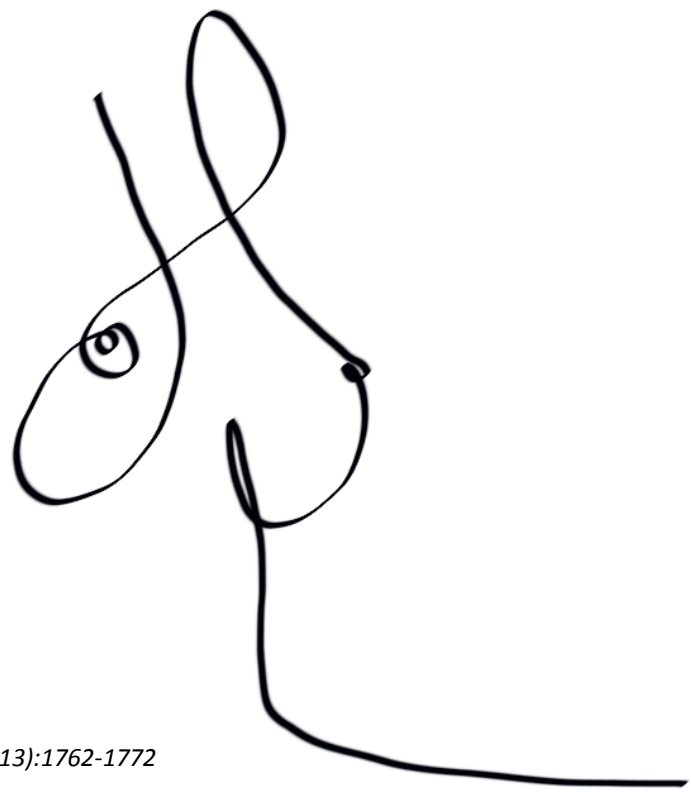
A comprehensive approach for quality assessment of breast cancer care

Heeg, E.

Chapter 8

Rates of re-excision and conversion to mastectomy after breast-conserving surgery with or without oncoplastic surgery: a nationwide population-based study



Erik Heeg
Maj-Britt Jensen
Lisbet R. Hølmich
Anne Bodilsen
Rob A.E.M. Tollenaar
Anne V. Laenkholm
Birgitte V. Offersen
Bent Ejlertsen
Marc A.M. Mureau
Peer M. Christiansen

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Abstract

Background

There is no consensus regarding the impact of oncoplastic surgery (OPS) on rates of re-excision and conversion to mastectomy following breast-conserving surgery (BCS). Here these two outcomes after BCS and OPS were compared in a nationwide population-based setting.

Methods

In Denmark, all OPS is registered and categorized into volume displacement, volume reduction or volume replacement. Patients who underwent BCS or OPS between 2012 and 2018 were selected from the Danish Breast Cancer Group database. Multivariable analyses were performed to adjust for confounders, and propensity score matching to limit potential confounding by indication bias.

Results

A total of 13,185 patients (72.5%) underwent BCS and 5,003 (27.5%) OPS. Volume displacement was used in 4,171 patients (83.4%), volume reduction in 679 (13.6%) and volume replacement in 153 (3.1%). Re-excision rates were 15.6 and 14.1% after BCS and OPS respectively. After adjusting for confounders, patients were less likely to have a re-excision following OPS than BCS (odds ratio (OR) 0.80, 95%-CI 0.72-0.88), specifically after volume displacement and reduction. The rate of conversion to mastectomy was similar after OPS and BCS (3.2 versus 3.7%; p=0·105), but with a lower risk in adjusted analysis (OR 0.69, 0.58 to.0·84), specifically after volume displacement and reduction procedures. Findings were similar after propensity score matching.

Conclusion

A modest decrease in re-excision rate and less frequent conversion to mastectomy were observed after OPS compared with BCS.

Introduction

Randomized trials[1-5] conducted in the 1980s established breast-conserving surgery (BCS) followed by radiotherapy as the preferred treatment for early-stage breast cancer. Improved breast cancer survival rates[6,7] have led to an increased focus on cosmetic outcomes after treatment.[8] Consequently, a challenging balance has emerged between achieving complete resection of the tumor with appropriate tumor-free margins and a favorable cosmetic result. Not every patient is eligible for BCS owing to anatomical and tumor characteristics.[9]

Oncoplastic surgery (OPS) improves cosmetic outcomes and is nowadays used in up to 34% of patients with breast cancer undergoing BCS.[10-14] Previous studies[15,16] have demonstrated that by using OPS breast conservation becomes an alternative to mastectomy in patients with large and multifocal tumors. Compared with BCS, OPS is associated with larger resections,[17,18] and good long-term survival outcomes[11,13,18,19] and quality of life.[20-22] Achieving larger tumor resections with OPS may also reduce the number of re-excisions owing to insufficient margins. High-quality evidence regarding the impact of OPS on re-excisions is, however, sparse.[18,19]

Between 2000 and 2009, re-excision after BCS occurred in about 17% of patients with breast cancer in Denmark,[23] which is within the reported range of 5-35%.[22,24-26] Re-excision requiring mastectomy is commonly defined as conversion to mastectomy. Re-excision and conversion to mastectomy are associated with more morbidity, complications, poorer aesthetic outcome, greater patient distress and increased healthcare costs.[27,28] Furthermore, for patients in whom free margins were not achieved during primary BCS, an increased risk of ipsilateral breast tumor recurrence has been reported.[23]

In Denmark, OPS techniques have been registered prospectively by the Danish Breast Cancer Group (DBCG) for all patients undergoing BCS since July 2010. The primary goal of the present study was to compare re-excision rates after BCS versus OPS in patients with early-stage breast cancer, in a population-based national setting. A further aim was to investigate whether OPS results in a lower conversion to mastectomy rate (CMR) than BCS. As several studies[11-13,29] have shown that patients may not have the same likelihood of receiving OPS based on their baseline characteristics, additional propensity score matching was used to limit the potential confounding by indication bias.

Methods

Since 1978, the DBCG has collected clinicopathological and treatment characteristics and follow-up data prospectively from all patients diagnosed with a primary invasive breast cancer.[30] OPS is categorized into three types: volume displacement, defined as local rearrangement of tissue near the lumpectomy cavity in order to close the defect; volume reduction, defined as the use of a breast reduction technique to remove tumor and improve breast shape at the same time; and volume replacement, defined as tissue transfer from outside the breast into the breast (such as local perforator flaps). A more detailed description of data collection by the DBCG has been published.[30,31] The study was approved by the Scientific Committee of Surgery within the DBCG and the Danish Clinical Registries.

Study population

All women with invasive breast cancer without distant metastasis, who underwent primary BCS between January 2012 and December 2018, identified from the DBCG database were included. Patients who received neoadjuvant therapy or surgical biopsy as the only surgical procedure were excluded. Patients were categorized into four groups: BCS (without OPS), OPS with volume displacement, OPS with volume reduction, and OPS with volume replacement.

Outcomes

The primary outcome was re-excision, defined as a second BCS procedure or mastectomy following the primary BCS within 2 months of the initial operation. This interval was chosen to limit potential re-excisions owing to breast cancer recurrence. Information about re-excision, including type, was retrieved from Danish National Patient Registry.[32] Re-excision rates among patients aged over 50 years might be influenced by use of boost radiation for treatment of insufficient margins, so secondary interventions (re-excision or boost radiation) were compared in patients aged 50 years or older undergoing BCS or OPS. The secondary outcome, CMR, was defined as the rate of mastectomy following the primary BCS within 2 months of the initial operation.

Confounders

Co-morbidity was classified according to the Charlson Co-morbidity Index (CCI).[33] Histological subtypes, such as papillary, medullary and mucinous subtypes, were categorized as ‘other’. In Denmark, grading is applied to invasive ductal and lobular

carcinomas, but not to subtypes classified as 'other', according to the modified version of the Bloom Richardson scoring system of Elston and Ellis.[34] Breast cancer was classified as estrogen receptor-positive when at least 10% of cells stained positive in immunohistochemical analyses. Expression of human epidermal growth factor receptor 2 (HER2) was determined according to standard recommendations.[35] Tumor size and lymph node status were categorized according to the seventh edition of the AJCC cancer staging classification.[36] Any missing characteristics were classified as unknown.

Guidelines

In accordance with Danish guidelines,[30,31] re-excision was advised if invasive carcinoma was identified at the inked margins or ductal carcinoma in situ (DCIS) within 2 mm from the margin. Danish guidelines also recommend boost radiation in all patients younger than 50 years after BCS with or without OPS; and in those with a microscopic free margin of less than 2 mm for invasive breast cancer or DCIS, irrespective of age.[37,38]

Statistical analysis

Patient and tumor characteristics were compared between BCS and OPS groups using $\chi 2$ test for categorical variables, and Mann–Whitney U test or Kruskal–Wallis test for continuous variables. Unknown characteristics were included in the descriptive statistics. Two-sided $P < 0{\cdot}050$ was considered statistically significant. To adjust for confounders, a multivariable logistic regression model was used to estimate whether patients who underwent OPS were more likely to have a re-excision than those who had BCS. Results were expressed as odds ratios (ORs) with 95% confidence intervals, and the Wald test was used for analysis of statistical significance. The latter analyses were repeated for the secondary outcome CMR. Patients with unknown variables were included as a separate category in all analyses.

To evaluate whether associations were subject to confounding by indication, meaning that not all patients were equally likely to have received OPS, analyses were repeated in propensity score-matched cohorts. Patients who underwent BCS were matched with those who had OPS as a whole and by each type of OPS. Patients were matched on the likelihood of undergoing OPS using the following co-variables: year of operation, age, CCI score, histological finding, differentiation grade, estrogen receptor positivity, HER2 status, T and N status.[39,40] Patients who underwent BCS were matched 1:1 with those who had OPS using a caliper width of 0.2 times the standard deviation of the logit of the propensity score.[41] Potential imbalances in characteristics before and after matching were shown using a standardized difference; a value of 10% or more was

indicative of an imbalance in characteristics.[42] All analyses were performed using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

A total of 18,188 patients met the inclusion criteria, of whom 13,185 (72.5%) underwent BCS and 5,003 (27.5%) OPS. Patients who had BCS were older than those who had OPS (mean (s.d.) 62.1 (11.5) versus 59.9 (11.5) years; p<0.001) (Table 8.1). Patients who underwent OPS had a lower co-morbidity score than those who had BCS (p<0.001), but poorer prognostic tumor factors, including higher differentiation grade (p<0.001), larger tumor size (p<0.001) and more lymph node involvement (p<0.001). The use of OPS decreased significantly from 30.3% in 2012 to 26.4% in 2018 (p<0.001).
OPS was performed with volume displacement in 4,171 patients (83.4%), volume reduction in 679 (13.6%) and volume replacement in 153 (3.1%). Patients who underwent OPS with volume reduction or replacement had lower co-morbidity scores (p=0.020), larger tumors (p<0.001) and more lymph node involvement (p<0.001) than those who had volume displacement (Table 8.2). Baseline characteristics of patients who underwent the three types of OPS are provided in Table 8.2.
In total, 2,763 patients (15.2%) underwent re-excision, in whom the final surgical treatment was BCS in 2,108 patients (76.3%) and mastectomy in 655 (23.7%). The re-excision rate was 15.6% for patients who underwent BCS and 14.1% among those who had OPS (p=0.012). Re-excision rates varied according to OPS technique: 14.5% for volume displacement, 10.3% for volume reduction and 20.9% for volume replacement (Table 8.3). The unadjusted re-excision rate did not change significantly over time (p=0.438).
Multivariable analysis showed that patients who underwent OPS were less likely to undergo re-excision than those who had BCS (adjusted OR 0.80, 95%-CI 0.72-0.88). Subsequent analyses showed that patients who underwent OPS with volume displacement (OR 0.83, 95%-CI 0.75-0·92) or volume reduction (OR 0.50, 95%-CI 0.39-0.65) were less likely to undergo re-excision than those who had BCS (Table 8.3). Patients who underwent OPS with volume replacement had the same likelihood of re-excision as the BCS group (OR 1.16, 95%-CI 0.78-1.73).
Other characteristics associated with re-excision were lobular or other histological subtype, higher differentiation grade, unknown estrogen receptor status, positive HER2 status, larger tumor size and lymph node involvement (Table 8.3). Re-excisions were less likely with increasing age. Year of surgery and co-morbidity were not associated with re-excision.

Table 8.1. Baseline characteristics of patients who underwent breast-conserving surgery or oncoplastic surgery.

	All patients (n=18,88)	BCS (n=13,185)	BCS with OPS (n=5,003)	p-value†
Year of operation				<0.001
2012	2,667 (14.7)	1,858 (14.1)	809 (16.2)	
2013	2,733 (15.0)	2,052 (15.6)	681 (13.6)	
2014	2,751 (15.1)	1,933 (14.7)	818 (16.4)	
2015	2,626 (14.4)	1,909 (14.5)	717 (14.3)	
2016	2,533 (13.9)	1,852 (14.0)	681 (13.6)	
2017	2,476 (13.6)	1,813 (13.8)	663 (13.3)	
2018	2,402 (13.2)	1,768 (13.4)	634 (12.7)	
Age (years)*	61.5 (11.5)	62.1 (11.5)	59.9 (11.5)	<0.001‡
Charlson Co-morbidity				<0.001
Index Score				
0	13,987 (76.9)	9,942 (75.4)	4,045 (80.9)	
1	2,500 (13.7)	1,910 (14.5)	590 (11.8)	
2	1,118 (6.1)	868 (6.6)	250 (5.0)	
≥3	583 (3.2)	465 (3.5)	118 (2.4)	
Histological finding				<0.001
ductal	14,777 (81.2)	10,669 (80.9)	4,108 (82.1)	
lobular	1,888 (10.4)	1,339 (10.2)	549 (11.0)	
other	1,505 (8.3)	1,161 (8.8)	344 (6.9)	
unknown	18 (0.1)	16 (0.1)	2 (0.0)	
Differentiation grade				<0.001
I	4,809 (26.4)	3,683 (27.9)	1,126 (22.5)	
II	7,958 (43.8)	5,700 (43.2)	2,258 (45.1)	
III	3,747 (20.6)	2,496 (18.9)	1,251 (25)	
not determined	1,505 (8.3)	1,161 (8.8)	344 (6.9)	
unknown	169 (0.9)	145 (1.1)	24 (0.5)	
Oestrogen receptor (%)				<0.001
<10	2,272 (12.5)	1,562 (11.8)	710 (14.2)	
≥10	15,867 (87.2)	11,583 (87.8)	4,284 (85.6)	
unknown	49 (0.3)	40 (0.3)	9 (0.2)	
HER2 status				<0.001
negative	16,086 (88.4)	11,751 (89.1)	4,335 (86.6)	
positive	1,916 (10.5)	1,281 (9.7)	635 (12.7)	
unknown	186 (1.0)	153 (1.2)	33 (0.7)	
T category				<0.001
T1	14,302 (78.6)	10,854 (82.3)	3,448 (68.9)	
T2	3,790 (20.8)	2,264 (17.2)	1,526 (30.5)	
T3	85 (0.5)	57 (0.4)	28 (0.6)	
Unknown	11 (0.1)	10 (0.1)	1 (0.0)	
N category				<0.001
N0	12,649 (69.5)	9,397 (71.3)	3,252 (65.0)	
N1	4,220 (23.2)	2,818 (21.4)	1,402 (28.0)	
N2	673 (3.7)	436 (3.3)	237 (4.7)	
N3	313 (1.7)	226 (1.7)	87 (1.7)	
Unknown	333 (1.8)	308 (2.3)	25 (0.5)	

Values in parentheses are percentages unless indicated otherwise; *values are mean (s.d.). BCS, breast-conserving surgery; OPS, oncoplastic surgery; HER2, human epidermal growth factor receptor 2. † χ^2 test, except; ‡ Mann–Whitney *U* test.

Table 8.2 Baseline characteristics according to type of oncoplastic surgery.

	Volume displacement (n=4,171)	Volume reduction (n=679)	Volume replacement (n=153)	p-value†
Year of operation				<0.001
2012	658 (15.8)	113 (16.6)	38 (24.8)	
2013	536 (12.9)	119 (17.5)	26 (17.0)	
2014	680 (16.3)	111 (16.3)	27 (17.6)	
2015	609 (14.6)	88 (13.0)	20 (13.1)	
2016	561 (13.5)	97 (14.3)	23 (15.0)	
2017	583 (14.0)	72 (10.6)	8 (5.2)	
2018	544 (13.0)	79 (11.6)	11 (7.2)	
Age (years)*	60.1 (11.5)	58·9 (11.2)	57·4 (10.3)	<0.001‡
Charlson Co-morbidity				0.020
Index score				
0	3,355 (80.4)	557 (82)	133 (86.9)	
1	515 (12.3)	63 (9.3)	12 (7.8)	
2	198 (4.7)	44 (6.5)	8 (5.2)	
≥3	103 (2.5)	15 (2.2)	0 (0)	
Histological finding				0.909
ductal	3,418 (81.9)	563 (82.9)	127 (83.0)	
lobular	456 (10.9)	75 (11.0)	18 (11.8)	
other	295 (7.1)	41 (6.0)	8 (5.2)	
unknown	2 (0)	0 (0)	0 (0)	
Differentiation grade				0.071
I	963 (23.1)	131 (19.3)	32 (20.9)	
II	1,884 (45.2)	299 (44.0)	75 (49.0)	
III	1,010 (24.2)	204 (30.0)	37 (24.2)	
not determined	295 (7.1)	41 (6.0)	8 (5.2)	
unknown	19 (0.5)	4 (0.6)	1 (0.7)	
Oestrogen receptor (%)				0.752
<10	592 (14.2)	95 (14.0)	23 (15.0)	
≥10	3,570 (85.6)	584 (86.0)	130 (85.0)	
unknown	9 (0.2)	0 (0)	0 (0)	
HER2 status				0.721
negative	3,620 (86.8)	581 (85.6)	134 (87.6)	
positive	522 (12.5)	94 (13.8)	19 (12.4)	
unknown	29 (0.7)	4 (0.6)	0 (0)	
T category				<0.001
T1	3000 (71.9)	370 (54.5)	78 (51.0)	
T2	1152 (27.6)	300 (44.2)	74 (48.4)	
T3	18 (0.4)	9 (1.3)	1 (0.7)	
unknown	1 (0)	0 (0)	0 (0)	
N category				0.006
N0	2749 (65.9)	417 (61.4)	86 (56.2)	
N1	1,134 (27.2)	215 (31.7)	53 (34.6)	
N2	190 (4.6)	39 (5.7)	8 (5.2)	
N3	74 (1.8)	7 (1.0)	6 (3.9)	
unknown	24 (0.6)	1 (0.1)	0 (0)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). HER2, human epidermal growth factor receptor 2. † $\chi 2$ test, except; ‡ Kruskal–Wallis test.

A shift from an imbalance in characteristics before propensity score matching to a balance after matching was observed when the BCS group was matched with the OPS group as a whole, and by type of OPS (Tables S8.1–S8.4, supporting information). In the matched cohort with OPS as a whole, re-excision was less likely after OPS than BCS (OR 0.79, 95%-CI 0·71-0·88), similar to the results of multivariable analysis of the unmatched study population. Matched patients who underwent OPS with volume displacement (OR 0.80, 95%-CI 0.71-0.90) or volume reduction (OR 0.46, 95%-CI 0.34-0.63) were less likely to undergo re-excision than the BCS group, whereas patients who underwent OPS with volume replacement had the same likelihood of re-excision as patients who had BCS (OR 1.13, 95%-CI 0.65-1.98).

Further analyses showed similar use of secondary interventions in patients older than 50 years undergoing BCS or OPS (16.4 versus 15.9%; p=0.430). However, among patients who had secondary interventions, boost radiation was used less often in patients who underwent BCS compared with those who had OPS (14.7 versus 21.2%; p<0·001).

In total, conversion to mastectomy was performed in 655 patients (3.6%). The CMR was 3.7 and 3.2% after BCS and OPS respectively (p=0.105). Different CMRs were observed among the OPS techniques: 3.2% for volume displacement, 2.9% for volume reduction and 5.9% for volume replacement. Over time, the unadjusted CMR decreased significantly from 4.3 to 2.7% (p=0.003) (Table S8.5, supporting information).

Table 8.3. Univariable and multivariable logistic regression analyses of characteristics predictive of re-excision.

	Re-excision		Odds ratio† Univariable analysis	Odds ratio† Multivariable analysis	
	No (n=15,425)	Yes (n=2,763)	(n=18,188)	(n=18,188)	p-value‡
Type of surgery					<0.001
BCS	11,128 (84.4)	2,057 (15.6)	1.00 (reference)	1.00 (reference)	
volume displacement	3,567 (85.5)	604 (14.5)	0.92 (0.83-1.01)	0.83 (0.75-0.92)	
volume reduction	609 (89.7)	70 (10.3)	0.62 (0.48-0.80)	0.50 (0.39-0.65)	
volume replacement	121 (79.1)	32 (20.9)	1.43 (0.97-2.12)	1.16 (0.78-1.73)	
Year of operation					0.202
2012	2,295 (86.1)	372 (13.9)	1.00 (reference)	1.00 (reference)	0.202
2013	2,332 (85.3)	401 (14.7)	1.06 (0.91-1.24)	1.07 (0.92-1.25)	
2014	2,330 (84.7)	421 (15.3)	1.12 (0.96-1.30)	1.12 (0.96-1.31)	
2015	2,208 (84.1)	418 (15.9)	1.17 (1.00-1.36)	1.19 (1.02-1.39)	
2016	2,144 (84.6)	389 (15.4)	1.12 (0.96-1.31)	1.13 (0.97-1.33)	
2017	2,083 (84.1)	393 (15.9)	1.16 (1.00-1.36)	1.21 (1.04-1.42)	
2018	2,033 (84.6)	369 (15.4)	1.12 (0.96-1.31)	1.19 (1.01-1.39)	
Age (years)*	61.8 (11.6)	59.9 (11.2)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	<0.001
Charlson Co-morbidity Index score					0.061
0	11 790 (84·3)	2,197 (15.7)	1.00 (reference)	1.00 (reference)	
1	2148 (85·9)	352 (14.1)	0.88 (0.78-0.99)	0.94 (0.83-1.07)	
2	962 (86·0)	156 (14.0)	0.87 (0.73-1.04)	0.96 (0.81-1.15)	
≥3	525 (90·1)	58 (9.9)	0.59 (0.45-0.78)	0.69 (0.52-0.91)	

Table 8.3. (continued)

	Re-excision		Odds ratio† Univariable analysis	Multivariable analysis	
	No (n=15,425)	Yes (n=2,763)	(n=18,188)	(n=18,188)	p-value‡
Histological finding					<0.001
ductal	12,614 (85.4)	2,163 (14.6)	1.00 (reference)	1.00 (reference)	
lobular	1,527 (80.9)	361 (19.1)	1.38 (1.22-1.56)	1.40 (1.23-1.59)	
other	1,269 (84.3)	236 (15.7)	1.09 (0.94-1.26)	1.45 (1.22-1.71)	
unknown	15 (83.3)	3 (16.7)	1.17 (0.34-4.03)	0.18 (0.04-0.78)	
Differentiation grade					<0.001
I	4,246 (88.3)	563 (11.7)	1.00 (reference)	1.00 (reference)	
II	6,658 (83.7)	1,300 (16.3)	1.35 (1.23-1.48)	1.32 (1.19-1.47)	
III	3,141 (83.8)	606 (16.2)	1.33 (1.19-1.49)	1.18 (1.03-1.36)	
not determined	1,269 (84.3)	236 (15.7)	-	-	
unknown	111 (65.7)	58 (34.3)	3.61 (2.60-5.00)	3.69 (2.57-5.3)	
Oestrogen receptor (%)					0.005
<10	1,902 (83.7)	370 (16.3)	1.10 (0.98-1.24)	0.97 (0.85-1.12)	
≥10	13,490 (85.0)	2,377 (15.0)	1.00 (reference)	1.00 (reference)	
unknown	33 (67.3)	16 (32.7)	2.75 (1.51-5.01)	3.69 (1.66-8.21)	
HER2 status					<0.001
negative	13,775 (85.6)	2,311 (14.4)	1.00 (reference)	1.00 (reference)	
positive	1,496 (78.1)	420 (21.9)	1.67 (1.49-1.88)	1.60 (1.42-1.81)	
unknown	154 (82.8)	32 (17.2)	1.24 (0.84-1.82)	0.85 (0.52-1.38)	
T category					<0.001
T1	12,284 (85.9)	2,018 (14.1)	1.00 (reference)	1.00 (reference)	
T2	3,097 (81.7)	693 (18.3)	1.36 (1.24-1.50)	1.33 (1.20-1.48)	
T3	37 (43.5)	48 (56.5)	7.90 (5.13-12.16)	7.16 (4.58-11.18)	
Unknown	7 (63.6)	4 (36.4)	3.48 (1.02-11.89)	2.58 (0.64-10.37)	
N category					<0.001
N0	10,865 (85.9)	1,784 (14.1)	1.00 (reference)	1.00 (reference)	
N1	3,501 (83.0)	719 (17.0)	1.25 (1.14-1.38)	1.20 (1.09-1.33)	
N2	521 (77.4)	152 (22.6)	1.78 (1.47-2.14)	1.51 (1.24-1.84)	
N3	243 (77.6)	70 (22.4)	1.75 (1.34-2.30)	1.39 (1.05-1.84)	
Unknown	295 (88.6)	38 (11.4)	0.79 (0.59-1.10)	0.75 (0.52-1.09)	

Values in parentheses are percentages unless indicated otherwise. BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2. * Values are mean(s.d.) and † values in parentheses are 95%-CIs; † Adjusted for type of surgery, year of operation, age, histological finding, differentiation grade, estrogen receptor, HER2 status, T and N category; ‡ Wald test.

Multivariable analysis showed that patients who underwent OPS were less likely to undergo conversion to mastectomy than those who had BCS (OR 0.69, 95%-CI 0.58-0.84). Similar results were found for subgroups who had OPS with volume displacement (OR 0.71, 95%-CI 0.58-0.87) or volume reduction (OR 0.53, 95%-CI 0.33-0.84) (Table S8.5, supporting information). There was no difference in CMR between OPS with volume replacement and BCS (OR 1.07, 95%-CI 0.53-2.13). Conversion to mastectomy was more likely in patients with poor prognostic characteristics, including lobular histology (p<0.001), larger tumor (p<0·001) and more lymph node involvement (p<0.001). In the matched cohorts (Tables S8.1-S8.4, supporting information), results of multivariable analyses were similar to those for the unmatched groups, in comparisons of OPS as a whole versus BCS (OR 0.70, 95%-CI 0.57-0.86), and OPS with volume

displacement (OR 0.67, 95%-CI 0.54-0.84), volume reduction (OR 0.51, 95%-CI 0.30-0.89) or volume replacement (OR 1.13, 95%-CI 0.43-3.02) versus BCS.

Discussion

In this population-based cohort study, re-excision or conversion to mastectomy was less likely among patients who underwent OPS than BCS, although differences were modest. The re-excision rate and CMR were lower among patients who underwent OPS using volume displacement and reduction techniques, but both rates were similar after BCS and OPS with volume replacement, although numbers in the latter group were small. This large population-based study adjusted for confounders, and limited confounding by indication bias by means of propensity score matching.

Although no long-term differences in recurrence rates and survival between BCS and OPS have been reported,[13,19,22,43-45] current evidence regarding the impact of OPS on the re-excision rate is limited because the data are from single-center studies with relatively few patients undergoing OPS (ranging from 31 to 1177), and in most studies the methodology was weak.[11,13,44,46-48] The present results are in line with a meta-analysis[19] from 2018 that found a significantly lower risk of re-excision in patients who underwent OPS compared with those who had BCS (relative risk 0.66, 95%-CI 0.48-0.90). However, more recently, comparable re-excision rates after BCS and OPS were reported in two studies from Finland[13] and Iceland.[11] In contrast to the present study, only relatively small numbers of patients were included, without extensive adjustment for confounders.

Since 2011, Danish guidelines[31] have stated that OPS should be considered when, for example, tumor size and location do not allow a satisfactory cosmetic result with BCS. In the present study, use of OPS among patients who underwent BCS decreased between 2012 and 2018 (from 30.3 to 26.4%), specifically in volume reduction and replacement techniques. A large multicenter study[10] from the USA showed a significant rise in the OPS rate from 4.3 to 9.0% between 2005 and 2016. Among those who underwent OPS, the percentage who had volume displacement was similar to that in the present study (85.2 and 83.4% respectively). Nonetheless, the overall use of OPS here was still substantially higher than in most previous studies.[18,19]

Boost radiation is associated with serious side-effects such as fibrosis, radiation heart disease and second non-breast cancer,[49,50] and so re-excision may have been preferred over boost radiation, specifically in patients with a tumor bed in front of the heart.[51] Nonetheless, in the present study, the rate of secondary interventions among patients older than 50 years was similar in those undergoing BCS and OPS, although boost

radiation was preferred to re-excision in the event of insufficient margins for those who underwent OPS. This was slightly surprising, as radiotherapy planning is challenging after OPS, because identification of the tumor bed can be difficult.[52] These findings highlight the challenge in balancing morbidity from re-excision with that of boost radiation, and the importance of close collaboration between surgeons and radiation oncologists. Any decision regarding re-excision or boost radiation should be made at a multidisciplinary team meeting.

Heterogeneous definitions of insufficient margins, ranging from 'tumor within 10mm from the ink margin' to 'tumor on ink', may partly explain the difference between the findings here and those of other studies.[18,19] The present overall re-excision rate of 15.2% is within the range (0-15.7%) reported in other studies that used the same definition of 'tumor on ink'.[13,53-55] The associations between poor prognostic factors, such as larger tumor or lymph node involvement, and re-excision and conversion to mastectomy are in line with previous findings.[18,53,55] Future guidelines may highlight the additional risk when considering OPS in these patients.

The overall CMR of 3.6% in this analysis is well below the mean of 6.2% and within the range of 0-34.2% reported in previous studies, and a systematic review of 55 studies.[18] However, it is not in line with the results of a meta-analysis from 2014,[17] which found a higher CMR for OPS with volume reduction and volume replacement compared with BCS. This may be explained partly by the fact that most included studies did not adjust for confounders and did not exclude patients diagnosed with *in situ* disease alone, because such patients are less likely to have a re-excision rate similar to that for invasive breast cancer.[56]

The differing rates of re-excision between OPS techniques might be explained by the small absolute numbers, and consequently wide confidence intervals. Another explanation could be differences in patient or tumor factors used for surgical procedure selection. Breast and tumor size, tumor location and glandular density are, among other factors, used in selection of the preferred OPS technique,[16,57] but also affect the likelihood of having a secondary mastectomy. For instance, patients with smaller breasts who require OPS with volume replacement may be less eligible for a secondary BCS, and may therefore undergo a secondary mastectomy when indicated.

The present data support the theory that OPS is associated with fewer re-excisions, although other explanations are possible. Patients and surgeons might be less willing to accept re-excisions following OPS because of the primary focus on the cosmetic result. Unfortunately, tumor margin data for the primary procedure are incomplete in the DBCG database for the early years of the present study and could therefore not be included.

Future studies should evaluate whether the effect of OPS on re-excision is similar in patients treated with and with- out neoadjuvant therapy, as patients who are considered candidates for neoadjuvant therapy, such as those with locally advanced tumors,[58] are also candidates for OPS. Neoadjuvant chemotherapy can be used for tumor downstaging, making more patients eligible for BCS without OPS. It could therefore be argued that there might be less need for OPS in the future as use of neoadjuvant chemotherapy in most high-income countries has been increasing in recent years.[8,57] Neoadjuvant chemotherapy has only been used for breast cancer downstaging in Denmark more recently,[59,60] and patients receiving such treatment were not included in the present study. The increasing use of neoadjuvant chemotherapy might, however, explain the slight decrease in OPS in more recent years in this study.

The changing paradigm from primary BCS to more mastectomy seen in, for instance, the USA could also have influenced the present findings.[61] Earlier reports from the DBCG database, however, showed that the proportion of patients undergoing primary mastectomy remained stable at around 25% in Denmark during the inclusion period of the present study.[59,60]

This study has several limitations. Several factors, such as breast size,[22] smoking status[11] and surgeons' preference,[62] are known to affect both the choice of surgery and outcomes. Likewise, local resources (such as operating times) and level of experience among staff members can affect both the use of OPS and re-excision rates. Unfortunately, information on these potential confounders was not available. Moreover, the rationale behind the choice of a specific surgical technique (such as racket mammoplasty or reduction with superior pedicle flap) is not registered by the DBCG. Residual confounding by indication could have been present as the matched analyses could only include available variables.

The present findings do not support the use of OPS in all patients undergoing BCS, but rather highlight the safety of OPS for those in whom a satisfactory cosmetic result could not be achieved with BCS alone. This study does not encourage the use of OPS in every patient, but emphasizes its appropriate use in selected patients who otherwise would not be eligible for breast conservation.

Supporting information

Table S8.1. Baseline characteristics of patients who underwent BCS and oncoplastic surgery before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=5,003)	Standardized difference	BCS (n=5,003)	OPS (n=5,003)	Standardized difference
Year of operation						
2012	1,858 (14.1)	809 (16.2)	0.058	829 (16.6)	809 (16.2)	0.011
2013	2,052 (15.6)	681 (13.6)	0.055	655 (13.1)	681 (16.4)	0.015
2014	1,933 (14.7)	818 (16.4)	0.047	773 (15.5)	818 (16.4)	0.025
2015	1,909 (14.5)	717 (14.3)	0.004	735 (14.7)	717 (14.3)	0.010
2016	1,852 (14.0)	681 (13.6)	0.013	673 (13.5)	681 (13.6)	0.005
2017	1,813 (13.8)	663 (13.3)	0.015	701 (14.0)	663 (13.3)	0.022
2018	1,768 (13.4)	634 (12.7)	0.022	637 (12.7)	634 (12.7)	0.002
Age, mean (SD)	62.1 (11.5)	59.9 (11.5)	0.190	59.8 (11.8)	59.9 (11.5)	0.008
CCI						
0	9,942 (75.4)	4,045 (80.9)	0.132	4,081 (81.6)	4,045 (80.9)	0.018
1	1,910 (14.5)	590 (11.8)	0.080	572 (11.4)	590 (11.8)	0.011
2	868 (6.6)	250 (5.0)	0.068	237 (4.7)	250 (5.0)	0.012
≥3	465 (3.5)	118 (2.4)	0.069	113 (2.3)	118 (2.4)	0.007
Histological finding						
ductal	10,669 (80.9)	4,108 (82.1)	0.031	4,144 (82.8)	4,108 (82.1)	0.019
lobular	1,339 (10.2)	549 (11.0)	0.027	532 (10.6)	549 (11.0)	0.011
other	1,161 (8.8)	344 (6.9)	0.072	325 (6.5)	344 (6.9)	0.015
unknown	16 (0.1)	2 (0.0)	0.029	2 (0.0)	2 (0.0)	<0.001
Differentiation grade						
I	3,683 (27.9)	1,126 (22.5)	0.125	1,148 (22.9)	1,126 (22.5)	0.010
II	5,700 (43.2)	2,258 (45.1)	0.038	2,303 (46.0)	2,258 (45.1)	0.018
III	2,496 (18.9)	1,251 (25)	0.147	1,202 (24.0)	1,251 (25.0)	0.023
ND	1,161 (8.8)	344 (6.9)	0.072	325 (6.5)	344 (6.9)	0.015
unknown	145 (1.1)	24 (0.5)	0.070	25 (0.5)	24 (0.5)	0.003
Oestrogen receptor (%)						
<10	1,562 (11.8)	710 (14.2)	0.070	662 (13.2)	710 (14.2)	0.028
≥10	11,583 (87.8)	4,284 (85.6)	0.066	4,334 (86.6)	4,284 (85.6)	0.029
unknown	40 (0.3)	9 (0.2)	0.025	7 (0.1)	9 (0.2)	0.010
HER2 status						
negative	11,751 (89.1)	4,335 (86.6)	0.076	4,399 (87.9)	4,335 (86.6)	0.038
positive	1,281 (9.7)	635 (12.7)	0.094	577 (11.5)	634 (12.7)	0.036
unknown	153 (1.2)	33 (0.7)	0.053	27 (0.5)	33 (0.7)	0.016
T category						
T1	10,854 (82.3)	3,448 (68.9)	0.316	3,458 (69.1)	3,448 (68.9)	0.004
T2	2,264 (17.2)	1,526 (30.5)	0.317	1,512 (30.2)	1,526 (30.5)	0.006
T3	57 (0.4)	28 (0.6)	0.018	32 (0.6)	28 (0.6)	0.010
unknown	10 (0.1)	1 (0.0)	0.026	1 (0.0)	1 (0.0)	<0.001
N category						
N0	9,397 (71.3)	3,252 (65.0)	0.135	3,290 (65.8)	3,252 (65.0)	0.016
N1	2,818 (21.4)	1,402 (28.0)	0.155	1,397 (27.9)	1,402 (28.0)	0.002
N2	436 (3.3)	237 (4.7)	0.073	218 (4.4)	237(4.7)	0.018
N3	226 (1.7)	87 (1.7)	0.002	75 (1.5)	87 (1.7)	0.019
unknown	308 (2.3)	25 (0.5)	0.156	23 (0.5)	25 (0.5)	0.006

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS as a whole using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.2. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume displacement before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=4,171)	Standardized difference	BCS (n=4,171)	OPS (n=4,171)	Standardized difference
Year of operation						
2012	1,858 (14.1)	658 (15.8)	0,047	693 (16.6)	658 (15.8)	0.023
2013	2,052 (15.6)	536 (12.9)	0,078	515 (12.3)	536 (12.9)	0.015
2014	1,933 (14.7)	680 (16.3)	0,045	629 (15.1)	680 (16.3)	0.034
2015	1,909 (14.5)	609 (14.6)	0.003	621 (14.9)	609 (14.6)	0.008
2016	1,852 (14.0)	561 (13.5)	0.017	554 (13.3)	561 (13.5)	0.005
2017	1,813 (13.8)	583 (14.0)	0.007	600 (14.4)	583 (14.0)	0.012
2018	1,768 (13.4)	544 (13.0)	0.011	559 (13.4)	544 (13.0)	0.011
Age, mean (SD)	62.1 (11.5)	60.1 (11.5)	0.168	60.0 (11.6)	60.1 (11.5)	0.016
CCI						
0	9,942 (75.4)	3,355 (80.4)	0.122	3,394 (81.4)	3,355 (80.4)	0.024
1	1,910 (14.5)	515 (12.3)	0.063	514 (12.3)	515 (12.3)	0.001
2	868 (6.6)	198 (4.7)	0.079	166 (4.0)	198 (4.7)	0.038
≥3	465 (3.5)	103 (2.5)	0.062	97 (2.3)	103 (2.5)	0.009
Histological finding						
ductal	10,669 (80.9)	3,418 (81.9)	0.026	3,478 (83.4)	3,418 (81.9)	0.038
lobular	1,339 (10.2)	456 (10.9)	0.025	413 (9.9)	456 (10.9)	0.034
other	1,161 (8.8)	295 (7.1)	0.064	278 (6.7)	295 (7.1)	0.016
unknown	16 (0.1)	2 (0)	0.025	2 (0.0)	2 (0.0)	<0.001
Differentiation grade						
I	3,683 (27.9)	963 (23.1)	0.111	943 (22.6)	963 (23.1)	0.011
II	5,700 (43.2)	1,884 (45.2)	0.039	1,9367 (46.4)	1,884 (45.2)	0.026
III	2,496 (18.9)	1,010 (24.2)	0.129	996 (23.9)	1,010 (24.2)	0.008
ND	1,161 (8.8)	295 (7.1)	0.064	278 (6.7)	295 (7.1)	0.016
unknown	145 (1.1)	19 (0.5)	0.073	17 (0.4)	19 (0.5)	0.007
Oestrogen receptor (%)						
<10	1,562 (11.8)	592 (14.2)	0.070	573 (13.7)	592 (14.2)	0.013
≥10	11,583 (87.8)	3,570 (85.6)	0.067	3,587 (86.0)	3,570 (85.6)	0.012
unknown	40 (0.3)	9 (0.2)	0.017	11 (0.3)	9 (0.2)	0.010
HER2 status						
negative	11,751 (89.1)	3,620 (86.8)	0.072	3,647 (87.4)	3,620 (86.8)	0.019
positive	1,281 (9.7)	522 (12.5)	0.089	501 (12.0)	522 (12.5)	0.015
unknown	153 (1.2)	29 (0.7)	0.049	23 (0.6)	29 (0.7)	0.018
T category						
T1	10,854 (82.3)	3,000 (71.9)	0.249	3,050 (73.1)	3,000 (71.9)	0.027
T2	2,264 (17.2)	1,152 (27.6)	0.253	1,105 (26.5)	1,152 (27.6)	0.025
T3	57 (0.4)	18 (0.4)	<0.001	14 (0.3)	18 (0.4)	0.016
unknown	10 (0.1)	1 (0)	0.023	2 (0.0)	1 (0.0)	0.013
N category						
N0	9,397 (71.3)	2,749 (65.9)	0.116	2,786 (66.8)	2,749 (65.9)	0.019
N1	2,818 (21.4)	1,134 (27.2)	0.136	1,123 (26.9)	1,134 (27.2)	0.006
N2	436 (3.3)	190 (4.6)	0.064	174 (4.2)	190 (4.6)	0.019
N3	226 (1.7)	74 (1.8)	0.005	69 (1.7)	74 (1.8)	0.009
unknown	308 (2.3)	24 (0.6)	0.147	19 (0.5)	23 (0.6)	0.017

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume displacement using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.3. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume reduction before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=679)	Standardized difference	BCS (n=679)	OPS (n=679)	Standardized difference
Year of operation						
2012	1,858 (14.1)	113 (16.6)	0.071	109 (16.1)	113 (16.6)	0.016
2013	2,052 (15.6)	119 (17.5)	0.053	113 (16.6)	119 (17.5)	0.023
2014	1,933 (14.7)	111 (16.3)	0.047	104 (15.3)	111 (16.3)	0.028
2015	1,909 (14.5)	88 (13.0)	0.044	92 (13.5)	88 (13.0)	0.017
2016	1,852 (14.0)	97 (14.3)	0.007	103 (15.2)	97 (14.3)	0.025
2017	1,813 (13.8)	72 (10.6)	0.096	71 (10.5)	72 (10.6)	0.005
2018	1,768 (13.4)	79 (11.6)	0.054	87 (12.8)	79 (11.6)	0.036
Age, mean (SD)	62.1 (11.5)	58.9 (11.2)	0.277	59.5 (12.0)	58.9 (11.2)	0.045
CCI						
0	9,942 (75.4)	557 (82)	0.162	576 (84.8)	557 (82.0)	0.075
1	1,910 (14.5)	63 (9.3)	0.161	42 (6.2)	63 (9.3)	0.116
2	868 (6.6)	44 (6.5)	0.004	48 (7.1)	44 (6.5)	0.023
≥3	465 (3.5)	15 (2.2)	0.079	13 (1.9)	15 (2.2)	0.021
Histological finding						
ductal	10,669 (80.9)	563 (82.9)	0.052	575 (84.7)	563 (82.9)	0.048
lobular	1,339 (10.2)	75 (11.0)	0.029	75 (11.0)	75 (11.0)	<0.001
other	1,161 (8.8)	41 (6.0)	0.106	29 (4.3)	41 (6.0)	0.080
unknown	16 (0.1)	0 (0)	0.049	-	-	-
Differentiation grade						
I	3,683 (27.9)	131 (19.3)	0.205	133 (19.6)	131 (19.3)	0.007
II	5,700 (43.2)	299 (44.0)	0.016	313 (46.1)	299 (44.0)	0.041
III	2,496 (18.9)	204 (30.0)	0.261	201 (29.6)	204 (30.0)	0.010
ND	1,161 (8.8)	41 (6.0)	0.106	29 (4.3)	41 (6.0)	0.080
unknown	145 (1.1)	4 (0.6)	0.056	3 (0.4)	4 (0.6)	0.021
Oestrogen receptor (%)						
<10	1,562 (11.8)	95 (14.0)	0.064	100 (14.7)	95 (14.0)	0.021
≥10	11,583 (87.8)	584 (86.0)	0.055	579 (85.3)	584 (86.0)	0.021
unknown	40 (0.3)	0 (0)	0.078	-	-	-
HER2 status						
negative	11,751 (89.1)	581 (85.6)	0.107	597 (87.9)	581 (85.6)	0.070
positive	1,281 (9.7)	94 (13.8)	0.128	79 (11.6)	94 (13.8)	0.066
unknown	153 (1.2)	4 (0.6)	0.061	3 (0.4)	4 (0.6)	0.021
T category						
T1	10,854 (82.3)	370 (54.5)	0.627	370 (54.5)	370 (54.5)	<0.001
T2	2,264 (17.2)	300 (44.2)	0.613	300 (44.2)	300 (44.2)	<0.001
T3	57 (0.4)	9 (1.3)	0.096	9 (1.3)	9 (1.3)	<0.001
unknown	10 (0.1)	0 (0)	0.039	-	-	-
N category						
N0	9,397 (71.3)	417 (61.4)	0.210	428 (63.0)	417 (61.4)	0.033
N1	2,818 (21.4)	215 (31.7)	0.235	210 (30.9)	215 (31.7)	0.016
N2	436 (3.3)	39 (5.7)	0.117	37 (5.4)	39 (5.7)	0.013
N3	226 (1.7)	7 (1.0)	0.059	3 (0.4)	7 (1.0)	0.069
unknown	308 (2.3)	1 (0.1)	0.199	1 (0.1)	1 (0.1)	<0.001

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume reduction using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.4. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume replacement before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=153)	Standardized difference	BCS (n=153)	OPS (n=153)	Standardized difference
Year of operation						
2012	1,858 (14.1)	38 (24.8)	0.274	37 (24.2)	38 (24.8)	0.015
2013	2,052 (15.6)	26 (17.0)	0.039	29 (19.0)	26 (17.0)	0.051
2014	1,933 (14.7)	27 (17.6)	0.081	22 (14.4)	27 (17.6)	0.089
2015	1,909 (14.5)	20 (13.1)	0.041	22 (14.4)	20 (13.1)	0.038
2016	1,852 (14.0)	23 (15.0)	0.028	28 (18.3)	23 (15.0)	0.088
2017	1,813 (13.8)	8 (5.2)	0.294	4 (2.6)	8 (5.2)	0.135
2018	1,768 (13.4)	11 (7.2)	0.206	11 (7.2)	11 (7.2)	<0.001
Age, mean (SD)	62.1 (11.5)	57.4 (10.3)	0.432	57.3 (13.3)	57.4 (10.3)	<0.001
CCI						
0	9,942 (75.4)	133 (86.9)	0.298	134 (87.6)	133 (86.9)	0.020
1	1,910 (14.5)	12 (7.8)	0.212	11 (7.2)	12 (7.8)	0.025
2	868 (6.6)	8 (5.2)	0.057	8 (5.2)	8 (5.2)	<0.001
≥3	465 (3.5)	0 (0)	0.270	-	-	-
Histological finding						
ductal	10,669 (80.9)	127 (83.0)	0.054	125 (81.7)	127 (83.0)	0.034
lobular	1,339 (10.2)	18 (11.8)	0.052	21 (13.7)	18 (11.8)	0.059
other	1,161 (8.8)	8 (5.2)	0.140	7 (4.6)	8 (5.2)	0.030
unknown	16 (0.1)	0 (0)	0.049	-	-	-
Differentiation grade						
I	3,683 (27.9)	32 (20.9)	0.164	25 (16.3)	32 (20.9)	0.118
II	5,700 (43.2)	75 (49.0)	0.116	86 (56.2)	75 (49.0)	0.144
III	2,496 (18.9)	37 (24.2)	0.128	34 (22.2)	37 (24.2)	0.046
ND	1,161 (8.8)	8 (5.2)	0.140	7 (4.6)	8 (5.2)	0.030
unknown	145 (1.1)	1 (0.7)	0.048	1 (0.7)	1 (0.7)	<0.001
Oestrogen receptor (%)						
<10	1,562 (11.8)	23 (15.0)	0.094	23 (15.0)	23 (15.0)	<0.001
≥10	11,583 (87.8)	130 (85.0)	0.084	130 (85.0)	130 (85.0)	<0.001
unknown	40 (0.3)	0 (0)	0.078	-	-	-
HER2 status						
negative	11,751 (89.1)	134 (87.6)	0.048	136 (88.9)	134 (87.6)	0.041
positive	1,281 (9.7)	19 (12.4)	0.086	17 (11.1)	19 (12.4)	0.041
unknown	153 (1.2)	0 (0)	0.153	-	-	-
T category						
T1	10,854 (82.3)	78 (51.0)	0.705	80 (52.3)	78 (51.0)	0.026
T2	2,264 (17.2)	74 (48.4)	0.705	72 (47.1)	74 (48.4)	0.026
T3	57 (0.4)	1 (0.7)	0.030	1 (0.7)	1 (0.7)	<0.001
unknown	10 (0.1)	0 (0)	0.040	-	-	-
N category						
N0	9,397 (71.3)	86 (56.2)	0.317	92 (60.1)	86 (56.2)	0.080
N1	2,818 (21.4)	53 (34.6)	0.299	39)25.5)	53 (34.6)	0.201
N2	436 (3.3)	8 (5.2)	0.095	10 (6.5)	8 (5.2)	0.056
N3	226 (1.7)	6 (3.9)	0.134	12 (7.8)	6 (3.9)	0.167
unknown	308 (2.3)	0 (0)	0.219	-	-	-

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume replacement using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.5. Univariable and multivariable analyses of characteristics predictive of conversion to mastectomy.

	Conversion to mastectomy [a]		Odds ratio (95%-CI)		
	No (n=17,533)	Yes (n=655)	Univariable (n=18,188)	Multivariable [b] (n=18,188)	p-value[‡]
Type of surgery					0.001
BCS	12,692 (96.3)	493 (3.7)	1.00 (reference)	1.00 (reference)	
volume displacement	4,038 (96.8)	133 (3.2)	0.85 (0.70-1.03)	0.71 (0.58-0.87)	
volume reduction	659 (97.1)	20 (2.9)	0.78 (0.50-1.23)	0.53 (0.33-0.84)	
volume replacement	144 (94.1)	9 (5.9)	1.61 (0.82-3.17)	1.07 (0.53-2.13)	
Year of operation					0.200
2012	2,551 (95.7)	116 (4.3)	1.00 (reference)	1·00 (reference)	
2013	2,626 (96.1)	107 (3.9)	0.9 (0.69-1.17)	0·92 (0.70-1.21)	
2014	2,646 (96.2)	105 (3.8)	0.87 (0.67-1.14)	0·89 (0.68-1.18)	
2015	2,539 (96.7)	87 (3.3)	0.75 (0.57-1.00)	0·78 (0.58-1.04)	
2016	2,447 (96.6)	86 (3.4)	0.77 (0.58-1.03)	0·79 (0.59-1.06)	
2017	2,386 (96.4)	90 (3.6)	0.83 (0.63-1.10)	0·90 (0.68-1.21)	
2018	2,338 (97.3)	64 (2.7)	0.60 (0.44-0.82)	0·66 (0.48-0.91)	
Age, mean (SD)	61.6 (11.5)	59.2 (12.4)	0.98 (0.98-0.99)	0·98 (0.97-0.99)	<0.001
CCI					0.550
0	13,468 (96.3)	519 (3.7)	1.00 (reference)	1.00 (reference)	
1	2,421 (96.8)	79 (3.2)	0.85 (0.67-1.08)	0.93 (0.73-1.20)	
2	1,075 (96.2)	43 (3.8)	1.04 (0.76-1.43)	1.20 (0.86-1.66)	
≥3	569 (97.6)	14 (2.4)	0.64 (0.37-1.09)	0.82 (0.48-1.42)	
Histological finding					<0.001
ductal	14,312 (96.9)	465 (3.1)	1.00 (reference)	1.00 (reference)	
lobular	1,753 (92.8)	135 (7.2)	2.37 (1.95-2.89)	2.34 (1.89-2.90)	
other	1,451 (96.4)	54 (3.6)	1.15 (0.86-1.53)	1.58 (1.12-2.38)	
unknown	17 (94.4)	1 (5.6)	1.81 (0.24-13.63)	0.12 (0.01-1.44)	
Differentiation grade					<0.001
I	4,696 (97.7)	113 (2.3)	1.00 (reference)	1.00 (reference)	
II	7,631 (95.9)	327 (4.1)	1.58 (1.31-1.91)	1.42 (1.13-1.77)	
III	3,604 (96.2)	143 (3.8)	1.46 (1.16-1.83)	1.15 (0.87-1.54)	
not determined	1,451 (96.4)	54 (3.6)	-	-	
unknown	151 (89.3)	18 (10.7)	4.39 (2.63-7.32)	3.87 (2.13-7.05)	
Oestrogen receptor (%)					0.120
<10	2,179 (95.9)	93 (4.1)	1.18 (0.94-1.47)	1.07 (0.83-1.39)	
≥10	15,311 (96.5)	556 (3.5)	1.00 (reference)	1.00 (reference)	
unknown	43 (87.8)	6 (12.2)	3.84 (1.63-9.07)	3.24 (1.03-10.19)	
HER2					<0.001
negative	15,548 (96.7)	538 (3.3)	1.00 (reference)	1.00 (reference)	
positive	1,812 (94.6)	104 (5.4)	1.66 (1.34-2.06)	1.63 (1.29-2.05)	
unknown	173 (93.0)	13 (7.0)	2.17 (1.23-3.84)	1.38 (0.66-2.88)	
T-stage					<0.001
T1	13,895 (97.2)	407 (2.8)	1.00 (reference)	1.00 (reference)	
T2	3,579 (94.4)	211 (5.6)	2.01 (1.70-2.39)	1.84 (1.52-2.22)	
T3	51 (60.0)	34 (40.0)	22.76 (14.59-35.52)	15.77 (9.72-25.59)	
unknown	8 (72.7)	3 (27.3)	12.80 (3.38-48.43)	7.48 (1.61-34.82)	
N-stage					<0.001
N0	12,292 (97.2)	357 (2.8)	1.00 (reference)	1.00 (reference)	
N1	4,027 (95.4)	193 (4.6)	1.65 (1.38-1.97)	1.49 (1.24-1.80)	
N2	609 (90.5)	64 (9.5)	3.62 (2.74-4.78)	2.54 (1.88-3.42)	
N3	283 (90.4)	30 (9.6)	3.65 (2.47-5.40)	2.29 (1.51-3.49)	
unknown	322 (96.7)	11 (3.3)	1.18 (0.64-2.17)	0.92 (0.47-1.80)	

Values in parentheses are 95 percent confidence intervals unless indicated otherwise. Abbreviations: breast-conserving surgery, BCS; standard deviation, SD; odds ratio, OR; confidence interval, CI. [a] Values are numbers and row percentages in parentheses. [b] Multivariable analyses were adjusted for type of surgery, year of operation, age, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-stage; [‡]Wald test.

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