Radiotherapy and Oncology 131 (2019) 229–236

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

# Post-mastectomy radiation therapy with or without implant-based reconstruction is safe in terms of clinical target volume coverage and survival – A matched cohort study

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ARTICLE INFO

*Article history:*
Received 7 January 2018
Received in revised form 24 June 2018
Accepted 4 July 2018
Available online 25 July 2018

*Keywords:*
Breast cancer
Radiation therapy
Clinical target volume
Immediate breast reconstruction
Implant
Overall survival

ABSTRACT

*Background and purpose:* Patients with breast cancer receiving mastectomy in our institution are offered immediate breast reconstruction (IBR). IBR may have an impact on the optimisation of radiation therapy (RT). Therefore, we aimed to evaluate the clinical target volume (CTV) dose coverage when disregarding the dose received by the breast implant in women treated for breast cancer. Furthermore, to investigate the safety of immediate breast reconstruction (IBR) with an implant (IBR+) in terms of recurrence and survival compared to patients without an implant (IBR−).

*Patients and methods:* This matched-cohort included 128 patients with IBR+ and 252 IBR− patients (controls). The potential confounding effects of tumour stage and treatment were controlled for. For IBR+ patients, the implant volume was excluded from the CTV in the RT planning images, and the RT target coverage ($V_{95\%}$: CTV covered by ≥the 95% isodose) was compared between the IBR+ and IBR− groups.

*Results:* A limited under dosage was observed in patients without lymph-node irradiation; the $V_{95\%}$ mean values for the CTV subtracting the implant were 84% and 92%, for IBR+ and IBR− groups, respectively. Median follow-up duration was 5.8 years (0.1–7.5 years). In comparing IBR+ and IBR− groups, no statistically significant differences were found in the incidence of recurrence rate ratios or recurrence free survival (log-rank $p = 0.142$), overall survival (log-rank $p = 0.096$), or breast cancer specific survival (log-rank $p = 0.147$).

*Conclusions:* Post-mastectomy radiation therapy and implant-based reconstruction lead to minor under dosage of the target, due to the projection of the subcutaneous tissue in the presence of the implant. However, recurrence and survival rates were equally distributed among IBR+ and IBR− patients indicating that the overall treatment protocol used in our institution is safe.

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Patients with breast cancer receiving mastectomy in our institution are offered immediate breast reconstruction (IBR) unless significant comorbidity or adjuvant therapies preclude this option [1]. In addition, post-mastectomy radiation therapy (PMRT) for breast cancer in combination with lymph node involvement results in increased local relapse control and overall survival [2–4]. IBR is a cost-effective measure [5] that improves quality of life and self-perceived body image [6,7]. Nevertheless, adverse events must be considered such as risk of delayed PMRT due to surgical complications and risk of reconstruction failure [8]. One concern when choosing IBR followed by PMRT is that the procedure could have an impact on disease control. Two meta-analyses have reported that local recurrence rates [9] and survival [10] did not differ between patients with or without reconstruction. However, a maximum of 30% of the patients included in those studies were treated with radiation therapy (RT). Another concern is that IBR might

*Abbreviations:* IBR, immediate breast reconstruction; PMRT, post-mastectomy radiation therapy; OAR, organs-at-risk; RT, radiation therapy; CTV, clinical target volume; HER2, human epidermal growth factor receptor 2; Gy, gray; PTV, planning target volume; AAA, analytical anisotropic algorithm; DVH, dose volume histograms; CW, chest wall; IRR, incidence rate ratios; TRAM, transverse rectus abdominis myocutaneous; DFS, disease free survival; OS, overall survival; CI, confidence interval.

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https://doi.org/10.1016/j.radonc.2018.07.005
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affect the optimisation of RT. One institution found excellent chest wall (CW) radiation coverage and acceptable doses to organs-at-risk (OAR) in women with implants when using intensity modulated RT [11,12]. In a study from our institution, no significant differences were found in doses to OAR in patients without implants (IBR−) versus IBR patients with implant (IBR+), although the clinical target volume (CTV) was significantly larger in the IBR+ group than in the IBR− group when the implant was included in the CTV [13].

Radiation therapy guidelines for the delineation of CTV do not specifically deal with the issue of implants, which often lead to discussions among the multidisciplinary teams when analysing the dose distribution in RT plans in IBR+ patients. Specifically, there is a lack of a standard on if and how to take into account the implant when delineating the CTV in IBR+ patients, and the required CTV dose coverage if the implant shall be subtracted. Finally, clinical outcomes in IBR+ patients in a matched control setting are also limited. In the present study we focused on the evaluation of the RT CTV dose coverage disregarding the dose received by the implant and elucidated if IBR+ is associated with increased breast cancer recurrence and/or decreased overall survival in comparison with IBR− patients.

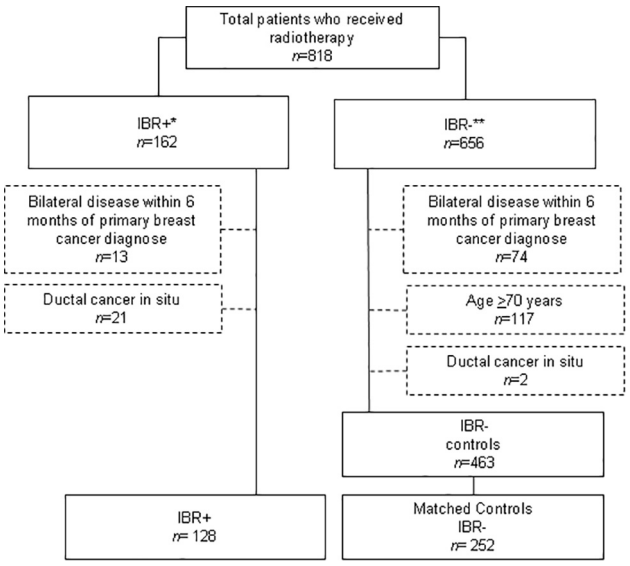


**Fig. 1.** Flow chart of the study population.

## Methods

### *Patients*

All women diagnosed with breast cancer within the Stockholm-Gotland area and receiving PMRT in the time period of 2009–2011 were eligible and our subjects were selected among these. Patients, tumour characteristics, and type of surgical and oncological treatment were obtained from the Swedish National Breast Cancer Registry [14] and from medical records. This study cohort was identified and used in a previous analysis of radiation dose in OAR in patients with or without IBR. Detailed information about patient collection, inclusion and exclusion criteria, radiation treatment, surgical technique and RT planning-procedures are found in the initial publication [13].

This study was approved by the Regional Research Ethics Committee in Stockholm 2010/1242-31, 2011/1861-32, 2017/455-32.

### *Study design*

The study population in this matched cohort study consisted of 128 IBR+ patients and 252 IBR− controls. The original patient cohort included 162 IBR+ patients and 656 IBR− patients [13]. For the present study, however, all patients with bilateral tumours within six months before or after breast cancer diagnosis, as well as patients with ductal carcinoma in situ, and patients ≥70 years of age were excluded. The remaining eligible patients included 463 IBR− and 128 IBR+ patients. The IBR+ patients were matched to 1–2 IBR− patients based on age at diagnosis and lymph-node status (negative or positive), resulting in 252 matched pairs of study (comparators) (Fig. 1). The potential confounding effects of year of mastectomy, tumour size, preoperative treatment, adjuvant treatment, and human epidermal growth factor receptor 2 (HER2) positivity were further controlled for by adjustment in regression models.

### *Surgery and breast implants*

All patients received mastectomy, and if the sentinel node was positive or positive axillary lymph nodes were detected preoperatively; an axillary lymph node dissection was performed. Three possible types of implants were used: type 1, temporary expander with an integrated magnetic port ($n = 21$); type 2, permanent expander implant with silicone gel and saline with a remote injection port placed subcutaneously on the chest wall ($n = 79$); and type 3, permanent silicone gel implants with a predefined volume ($n = 28$). All implants were placed under total muscular cover, e.g. the pectoralis muscle and were of anatomical shape. Expansion was always completed before RT. Implant type and size was discussed and decided mutually between the breast surgeon and the patient. The volumes for delineated implants ranged between 109 cc and 716 cc, the mean volume was 360 cc, and median volume was 355 cc.

### *Systemic therapy*

Patients received chemotherapy including anthracyclines with or without taxane based regimens according to international and national guidelines [15]. One-year treatment of trastuzumab was given to all patients with HER2 positive tumours when chemotherapy was indicated. Adjuvant hormonal therapy was indicated for all patients with oestrogen receptor-positive tumours [16]. Depending on menopausal status, tamoxifen or aromatase inhibitors were given after completion of chemotherapy.

### *Indications for post mastectomy radiotherapy*

PMRT was indicated for all patients with stage III tumours. PMRT in T1 and T2 tumours was optional for patients with 1–3 lymph node metastases in combination with 2 or more high risk parameters such as high proliferation, young age, oestrogen receptor negative or grade III tumours [4]. In patients with T3 tumours in combination with node-negative disease, only chest wall (CW) irradiation was indicated. The same RT-treatment protocol was applied for the duration of the present study [17].

### *Clinical target volume, radiation therapy technique and planning*

All patients received a complete course of RT with 2 Gy daily fractions in 25 fractions. The 3D-CT based RT treatment was based on an isocentric technique, with 2.5–3.0 mm thickness slice, and set-up starting from external origo (reference point of the coordinate system). 6-MV photons were used and some patients received additional 15-MV or 18-MV photon fields. All treatment plans were created in Eclipse (Varian) and the dose was calculated with the Analytical Anisotropic Algorithm (AAA) algorithm. Chest wall RT

was performed by using two tangential fields. When CTV included the lymph nodes, an isocentric technique with two tangential fields covering CW and three fields covering respectively the lymph nodes in the infra- and supraclavicular fossa and the axilla was used. In accordance with the local practice at our institution, the internal mammary nodes were not specifically targeted. Boost was given to patients if there was a positive margin close to the chest wall. The boost was given towards the same target i.e., CW and/or lymph nodes, regardless of IBR or not. The same RT technique was used as described above. The boost radiation dose was 2 Gy/day with a final boost dose ranging between 6 Gy and 16 Gy depending on the grade of side effects to the skin. Bolus was used in patients with a thin CW; this might imply the risk of full dose coverage to CTV close to the patient́s surface. The thickness of the bolus was 3–5 mm. If bolus was indicated, it was used daily during the whole radiation treatment course.

The CTV defines the volume of the tissue which is indicated to be treated (excluding geometrical margins); unless other specifications it includes the breast implant, when present. CTV was defined as "CW-only" for local RT plans or as "CW plus lymph nodes" for loco-regional RT. In patients with IBR+, CTV was delineated including the breast implant according to routine procedures used in our institution. Planning target volume (PTV) included an additional 5–7 mm margin around CTV. The treatment aim was to keep the dose to the CTV between 95% and 105% of the prescribed dose. CTV coverage was defined as the volume of CTV covered by $\geq$ the 95% isodose (CTV $V_{95\%}$). Dose Volume Histograms (DVH) and dose statistics for CTV coverage were retrieved from the ARIA treatment planning system. As an example, the CTV delineation and the dose distribution on a transversal slice in an IBR+ patient and in an IBR− patient can be seen in Fig. 2A and B.

In the present study for IBR+ patients, $V_{95\%}$ was extracted both for CTV and for CTV excluding the implant. The implant was outlined retrospectively (all by the same person). Other DVH-parameters to describe the CTV dose distribution included the mean dose and $V_{105\%}$ (indicating the level of target dose homogeneity).

### *Follow up procedures and definitions of survival*

Endpoints in survival analyses were recurrence-free survival (RFS), breast cancer specific survival (BCSS), and overall survival (OS) in both IBR+ and IBR− patients. All patients received yearly follow-ups, which included mammography of the contralateral breast. Additional imaging or blood tests were performed if signs of recurrence were apparent. Local failure was defined as metastases on the CW. Loco-regional failure was defined as any metastases within the infra- or supraclavicular region or axilla, and any other metastases were considered distant.

### *Statistical analyses*

The IBR+ and IBR− groups were compared in terms of target coverage to determine whether the presence of the implant during RT influences the ability to fulfill treatment aims.

A two-tailed Student's *t*-test was used to highlight any differences in DVH parameters between IBR+ and IBR− patients. In the patients where the CTV included lymph nodes as well as CW, the effect of the implant on DVH parameters was expected to be smaller due to the smaller fraction of the volume represented by the implant. Therefore, a separate analysis was performed on patients with lymph-node irradiation.

Cox regression models were used to estimate the rate of recurrence among IBR+ women compared to IBR− women. Follow-up time was calculated from the date of mastectomy until the date of first recorded recurrence, death, or end of the study on June 30, 2016 (whichever occurred first).

Results are presented as incidence rate ratios (IRR) with 95% confidence intervals (CI). We used three different models to sequentially assess potential confounding effects between IBR+ and IBR− patients. Model 1 was adjusted for the matching variables, Model 2 was further adjusted for the year of mastectomy, tumour size (pT1, pT2, pT3), the usage of preoperative therapy and adjuvant chemotherapy, and Model 3 included also HER2 and oestrogen receptor status. The variables included in the Cox models were determined *a priori* based on their potential relevance as confounding factors for the association between IBR and the risk of recurrence. No variables were included in the models solely based on the observed level of statistical significance. The proportional hazards assumption was evaluated by applying the Grambsch-Therneau test on the Schoenfeld residuals obtained from each model.

Kaplan–Meier estimates and model-based predictions of RFS, OS, and BCSS were estimated by IBR exposure status. The adjusted survival curves were estimated using a flexible parametric survival model adjusted for the same covariates as the fully adjusted Cox regression model (i.e., Model 3) [18]. Log rank tests and Wald tests were applied to test for differences in survival (Kaplan–Meier and adjusted survival curves, respectively).

## Results

### *Baseline demographics*

Analysis of tumour characteristics, oncology and RT treatment of the study population revealed no significant differences in the distribution of matching factors between the IBR+ and the matched IBR− groups (Table 1). Median follow-up duration was 5.8 years (range: 0.1–7.5 years). These findings indicate that the matched control process was satisfactory.

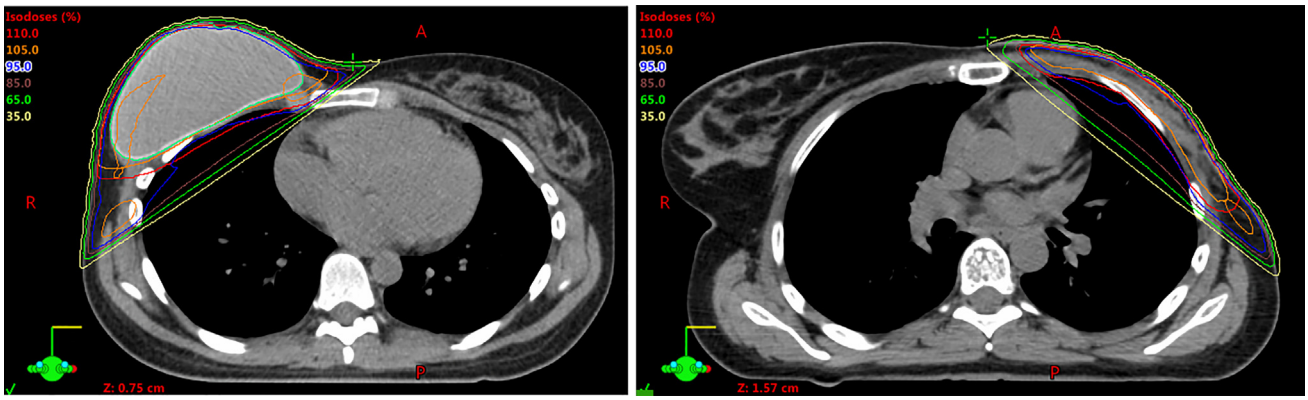


**Fig. 2.** A and B. The CTV delineation and the dose distribution on a transversal slice in an IBR+ patient and in an IBR− patient.

*Dosimetric characteristics of clinical target volume including and excluding implant*

Due to the presence of the implant for the IBR+ patients, we found a significantly larger CTV for IBR+ patients than for IBR− patients, both in the CW and CW plus lymph nodes cases (Table 2. Upper portion). When the implant was excluded, the CTV was somewhat smaller in the IBR+ group with only CW RT (Table 2. Lower portion).

A significant difference was observed between IBR+ and IBR− groups in terms of $V_{95\%}$ when the implant was excluded from the CTV (Table 2. Lower portion). This indicates that the treatment aim for target coverage is not achieved to the same extent for IBR+ patients as for IBR− patients. A limited under dosage follows, as indicated by the slightly lower mean dose. The target dose homogeneity ($V_{105}$%) seems better for IBR+ patients than for IBR− patients (CW irradiation). However, excluding the implant reveals that the exposure to high doses for the CW is similar in the two groups.

*Events of recurrence in women with or without IBR*

In total, there were 42 patients with recurrences (local or regional lymph node or distant). In IBR+ patients with local or regional lymph node recurrences, 3 women were reconstructed with permanent implants, and 3 women with temporary implants. Hence, no patients with local or regional lymph node recurrences had an implant with magnetic port (Table 3). The dose data for the 6 IBR+ patients and the 6 IBR− patients with local or regional lymph node recurrences are presented in a supplementary table (Supplementary Table S1). We observed no statistically significant differences in the incidence of recurrence between the IBR+ or IBR− groups in the unadjusted ($IRR_{model1}$: 0.59, 95% CI: 0.29–1.21) or adjusted Cox regression models ($IRR_{model4}$: 0.85, 95% CI: 0.40–1.82) (Table 4).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.07.005.

**Table 1**
Patient and tumour characteristics in the study cohort.

| | The whole study population | | IBR+** | | IBR−* | |
|---|---|---|---|---|---|---|
| | No. (%) | Recurrences | No. (%) | Recurrences | No. (%) | Recurrences |
| Total | 380 | 42 | 128[Y] | 10 | 252 | 32 |
| Age at diagnosis | | | | | | |
| Median (range) | 46 (21–68) | | 46 (21–68) | | 47 (24–68) | |
| <55 | 301 (79.2) | 36 | 106 (82.8) | 10 | 195 (77.4) | 26 |
| 55+ | 79 (20.8) | 6 | 22 (17.2) | 0 | 57 (22.6) | 6 |
| Year of mastectomy | | | | | | |
| 2009 | 125 (32.9) | 18 | 49 (38.3) | 4 | 76 (30.2) | 14 |
| 2010 | 134 (35.3) | 15 | 37 (28.9) | 4 | 97 (38.5) | 11 |
| 2011 | 121 (31.8) | 9 | 42 (32.8) | 2 | 79 (31.4) | 7 |
| Tumour size | | | | | | |
| pT1 | 179 (47.1) | 17 | 65 (50.8) | 4 | 114 (45.2) | 13 |
| pT2 | 138 (36.3) | 17 | 45 (35.2) | 4 | 93 (36.9) | 13 |
| pT3 | 37 (9.7) | 4 | 13 (10.2) | 1 | 24 (9.5) | 3 |
| Missing | 25 (6.8) | 4 | 5 (3.9) | 1 | 21 (8.3) | 3 |
| Lymph nodes | | | | | | |
| pN0 | 165 (43.4) | 11 | 57 (44.5) | 3 | 108 (42.9) | 8 |
| pN+ | 215 (56.6) | 31 | 71 (55.5) | 7 | 144 (57.1) | 24 |
| Side | | | | | | |
| Right | 180 (47.4) | 18 | 71 (55.5) | 5 | 109 (43.3) | 13 |
| Left | 200 (52.6) | 24 | 57 (44.5) | 5 | 143 (56.7) | 19 |
| HER2 | | | | | | |
| No | 293 (77.1) | 32 | 98 (76.6) | 8 | 195 (77.4) | 24 |
| Yes | 87 (22.9) | 10 | 30 (23.4) | 2 | 57 (22.6) | 8 |
| Preoperative chemotherapy treatment | | | | | | |
| No | 221 (58.2) | 13 | 97 (75.8) | 5 | 124 (49.2) | 8 |
| Yes | 159 (41.8) | 29 | 31 (24.2) | 5 | 128 (50.8) | 24 |
| Adjuvant chemotherapy treatment | | | | | | |
| No | 189 (49.7) | 28 | 48 (37.5) | 5 | 141 (55.9) | 23 |
| Yes | 187 (49.2) | 14 | 79 (61.7) | 5 | 108 (42.9) | 9 |
| Missing | 4 (1.1) | 0 | 1 (0.8) | 0 | 3 (1.2) | 0 |
| Endocrine therapy | | | | | | |
| No | 81 (21.3) | 12 | 32 (25.0) | 6 | 49 (19.4) | 6 |
| Yes | 295 (77.6) | 30 | 95 (74.2) | 4 | 200 (79.4) | 26 |
| Missing | 4 (1.1) | 0 | 1 (0.8) | 0 | 3 (1.2) | 0 |
| RT target | | | | | | |
| Chest wall | 114 (30.0) | 3 | 52 (40.6) | 3 | 62 (24.6) | 0 |
| Chest wall + lymph nodes | 266 (70.0) | 39 | 76 (59.4) | 7 | 190 (75.4) | 32 |
| Bolus[#] | | | | | | |
| No | 362 (95.3) | 39 | 126 (98.4) | 10 | 236 (93.7) | 29 |
| Yes | 18 (4.7) | 3 | 2 (1.6) | 0 | 16 (6.4) | 3 |
| Boost dose | | | | | | |
| No | 371 (97.6) | 41 | 126 (98.4) | 10 | 245 (97.2) | 31 |
| Yes | 9 (2.4) | 1 | 2 (1.6) | 0 | 7 (2.8) | 1 |

IBR−*; No immediate breast reconstruction, IBR+**; Immediate breast reconstruction with implant.
Abbreviations: p, pathological; RT, radiation therapy; HER2, human epidermal growth factor receptor 2.
[Y] Of which $n = 21$ with temporary expander with an integrated magnetic port, $n = 79$ with permanent expander implant with silicone gel and saline with a remote injection port placed subcutaneously on the chest wall, $n = 28$ with permanent silicone gel implants with a predefine volume.
[#] Bolus; was used in patients with thin chest wall, the bolus was 3–5 mm and was used daily during the whole radiation treatment course.

**Table 2**
Clinical target volume (CTV) in IBR+ and IBR− groups, and CTV excluding the implant in the IBR+ group receiving radiation therapy.

| | Chest wall (CTV) | | | Chest wall plus lymph nodes (CTV) | | |
|---|---|---|---|---|---|---|
| | IBR+** N = 52 | IBR−* N = 62 | P | IBR+** N = 76 | IBR−* N = 190 | P |
| Volume ($cm^3$) | 670 (2 5 5) | 419 (2 6 4) | <0.01 | 1097 (2 9 2) | 760 (2 8 0) | <0.01 |
| Mean dose (Gy) | 50.1 (0.9) | 50.4 (0.9) | 0.06 | 50.4 (0.6) | 50.3 (0.7) | 0.34 |
| $V_{95}$ (%) [a] | 91.6 (5.5) | 92.9 (7.1) | 0.72 | 93.7 (3.4) | 92.9 (4.7) | 0.16 |
| $V_{105}$ (%) [b] | 10.0 (5.7) | 15.3 (12.2) | 0.01 | 11.8 (6.7) | 11.8 (6.2) | 0.99 |
| | Chest wall (CTV) | | | Chest wall plus lymph nodes (CTV) | | |
| | IBR+** N = 52 CTV excluding implant | IBR−* N = 62 | P | IBR+** N = 76 CTV excluding implant | IBR−* N = 190 | P |
| Volume ($cm^3$) | 333 (194) | 419 (264) | 0.06 | 717 (235) | 760 (280) | 0.25 |
| Mean dose (Gy) | 49.7 (1.2) | 50.4 (0.9) | <0.01 | 50.2 (0.7) | 50.3 (0.7) | 0.31 |
| $V_{95}$ (%) | 83.8 (9.7) | 92.0 (7.1) | <0.01 | 90.6 (5.3) | 92.9 (4.7) | <0.01 |
| $V_{105}$ (%) | 14.5 (8.5) | 15.3 (12.2) | 0.70 | 12.5 (6.2) | 11.8 (6.2) | 0.39 |

* IBR−; no immediate breast reconstruction.
** IBR+; immediate breast reconstruction with implant.
[a] The irradiated volume with 95% of the prescribed dose.
[b] The irradiated volume with 105% of the prescribed dose.

**Table 3**
Description of events in IBR+ and IBR− groups.

| Description of recurrences | All patients n = 380 (%) | IBR**+ n = 128 (%) | IBR−* n = 252 (%) |
|---|---|---|---|
| Local | 4 (1.1) | 1[a] (0.8) | 3 (1.2) |
| Regional lymph node | 8 (2.1) | 5 (3.9) | 3 (1.2) |
| Distant | 38 (10.0) | 7 (5.5) | 31 (12.3) |
| Local and distant | 3 (0.8) | 0 | 3 (1.2) |
| Other primary tumour | 2 (0.5) | 0 | 2 (0.8) |
| Death (death any cause) | 30 (7.9) | 6 (4.7) | 24 (9.5) |
| Death breast cancer | 28 (7.4) | 6 (4.7) | 22 (8.7) |

* IBR−; no immediate breast reconstruction.
** IBR+; immediate breast reconstruction with implant.
[a] The local recurrence was located "above the implant" i.e., between the skin and the upper surface of the breast implant.

*Survival in women with IBR+ and IBR−*

There was no significant difference in RFS (log-rank, $p = 0.142$; wald, $p = 0.718$) (Fig. 3), or OS (log-rank, $p = 0.096$; wald, $p = 0.382$) or BCSS (log-rank $p = 0.147$, wald $p = 0.558$) (Fig. 4) in comparing women with IBR+ and IBR− in both unadjusted (Kaplan–Meier) and adjusted analyses. A total of 30 patients died during follow-up and among those, 28 women died from breast cancer and the remaining two died from other primary cancers (lung cancer and colorectal cancer) (Table 3).

When evaluating the treatment plans of the patients who had recurrence of any type, no loss of target coverage was observed outside the build-up region (i.e., the volume close to the patient surface where full radiation dose has not yet been reached), excluding the RT treatment plan as a potential cause of recurrence for these patients.

## Discussion

In our study, we found no statistically significant difference in OS between IBR+ and IBR− groups. In dosimetric terms, a limited but significant reduction in the coverage of CTV excluding the implant ($V_{95\%}$) and in mean CTV dose were found in the IBR+ group. Since the implant reshapes the chest wall to be treated into a thin rim, which to a large extent coincides with the build-up region, the reduction in CTV coverage was expected. However, the extent of the resulting target under dosage had not previously been quantified; in fact, the treatment plan quality assurance (QA) is performed on CTV including the implant. The routine treatment plan QA includes checking conformance to RT protocols (i.e. compliance of the RT plan to dose/volume constraints and other parameters of interest), the quality of the dose distribution as well as reviewing the patient's medical history in a multidisciplinary meeting. However, since no corresponding increase in recurrences or reduction in OS was observed in the IBR+ group, the limited difference in target dose coverage does not appear to have any clinical significance. Hence, our results indicate that the RT protocol and treatment procedure, used in our institution, for IBR+ patients are safe.

Unlike in prior studies that reported no differences in OS in IBR+ patients compared to IBR− patients, in the present study all patients received irradiation and CTV coverage was studied in detail. In addition, our study population is derived from a consecutive series of patients presented over a relatively short period (three years) in which treatment protocols were the same. Matching age and lymph-node status and subsequently performing confounder analyses of TNM, HER2, and preoperative treatment and adjuvant chemotherapy resulted in a robust dataset for the analyses.

Only one previous study investigated disease free survival (DFS) and OS in IBR patients who all received RT as part of the breast cancer treatment [19]. However, in that study, patients received either immediate autologous reconstruction with transverse rectus abdominis myocutaneous (TRAM) flap or no reconstruction. The authors observed no differences in DFS or OS between the groups [19].

In a meta-analysis including 19 publications, Zhang et al. concluded that IBR+ does not affect the OS and DFS [10]. However, none of the studies included in that meta-analysis had a patient cohort where all subjects received RT as part of the breast cancer treatment. In addition, detailed data about RT were missing in several of the studies in this meta-analysis, which could lead to a potential bias in the meta-analyses. Therefore, a direct comparison between our study and those of others is of limited value.

While most studies show no significant differences in OS between IBR+ and IBR−, one large register study found a higher OS in the IBR+ group than in the IBR− group although few confounders were controlled for. Furthermore, the authors indicated a possible socioeconomic confounder effect and their results should be cautiously interpreted [20]. In addition, only 17% of the patients received RT and thus that study is not comparable with our results. In other publications analysing OS in IBR+ and IBR− patients, the range of patients receiving RT was only 20–30% and hence not fully comparable with our results. However, these groups used the same type of implants as in the present

**Table 4**
Incidence of relapse [Rate Ratios (IRR) and 95% Confidence Intervals (CI)] in women who had mastectomy ($n = 380$) between 21 and 68 years of age.

| | Model 1[1] IRR (95% CI) | Model 2[2] IRR (95% CI) | Model 3[3] IRR (95% CI) | Model 4[4] IRR (95% CI) |
|---|---|---|---|---|
| Immediate Breast reconstruction (IBR) | | | | |
| IBR−[**] | 1.00 (reference)[*] | 1.00 (reference) [*] | 1.00 (reference) [*] | 1.00 (reference) |
| IBR+[***] | 0.59 (0.29–1.21) | 0.59 (0.29–1.20) | 0.85 (0.40–1.80) | 0.85 (0.40–1.82) |
| Age at mastectomy | | 0.95 (0.92–0.98) | 0.96 (0.93–0.99) | 0.97 (0.92–0.99) |
| Lymph nodes | | | | |
| pN0 | | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| pN1+ | | 2.30 (1.15–4.57) | 2.61 (1.26–5.43) | 2.60 (1.25–5.44) |
| Year of mastectomy | | | | |
| 2009 | | | 1.00 (reference) | 1.00 (reference) |
| 2010 | | | 0.95 (0.46–1.95) | 0.95 (0.46–1.96) |
| 2011 | | | 0.47 (0.20–1.07) | 0.47 (0.20–1.07) |
| Tumour size | | | | |
| pT1 | | | 1.00 (reference) | 1.00 (reference) |
| pT2 | | | 1.46 (0.73–2.94) | 1.46 (0.73–2.94) |
| pT3 | | | 1.09 (0.36–3.33) | 1.09 (0.36–3.32) |
| Missing | | | 1.54 (0.49–4.85) | 1.56 (0.48–5.00) |
| Preoperative treatment with chemotherapy | | | | |
| No | | | 1.00 (reference) | 1.00 (reference) |
| Yes | | | 4.42 (1.29–15.16) | 4.47 (1.26–15.85) |
| Adjuvant treatment | | | | |
| No | | | 1.00 (reference) | 1.00 (reference) |
| Yes | | | 1.36 (0.41–4.44) | 1.38 (0.40–4.71) |
| Missing | | | NA | NA |
| HER2 | | | | |
| No | | | | 1.00 (reference) |
| Yes | | | | 0.97 (0.45–2.10) |

*Abbreviations*: HER2, human epidermal growth factor receptor 2; NA, not applicable.
[1] Unadjusted for confounders.
[2] Adjusted for matching factors age at mastectomy and lymph node status (from medical records).
[3] Further adjusted for tumour size, calendar period of mastectomy and preoperative treatment with chemotherapy and adjuvant chemotherapy treatment.
[4] Further adjusted for HER2 status.
[*] No evidence against the proportional hazards assumption (Grambsch-Therneau test).
[**] IBR− no immediate breast reconstruction.
[***] IBR+ immediate breast reconstruction with implant.

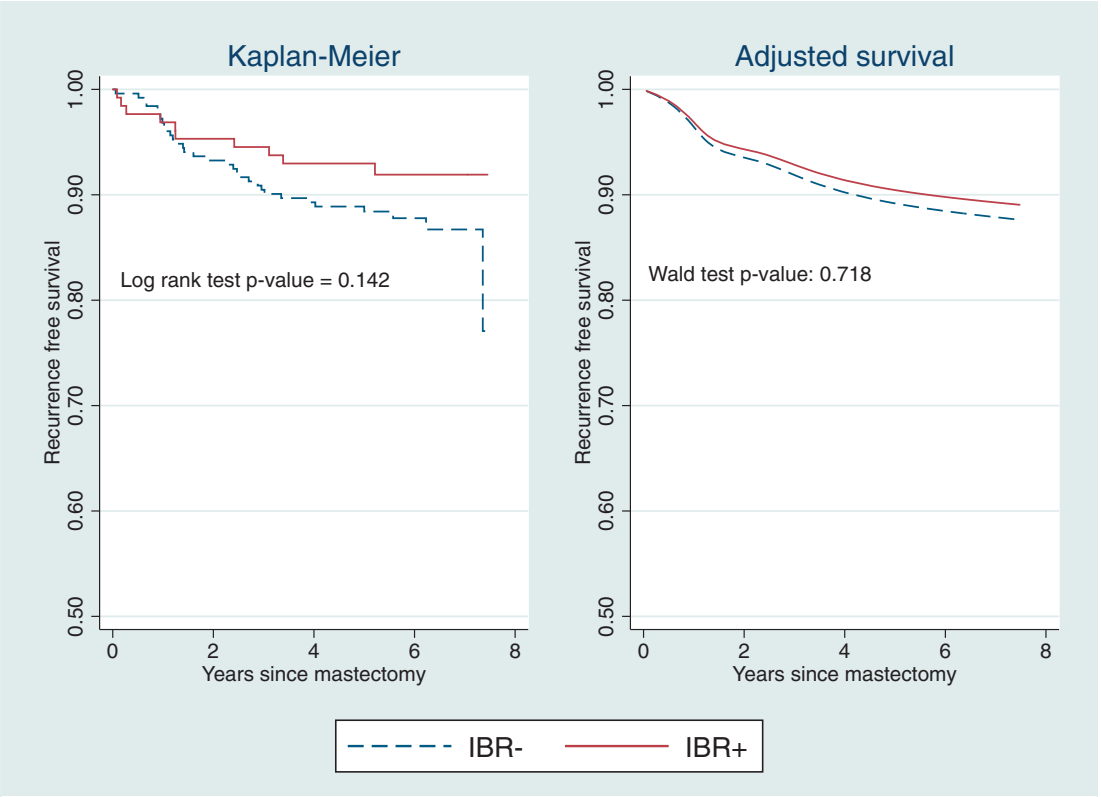


**Fig. 3.** Recurrence free survival in IBR+ and IBR− groups.

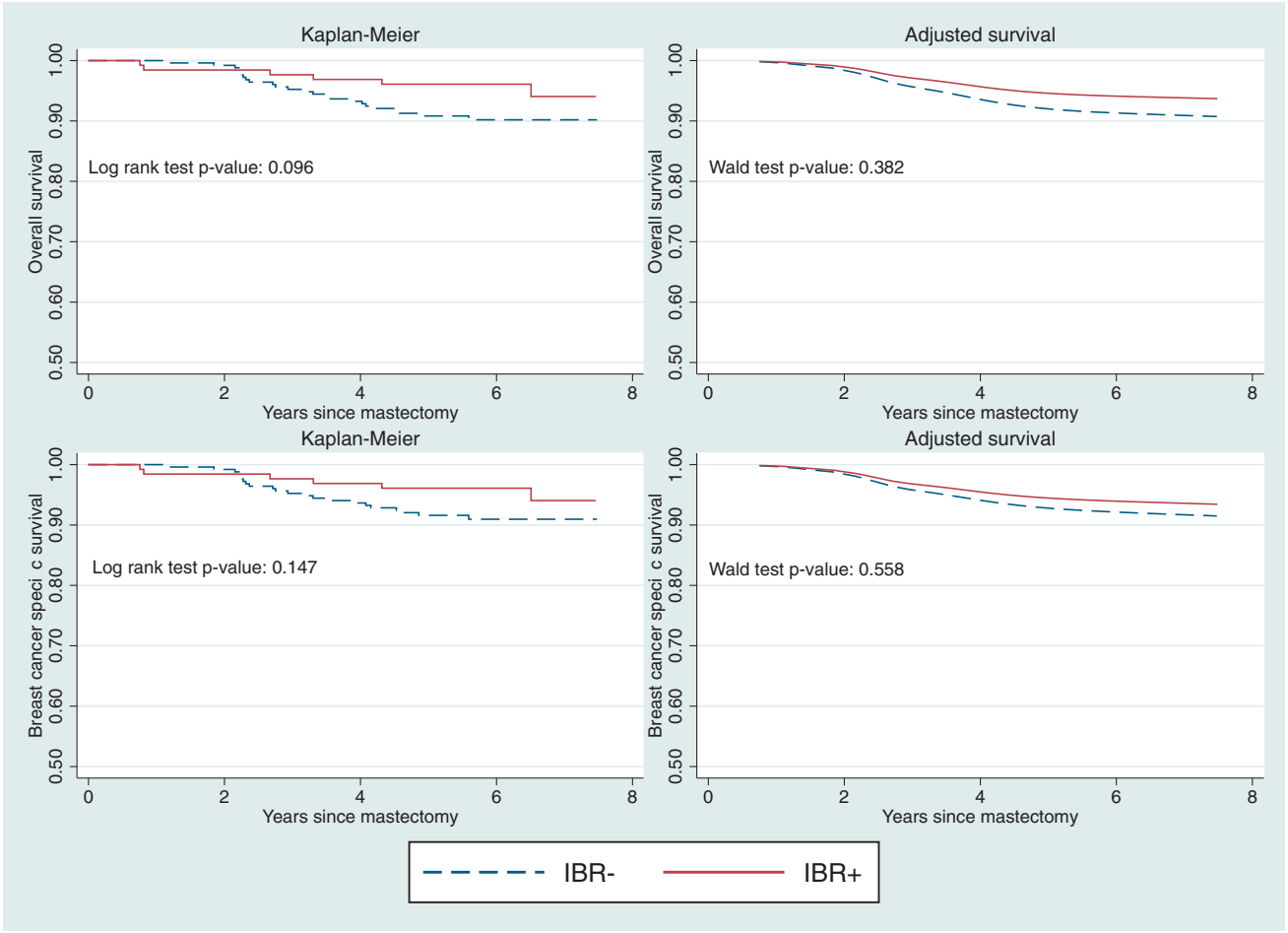


**Fig. 4.** Overall survival and breast cancer free survival in IBR+ and IBR− groups.

study [21,22]. In the earlier study from our institution no differences in OS between IBR+ and IBR− were found. Notably, the study cohort was selected during 1990–2004 with 32.8% patients treated with PMRT. Despite the revised oncology treatment protocols since that time period, similar OS results were found in both studies [23].

There are no other reports that combine quantitative information about dose coverage and survival analyses in patients treated for breast cancer. Other groups have investigated the RT dose in reconstructed breast cancer patients ($n = 196$), but without a matched-control design [12] and/or with small number of patients studied ($n = 41$) [11].

One of the three implant types used in our study had a magnetic port, previously shown to attenuate the radiation beam, [24–26] which may cause incorrect modelling by the treatment planning system [27]. For a tangential beam arrangement, the local dose reduction due to the magnetic port is in the 7–10% range [25,26]. The uncertainty in calculated dose due to the magnetic port was not considered in the current study, and consequently the CTV dose was likely slightly overestimated in a subgroup of patients. This would slightly increase the observed magnitude in CTV dose reduction in the overall IBR+ group compared to the IBR− group. Nevertheless, no local or regional node recurrences were observed in patients with a magnetic port.

Limitations with our study are lack of randomisation, non-prospective design, and a relatively short follow-up period. Due to ethical reasons, randomisation was not possible in this patient group and the match-cohort design sufficiently accounted for much of the potential bias.

In conclusion, PMRT in IBR+ patients lead to a limited under dosage of the target, due to the projection of the subcutaneous tissue in the presence of the implant. However, no association with a higher incidence of recurrence or impaired survival was associated with IBR+. Thus, patients in our institution can be informed that the overall treatment protocol is safe in terms of survival when choosing IBR followed by RT. Larger prospective studies are needed to confirm our results.

## Acknowledgments

The authors wish to thank Kamilla Krawiec at the Regional Cancer Centre of Stockholm Gotland for valuable assistance in this work.

## Funding

This work was supported by The Ulrika Foundation.

## Disclosure

Niina Rintelä has stocks in Raysearch Laboratories, Sandra Eloranta has a consulting role at Scandinavian Development Services and is a project coordinator of a public–private real world evidence collaboration between Karolinska Institutet and Janssen Pharmaceuticals. All remaining authors have declared no conflicts of interest.

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