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ORIGINAL ARTICLE – BREAST ONCOLOGY

TARGIT-R (Retrospective): North American Experience with Intraoperative Radiation Using Low-Kilovoltage X-Rays for Breast Cancer

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ABSTRACT

Background. Single-dose intraoperative radiotherapy (IORT) is an emerging treatment for women with early stage breast cancer. The objective of this study was to define the frequency of IORT use, patient selection, and outcomes of patients treated in North America.

Methods. A multi-institutional retrospective registry was created, and 19 institutions using low-kilovoltage IORT for the treatment of breast cancer entered data on patients treated at their institution before July 31, 2013. Patient selection, IORT treatment details, complications, and recurrences were analyzed.

Results. From 2007 to July 31, 2013, a total of 935 women were identified and treated with lumpectomy and IORT. A total of 822 patients had at least 6 months' follow-up documented and were included in the analysis. The number of IORT cases performed increased significantly over time ($p < 0.001$). The median patient age was 66.8 years. Most patients had disease that was <2 cm in size (90 %) and was estrogen positive (91 %); most patients had invasive ductal cancer (68 %). Of those who had a sentinel lymph node procedure performed, 89 % had negative sentinel lymph nodes. The types of IORT performed were primary IORT in 79 %, secondary IORT in 7 %, or planned boost in 14 %. Complications

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were low. At a median follow-up of 23.3 months, crude in-breast recurrence was 2.3 % for all patients treated.

Conclusions. IORT use for the treatment of breast cancer is significantly increasing in North America, and physicians are selecting low-risk patients for this treatment option. Low complication and local recurrence rates support IORT as a treatment option for selected women with early stage breast cancer.

For patients with breast cancer who elect to undergo breast conservation, adjuvant radiation has been shown to decrease the risk of local recurrence. Conventional radiation is typically delivered to the whole breast in daily treatments for up to 6 weeks. This technique offers good local tumor control, with recurrence rates of less than 1 % per year.[1,2] In older women with estrogen-positive, early stage breast cancer, this risk of recurrence with the addition of radiation is even lower.[3,4]

Although external-beam radiotherapy (EBRT) has been shown to decrease the overall risk of breast cancer recurrence,[5] it may not be feasible or appropriate for all patients. Some women elect to have a mastectomy specifically to avoid undergoing EBRT, and up to 30 % of patients undergoing lumpectomy do not complete the prescribed course of radiation for various reasons, particularly those who live far from a cancer center.[6–8] Additionally, EBRT takes weeks to complete and can increase the long-term risks of cardiovascular disease,[9] pulmonary issues,[10,11] and development of other subsequent cancers.[12]

Studies have shown that the highest risk of a local in-breast recurrence is at the lumpectomy site, and techniques such as accelerated partial breast irradiation have been developed to focus radiation to only the lumpectomy cavity, with favorable rates of local control in appropriately selected patients.[13–16] This focused radiation can spare other surrounding tissues from the effects of radiation and can offer a more convenient treatment for patients. Intraoperative radiotherapy (IORT) involves the collaboration of both the breast surgeon and radiation oncologist to deliver a single dose of radiation directly to the lumpectomy cavity at the time of surgery, completing local therapy in 1 day.

The role for IORT in the treatment of early stage breast cancer was prospectively evaluated in the international TARGIT-A trial, which randomized 3,451 patients to receive either a single dose of 20 Gy radiation to the surface of the lumpectomy cavity with 50 kV x-rays using the Intrabeam IORT system (Carl Zeiss Meditec, Oberkochen, Germany) or conventional external-beam whole breast radiotherapy over 5–6 weeks.[16–19] TARGIT-A also investigated the timing of the delivery of IORT. Patients could receive IORT either at the time of their lumpectomy (pre-pathology) or as a second surgical procedure, once final pathology is known (post-pathology). An analysis of timing of IORT delivery in the TARGIT-A trial showed that pre-pathology IORT is most effective.[16,17] Furthermore, IORT can be delivered as a single dose during surgery, serving as the boost radiation dose followed by whole breast EBRT for tumors with high-risk features.[20]

In the TARGIT-A trial, only 10 % (220/2232) of the participants were from North America.[16] Aside from this trial, little is currently known about the use of IORT in North America. Information on current IORT use, case selection, safety, and outcomes is limited to several small, published series.[21–23] The objective of this study was to define the frequency of IORT use, patient selection, current applications, and outcomes of patients treated in North America with IORT using the Intrabeam system.

METHODS

In 2013 all institutions across North America that were performing IORT for breast cancer using the Intrabeam system were invited to participate in this study. Approval for this study was obtained from the institutional review board at our institution as well as from all participating centers. Institutions then retrospectively entered data on patients who had been treated with breast IORT using Intrabeam at their center before July 31, 2013, via a shared secure online electronic data collection system (REDCap™).[24] Eligibility for receiving IORT was determined by the individual institutions.

Patient demographics, tumor histology and size, disease stage, surgical procedure, IORT treatment type and details, complications, outcomes, recurrence, and follow-up data were collected and then analyzed. Complications were defined as the presence of any seroma or hematoma at any time, or an infection requiring the use of intravenous antibiotics. Increases in the per-quarter rates at which IORT procedures were performed were modeled using a negative binomial model. Recurrences by IORT type were evaluated by the log-rank test and Kaplan–Meier estimates. All analyses were performed using R software version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria), and a 5 % significance level was used for all testing.

RESULTS

In 2013, a total of 19 of the 30 known institutions that were performing IORT using the Intrabeam system in the United States and Canada agreed to participate. This group included both academic and community practice

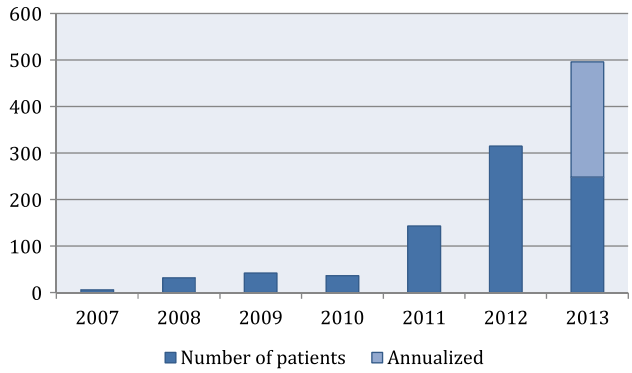

FIG. 1 Number of women treated in United States has increased statistically over the years ($p = 0.005$); 2007 = 6, 2008 = 32, 2009 = 42, 2010 = 36, 2011 = 143, 2012 = 315, 2013 = 248 (annualized = 496)

organizations (Table 1). A total of 935 women were identified as treated with lumpectomy and IORT before July 31, 2013, and were entered into the registry. Of those, 822 patients had a minimum of at least 6 months' follow-up documented and were included in this analysis.

In North America, the first patients documented in this series as treated with IORT started in 2007 with only 6 women. Figure 1 shows that IORT use has increased significantly over time ($p < 0.005$), with an annualized estimate of close to 500 cases performed in 2013.

Table 2 shows the characteristics of the types of patients and tumors treated with IORT. All patients who received IORT were women with a median age at the time of treatment of 66.8 years (range 32–95 years). Most patients had an invasive ductal cancer (68 %), with tumors <2 cm in size (90 %). Tumors were most commonly estrogen receptor (ER) positive (91 %), progesterone receptor (PR) positive (83 %), and HER2 (human epidermal growth factor receptor 2) receptor nonamplified (89 %). Most women had tumors of grade 1 or 2 (83 %) with no lymphovascular invasion (91 %). Of those who had a sentinel lymph node procedure performed (90 %), 89 % had negative sentinel lymph nodes. Overall, 52 % of patients who received IORT underwent preoperative magnetic resonance imaging (MRI). The average IORT treatment delivery time was 29.2 min, with the most use common use of the 3.5 cm (23 %) and 4 cm (35 %) applicator sizes.

Three types of IORT were performed (Fig. 2). A total of 647 patients (79 %) received pre-pathology (primary) IORT. Of the patients who received primary IORT, in 537 (83 %), this was the only radiation they received. Additionally, 110 patients (17 %) who were treated with primary IORT subsequently received EBRT. In these cases, the primary IORT served as a boost followed by EBRT. The reasons for receiving additional radiation among these patients included positive lumpectomy margins (35 %), positive sentinel lymph nodes (39 %), or a change in final pathology diagnosis (26 %). A total of 60 patients (7 %) received post-pathology (secondary) IORT as a delayed procedure, and 115 (14 %) received it as a planned boost followed by EBRT.

TABLE 1 Nineteen North American institutions that participated in TARGIT-R

The Cleveland Clinic, Cleveland, OH
Summit Medical Center, Bay Area Breast Surgeons, Emeryville, CA
Northwestern Memorial Hospital, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL
Memorial University Medical Center, Savannah, GA
Lafayette Surgical Clinic, Lafayette, IN
Community Physician Network Breast Care, Community Health Network, Indianapolis, IN
Moffitt Cancer Center, Tampa, FL
Ashikari Breast Center, Dobbs Ferry, NY
Mercy Medical Center, Baltimore, MD
Trinity Medical Center, Birmingham, AL
The Sentara Dorothy G. Hoefer Comprehensive Breast Center, Newport News, VA
Advocate Good Shepherd Hospital, Barrington, IL
University of California Irvine Medical Center, Irvine, CA
Princess Margaret Cancer Centre, Toronto, ON, Canada
Sutter Cancer Center, Sacramento, CA
Medstar Georgetown University Hospital, Washington, DC
University of Florida, Gainesville, FL
St. Luke's University Health Network, Bethlehem, PA
MedStar Washington Hospital Center, Washington, DC

TABLE 2 Patient and tumor characteristics of women treated with intraoperative radiotherapy

Characteristic	%
Age (years)	
<50	7
50–65	38
65–75	35
≥75	20
Tumor size (cm)	
<1	46
1–2	44
2–3	8
≥3	2
Tumor type	
Invasive ductal	68
Invasive lobular	3
DCIS	9
Mixed[a]	18
Other	2
Tumor grade	
1	38
2	45
3	17
Estrogen receptor (%)	
Positive	91
Negative	9
Progesterone receptor (%)	
Positive	83
Negative	17
HER2 (%)	
Amplified	6
Nonamplified	90
Equivocal	4
Lymphovascular invasion (%)	
Present	9
Absent	91
Sentinel lymph node biopsy (%)	
Not performed	10
0	79
1–3	10
>3	1

DCIS ductal carcinoma-in situ, *HER2* human epidermal growth factor receptor 2

[a] Mixed includes tumors that were invasive ductal cancer coexisting with either invasive lobular cancer or DCIS

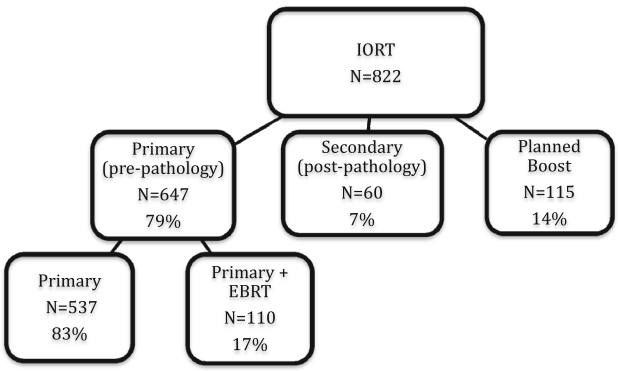

FIG. 2 Types of IORT performed. Primary IORT indicates IORT provided at time of lumpectomy; secondary IORT, IORT provided as second surgery after pathology on initial lumpectomy is known; planned boost, IORT provided with intention to replace EBRT boost; unplanned boost, IORT provided intended to be primary IORT but because of unfavorable lumpectomy pathology results, subsequent EBRT was provided. *EBRT* external-beam radiotherapy, *IORT* intraoperative radiotherapy

Overall, reported postoperative wound complications among all groups were low, and few patients had more than 1 complication. The most common complications included presence of postoperative seroma in 9 %, hematoma in 1.5 %, and infection requiring intravenous antibiotics in 2.8 %.

The median follow-up time for this study was 23.3 months (range 6 months to 5.4 years). The overall crude recurrence rates at the 23.3-month follow-up for all types of IORT are as follows: in-breast recurrence 2.3 % (19/822), axillary nodal recurrence 0.2 % (2/822), contralateral breast new primary lesion 0.9 % (8/822), and metastatic disease 0.3 % (8/822). Of the 19 patients with an in-breast recurrence, 4 also included a combined other-site recurrence. The median time to recurrence was 19.4 months, with the first recurrence occurring at 4.8 months. There were 15 deaths reported in this patient population during the study time period, with 1 death attributable to breast cancer.

When the recurrences were evaluated by IORT type (Table 3), the recurrence rate for primary IORT was 2.4 %, secondary IORT 6.6 %, primary IORT followed by EBRT 1.7 %, and boost with EBRT 1.8 % ($p = 0.92$). Of the 19 recurrences, 13 recurrences occurred > 1 cm from the lumpectomy site, 5 occurred <1 cm from the lumpectomy site, and 1 site was not specified. Additionally, a total of 7 (37 %) of 19 patients with recurrence had a preoperative MRI performed and 12 did not. The original tumor characteristics of the 13 patients with a local recurrence who received primary IORT were as follows: 3 had ER-negative tumors and did not receive additional radiation or chemotherapy, 4 patients had ER-positive tumors and did not take recommended antiendocrine therapy, and 1 patient with axillary sentinel lymph node metastasis did not undergo any additional treatment with EBRT.

TABLE 3 Evaluation of ipsilateral breast recurrences by IORT type at 23.3 months' follow-up

Characteristic	Primary IORT ($n = 537$)	Primary IORT + EBRT ($n = 110$)	Secondary IORT ($n = 60$)	Intended boost IORT ($n = 115$)	Total ($n = 822$)
No. of ipsilateral breast recurrence	13	1	4	1	19
% recurrence (%)	2.4	0.9	6.6	0.9	2.3
Initial tumor characteristics					
ER positive	10	0	3	1	14
ER negative	3	1	1	0	5
HER2 positive	1 equivocal	0	0	0	1
Positive margins	1	1	0	0	2
Positive lymph node	0	1	0	1	2
SLNB not performed	3	0	2	0	5
Noncompliant with antiestrogen therapy	4	0	0	0	4
Recurrence data					
Recurrence <1 cm from scar	3	0	1	1	5
Recurrence >1 cm from scar	10	0	3	0	13
Recurrence location not specified	0	1	0	0	1

Baseline tumor characteristics and initial treatment data and recurrence location for patients with ipsilateral breast recurrence

EBRT external-beam radiotherapy, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *IORT* intraoperative radiotherapy, *SLNB* sentinel lymph node biopsy

DISCUSSION

This is the largest study to evaluate the use and outcomes of patients treated with IORT for breast cancer in North America. Rates of IORT use for breast cancer treatment are increasing significantly in North America. The patterns of care reported in this study suggest that most clinicians are selecting low-risk women who have a favorable, early stage breast cancer.

IORT is intended to be provided as a risk-adapted treatment approach, which enables the addition of conventional EBRT if additional risk factors are identified postoperatively. In this study, 17 % of patients who received primary IORT were recommended to receive EBRT as a result of unfavorable final pathology, such as positive lumpectomy margins, positive lymph nodes, or high-risk tumor biology. Similarly, in the TARGIT-A trial, 15.2 % of patients received EBRT as a result of unfavorable final pathology.[16]

Timing of IORT has shown to be an important factor in risk of local recurrence.[17] The theory is that this may be due to IORT alteration of the microenvironment through the modulation of the wound-healing response at the time of the initial surgery.[25] In this study, the recurrence rate for primary IORT versus secondary IORT was 2.4 vs. 6.6 %, respectively. Although this difference in treatment timing is not statistically significant, the trend is similar to the results reported in the TARGIT-A trial. IORT performed concurrently at the time of lumpectomy is recommended.

Additionally, we found low rates of perioperative complications among patients treated with IORT. The complication rates in this North American registry are similar to those reported in the context of the TARGIT-A trial.[16] Because of the retrospective nature of this study, a limitation is that not all institutions had data available to formally evaluate radiation toxicity, fibrosis, or cosmesis, although other studies have reported these outcomes to actually be improved with IORT compared to EBRT.[21,26,27]

The crude rate of local recurrence for all patients in this series is 2.3 % at a follow-up of 23.3 months. It is noteworthy that many of the patients in this series who had a local recurrence were (1) determined to be higher risk of recurrence on final pathology (positive lumpectomy margins or positive sentinel lymph nodes) and elected not to receive recommended additional surgery or EBRT (2) ER receptor positive and were noncompliant with antiendocrine therapy, or (3) ER receptor negative and did not receive adjuvant EBRT or adjuvant chemotherapy. This series differs from the prospective clinical trial setting in that it is a retrospective analysis of the results of a novel treatment technique implemented into clinical practice. It is, importantly, reflective of actual clinical practice patterns in North America. For instance, patients treated in our study had pure ductal carcinoma-in situ (DCIS), higher incidence of mixed tumor type (invasive ductal, invasive lobular, or DCIS components), some patients did not have sentinel lymph node biopsy performed or EBRT provided

for high-risk features, and not all patients took endocrine therapy as recommended. Adherence to adjuvant endocrine therapy for hormone-positive breast cancer and the utilization of adjuvant EBRT in those with high-risk pathologic features (i.e., positive lymph nodes or surgical margins) may help maximize local control in the population of patients treated with IORT.

Many patients in this study were over the age of 65 years (55 %). Although radiotherapy in this cohort of patients with estrogen-positive cancer has not been associated with an increase in survival, it is associated with an improvement in local control.[3,4] Local control among patients over 70 years of age obviously remains a concern to physicians, as recent studies have shown that among the National Comprehensive Cancer Network participating institutions, 79 % of women over the age of 70 years and 41 % of women over the age of 80 years continue to receive adjuvant EBRT after lumpectomy.[28] The use of IORT in this cohort of patients is a good alternative to EBRT because it is safe, less costly, and can be completed without the need for multiple visits to the cancer facility for treatment planning and radiation.[29] Additionally, outcomes and complications of IORT performed in women over 70 years old versus younger than 70 years have been reported to be similar.[30,31]

Patients with breast cancer have many options for treatment, each option with benefits, risks, harms, and associated costs. These data support the idea that IORT with Intrabeam is a rational option for selected patients with early stage breast cancer. IORT should be used as part of risk-adapted therapy and in conjunction with other recommendations for adjuvant therapy to offer patients the best possible outcomes. In light of these data, we anticipate patients and providers will continue to select IORT as part of their treatment for early stage breast cancer and that utilization of IORT will continue to increase in North America.

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