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Intraoperative Radiotherapy for Breast Cancer Treatment in a Rural Community

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Abstract

Background.—Access to health care poses particular challenges for patients living in rural communities. Intraoperative radiotherapy (IORT) offers a treatment alternative to traditional whole-breast radiation therapy (WBRT) for select patients. This study aimed to analyze the use of IORT for patients undergoing breast-conserving surgery at an academic institution located in a rural state.

Methods.—A retrospective review analyzed all patients at a single institution with a diagnosis of ductal carcinoma in situ (DCIS) or invasive breast cancer from April 2012 to January 2017 who were undergoing breast-conserving surgery with either IORT or WBRT. Student's *t* test or Fisher's exact test was used to make statistical comparisons.

Results.—Patients undergoing IORT (*n* = 117) were significantly older than patients treated with WBRT (*n* = 191) (65.6 vs 58.6 years; *p* < 0.001) and had smaller tumors on both preoperative imaging (1.04 vs 1.66 cm; *p* < 0.05) and final pathology (0.99 vs 1.48 cm; *p* < 0.05). Patients receiving IORT lived farther from the treating facility than patients treated with WBRT (67.2 vs 30.8 miles; *p* < 0.05). To account for biases created in the IORT selection criteria, subgroup analysis was performed for women receiving WBRT who fulfilled IORT selection criteria, and distance traveled remained significant (67.2 vs 31.4 miles; *p* < 0.05). Neither recurrence nor survival differed between the IORT and WBRT groups. Medicare reimbursement for IORT was approximately 50% more than for WBRT.

Conclusions.—For women from rural communities, IORT appears to be an attractive option because these women tend to be older and to live farther from the treatment facility.

Breast-conserving therapy in combination with radio-therapy has early beginnings dating back to the 1920s.¹ Since that time, the evolution of breast cancer treatment has focused on improvements in early detection, better patient selection, more effective hormonal therapy and chemotherapy, and less invasive surgery. A number of clinical trials have established

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CONFLICT OF INTEREST

There are no conflicts of interest.

that breast-conserving surgery (BCS) followed by adjuvant radiation therapy provides survival rates equal to those for mastectomy used to treat early-stage breast cancer.²⁻⁴

The NSABP B-06 trial demonstrated no statistically significant difference in overall survival, disease-free survival, or distant disease-free survival between patients who underwent a total mastectomy and those treated with lumpectomy.³ After 20 years of follow-up evaluation, ipsilateral breast tumor recurrence showed a statistically significant improvement among women who underwent lumpectomy with whole-breast radiation versus those who underwent lumpectomy alone.³ This result prompted further trials evaluating the effects of whole-breast radiation therapy (WBRT) versus intraoperative radiotherapy (IORT) for early-stage breast cancer treated with BCS.

Two randomized clinical trials have addressed this question: TARGeted Intraoperative radioTherapy (TARGIT-A) and ELection IntraOperative radioTherapy (ELIOT) trials.^{5,6} Both trials demonstrated a higher in-breast recurrence rate in the IORT group than in the WBRT group, ultimately suggesting the need to have better selection criteria for patients undergoing IORT.^{6,7}

Women with breast cancer living in rural areas often forgo radiation or choose to undergo mastectomy due to challenges of access caused by the distance to a radiation facility.⁸ According to the 2010 Census, approximately one third of the population in Iowa resides in a rural community.⁹ Patients in rural communities in Iowa have a median driving time of 52 min for care by an oncologist.¹⁰ The University of Iowa is the primary academic referral center for the state of Iowa and western Illinois, serving an overwhelmingly rural population. It also was the first institution in the state to offer IORT, which may be a particularly attractive option for women living in rural communities.

We aimed to report our findings from one of the main referral centers in Iowa to offer IORT and to describe patient characteristics that may influence the decision to use IORT.

METHODS

Patients

After institutional review board approval was received, a retrospective review of electronic medical records was performed for 308 consecutive patients with a diagnosis of primary breast cancer undergoing BCS with adjuvant radiation at the University of Iowa Hospital and Clinics from April 2012 to January 2017. The identified patients had undergone IORT at the time of surgery or received postoperative WBRT.

We developed inclusion criteria based on evidence in the literature reporting results of accelerated partial breast radiation.^{5,6,11,12} Our institutional eligibility criteria for IORT were as follows: age of 50 years or older, evidence of invasive ductal carcinoma or ductal carcinoma in situ (DCIS), tumor size of 3.5 cm or smaller for invasive cancer (based on the size limit used in the TARGIT-A trial⁵) or smaller than 3 cm for DCIS, no more than focal lymphovascular space invasion, estrogen receptor (ER)- and progesterone receptor (PR)-positive tumors, no evidence of multicentric disease that would preclude a single

lumpectomy, no clinical or radiologic evidence of axillary nodal involvement, no history of systemic neoadjuvant therapy used to treat the current cancer, no history of previous ipsilateral breast cancer or radiation, and no known BRCA or other high risk-mutation (Table 1). Breast magnetic resonance imaging (MRI) was not required for inclusion. However, the criteria were written such that patients not otherwise eligible could receive IORT in special circumstances if approved by the members of our institutional tumor board. Sentinel node positivity and positive margins at the time of the index surgery necessitating reoperation were used as criteria for WBRT after IORT.

For IORT, the IntraBeam Photon Radiosurgery System (Zeiss Inc., Oberkochen, Germany) was used with an applicator appropriately sized to the lumpectomy cavity, leaving at least 1 cm of tissue between the lumpectomy cavity and the skin. Demographic patient data were collected retrospectively through review of the electronic medical record and included age, hometown, and driving distance to the operating institution. Tumor characteristics were collected including tumor size on preoperative imaging, evidence of invasive cancer or nodal metastasis on pathology, and hormone status. Data on the type and timing of radiation received also were recorded.

After collection of the data, the patients were divided into two groups according to the type of radiation received (IORT or postoperative WBRT). All analyses were performed according to stratification into these two groups. Additional analysis was performed comparing the IORT group with the age- and stage-matched patients who received WBRT.

Statistical Analysis

The WBRT and IORT cohorts were compared using Chi-square and Fisher's exact test for categorical variables and Student's *t* test for continuous variables. The age- and stage-matched WBRT patients were subsequently compared with the IORT patients.

RESULTS

The inclusion criteria was met by 308 patients, 117 of whom received IORT and 191 of whom received WBRT. The patients receiving IORT were significantly older than those undergoing WBRT (mean age, 65.6 vs 58.6 years; $p < 0.05$) (Table 2). The patients receiving IORT and those undergoing WBRT had similar rates of invasive breast cancer pathology (78.6 vs 78.5%; $p = 0.98$). However, the patients receiving IORT had smaller tumors determined by preoperative imaging (mean, 1.04 vs 1.66 cm; $p < 0.05$) and by final pathology (mean, 0.99 vs 1.48 cm; $p < 0.05$).

As a result of the IORT eligibility criteria, the patients receiving IORT were more likely to have ER-positive (95.7 vs 73.8%; $p < 0.05$) and PR-positive (91.4 vs 61.8%; $p < 0.05$) tumors. The incidence of patients who had tumors with human epidermal growth factor receptor 2 (HER2) overexpression was lower in the IORT group than in the WBRT group (5.1 vs 15.7%; $p < 0.05$). Although institutional IORT selection criteria require ER and PR positivity for IORT eligibility, four patients receiving IORT were negative for both ER and PR staining, and five patients were ER-positive but negative for PR staining.

The patients receiving WBRT were significantly more likely to have more advanced disease, with a greater number of patients having positive nodes at the time of resection (10/117 IORT vs 34/191 WBRT; $p < 0.05$). Four patients (3.4%) receiving IORT and 28 patients (14.7%) receiving WBRT ($p < 0.05$) went on to have further operative reexcision of margins based on final pathology. Of the patients who underwent IORT, 11 (9.4%) subsequently proceeded with WBRT. Of these 11 patients, 4 had positive margins at the initial surgery, requiring reexcision, and 4 had positive sentinel lymph nodes at the time of surgery. The remaining three patients had close margins or high-risk lesions, and a decision was made to add WBRT. One patient from the IORT arm of the study had an in-breast recurrence, and one patient had a distant metastasis, compared with four patients in the WBRT arm who had an in-breast recurrence and two who had distant metastasis (Table 3). The two groups showed no statistically significant difference in overall survival.

The patients receiving IORT were more likely to travel a greater distance to receive their oncologic care (mean distance to treatment facility, 67.2 miles for IORT vs 30.8 miles for WBRT; $p < 0.05$). In an attempt to control for the inclusion criteria, a subgroup analysis of the patients in the WBRT group who fulfilled the IORT inclusion criteria (age ≥ 50 years; tumor by imaging < 3.5 cm; clinically node-negative; no neoadjuvant chemotherapy) was performed.

In the comparison of the IORT patients and the WBRT patients who fulfilled the IORT criteria, a statistically significant difference persisted in age, distance traveled to the treating facility, and mean tumor size on preoperative imaging (Table 2). This secondary comparison showed no statistically significant differences in the percentages of patients with invasive cancer, ER-positive patients, HER2-positive patients, or patients with node-positive disease. The WBRT group meeting the IORT criteria continued to have a greater need for reexcision. The IORT group had a slightly longer follow-up period than the modified WBRT group (33 vs 25 months; $p < 0.05$) (Table 3). However, no differences in locoregional recurrence, distant metastases, or overall survival were observed.

Medicare reimbursement was compared for IORT and WBRT. Based on the expected reimbursement for physician services and hospital charges, the total Medicare reimbursement for IORT was estimated to be \$8406.92 (Table 4). A similar expected Medicare reimbursement analysis of WBRT showed a reimbursement of \$4221.31. These data indicate that costs to Medicare for IORT are approximately twice that for WBRT, mostly driven by the hospital reimbursement for CPT code 77424, intraoperative radiation treatment delivery, X-ray, and single treatment session. To determine the actual revenue realized, the total revenue from radiation oncology treatments for 9 Medicare patients who had IORT and 10 Medicare patients treated with WBRT were randomly chosen from the patients treated between 2012 and 2017. The average Medicare revenue for IORT was \$9063.81 compared with \$6000.45 for WBRT, confirming a 50% increase in Medicare costs for IORT versus WBRT.

DISCUSSION

The IORT procedure was introduced as an alternative to WBRT, offering the possibility of a single intraoperative treatment compared with the standard 5-to 6-week course of WBRT.¹³ As new technologies for breast care are introduced, it is important to evaluate the impact of these new approaches in various practice settings.

Many patients treated at the University of Iowa come from rural communities, and clinicians face significant challenges providing health care to patients from small towns that are relatively geographically isolated.⁸ Patients living in rural communities tend to be older, to be socioeconomically disadvantaged, to experience challenges to health care access with lower quality of care, and to have less education, and cancer patients, tend to present at later stages of disease.^{14–17}

Transportation for health care services was noted to be a particularly significant barrier for rural patients.^{8,18} With regard to radiation, one study of cancer patients in Iowa reported that patients living in rural communities traveled three times farther for their radiation treatment than patients in urban communities.¹⁹ Other studies have shown that rural patients, particularly older patients with less socioeconomic support, have a lower rate of receiving recommended radiation for cancer.^{8,20}

The IORT procedure may offer significant advantages for patients living in rural areas who may have problems related to the distance they need to travel for WBRT. In the current study, the patients treated by IORT lived more than twice as far from the treatment facility as the patients undergoing WBRT. This difference persisted when the analysis considered the subset of patients receiving WBRT who fulfilled the clinical criteria for IORT. The findings lead us to the conclusion that IORT is a particularly attractive option for women with breast cancer living in rural communities.

Randomized clinical trials have provided data supporting the clinical efficacy of IORT compared with WBRT. The TARGeted Intraoperative radioTherapy Alone (TARGIT-A) trial randomized patients 45 years of age or older undergoing breast conservation to IORT rather than WBRT.¹¹ The patients in the IORT group had an increase in locoregional recurrence (3.3 vs 1.3%; $p < 0.04$). However, no difference in overall survival was observed. Interestingly, the patients in the IORT group had significantly reduced non-breast cancer mortality, with fewer grade 3 or 4 skin complications.

Similar results were reported for the European Institute of Oncology Trial using electron intraoperative radiotherapy (ELIOT).⁶ The authors reported a significant increase in ipsilateral breast tumor recurrence (IBTR) of 4.4% in the IORT group compared with a 0.4% IBTR in the WBRT group. However, the overall survival did not differ between the treatment groups. The ELIOT trial also reported fewer skin complications in the IORT-treated group. Local wound complications for IORT are influenced by the size of the applicator, which relates to the dose of radiation.²¹ These trials concluded that IORT is an acceptable treatment method for selected patients with a relatively low-risk prognosis.^{7,22}

The American Society for Radiation Oncology (ASTRO) consensus statement advocated the use of low-energy IORT (as in this study) in the context of a prospective registry or clinical trial.²³ Furthermore, ASTRO advises that low-energy IORT should be used only for “suitable” patients, which would have excluded certain patients in the TARGIT-A trial. However, these recommendations are controversial, with a recognition that low-energy TARGIT IORT provides acceptable results for well-selected patients.²⁴

Interestingly, we did not observe differences between IORT and WBRT in either in-breast recurrence or overall survival. Our study actually demonstrated a trend for a lower rate of in-breast recurrence (0.85% for IORT vs 2.09% for WBRT patients). Most likely, patient selection resulted in our observed low incidence of in-breast recurrence. The average age of our IORT group was 65.6 years, and the CALGB 9343 trial reported that 70 or more patients treated with tamoxifen alone had the same survival as those treated with tamoxifen plus radiation, although local recurrence was reduced with radiation.²⁵

Our protocol for IORT selected for patients with ER-and PR-positive tumors. Consistent with this conclusion, the subset analysis of PR-positive patients in the TARGIT trial demonstrated no difference in local recurrence between the patients treated with IORT and those treated with WBRT.⁵

Recent studies have confirmed a 5-year local recurrence rate lower than 2% for IORT among patients older than 50 years without lobular histology, a tumor size of 2 cm or smaller, node negativity, non-triple-negative histology, low tumor grade, and ki67 of 20% or less.²⁶ On the other hand, a study of patients in Taiwan treated with IORT reported excellent results for patients with more liberal selection criteria that included younger patients with relatively larger tumors.²⁷

The data from clinical trials indicate an acceptable local recurrence rate for patients treated with IORT. Furthermore, patients treated with IORT whose pathologic findings are worrisome have the option of additional WBRT. The rate of additional external radiotherapy for patients treated with IORT varies from 3 to 15% in the literature.^{11,27} However, WBRT after IORT is associated with an increased rate of seroma formation.²⁸ In our series, 9.4% (11/117) of all IORT patients received additional WBRT. Hence, patient selection, additional external beam radiotherapy, and systemic therapy with hormonal and chemotherapy results in a low in-breast recurrence rate for patients treated with IORT.

Several studies have reported that IORT results in better quality of life and lower cost than WBRT. One study estimated the cost for IORT to be less than 20% of the cost for WBRT.²⁹ Even when the analysis accounted for capital equipment costs, increased local recurrence rate, and operative time, IORT was found to be more effective and less expensive than WBRT.³⁰ Similar findings were reported showing increased quality of life and lower cost for IORT compared with standard WBRT for patients treated in the United Kingdom.³¹

In the current study, Medicare reimbursement for IORT was estimated to be approximately 50% more than for WBRT. Although a formal institutional cost analysis was beyond the scope of the current study, the findings suggest that in our practice, IORT has a higher cost

burden to Medicare. Although this cost analysis did not account for differences in recurrences, we did not find a statistically significant difference in recurrence rates.

This study had some potential limitations. Some patients in our study, especially those who had surgery in the last couple of years, had a short follow-up time, and this may have affected differences in recurrence. Although the mean follow-up time was 33 months for the patients receiving IORT and 29 months for those receiving WBRT, additional time may be needed to realize a difference, if any, in terms of in-breast recurrence, distant recurrence, and death.

Another limitation was the retrospective nature of our study. Our study had a degree of selection bias because the outcomes and patient characteristics may not have been representative of patients nationwide. However, it did achieve the purpose of addressing the specific question of the choices that patients make in a largely rural community. Ultimately, we discovered that women electing to undergo IORT are significantly older and live farther from the treating institution than women who elect postoperative whole-breast radiation. Hence, IORT may gain popularity for the rural elderly population.

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TABLE 1

Eligibility criteria for intraoperative radiotherapy (IORT)

University of Iowa Hospitals and Clinics Multidisciplinary Breast Service Guidelines for Targeted Intraoperative Radiation Therapy Following Breast-Conserving Surgery	
1. Age 50 years or older	
2. Invasive ductal carcinoma or ductal carcinoma in situ (DCIS) (no lobular cancer)	
3. T1 and T2 tumors (< 3.5 cm in size) for invasive cancer, or < 3 cm for DCIS	
4. No more than focal lymphovascular space invasion (LVSI) on core biopsy	
5. Estrogen receptor and progesterone positive tumors only	
6. No evidence of multicentric disease by clinical examination or imaging that may preclude excision with negative margins using a single lumpectomy	
7. No clinical or radiologic evidence of axillary nodal involvement	
8. Unilateral breast cancer only at the time of diagnosis (metachronous cancers on the contralateral side are eligible if they meet all other criteria)	
9. No history of neoadjuvant systemic therapy to treat the current cancer	
10. No prior history of ipsilateral breast cancer or radiation	
11. No known BRCA 1/2 or other high-risk mutation	

These are guidelines only. Final decisions regarding individual patient care will be guided by consensus after case presentation and group discussion by the multidisciplinary breast tumor board

TABLE 2
 Characteristics of intraoperative radiotherapy (IORT) versus whole-breast radiation therapy (WBRT) patients

Patient characteristics	Patients receiving IORT (<i>n</i> = 117)		Patients receiving WBRT (<i>n</i> = 191)		Age- & stage-matched patients receiving WBRT (<i>n</i> = 87) ^a	
	<i>n</i> (%)		<i>n</i> (%)	<i>p</i> value	<i>n</i> (%)	<i>p</i> value
Age (mean)	65.6		58.6	<0.05	63.6	0.05
Distance traveled to treating facility (miles)	67.2		30.8	<0.05	31.4	<0.05
Mean tumor size on imaging (cm)	1.04		1.66	<0.05	1.41	<0.05
Invasive breast cancer on pathology	92 (78.6)		150 (78.5)	0.98	63 (72.4)	0.30
Mean tumor size on final pathology (cm)	0.99		1.48	<0.05	1.02	0.95
Hormone receptors						
ER-positive	112 (95.7)		141 (73.8)	<0.05	85 (97.7)	0.70
PR-positive	107(91.4)		118 (61.8)	<0.05	70 (80.4)	<0.05
HER2-positive	6 (5.1)		30 (15.7)	<0.05	10 (11.5)	0.09
Patients with nodal metastases	10		34	<0.05	14	0.10
Patients requiring reexcision	4		28	<0.05	13	<0.05

ER estrogen receptor, PR progesterone receptor

^aIncluding all patients 50 years of age, preoperative tumor size < 3.5 cm, clinically node-negative, no neoadjuvant therapy. All *p* values compared with IORT

TABLE 3
Postoperative outcomes for intraoperative radiotherapy (IORT) versus whole-breast radiation therapy (WBRT) patients

Patient characteristics	Patients receiving IORT (<i>n</i> = 117)	Patients receiving WBRT (<i>n</i> = 191)	<i>p</i> value	Age- and stage-matched patients receiving WBRT (<i>n</i> = 87) ^a	<i>p</i> value
Mean follow-up time (months)	33	29	<0.05	25	<0.05
In-breast recurrence	1	4	0.65	0	1.00
Distant recurrence	1	2	1.00	0	1.00
Deaths	2	6	0.70	2	1.00

^aIncluding all patients 50 years of age, preoperative tumor size < 3.5 cm, clinically node-negative, no neoadjuvant therapy. All *p* values compared with IORT

TABLE 4

Expected medicare reimbursement

Code	PB Medicare (\$)	HB Medicare (\$)
Intraoperative radiotherapy		
77263	159.85	Not paid under OPPS
77336	71.72	113.55
77300	31.48	113.55
77424	0.00	7200.10
77470	102.50	477.65
77332	22.95	113.55
Total	388.50	8018.42
Whole-breast radiotherapy		
77280-sim	35.33	113.55
77280-verify	35.33	113.55
77263	159.85	Not paid under OPPS
77295	215.84	1029.65
77300	31.48	113.55
77334	57.96	300.88
77412	0.00	197.49
77387	0.00	Packaged
77014	42.82	Packaged
77336	71.72	113.55
77427	178.63	Not paid under OPPS
Boost		
77307	146.19	300.88
77334	57.96	300.88
77412	0.00	197.49
77387	0.00	Packaged
77014	42.82	Packaged
77336	71.72	113.55
77427	178.63	Not paid under OPPS
Total	1326.28	2895.03
Code	Code-modifier	Code description
77014	77014-26	CT scan for therapy guide
77263	77263	Radiation therapy planning
77280	77280-26	Set radiation therapy field
77295	77295-26	3-D radiotherapy plan
77300	77300-26	Radiation therapy dose plan
77307	77307-26	Teletherapy isodose plan, complex
77332	77332-26	Radiation treatment aid(S)
77334	77334-26	Radiation treatment aid(S)
77336	77336	Radiation physics consult

77387	77387–26	Guidance for localization of target volume for delivery of radiation treatment
77412	77412	Radiation treatment Delivery
77424	77424	Intraoperative radiation treatment delivery by X-ray
77427	77427	Radiation treatment management, 5 treatments
77470	77470–26	Special radiation treatment

PB physician-based reimbursement, *HB* hospital-based reimbursement, *OPPS* outpatient prospective payment system, *CT* computed tomography