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Original Article

Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study

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Abstract

Background: Radiotherapy (RT) is a risk factor for impaired outcomes after implant-based immediate breast reconstruction (IBR). Large studies including long-term follow-up are relatively scarce. The purpose of this analysis was to assess long-term effects of RT in implant-based IBR, distinguishing between implant removal because of postoperative complications *versus* patient preference.

Methods: This population-based cohort study included all patients with breast cancer who underwent implant-based IBR in Stockholm between 2005 and 2015. Data were collected through national registers and medical charts. The main endpoint was implant removal owing to postoperative complications (wound breakdown, infection, bleeding) or patient preference (dissatisfaction, pain, capsular contracture), with or without conversion to autologous reconstruction.

Results: Some 1749 implant-based IBRs in 1687 women were included. Median follow-up was 72 (range 1–198) months. Reconstructions were divided according to receipt of RT: No RT ($n = 856$, 48.9 per cent), adjuvant RT ($n = 749$, 42.8 per cent), and previous RT ($n = 144$, 8.2 per cent). Implant removal occurred after 266 reconstructions (15.2 per cent); 68 (7.9 per cent) in the no RT, 158 (21.1 per cent) in the adjuvant RT, and 40 (27.8 per cent) in the previous RT group. Implant removal was because of postoperative complications in 152 instances (57.1 per cent) and was most common in the first 3 years. This was especially observed in the previous RT group, where 15 of 23 implant removals occurred during the first 6 months. Implant removal owing to patient preference (114 of 266, 42.9 per cent) became more common with increasing follow-up.

Conclusion: Implant removal after implant-based IBR is significantly associated with RT. The reason for implant removal shifts over time from postoperative complications to patient preference.

Introduction

About one-third of patients diagnosed with primary breast cancer undergo mastectomy[1]. International guidelines[2,3] state that the patient should be counselled about reconstructive options when a mastectomy is performed, with the aim of empowering patients to make an informed decision. Reconstructive counselling should consider aspects of timing (immediate *versus* delayed breast reconstruction) and method (implant-based *versus* autologous reconstruction), but also the individual risk profile and physical prerequisites for available reconstructive methods. Immediate breast reconstruction (IBR) is increasingly being performed[4,5]. Even though postoperative complications may interfere with the start of adjuvant treatment on an individual level, this does not affect oncological outcome on a group level[6]. In Sweden, IBR is nearly exclusively based on implants, and IBR rates have increased from 6 per cent in 2010 to 12 per cent in 2020, with the highest rate in the Stockholm region (31 per cent)[1].

Although radiotherapy (RT) offers a clinically relevant reduction in the risk of locoregional recurrence after mastectomy, it significantly impairs the results of reconstruction[7–10]. Adverse long-term effects of RT are most pronounced in implant-based reconstruction, and include capsular contracture, pain, and reduced patient satisfaction. These symptoms commonly lead to revisional surgery or implant removal, with or without conversion to an autologous reconstruction. Therefore, it has been a long-standing discussion whether or not to offer implant-based IBR in the setting of postmastectomy RT (PMRT). Immediate autologous options imply more extensive surgery and are not widely available. In addition, not all patients have the

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prerequisites for or the desire to choose such options, and there is also controversy regarding whether or not to expose an autologous flap to PMRT. Thus, implant-based options may be here to stay. This was recently debated at the international Oncoplastic Breast Consortium Consensus Conference, where panellists agreed that implant-based IBR is a valid option in the face of PMRT, despite the known negative effects on reconstructive and patient-reported outcomes[11].

The existing literature on breast reconstruction in the face of PMRT is compromised by substantial heterogeneity in reconstructive methods and timing, limited population sizes, and/or limited follow-up. Implant-based as opposed to autologous breast reconstruction is prone to repeated revisional operations, which contributes to an increased cumulative risk of postoperative complications and, ultimately, failure of reconstruction, especially in the context of PMRT[12]. It is, therefore, very important to assess long-term outcomes. The aim of the present analysis was to provide population-based outcome data from a large and uniquely homogeneous cohort of women undergoing implant-based IBR.

Methods

This population-based cohort study included all women with a diagnosis of invasive or *in situ* breast cancer undergoing therapeutic mastectomy with implant-based IBR at one of the four surgical units performing breast cancer surgery (Capio St Göran's Hospital, Stockholm South General Hospital, Karolinska University Hospital, Danderyd Hospital) in Stockholm, Sweden, from 1 January 2005 to 31 December 2015. All patients with breast cancer residing in the Stockholm region were treated at one of these four hospitals in this time interval. Patients with primary or recurrent breast cancer were eligible. Patients with bilateral disease were registered as two cases if both sides fulfilled the inclusion criteria; otherwise, only the eligible side was registered. Risk-reducing mastectomies were not eligible. Patients were identified via inpatient admissions included in the National Patient Register at the Swedish National Board of Health and Welfare. Subsequently, medical records were collected from the hospitals, and were scrutinized individually to correctly identify and exclude those not fulfilling the above inclusion criteria.

Clinical data were extracted by individual review of the complete medical files and registered in an electronic case report form (eCRF) managed by the Clinical Trials Unit at Karolinska University Hospital, Stockholm, Sweden, in accordance with applicable legislation. Data comprised patient age, date and type of surgery, tumour and treatment characteristics, details of the immediate reconstructive surgery performed, risk factors and postoperative complications, as well as follow-up regarding ipsilateral (implant removal, revisional surgery, autologous reconstruction) and contralateral (any symmetrizing procedure) operations, recurrence, survival, and dates of last follow-up. Data collection was undertaken by all authors and submitted to subsequent quality control by means of predefined feasibility checks and selective source data verification. To obtain as complete data as possible, data were also cross-linked to the National Quality Register for Breast Cancer (NKBC).

For the present analysis, patients were grouped according to RT received: no RT, adjuvant RT or previous RT (such as for a previous ipsilateral breast cancer treated with breast conservation, sarcoma or lymphoma). Nipple-sparing mastectomy was defined based on the final procedure; subsequent removal of the nipple, owing to a positive retroareolar biopsy, altered the categorization from nipple-sparing to skin-sparing. Indications for PMRT at the time were T3 tumours, positive nodal status, multifocality, and *in situ* disease exceeding 10 cm in extent or covering at least 25 per cent of the breast.

Postoperative infections within 90 days were classified into four groups: no postoperative infection; clinically suspected but unconfirmed infection treated with oral antibiotics; confirmed infection (confirmed by culture and/or raised serum C-reactive protein levels) treated with oral antibiotics; and confirmed infection treated with intravenous antibiotics.

Implants were grouped into three categories: permanent implants (fixed-volume silicone implants); temporary expander implants (saline expanders commonly featuring an integrated magnetic filling port, designated by the manufacturer to be exchanged to a permanent implant); and permanent expander implants (expanders composed of both silicone and saline, designated for permanent use by the manufacturers, often equipped with a filling tube that is removed separately).

The reason for implant removal was considered to be either a postoperative surgical complication (infection, wound dehiscence, bleeding) after the IBR itself or any ipsilateral revisional procedure during follow-up, or patient preference (wish for removal of implant or conversion to autologous reconstruction owing to dissatisfaction, pain, or capsular contracture) in order to distinguish between forced and scheduled implant removal. Thus, if capsular contracture led to the scheduled removal of an implant with or without conversion to autologous reconstruction, the reason was considered to be patient preference; if, on the other hand, it led to revisional surgery resulting in surgical complications, such as wound breakdown, infection or bleeding, implant removal was considered to be due to a postoperative complication. Implant removal could be combined with simultaneous or subsequent conversion to autologous reconstruction. Implant removal owing to recurrence was not considered in this analysis.

Ethical permission for this study was obtained from the Swedish Ethical Review Authority in 2015 (2015/1183-31/4), with amendments in 2016 (2016/1374-32), 2017 (2017/2318-32), and 2018 (2018/42-32). The eCRF is registered as Stockholm Breast Reconstruction Database at Karolinska Institutet, Stockholm, Sweden. No informed consent was required under Swedish and European Union legislation.

Statistical analysis

Data are presented as numbers with percentages, median (range) or mean(s.d.). The Kruskal–Wallis test was used to compare continuous variables (such as age, tumour size, and BMI) between the three RT groups, whereas the χ^2 test or Fisher's exact test was used, as appropriate, to assess the distribution of categorical variables (such as histological grade and hormone receptor status).

For the binary outcomes postoperative infection within 90 days and reoperation within 30 days, univariable and multivariable logistic regression analyses were performed, and associations are presented as ORs with 95 per cent confidence intervals. The multivariable model was adjusted for RT, patient factors (age, BMI, and smoking), medications, and surgical variables. For the outcome implant removal with or without simultaneous or subsequent conversion to autologous reconstruction during follow-up, any implant removal, irrespective of reason, was included in a single category. Time from mastectomy to first

implant removal was calculated with censoring at death or end of follow-up (last date of documented patient contact). Associations between implant removal rates and RT, patient factors, medications, and surgical and oncological treatments were assessed in univariable and multivariable Cox regression analyses, with estimation of HRs and 95 per cent confidence intervals. Thereafter, separate Cox regression analyses were undertaken according to reason for implant removal; those due to postoperative complication or patient preference were considered separately. As the number revisional procedures and time interval between them could vary substantially, and considering that every revisional procedure entering the implant cavity poses a risk of postoperative complications and subsequent implant removal, the number of revisional operations was entered into the Cox model as a time-varying co-variate after time-splitting at dates of first and second revisional procedures. The cumulative risk of implant removal was estimated as 1 minus the Kaplan–Meier estimate, and compared among RT groups using the log rank test.

Results

Overall, 1749 implant-based IBRs in 1687 women were included. Median follow-up was 72 (range 1–198) months. Some 856 reconstructions were included in the no RT group (48.9 per cent), 749 in the adjuvant RT group (42.8 per cent), and 144 in the previous RT group (8.2 per cent). The percentage of women receiving adjuvant RT increased over time; it was 30.6 per cent in the years 2005–2007, 39.2 per cent in 2008–2010, 46.7 per cent in 2011–2013, and 54.1 per cent in 2014–2015 ($P < 0.001$). Similarly, the use of neoadjuvant chemotherapy increased, being administered in 7.7, 10.2, 14.4, and 27.2 per cent respectively ($P < 0.001$). The adjuvant RT group differed significantly in several oncological aspects, and featured the most advanced disease characteristics such as nodal status, tumour size, and subtype in the youngest individuals (*Table 1*). A total of 177 patients died from any cause (no RT: 71, 8.3 per cent; adjuvant RT: 85, 11.3 per cent; previous RT: 21, 14.6 per cent), and 120 deaths were related to breast cancer (no RT: 36, 4.2 per cent; adjuvant RT: 71, 9.5 per cent; previous RT: 13, 9.0 per cent).

Risk factors for implant removal and outcome of reconstruction are shown by RT group in *Table 2*. Patients receiving adjuvant RT had the lowest proportion of nipple-sparing mastectomies and the highest specimen weight. In according with local practice at the time, permanent implants were least common in the adjuvant RT group. The proportion of patients not undergoing any revisional surgery was highest in the no RT group. The majority of implants were placed with full muscular coverage, and the use of acellular dermal or synthetic matrix was relatively rare. However, the latter increased over time, being 0 per cent in the years 2005–2007, 0.2 per cent in 2008–2010, 3.6 per cent in 2011–2013, and 14.2 per cent in 2014–2015 ($P < 0.001$). In addition to the reported nipple-sparing mastectomies, the nipple had to be removed in 35 breasts with positive retroareolar biopsies. None of these suffered an implant failure.

Implant removal occurred after 266 reconstructions (15.2 per cent) overall: 68 (7.9 per cent) in the no RT group, 158 (21.1 per cent) in the adjuvant RT group, and 40 (27.8 per cent) in the previous RT group. Median time to implant removal was 12 (range 0–158), 25 (0–154), and 9 (0–149) months respectively ($P < 0.001$). The primary reason for implant removal was a postoperative complication in 152 breasts (57.1 per cent). Median time to implant removal for this reason was 7.3 (0.2–158.0) months in the no RT group, 14.2 (0.5–111.1) months in the adjuvant RT group, and 2.7 (range 0.5–149.7) months in the previous RT group. Patient preference was the indication for removal in 114 instances (42.9 per cent), with a median time to implant removal of 51.5 (12.4–148.1) months in the no RT group, 58.5 (10.3–188.8) months in the adjuvant RT group, and 34.9 (7.9–188.8) months in the previous RT group. In a minority of women undergoing implant removal because of postoperative complications, conversion to autologous reconstruction was performed (no RT: 8 of 47, 17.0 per cent; adjuvant RT: 36 of 82, 44 per cent; previous RT: 5 of 23, 21.7 per cent; $P < 0.001$). Among those whose preference it was to have the implant removed, conversion to an autologous reconstruction was significantly more common (no RT: 15 of 21, 71.4 per cent; adjuvant RT: 63 of 76, 83 per cent; previous RT: 14 of 17, 82.4 per cent; $P < 0.001$).

The cumulative risk of implant removal was significantly higher in both irradiated groups, irrespective of the reason for removal (*Table 3*). Implant removal because of postoperative complications was most common in the first 3 years after implant-based IBR, and especially so in the previous RT group, where 15 of 23 implant removals occurred during the first 6 months. Implant removal owing to patient preference became increasingly more common with longer follow-up (*Fig. 1*). Comparing 5- and 10-year risks of implant removal, the relative increase between time points was more pronounced in women choosing to undergoing implant removal (increase by a factor of 2.4–2.5) than in those having implant removal because of postoperative complications (increase by a factor of 1.2–1.5) (*Table 3*). The relative increase in cumulative risk of implant removal from 5 to 10 years was similar in the three RT groups.

Adjuvant and previous RT was associated with implant removal (adjuvant RT: HR 2.79, 95 per cent c.i. 2.10 to 3.71; previous RT: HR 3.89, 2.63 to 5.76), and also after adjustment for other risk factors (adjuvant RT: HR 2.44, 1.70 to 3.52; previous RT: HR 4.08, 2.53 to 6.58) (*Table 4*). Further independent risk factors were the use of foreign material (acellular dermal or synthetic matrix), two or more ipsilateral revisional procedures, smoking, preobesity, and obesity. The same independent risk factors were confirmed in analyses considering only implant removal because of postoperative complications, with the addition of age 65 years or more as a risk factor (*versus* age below 40 years: adjusted HR 2.51, 1.07 to 5.88; $P = 0.035$). RT remained significantly associated with implant removal owing to patient preference (adjuvant RT: adjusted HR 3.39, 1.82 to 6.33, $P < 0.001$; previous RT: adjusted HR 5.80, 2.64 to 12.77, $P < 0.001$) as did diabetes (adjusted HR 4.85, 1.07 to 22.04; $P = 0.041$) and preobesity (adjusted HR 1.68, 1.00 to 2.80; $P = 0.048$). There were no independent associations with overall implant failure when calendar interval was integrated into the model with censoring of all cases at 5 years of follow-up. For implant failure owing to complications, however, there was a time trend towards increased risk (2008–2010: adjusted HR 1.41, 0.67 to 2.99, $P = 0.369$; 2011–2013: adjusted HR 1.92, 0.92 to 4.03, $P = 0.084$; 2014–2015: adjusted HR 2.44, 1.10 to 5.40, $P = 0.028$) compared with 2005–2007. No such effect was noted for implant removal requested by the patient.

Postoperative infection occurred within 90 days after 365 of 1744 reconstructions (20.9 per cent; 5 missing cases). Previous RT was associated with a higher risk of infection in univariable analysis (OR 1.79, 95 per cent c.i. 1.23 to 2.61; $P = 0.002$), but not after adjusting for all variables in *Table 2*

Table 1 Patient, treatment, and tumour characteristics

	No RT (*n* = 856)	Adjuvant RT (*n* = 749)	Previous RT (*n* = 144)	P¶
Follow-up (months), median (range)	71 (1–198)	72 (1–190)	77.5 (3–188)	0.480#
Calendar interval				<0.001
2005–2007	220 (25.7)	113 (15.1)	36 (25.0)	
2008–2010	259 (30.3)	194 (25.9)	42 (29.2)	
2011–2013	224 (26.2)	233 (31.1)	42 (29.2)	
2014–2015	153 (17.9)	209 (27.9)	24 (16.7)	
Age (years), median (range)	50 (21–79)	47 (21–78)	55 (28–74)	<0.001#
< 40	102 (11.9)	149 (19.9)	4 (2.8)	<0.001
40–49	305 (35.6)	336 (44.9)	46 (31.9)	
50–64	369 (43.1)	221 (29.5)	77 (53.5)	
65+	80 (9.3)	43 (5.7)	17 (11.8)	
Invasiveness				<0.001
In situ only	269 (31.4)	70 (9.3)	43 (29.9)	
Invasive	587 (68.6)	679 (90.7)	101 (70.1)	
Focality*				<0.001
Unifocal	429 (73.1)	316 (46.5)	78 (77.2)	
Multifocal	153 (26.1)	353 (52.0)	21 (20.8)	
Missing	5 (0.9)	10 (1.5)	2 (2.0)	
Histology*†				0.028
Ductal	458 (78.0)	523 (77.0)	87 (86.1)	
Lobular	81 (13.8)	105 (15.5)	10 (9.9)	
Mixed	18 (3.1)	36 (5.3)	1 (1.0)	
Other	30 (5.1)	15 (2.2)	3 (3.0)	
Tumour category*†				<0.001
T1	391 (66.6)	262 (38.6)	83 (82.2)	
T2	188 (32.0)	297 (43.7)	16 (15.8)	
T3	5 (0.9)	115 (16.9)	1 (1.0)	
Missing	3 (0.5)	5 (0.7)	1 (1.0)	
Tumour size (mm), median (range)*‡	15 (0.5–81)	21 (1–130)	12 (1–80)	<0.001#
Clinical nodal status				<0.001
cN0	832 (97.2)	578 (77.2)	140 (97.2)	
cN1	15 (1.8)	154 (20.6)	1 (0.7)	
Missing	9 (1.1)	17 (2.3)	3 (2.1)	
Pathological nodal status‡§				<0.001
pN0	681(88.8)	282 (49.8)	61 (83.6)	
pN1	81 (10.6)	205 (36.2)	9 (12.3)	
pN2	0 (0)	62 (11.0)	1 (1.4)	
pN3	4 (0.5)	15 (2.7)	0 (0)	
Missing	1 (0.1)	2 (0.4)	2 (2.7)	
Axillary surgery				<0.001
Sentinel node biopsy only	648 (75.7)	255 (34.0)	55 (38.2)	
Axillary lymph node dissection	142 (16.6)	489 (65.3)	22 (15.3)	
None	66 (7.7)	5 (0.7)	67 (46.5)	
Grade*†				<0.001
1	94 (16.0)	52 (7.7)	21 (20.8)	
2	299 (50.9)	319 (47.0)	40 (39.6)	
3	182 (31.0)	277 (40.8)	38 (37.6)	
Missing	12 (2.0)	31 (4.6)	2 (2.0)	
Tumour subtype*†				0.002
HR+ HER2–	404 (68.8)	431 (63.5)	69 (68.3)	
HR+ HER2+	59 (10.1)	98 (14.4)	6 (5.9)	
HR– HER2–	49 (8.3)	63 (9.3)	18 (17.8)	
HR–HER2+	47 (8.0)	69 (10.2)	5 (5.0)	
Missing	28 (4.8)	18 (2.7)	3 (3.0)	
Ki-67 (%), mean(s.d.)*†	24.7 (20.5)	31.1 (22.6)	27.6 (24.3)	0.489#
Neoadjuvant chemotherapy*				<0.001
Yes	21 (3.6)	175 (25.8)	4 (4.0)	<0.001
No	566 (96.4)	504 (74.2)	97 (96.0)	
Chemotherapy at any time*				<0.001
Yes	283 (48.2)	562 (82.8)	50 (49.5)	
No	300 (51.1)	110 (16.2)	47 (46.5)	
Missing	4 (0.7)	7 (1.0)	4 (4.0)	
Endocrine treatment*				0.096
Yes	472 (80.4)	548 (8.4)	73 (72.3)	
No	109 (18.6)	128 (18.9)	28 (27.7)	
Missing	6 (1.0)	3 (0.4)	0 (0)	
Anti-HER2 therapy*				<0.001
Yes	81 (13.8)	143 (21.1)	10 (9.9)	
No	455 (77.5)	493 (72.6)	84 (83.2)	
Missing	51 (8.7)	43 (6.3)	7 (6.9)	

Values are *n* (%) unless otherwise indicated. Percentages may not always add up to 100 per cent owing to rounding. *Invasive disease only. †Calculated based on surgical specimen in patients who had primary surgery, and on pretreatment core needle biopsy for those who had neoadjuvant therapy. ‡Primary surgery only. §Cases without any axillary staging excluded. RT, radiotherapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2. ¶χ^2 test or Fisher's exact test, except #Kruskal–Wallis test.

Table 2 Surgical details, number of revisions, and risk factors by radiotherapy group

	No RT (*n* = 856)	Adjuvant RT (*n* = 749)	Previous RT (*n* = 144)	P*
Type of implant				<0.001
Permanent	213 (24.9)	130 (17.4)	53 (36.8)	
Permanent expander	395 (46.1)	383 (51.1)	47 (32.6)	
Temporary expander	234 (27.3)	228 (30.4)	40 (27.8)	
Missing	14 (1.6)	8 (1.1)	4 (2.8)	
Nipple-sparing mastectomy				0.019
Yes	124 (14.5)	83 (11.1)	27 (18.8)	
No	732 (85.5)	666 (88.9)	117 (81.2)	
Acellular dermal or synthetic matrix				0.099
Yes	35 (4.1)	28 (3.7)	11 (7.6)	
No	821 (95.9)	721 (96.3)	133 (92.4)	
Implant position				0.003
Complete muscle coverage	811 (94.7)	709 (94.7)	129 (89.6)	
Partly submuscular (including dermal sling)	45 (5.3)	40 (5.3)	14 (9.7)	
Prepectoral	0 (0)	0 (0.0)	1 (0.7)	
Revisional surgery				0.003
0	320 (37.4)	200 (26.7)	49 (34.0)	
1	443 (51.8)	431 (57.5)	81 (56.3)	
≥ 2	93 (10.8)	118 (15.8)	14 (9.7)	
Mastectomy specimen weight (g), median (range)	337 (66–1508)	363 (67–2232)	280 (75–1048)	<0.001†
< 300	320 (37.4)	230 (30.7)	70 (48.6)	<0.001
300–499	253 (29.6)	276 (36.8)	32 (22.2)	
> 500	163 (19.0)	180 (24.0)	19 (13.2)	
Missing	120 (14.0)	63 (8.4)	23 (16.0)	
Implant volume (cc), median (range)	332.5 (100–660)	350 (100–685)	300 (100–565)	<0.001†
Smoking				0.058
Non-smoker	627 (73.2)	596 (79.6)	109 (75.7)	
Active smoker	83 (9.7)	60 (8.0)	10 (6.9)	
Previous smoker	101 (11.8)	67 (8.9)	9 (6.3)	
Missing	45 (5.3)	26 (3.5)	16 (11.1)	
Diabetes				0.683
No	828 (96.7)	732 (97.7)	1 (0.7)	
Yes	9 (1.1)	5 (0.7)	140 (97.2)	
Missing	19 (2.2)	12 (1.6)	3 (2.1)	
Antihypertensive medication				0.007
No	759 (88.7)	695 (92.8)	5 (3.5)	
Yes	77 (9.0)	42 (5.6)	136 (94.4)	
Missing	20 (2.3)	12 (1.6)	3 (2.1)	
Immunosuppressive medication				0.736
No	823 (96.1)	719 (96.0)	2 (1.4)	
Yes	12 (1.4)	14 (1.9)	139 (96.5)	
Missing	21 (2.5)	16 (2.1)	3 (2.1)	
BMI (kg/m^2), median (range)	23 (16–38)	23 (17–45)	23 (17–40)	0.518†
< 18.5	17 (2.0)	12 (1.6)	5 (3.5)	0.431
18.5–24.9	506 (59.1)	440 (58.7)	80 (55.6)	
25.0–29.9	209 (24.4)	205 (27.4)	43 (29.9)	
≥ 30.0	45 (5.3)	46 (6.1)	5 (3.5)	
Missing	79 (9.2)	46 (6.1)	11 (7.6)	

Values are *n* (%) unless otherwise indicated. RT, radiotherapy. *χ^2 test or Fisher's exact test, except †Kruskal–Wallis test.

Table 3 Cumulative risk of implant removal at 5 and 10 years, overall and by reason for removal

	Implant removal overall (%)		Removal owing to postoperative complications (%)		Removal owing to patient preference (%)	
	5 years	10 years	5 years	10 years	5 years	10 yeary
No RT	7.0	10.2 (1.5)	5.4	6.3 (1.2)	1.7	4.1 (2.4)
Adjuvant RT	16.3	27.7 (1.7)	10.4	13.5 (1.3)	6.6	16.5 (2.5)
Previous RT	18.5	33.0 (1.8)	12.0	17.6 (1.5)	7.4	18.7 (2.5)

Values in parentheses are the relative increase in cumulative risk from 5 to 10 years (risk ratio for 10 *versus* 5 years). RT, radiotherapy.

plus age, RT, primary treatment, and axillary surgery (OR 1.47, 0.87 to 2.50; $P = 0.154$). Independent risk factors were nipple-sparing mastectomy (OR 1.62, 1.13 to 2.34; $P = 0.009$), a high specimen weight (300–499 *versus* less than 300 g: OR 1.68, 1.17 to 2.41, $P = 0.005$; 500 or more *versus* less than 300 g: OR 2.24, 1.46 to 3.45, $P < 0.001$), smoking (OR 2.00, 1.31 to 3.00; $P = 0.001$), and the use of permanent implants as opposed to permanent expander devices (OR 1.60, 1.10 to 2.34; $P = 0.015$).

Reoperation within 30 days was necessary after 83 reconstructions (4.7 per cent). The primary reason was bleeding (33, 40 per cent), infection (30, 36 per cent), wound necrosis (8, 10 per cent), unspecified (7, 8 per cent), wound dehiscence (4, 5 per cent), and seroma (1, 1 per cent). Previous RT was not associated with an increased risk of reoperation. In multivariable logistic regression analysis including the same variables as above, only older age was identified as an independent risk factor for reoperation (50–64 *versus* less than 40 years: OR 4.59, 1.56 to 13.52, $P = 0.006$; 65 or more *versus* less than 40 years: OR 4.55, 1.28 to 16.17, $P = 0.019$).

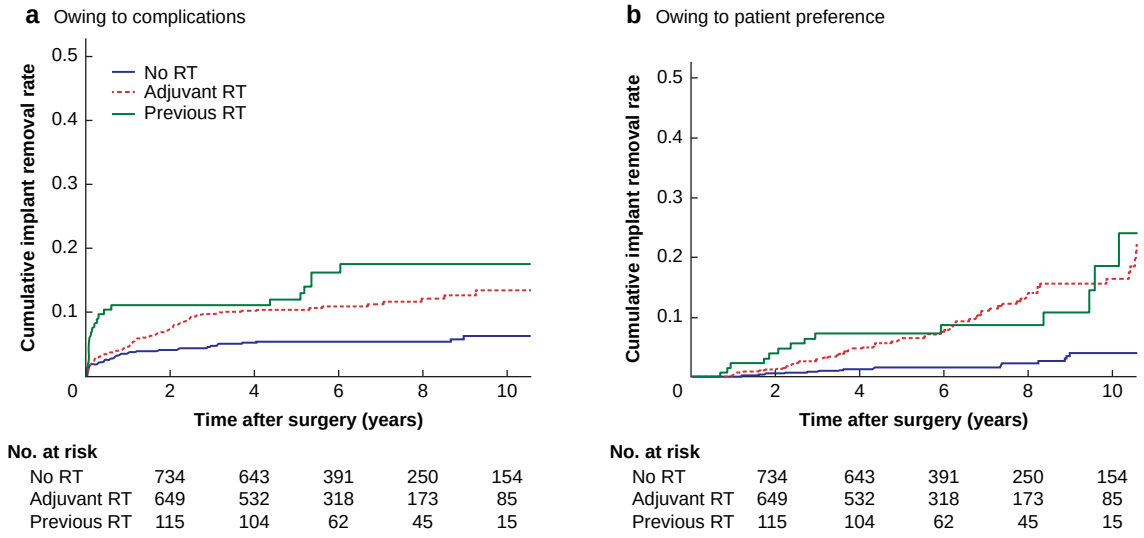

Fig. 1 Cumulative implant removal rates over time by radiotherapy group

Implant removal owing to **a** postoperative complications and **b** patient preference. RT, radiotherapy.

Discussion

In this large, population-based cohort of women with breast cancer undergoing implant-based IBR, RT was confirmed as a significant risk factor for implant removal, also after extended follow-up. Importantly, temporal outcome patterns for implant removal owing to postoperative complications or patient preference were significantly different, as were rates of conversion to autologous reconstruction. It is therefore relevant to differentiate outcomes based on the reason for implant removal. In many publications, however, all instances of implant removal are merged into the term reconstructive failure.

In discussing implant removal or failure of reconstruction, it is important to consider the intention of the first reconstructive step. In the delayed-immediate concept, immediate IBR using a tissue expander (stage 1) is planned with a subsequent exchange to autologous tissue after PMRT or exchange to a permanent implant if no PMRT is given (stage 2)[13]. In this situation, planned implant removal including conversion to an autologous reconstruction should not be regarded as a reconstructive failure. In the Stockholm region, the concept of 'optional delayed-immediate' has been practised since the 1990s. This concept is similar to that described above, but with stage 2 based on the postoperative aesthetic and patient-experienced outcomes, and not preplanned.

The most common long-term consequence of RT after implant-based IBR is capsular contracture. As measurement of capsular contracture according to Spear and Baker[14] is highly subjective, and more objective measures such as applanation tonometry are rarely applied, the present analysis focused on the most severe consequence of capsular contracture, namely implant removal. Another measure of capsular contracture is patient-reported discomfort, decreased aesthetics, and pain, which were not included in the present work. Patient-reported outcomes have been reported previously from a subset of the present cohort and showed that RT is a major factor for reducing patient satisfaction, although a large proportion of women would choose the same reconstruction again and recommend it to others in a similar situation[10]. In addition, patient-reported outcomes were stable over time in a longitudinal analysis, even among women who had received RT[15]. One relatively modern attempt to mitigate capsular contracture is to use acellular dermal matrix or synthetic meshes. In the present analysis, however, this led to a significantly higher risk of implant failure owing to complications, a finding reported in some prospective trials[16] but not in others[17]. The observed effect may be part of a learning curve as the number of procedures in the relevant years was small, but caution is necessary when using auxiliary material such as acellular dermal matrix or synthetic meshes. In recent years, there has been an additional shift towards prepectoral implant placement in combination with acellular dermal matrix or synthetic meshes. Thus, postoperative complication and implant failure rates from prospective trials, such as the OPBC02-PREPEC trial[18], are urgently awaited. As confirmed in the present analysis, a major problem with implant-based IBR in the context of RT is that long-term effects such as capsular contracture will continue to generate the need for revisional surgery and/or conversion to autologous reconstruction even after many years. Revisional surgery poses a significant risk of implant loss owing to postoperative complications and so the risk of reconstructive failure is never eliminated[12]. Autologous reconstruction, on the other hand, tends to come with a higher risk of postoperative complications but far fewer negative long-term consequences and less need for revisional surgery[19,20].

A major strength of this work is the population-based setting, including all patients with breast cancer undergoing implant-based IBR in the Stockholm region during the study interval. This is one of the largest and most homogeneous cohorts evaluated so far. Long-term follow-up was achieved by individual scrutiny of medical records, and resulted in high-quality data ascertainment. Any retrospective data collection is prone to selection bias and cohorts may differ in ways that cannot be adjusted for in analysis. In this study, however, selection bias was mitigated by covering an entire region over an 11-year time frame, thus creating a population-based sample. Furthermore, if data from medical records were missing, the information was completed by addition of prospectively collected register data linked to the

Table 4 Factors associated with implant removal owing to complication or patient preference with or without autologous re-reconstruction

	Univariable analysis			Multivariable analysis§		
	No. of reconstructions*	HR†	P	No. of reconstructions*	HR†	P
RT						
No RT	856 (68)	1.00 (reference)		636 (56)	1.00 (reference)	
Adjuvant RT	749 (158)	2.79 (2.10, 3.71)	<0.001	631 (132)	2.44 (1.70, 3.52)	<0.001
Previous RT	144 (40)	3.89 (2.63, 5.76)	<0.001	100 (29)	4.08 (2.53, 6.58)	<0.001
Acellular dermal or synthetic matrix						
No	1675 (248)	1.00 (reference)		1304 (201)	1.00 (reference)	
Yes	74 (18)	2.15 (1.33, 3.48)	0.002	63 (16)	2.43 (1.39, 4.25)	0.002
Hospital						
1	768 (131)	1.00 (reference)		652 (113)	1.00 (reference)	
2	369 (45)	0.66 (0.47, 0.92)	0.015	272 (33)	0.66 (0.42, 1.02)	0.060
3	399 (58)	0.85 (0.63, 1.16)	0.317	288 (44)	0.82 (0.55, 1.23)	0.341
4	213 (32)	0.80 (0.54, 1.18)	0.258	155 (27)	0.98 (0.59, 1.60)	0.921
Axillary lymph node dissection						
No	1096 (136)	1.00 (reference)		840 (110)	1.00 (reference)	
Yes	653 (130)	1.59 (1.25, 2.02)	<0.001	527 (107)	1.08 (0.77, 1.52)	0.643
Nipple-sparing mastectomy						
No	1515 (237)	1.00 (reference)		1174 (192)	1.00 (reference)	
Yes	234 (29)	0.88 (0.60, 1.30)	0.527	193 (25)	1.04 (0.65, 1.67)	0.863
Mastectomy specimen weight (g)						
< 300	620 (65)	1.00 (reference)		549 (60)	1.00 (reference)	
300–499	561 (91)	1.58 (1.15, 2.18)	0.005	492 (86)	1.42 (0.98, 2.06)	0.065
500+	362 (77)	2.11 (1.52, 2.94)	<0.001	326 (71)	1.49 (0.97, 2.29)	0.072
Type of breast implant						
Permanent expander	825 (137)	1.00 (reference)		636 (106)	1.00 (reference)	
Permanent implant	396 (48)	0.70 (0.51, 0.98)	0.036	323 (42)	0.87 (0.57, 1.34)	0.527
Temporary expander	502 (79)	0.95 (0.72, 1.26)	0.736	408 (69)	0.85 (0.58, 1.23)	0.382
Ipsilateral revisional surgery‡						
0	1749 (146)	1.00 (reference)		1367 (118)	1.00 (reference)	
1	1125 (88)	1.13 (0.82, 1.57)	0.463	893 (73)	1.16 (0.79, 1.70)	0.444
≥ 2	196 (32)	2.83 (1.81, 4.43)	<0.001	156 (26)	3.03 (1.81, 5.09)	<0.001
Neoadjuvant chemotherapy						
No	1546 (225)	1.00 (reference)		1182 (179)	1.00 (reference)	
Yes	203 (41)	1.52 (1.09, 2.13)	0.013	185 (38)	1.12 (0.75, 1.69)	0.573
Endocrine therapy						
No	545 (68)	1.00 (reference)		404 (53)	1.00 (reference)	
Yes	1193 (197)	1.32 (1.00, 1.74)	0.049	963 (164)	1.03 (0.75, 1.42)	0.842
Smoking						
Non-smoker	1332 (193)	1.00 (reference)		1095 (160)	1.00 (reference)	
Active smoker	153 (36)	1.63 (1.14, 2.33)	0.007	125 (31)	1.85 (1.24, 2.75)	0.002
Previous smoker	177 (29)	1.14 (0.77, 1.68)	0.524	147 (26)	1.22 (0.79, 1.87)	0.367
Diabetes						
No	1700 (257)	1.00 (reference)		1356 (214)	1.00 (reference)	
Yes	15 (3)	1.24 (0.40, 3.88)	0.710	11 (3)	1.88 (0.58, 6.15)	0.296
Antihypertensive medication						
No	1590 (233)	1.00 (reference)		1281 (195)	1.00 (reference)	
Yes	124 (27)	1.54 (1.03, 2.29)	0.034	86 (22)	1.38 (0.86, 2.23)	0.184
Immunosuppressive medication						
No	1681 (250)	1.00 (reference)		1347 (212)	1.00 (reference)	
Yes	28 (9)	2.34 (1.20, 4.56)	0.012	20 (5)	1.84 (0.74, 4.60)	0.189
BMI (kg/m^2)						
< 18.5	34 (5)	1.36 (0.56, 3.32)	0.503	29 (3)	0.95 (0.29, 3.07)	0.926
18.5–24.9	1026 (126)	1.00 (reference)		873 (112)	1.00 (reference)	
25.0–29.9	457 (95)	1.78 (1.36, 2.32)	<0.001	385 (81)	1.38 (1.00, 1.89)	0.050
≥ 30.0	96 (25)	2.22 (1.45, 3.42)	<0.001	80 (21)	1.90 (1.13, 3.20)	0.016
Age (years)						
< 40	255 (34)	1.00 (reference)		218 (29)	1.00 (reference)	
40–49	687 (95)	1.07 (0.72, 1.58)	0.747	557 (82)	1.12 (0.73, 1.73)	0.606
50–64	667 (114)	1.35 (0.92, 1.99)	0.121	490 (89)	1.31 (0.83, 2.07)	0.245
≥ 65	140 (23)	1.39 (0.82, 2.36)	0.223	102 (17)	1.52 (0.80, 2.87)	0.200

Values in parentheses are *number of implant removals and †95 per cent confidence intervals. ‡Time-varying co-variate; due to time-splitting, the same patient may occur in more than one category if exposed to one, two or more revisional procedures. Events are only counted once, that is in the category in which they occur. RT; radiotherapy. §Multivariable Cox regression model adjusted for all variables in table.

cohort. Data on BMI, smoking, mastectomy specimen weight, and duration of operation were limited because they could not be extracted from registers, and were often not documented in medical records during the earlier parts of the study, which may have reduced the statistical power of the adjusted models. A further limitation is that this work did not include patient-reported outcomes, which are an important part of the assessment of outcomes of reconstruction. Two previous publications[10,15] on patient-reported outcomes from a subpopulation of the present cohort have contributed to understanding the priorities and significance of reconstructive outcome from the patient perspective. Importantly, it is a challenge to differentiate between postoperative complications and patient preference as reasons for implant removal. In this study, these two main entities were strictly defined. Thus, if capsular contracture led to the planned removal of an implant, patient preference was deemed the reason for implant removal; if, on the other hand, it led to revisional surgery resulting in surgical complications, such as wound breakdown, infection or bleeding, postoperative complication was considered to be the reason. Thereby, the distinction between forced and scheduled implant removal was made.

This study has shown that RT is a significant risk factor for implant removal after implant-based IBR, and that the reasons for, and consequences of, implant removal shift over time.

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Disclosure

The authors declare no conflict of interest.

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