Published in final edited form as:

Brachytherapy. 2013 ; 12(4): 293–302. doi:10.1016/j.brachy.2013.01.168.

Survival after Partial Breast Brachytherapy in Elderly Patients with Non-Metastatic Breast Cancer

Nengliang Yao¹, Heath B. Mackley², Roger T. Anderson³, and Abram Recht⁴

¹Pennsylvania State University, Department of Health Policy and Administration

²Pennsylvania State University, Division of Radiation Oncology

³Pennsylvania State University, Department of Public Health Science

⁴Department of Radiation Oncology, Harvard Medical School, and Beth Israel Deaconess Medical Center, Boston MA

Abstract

Background—Despite growing utilization of accelerated partial breast irradiation using brachytherapy (APBI-Brachy) for elderly breast cancer patients, there are limited data from randomized phase III trials to support its routine use. This study uses population-based data to examine whether APBI-Brachy results in comparable survival rates compared to whole breast irradiation (WBI).

Methods—A sample of 29,647 female patients diagnosed with non-metastatic breast cancer in 2002–2007 treated with breast -conserving surgery and radiotherapy was identified in the SEER-Medicare dataset. Log-rank tests, Cox proportional hazards models, instrumental variable analysis, and subgroup analysis were used to study the comparative effectiveness of APBI-Brachy and WBI.

Results—During a median follow-up of 3.6 and 4.8 years, 123 (7.7%) and 3438 (13.6%) patients died following APBI-Brachy and WBI, respectively. Recurrence-free survival (p-value=0.9711) and overall survival rates (p-value=0.0551) did not differ significantly between the two radiation modalities. After accounting for tumor characteristics, patient characteristics, community factors, and comorbidities, the recurrence-free survival (HR=1.05; 95% CI, 0.90–1.23; p=0.5125) and overall survival (HR= 0.87; 95% CI, 0.72–1.04; p=0.1332) were still not significantly different between patients treated with APBI-Brachy and WBI.

Conclusion—Partial breast brachytherapy and WBI resulted in similar recurrence-free and overall survival rates in this cohort of elderly breast cancer patients, even after adjustment for the more favorable characteristics of patients in the former group. These findings will need to be confirmed by the randomized trials comparing these modalities.

Corresponding author: Nengliang Yao, Department of Health Policy and Administration, College of Health and Human Development, The Pennsylvania State University, 604 Ford Building, University Park, PA 16802, Phone: (814) 380 1251, Fax: (814) 863 2905, ayao@psu.edu.

The authors have no financial disclosures.

Keywords

Brachytherapy; breast-conserving therapy; accelerated partial breast irradiation; breast carcinoma; effectiveness

Introduction

Radiation therapy has played an important role in improving survival and local control rates among female breast cancer patients in multiple randomized trials.¹ Whole breast irradiation (WBI) has been recommended for patients with early-stage cancers after breast-conserving surgery in practice guidelines.^{2–4} However, WBI involves a 4–7 week course of daily treatment, depending on the schedule chosen. It has been suggested that this burden is an important cause of lack of adherence for receiving appropriate adjuvant radiation therapy.⁵ Accelerated partial breast irradiation (APBI) is an alternative to WBI, which significantly decreases the number of patient visits and thus could potentially reduce the incidence of radiation therapy omission after breast conserving surgery (BCS). In contrast to 16–36 fractions of radiotherapy in WBI, APBI usually involves twice-daily treatments over 5 days. Accelerated partial breast brachytherapy (APBI-Brachy) is a procedure in which physicians place catheters or a balloon applicator inside the breast to deliver radiation to the operative cavity and surrounding tissue using a radioactive isotope. APBI-Brachy has become an increasingly popular alternative to WBI in the United States.⁶

Despite its increasing utilization, the use of APBI-Brachy as the sole radiation treatment after BCS remains controversial. Recent clinical trials found that APBI brachytherapy provides similar local control rates compared to WBI.^{7–11} However, a recent population study using Medicare claims data found that APBI-Brachy is associated with a two-fold increased risk for subsequent mastectomy compared with WBI in elderly patients.¹² Their study was criticized by the American Brachytherapy Society for not controlling for important tumor characteristics.¹³ The results of large phase III randomized trials being conducted in North America and Europe which compare WBI to APBI will take many more years to emerge.¹⁴

We therefore feel that an immediate need exists for a population-based study to compare the effectiveness of APBI-Brachy with that of standard WBI. We used the linked Surveillance, Epidemiology, and End Results Program (SEER)-Medicare database to examine this issue after accounting for tumor, patient, and comorbidity factors. Instrumental variable analyses and subgroup analyses were used in this study to control for the selection bias in the observational data.^{15,16} Instrumental variable analysis mimics the key feature of randomization by finding a variable that affects treatment assignment but has no independent effect on outcomes. Subgroup analyses analyzed the survival outcomes among the patients that fit most closely into the “suitable” category of the ASTRO consensus guidelines.

Methods

Data Source

Data for this study were taken from the linked SEER-Medicare database. The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The current SEER-Medicare database 2011 edition contains SEER registry information for patients with a first breast cancer diagnosed between 2002–2007 and Medicare claims of those patients from 2001–2009. Patients' census tract information and sociodemographic information of patients' census tract is also included. The SEER program of the National Cancer Institute (NCI) currently collects and publishes cancer incidence and survival data from 18 population-based cancer registries covering approximately 28% of the U.S. population.¹⁷ SEER regions include the states of California, Connecticut, Hawaii, Iowa, Louisiana, New Jersey, New Mexico, Utah; multi-county areas of Atlanta and rural Georgia and Detroit; and American Indians/Alaska Natives in Arizona and Alaska. Medicare is the primary health insurer for 97% of the population 65 and older. The Medicare program is likely to have complete claims information for patients not enrolled in a health maintenance organization and have therefore, been used extensively in cancer care research. The SEER-Medicare data have also been used to study recurrence and survival among breast cancer patients.^{18–20}

The Pennsylvania State University Institutional Review Board approved this study, and the National Cancer Institute, Centers for Medicare & Medicaid Services, and individual SEER cancer registries approved data requests. This manuscript was reviewed by the SEER-Medicare program to ensure the confidentiality of patients and providers in SEER areas.

Cohort selection

A sample of 26,931 female patients age 65 years or older was identified. We limited the analysis to those most likely to have complete claims, namely patients who had continuous Medicare Part A and Part B enrollment and no enrollment in a health maintenance organization from diagnosis through death or to the end of this study (31 December 2009). The cohort was restricted to patients who underwent radiotherapy within six months after their last BCS. Patients who died and who had a secondary diagnosis of cancer or subsequent mastectomy within this six month period were excluded, because they may have elevated risk of mortality compared to a typical non-metastatic breast cancer patient. Patients receiving chemotherapy were also excluded because adjuvant chemotherapy is generally given before WBI but usually after APBI-Brachy and hence this difference in timing of when radiation is given might affect the risk of local recurrence between these two modalities. Confirmation that breast-conserving surgery and radiotherapy were performed was obtained from Medicare claims by examining claims made under specific HCPCS and ICD-9 inpatient and outpatient procedure codes (Table 1).

Outcome variable and other covariates

The outcome variables examined were recurrence-free survival and overall survival. A recurrence (local, regional, distant, or new contralateral breast cancer) is defined as having a subsequent mastectomy in Medicare claims or a second confirmed diagnosis of breast

cancer in the cancer registry filed more than six months from the last breast-conserving surgery.^{18–20} A recent paper found this algorithm can identify breast cancer recurrence with high sensitivity, specificity, and positive predictive value when validated against medical record review.²¹ Similar algorithms have been used in previously published SEER-Medicare analyses as a surrogate for local failure.^{18–20,22} Recurrence-free survival is defined as the interval from date of diagnosis until the first evidence of any recurrence or death from any cause more than 6 months after BCS, so it is jointly determined by recurrence and death. Overall survival is defined as the interval from date of diagnosis until the first evidence of death from any cause more than 6 months after BCS. Date of death is recorded in the SEER registry and Medicare claims. Breast cancer-specific survival was not analyzed because of the frequent absence of information as to the cause of death in the data.

The explanatory variable of main interest was the type of radiation therapy that patients received after BCS. Patients are defined as treated with WBI or APBI-Brachy if procedure claims were recorded within 6 months of the date of BCS. APBI-Brachy was considered to be the sole radiation modality used if there were at least 5 and no more than 10 fractions of APBI and no billing records for WBI. WBI was considered to be the sole radiation modality used if there were at least 11 fractions of external beam radiation given in 15–50 days and no billing records for APBI-Brachy.

Other explanatory variables in this study included patient characteristics, tumor characteristics, and comorbidity. Patient characteristics included race, age at diagnosis, year of diagnosis, registry of residence, median household income of the patient's census tract, and metropolitan status of patient's residence. Tumor characteristics included tumor size, histology, grade, stage, receptor status, and lymph node involvement. The Charlson comorbidity score in this study was derived from Medicare claims data during the 12 months preceding diagnosis.²³

Statistical Analysis

Rates of recurrence, recurrence-free survival, and overall survival were calculated using Kaplan-Meier estimation. The statistical significance of differences between these rates was calculated using the log-rank tests. Cox proportional hazards model estimates were used to show how treatment and other covariates were related to outcome. Patients were censored at the first evidence of recurrence, death, or end of the study in the log-rank test and the hazards models. All analyses were conducted using SAS software version 9.2, and all statistical tests assumed a two-tailed $\alpha=0.05$.

To further assess the validity of the findings and reduce the influence of selection bias, we also performed an instrumental variable analysis.^{15,16} Relative distance to an APBI-Brachy physician is used as an instrumental variable in the analysis. We defined this as the distance from the patient's residence to the nearest physician performing at least 5 APBI-Brachys the year of treatment or the past year of treatment minus the distance from the patient's residence to the nearest physician performing any WBI. We calculated distances using the proximity tool in the ArcGIS 10, which measures the number of miles between the centers of patient's census tract and the ZIP code of physician's practice.

Distance from patient's residence to the nearest facility is one of the most common instrumental variables used in previous health care research.¹⁶ To assess its validity as an instrument in this study, we confirmed that the relative distance was strongly associated with receipt of APBI-Brachy (χ^2 test; $P < 0.0001$); patients living closer to a provider of APBI-Brachy were more likely to receive this treatment. This relationship persisted in a multivariate regression that adjusted for patient characteristics, tumor characteristics, and community factors (F statistic=83.4). Furthermore, in a standard multivariate proportional hazards model, we observed no significant association between the instrument variable and survival (recurrence free survival: HR, 0.92; 95% CI, 0.67–1.27; p-value=0.6040; overall survival: HR, 0.87, 95% CI, 0.60–1.24, p-value=0.4307). The relative distance is also relatively independent of a current patient's tumor factors, comorbidities and other characteristics. Taken together, these findings suggest that relative distance is a valid instrument variable.

Applying instrumental variable analysis in a hazards model requires a two-stage residual inclusion estimation approach.^{15,24} The first-stage equation predicts the likelihood of receiving the radiation therapy as a function of the relative distance to radiotherapy facility and other factors, and the second-stage equation estimates the effect of the treatment on the recurrence-free survival or overall survival rates incorporating the “residuals” generated from the first-stage equation.

To further analyze the survival after APBI-Brachy in our study sample, we performed a subgroup analysis for the patients that fit most closely into the “suitable” category of the ASTRO consensus guidelines. These patients were diagnosed with T1N0 invasive ductal carcinomas that were well or moderately-well differentiated and ER positive. (Other details of histology used in the ASTRO classification, such as margin width and the presence of lymphovascular invasion, were not available to us.) We performed standard multivariable proportional hazards models to study recurrence-free survival and overall survival in this narrowly-defined cohort of patients.

Results

A total of 26,931 women met our study's eligibility criteria; 1594 patients (5.9%) were treated with APBI-Brachy and 25,339 patients (94.1%) were treated with standard WBI. Table 2 describes the patients' demographic characteristics and tumor characteristics by the type of radiation therapy given. The proportion of patients treated with APBI-Brachy rose substantially over time (from 1.3% of patients diagnosed in 2002 to 11.2% of patients diagnosed in 2007). Patients who received APBI-Brachy were 0.4 years younger than recipients of WBI (73.76 years versus 74.14 years, $p = 0.0184$). About 90% of patients were White, and the distributions of race/ethnicity are not significantly different in the two treatment groups. 85.3% of patients received APBI-Brachy were diagnosed with an invasive breast cancer, higher than WBI patients (80.3%, $p < 0.0001$). 82.1% of patients who received APBI-Brachy were diagnosed with a tumor 0–2 cm in size, higher than WBI patients (73.0%, $p < 0.0001$). There were more ductal carcinoma patients in the APBI-brachy group than in the WBI group (70.1% versus 62.0%, $p < 0.0001$). 79.1% of patients who received APBI-Brachy did not have lymph node involvement, which was higher than for WBI

patients (66.1%, $p < 0.0001$). There were more patients with ER-positive cancers in the APBI-brachy group than in the WBI group (80.4% versus 76.0%, $p < 0.0001$). 75.85% of APBI-Brachy patients' tumor were differentiated or moderately differentiated, higher than among WBI patients (69.1%, $p < 0.0001$). About 17% of patients were free of comorbid conditions, and the distributions of comorbidities are not significantly different in the two treatment groups. The median household income of the patient's census tract was also similar in both treatment groups (\$55620 versus \$55853, $p = 0.7203$). However, 92.6% of patients who received APBI-Brachy resided in metropolitan areas, higher than for WBI patients (88.5%, $p < 0.0001$). Finally, the distributions of cancer registries were significantly different between the two treatment groups ($p < 0.0001$).

The median follow-up time for the whole study cohort was 4.7 years (interquartile range, 3.3–6.3 years). For the patients who received APBI-Brachy, 53 had any cancer recurrence and 123 died from any cause during a median follow-up of 3.6 years (interquartile range, 2.7–4.9 years). For the WBI patients, 636 patients had any recurrence and 3438 patients died from any cause during a median follow-up of 4.8 years (interquartile range, 3.3–6.4 years). Figure 1 displays the Kaplan-Meier curves and compares the recurrence-free survival and overall survival for the two radiation modalities. The unadjusted analysis showed that patients treated with APBI-Brachy had a higher recurrence rate than WBI patients ($p < 0.0001$). Recurrence-free survival ($p = 0.9711$) and overall survival ($p = 0.0551$) did not differ significantly between the two radiation modalities.

Adjusted risks of any recurrence and all-cause death were determined using standard multivariate Cox proportional hazards models, including tumor, demographic, socioeconomic, comorbidity, and treatment covariates. Table 3 displays the predictors of recurrence-free survival from the hazards model. The risk in patients treated with APBI-Brachy was not significantly different from patients treated with WBI (HR= 1.05; 95% CI, 0.90–1.23; $p = 0.5125$). Factors independently associated with an increased risk in the model included old age, invasive cancer, tumor size greater than 2 cm but smaller than 5 cm, lymph node involvement, ductal histology, negative estrogen receptor status, undifferentiated tumor, the existence of comorbid conditions, residing in the Louisiana registry area, and living in a census tract below the national median household income. Race, year of diagnosis, and metropolitan status of patient's residence were not significantly associated with an increased risk. The instrumental variable analysis suggested that results in the standard model were essentially unchanged (HR= 0.85; 95% CI, 0.36–2.01; $p = 0.7032$).

Table 4 displays the predictors of overall survival from the hazards model. The risk in patients treated with APBI-Brachy was not significantly different from patients treated with WBI (HR= 0.87; 95% CI, 0.72–1.04; $p = 0.1332$). Other significant factors in this model are similar to the model of recurrence free survival. The instrumental variable analysis suggested that results in the standard multivariate proportional hazards model were essentially unchanged (HR= 0.59; 95% CI, 0.22–1.57; $p = 0.2919$).

Table 5 presents the results of the subgroup analysis for the “suitable” patients to determine whether the APBI-Brachy is associated with comparable survival benefits relative to WBI. Of these 5374 patients (4376 WBI patient and 527 APBI-Brachy patients), 4806 have full

information to perform multivariate hazards model regression. After adjusting for patient's age, tumor size, comorbidity, and census tract's median household income, outcome for patients treated with APBI-Brachy was not significantly different from that of patients treated with WBI (recurrence-free survival: HR, 1.12; 95% CI, 0.82–1.54; $p=0.4697$; overall survival: HR, 0.89, 95% CI, 0.61–1.30, $p=0.5459$).

Discussion

The proportion of Medicare patients receiving APBI-Brachy in our study increased from less than 1% of patients in 2001 to 11.2% in 2007, which is consistent with previous studies.^{6,12,25} A recent population study by researchers from MD Anderson Cancer Center (MDACC) found that the 5-year overall survival rate was similar between patients treated with APBI-Brachy and WBI in a multivariate analysis,¹² but this analysis failed to control for important prognostic factors such as tumor characteristics.¹³ We found that receipt of APBI-Brachy results in similar survival outcomes compared to standard WBI after accounting for tumor characteristics, patient characteristics, community factors, and comorbidities. Since selection bias may still play a major role in accounting for differences of outcome in observational studies,²⁶ we used instrumental variable analyses and subgroup analyses to reduce the influence of selection bias caused by unobserved confounders. The “suitable” patients in the subgroup analyses were a more homogeneous group, and analyzing them separately has helped address some of the issues about selection bias. Therefore, the present study is more rigorously adjusted to consider observable and unobservable confounding factors.

The paper by MDACC researchers, along with another recent population study by researchers from Yale, have also found that treatment with brachytherapy compared with WBI was associated with increased complications,^{12,27} but they fail to control for important tumor characteristics because Medicare claims data do not contain such information. Additional study is warranted in the next few years to compare the complication rates between brachytherapy and WBI using SEER-Medicare linked data to adjust for potential confounders such as tumor stage.

This study has several limitations. The follow-up time is relatively short, so additional differences between the two treatment groups may emerge at later time points. Because of the coding issues in the claims data, we were not able to control for hormone therapy use, although we were able to exclude patients receiving chemotherapy. We were not able to compare all APBI techniques, such as intraoperative radiation therapy.²⁸ We also cannot distinguish two types of brachytherapy (balloon based and multicatheter based) because of ambiguities in the procedure codes. Our definitions of surgery and radiation are determined by claims, not by chart review; however, Medicare claims are generally thought to be accurate because they are tied to physician payment. The algorithm of recurrence does not distinguish between ipsilateral and contralateral events; however, the risk of contralateral breast cancer should not be affected by the radiation therapy modality, so the difference between two modalities should reflect only ipsilateral local failure rates if the two populations are not different in their risk of contralateral breast cancer. Finally, the results from the present study may not apply to younger patients.

In summary, partial breast brachytherapy resulted in similar outcomes to standard WBI in this cohort of elderly breast cancer patients after accounting for tumor characteristics, patient characteristics, community factors, and comorbidities. This finding will eventually need to be confirmed by randomized trials. However, our work supports the cautious use of partial breast brachytherapy until such data are available.

List of Abbreviations Used

WBI	Whole breast irradiation
APBI	Accelerated partial breast irradiation
APBI-Brachy	Accelerated partial breast irradiation using brachytherapy
BCS	Breast conserving surgery
SEER	Surveillance, Epidemiology, and End Results Program
NCI	National Cancer Institute
HCPSC	Healthcare Common Procedure Coding System
HR	Hazards Ratio
ASTRO	American Society for Radiation Oncology

References

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005; 366:2087–2106. [PubMed: 16360786]
2. National Institute of Health. NIH consensus conference. Treatment of early-stage breast cancer. *JAMA*. 1991; 265:391–395. [PubMed: 1984541]
3. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 1. 2011. 2012. (Accessed February 9, 2011, at http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.)
4. Breast cancer treatment (PDQ®): Health professional version 2011. 2012. (Accessed July 9, 2012, at <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page6>.)
5. Arthur DW, Vicini FA. Accelerated partial breast irradiation as a part of breast conservation therapy. *J Clin Oncol*. 2005; 23:1726–1935. [PubMed: 15755981]
6. 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. [PubMed: 21135274]
7. Ferraro DJ, Garsa AA, DeWees TA, et al. Comparison of accelerated partial breast irradiation via multicatheter interstitial brachytherapy versus whole breast radiation. *Radiat Oncol*. 2012; 7:53. [PubMed: 22458887]
8. McHaffie DR, Patel RR, Adkison JB, et al. Outcomes after accelerated partial breast irradiation in patients with ASTRO consensus statement cautionary features. *Int J Radiat Oncol Biol Phys*. 2011; 81:46–51. [PubMed: 20732760]
9. Strnad V, Hildebrandt G, Potter R, et al. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys*. 2011; 80:17–24. [PubMed: 20605365]
10. Shah C, Antonucci JV, Wilkinson JB, et al. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. *Radiother Oncol*. 2011; 100:210–214. [PubMed: 21497927]

11. Polgar C, Major T, Fodor J, et al. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol.* 2010; 94:274–279. [PubMed: 20181401]
12. Smith GL, Xu Y, Buchholz TA, et al. Association between treatment with brachytherapy vs whole-breast irradiation and subsequent mastectomy, complications, and survival among older women with invasive breast cancer. *JAMA.* 2012; 307:1827–1837. [PubMed: 22550197]
13. ABS Response to Breast Brachytherapy Article in JAMA. May 2. 2012 2012. (Accessed June 8, 2012, at http://www.americanbrachytherapy.org/publications/APBI-ABS_statement_05-12.pdf.)
14. RTOG 0413 Protocol Information. 2011. (Accessed February 21, 2012, at <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0413>.)
15. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. *J Health Econ.* 2008; 27:531–543. [PubMed: 18192044]
16. Hadley J, Yabroff KR, Barrett MJ, et al. Comparative effectiveness of prostate cancer treatments: evaluating statistical adjustments for confounding in observational data. *J Natl Cancer Inst.* 2010; 102:1780–1793. [PubMed: 20944078]
17. Surveillance, Epidemiology, and End Results Program. 2005. (Accessed July 21, 2011, at http://seer.cancer.gov/about/SEER_brochure.pdf.)
18. Smith BD, Gross CP, Smith GL, et al. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst.* 2006; 98:681–690. [PubMed: 16705122]
19. Stokes ME, Thompson D, Montoya EL, et al. Ten-year survival and cost following breast cancer recurrence: estimates from SEER-medicare data. *Value Health.* 2008; 11:213–220. [PubMed: 18380633]
20. Punglia RS, Saito AM, Neville BA, et al. Impact of interval from breast conserving surgery to radiotherapy on local recurrence in older women with breast cancer: retrospective cohort analysis. *BMJ.* 2010; 340:c845. [PubMed: 20197326]
21. Chubak J, Yu O, Pocobelli G, et al. Administrative Data Algorithms to Identify Second Breast Cancer Events Following Early-Stage Invasive Breast Cancer. *J Natl Cancer Inst.* 2012; 104(12): 931–940. [PubMed: 22547340]
22. Gooden KM, Howard DL, Carpenter WR, et al. The effect of hospital and surgeon volume on racial differences in recurrence-free survival after radical prostatectomy. *Med care.* 2008; 46:1170–1176. [PubMed: 18953228]
23. Klabunde CN, Potosky AL, Legler JM, et al. Development of a comorbidity index using physician claims data. *J Clin Epidemiol.* 2000; 53:1258–1267. [PubMed: 11146273]
24. Terza JV, Bradford WD, Dismuke CE. The use of linear instrumental variables methods in health services research and health economics: a cautionary note. *Health Serv Res.* 2008; 43:1102–1120. [PubMed: 18546544]
25. Abbott AM, Habermann EB, Tuttle TM. Trends in the use of implantable accelerated partial breast irradiation therapy for early stage breast cancer in the United States. *Cancer.* 2011; 117:3305–3310. [PubMed: 21287535]
26. Giordano SH, Kuo YF, Duan Z, et al. Limits of observational data in determining outcomes from cancer therapy. *Cancer.* 2008; 112:2456–2466. [PubMed: 18428196]
27. Presley CJ, Soulos PR, Herrin J, et al. Patterns of Use and Short-Term Complications of Breast Brachytherapy in the National Medicare Population From 2008–2009. *Journal of Clinical Oncology.* 2012; 30(35):4302–4307. [PubMed: 23091103]
28. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet.* 2010; 376:91–102. [PubMed: 20570343]

Figure 1.
Kaplan-Meier Estimates of Any Recurrence, Recurrence-Free Survival, and Overall Survival for BCS Patients Treated With WBI vs APBI-Brachy

Table 1

Claims Codes Used to Classify Treatment Modalities *

Procedures	ICD-9 Procedure Codes	CPT/HCPCS Codes
Whole-Breast Irradiation	9221–9226, 9228, 9229	77427, 77431–77432, 77401–77409, 77411–77414, 77416, 77418, 77470, 77499, 77520, 77522–3, 77525, 77750, 77789, 77790
Brachytherapy	9227	19296–19298, 77326–77328, 77761–77763, 77776–77778, 77781–77784, Q3001, C9714–C9715
Breast-Conserving Surgery	8520–8523, 8525	2002–2006: 19110, 19120, 19125, 19160, 19162 2007–2008: 19110, 19120, 19125, 19301, 19302
Chemotherapy	9925	96400–96549, Q0083–Q0085, J8520, J8521, J8530, J8540, J8560, J8597, J8610, J8999; J9000–J9999 but excluding J9003, J9165, J9175, J9202, J9209, J9212–J9226, J9240, J9395

* CPT = Common Procedural Terminology;

HCPCS = Healthcare Common Procedural Coding System;

ICD = International Classification of Diseases;

Table 2

Patient Characteristics by Treatment Group (n=26,931)

	No. (%) of Women			P-value ^d	
	WBI	APBI-Brachy			
Sociodemographic characteristics					
Age, mean (SD), years	74.13	6.04	73.76	6.24	0.0184
Race					0.1283
White	22699	89.58	1451	91.03	
Non-white	2625	10.36	143	8.97	
Unknown	15	0.06	0	0	
Year of diagnosis					<.0001
2002	4636	18.30	62	3.89	
2003	4516	17.82	130	8.16	
2004	4321	17.05	211	13.24	
2005	4118	16.25	304	19.07	
2006	3931	15.51	404	25.35	
2007	3817	15.06	483	30.30	
Tumor characteristics					
Invasive cancer					<.0001
Yes	20358	80.34	1360	85.32	
No	4981	19.66	234	14.68	
Tumor size					
0–2cm	18411	72.96	1308	82.06	
>2–5cm	4628	18.34	184	11.54	
>5cm	765	3.03	28	1.76	
Unknown	1429	5.66	74	4.64	
Histology					<.0001
Ductal	15717	62.03	1118	70.14	
Lobular	1882	7.43	69	4.33	
Others	7740	30.55	407	25.53	
No. of positive lymph nodes					<.0001

	No. (%) of Women			P-value ^a
	WBI	APBI-Brachy		
0	16758	66.14	1260	79.05
1-3	2101	8.29	63	3.95
>=4	393	1.55	0	0
Unknown	6087	24.02	271	17
Estrogen receptor status				<.0001
Positive	19246	75.95	1282	80.43
Negative	2253	8.89	147	9.22
Unknown	3840	15.15	165	10.35
Grade				<.0001
Differentiated/moderately differentiated	17515	69.12	1209	75.85
Undifferentiated/poorly differentiated	151	0.60	10	0.63
Unknown/inapplicable	7673	30.28	375	23.53
Comorbidity				0.9058
0	4430	17.48	278	17.44
1-3	14437	56.98	901	56.52
>=4	6472	25.54	415	26.04
Community characteristics				
Median income in census tract (US\$)	55620	55853	25291	25158
Under the 2000 US median household income				0.7203
Yes	8431	33.27	520	32.62
No	16908	66.73	1074	67.38
Metropolitan area				<.0001
Yes	22430	88.52	1477	92.66
No	2909	11.48	117	7.34
Cancer registry				<.0001
San Francisco	914	3.61	41	2.57
Connecticut	2137	8.43	70	4.39
Detroit	1769	6.98	110	6.90
Hawaii	374	1.48	N/A	N/A
Iowa	1503	5.93	32	2.01

	No. (%) of Women			P-value ^a
	WBI	APBI-Brachy		
New Mexico	465	60	3.76	
Seattle	1689	96	6.02	
Utah	557	64	4.02	
Atlanta	730	136	8.53	
San Jose	623	28	1.76	
Los Angeles	1951	121	7.59	
Rural Georgia	40	N/A	N/A	
Greater California	5050	432	27.1	
Kentucky	1576	87	5.46	
Louisiana	1328	135	8.47	
New Jersey	4633	171	10.73	

^aP value from χ^2 tests and t-tests.

N/A. Data suppressed to conform to CMS small cell size policy

Table 3

Multivariate Proportional Hazards Regression: Predictors of Recurrence-Free Survival

Treatment	No. of Patients	No. of Events	Standard model			Instrumental variable analysis		
			Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Treatment								
WBI	25339	4074	1.00	reference		1.00	reference	
APBI-Brachy	1592	176	1.05	0.90	0.5125	0.85	0.36	0.7032
Sociodemographic characteristics								
Age, per each additional year of age	26931	4250	1.06	1.05	<.0001	1.06	1.05	<.0001
Race								
White	24150	3778	1.00	reference		1.00	reference	
Non-white	2766	468	0.98	0.88	0.7206	1.01	0.91	0.9193
Unknown	15	4	1.55	0.58	0.3856	1.51	0.56	0.4106
Year of diagnosis								
2002	4698	1254	0.96	0.82	0.6559	0.94	0.77	0.5450
2003	4647	1046	1.05	0.89	0.5389	1.02	0.85	0.8119
2004	4531	840	1.16	0.99	0.0697	1.15	0.96	0.1245
2005	4420	559	1.07	0.90	0.4578	1.06	0.89	0.5446
2006	4335	358	1.04	0.87	0.6497	1.04	0.87	0.6847
2007	4300	193	1.00	reference		1.00	reference	
Tumor characteristics								
Invasive cancer								
Yes	21717	3588	1.34	1.19	<.0001	1.33	1.17	<.0001
No	5214	662	1.00	reference		1.00	reference	
Tumor size								
0–2cm	19718	2776	1.00	reference		1.00	reference	
>2–5cm	4812	1099	1.35	1.26	<.0001	1.35	1.25	<.00041
>5cm	792	146	1.27	1.07	0.0066	1.27	1.07	0.0073
Unknown	1503	200	1.04	0.88	0.6451	1.04	0.88	0.6885
Histology								
Ductal	16835	2740	1.00	reference		1.00	reference	

	No. of Patients	No. of Events	Standard model			Instrumental variable analysis			
			Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value	
Lobular	1949	302	0.85	0.76	0.97	0.85	0.75	0.97	0.0120
Others	8147	1208	0.90	0.83	0.96	0.91	0.84	0.97	0.0068
No. of positive lymph nodes									
0	18017	2439	1.00	reference		1.00	reference		
1–3	2164	479	1.36	1.23	1.50	1.32	1.19	1.47	<.0001
>=4	392	174	2.66	2.26	3.13	2.63	2.19	3.15	<.0001
Unknown	6358	1158	1.40	1.29	1.53	1.39	1.27	1.52	<.0001
Estrogen receptor status									
Positive	2401	544	1.00	reference		1.00	reference		
Negative	20525	2998	1.45	1.31	1.60	1.44	1.30	1.59	<.0001
Unknown	4005	708	1.00	0.91	1.10	0.99	0.89	1.09	0.99
Grade									
Differentiated/moderately differentiated	18722	2692	1.00	reference		1.00	reference		
Undifferentiated/poorly differentiated	161	109	5.21	4.28	6.36	5.13	4.19	6.27	<.0001
Unknown/inapplicable	8048	1449	1.11	1.04	1.19	1.11	1.04	1.20	0.0030
Comorbidity									
0	4708	339	1.00	reference		1.00	reference		
1–3	15336	2003	1.54	1.37	1.73	1.57	1.40	1.77	<.0001
>=4	6887	1908	2.98	2.65	3.36	3.04	2.69	3.43	<.0001
Community characteristics									
Under the 2000 US median household income									
Yes	8948	1608	1.12	1.05	1.21	1.13	1.05	1.21	0.0010
No	17983	2642	1.00	reference		1.00	reference		
Metropolitan area									
Yes	23905	3776	0.98	0.88	1.10	0.99	0.88	1.11	0.8734
No	3026	474	1.00	reference		1.00	reference		
Cancer registry									
San Francisco	955	146	1.00	reference		1.00	reference		
Connecticut	2207	342	0.95	0.79	1.16	0.94	0.77	1.15	0.5370
Detroit	1879	303	0.93	0.76	1.13	0.92	0.74	1.13	0.3993

	No. of Patients	No. of Events	Standard model			Instrumental variable analysis		
			Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Hawaii	380	47	0.85	0.61	1.19	0.3459	0.81	0.58
Iowa	1536	221	1.03	0.83	1.29	0.7828	1.01	0.80
New Mexico	525	79	0.87	0.66	1.15	0.3252	0.87	0.65
Seattle	1785	261	1.05	0.86	1.29	0.6411	1.03	0.84
Utah	621	88	0.97	0.74	1.26	0.8033	0.96	0.73
Atlanta	867	130	1.13	0.89	1.44	0.3151	1.13	0.87
San Jose	651	98	1.09	0.84	1.41	0.5209	1.07	0.82
Los Angeles	2072	328	0.98	0.80	1.19	0.8221	0.94	0.76
Rural Georgia	45	8	1.04	0.50	2.13	0.9237	1.03	0.50
Greater California	5481	859	1.08	0.90	1.29	0.4102	1.06	0.88
Kentucky	1662	254	0.99	0.80	1.23	0.9487	0.98	0.79
Louisiana	1461	276	1.23	1.00	1.51	0.0480	1.22	0.98
New Jersey	4804	810	1.06	0.89	1.26	0.5383	1.04	0.86
								1.25
								0.6948

Table 4

Multivariate Proportional Hazards Regression: Predictors of Overall Survival

Treatment	No. of Patients	No. of Death	Standard model			Instrumental variable analysis		
			Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Treatment								
WBI	25339	3438	1.00	reference		1.00	reference	
APBI-Brachy	1594	123	0.87	0.72	1.04	0.59	0.22	1.57
					0.1332			0.2919
Sociodemographic characteristics								
Age, per each additional year of age	26933	3561	1.07	1.06	1.08	1.07	1.06	1.08
					<.0001			<.0001
Race								
White	24150	3162	1.00	reference		1.00	reference	
Non-white	2768	396	0.99	0.88	1.11	1.01	0.90	1.13
					0.8437			0.8898
Unknown	15	3	1.38	0.44	4.29	1.32	0.42	4.13
					0.5805			0.6288
Year of diagnosis								
2002	4698	1089	0.82	0.68	0.98	0.78	0.63	0.97
					0.0318			0.0280
2003	4646	896	0.92	0.76	1.10	0.88	0.71	1.08
					0.3506			0.2261
2004	4532	678	0.99	0.82	1.19	0.96	0.79	1.17
					0.9010			0.7111
2005	4422	439	0.93	0.77	1.12	0.91	0.75	1.11
					0.4342			0.3532
2006	4335	306	1.05	0.86	1.28	1.04	0.86	1.27
					0.6320			0.6750
2007	4300	153	1.00	reference		1.00	reference	
Tumor characteristics								
Invasive cancer								
Yes	21718	3113	1.73	1.50	2.00	1.71	1.48	1.98
					<.0001			<.0001
No	5215	448	1.00	reference		1.00	reference	
Tumor size								
0–2cm	19719	2282	1.00	reference		1.00	reference	
>2–5cm	4812	1000	1.44	1.33	1.56	1.43	1.32	1.56
					<.0001			<.0001
>5cm	793	123	1.29	1.07	1.55	1.28	1.06	1.54
					0.0087			0.0119
Unknown	1503	132	1.00	0.81	1.22	0.98	0.80	1.20
					0.9627			0.8419
Histology								
Ductal	16835	2331	1.00	reference		1.00	reference	

	Standard model				Instrumental variable analysis			
	No. of Patients	No. of Death	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Lobular	1951	260	0.81	0.71	0.93	0.81	0.71	0.93
Others	8147	970	0.88	0.82	0.95	0.89	0.82	0.97
No. of positive lymph nodes								
0	18018	2020	1.00	reference		1.00	reference	
1-3	2164	441	1.42	1.27	1.58	1.37	1.23	1.54
>=4	393	169	2.86	2.41	3.38	2.78	2.30	3.37
Unknown	6358	931	1.45	1.32	1.59	1.45	1.31	1.59
Estrogen receptor status								
Positive	20528	2553	1.00	reference		1.00	reference	
Negative	2400	443	1.35	1.22	1.51	1.34	1.20	1.50
Unknown	4005	565	1.03	0.93	1.15	1.01	0.91	1.13
Grade								
Differentiated/moderately differentiated	18724	2265	1.00	reference		1.00	reference	
Undifferentiated/poorly differentiated	161	74	3.34	2.63	4.24	3.36	2.64	4.27
Unknown/inapplicable	8048	1222	1.14	1.06	1.23	1.14	1.06	1.23
Comorbidity								
0	4708	232	1.00	reference		1.00	reference	
1-3	15338	1592	1.72	1.50	1.98	1.78	1.55	2.06
>=4	6887	1737	3.71	3.23	4.27	3.86	3.34	4.45
Community characteristics								
Under the 2000 US median household income								
Yes	8951	1377	1.14	1.06	1.23	1.14	1.05	1.23
No	17982	2184	1.00	reference		1.00	reference	
Metropolitan area								
Yes	23907	3164	0.97	0.85	1.09	0.98	0.86	1.11
No	3026	397	1.00	reference		1.00	reference	
Cancer registry								
San Francisco	955	120	1.00	reference		1.00	reference	
Connecticut	2207	282	0.97	0.79	1.21	0.95	0.76	1.18
Detroit	1879	259	0.96	0.77	1.19	0.94	0.75	1.18

	Standard model				Instrumental variable analysis					
	No. of Patients	No. of Death	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value		
Hawaii	380	40	0.90	0.62	1.29	0.5590	0.84	0.58	1.23	0.3715
Iowa	1535	180	1.08	0.85	1.38	0.5328	1.04	0.81	1.34	0.7553
New Mexico	525	65	0.90	0.66	1.22	0.4869	0.89	0.65	1.23	0.4944
Seattle	1785	211	1.06	0.85	1.33	0.6043	1.03	0.82	1.31	0.7849
Utah	621	68	0.93	0.69	1.26	0.6311	0.92	0.68	1.25	0.5967
Atlanta	866	112	1.29	1.00	1.68	0.0524	1.30	0.98	1.72	0.0684
San Jose	651	84	1.16	0.88	1.53	0.3002	1.13	0.85	1.50	0.4156
Los Angeles	2072	286	1.05	0.84	1.30	0.6843	0.99	0.79	1.25	0.9511
Rural Georgia	45	5	0.77	0.31	1.90	0.5690	0.76	0.31	1.89	0.5608
Greater California	5482	720	1.11	0.91	1.35	0.2906	1.09	0.89	1.34	0.4177
Kentucky	1663	226	1.10	0.88	1.39	0.4102	1.07	0.84	1.36	0.5723
Louisiana	1463	231	1.28	1.02	1.60	0.0337	1.26	0.99	1.60	0.0558
New Jersey	4804	672	1.07	0.88	1.30	0.5156	1.03	0.84	1.27	0.7522

Table 5

Multivariate Proportional Hazards Regressions: Suitable Patients ^a (N=4802)

	Recurrence-Free Survival			Overall Survival		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Age, per each additional year of age	1.06	1.04	1.08	1.08	1.06	1.10
Treatment						
WBI	1.00	reference		1.00	reference	
APBI-Brachy	1.12	0.82	1.54	0.89	0.61	1.30
Tumor size						
Smaller than 5mm	1.00	reference		1.00	reference	
5–10mm	0.94	0.65	1.37	1.23	0.78	1.94
>10mm	1.14	0.80	1.63	1.44	0.93	2.24
Comorbidity						
0	1.00	reference		1.00	reference	
1–3	1.62	1.13	2.31	2.24	1.39	3.61
≥4	3.23	2.25	4.65	5.08	3.14	8.22
Under the 2000 US median household income						
Yes	1.34	1.10	1.64	1.31	1.05	1.63
No	1.00	reference		1.00	reference	

^aPatients diagnosed with T1N0, invasive ductal, well or moderately-well differentiated, and ER positive