Clinical Outcomes of Breast-Conserving Surgery with Synchronous 50-kV X-ray Intraoperative Partial Breast Irradiation in Patients Aged 64 Years or Older with Low-Risk Breast Cancer

Breast Cancer: Basic and Clinical Research
Volume 18: 1–8

DOI: 10.1177/11782234231224267
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ABSTRACT

BACKGROUND: Breast-conserving surgery with synchronous 50-kV X-ray intraoperative radiation therapy (TARGIT-IORT) is a convenient form of partial breast irradiation; however, the existing literature supports a wide range of local control rates.

OBJECTIVES: We investigated the treatment effectiveness and toxic effects of TARGIT-IORT in a patient cohort aged 64 years or older with low-risk breast cancer.

DESIGN: Retrospective analysis.

METHODS: Patients who received breast-conserving surgery with synchronous TARGIT-IORT at a single institution from 2016 to 2019 were reviewed. Additional whole breast irradiation was recommended at the discretion of the treating radiation oncologist. Baseline patient demographics and treatment details were recorded. Acute and chronic toxicities, measured using the Common Terminology Criteria for Adverse Events version 3.0 or 4.0 and breast cosmetic outcomes, using the Harvard Cosmesis score, were recorded. Locoregional recurrence, distant metastasis, and overall survival were recorded, and 5-year rates were estimated using the Kaplan-Meier method.

RESULTS: 61 patients were included with a median follow-up of 3.5 years and median age of 72 years. Eight (13%) patients received additional whole breast irradiation, and fifty-four (89%) received adjuvant hormone therapy. There were no local, regional, or distance recurrences. One patient died of complications from COVID-19 infection. Grade 2 + acute and chronic toxicities were observed in 6 (12%) and 7 (14%) patients, respectively. One patient experienced a grade 3 acute toxicity. Cosmetic outcome was "excellent" or "good" in 45 (92%) patients.

CONCLUSIONS: Breast TARGIT-IORT was well tolerated and conferred excellent disease control in this cohort of patients with low-risk breast cancer. While continued follow-up is required, TARGIT-IORT may be an appropriate treatment option for this population.

KEYWORDS: Intraoperative radiation therapy, TARGIT-IORT, breast cancer, brachytherapy, breast TARGIT-IORT, partial breast irradiation

RECEIVED: May 16, 2023. **ACCEPTED:** December 15, 2023.

TYPE: Original Research Article

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

COMPETING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

In appropriately selected patients undergoing breast-conserving surgery, accelerated partial breast irradiation (APBI) constitutes a standard adjuvant treatment option. A consensus statement from The American Society for Radiation Oncology outlines criteria to identify suitable candidates for APBI, which includes patients aged 50 years or older with low-risk, pure ductal carcinoma in-situ (DCIS), or estrogen-receptor-positive invasive ductal tumors 2 cm or less in size.[1] APBI with multicatheter interstitial brachytherapy, single-entry interstitial brachytherapy, and intensity modulated external beam techniques have been shown to result in similarly low local recurrence and toxicity rates, compared with whole breast irradiation.[2-4] APBI has the possible benefit of reducing the radiation dose delivered to critical organs at risk, including the heart, lung, and total breast volume. Intraoperative radiation therapy (IORT) is a form of APBI in which the surgical cavity is focally targeted, typically as a single fraction at the time of breast-conserving surgery while the patient is under general anesthesia. IORT when offered as monotherapy avoids the daily hospital visits required for fractionated external beam irradiation, which typically span 1 to 4 weeks for this patient population.[5-7]

TARGIT-A was a multicenter prospective, randomized trial that compared low energy X-ray IORT delivered with an Intrabeam device (TARGIT-IORT) to adjuvant whole breast irradiation.[8] The study included 2298 patients aged 45 years or older with invasive ductal carcinoma measuring 3.5 cm or less. Depending on the center, randomization occurred either before the initial surgery (prepathology) or after the initial surgery (postpathology). In the former case, patients randomized to TARGIT-IORT received the single fraction during the same operative procedure as the breast-conserving surgery. Patients with prespecified adverse tumor features on final pathology underwent additional whole breast irradiation with standard techniques. Patients in the postpathology stratum had a second procedure to deliver TARGIT-IORT once final pathology from the breast-conserving surgery was available. For all patients, the 5-year risk for local recurrence was 1.3% in the whole breast irradiation arm versus 3.3% in the TARGIT-IORT arm, which met the prespecified criteria for noninferiority. When limiting the analysis to patients in the prepathology stratum, the 5-year risk for local recurrence was 1.1% with whole breast irradiation versus 2.1% with TARGIT-IORT. The updated results from TARGIT-A supported its initial findings.[9]

Although adjuvant radiation treatment may be de-escalated with APBI in appropriate patients, it may also be omitted altogether in older patients with small, hormone receptor positive tumors who undergo adjuvant endocrine therapy (ET).[10,11] The CALGB 9343 and PRIME II prospective randomized clinical trials demonstrated that omission of radiation therapy after breast-conserving surgery led to worse local control but no difference in overall survival in patients older than 70 years and 65 years, respectively, with low-risk breast cancer. Some patients, however, remain motivated to receive adjuvant therapy as a means of avoiding recurrent disease, which may require salvage surgery. One retrospective study demonstrated that more than 74% of patients aged 65 years or older chose IORT when presented as an option for adjuvant treatment after breast-conserving surgery, demonstrating the convenience of the option.[12] At our institution, we have typically offered TARGIT-IORT as monotherapy for patients aged 64 years or older who are suitable for APBI and who generally meet criteria for omission of adjuvant radiation therapy. In this study, we report mature effectiveness and toxicity outcomes for these patients.

Materials and Methods

Patients and treatment technique

This was an institutional-review-board approved retrospective review of all patients undergoing breast TARGIT-IORT at a single institution from September 2016 to December 2019. TARGIT-IORT was offered to patients based on a multidisciplinary discussion between the breast surgeon and radiation oncologist. The technique of IORT used was modeled off that described by Vaidya et al.[13,14] All patients underwent TARGIT-IORT during the same operation as their breast conservation surgery. Applicator size was decided and agreed on by the breast surgeon and radiation oncologist and ranged from 1.5 to 5 cm. Following breast-conserving surgery, the skin flaps were everted and wet gauze was used to keep the skin surface away. A tungsten shield was used to prevent backscatter. After assessing for adequate skin spacing, a dose of 20 Gy prescribed to the surface was delivered in a single fraction using a 50-kVp X-ray Intrabeam device. Additional whole breast with or without regional nodal irradiation was recommended at the discretion of the treating radiation oncologist based on the presence of unexpected adverse features on final pathology, with the TARGIT-IORT treatment acting as the surgical cavity boost.

Follow-up and evaluation of outcomes

Patients had follow-up visits every 3 to 6 months for the first year after treatment and annually in subsequent years. Annual mammography was performed after treatment with additional breast ultrasonography and magnetic resonance imaging (MRI) at the discretion of the treating breast surgeon and radiation oncologist. Local, regional, and distant recurrence events were recorded. Toxic effects were documented by the treating radiation oncologist at each follow-up visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 until February 2018, at which time CTCAE version 4.0 was used. Cosmetic outcome was also assessed at each radiation oncology follow-up visit, using a 4-point scale of Excellent, Good, Fair, or Poor per the Harvard Cosmesis score.[15]

Statistical analyses

Overall survival was estimated with the Kaplan-Meier method. All statistical analyses were performed using GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA).

Results

A total of 61 patients were included in this analysis with a median follow-up of 3.5 years (interquartile range 2.3-4.2 years). Baseline patient characteristics are outlined in Table 1. The median age was 72 years. Fifty-eight (95%) patients had invasive ductal carcinoma, 2 (3%) patients had pure DCIS, and 1 (2%) patient had invasive lobular carcinoma. Of patients with invasive disease, 6 (10%) had AJCC pathologic stage IIA disease, while the remaining patients had stage IA disease. Sixty (98%) patients were estrogen receptor positive, and 3 (5%) were HER-2 positive. Fifty-six (92%) patients underwent sentinel lymph node sampling, and 2 (3%) patients were found to have lymph node positive disease. Seven (11%) patients had positive surgical margins, and each of these patients underwent re-excision with subsequent negative margins. Eight (13%) patients underwent additional whole breast irradiation after IORT, with 1 (2%) patient also undergoing regional nodal irradiation due to a positive sentinel lymph node. Three (5%) patients underwent adjuvant chemotherapy. Fifty-four (89%) patients initiated ET with a median duration of treatment of 2.5 years. Fifteen (28%) patients who had initiated ET therapy had discontinued it prior

Table 1. Baseline patient, tumor, and treatment characteristics (n=61).

CHARACTERISTIC	MEDIAN (IQR) OR N (%)
Age, years	72 (69-74)
Sex	
Female	61 (100)
Male	0 (0)
Follow-up, months	42 (28-50)
Laterality of primary tumor	
Right	30 (49.2)
Left	31 (50.8)
Quadrant of primary tumor	
Upper outer	27 (44.3)
Lower outer	5 (8.2)
Upper inner	17 (27.9)
Lower inner	5 (8.2)
Central	7 (11.5)
Histologic type	
Invasive ductal	58 (95.1)
Invasive lobular	1 (1.6)
DCIS	2 (3.3)
Tumor grade	
1	29 (47.5)
2	29 (47.5)
3	2 (3.3)
Unknown	1 (1.6)
Pathologic stage	
0	2 (3.3)
IA	53 (86.9)
IB	0 (0)
IIA	6 (9.8)
Pathologic T stage	
Tis	2 (3.3)
T1a	10 (16.4)
T1b	23 (37.7)
T1c	21 (34.4)
T2	5 (8.2)
Pathologic N stage	
N0	58 (95.1)
N0(i+)	1 (1.6)
N1(mi)	0 (0)
N1a	1 (1.6)
NX	1 (1.6)
Number of lymph nodes removed	
0	5 (8.2)
1	19 (31.1)
2	23 (37.7)
3	9 (14.8)
4	4 (6.6)
5	1 (1.6)
Number of lymph nodes positive	
0	59 (96.7)
1	2 (3.3)
Surgical margin status	
Positive	7 (11.5)
<1 mm	9 (14.8)
1-2 mm	10 (16.4)
>2 mm	35 (57.4)
ER status	
Positive	60 (98.4)
Negative	1 (1.6)
PR status	
Positive	55 (90.2)
Negative	6 (9.8)
HER-2 status	
Positive	3 (4.9)
Negative	57 (93.4)
Unknown	1 (1.6)
LVSI	
Yes	5 (8.2)
No	56 (91.8)
DCIS	
Yes	34 (57.6)
No	25 (42.4)
EIC	
Yes	7 (11.9)
No	52 (88.1)

(Continued)

(Continued)

Table 1. (Continued)

CHARACTERISTIC	MEDIAN (IQR) OR N (%)
Oncotype DX score	
<16	11 (18.0)
16-25	7 (11.5)
>25	2 (3.3)
Unknown	41 (67.2)
Adjuvant whole breast radiation	
Yes	8 (13.1)
No	53 (86.9)
Hormone therapy	
Yes	54 (88.5)
No	7 (11.5)
Duration, months	30 (22-43)
Chemotherapy	
Yes	3 (4.9)
No	58 (95.1)
ASTRO APBI suitable	
Yes	37 (60.7)
No	24 (39.3)
CALGB 9343 or PRIME-II candidate	
Yes	53 (86.9)
No	6 (9.8)
Not applicable	2 (3.3)

Abbreviations: APBI, accelerated partial breast irradiation; ASTRO, American Society for Radiation Oncology; DCIS, ductal carcinoma in-situ; EIC, extensive intraductal component; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; IQR, interquartile range; LVSI, lymphovascular space invasion; PR, progesterone receptor.

to completing the recommended treatment duration due to side effects. Fifty-three (90%) patients with invasive disease met inclusion criteria for either the CALGB C9343 or PRIME-II clinical trials, and therefore would have been candidates for omission of adjuvant radiation therapy. Thirty-seven (61%) patients were "suitable" candidates for APBI per the ASTRO consensus update.

There were no local, regional, or distant recurrences. No patients died of breast cancer, and 1 patient died 18 months after IORT due to complications of COVID-19 infection. The Kaplan-Meier estimate of survival is shown in Figure 1. The breakdown of acute and chronic treatment toxicity is shown in Tables 2 and 3. Acute toxicity was defined as occurring during radiation treatment or at the first follow-up visit 3 months after completing radiation treatment. Chronic toxicity was defined as occurring more than 3 months out from treatment completion.

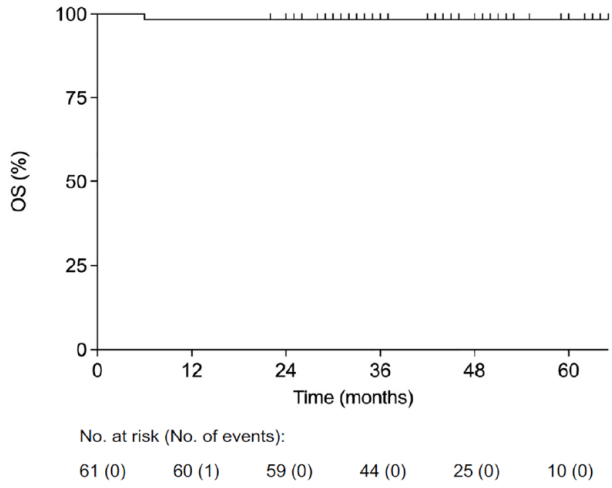

Figure 1. Kaplan-Meier overall survival estimate.

Forty-nine (80%) patients had at least 1 follow-up visit with a radiation oncologist with toxicity recorded.

Six (12%) patients experienced at least 1 grade 2 + acute toxicity, and 1 (2%) patient experienced a grade 3 acute toxicity, which was grade 3 breast pain reported at the first post-IORT follow-up visit. The breast pain had completely resolved in this patient at subsequent follow-up. Three (6%) patients had grade 2 breast edema, 2 (4%) patients had grade 2 breast hyperpigmentation, and 1 (2%) patient had grade 2 radiation dermatitis. There were no cases of acute grade 2 + fatigue or breast hypopigmentation. Seven (14%) patients experienced at least 1 grade 2 chronic toxicity, and no patient experienced any grade 3 + chronic toxicities. Five (10%) patients had grade 2 breast volume reduction, 2 (4%) patients had grade 2 fibrosis, 1 (2%) patient had grade 2 nipple deformity, and 1 (2%) patient had grade 2 telangiectasia. There was no grade 2 + fat necrosis and no accounts of arm lymphedema, myositis, rib fracture, or pneumonitis. Cosmetic outcomes were available for 49 patients and rated as "excellent" or "good" in 45 (92%) patients and "fair" in 4 (8%) patients. There were no patients with a "poor" cosmetic outcome. Toxicity data were available for 6 of the 8 patients who received additional whole breast irradiation after IORT, and none of these patients experienced any grade 2 + acute or chronic toxicities. Cosmetic outcome in this subset was "excellent" in 3 (50%) patients and "good" in 3 (50%) patients.

Discussion

In our cohort of patients aged 64 years or older with low-risk disease, we found that breast-conservation surgery with synchronous TARGIT-IORT resulted in low rates of acute and chronic toxicity, in-line with the prior published data.[16,17] We also observed no recurrences. Multiple studies have assessed the effectiveness of breast TARGIT-IORT with low energy photons. Although TARGIT-A had shown noninferior 5-year local recurrence and noninferior 10-year local recurrence free survival, the 5-year rate of local recurrence was numerically higher with IORT, and the median follow-up for determining risk of

Table 2. Acute toxicities.

ACUTE TOXICITY	N (%)
Fatigue	
None	41 (83.7)
Grade 1	8 (16.3)
Grade 2	0 (0)
Grade ⩾3	0 (0)
Breast pain	
None	32 (65.3)
Grade 1	16 (32.7)
Grade 2	0 (0)
Grade ⩾3	1 (2)
Breast edema	
None	33 (67.3)
Grade 1	13 (26.5)
Grade 2	3 (6.1)
Grade ⩾3	0 (0)
Radiation dermatitis	
None	43 (87.8)
Grade 1	5 (10.2)
Grade 2	1 (2)
Grade ⩾3	0 (0)
Hyperpigmentation	
None	36 (73.5)
Grade 1	11 (22.4)
Grade 2	2 (4.1)
Grade ⩾3	0 (0)
Hypopigmentation	
None	49 (100)

Table 3. Chronic toxicities.

CHRONIC TOXICITY	N (%)
Induration/fibrosis	
None	19 (38.8)
Grade 1	28 (57.1)
Grade 2	2 (4.1)
Grade ⩾3	0 (0)
Volume reduction	
None	26 (54.2)
Grade 1	17 (35.4)
Grade 2	5 (10.4)
Grade ⩾3	0 (0)
Fat necrosis	
None	47 (95.9)
Grade 1	2 (4.1)
Grade 2	0 (0)
Grade ⩾3	0 (0)
Telangiectasia	
None	46 (93.9)
Grade 1	2 (4.1)
Grade 2	1 (2)
Grade ⩾3	0 (0)
Nipple deformity	
None	31 (93.9)
Grade 1	1 (3)
Grade 2	1 (3)
Grade ⩾3	0 (0)
Arm lymphedema	
None	48 (100)
Myositis/chest wall pain	
None	49 (100)
Rib fracture	
None	49 (100)
Pneumonitis	
None	9 (100)

local recurrence was only 5 years. Other institutions have published retrospective breast IORT outcomes, including the Cleveland Clinic, which reported a 2% local recurrence rate in a cohort of 201 patients at median 1.9-year follow-up.[18] Rabin Medical Center in Israel reported no local recurrences in 158 patients at a mean of 2.5-year follow-up.[19] Chowdhry et al[20] retrospectively reviewed 110 patients with median follow-up of 2.5 years and found a 5-year risk of local failure of 3.7%. Falco et al[21] found a 1% local failure rate at median 74-month follow-up in 199 patients above the age of 60 years; however, 48.7% of these patients received additional whole breast irradiation.

TARGIT-R was a multiinstitutional retrospective registry intended to provide "real-world" clinical practice outcomes with TARGIT-IORT performed in North America.[22] This study

Table 4. Summary of breast IORT studies.

STUDY	YEARS	DESIGN	IORT TECHNIQUE, DOSE	NO. OF PATIENTS	MEDIAN AGE (YEARS)	MEDIAN FOLLOW-UP (YEARS)	CLINICAL ENDPOINT	ADJUVANT WBRT (%)	HORMONE THERAPY (%)
Chowdry et al	2011-2017	Retrospective	XOFT©, 50 kV photons, 20 Gy	110	67	2.5	5-year local failure 3.7%	11	75.2
Silverstein et al	2010-2020	Prospective registry	XOFT©, 50 kV photons, 20 Gy	1400	65	5.2	5-year local recurrence 5.27%	11.9	N/R
Falco et al	2010-2017	Retrospective	Intrabeam, kV photons, 20 Gy	199	67.4	6.2	1% local failure at median 74-month follow-up	48.7	97
Nguyen et al	2013-2017	Prospective registry	XOFT©, 50 kV photons, 20 Gy	77	65	4.6	3.9% local failure at median 55-month follow-up	0	72
Obi et al	2011-2019	Retrospective	Intrabeam, 50 kV photons, 20 Gy	201	71	1.9	2.0% local recurrence at median 23-month follow-up	1	75.6
Melnik et al	2014-2018	Retrospective	X-ray energy, 20 Gy	158	68	2.5	0% local recurrence at mean 30-month follow-up	14.9	N/R
TARGIT-R	2007-2013	Retrospective	Intrabeam, low energy photons, N/R	477	68	5.1	5-year ipsilateral breast tumor recurrence 8%	0	69.4
TARGIT-A	2000-2012	Prospective	Intrabeam, 50 kV photons, 20 Gy	1140	N/R	5	5 year local recurrence 2.1%	15.2	81.5
Current study	2017-2019	Retrospective	Intrabeam, 50 kV photons, 20 Gy	61	72	3.5	No local recurrences at median 3.5-year follow-up	13.1	88.5

Abbreviations: IBTR, ipsilateral breast tumor recurrence; IORT, intraoperative radiation therapy; N/R, not reported; WBRT, whole breast radiation therapy.

showed an elevated 5-year IBTR rate of 8% in patients receiving primary IORT without additional whole breast irradiation. Published prospective and retrospective studies on low energy X-ray IORT are summarized in Table 4.

It is hypothesized that the difference in local recurrence rate with breast IORT on TARGIT-R compared with other published data may be at least partially explained by differences in patient populations and tumor aggressiveness. However, the patients included in the primary IORT arm of TARGIT-R appeared to have disease characteristics similar to our patient population. Their patient cohort had a median age of 68 years, a median tumor size of 1 cm, and 94% of their patients were estrogen receptor positive. Interestingly, they observed higher local recurrence rates in older patients, with patients aged 71 to 80 years having an 11% IBTR rate and patients aged >80 years having a 17% IBTR rate. TARGIT-R observed ET compliance to be an independent predictor of IBTR, with noncompliant patients having a 3.67 fold increased risk of IBTR. Our patient cohort had similar ET compliance to TARGIT-R, with 36% of patients either never initiating ET or discontinuing it early; however, no recurrences were observed at albeit shorter median follow-up of 3.5 years. The elevated IBTR rate observed on TARGIT-R in patients older than 70 years with seemingly low-risk tumors does not appear to be fully explained by ET compliance. The question of TARGIT-IORT efficacy in elderly patients with low-risk tumors was further assessed in the TARGIT-E single-arm prospective multicenter study, including 474 patients aged ⩾ 70 with T1, node-negative disease.[23] With median follow-up of 3.25 years, the actuarial local relapse-free survival after 5 years was 98.5%, although ET compliance was not reported. This low rate of local recurrence is in concordance with our study.

Other possible explanations for the higher recurrence rate with breast IORT in TARGIT-R include operator experience and ability to achieve tight conformality between the applicator and the surgical cavity, which is necessary for appropriate dose distribution. Without the aid of intraoperative imaging, operator experience becomes critical in ensuring optimal positioning of the applicator. The lack of image acquisition also precludes the generation of dose-volume histograms for most organs at risk. The skin may be everted and retracted away from the applicator, and the distance between the 2 can be approximated with a ruler or ultrasonography and used to ensure dose to the skin is within tolerance. Dose to the underlying lung and cardiac tissues, however, is left unmeasured. It is assumed to be very low, considering the steep attenuation of low energy X-rays across the thickness of the chest wall.[24,25] Another potential concern of low energy X-ray IORT is the steep dose fall-off. With a spherical applicator and a dose of 20 Gy prescribed to the surgical cavity surface, the dose falls to 6-7 Gy 1 cm from applicator surface, depending on the applicator size.[26] This translates to a significantly smaller biologically equivalent dose at this depth compared with the brachytherapy and external beam techniques used on various APBI protocols.[2-4,27] The premise of TARGIT-IORT rests on the idea that microscopic tumor foci may never progress to clinically significant cancers.[28,29]

It is important to note that most of the patients included in our study would have been candidates for other convenient forms of adjuvant APBI as well. A prospective, randomized clinical trial out of University of Florence looked at 520 patients above the age of 40 years with invasive ductal carcinoma or DCIS measuring less than 2.5 cm.[4] Patients were randomized to external beam APBI of 30 Gy in 5 fractions versus whole breast irradiation of 50 Gy in 25 fractions plus a 10 Gy boost to the surgical cavity. Accelerated partial breast irradiation resulted in a 10-year risk of IBTR of 3.7% versus 2.5% with whole breast irradiation, which were not significantly different. This APBI regimen allows for image guidance and the resulting target and organ at risk dose-volume analysis, but it does require additional clinic visits for treatments compared with IORT.

Limitations of our study include a relatively small sample size of 61 patients with limited follow-up of 3.5 years. Multiple prospective, randomized studies of breast IORT showed that patients remain at risk for IBTR beyond this time frame. Our clinical outcomes at 3.5-year follow-up are encouraging, though, and in-line with the TARGIT-A outcomes.[9]

Conclusions

Although local recurrence rates with breast IORT vary by patient population and possibly other technical factors, our data show that with an experienced multidisciplinary treatment team, breast IORT is well tolerated and results in a very low risk of recurrence in patients aged 64 years or older with low-risk disease. It is a convenient treatment option in this patient population, particularly for those who live great distances from a radiation treatment center.

Declarations

Ethics approval and consent to participate

This is an IRB-approved study by the Corewell Health East William Beaumont University Hospital IRB (IRB number 2011-051). The requirement for informed consent to participate has been waived by the Institutional Review Board.

Consent for publication

Not applicable.

Author contributions

Kamran Salari: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Acknowledgements
Not applicable.

Availability of data and materials
Not applicable.

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