Trends in the Use of Implantable Accelerated Partial Breast Irradiation Therapy for Early Stage Breast Cancer in the United States

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Abstract

Background

In 2002 the Food and Drug Administration approved an implantable balloon catheter that delivers accelerated partial breast irradiation (APBI) directly to the tumor bed and surrounding area after breast conserving surgery (BCS). Our aim was to determine the use of implantable APBI (IAPBI) in the United States and the patient and tumor factors associated with IAPBI use.

Methods

Using the Surveillance, Epidemiology, and End Results database, we conducted a retrospective analysis of patients who received whole breast radiation therapy (WBRT) or IAPBI after BCS for ductal carcinoma in situ, stage I or II breast cancer from 2000 to 2007. We determined WBRT and IAPBI rates across time and demographic and tumor factors using chi-square tests and Cochran-Armitage tests for trend for our unadjusted analyses. We used logistic regression for our multivariate analysis, allowing for adjustment for potential confounders.

Results

We identified 127,257 patients who met inclusion criteria. Over the study period the proportion of patients receiving IAPBI increased by 1600% (2000: 0.4%; 2007: 6.8%; $p < 0.001$). This trend remained significant when using logistic regression (OR = 20.3, 95% CI 15.5 to 26.6). The increase in IAPBI use was statistically significant across all stage

and age categories over 40 ($p< 0.001$). The use of IAPBI was most notable in older women (70-79 years) with a > 2100% increase in use during the study period (2000:0.4%; 2007: 9.0%; p-value <0.001). We also found significant variation in IAPBI use by region.

Conclusions

IAPBI use has markedly increased since 2000, particularly in the elderly population. The rapid and widespread adoption of IAPBI is concerning, because large multicenter randomized controlled trials have not yet demonstrated long-term effectiveness of IAPBI compared to WBRT.

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Introduction

Investigators from the National Surgical Adjuvant Breast Project Trial (NSABP) B-06 reported in 1985 that survival after breast conserving surgery (BCS) and whole breast radiation therapy (WBRT) was equivalent to mastectomy (1). The National Institute of Health then released a consensus statement in 1990 stating that BCS and WBRT was the preferred treatment for early stage breast cancer (2). As a result, the practice patterns in the United States changed dramatically, and BCS rates markedly increased (3). The benefit of WBRT has been established by several randomized trials that have demonstrated that local recurrence rates are higher in patients treated with BCS alone compared to BCS plus WBRT (1, 4-5).

Accelerated partial breast irradiation (APBI) may offer an alternative method of radiation delivery that is given directly to the tumor bed and in a shorter course of therapy. In 2002, the Food and Drug Administration (FDA) approved the use of a single balloon implantable catheter, MammoSite ®, for use in APBI therapy. The American Society of Breast Surgeons (ASBS) and the American Society of Radiation Oncology (ASTRO) support the use of APBI in select patients with invasive ductal cancer or ductal carcinoma in-situ (DCIS) (6-8). The indications for APBI are evolving and not uniform across oncology fields. The ASBS uses criteria based on the American Society of Brachytherapy guidelines and ASTRO's guidelines are based upon recommendations from a task force review of the APBI literature (8-10). A recent publication by Shaitelman et al. determined that when the ASTRO guidelines were retrospectively applied to patients treated in the ASBS MammoSite® Registry Trial, no subgroup of

patients was found to have an increased rate of ipsilateral breast tumor recurrence (IBTR) (11).

Our aim in the present study was to determine the use of implantable APBI (IAPBI) in the United States using a population-based dataset and to determine the patient and tumor factors associated with its use.

Methods

Database

The Surveillance, Epidemiology, and End Results (SEER) database was used to evaluate rates and trends of WBRT and IAPBI use in the United States from 2000 to 2007. The SEER cancer registries provide population-based cancer surveillance for 17 areas that represent approximately 26% of the United States (12). SEER collects information on patient, tumor, and treatment characteristics including: age, race, marital status, tumor grade, stage, and histology, receipt and type of radiotherapy administered, and type of surgery received.

Study Cohort

This study evaluated women who underwent BCS and radiation therapy (RT) for the treatment of breast cancer. Women with a diagnosis of DCIS, stage I, or stage II breast cancer, who were older than 18 years of age, with no prior history of cancer, including breast cancer, were eligible for the study. Radiation categories were limited to beam radiation or radioactive implants. Women with grade 4 tumors were excluded from the study due to the low frequency of this diagnosis and the concern that it may represent a metastatic nonbreast malignancy. Patients who received radioisotopes, combination therapy, or an unspecified type of RT were excluded from the analysis.

Statistical Analysis

We evaluated rates of WBRT and IAPBI across patient and tumor factors using chi-square tests. We calculated the percentage increase of IAPBI use from 2000 through 2007 using the Cochran-Armitage test for trend. We constructed a logistic regression model to compare the odds of receiving IAPBI versus WBRT for each year (2001-2007) compared to 2000. Logistic regression was also used to evaluate for predictors of IAPBI therapy including age, race, marital status, stage, and registry, controlling for patients' age, race, marital status, stage, and registry as potential confounders.

All statistical analyses were completed using SAS software (version 9.2). This study was exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board because we used preexisting data void of any personal identifiers.

Results

We identified 127,257 patients who met inclusion criteria during the study period. On bivariate analysis we found significant differences between patients who received WBRT compared to patients who received IAPBI. Patients differed in age, race, stage of disease, and marital status. Women in the IAPBI treatment group were more likely to be older, widowed, and have stage I disease. Whites were the predominant race in both groups and African Americans were equally represented (Table 1). We also found variation by geographic location. Only 0.5% of women treated with radiation in Hawaii received IAPBI, while 7.2% of women in metropolitan Atlanta were treated with IAPBI.

The proportion of patients receiving IAPBI increased by 1600% (2000: 0.4%; 2007: 6.8%; $p < 0.001$) while the proportion of patients receiving WBRT decreased (2000: 99.6%; 2007: 93.2%; $p < 0.001$) (Figure 1). Use of IAPBI increased among all age groups over 40 during the study period ($p < 0.001$) (Figure 2). Although the p-value for the age category 18-39 approaches statistical significance ($p=0.051$), only twenty-five patients were treated with IAPBI during 2000 to 2007 in this age group. The most notable increase in IAPBI use was among patients over 80 years of age (0.85%, 2000; 9.61% 2007, $p < 0.001$). Patients with stage I disease represented the largest group of patients who received IAPBI (3.5%, $p < 0.001$). The use of IAPBI increased among women with DCIS, stage I, and stage II breast cancer from 2000 to 2007 ($p < 0.001$).

We used logistic regression to evaluate several patient and tumor characteristics as predictors of the receipt of IAPBI therapy (vs. WBRT) while adjusting for potential confounders (Table 2). Trends in IAPBI use remained significant (OR = 20.3 for 2007 vs.

2000, 95% CI 15.5-26.6), and older age continued to be a predictor of use. Patients over 80 years of age were more likely than younger patients to receive IAPBI (OR 7.1 for 80+ vs. 18-39, 95% CI 4.6-10.7). Race was also a significant predictor; white women were more likely to receive IAPBI as compared to African Americans (OR 1.3, 95% CI 1.1-1.5). Women who were separated, divorced, or whose marital status was unknown were more likely than single women to receive IAPBI (OR 1.1 for separated/divorced/unknown vs. single, 95% CI 1.0-1.4). Married or widowed women were not more likely than single women to be treated with IAPBI.

Patients with DCIS or stage I disease were more likely than patients with stage II disease to be treated with IAPBI (DCIS vs. stage II OR 1.9, 95% CI 1.7-2.2; stage I vs. stage II OR 3.1, 95% CI 2.8 to 3.5). We did find geographic variation with IAPBI use (Table 3). For example, patients in Atlanta were more likely than patients in Hawaii to receive IAPBI (OR 10.5 for Atlanta vs. Hawaii, 95% CI 6.2-17.6).

Discussion

The results from our study demonstrate that IAPBI use dramatically increased in the United States from 2000 to 2007. This increase occurred among women of all ages but was statistically significant in women over 40 years of age and most notable in women over 80 years of age. Disease stage, marital status, race, and geographic location were also significant predictors of receipt of IAPBI therapy. Our findings indicate that IAPBI use is becoming a more widely used therapy modality for women who have undergone BCS.

Despite the demonstrated efficacy of WBRT after BCS, recent studies have found that an increasing number of women are not receiving WBRT after BCS (13, 14). The results of a study conducted by Freedman et al. demonstrate that the rates of WBRT after BCS are decreasing in the United States (1988, 79.4%; 2004, 66.4%; $p < 0.001$) (14). The reasons for omission of WBRT after BCS are not entirely clear. The current schedule of daily WBRT for 6 weeks probably contributes to the observed trends. Transportation to and from treatments, as well as the time needed to receive the radiation, may be difficult for some patients, particularly elderly or employed women. It has been demonstrated that patients who live far distances from RT centers are less likely to receive WBRT after BCS (15). Due to the complex multidisciplinary nature of breast cancer treatment, patient handoffs between surgeons, medical oncologists, and radiation oncologists may not occur smoothly. Finally, many patients may simply overestimate the frequency and severity of WBRT side effects.

Alternative strategies to deliver RT may ensure adequate local treatment after BCS. Hypofractionated RT delivered over 3 weeks, as compared to 6 weeks, represents an attractive alternative to WBRT after BCS. Whelan et al. reported the results of a clinical trial in which women with node negative breast cancer were randomized to traditional WBRT (50 Gy in 25 fractions over 35 days) or hypofractionated RT (42.5 Gy in 16 fractions over 22 days) after BCS; local recurrence rates at 10 years were not significantly different between the two groups (16). APBI is another method of delivering RT that may increase compliance rates due to its targeted effects directly to the tumor bed and shorter course of therapy. Several methods of delivering APBI are available including balloon implantable catheters, interstitial brachytherapy, 3-D conformal RT, and intraoperative RT (IORT). The implantable balloon devices are placed directly into the tumor bed at the time of BCS or shortly after. The interstitial method involves insertion of several after-loading catheters through the skin and into the tumor cavity. IORT is given after surgical resection as a single-fraction targeted dose to the site of tumor. Currently an international phase III prospective randomized trial, TARGIT, is evaluating the efficacy IORT compared to WBRT in control of local recurrence rates (17, 18). Implantable balloon catheters are probably the most commonly used method of IAPBI in clinical practice in the United States. Hologic estimates over 50,000 women to date have been treated with MammoSite ® (19). Although other balloon devices, such as Contura ®, have also been approved by the FDA, MammoSite is the most well-studied and probably most frequently used balloon catheter for IAPBI.

Several single and multi-institution studies have evaluated the effectiveness of the MammoSite ® device. A prospective study conducted by Benitez et al. reported no local or regional recurrences among the 36 patients with early stage breast cancer who were followed for a median of 5.5 years. Cosmetic outcomes of good to excellent were reported in 83.3% of these patients (20). Chao et al. followed 80 patients for a median of 22.1 months after BCS and treatment with MammoSite® and reported that two patients (2.5%) developed IBTR. Cosmetic outcomes were favorable with 88.2% of patients reporting good to excellent outcomes at 36 months (21). The ASBS MammoSite® brachytherapy registry is the largest cohort reported in the literature. At three years of follow-up on the entire cohort the IBTR rate was 2.15%. An additional year of follow-up on the first 400 patients reveals an IBTR rate of 2.65% (22). Cosmetic outcomes and complication rates were similar to other published results with IAPBI use. While these reports indicate outcomes comparable to WBRT, the large multi-centered randomized clinical trials with long-term follow-up are not yet available.

Currently the NSABP/Radiation Therapy Oncology Group (RTOG) is conducting a randomized clinical trial to evaluate the effectiveness of APBI in women treated with BCS. In NSABP-B39/RTOG 0413, women are randomized to WBRT or one of three methods of APBI: multi-catheter, MammoSite® balloon catheter, or 3-D conformal RT. Women with DCIS, stage I, or stage II disease are eligible for enrollment. The results from this study may establish APBI as a safe and effective alternative to WBRT.

We acknowledge some limitations of this study. Detailed patient and tumor information that may have influenced treatment decisions were not available from the

cancer registry database. Important factors regarding family history, genetic testing results, tamoxifen use, systemic chemotherapy, and mammographic findings were not available from this database. Also, the SEER registry classifications of RT are limited to beam radiation, radioactive implants, radioisotopes, combination, radiation not otherwise specified, other, and unknown. Although we can't be absolutely certain, radioactive implants in the form of balloon catheter therapy, specifically MammoSite ®, probably represented the most commonly used method of IABPI in our population during the study period. SEER does not record the number of radiation treatments received so we are unable to determine if patients received a full course of RT. By eliminating the radiation category of combination therapy we may be missing patients who did not tolerate WBRT and were then offered IAPBI, and, in fact, under-reporting the true rate of IAPBI. Additionally, data analysis in SEER relies on accurate coding of procedures. During the early use of the implantable balloon catheters, some cases may have been coded under a different radiation category instead of radioactive implants, again resulting in an under-estimation of the true increase in IAPBI use.

Conclusion

The rate of IAPBI therapy is increasing in the United States while the rate of WBRT is decreasing. IAPBI may be a favorable alternative to WBRT with a shorter course of therapy, acceptable cosmesis, and low complication rates. The follow-up data on recurrence rates, however, are still premature and cannot be adequately compared to traditional WBRT. Until the release of NSABP-B39/RTOG 0413, clinicians should be encouraged to enroll women in clinical trials and to avoid off-trial use of this therapy.

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Table 1: Cohort Demographics

Characteristics	WBRT N =123959 (%)	IAPBI N = 3298 (%)	p-value
Age			
18-39	5306 (4.3)	25 (0.76)	<0.0001
40-49	25320 (20.4)	369 (11.2)	
50-59	35790 (28.9)	892 (27.0)	
60-69	30298 (24.4)	991(30.0)	
70-79	20921(16.9)	743 (22.5)	
80+	6324 (5.1)	278 (8.4)	
Race			
White	104440 (84.3)	2940 (89.1)	< 0.0001
African American	9498 (7.7)	253 (7.7)	
Other/Unknown	10021 (8.1)	105 (3.2)	
Stage			
DCIS	23312 (18.8)	546 (16.6)	< 0.0001
Stage I	65238 (52.6)	2371 (71.9)	
Stage II	35409 (28.6)	381 (11.6)	
Marital Status			
Separated/Divorced/Unknown	17674 (14.3)	487 (14.8)	< 0.0001
Married	76541 (61.7)	1996 (60.5)	
Widowed	15433 (12.5)	516 (15.6)	
Single	14311 (11.5)	299 (9.1)	

Abbreviations: WBRT, whole breast radiation therapy; IAPBI, implantable accelerated partial breast irradiation; DCIS, ductal carcinoma in situ

Table 2: Multivariate Analysis Significant Predictors of IAPBI Use

	Odds Ratio	95% Confidence Interval
Age		
18-39	Ref	Ref
40-49	2.5	1.6, 3.7
50-59	4.0	2.7, 6.0
60-69	4.9	3.3, 7.3
70-79	5.8	3.9, 8.7
80+	7.1	4.6, 10.7
Marital Status		
Separated/Divorced/Unknown	1.2	1.0, 1.4
Married	1.1	0.99, 1.3
Widowed	1.1	0.93, 1.3
Single	Ref	Ref
Stage		
DCIS	1.9	1.7, 2.2
Stage I	3.1	2.8, 3.5
Stage II	Ref	Ref
Race		
White	1.3	1.1, 1.5
Other/Unknown	0.6	0.5, 0.8
African American	Ref	Ref

Abbreviations: IAPBI, implantable accelerated partial breast irradiation; Ref, referent; DCIS, ductal carcinoma in situ

Table 3: Use of IAPBI Compared to WBRT by Registry

Registry	WBRT N = 123959 (%)	IAPBI N = 3298 (%)	Multivariate Analysis OR (95% CI)
San Francisco	8925 (98.6)	125 (1.4)	1.8 (1.1, 3.1)
Connecticut	7931 (97.9)	170 (2.1)	2.4 (1.4, 4.1)
Metro Detroit	8072 (97.5)	209 (2.5)	3.2 (1.9, 5.5)
Hawaii	3165 (99.5)	16 (0.5)	Ref
Iowa	6006 (98.8)	73 (1.2)	1.3 (0.8, 2.3)
New Mexico	2111 (98.2)	38 (1.8)	2.4 (1.3, 4.3)
Seattle	9634 (97.3)	264 (2.7)	3.2 (1.9, 5.5)
Utah	2412 (95.9)	102 (4.1)	5.1 (2.9, 8.8)
Metro Atlanta	4836 (92.8)	374 (7.2)	10.5 (6.2, 17.6)
San Jose	4473 (99.0)	47 (1.0)	1.3 (0.7, 2.2)
Los Angeles	11264 (97.4)	296 (2.6)	3.5 (2.1, 5.9)
Greater California	28025 (97.2)	809 (2.8)	3.5 (2.1, 5.8)
Kentucky	5676 (96.6)	200 (3.4)	3.9 (2.3, 6.7)
Louisiana*	5106 (95.2)	259 (4.8)	6.8 (4.0, 11.5)
New Jersey	16323 (98.1)	316 (1.9)	2.3 (1.3, 3.8)

Abbreviations: IAPBI, implantable accelerated partial breast irradiation; WBRT, whole breast radiation therapy; OR, odds ratio; CI, confidence interval, Metro, metropolitan; Ref, referent

*2005 data excluded from Louisiana registry

Figure 1: Trends in the Use of Whole Breast Radiation Therapy Compared to Implantable Accelerated Partial Breast Irradiation

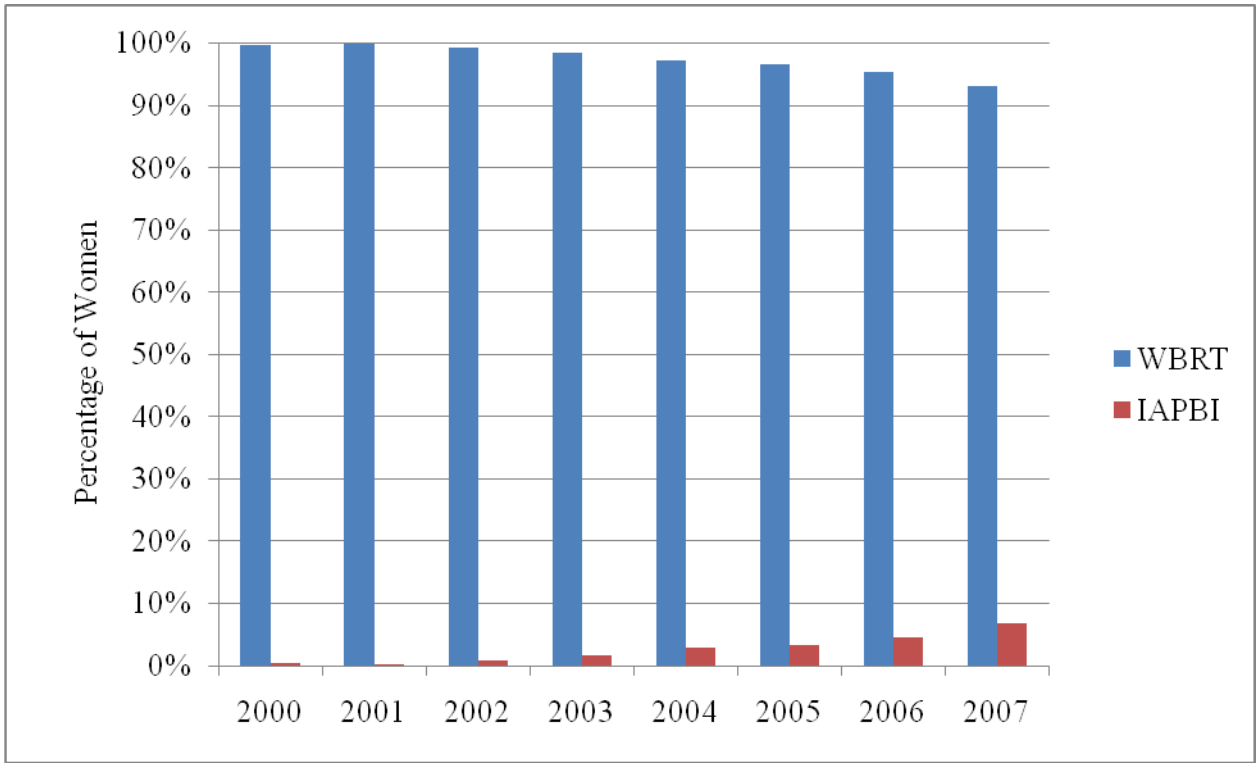

Figure 2: Implantable Accelerated Partial Breast Irradiation Use by Age from 2000 to 2007