare beneficiaries.

Methods

Data source

The SEER-Medicare database captures clinical, pathologic, and insurance claims data for incident cancers diagnosed in Medicare beneficiaries who reside within 1 of 16 geographic areas that account for 26% of the United States population. The case ascertainment rate is approximately 98% (13). In this study, the demographic and tumor characteristics for incident malignancies diagnosed from January 1, 2000, to December 31, 2008, were linked to Medicare treatment claims from January 1, 1999, to December 31, 2010.

Study sample

From 2000 to 2008, 195,217 women age $\geq$ 66 years received diagnoses of invasive or in situ breast cancer and reported in the SEER-Medicare cohort. We applied standard exclusions as outlined in Table E1 (available online at www.redjournal.org) to create an analytic cohort of 55,327 patients with early-stage disease (Tis-T2N0-1). We required that all patients maintain fee-for-service Medicare coverage from 12 months before through 24 months after diagnosis to permit ascertainment of comorbid illness before diagnosis and delayed breast reconstruction after diagnosis.

Outcomes

The primary outcome for this study was type of local treatment, defined as 1 of the following: (*1*) lumpectomy followed by external beam radiation; (*2*) mastectomy without reconstruction within 2 years of diagnosis; (*3*) mastectomy with reconstruction within 2 years of diagnosis; (*4*) lumpectomy followed by brachytherapy; or (*5*) lumpectomy with no adjuvant radiation therapy. For patients treated with mastectomy, we also required that they did not receive radiation within 12 months of surgery, inasmuch as the use of postmastectomy radiation would likely indicate a more advanced cancer. Type of surgery (lumpectomy vs mastectomy) was determined from both SEER data and Medicare claims within 12 months of diagnosis, with the most extensive surgery coded by either source considered to be the definitive surgery. Patients were considered to have received breast reconstruction if any claim for reconstruction was present within 24 months of diagnosis (Table E2; available online at www.redjournal.org).

Baseline covariables

The patient characteristics from the SEER data included age at diagnosis, race, sex, and year of diagnosis. Modified Charlson comorbidity index with Klabunde modification was determined from claims spanning an interval of 12 months to 1 month before diagnosis (14, 15). Tumor characteristics extracted from SEER included T stage and N stage, grade, histology, estrogen receptor (ER) status, and laterality. Lymphovascular space invasion and margin status are not reported. Area-level characteristics included urban/rural residence, median income, educational attainment, and county-level density of surgeons and radiation oncologists determined from the Area Resource File (16).

Determination of cost

The costs for each patient were calculated from a payer perspective using all inpatient, outpatient, and carrier claims within 2 years of diagnosis and were divided by calendar month to evaluate trends over time related to date of diagnosis. Costs were adjusted for geographic variation using the geographic adjustment factor for Part A claims and the geographic practice cost index for Part B claims and for inflation using the Prospective Pricing Index for Part A claims and the Medicare Economic Index for Part B claims (17, 18). Costs were also adjusted for differences in use of chemotherapy by normalizing costs of each local therapy to the utilization rate of chemotherapy in patients treated with lumpectomy plus external beam radiation. All costs are reported in 2014 dollars.

Statistical analysis

The baseline characteristics across treatment strata were compared with Pearson's χ^2 test. Trends in treatment utilization by calendar year quarter were determined with Joinpoint linear regression models (Joinpoint version 3.4.3). Adjusted associations between baseline characteristics and treatment strategy were estimated using polychotomous logistic regression. Lumpectomy followed by external beam radiation served as the referent group for this model because it was the most commonly used strategy and its use was relatively stable over time. Covariables were selected for inclusion in this model a priori on the basis of clinical relevance or if associated with the outcome in univariate analysis at $P<.20$. The model was iteratively refined to optimize fit.

To determine trends in costs, the total median 2-year costs by treatment strategy and year of diagnosis were calculated. Linear regression was used to determine direction and magnitude of cost growth over time. The trend line for lumpectomy and brachytherapy started at 2002 to ensure adequate numbers for meaningful regression; the U.S. Food and Drug Administration (FDA) first approved balloon brachytherapy for breast cancer in 2002.

All statistical tests were 2-sided with $P\leq.05$ and were conducted with SAS version 9.3 (Cary, NC). Our institutional review board granted this study exempt status.

Results

Baseline characteristics

Of 55,327 women, the median age was 75 years, and 48,792 (88.5%) were white. The number of patients receiving each treatment was as follows: 27,896 (50.3%) lumpectomy with external beam radiation, 18,356 (33.1%) mastectomy alone, 6159 (11.1%) lumpectomy alone, 1488 (2.7%) mastectomy with reconstruction, and 1455 (2.6%) lumpectomy with brachytherapy (Table 1).

Trends in local therapy

During the study interval, the proportion of patients undergoing mastectomy alone declined from 39.0% in 2000 to 28.2% in 2008, and the use of breast conserving local therapies rose from 58.7% to 68.2% (Fig. 1A). Specifically, lumpectomy plus external radiation rose from 47.9% in 2000 to a peak of 52.6% in 2003 before declining modestly to 50.4% of cases in 2008. This later decline was accompanied by a rise in breast conservation using brachytherapy. This strategy increased from fewer than 0.3% of cases in 2000 and 2001 to 6.1% of cases in 2008, which represented the fastest growth among all treatment options. Mastectomy followed by reconstruction accounted for 2.2% of cases in 2000 and 3.6% of cases in 2008, with most of this increase occurring during the final 2 years of the interval. Finally, the use of lumpectomy alone rose slightly, from 10.6% to 11.7% of cases during the study period.

When limited to only those patients for whom all of these treatments are considered guideline concordant (ie, age ≥70, stage T1N0, ER+), similar trends in local therapy strategies were observed, with the exception that there was a much more pronounced increase in the use of lumpectomy alone, with the percentage of patients treated with this strategy stable between 2000 and 2003 at 12.9%, then

Table 1 Baseline characteristics

Factor	Lumpectomy & external radiation, N=27,869		Mastectomy alone, N=18,356		Mastectomy & reconstruction, N=1488		Lumpectomy & brachytherapy, N=1455		Lumpectomy alone, N=6159		All patients, N=55,327		*P*
Patient and treatment factors													
Age, y													
66-69	7615	27.3%	3460	18.8%	690	46.4%	385	26.5%	545	8.8%	12,695	22.9%	<.001
70-74	8214	29.5%	4535	24.7%	469	31.5%	410	28.2%	774	12.6%	14,402	26.0%	
75-79	6919	24.8%	4664	25.4%	236	15.9%	349	24.0%	1159	18.8%	13,327	24.1%	
80-84	3908	14.0%	3543	19.3%	63	4.2%	221	15.2%	1608	26.1%	9343	16.9%	
85+	1213	4.4%	2154	11.7%	30	2.0%	90	6.2%	2073	33.7%	5560	10.0%	
Race													
White	25,002	89.7%	15,778	86.0%	1368	91.9%	1329	91.3%	5495	89.2%	48,972	88.5%	<.001
Black	1515	5.4%	1454	7.9%	74	5.0%	75	5.2%	400	6.5%	3518	6.4%	
Other/unknown	1352	4.9%	1124	6.1%	46	3.1%	51	3.5%	264	4.3%	2837	5.1%	
Charlson comorbidity index													
0	18,694	67.1%	10,612	57.8%	1067	71.7%	971	66.7%	3365	54.6%	34,709	62.7%	<.001
1	6110	21.9%	4599	25.1%	298	20.0%	337	23.2%	1542	25.0%	12,886	23.3%	
≥2	2585	9.3%	2529	13.8%	100	6.7%	147	10.1%	1030	16.7%	6391	11.6%	
Incomplete	480	1.7%	616	3.4%	23	1.5%	0	0.0%	222	3.6%	1341	2.4%	
Chemotherapy													
No	23,486	84.4	15,365	83.8	1130	75.9	1347	92.6	5947	96.6	47,275	85.5%	<.001
Yes	4356	15.7	2978	16.2	358	24.1	108	7.4	209	3.4	8009	14.5%	
Year of diagnosis													
2000	2777	10.0%	2262	12.3%	<150	<9%	<20	<2%	612	9.9%	5795	10.5%	<.001
2001	2978	10.7%	2502	13.6%	<170	<11%	<11	<1%	640	10.4%	6283	11.4%	
2002	3125	11.2%	2262	12.3%	150	10.1%	38	2.6%	653	10.6%	6228	11.3%	
2003	3223	11.6%	2082	11.3%	152	10.2%	87	6.0%	577	9.4%	6121	11.1%	
2004	3233	11.6%	2015	11.0%	166	11.2%	144	9.9%	690	11.2%	6248	11.3%	
2005	3062	11.0%	1864	10.2%	150	10.1%	187	12.9%	740	12.0%	6003	10.9%	
2006	3182	11.4%	1763	9.6%	148	9.9%	263	18.1%	779	12.6%	6135	11.1%	
2007	3123	11.2%	1835	10.0%	209	14.0%	334	23.0%	733	11.9%	6234	11.3%	
2008	3166	11.4%	1771	9.6%	227	15.3%	381	26.2%	735	11.9%	6280	11.4%	
Tumor factors													
Tumor size													
T1 (0.0-2.0 cm)	22,995	82.5%	11,866	64.6%	1026	69.0%	1312	90.2%	4898	79.5%	42,097	76.1%	<.001
T2 (2.1-5.0 cm)	4676	16.8%	6326	34.5%	443	29.8%	132	9.1%	1202	19.5%	12,779	23.1%	
Not specified	198	0.7%	164	0.9%	19	1.3%	11	0.8%	59	1.0%	451	0.8%	
Nodal status													
Pathologic N0	21,386	76.7%	13,493	73.5%	1192	80.1%	1301	89.4%	2737	44.4%	40,109	72.5%	<.001
Clinical N0	2524	9.1%	1184	6.5%	46	3.1%	95	6.5%	3090	50.2%	6939	12.5%	
Pathologic N1	3959	14.2%	3679	20.0%	250	16.8%	59	4.1%	332	5.4%	8279	15.0%	
Histology													
Ductal, tubular, mucinous	20,920	75.1%	12,653	68.9%	884	59.4%	1156	79.5%	4546	73.8%	40,159	72.6%	<.001
Lobular	2282	8.2%	1815	9.9%	184	12.4%	71	4.9%	480	7.8%	4832	8.7%	
Other invasive	3959	14.2%	2804	15.3%	260	17.5%	184	12.6%	923	15.0%	8130	14.7%	
DCIS	708	2.5%	1084	5.9%	160	10.8%	44	3.0%	210	3.4%	2206	4.0%	
Grade													
Low-intermediate	19,933	71.5%	11,438	62.3%	925	62.2%	1175	80.8%	4548	73.8%	38,019	68.7%	<.001
High	6197	22.2%	5249	28.6%	428	28.8%	223	15.3%	1069	17.4%	13,166	23.8%	
Other/unknown	1739	6.2%	1669	9.1%	135	9.1%	57	3.9%	542	8.8%	4142	7.5%	
Estrogen receptor status													
ER+	22,136	79.4%	12,722	69.3%	1086	73.0%	1245	85.6%	4717	76.6%	41,906	75.7%	<.001
ER−	3291	11.8%	2568	14.0%	228	15.3%	108	7.4%	466	7.6%	6661	12.0%	
Unspecified	2442	8.8%	3066	16.7%	174	11.7%	102	7.0%	976	15.8%	6760	12.2%	

(*continued on next page*)

Table 1 (*continued*)

Factor	Lumpectomy & external radiation, N=27,869		Mastectomy alone, N=18,356		Mastectomy & reconstruction, N=1488		Lumpectomy & brachytherapy, N=1455		Lumpectomy alone, N=6159		All patients, N=55,327		*P*
Area-level factors													
Type of patient residence													
Urban	25,823	92.7%	15,477	84.3%	1373	92.3%	1369	94.1%	5550	90.1%	49,592	89.6%	<.001
Rural	>2025	>5	2879	15.7%	115	7.7%	86	5.9%	609	9.9%	>5725	>5	
Unknown	<11	<5	0	0.0%	0	0.0%	0	0.0%	0	0.0%	<11	<5	
Density of surgeons													
Highest quartile	6125	22.0%	5598	30.5%	348	23.4%	351	24.1%	1413	22.9%	13,835	25.0%	<.001
2nd quartile	7222	25.9%	4542	24.7%	364	24.5%	414	28.5%	1711	27.8%	14,253	25.8%	
3rd quartile	7184	25.8%	3942	21.5%	375	25.2%	323	22.2%	1569	25.5%	13,393	24.2%	
4rth quartile	7338	26.3%	4274	23.3%	401	26.9%	367	25.2%	1466	23.8%	13,846	25.0%	
Density of radiation oncologists													
Highest quartile	5552	19.9%	6088	33.2%	328	22.0%	334	23.0%	1495	24.3%	13,797	24.9%	<.001
2nd quartile	7416	26.6%	4167	22.7%	393	26.4%	458	31.5%	1582	25.7%	14,016	25.3%	
3rd quartile	7600	27.3%	3764	20.5%	382	25.7%	298	20.5%	1642	26.7%	13,686	24.7%	
4th quartile	7301	26.2%	4337	23.6%	385	25.9%	365	25.1%	1440	23.4%	13,828	25.0%	
Residents with some college education													
1st quartile (0-8.1%)	8117	29.1%	3409	18.6%	517	34.7%	490	33.7%	1545	25.1%	14,078	25.4%	<.001
2nd quartile (8.2%-14.4%)	7190	25.8%	4108	22.4%	387	26.0%	375	25.8%	1527	24.8%	13,587	24.6%	
3rd quartile (14.5-24.0%)	6755	24.2%	4979	27.1%	294	19.8%	308	21.2%	1500	24.4%	13,836	25.0%	
4th quartile (>24.1%)	5807	20.8%	5860	31.9%	290	19.5%	282	19.4%	1587	25.8%	13,826	25.0%	
Income level													
1st quartile ($0-$35,453)	5672	20.4%	6069	33.1%	279	18.8%	258	17.7%	1556	25.3%	13,834	25.0%	<.001
2nd quartile ($35,454-$46,559)	6619	23.8%	4967	27.1%	317	21.3%	370	25.4%	1557	25.3%	13,830	25.0%	
3rd quartile ($46,560-$62,311)	7451	26.7%	4135	22.5%	371	24.9%	369	25.4%	1505	24.4%	13,831	25.0%	
4th quartile (>$62,312)	8127	29.2%	3185	17.4%	521	35.0%	458	31.5%	1541	25.0%	13,832	25.0%	

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor.
Cell sizes <11 have been suppressed in accordance with guidelines from SEER-Medicare.

increasing to a high of 18.7% in 2006 and subsequently falling slightly to 16.8% in 2008 (Fig. 1B).

Predictors of treatment

Polychotomous logistic regression using lumpectomy plus external radiation as the referent was used to identify predictors for the use of the other 4 treatment strategies (Table 2). The youngest patients and those with minimal comorbidities were more likely to undergo mastectomy with reconstruction. By contrast, older patients and those with more comorbidities were more likely to undergo shorter treatment strategies such as mastectomy alone, lumpectomy alone, or lumpectomy with brachytherapy. Additionally, lumpectomy with brachytherapy was strongly associated with a later year of diagnosis and with tumor features including smaller size, lower grade, ER positivity, node negativity, and ductal rather than lobular histology. Socioeconomic factors also correlated with treatment (Table 2). One notable finding was a correlation between regions with low incomes or rural settings and the use of mastectomy alone.

Cost of treatment

For the year 2008, the median total costs for each treatment strategy, from highest to lowest, were ranked as follows: lumpectomy with brachytherapy ($36,749), mastectomy with reconstruction ($35,030), lumpectomy with external beam radiation ($31,388), mastectomy alone ($21,993), and lumpectomy alone ($19,287). The majority of costs were accrued during the treatment phase (0-6 months after diagnosis) regardless of the chosen therapy (Figs. 2A and 2B). However, qualitative differences were preserved

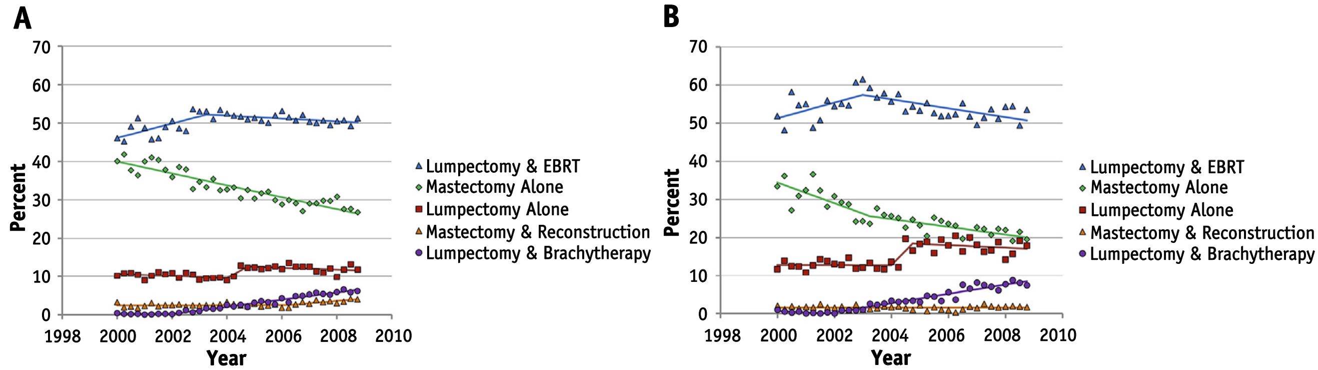

Fig. 1. (A) Proportion of Medicare patients who received each treatment for each annual quarter between 2000 and 2008. (B) Limited to favorable risk patients with T1 N0 estrogen receptor−positive breast cancer age ≥70 at diagnosis. *Abbreviation:* EBRT = external beam radiation therapy.

during the period associated with managing adverse events (6-24 months), with combination therapies attendant with higher costs (Fig. 2C). The cost of all treatment strategies grew at a rate faster than inflation, with the exception of lumpectomy with brachytherapy, whose cost was stable over time (Fig. 3).

Discussion

We used the SEER-Medicare database to characterize trends in local therapy and associated costs for older women with early-stage breast cancer diagnosed between 2000 and 2008 in the SEER-Medicare cohort. The main trend we observed was a steady decline in the use of mastectomy alone during this time frame, with increasing use of breast conserving strategies, particularly driven by the increasing use of lumpectomy with brachytherapy and lumpectomy alone. Although lumpectomy with brachytherapy was the most costly intervention before 2007, its inflation-adjusted cost was roughly stable over time, in contrast to the other strategies, whose growth in cost regularly exceeded inflation.

The groundbreaking National Surgical Adjuvant Breast and Bowel Project B-6 study demonstrated that patients with diagnoses of with early-stage breast cancer had statistically equivalent survival whether they were treated with mastectomy or lumpectomy followed by adjuvant radiation (19). After the study's publication in 1985, a steady rise in breast conservation was observed in the United States (20-22). The patients benefited from less extensive surgeries requiring shorter hospital stays, fewer operative adverse events, and likely better cosmetic outcomes. The costs during this era were comparable between the 2 approaches because savings from reduced length of hospitalization and faster surgical recovery were offset by the cost of radiation therapy among those who underwent breast conservation (23, 24).

In 2004, 2 landmark randomized clinical trials were published that sought to evaluate the need for whole breast irradiation specifically in older women with stage I ER-positive breast cancer (25, 26). These studies found that whole breast irradiation conferred a small (<5%) absolute reduction in risk of local recurrence at 5 years for older women, without an accompanying benefit in overall breast preservation or survival. The entry criteria for 1 of these trials, the Cancer and Leukemia Group B (CALGB) 9343, were subsequently incorporated into the National Comprehensive Cancer Network guidelines to define a group of older patients for whom radiation could be omitted (27), specifically women age ≥70 with clinical T1 N0, ER-positive disease resected with negative margins. Omission of radiation continues to be debated, however, with some experts arguing that the modest local control benefit conferred by radiation may justify its use for older patients with longer life expectancy (28).

Yet, despite the research demonstrating the safety of breast conservation, by the 2000s the trend favoring adoption of breast conservation reversed in several single-institution and population-based studies (5-9). The reasons for the renewed popularity of mastectomy were unclear, but possibilities included better techniques for breast reconstruction and improved access to reconstruction after the passage of the Women's Health and Cancer Rights Act in 1998 (29). Psychological factors favoring mastectomy may have included patients' anxieties over the malignant potential of residual breast tissue and the carcinogenicity of radiation. Advances in breast imaging, including the widespread use of breast magnetic resonance imaging, may also have contributed to these concerns (30). Finally, the logistics of conventional radiation therapy, which requires 6 weeks of therapy, may have steered some patients to shorter interventions (31).

By contrast, among the older Medicare population, we identified a trend in the opposite direction, with an 11% decline in the proportion of patients opting for mastectomy alone accompanied by a 10% rise in use of breast conserving strategies. This finding is similar to recent analyses by the National Cancer Database (32) and the SEER-Medicare database (33). A unique contribution of this

Table 2 Predictors of treatment strategy using polychotomous logistic regression with lumpectomy plus external beam radiation designated as referent group

Factor	Mastectomy alone			Mastectomy & reconstruction			Lumpectomy & brachytherapy			Lumpectomy alone		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient factors												
Age, y												
66-69	1			1			1			1		
70-74	1.23	1.17-1.31	<.0001	0.65	0.57-0.73	<.0001	1.02	0.89-1.18	.7611	1.28	1.14-1.44	<.0001
75-79	1.57	1.49-1.67	<.0001	0.4	0.34-0.46	<.0001	1.07	0.92-1.25	.3754	2.05	1.83-2.29	<.0001
80-84	2.22	2.08-2.37	<.0001	0.19	0.15-0.25	<.0001	1.14	0.96-1.36	.1338	4.21	3.77-4.70	<.0001
85+	4.4	4.04-4.81	<.0001	0.31	0.21-0.45	<.0001	1.56	1.22-2.00	.0003	12.69	11.3-14.3	<.0001
Race												
White	1			1			1			1		
Black	1.18	1.09-1.29	<.0001	0.85	0.66-1.1	.22	1.12	0.87-1.44	.38	1.12	0.98-1.29	.089
Other/unknown	1.57	1.44-1.72	<.0001	0.6	0.44-0.81	.0009	0.67	0.5-0.9	.0069	0.99	0.85-1.15	.86
Charlson comorbidity index												
0	1			1			1			1		
1	1.25	1.19-1.31	<.0001	0.92	0.81-1.06	.25	1.03	0.91-1.18	.6307	1.63	1.48-1.78	<.0001
≥2	1.52	1.42-1.62	<.0001	0.78	0.63-0.96	.021	1.04	0.86-1.25	.7006	NA	NA	NA
Incomplete	1.54	1.34-1.76	<.0001	0.85	0.55-1.32	.47	1.19	1.1-1.28	.8575	3.43	2.84-4.15	<.0001
Year of diagnosis												
2000	1			1			1			1		
2001	1.04	0.96-1.13	.37	1.09	0.86-1.40	.47	0.46	0.19-1.15	.098	1.05	0.91-1.20	.52
2002	0.92	0.84-0.99	.042	0.98	0.77-1.25	.87	2.25	1.21-4.17	.0098	1.21	1.06-1.40	.0068
2003	0.78	0.72-0.85	<.0001	0.98	0.77-1.25	.87	5.02	2.85-8.85	<.0001	1	0.86-1.15	.95
2004	0.78	0.71-0.85	<.0001	1.05	0.82-1.33	.73	8.55	4.92-14.85	<.0001	1.41	1.23-1.62	<.0001
2005	0.75	0.69-0.82	<.0001	0.95	0.75-1.22	.70	12.09	7.00-20.90	<.0001	1.67	1.45-1.91	<.0001
2006	0.69	0.63-0.75	<.0001	0.92	0.72-1.18	.50	16.44	9.56-28.26	<.0001	1.76	1.54-2.02	<.0001
2007	0.71	0.65-0.78	<.0001	1.31	1.04-1.65	.023	21.25	12.4-36.4	<.0001	1.67	1.45-1.92	<.0001
2008	0.68	0.62-0.74	<.0001	1.37	1.09-1.73	.0081	23.58	13.8-40.4	<.0001	1.78	1.55-2.05	<.0001
Tumor factors												
Tumor size												
T1 (0.0-2.0 cm)	1			1			1			1		
T2 (2.1-5.0 cm)	2.27	2.17-2.38	<.0001	2.01	1.78-2.27	<.0001	0.58	0.48-0.7	<.0001	1.04	0.96-1.13	.33
Not specified	1.71	1.37-2.14	<.0001	1.71	1.05-2.78	.032	0.65	0.35-1.2	.168	0.91	0.65-1.27	.58
Nodal status												
Pathologic N0	1			1			1			1		
Clinical N0	0.49	0.45-0.53	<.0001	0.48	0.35-0.65	<.0001	0.77	0.62-0.96	.018	5.66	5.25-6.1	<.0001
Pathological N+	1.32	1.25-1.40	<.0001	1.1	0.95-1.27	.21	0.28	0.21-0.36	<.0001	0.7	0.62-0.79	<.0001
Histology												
Ductal, tubular, mucinous	1			1			1			1		
Lobular	1.27	1.18-1.36	<.0001	1.79	1.5-2.13	<.0001	0.54	0.42-0.69	<.0001	0.83	0.74-0.94	.0034
Other invasive	1.17	1.11-1.24	<.0001	1.53	1.32-1.77	<.0001	0.9	0.76-1.05	.1844	1.02	0.94-1.12	.62
DCIS	2.27	2.04-2.53	<.0001	4.06	3.33-4.96	<.0001	0.9	0.65-1.23	.5041	2.47	2.08-2.92	<.0001
Grade												
Low-intermediate	1			1			1			1		
High	1.16	1.10-1.22	<.0001	1.16	1.02-1.33	.027	0.75	0.64-0.88	.0005	0.79	0.72-0.86	<.0001
Other/unknown	1.23	1.13-1.33	<.0001	1.29	1.06-1.58	.012	0.82	0.62-1.09	.1678	1.14	1.01-1.28	.039
Estrogen receptor status												
ER+	1			1			1			1		
ER−	1.19	1.12-1.27	<.0001	1.2	1.02-1.41	.032	0.65	0.52-0.8	<.0001	0.77	0.69-0.87	<.0001
Unspecified	1.82	1.71-1.94	<.0001	1.26	1.06-1.51	.011	1.34	1.08-1.66	.0076	1.64	1.49-1.8	<.0001
Area-level factors												
Type of patient residence												
Metropolitan	1			1			1			1		
Nonmetropolitan	1.4	1.3-1.52	<.0001	0.96	0.76-1.22	.73	0.62	0.48-0.8	.0003	1.14	1-1.3	.053

(*continued on next page*)

Table 2 (*continued*)

Factor	Mastectomy alone			Mastectomy & reconstruction			Lumpectomy & brachytherapy			Lumpectomy alone		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Density of surgeons												
Highest quartile	1			1			1			1		
2nd quartile	0.9	0.85-0.95	<.0001	0.95	0.8-1.12	.031	1.19	1.01-1.41	.0331	1.16	1.06-1.28	.002
3rd quartile	0.9	0.84-0.96	.51	1.03	0.86-1.24	.74	1.13	0.94-1.35	.2116	1.09	0.98-1.21	.13
4th quartile	0.92	0.86-0.99	.002	1.12	0.92-1.37	.2631	1.42	1.16-1.74	.0008	1.03	0.91-1.16	.64
Density of radiation oncologists												
Highest quartile	1			1			1			1		
2nd quartile	0.68	0.63-0.73	<.0001	0.85	0.71-1.03	.093	0.86	0.72-1.02	.083	0.86	0.77-0.95	.0051
3rd quartile	0.58	0.54-0.62	<.0001	0.76	0.62-0.92	.0064	0.53	0.43-0.65	<.0001	0.85	0.76-0.96	.0082
4th quartile	0.75	0.7-0.81	<.0001	0.76	0.62-0.95	.015	0.55	0.44-0.68	<.0001	0.73	0.64-0.83	<.0001
Residents with some college education												
1st quartile (0 to 8.1%)	1			1			1			1		
2nd quartile (8.2% to 14.4%)	1.04	0.97-1.1	.28	0.88	0.76-1.03	.104	0.83	0.71-0.97	.018	0.97	0.88-1.07	.58
3rd quartile (14.5 to 24.0%)	1.12	1.05-1.21	.001	0.73	0.61-0.88	.001	0.69	0.57-0.83	<.0001	0.94	0.84-1.05	.24
4th quartile (>24.1%)	1.2	1.11-1.3	<.0001	0.82	0.66-1.02	.067	0.74	0.59-0.91	.0057	1.07	0.95-1.21	.28
Income level												
1st quartile ($0 to $35,453)	1			1			1			1		
2nd quartile ($35,454 to $46,559)	0.87	0.82-0.92	<.0001	0.97	0.8-1.16	.72	1.15	0.96-1.38	.1371	0.98	0.89-1.08	.70
3rd quartile ($46,560 to $62,311)	0.74	0.69-0.79	<.0001	0.98	0.8-1.21	.86	0.91	0.74-1.12	.3808	0.86	0.77-0.96	.0084
4th quartile (>$62,312)	0.59	0.54-0.64	<.0001	1.1	0.88-1.38	.40	0.94	0.75-1.18	.5801	0.86	0.76-0.98	.024

Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HR = hazard ratio.

report, however, is the incorporation of data about the use of breast reconstruction after mastectomy and the accompanying cost data. For example, our data indicate that for each patient who chooses lumpectomy plus external beam radiation over mastectomy plus reconstruction, approximately $3600 is saved. This vital information serves as an important reminder of the practical benefits of organ preservation facilitated by radiation.

Notably, we did observe shifts over time in the relative proportions of the different breast conservation strategies used in the community. Breast conservation using external beam radiation declined modestly after 2003 in favor of strategies using lumpectomy alone or brachytherapy. The use of lumpectomy alone rose markedly after 2004, especially among favorable-risk patients who fit the CALGB 9343 entry criteria (25). This observation is in accordance with a prior study by Soulos et al (34), which also reported a modest trend toward the omission of radiation after the CALGB trial was published. However, another unique finding of the current study is that brachytherapy also rose significantly after 2004 among favorable-risk patients (Fig. 1B). This suggests that some practitioners, rather than omit radiation, may have instead selected brachytherapy, perhaps in an effort to garner the local control benefits of radiation while avoiding the toxicities and inconvenience of whole breast treatment.

In the larger cohort of patients not limited by CALGB criteria, there was also observed a movement in favor of breast brachytherapy in later years that appeared to be at the expense of external radiation (Fig. 1A). The time and effort required of the patient for several weeks of traditional external radiation therapy and its inferior reimbursement relative to brachytherapy may have influenced the adoption of the latter after its approval for use in the United States by the FDA.

Our second objective was to determine predictors of treatment strategy. We found that the youngest patients and those with the least comorbidities were more likely to receive mastectomy with reconstruction, echoing the findings of previously published studies that examined younger cohorts (5-9). We also found that patients with the least aggressive tumors (smaller size, lower grade, ER-positive, node-negative) were the most likely to undergo brachytherapy instead of conventional radiation, which may

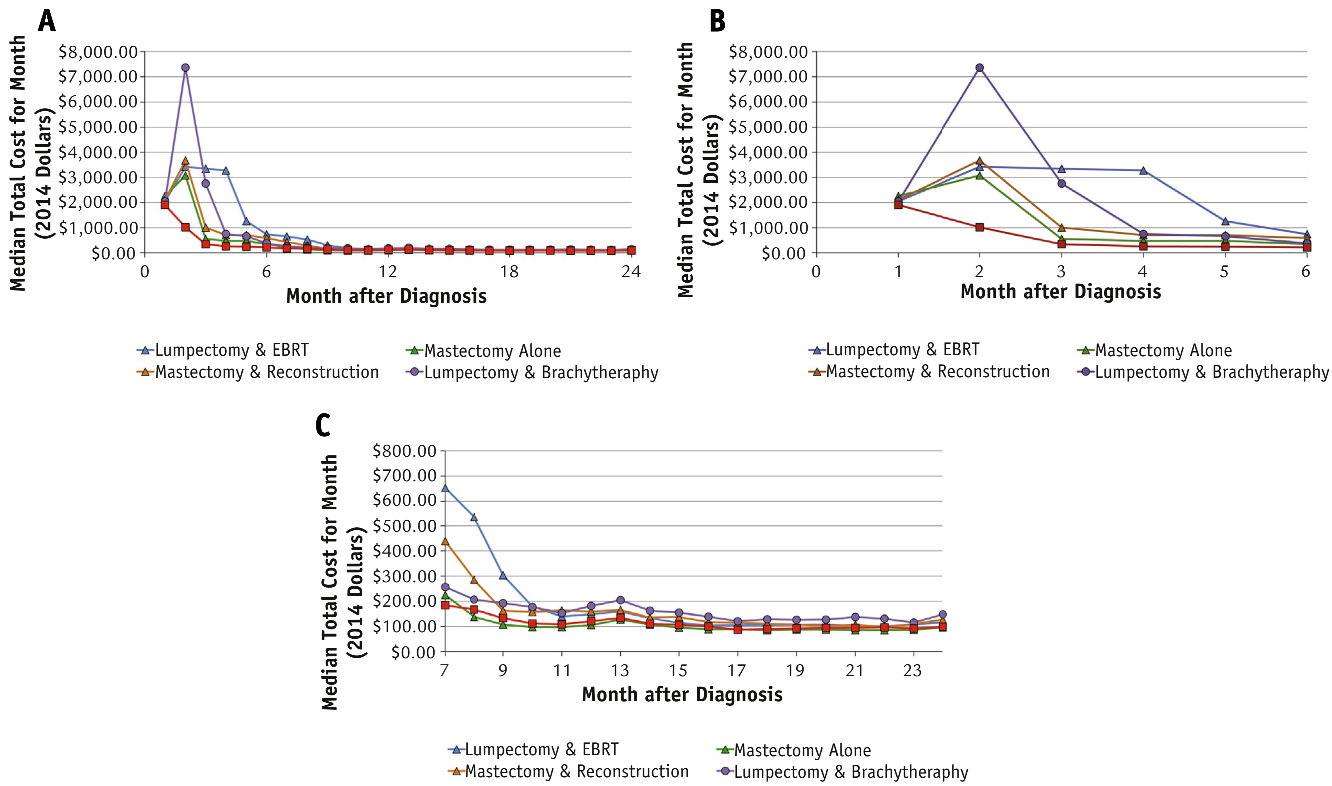

Fig. 2. (A) Median total cost by month of each treatment strategy during the first 24 months after diagnosis. (B, C) highlight trends during the first 6 months and between months 7 and 24, respectively. *Abbreviation:* EBRT = external beam radiation therapy.

reflect published consensus statements and general caution about using a new technology during its early adoption phase (3, 35, 36). A later year of diagnosis was very strongly correlated with brachytherapy, which, in similar fashion, implies improving physicians' comfort with this newer technique. Another important observation is that

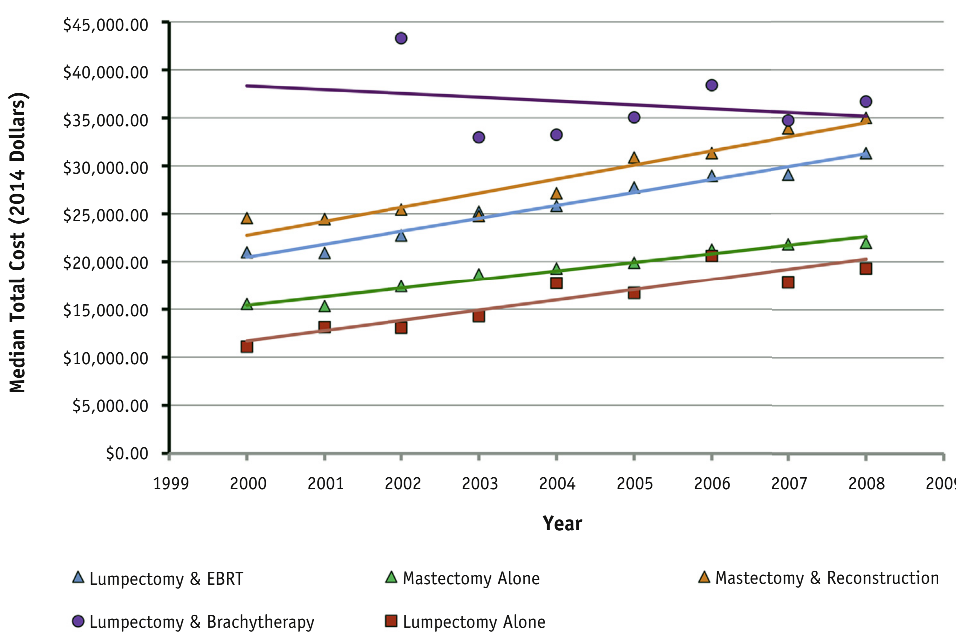

Fig. 3. Trends in median total cost for each treatment during the study interval. The lumpectomy and brachytherapy trend line starts in 2002, when balloon-based breast brachytherapy was approved by the U.S. Food and Drug administration. *Abbreviation:* EBRT = external beam radiation therapy.

factors signifying lower socioeconomic status such as low area-level income and rural residence were associated with the use of mastectomy alone in lieu of combination strategies using radiation or reconstruction. This finding reiterates an oft-described failure in the United States to diffuse innovations in breast cancer care to the least advantaged (37-39).

Our third objective was to examine the costs of these treatments. Lumpectomy plus brachytherapy was associated with the highest cost. However, an examination of trends revealed that brachytherapy exhibited a stable cost during the study period, in contrast to other treatments, whose cost curves consistently exceeded inflation. The relative stability in the cost of brachytherapy may be attributable to predictable Medicare fee schedules and a limited number of procedure codes. Declines in reimbursement for brachytherapy may have also offset inflationary trends. By contrast, the costs associated with lumpectomy and conventionally delivered radiation grew at a rate exceeding that of inflation. This trend is likely due to the adoption of 3-dimensional conformal and intensity modulated radiation techniques over the study period (40, 41). In the future, the cost curve for external beam radiation may more closely track with inflation as a result of bundled payments prompted by the Accountable Care Act and the publication of convincing studies supporting the use of hypofractionation in postmenopausal women (41-43).

This highlights a larger point: policymakers, payers, and physicians can control costs by promoting payment structures that encourage high-value interventions such as hypofractionation (44). For example, a potential policy intervention based on this data would be to develop a bundle for local therapy for older women with early breast cancer amenable to breast conserving therapy. Setting a price point comparable to the cost of lumpectomy plus hypofractionated whole breast irradiation in patients with life expectancies longer than 10 years could incentivize this high-value treatment while discouraging more expensive treatment. Setting a price point comparable to lumpectomy alone in patients with life expectancy less than 10 years and ER-positive disease could incentivize this high value treatment in patients unlikely to benefit from radiation. Importantly, the use of qualifiers such as life expectancy or other pertinent characteristics can help ensure that bundled payments do not fail to account for meaningful differences among individual patients.

We used a combination of SEER data plus Medicare billing claims to classify treatments, thereby reducing the likelihood of misclassification bias in comparison with studies that rely only on SEER coding (45, 46). Nevertheless, our study has certain limitations. First, the study cohort was limited to fee-for-service Medicare patients and may not generalize to younger patients or those covered by private insurance. Second, our cost analysis measured only expenses for which claims data were available. It did not include lost work time or discretionary health care expenses. Third, the period of time studied for cost calculations captured treatment-related costs and the costs of adverse events over the medium term. Inasmuch as differences in disease-free survival emerge later in the course of treated early-stage breast cancer, it is possible that expenses attributable to salvage therapy could change the relative cost profiles observed in our study. The cost of salvage therapy is expected to approximate the initial costs of therapy; for example, cost of salvage mastectomy is likely to be similar to the cost of mastectomy alone. However, because the risk of local recurrence is low, and the difference in local recurrence risk between treatments is small (4, 26), the overall impact of salvage therapies on cost differences is expected to be minimal. Fourth, claims for external beam partial breast irradiation are indistinguishable from claims for whole breast irradiation, and thus we did not attempt to distinguish between these 2 treatments. However, other studies indicate that the use of external beam partial breast irradiation was quite low during this time interval, and thus our findings regarding lumpectomy followed by external beam radiation likely primarily reflect the experience with delivering whole breast irradiation. Fifth, the costs of endocrine therapy were not included and can vary widely, from as little as $600 for 5 years of tamoxifen to as much as approximately $36,000 for 5 years of letrozole (47). Notably, given the expense of aromatase inhibitors, hypofractionated radiation may be a higher-value alternative for patients at very low risk of distant recurrence, for whom the primary intent of adjuvant therapy is to improve local disease control in the breast (41, 48). Finally, our discussion of value and bundled payments assumes that costs are defined by reimbursement dollars. Other models for calculating costs, such as time-driven activity-based costing, are also under investigation. Such diligence by health economists and policymakers is necessary in the creation of value-based payment models to ensure that those models benefit patients rather than deny needed care.

It is concluded that in this population-based cohort of older women with early breast cancer, the use of mastectomy decreased, accompanied by increases in breast conserving approaches, including both standard external beam radiation and newer treatment strategies such as lumpectomy with brachytherapy or lumpectomy alone. Although mastectomy with reconstruction has become more popular in younger women, it has not yet gained significant traction among the population studied here. Using the cost estimates provided in this report, price points for local therapy bundles can be constructed to incentivize treatment strategies that confer the highest value to patients.

References

1. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: Burdens upon an aging, changing nation. *J Clin Oncol* 2009;27:2758-2765.

2. Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202.
3. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009;74:987-1001.
4. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-2387.
5. Dragun AE, Huang B, Tucker TC, et al. Increasing mastectomy rates among all age groups for early stage breast cancer: A 10-year study of surgical choice. *Breast J* 2012;18:318-325.
6. Mahmood U, Hanlon AL, Koshy M, et al. Increasing national mastectomy rates for the treatment of early stage breast cancer. *Ann Surg Oncol* 2013;20:1436-1443.
7. Katipamula R, Degnim AC, Hoskin T, et al. Trends in mastectomy rates at the Mayo Clinic Rochester: Effect of surgical year and preoperative magnetic resonance imaging. *J Clin Oncol* 2009;27:4082-4088.
8. Kummerow KL, Du L, Penson DF, et al. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg* 2015;150:9-16.
9. McGuire KP, Santillan AA, Kaur P, et al. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. *Ann Surg Oncol* 2009;16:2682-2690.
10. Porter ME, Lee TH. Why strategy matters now. *N Engl J Med* 2015;372:1681-1684.
11. Newcomer LN, Gould B, Page RD, et al. Changing physician incentives for affordable, quality cancer care: Results of an episode payment model. *J Oncol Pract* 2014;10:322-326.
12. Dieng M, Trevena L, Turner RM, et al. What Australian women want and when they want it: Cervical screening testing preferences, decision-making styles and information needs. *Health Expect* 2013;16:177-188.
13. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40. IV-3-18.
14. Klabunde CN, Potosky AL, Legler JM, et al. Development of a comorbidity index using physician claims data. *J Clin Epidemiol* 2000;53:1258-1267.
15. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: An overview. *Med Care* 2002;40. IV-26-35.
16. Smith GL, Xu Y, Buchholz TA, et al. Brachytherapy for accelerated partial-breast irradiation: A rapidly emerging technology in breast cancer care. *J Clin Oncol* 2011;29:157-165.
17. Brown ML, Riley GF, Schussler N, et al. Estimating health care costs related to cancer treatment from SEER-Medicare data. *Med Care* 2002;40. IV-104-117.
18. Warren JL, Yabroff KR, Meekins A, et al. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100:888-897.
19. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985;312:665-673.
20. Freedman RA, He Y, Winer EP, et al. Trends in racial and age disparities in definitive local therapy of early-stage breast cancer. *J Clin Oncol* 2009;27:713-719.
21. Lazovich D, Solomon CC, Thomas DB, et al. Breast conservation therapy in the United States following the 1990 National Institutes of Health Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma. *Cancer* 1999;86:628-637.
22. Foote RL, Johnson RE, Donohue JH, et al. Trends in surgical treatment of breast cancer at Mayo Clinic 1980-2004. *Breast* 2008;17:555-562.
23. Barlow WE, Taplin SH, Yoshida CK, et al. Cost comparison of mastectomy versus breast-conserving therapy for early-stage breast cancer. *J Natl Cancer Inst* 2001;93:447-455.
24. Palit TK, Miltenburg DM, Brunicardi FC. Cost analysis of breast conservation surgery compared with modified radical mastectomy with and without reconstruction. *Am J Surg* 2000;179:441-445.
25. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971-977.
26. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-970.
27. Carlson RW, Anderson BO, Burstein HJ, et al. Breast cancer. *J Natl Compr Canc Netw* 2005;3:238-289.
28. Scalliet PG, Kirkove C. Breast cancer in elderly women: Can radiotherapy be omitted? *Eur J Cancer* 2007;43:2264-2269.
29. Yang RL, Newman AS, Lin IC, et al. Trends in immediate breast reconstruction across insurance groups after enactment of breast cancer legislation. *Cancer* 2013;119:2462-2468.
30. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: Meta-analysis of surgical outcomes. *Ann Surg* 2013;257:249-255.
31. Goyal S, Chandwani S, Haffty BG, et al. Effect of travel distance and time to radiotherapy on likelihood of receiving mastectomy. *Ann Surg Oncol* 2015;22:1095-1101.
32. Lautner M, Lin H, Shen Y, et al. Disparities in the use of breast-conserving therapy among patients with early-stage breast cancer. *JAMA Surg* 2015;150:778-786.
33. Showalter SL, Grover S, Sharma S, et al. Factors influencing surgical and adjuvant therapy in stage I breast cancer: A SEER 18 database analysis. *Ann Surg Oncol* 2013;20:1287-1294.
34. Soulos PR, Yu JB, Roberts KB, et al. Assessing the impact of a cooperative group trial on breast cancer care in the Medicare population. *J Clin Oncol* 2012;30:1601-1607.
35. Arthur DW, Koo D, Zwicker RD, et al. Partial breast brachytherapy after lumpectomy: Low-dose-rate and high-dose-rate experience. *Int J Radiat Oncol Biol Phys* 2003;56:681-689.
36. Dickler A, Kirk MC, Chu J, et al. The MammoSite breast brachytherapy applicator: A review of technique and outcomes. *Brachytherapy* 2005;4:130-136.
37. Albain KS, Green SR, Lichter AS, et al. Influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast-sparing treatment in women enrolled in adjuvant breast cancer studies: An analysis of two intergroup trials. *J Clin Oncol* 1996;14:3009-3017.
38. Black DM, Jiang J, Kuerer HM, et al. Racial disparities in adoption of axillary sentinel lymph node biopsy and lymphedema risk in women with breast cancer. *JAMA Surg* 2014;149:788-796.
39. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst* 2002;94:490-496.
40. Smith BD, Pan IW, Shih YC, et al. Adoption of intensity-modulated radiation therapy for breast cancer in the United States. *J Natl Cancer Inst* 2011;103:798-809.
41. Porter ME. What is value in health care? *N Engl J Med* 2010;363:2477-2481.
42. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086-1094.
43. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: A randomized clinical trial. *JAMA Oncol* 2015;1:931-941.

44. Diaby V, Tawk R, Sanogo V, et al. A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. *Breast Cancer Res Treat* 2015; 151:27-40.
45. Walker GV, Giordano SH, Williams M, et al. Muddy water? Variation in reporting receipt of breast cancer radiation therapy by population-based tumor registries. *Int J Radiat Oncol Biol Phys* 2013;86:686-693.
46. Jagsi R, Abrahamse P, Hawley ST, et al. Underascertainment of radiotherapy receipt in Surveillance, Epidemiology, and End Results registry data. *Cancer* 2012;118:333-341.
47. Drug Pricing. Available at: www.goodrx.com. Accessed October 17, 2015.
48. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol* 2010;28:4120-4128.