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Clinical Investigation

Contemporary Toxicity Profile of Breast Brachytherapy Versus External Beam Radiation After Lumpectomy for Breast Cancer

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Summary

We compared toxicities after brachytherapy with those after external beam radiation (EBRT) in 64,112 breast cancer patients, based on insurance claims data. Brachytherapy was associated with excess infectious adverse events in patients treated through 2007, after which the infectious risks declined in brachytherapy patients, becoming comparable with infectious risks with EBRT. By contrast, brachytherapy maintained 2-fold increased odds of noninfectious postoperative adverse events, most

Purpose: We compared toxicities after brachytherapy versus external beam radiation therapy (EBRT) in contemporary breast cancer patients.

Methods and Materials: Using MarketScan healthcare claims, we identified 64,112 women treated from 2003 to 2012 with lumpectomy followed by radiation (brachytherapy vs EBRT). Brachytherapy was further classified by multichannel versus single-channel applicator approach. We identified the risks and predictors of 1-year infectious and noninfectious postoperative adverse events using logistic regression and temporal trends using Cochran-Armitage tests. We estimated the 5-year Kaplan-Meier cumulative incidence of radiation-associated adverse events.

Results: A total of 4522 (7.1%) patients received brachytherapy (50.2% multichannel vs 48.7% single-channel applicator). The overall risk of infectious adverse events was higher after brachytherapy than after EBRT (odds ratio [OR] = 1.21; 95% confidence interval [CI] 1.09-1.34, $P<.001$). However, over time, the frequency of infectious adverse events after brachytherapy decreased, from 17.3% in 2003 to 11.6% in 2012, and was stable after EBRT at 9.7%. Beyond 2007, there were no longer excess infections with brachytherapy ($P=.97$). The overall risk of noninfectious adverse events was higher after brachytherapy than after EBRT (OR = 2.27; 95% CI 2.09-2.47, $P<.0001$). Over time, the frequency of noninfectious adverse events detected increased: after multichannel brachytherapy, from 9.1% in 2004 to 18.9% in 2012 (Ptrend = .64); single-channel brachytherapy, from 12.8% to 29.8% (Ptrend<.001); and EBRT, from 6.1% to 10.3% (Ptrend<.0001). The risk

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commonly development of seroma. Seroma increased the risk of breast pain.

was significantly higher with single-channel than with multichannel brachytherapy (hazard ratio = 1.32; 95% CI 1.03-1.69, $P = .03$). Of noninfectious adverse events, 70.9% were seroma. Seroma significantly increased breast pain risk ($P < .0001$). Patients with underlying diabetes, cardiovascular disease, and treatment with chemotherapy had increased infectious and noninfectious adverse events. The 5-year incidences of fat necrosis, breast pain, and rib fracture were slightly higher after brachytherapy than after EBRT (13.7% vs 8.1%, 19.4% vs 16.0%, and 1.6% vs 1.3%, respectively), but the risks were not significantly different for multichannel versus single-channel applicators.

Conclusion: Toxicities after breast brachytherapy were distinct from those after EBRT. Temporal toxicity trends may reflect changing technology and evolving practitioner experience with brachytherapy. © 2016 Elsevier Inc. All rights reserved.

Introduction

Accelerated partial breast brachytherapy is an adjuvant treatment after lumpectomy for early breast cancer in eligible patients (1). Breast brachytherapy offers considerable convenience benefits over the historical standard adjuvant treatment option, external beam radiation therapy (EBRT), with brachytherapy completed within 1 week compared with 3 to 6 weeks of EBRT. Both treatment options offer similar, excellent local control rates, particularly in appropriately selected low-risk patients (2-4).

However, both physicians and patients typically consider more than local control outcomes when selecting between local treatment options. Differences in treatment toxicities emerge to the forefront for informing risk-to-benefit ratios and patient preferences for treatment, especially when the oncologic outcomes are similarly good, as is the case for brachytherapy versus EBRT in low-risk patients with early-stage breast cancer. Although toxicities with EBRT after lumpectomy are well known (5, 6), a thorough understanding of toxicities associated with breast brachytherapy requires further study, for several reasons. First, although single-arm registry toxicity data exist for patients treated with breast brachytherapy, direct comparisons with EBRT are scarce (3). Directly comparative data are needed to help quantify the relative risks and benefits of the 2 candidate treatments. Additionally, there is a particular need to characterize temporal changes in the toxicity profile of breast brachytherapy, to inform our understanding of this newer therapy as currently practiced by physicians in the United States. Trends over time could reflect evolution of the technology itself, including the recent advancement of multichannel brachytherapy applicators, or advancement of practitioners who have undergone a learning curve. Both such changes over time could have a substantial impact on the current toxicity profile of brachytherapy.

We therefore sought to compare the toxicity profiles of breast brachytherapy with those of EBRT in a population-based cohort of breast cancer patients treated with lumpectomy. Our objective was to characterize the risks and temporal trends of postoperative and postradiation adverse events in each group. Additionally, for patients treated with brachytherapy, we sought to ascertain whether differences in adverse events existed between patients treated with multichannel applicators and those treated with single-channel applicators, particularly given that multichannel applicators represent newer technology and practice.

Methods and Materials

Dataset

MarketScan Commercial Claims and Encounters database (Truven Health Analytics) is an employment-based, deidentified health care claims database covering employees, spouses, and dependent beneficiaries. Beneficiaries were identified from 45 employers in the United States (inclusive of approximately 100 payers), and a convenience sample of 28 million insured lives in the United States was selected. Data are obtained from employers, health plans, and state Medicaid agencies. For each patient, adjudicated service-level inpatient and outpatient claims were included (7). Medicare beneficiaries (patients aged ≥65 years) were not included in this dataset.

Study patients

We examined diagnosis and procedure claims on women aged 18 to 64 with breast cancer treated between 2003 and 2012 with lumpectomy followed by radiation therapy (RT). A total of 83,030 patients who had continuous insurance coverage from 3 months before to 12 months after the lumpectomy date were included. From this group, to focus our analysis on patients treated with radiation for definitive, breast-conserving intent, we excluded patients for the following reasons: mastectomy conducted before the first radiation treatment (n = 7027), metastatic cancer (n = 6724), no radiation simulation codes (n = 2988), or no RT delivery codes (n = 549). We also excluded patients treated with both EBRT and brachytherapy (n = 1630). Our

final sample yielded 64,112 patients (Table E1; available online at www.redjournal.org).

Radiation treatment

We identified the type of radiation treatment using the International Classification of Diseases 9th edition or the Current Procedural Terminology procedure codes claims related to radiation treatment within 12 months of lumpectomy date and classified treatment as EBRT or brachytherapy (Table E2; available online in the Supplemental Material at www.redjournal.org). We further specified claims indicating treatment using intensity modulated radiation therapy (IMRT) in EBRT patients, and claims indicating treatment using a

Table 1 Characteristics of breast cancer patients

Characteristic	Brachytherapy (n=4522)		EBRT (n=59,590)		*P*
	n	%	n	%	
Treatment					
Age group, y					<.0001
18-44	156	4	8040	14	
45-49	553	12	10,354	17	
50-54	1052	23	13,246	22	
55-59	1377	31	15,222	26	
60-64	1384	31	12,728	21	
Endocrine therapy					<.0001
Endocrine−	1798	40	25,952	44	
Endocrine+	2724	60	33,638	57	
IMRT					
No	-	-	52,546	88	-
Yes	-	-	7044	12	
Brachytherapy*					
Single-channel	2203	49	-	-	
Multichannel	2269	50	-	-	
Systemic chemotherapy					<.0001
No	3609	80	35,650	60	
Yes	913	20	23,940	40	
Trastuzumab					
No	4344	96	55,451	93	<.0001
Yes	178	4	4139	7	
Axillary lymph node involvement					<.0001
No	4424	98	51,069	86	
Yes	98	2	8521	14	
Axillary lymph node surgery					.47
No	909	20	12,245	21	
Yes	3613	80	47,345	80	
Comorbidities					
Modified Charlson comorbidity score					.0001
0	4345	96	57,848	97	
1+	177	4	1742	3	
Cardiovascular disease					<.01
No	4249	94	56,593	95	
Yes	273	6	2997	5	
Diabetes					<.0001
No	4057	90	54,800	92	
Yes	465	10	4790	8	
Social/demographic					
Region					<.0001
Northeast	523	12	10,063	17	
Midwest	984	22	15,222	26	
South	2241	50	22,895	38	
West	682	15	10,398	18	
Unknown	92	2	1012	2	

Abbreviations: EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy.
* 50 patients treated with brachytherapy could not be classified as receiving single-channel or multichannel therapy.

multichannel or a single-channel applicator in brachytherapy patients.

Outcomes

We identified infectious and noninfectious postoperative adverse events (Table E2; available online in the Supplementary Material at www.redjournal.org) based on claims that occurred between the lumpectomy date and 1 year postoperatively. We also separately analyzed claims for seroma (Table E2; available online in the Supplemental Material at www.redjournal.org), which was the most common noninfectious adverse event. We further identified claims codes for postradiation adverse events including pneumonitis, fat necrosis, breast pain, and rib fracture (Table E2; available online in the Supplemental Material at www.redjournal.org) that occurred between the first date of radiation treatment and 5-year follow-up.

Covariates

We searched inpatient and outpatient claims to determine covariates, including age at the time of lumpectomy, endocrine therapy, chemotherapy (separately specifying trastuzumab, anthracyclines, and taxanes), axillary lymph node surgery, and axillary lymph node involvement. Patients were defined as receiving endocrine therapy if claims of tamoxifen, anastrozole, letrozole, or exemestane existed from 3 months before to 12 months after lumpectomy in inpatient or outpatient claims files or National Drug Code pharmacy file. A modified Charlson comorbidity score was calculated based on claims made during the 3 months before lumpectomy (8). Cardiovascular disease and diabetes diagnoses were also specifically coded.

Statistical analysis

Univariate associations between covariates and radiation treatment type (EBRT vs brachytherapy) were tested by use of the Pearson χ^2 test. For patients treated with brachytherapy, Cochran-Armitage tests were conducted to evaluate time trends for the use of multichannel applicators and single-channel applicators. For postoperative adverse events, the probabilities of having postoperative infectious adverse events and postoperative noninfectious adverse events were determined separately by the use of 2 logistic models adjusted for covariates, determined on the basis of clinical significance (2) and statistical significance in univariate associations ($P<.25$). Goodness-of-fit was assessed with the Hosmer and Lemeshow test. Temporal trends for postoperative adverse events were examined with Cochran-Armitage tests for trend. To estimate the risk of postradiation adverse events in each group, 1-year, 3-year, and 5-year cumulative incidences were determined by use of the Kaplan-Meier method for pneumonitis, fat necrosis, breast pain, and rib fracture. Patients were censored at the earliest of any of the following: loss of part A or B coverage, conversion to health maintenance organization coverage, death, or the end of the study period. The univariate association of seroma with frequency of breast pain after diagnosis was compared with the Pearson χ^2 test for patients treated with EBRT and patients treated with brachytherapy. We further investigated the 1-year, 2-year, and 3-year cumulative incidences of breast pain by comparing patients treated in an earlier time period (2003-2007) with patients in the more recent era (2008-2012). The 5-year cumulative incidence was not compared because of the inadequate number of patients treated in 2008-2012 with 5-year follow-up. The cutpoint between the 2 time periods, the transition from the years 2007 to 2008, correlated with

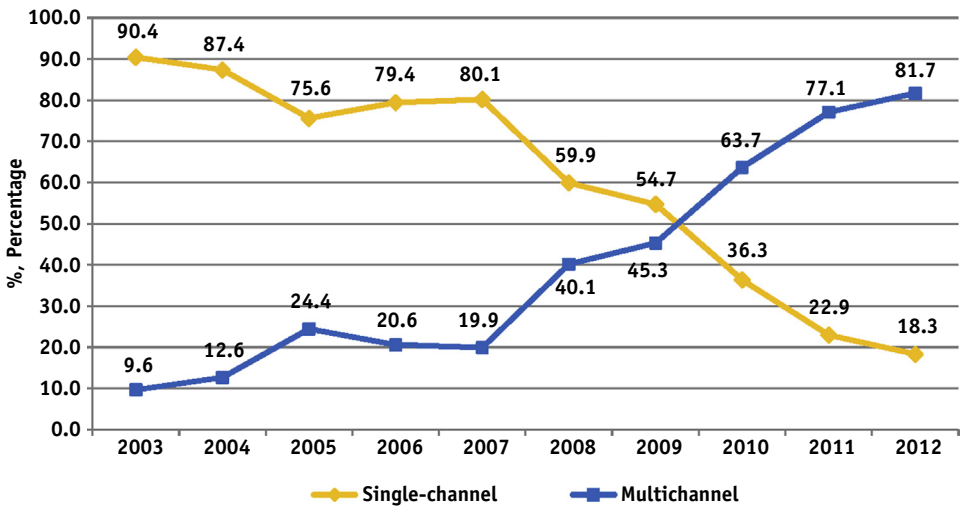

Fig. 1. Temporal trends in brachytherapy use between 2003 and 2010, stratified by brachytherapy applicator type.

changes in available brachytherapy devices such as the multilumen catheter.

To ascertain the effects of advanced technologies on postoperative infectious and noninfectious adverse events, additional multivariable logistic regression models were used to compare toxicities associated with the use of multichannel versus single-channel applicators and also to compare IMRT versus 3-dimensional (3-D) conformal RT. The 1-year, 3-year, and 5-year cumulative incidences of postradiation toxicities were also determined, comparing multichannel versus single-channel applicators, and also comparing IMRT versus 3-D conformal RT. All *P* values were 2-sided at the 5% significance level. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC). This study was deemed exempt by the University of Texas MD Anderson Cancer Center Institutional Review Board.

Results

Of 64,112 patients who received lumpectomy, 4522 (7.1%) patients received brachytherapy (2269 [50.2%] with a multichannel applicator and 2203 [48.7%] with a single-channel applicator), and 59,590 (92.9%) patients received EBRT (11.8% with IMRT). The median follow-up times were 31 months (range, 13-132 months) for EBRT patients and 32 months (range, 13-132 months) for brachytherapy patients.

The patients treated with brachytherapy were younger and more likely to receive endocrine therapy but were less likely to receive systemic chemotherapy or to have a claim indicating axillary nodal involvement. The patients treated with brachytherapy more likely had cardiovascular disease and diabetes (Table 1). Between 2003 and 2010, multichannel applicator use increased from 9.6% to 81.7%, and single-channel applicator use decreased from 90.4% to 18.3% ($P<.0001$ for trend) (Fig. 1).

Postoperative infectious adverse events

The patients receiving brachytherapy demonstrated a higher risk of infectious adverse events within the first year after lumpectomy, and the association remained significant after covariate adjustment (odds ratio [OR], 1.21; 95% confidence interval [95% CI], 1.09-1.34, $P<.001$) (Table 2). The patients also had a higher risk of infectious adverse events if they received chemotherapy (OR, 1.20; 95% CI, 1.12-1.28, $P<.0001$), had cardiovascular disease (OR, 1.26; 95% CI, 1.13-1.40, $P<.0001$), or diabetes (OR, 1.55; 95% CI, 1.43-1.69, $P<.0001$).

Temporal trends

Between 2003 and 2012, the incidence of postoperative infectious adverse events for patients who received brachytherapy generally decreased from 17.3% to 11.6%. By contrast, the incidence of postoperative infectious adverse events for patients who received EBRT was generally stable, ranging from 8.5% to 10.1% over the same period (9.7% overall). Accordingly, excess infectious adverse events in patients treated with brachytherapy, determined by use of the difference in incidence of infectious adverse events between the 2 groups, significantly decreased from 7.2% in 2003 to 1.8% in 2012. In addition, from 2007 to 2012, patients treated with brachytherapy no longer had significant excess infection risk ($P=.97$) (Fig. 2a and 2b).

Table 2 Multivariable analysis for factors associated with infectious adverse events

Factor	OR	95%	CI	*P*
Radiation therapy				
Brachytherapy (vs EBRT)	1.21	1.09	1.34	<.001
Age group				
45-49 (vs 18-44)	1.03	0.93	1.13	.57
50-54 (vs 18-44)	1.01	0.92	1.10	.91
55-59 (vs 18-44)	0.97	0.88	1.06	.47
60-64 (vs 18-44)	1.02	0.93	1.12	.68
Year of diagnosis				
2004 (vs 2003)	0.80	0.69	0.94	<.01
2005 (vs 2003)	0.96	0.82	1.13	.63
2006 (vs 2003)	0.83	0.71	0.97	.02
2007 (vs 2003)	0.94	0.82	1.09	.43
2008 (vs 2003)	0.95	0.82	1.09	.43
2009 (vs 2003)	0.95	0.83	1.09	.49
2010 (vs 2003)	0.97	0.84	1.11	.64
2011 (vs 2003)	0.98	0.85	1.12	.73
2012 (vs 2003)	0.94	0.82	1.09	.40
Axillary lymph node involvement				
Yes (vs no)	1.34	1.24	1.45	<.0001
Axillary lymph node surgery				
Yes (vs no)	1.22	1.13	1.32	<.0001
Chemotherapy				
Yes (vs no)	1.20	1.12	1.28	<.0001
Endocrine therapy				
Yes (vs no)	0.99	0.93	1.04	.60
Trastuzumab				
Yes (vs no)	1.10	0.99	1.21	.08
Cardiovascular disease				
Yes (vs no)	1.26	1.13	1.40	<.0001
Diabetes				
Yes (vs no)	1.55	1.43	1.69	<.0001
Region				
Midwest (vs northeast)	1.05	0.97	1.15	.22
South (vs northeast)	1.00	0.93	1.08	.98
West (vs northeast)	0.98	0.89	1.07	.63

Abbreviation: EBRT = external beam radiation therapy.

Subsidiary model: multichannel brachytherapy compared with single-channel brachytherapy, odds ratio (OR) = 0.89; 95% confidence interval (CI); range, 0.72-1.11; $P=.29$.

Postoperative noninfectious adverse events

The patients receiving brachytherapy also demonstrated a higher risk of noninfectious adverse events detected within

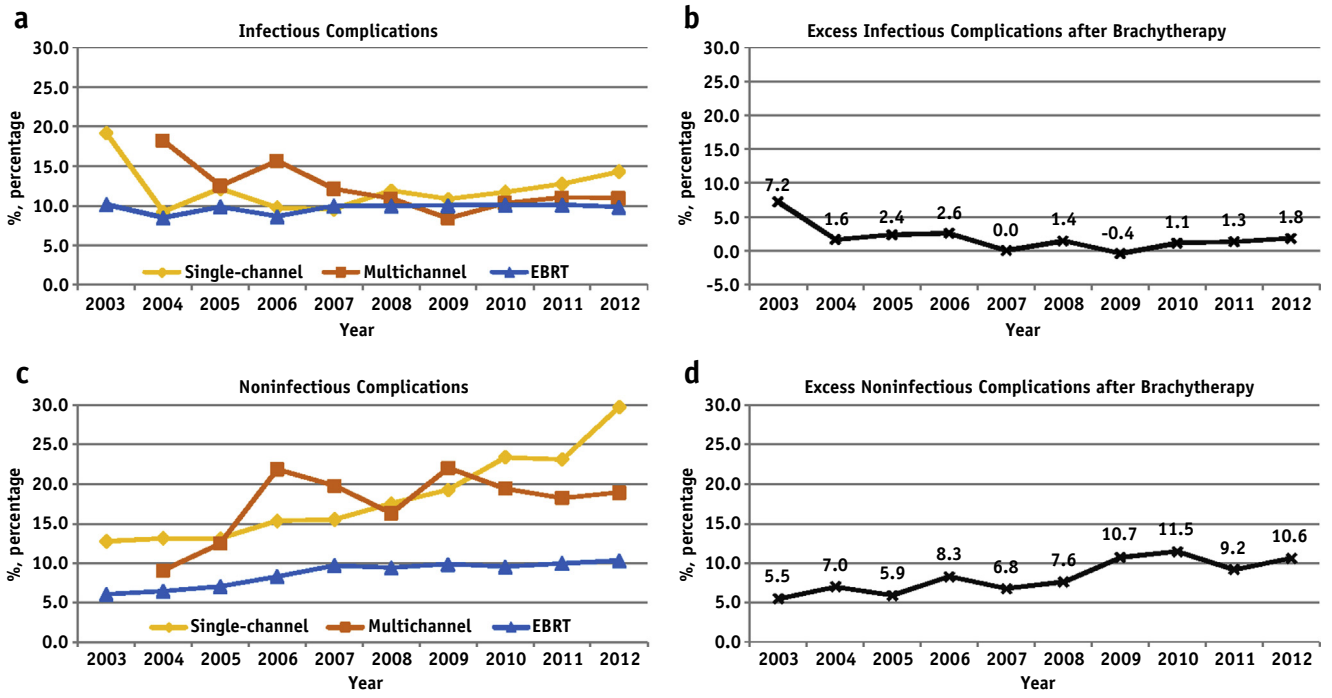

Fig. 2. Temporal trends for infectious and noninfectious complications. (a, Infectious complications Cochran-Armitage trend test: brachytherapy single-channel, $P = .56$; brachytherapy multichannel, $P = .67$; EBRT, $P = .03$. b, Excess infectious complications between patients treated with brachytherapy and patients treated with EBRT. c, Noninfectious complications: brachytherapy single-channel, $P < .001$; brachytherapy multichannel, $P = .64$; EBRT, $P < .0001$. d, Excess noninfectious complications between patients treated with brachytherapy and patients treated with EBRT). *Abbreviation:* EBRT = external beam radiation therapy.

the first year after lumpectomy, and this association remained significant after adjustment for covariates (OR, 2.27; 95% CI, 2.09-2.47, $P<.0001$). A higher risk of noninfectious adverse events was also associated with any chemotherapy (OR, 1.15; 95% CI, 1.08-1.23, $P<.0001$), cardiovascular disease (OR, 1.28; 95% CI, 1.15-1.43, $P<.0001$) and diabetes (OR, 1.33; 95% CI, 1.22-1.46, $P<.0001$) (Table 3). No significant association was detected specifically for trastuzamab, anthracyclines, or taxanes.

Seroma was the most common noninfectious adverse events, representing 70.9% of noninfectious adverse events in all patients, 83.5% of noninfectious adverse events in brachytherapy patients (multichannel applicator, 83.3%; single-channel applicator, 83.9%), and 69.0% of noninfectious adverse events in EBRT. Of patients with seroma, 77.7% had no other adverse event or postradiation toxicity preceding the seroma. Additionally, of patients with seroma, some had additional adverse events after the development of seroma, most commonly breast pain (17.8%), infection (17.3%), and fat necrosis (7.8%). Other common noninfectious adverse events included hematoma, the second most common (19.5%), and nonhealing surgical wounds (7.5%).

Temporal trends

Between 2003 and 2012, the incidence of postoperative noninfectious adverse events detected increased. For patients who received brachytherapy, the detected incidence increased overall from 11.5% to 20.9% (Cochran-Armitage trend test, $P<.001$), from 9.1% to 18.9% for multichannel catheter use (Cochran-Armitage trend test, $P=.64$), and 12.8% to 29.8% for single-channel catheter use (Cochran-Armitage trend test, $P<.001$) (Fig. 2c). For patients who received EBRT, the detected incidence of noninfectious adverse events also increased, but to a lesser magnitude, from 6.1% to 10.3% (Cochran-Armitage trend test, $P<.0001$). Accordingly, the excess noninfectious adverse events detected in patients treated with brachytherapy increased from 5.5% in 2003 to 10.6% in 2012 (Fig. 2d). The temporal trends were consistent for seroma, which increased from 7.7% to 17.9% for patients who received brachytherapy and from 3.7% to 7.8% for patients who received EBRT (Cochran-Armitage trend test, $P<.0001$ for both) (Fig. 3). The increase in detection was associated with an increased use of imaging surveillance modalities (ultrasonography and mammography) ($P<.001$). However, in a subsidiary model adjusted for use of imaging surveillance modalities, patients receiving brachytherapy still demonstrated a higher risk of noninfectious adverse events compared with patients receiving EBRT (OR, 2.19; 95% CI, 2.01-2.38, $P<.0001$).

Postradiation adverse events

The 3-year and 5-year cumulative incidences of fat necrosis, breast pain, and rib fracture were slightly higher after

Table 3 Multivariable analysis for factors associated with noninfectious adverse events

Factor	OR	95%	CI	*P*
Radiation therapy				
Brachytherapy (vs EBRT)	2.27	2.09	2.47	<.0001
Age group				
45-49 (vs 18-44)	1.05	0.95	1.16	.35
50-54 (vs 18-44)	1.08	0.99	1.19	.10
55-59 (vs 18-44)	0.98	0.89	1.08	.67
60-64 (vs 18-44)	1.04	0.95	1.15	.39
Year of diagnosis				
2004 (vs 2003)	1.07	0.89	1.30	.46
2005 (vs 2003)	1.19	0.99	1.45	.07
2006 (vs 2003)	1.43	1.20	1.71	<.0001
2007 (vs 2003)	1.64	1.38	1.94	<.0001
2008 (vs 2003)	1.61	1.36	1.90	<.0001
2009 (vs 2003)	1.78	1.51	2.09	<.0001
2010 (vs 2003)	1.72	1.46	2.02	<.0001
2011 (vs 2003)	1.75	1.49	2.06	<.0001
2012 (vs 2003)	1.85	1.56	2.18	<.0001
Axillary lymph node involvement				
Yes (vs no)	1.28	1.19	1.39	<.0001
Axillary lymph node surgery				
Yes (vs no)	1.23	1.14	1.33	<.0001
Chemotherapy				
Yes (vs no)	1.15	1.08	1.23	<.0001
Endocrine therapy				
Yes (vs no)	0.98	0.93	1.04	.49
Trastuzumab				
Yes (vs no)	0.91	0.81	1.01	.08
Cardiovascular disease				
Yes (vs no)	1.28	1.15	1.43	<.0001
Diabetes				
Yes (vs no)	1.33	1.22	1.46	<.0001
Region				
Midwest (vs northeast)	1.20	1.10	1.31	<.0001
South (vs northeast)	1.20	1.10	1.30	<.0001
West (vs northeast)	1.18	1.07	1.29	.0007

Abbreviations: EBRT = external beam radiation therapy.

Subsidiary models: multichannel brachytherapy compared with single-channel brachytherapy, odds ratio (OR) = 0.95 (95% confidence interval (CI): 0.80-1.12, $P = .53$).

brachytherapy than after EBRT. At 5 years, the cumulative incidences were 13.7% versus 8.1%, 19.4% versus 16.0%, and 1.6% versus 1.3%, respectively ($P<.001$ for all comparisons). By contrast, the cumulative incidence of pneumonitis was lower (Table 4).

Breast pain

An increased risk of breast pain was found in patients with seroma: 20.1% of patients with seroma had claims of breast pain compared with 11.8% of patients without seroma ($P<.0001$) (Table E4; available online in the Supplemental Material at www.redjournal.org). The absolute proportion of patients with seroma having breast pain was higher in patients treated with brachytherapy (22.8% of patients with seroma vs 14.0% of patients without seroma, $P<.0001$) than in patients treated with EBRT (19.6% of patients with seroma vs 11.2% of patients without seroma, $P<.0001$) (Table E5; available online in the Supplemental Material at www.redjournal.org).

Advanced technologies

Multichannel versus single-channel applicators

Among patients treated with brachytherapy, no significant differences in postoperative infectious or noninfectious adverse events were found between patients treated with multichannel applicators and those treated with single-channel applicators. For postradiation adverse events, again there were no significant differences, although the absolute 5-year cumulative incidence rate of fat necrosis was slightly lower for multichannel brachytherapy (11.9%) than for single-channel brachytherapy (14.5%).

IMRT versus 3-D conformal RT

Patients receiving IMRT demonstrated no significant difference in any postoperative adverse events compared with patients receiving 3-D conformal RT after adjustment for multiple covariates. However, the 3-year and 5-year cumulative incidences of fat necrosis and breast pain were slightly higher after IMRT than after 3-D conformal RT. For example, at 5 years, the cumulative incidences were 9.3% versus 8.0% and 16.7% versus 15.8%, respectively ($P<.01$ for both comparisons). Fraction number was not associated with a risk of adverse events.

Discussion

Toxicities found after breast brachytherapy were distinct from toxicities found after EBRT in our contemporary cohort of breast cancer patients. The overall relative toxicity risks were higher after brachytherapy for 1-year postoperative adverse events and for longer-term risks of breast pain, fat necrosis, and rib fracture. The absolute differences between treatment groups were, however, still small. The temporal trends suggested that advances in provider experience may have mitigated excess postoperative infection risk associated with brachytherapy. By contrast, seroma risk after brachytherapy persistently exceeded the risk after EBRT over the entire study period. Seroma still occurred in approximately 1 of every 6 patients treated with brachytherapy (and 1 of 4 patients with single-channel applicators) in 2012, the most recent year studied in this cohort. Furthermore, seroma development was associated with increased risk of breast pain. Data were not available to investigate whether these differences in toxicity profiles ultimately affected long-term patient cosmesis, quality of life, and patient perception of treatment decisions, but the need for future exploration of such questions is highlighted by our findings.

Our findings build on toxicity data reported in prior analyses. In some of the earliest reported data for balloon-based breast brachytherapy in a single-arm study in the

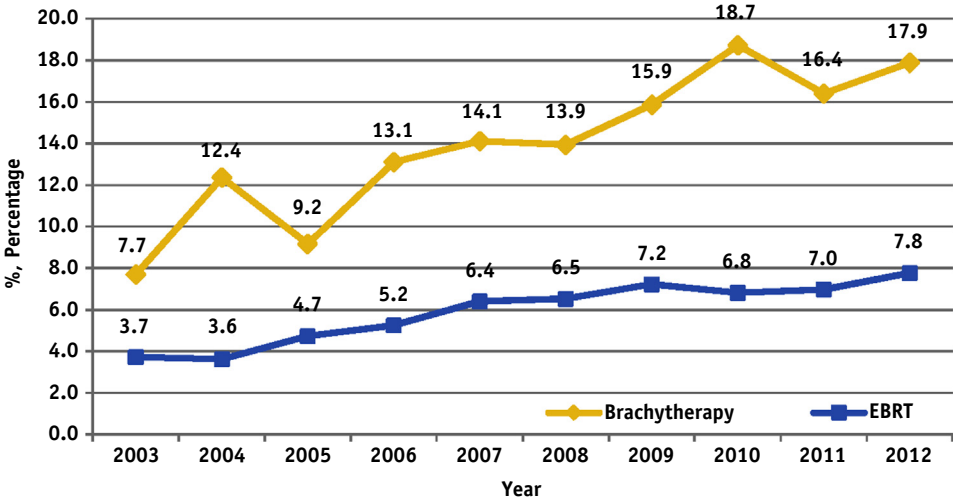

Fig. 3. Temporal trends for seroma adverse events. *Abbreviation:* EBRT = external beam radiation therapy.

United States, adverse event profiles were considered acceptable (9). However, additional recent retrospective data sought to directly compare toxicities in patients treated with brachytherapy versus EBRT, and these studies consequently raised concerns about significantly higher toxicity risks after brachytherapy (2, 10-12). Wound, skin, infectious, and postradiation adverse events occurred more frequently after brachytherapy in these studies (2, 10-12). In previous reports, infectious adverse events after brachytherapy ranged from 0% to 16%, with higher infection rates reported in earlier studies of patients treated between 2002 and 2003 (3, 11, 13-17). Our analysis supports the premise that infectious adverse events have significantly decreased since the earliest treatment era, likely along with the implementation of closed-cavity placement, prophylactic antibiotics, and meticulous catheter care practices (18).

Yet, by contrast, we found that the incidence of noninfectious adverse events, specifically those classified by diagnosis claims as seroma, increased in detection over time. A higher absolute seroma incidence was detected in patients treated with brachytherapy over the entire study period. Prior studies have reported variable seroma incidences after brachytherapy, ranging from 4.8% to 78% (19-22), generally with more than 20% risk after 12 months of follow-up (3, 23). Although the overall seroma incidence in our study falls within this range, the underlying cause of the temporal increase found in our analysis was unclear: whether changes in patient selection, technique, or detection of seroma have changed over time. Previously identified factors associated with increased seroma development include body weight, larger tumor size, skin spacing, balloon fill, postoperative infection, timing of catheter placement, and catheter placement technique (17, 20, 24). Chemotherapy use was noted in prior studies as a risk factor for brachytherapy toxicities including seroma (15, 24-26). Although we also found a similar association, this result should be interpreted cautiously and not necessarily causally. The longer-term implications of seroma development on cosmesis and long-term fibrosis and breast pain are unclear, and whether such potential secondary effects need to be mitigated also requires additional investigation.

In our study, the magnitudes of risks of post-radiation adverse events were consistent with risks reported in prior studies (16, 27-30). The absolute 3-year and 5-year risks of fat necrosis, breast pain, and rib fracture after brachytherapy were all comparable to slightly lower in patients treated with multichannel brachytherapy compared with single-channel brachytherapy. It is important to note that these absolute differences in risk were not statistically significant, although only small sample sizes were available for these comparisons. Still, our results do not rule out that improved operator experience over time, along with the potential for improved target coverage and dose homogeneity with multichannel brachytherapy (31, 32) could ultimately translate into more favorable clinical outcomes in the most contemporary practice of brachytherapy. Longer follow-up is needed to provide additional insight into this comparison, and our subgroup analysis should be interpreted only as exploratory and hypothesis generating. Long-term follow-up will reflect the additional experience and diffusion of breast brachytherapy into current practice, continued advances in catheter technology, and improvements in individual operator's experience and practitioner's technique. We found no increase in radiation-associated toxicities for IMRT versus 3-D conformal RT. Previous studies have suggested a more favorable acute skin toxicity profile and cosmesis with IMRT (33, 34), but, consistent with our results, have never demonstrated improvement in fat necrosis, breast pain, rib fracture, or seroma risks.

We were limited only to toxicities identifiable through claims. Severity, grade, cancer staging, and patient-measured versus provider-measured outcomes (including cosmesis) were not available in this database. Future prospective studies providing such details can provide

Table 4 One-year, 3-year, and 5-year actuarial events risk for pneumonitis, fat necrosis, rib fracture, and breast pain

Toxicity	1 year %	3 year %	5 year %	*P* value (between RT subgroups*)	*P* value (between RT types†)
Pneumonitis					<.01
EBRT	0.20	0.32	0.38	.72	
3-D conformal	0.20	0.32	0.38		
IMRT	0.20	0.31	0.37		
Brachytherapy	0.00	0.02	0.24	.29	
Single-channel	0.00	0.05	0.32		
Multichannel‡	-	-	-		
Fat necrosis					<.0001
EBRT	4.43	6.64	8.12	<.0001	
3-D conformal	4.32	6.46	7.97		
IMRT	5.33	8.01	9.32		
Brachytherapy	5.00	9.24	13.73	.86	
Single-channel	4.77	9.37	14.54		
Multichannel	5.20	8.90	11.92		
Breast pain					<.0001
EBRT	5.99	12.33	15.96	<.01	
3-D conformal	5.96	12.15	15.83		
IMRT	6.26	13.66	16.73		
Brachytherapy	9.16	16.62	19.42	.77	
Single-channel	9.03	16.64	19.12		
Multichannel	9.17	16.22	19.48		
Rib fracture					<.001
EBRT	0.22	0.79	1.26	.80	
3-D conformal	0.21	0.80	1.25		
IMRT	0.23	0.66	1.39		
Brachytherapy	0.51	1.26	1.63	.20	
Single-channel	0.64	1.56	1.84		
Multichannel	0.40	0.97	1.27		

Abbreviations: EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; RT = radiation therapy.
* 3-D Conformal versus IMRT, single-channel versus multichannel brachytherapy.
† EBRT versus brachytherapy.
‡ Insufficient events for estimate.

important complementary information to our population-based study. Our claims-based data may have favored detection of toxicities causing severe enough clinical sequelae to require intervention and may not have captured less severe grades of toxicity. Variations in toxicity documentation and claims coding practices may have also translated into heterogeneity in outcomes classification, a potential nondifferential bias. Claims data precluded brachytherapy treatment details, for example, details on balloon-based versus strut-based devices, or other characteristics that may modify the risk of outcomes, including seroma. Finally, given that our cohort was selected from a private insurance claims dataset, our follow-up window was limited to the duration of a patient's private insurance coverage, and therefore long-term toxicities beyond 3 to 5 years, especially for newer techniques such as multichannel applicators, require additional study.

In summary, we found that postoperative adverse event and postradiation toxicity profiles after breast brachytherapy were distinct from those after EBRT. The overall risks for our era of study still demonstrated some increased adverse events detected in patients treated with brachytherapy, but the absolute differences were generally small. The temporal trends potentially reflected the evolving use of this newer therapy. Clinical consideration of brachytherapy as a treatment option requires careful discussion of both the historical and emerging toxicity profiles and of the ongoing uncertainties about the risk of long-term adverse events.

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