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Original research article

Frequency of whole breast irradiation (WBRT) after intraoperative radiotherapy (IORT) is strongly influenced by institutional protocol qualification criteria

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ARTICLE INFO

Article history:
Received 24 July 2017
Received in revised form
20 September 2017
Accepted 26 November 2017
Available online 15 December 2017

Keywords:
Breast cancer
Accelerated partial breast irradiation
Intraoperative radiotherapy
Whole breast irradiation

ABSTRACT

Background: Accelerated partial breast irradiation (APBI) is a promising method of adjuvant radiotherapy for select patients. Intraoperative radiotherapy (IORT) is a form of APBI, and appropriate patient selection is important.

Aim: The aim of our study was to analyse the influence of our protocol on the frequency of WBRT after IORT and our protocol's correlation with the reported use of WBRT according to TARGIT guidelines. We also aimed to verify how changes in our protocol influenced the frequency of WBRT.

Material and methods: Between April 20, 2010 and May 10, 2017, we identified 207 patients irradiated with IORT for APBI.

Results: Ninety-one patients (44%) met the criteria for APBI only, while 116 (56%) should have been offered additional WBRT. Retrospective analysis showed that WBRT was applied statistically significantly less frequently compared with strict protocol indications: 99 patients (47.8%) received APBI only and 108 (51.2%) underwent adjuvant WBRT ($p < 0.0001$). Applying the TARGIT trial guidelines, 69 patients (33.4%) should have been offered WBRT ($p < 0.0001$), which is twice the number of patients treated with WBRT in our study. Changing the protocol to less restrictive criteria would have statistically significantly decreased the number of patients (95, 46%) offered WBRT ($p < 0.0001$).

Conclusions: Following international guidelines, 46% of patients should receive WBRT after IORT, which is 1.5–2 times more than for the TARGIT criteria. In our analysis, a high percentage of patients (19%) did not receive WBRT after IORT despite the protocol recommendations. The chosen protocol strongly influences the frequency of adjuvant WBRT.

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https://doi.org/10.1016/j.rpor.2017.11.003

1. Background

The value of whole breast radiotherapy (WBRT) after breast-conserving surgery (BCS) for invasive breast cancer (IBC) has been confirmed in multiple clinical trials and meta-analyses.[1–3] Based on these studies, all patients should be offered adjuvant radiotherapy after BCS for IBC. However, the disadvantages of adjuvant WBRT include exposure of healthy tissue to irradiation (lung, heart, chest wall) and the time needed to conduct at least 15 fractions (3 weeks).[4] Considering the limitations of WBRT and the biology of IBC, researchers began irradiating only the primary tumour and surrounding healthy tissue, which is called accelerated partial breast irradiation (APBI).

Several scientific societies have published recommendations for patient qualification for APBI, including the European Organisation for Research and Treatment of Cancer (ESTRO) and the American Society for Radiation Oncology (ASTRO).[5,6] These societies divide candidates for APBI into three groups: "suitable", "cautionary", and "unsuitable", depending on the histological tumour type, diameter, presence of ductal carcinoma in situ (DCIS), excision margin, oestrogen receptor-positive status, lymphatic vessel invasion, lymph node status, age, and BRCA1 gene status.

The advantages/disadvantages of APBI have been evaluated in randomised trials using different methods and different groups of patients. Linear accelerator-based APBI was evaluated in two trials with conflicting results. Conformal radiotherapy appeared to induce unacceptable cosmetic effects,[7] while intensity-modulated radiotherapy (IMRT) showed comparable efficacy to WBRT with better cosmetic effects.[8] Recently, brachytherapy (either high-dose rate or pulsed-dose rate) was confirmed as an acceptable alternative to WBRT in "suitable" patients with IBC.[9] Both IMRT and brachytherapy can be used after BCS when all risk factors are known, and the qualification procedure is relatively simple.

Intraoperative radiotherapy (IORT), applied at the time of BCS, enables localised irradiation precisely in the tumour cavity and is biologically optimal.[10] However, certain factors are unknown when using APBI, including histological tumour type, DCIS status, excision margin, lymphatic vessel invasion, and lymph node status. Currently, two systems of IORT are available: electron-based: (Mobetron; Sunnyvale, CA, USA, and a mobile dedicated accelerator, Novak LIAC; Sordina IORT Technologies, SpA, Vicenza, Italy), or kilovoltage photon-based (INTRABEAM; Carl Zeiss, Oberkochen, Germany). Studies evaluating electron-based IORT were among the first to be published.[11] One trial confirmed that APBI is an acceptable treatment option for "suitable" candidates and that its use in other groups of patients should be carefully considered.[12]

The targeted intraoperative radiotherapy (TARGIT) trial verified the value of kilovoltage photon-based IORT for APBI.[13] The advantage of the method is that it can be followed with WBRT.[14,15] The TARGIT trial protocol recommends using WBRT after IORT in cases of extensive intraductal component, resection margins <1 mm, and lobular cancer. In the trial, each participating centre was able to apply its own recommendations, and overall, 15.2% of patients in the TARGIT trial received WBRT after IORT.[13]

2. Aim

The aim of our study was to analyse how our protocol influenced the frequency of WBRT use after IORT and to assess our protocol's correlation with WBRT use following the TARGIT guidelines. We also aimed to verify how changes in the protocol influenced the frequency of WBRT use.

3. Materials and methods

This was a retrospective medical record analysis. The data were analysed and reported anonymously; therefore, no additional patient informed consent was required.

Beginning in April 2010, IBC patients in our hospital have been treated with the INTRABEAM system (INTRABEAM; Carl Zeiss Surgical, Oberkochen, Germany). The criteria for APBI were defined according to the ESTRO and ASTRO recommendations (Table 1).[5,6] Patients who did not meet these criteria did not qualify for APBI. Patients were consulted in two multidisciplinary team (MDT) meetings: before and after operation. BCS included tumour resection, intraoperative radiological specimen analysis, sentinel lymph node biopsy, and APBI. During the second MDT meeting, WBRT indications were assessed. If pathological report findings did not meet eligibility criteria for APBI only (Table 1), patients were qualified for WBRT. If the only criteria for WBRT qualification was age, patients between 50 and 60 years were given the option to decline WBRT.

Between April 20, 2010 and May 10, 2017, 207 patients received irradiation according to the APBI protocol. Of these, 99 patients (47.8%) underwent APBI only, while 108 (51.2%) received adjuvant WBRT after IORT. Group characteristics are presented in Table 2.

IORT was performed using INTABEAM system, which emits low-energy photons (30–50 kV) with a steep fall-off in soft tissues. After the resection of tumour, the cavity was examined and the applicator was installed. The diameter of applicator was chosen depending on cavity volume. The specimen of resected tissue was verified for margins with the Trident specimen radiography system (Hologic, Inc., Malborough, USA). 50 kV photons were used and the dose of 20 Gy was prescribed on the surface of applicator. Irradiation time depended on the

Table 1 – Eligibility criteria for APBI based on the West Pomeranian Oncology Center protocol.

Tumour type	Ductal, tubular, mucinous carcinoma No lobular, medullar carcinoma
ER	Positive
Her-2	No overexpression
Tumour size	≤20 mm
Margins	>2 mm
LN status	pN0
LVI	No
DCIS	<5% in tumour, no outside of the tumour
Age	Above 60

APBI, accelerated partial breast irradiation; ER, oestrogen receptor; LN, lymph node; LVI, lymphatic vessel invasion; DCIS, ductal carcinoma in situ.

Table 2 – Group characteristics.

Factor	Number
All	207
Age	
<60 years	30 (14.5%)
60–75 years	154 (74.4%)
>75 years	23 (11.1%)
Histology – core biopsy	
Ductal	191 (92.3%)
Tubular	7 (3.4%)
Mucinous	9 (4.3%)
pT	
1a	8 (3.9%)
1b	84 (40.6%)
1c	115 (55.5%)
pN	
0	180 (87%)
1mic	7 (3.4%)
1	12 (5.8%)
2	8 (3.9%)
Lobular	
No	185 (89.4%)
Yes	22 (10.6%)
Any DCIS	
No	129 (62.3%)
Yes	78 (37.7%)
Protocol important DCIS	
No	169 (81.6%)
Yes	38 (18.4%)
LVI	
No	194 (93.7%)
Yes	13 (6.3%)
Margin	
>2 mm	144 (69.6%)
≤2 mm	63 (30.4%)
≥1 mm	21 (10.1%)
<1 mm	186 (89.9%)

DCIS, ductal carcinoma in situ; LVI, lymphatic vessel invasion.

diameter of applicator and varied between nineteen and forty minutes. The most frequently used applicators had diameters of either 3.5 or 4 cm.

Out of 27 patients with metastases in the axillary lymph nodes, 12 underwent radical axillary lymphadenectomy (10 with macrometastases and 2 with micrometastases).

In a group of patients who underwent WBRT, the planning computed tomography scan was obtained with 5-mm-thickslices on a personalised immobilisation device with one or two arms raised. The clinical target volume included the whole breast tissue and was expanded by 5 mm to create the planning target volume. For 27 patients with lymph node metastases, the clinical target volume was expanded to include also the ipsilateral axillary and supraclavicular lymph nodes. Organs at risk (OARs) included the lung, heart, coronary arteries, and contralateral breast. The plans were prepared in three-dimensional (3D) planning systems either by Prowess Panther (Radiology Oncology Systems, Inc., San Diego, CA, USA) or Oncentra Masterplan (Oncentra MasterPlan, Nucletron, Veenendaal, The Netherlands). Whole breast was treated with a total dose of 46 for negative axillary lymph nodes and 50 Gy in 2-Gy daily fractions for patients with axillary lymph nodes metastases. For each patient, dose–volume histograms for the target and OARs were obtained. Choice of irradiation technique (intensity modulated radiotherapy or 3D conformal radiotherapy) depended on the fulfilment of dose constrains for the OARs and target volume. WBRT was performed on Siemens linear accelerators (Siemens Health-care, Erlangen, Germany) using either 6 or 7 MeV photons. Mean time from IORT to the first fraction of WBRT was 53 days (24–244 days).

Table 3 – WBRT according to the West Pomeranian protocol.

Protocol factor	APBI only	IORT + WBRT	*p*-value
Whole group			
APBI	77	14	<0.0001
IORT + WBRT	22	94	
DCIS			
Yes	22	56	<0.0001
No	77	52	
DCIS protocol			
Yes	8	30	0.0003
No	91	78	
Margin			
>2 mm	84	60	<0.0001
≤2 mm	15	48	

WBRT, whole-breast radiotherapy; APBI, accelerated partial breast irradiation; IORT, intraoperative radiotherapy; DCIS, ductal carcinoma in situ.

3.1. *Statistical analyses*

χ^2 or Fisher's exact tests were used to compare differences between APBI (IORT only) and WBRT (IORT + WBRT) groups. The level of significance was set at 5%. Statistical analyses were performed using MedCalc for Windows, version 17.6 (MedCalc Software, Ostend, Belgium).

4. Results

According to the APBI protocol, 91 patients (44%) met the criteria for APBI only, while 116 patients (56%) should have been offered additional WBRT during their MDT meetings. Our retrospective analysis showed that WBRT was used statistically significantly less often in the analysed group compared with strict protocol indications: 99 patients (47.8%) received APBI only and 108 (51.2%) underwent adjuvant WBRT ($p < 0.0001$) (Table 3). Fourteen patients (15.4%) who were candidates for APBI only underwent adjuvant WBRT, while 22 patients (19%) did not, despite existing risk factors. In patients with lymph node metastasis and positive lymphatic vessel invasion, all 27 (13%) and 13 (6.3%) patients, respectively, underwent adjuvant WBRT. Only 1/22 patients with additional lobular cancer confirmed on postoperative histopathology refused WBRT. Patients meeting the criteria for WBRT and not receiving this treatment included eight cases of 5–30% DCIS tumour component, thirteen cases with resection margins of 1–2 mm, and two cases with both a DCIS component and 1–2 mm resection margins. Patients receiving WBRT without meeting the protocol criteria included eight patients with <5% DCIS tumour component and three patients <60 years of age. In three patients, there were no risk factors precluding WBRT. In the analysed group, interpretation of the pathological report

Table 4 – Comparison of APBI vs WBRT according to the TARGIT trial protocol and our modified institutional protocol.

Actual protocol	APBI	IORT + WBRT	*p*-value
TARGIT protocol			
APBI	91	47	<0.0001
IORT + WBRT	0	69	
New protocol			
APBI	91	21	<0.0001
IORT + WBRT	0	95	

APBI, accelerated partial breast irradiation; WBRT, whole-breast radiotherapy; TARGIT, targeted intraoperative radiotherapy; IORT, intraoperative radiotherapy.

according to protocol was not consistent in the DCIS and resection margin cases (Table 3). Patients with DCIS outside the tumour were more frequently qualified for WBRT compared with patients with intratumoural DCIS.

The TARGIT criteria for APBI vs. WBRT were fulfilled in 138 (66.6%) and 69 (33.4%) patients, respectively. The protocol we used increased the number of patients (47) who underwent WBRT compared with the TARGIT trial protocol (Table 4).

Following our analysis, we proposed changing the APBI protocol regarding DCIS and margin resection. APBI qualifying factors in the new protocol are: intratumoural DCIS component <25% (DCIS outside the tumour is not acceptable), resection margin ≥2 mm (in cases of chest wall tumours, 1 mm margins are acceptable), and age > 50 years. These changes would have resulted in avoiding WBRT in an additional 21 patients, but with 95 patients (46%) still receiving irradiation.

5. Discussion

APBI delivered with IORT is less time-consuming compared with WBRT.[16] However, APBI should be reserved for precisely-selected patients. Contrary to the findings of the ELIOT trial,[11] it is safe to deliver WBRT after kilovoltage IORT. WBRT after IORT has been shown effective, with a 2.6% 5-year recurrence rate[14] and good cosmetic effects,[15] in an unselected group of patients. Because IORT is an intraoperative procedure, most important risk factors are not precisely known. The ability to consider adjuvant WBRT gives physicians greater confidence knowing that patients will not receive inferior treatment regarding time to recurrence, if IORT is applied. However, the remaining questions include which patients should receive adjuvant WBRT and what factors are important for decision making.

The published recommendations (ESTRO or ASTRO) define APBI only for the "suitable" group of patients. Despite this, trials involving APBI given post-BCS differ widely in enrolment criteria. Strnad et al. used brachytherapy for APBI in a group of patients that included 6% pure DCIS, 6% oestrogen receptor-negative, 13% lobular cancer component, and 1% with micrometastases to the axillary lymph nodes.[9] Livi et al. applied IMRT for APBI in a group of patients that included 12.3% with DCIS, 18.2% with lobular cancer component, and 12.7% with axillary lymph node metastases.[8] Both trials used different inclusion and exclusion criteria, and the TARGIT trial included obligatory exclusion criteria for every participant: tumour-free margin <1 mm, extensive intraductal component, and unexpected lobular cancer component.[13] The participating oncology centres in the TARGIT trial were also able to add their own additional criteria e.g., patients from Germany also qualified to receive adjuvant WBRT in cases of positive lymphatic vessel invasion, axillary lymph node metastases, and margins closer than 1 cm.[17]

In the TARGIT-A trial, based on the criteria of the TARGIT trial, only 14.2% of patients received WBRT post-IORT, despite the fact that 19% were axillary lymph node metastasis-positive, 7% had a lobular cancer component, 14% had positive lymphatic vessel invasion, and 7.1% required re-excision because of close margins.[18] In contrast, in the experimental APBI arm, 76.7% of patients received IORT only.[18]

In our institution, we decided that patients with HER-2 overexpression or who were oestrogen receptor-negative would not qualify for APBI because of a lack of clinical safety data. We were also more restrictive with histopathologically-confirmed DCIS. As a result, 56% of our patients fulfilled the criteria for APBI only. If we applied the TARGIT criteria used in Germany,[17] one third of patients should have been offered WBRT, which is still twice more than in the APBI arm. The frequency of risk factors in our cohort and the TARGIT APBI arm did not differ noticeably, i.e. the lymph node metastasis rate in the TARGIT trial was 19% vs. 13% in our group, lymphatic vessel invasion positivity was 14% vs. 6.3%, lobular cancer component was 7% vs. 10.6%, resection margin positivity was 9.5% vs. 10.2%, and DCIS presence was 50% vs. 37%.[18]

Sperk et al. analysed a cohort of patients regarding the use of IORT in early breast cancer.[19] Results showed that 15.8% and 34.2% of patients fulfilled the ASTRO and ESTRO criteria, respectively, for APBI. The criteria did not include a margin factor, lymphatic vessel invasion, or the ability to perform APBI. Leonardi et al. showed, in the ELIOT trial, that 31.5% of patients were "suitable" for APBI according to the ESTRO criteria.[12] In our study, patients with HER-2 overexpression were excluded from receiving APBI.

For 18% of our patients, we saw incompatibility when comparing our institution's protocol with the actual treatment. To some extent, this can be explained by patients' preferences, similar to the TARGIT trial and Livi et al. trial where 8.5–8.9% and 5.4% of patients, respectively, did not receive treatment according to the protocol.[8,18] Most patients who did not receive WBRT in our group met the criteria for APBI only according to the TARGIT trial criteria. Therefore, differences in institutional protocol vs. the TARGIT protocol could result from both patient and physician decisions.

Care is needed when introducing a new treatment modality. Having that in mind, in 2010, our protocol was very restrictive, which led to quite a high percentage of patients receiving WBRT. As new data from the TARGIT trial were published, we relaxed the criteria regarding DCIS, resection margin, and age. We decided to accept margins of 1 mm in the chest wall if the pectoralis fascia is resected. Based on our new protocol, 46% of the patients in the current study would have been candidates for adjuvant WBRT; however, this is still 1.5 times more than using the TARGIT trial criteria.

6. Conclusions

Different trials using multiple treatment modalities used qualification criteria incompatible with the ESTRO and ASTRO recommendations.[8,9,18] Following the TARGIT trial criteria, it remains difficult to conclude which of patients should have been offered WBRT after IORT.[17,18] Following the ESTRO and ASTRO recommendations, 46% of our patients should receive WBRT after IORT, which is 1.5–2 more than following the TARGIT criteria. In our analysis, a high percentage of patients (19%) did not receive WBRT after IORT despite meeting the protocol recommendations. The chosen protocol strongly influences the frequency of adjuvant WBRT use.

Ethical approval

For this type of study formal consent is not required.

Conflict of interest

None declared.

Financial disclosure

None declared.

Acknowledgements

We thank Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

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