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Original Article

Recurrence and survival after standard versus oncoplastic breast-conserving surgery for breast cancer

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Abstract

Background: Oncoplastic techniques in breast-conserving surgery (BCS) are used increasingly for larger tumours. This large cohort study aimed to assess oncological outcomes after oncoplastic BCS (OPS) *versus* standard BCS.

Methods: Data for all women who had BCS in three centres in Stockholm during 2010–2016 were extracted from the Swedish National Breast Cancer Register. All patients with T2–3 tumours, all those receiving neoadjuvant treatment, and an additional random sample of women with T1 tumours were selected. Medical charts were reviewed for local recurrences and surgical technique according to the Hoffman–Wallwiener classification. Date and cause of death were retrieved from the Swedish Cause of Death Register.

Results: The final cohort of 4178 breast cancers in 4135 patients was categorized into three groups according to surgical technique: 3720 for standard BCS, 243 simple OPS, and 215 complex OPS. Median duration of follow up was 64 (range 24–110) months. Node-positive and large tumours were more common in OPS than in standard BCS ($P < 0.001$). There were 61 local recurrences: 57 (1.5 per cent), 1 (0.4 per cent) and 3 (1.4 per cent) in the standard BCS, simple OPS and complex OPS groups respectively ($P = 0.368$). Overall, 297 patients died, with an unadjusted 5-year overall survival rate of 94.7, 93.1 and 92.6 per cent respectively ($P = 0.350$). Some 102 deaths were from breast cancer, with unadjusted 5-year cancer-specific survival rates of 97.9, 98.3 and 95.0 per cent respectively ($P = 0.056$).

Discussion: Oncoplastic BCS is a safe surgical option, even for larger node-positive tumours, with low recurrence and excellent survival rates.

Introduction

Breast-conserving surgery (BCS) followed by whole-breast irradiation is the recommended surgical strategy for early breast cancer. Although early follow-up reports confirmed the oncological equivalence of BCS and mastectomy, they also pointed to a slightly increased risk of ipsilateral in-breast recurrence after BCS[1]. This observation has been contradicted by more recent retrospective studies of large cohorts. These studies have shown not only no difference in local recurrence risk between mastectomy and BCS, but also a higher overall survival (OS) rate after BCS, most probably due to earlier detection and improved oncological treatments[2,3].

The cosmetic outcome after breast surgery strongly influences patient satisfaction and quality of life[4,5]. Following standard BCS, poor cosmetic outcomes have been reported to affect around 30 per cent of women[5–7]. To improve quality of life is especially important, considering the growing number of long-time survivors living with the consequences of their cancer treatment. Today, oncoplastic techniques are increasingly implemented in BCS, enabling surgeons to achieve better cosmesis while maintaining excellent oncological results. On average, oncoplastic BCS (OPS) has been shown to result in higher resection volumes and larger resection margins, as well as a significantly reduced re-excision rate[8–11]. A consequence of this development is that previous indications for BCS have been widened, and today BCS is generally offered to women with larger tumours than those included in the ground-breaking randomized trials by Veronesi and colleagues[12] and Fisher co-workers[1], even though oncoplastic techniques may

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also be chosen for women with smaller tumours in unfavourable locations. In fact, there are indications that tumours treated with OPS may be more similar with respect to size and tumour biology to those treated by mastectomy than those treated with standard BCS[13].

There are a number of retrospective studies reporting on the oncological safety of OPS[10,14], but data are still deemed insufficient[11,15]. The aim of this study was therefore to assess local recurrence and survival rates after OPS with a special focus on larger tumours, using thoroughly validated surgical and oncological outcomes in a large cohort of patients with breast cancer from the three large-volume breast centres in Stockholm, Sweden.

Methods

This was a register-based cohort study with local recurrence as the primary endpoint, and overall and breast cancer-specific survival as secondary endpoints. Data were used from the Swedish National Breast Cancer Register (NKBC), which includes patients with a diagnosis of invasive or non-invasive primary breast cancer, with national coverage since 1992 and harmonized online reporting since 2008. The NKBC contains information on age, sex, primary tumour and lymph node characteristics, surgical intervention, adjuvant and neoadjuvant treatment, and follow-up data. The completeness for all primary breast cancer cases is estimated to be 98–99 per cent[16]. Validations of the NKBC in 2015 and 2019 demonstrated a high data quality, with an overlap between NKBC data and validation data of more than 90 per cent[17,18].

Inclusion criteria for data extraction in this study were: patients diagnosed in 2010–2016 with primary invasive breast cancer as reported to the NKBC, operated on with BCS as the final surgical intervention at one of the three breast centres in Stockholm (Karolinska University Hospital, Capio St Göran's Hospital and South General Hospital), and planned for radiotherapy according to NKBC data (5428 patients). The extracted variables included tumour and treatment data for each patient as well as follow-up records.

As the NKBC does not register information on margin status and type of surgery (that is, different oncoplastic procedures *versus* standard BCS), and to confirm and complete data on local recurrences, a thorough medical chart review was undertaken by five specialists in general and breast surgery and one breast research nurse. Oncoplastic BCS is rare in the smallest tumours, which are nonetheless very common, so a random sample of approximately 25 per cent of patients with tumours of 10 mm or less was selected for this review. In contrast, medical chart review included all patients with tumours larger than 10 mm, as well as all those receiving neoadjuvant treatment, as pathological tumour size does not represent the initial tumour stage. The final cohort of patients eligible for medical chart review was 4294; medical charts were identified and scrutinized for all patients. In this phase, an additional 116 cases were excluded (*Fig. 1*). Remaining patients were then categorized into three groups according to surgical technique: standard BCS, defined as grade 1 and 2 according to the Hoffman–Wallwiener classification[19]; simple OPS, representing grades 3 and 4; and complex OPS, grades 5 and 6. As described in the original Hoffman–Wallwiener publication[19], grades 1 and 2 constituted simple excision or intramammary reconstruction with less than 25 per cent mobilization of the glandular body, grades 3 and 4 constituted mastopexy techniques such as inverted T incisions and round block or doughnut mastopexies, and grades 5 and 6 were mainly therapeutic mammaplasty techniques, but also partial flap reconstructions.

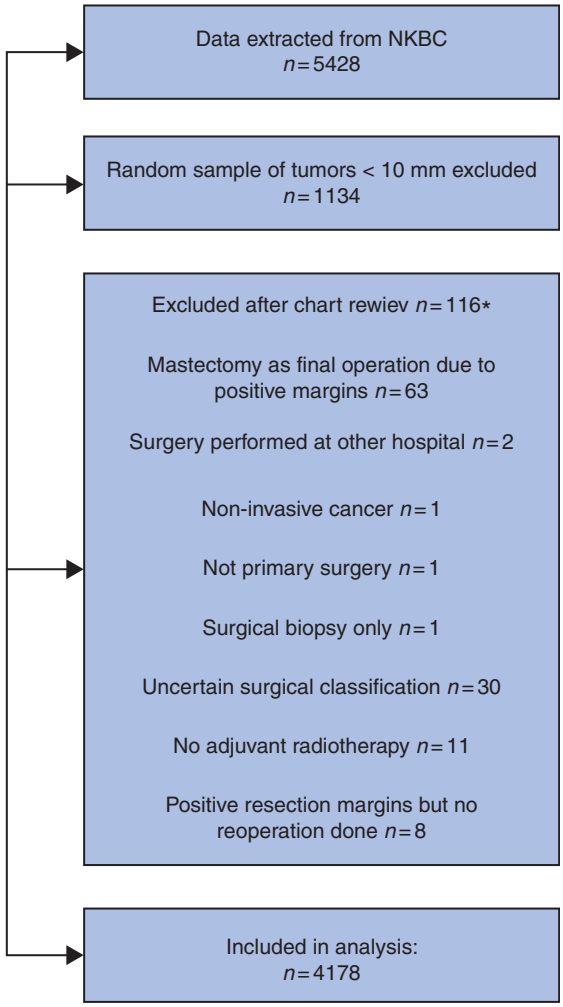


Fig. 1 Flow diagram for selection of the study cohort from all patients with primary breast cancer treated with breast-conserving surgery followed by whole-breast irradiation at three breast centres in Stockholm, Sweden, 2010–2016

*One patient had two of the exclusion criteria. NKBC, Swedish National Breast Cancer Register.

Variables extracted from medical charts included the closest peripheral margin (deep and superficial margins were disregarded), postoperative radiotherapy (radiation target classified as local (whole breast) or locoregional (including nodal fields), boost and total received dose), and local recurrence. Patients with bilateral cancers were regarded as two separate cases, one for each side. Local recurrence was calculated per case, and OS was calculated per person. A local recurrence was defined as a new invasive or non-invasive breast cancer in the ipsilateral breast. Women were followed for local recurrence until the date of medical chart review, the end of March 2019.

Dates and causes of death were obtained from the Total Population Register at Statistics Sweden and the Swedish Cause of Death Register at the National Board of Health and Welfare, and linked individually to the cohort using the personal identification number assigned to all Swedish residents and included in all registers. The date of register data extraction was 20 September 2019.

The study was approved by the regional Ethical Review Authority in Stockholm (2017/2493-31).

Statistical analysis

Data are presented as numbers and percentages for categorical variables, and as median (range) values for continuous variables. Tumour and treatment characteristics were compared by non-parametrical tests: the Kruskal–Wallis test for continuous variables, and χ^2 and Fisher's exact tests for categorical variables. Time to local recurrence was calculated from date of surgery to recurrence, death or end of follow-up (at medical chart review), whichever came first. OS was calculated from date of surgery until death from any cause or the end of follow-up at the date of register data extraction, and breast cancer-specific survival until death from breast cancer or end of follow-up. Five-year local recurrence-free, overall, and breast cancer-specific survival proportions were estimated using the Kaplan–Meier method for each type of surgery, and compared with the log rank test. Subsequently, both univariable and multivariable Cox proportional hazard regression analyses were performed to investigate associations between tumour, treatment and patient factors and the outcomes. Time from surgery was used as the underlying timescale, and associations are reported as hazard ratios (HRs) with 95 per cent confidence intervals. All statistical analyses were performed using IBM® SPSS® Statistics version 25 (IBM, Armonk, NY, USA). Two-tailed *P* values of less than 0.050 were considered statistically significant.

Results

An overall total of 4178 breast cancers in 4135 women were analysed: 3720 cases (89.0 per cent) were standard BCS (Hoffmann–Wallwiener grade 1–2), 243 (5.8 per cent) were simple OPS (grade 3–4), and 215 (5.1 per cent) were complex OPS (grade 5–6). Overall median duration of follow-up to medical chart review was 64 (range 24–110) months: 67 months for standard BCS, 55 for simple OPS, and 59 for complex OPS. Overall median follow-up to survival data extraction was 71 (range 32–116) months; 74, 62 and 66 months for standard BCS, simple OPS and complex OPS respectively. Larger, multifocal and node-positive tumours were significantly more common in the OPS groups than in the standard BCS group (*Table 1*). Women operated with OPS were younger and more likely to have oestrogen receptor-negative and human epidermal growth factor receptor 2-positive tumours with a higher Ki67 proliferation index, the consequences of which are mirrored both in the frequency of neoadjuvant chemotherapy and in differences in adjuvant treatment (*Table 1*). Despite including only 25 per cent of all registered tumours of 10 mm or less in size, T1 tumours still constituted the largest part of the total 4178 cases (2927, 70.1 per cent), whereas T2 tumours (1200, 28.7 per cent) and T3 tumours (51, 1.2 per cent) represented a minority. Tumour sizes differed between the surgical groups as shown in *Fig. 2*.

The use of OPS increased over time; although all oncoplastic procedures together represented only 5.8 per cent of all breast-conserving operations in 2010, this had increased gradually to 17.8 per cent by 2016 ($P < 0.001$).

There were 61 local recurrences: 57 (1.5 per cent) after standard BCS, one (0.4 per cent) after simple OPS, and three (1.4 per cent) after complex OPS ($P = 0.368$). For T1 tumours, 39 local recurrences occurred after standard BCS (1.5 per cent), but none in either OPS group. For T2 tumours, 22 local recurrences were found, 18 of which occurred after standard BCS (1.8 per cent), one after simple (1 per cent), and three after complex OPS (2.8 per cent) ($P = 0.678$). There were no local recurrences in patients with T3 tumours. The 5-year local recurrence-free survival rate did not differ, with 98.4, 99.6 and 98.5 per cent in the standard BCS, simple OPS and complex OPS group respectively ($P = 0.484$) (*Fig. 3*). Peripheral resection margins were significantly largest in the complex OPS group (median 10 (range 0.1–45) mm), compared with margins in the standard BCS group (9 (0.1–62) mm; $P = 0.016$) and the simple OPS group (7 (0.1–55) mm; $P = 0.001$), which had the closest margins.

No data were available on the conversion of BCS to mastectomy owing to positive margins. The rate of re-excision did not differ between the groups ($P = 0.680$): 197 of 3720 (5.3 per cent) for standard BCS, 16 of 243 (6.6 per cent) for simple OPS, and 11 of 215 (5.1 per cent) for complex OPS. By the end of follow-up, 297 patients had died: 262 (7.0 per cent) in the standard BCS group, 17 (7.0 per cent) in the simple OPS group, and 18 (8.4 per cent) in the complex OPS group. This resulted in 5-year OS rates of 94.7, 93.1 and 92.6 per cent in the three groups respectively ($P = 0.350$). (*Fig. 4*) Of all deaths, 102 were due to breast cancer, with 5-year breast cancer-specific survival rates of 97.9, 98.3 and 95.0 per cent respectively ($P = 0.056$) (*Fig. 5*).

For the primary endpoint of local recurrence, only unadjusted regression analysis could be performed owing to the extremely low number of events in the OPS groups (*Table 2*). Although based

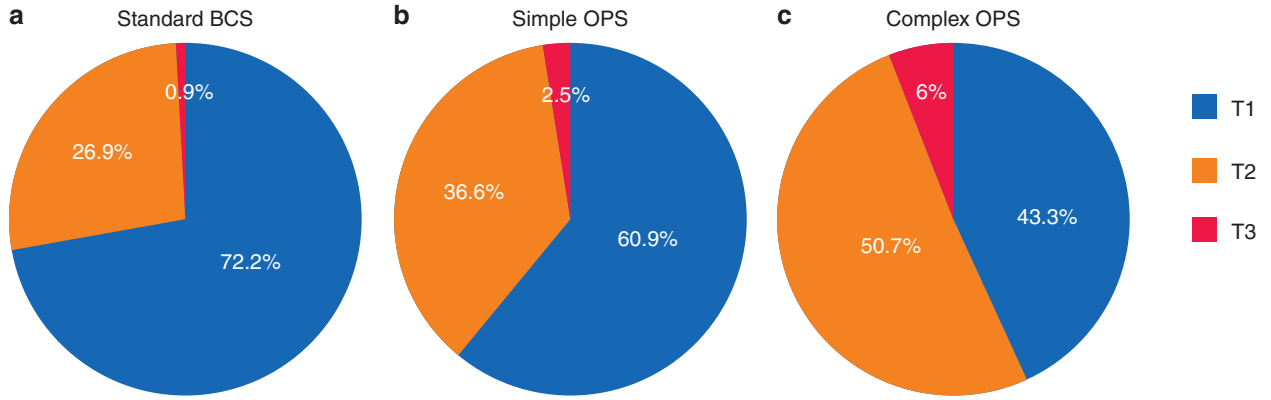


Fig. 2 Distribution of tumour categories in the three surgical groups

a Standard breast-conserving surgery (BCS); **b** simple oncoplastic BCS (OPS); **c** complex OPS. pT category is shown for primary surgery and cT category for patients treated with neaodjuvant chemotherapy. $P<0.001$.

Table 1 Patient and tumour characteristics according to type of operation

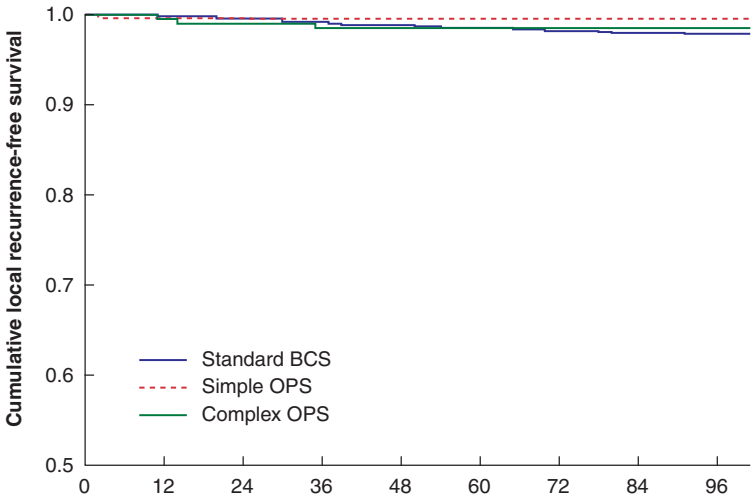
	Standard BCS ($n = 3720$)	Simple OPS ($n = 243$)	Complex OPS ($n = 215$)	P¶
Patient age (years)*	63 (23–91)	59 (29–85)	58 (30–81)	<0.001#
<41	149 (4.0)	20 (8.2)	20 (9.3)	
41–50	620 (16.7)	46 (18.9)	43 (20.0)	
51–65	1447 (38.9)	111 (45.7)	101 (47.0)	
>65	1504 (40.4)	66 (27.2)	51 (23.7)	
Invasive tumour size (mm)*†	16 (1–80)	18 (7–100)	21 (2–86)	<0.001#
Tumour category‡				<0.001
T1	2686 (72.2)	148 (60.9)	93 (43.3)	
T2	1002 (26.9)	89 (36.6)	109 (50.7)	
T3	32 (0.9)	6 (2.5)	13 (6.0)	
Node category‡				<0.001
N0	2772 (74.6)	159 (65.4)	136 (63.3)	
N+	942 (25.4)	84 (34.7)	79 (36.7)	
Missing	6	0	0	
Histological subtype				0.830
Ductal	2961 (79.9)	200 (82.6)	171 (80.3)	
Lobular	399 (10.8)	24 (9.9)	24 (11.3)	
Other	347 (9.4)	18 (7.4)	18 (8.5)	
Missing	13	1	2	
Nottingham histological grade				0.062
1	688 (19.4)	27 (12.9)	29 (16.7)	
2	1825 (51.6)	117 (56.0)	83 (47.7)	
3	1025 (29.0)	65 (31.1)	62 (35.6)	
Missing	182	34	41	
Tumour multifocality				<0.001
Yes	274 (7.4)	30 (12.7)	28 (13.5)	
No	3425 (92.6)	207 (87.3)	180 (86.5)	
Missing	21	6	7	
ER status§				0.018
Positive	3261 (87.9)	203 (83.9)	176 (82.6)	
Negative	448 (12.1)	39 (16.1)	37 (17.4)	
Missing	11	1	2	
PR status§				0.319
Positive	2642 (71.3)	165 (68.2)	144 (67.6)	
Negative	1063 (28.7)	77 (31.8)	69 (32.4)	
Missing	15	1	2	
HER2 amplification§				0.001
Yes	389 (10.7)	43 (17.8)	32 (15.4)	
No	3246 (89.3)	198 (82.2)	176 (84.6)	
Missing	85	2	7	
Ki67*§	20 (1–97)	27 (1–90)	30 (1–100)	<0.001#
Tumour surrogate subtype				0.003
ER/PR+ HER2−	2925 (80.5)	175 (72.6)	151 (72.9)	
ER/PR+ HER2+	285 (7.8)	29 (12.0)	21 (10.1)	
ER/PR− HER2+	104 (2.9)	14 (5.8)	11 (5.3)	
ER/PR− HER2−	318 (8.8)	23 (9.5)	24 (11.6)	
Missing	88	2	8	
Radiotherapy field				<0.001
Breast only	3106 (83.7)	185 (76.4)	159 (74.0)	
Breast and regional lymph nodes	604 (16.3)	57 (23.6)	56 (26.0)	
Missing	10	1	0	
Radiation dose and fractionation				0.025
Hypofractionation	1640 (44.5)	95 (39.3)	90 (42.3)	
Standard fractionation	1332 (36.2)	88 (36.4)	69 (32.4)	
Hypofractionation + boost	345 (9.4)	28 (11.6)	18 (8.5)	
Standard fractionation + boost	366 (9.9)	31 (12.8)	36 (16.9)	
Missing	37	1	2	
Endocrine treatment				0.022
Yes	3265 (88.2)	203 (84.2)	179 (83.3)	
No	435 (11.8)	38 (15.8)	36 (16.7)	
Missing	20	2	0	
Chemotherapy				<0.001
Yes	1599 (43.5)	140 (58.3)	141 (65.9)	
No	2076 (56.5)	100 (41.7)	73 (34.1)	
Missing	45	3	1	
Neoadjuvant chemotherapy				
Yes	168 (4.5)	32 (13.2)	41 (19.1)	<0.001
No	3552 (95.5)	211 (86.8)	174 (80.9)	

(continued)

Table 1 (continued)

	Standard BCS ($n=3720$)	Simple OPS ($n=243$)	Complex OPS ($n=215$)	P¶
Anti-HER2 targeted therapy				<0.001
Yes	360 (9.7)	40 (16.6)	34 (15.8)	
No	3340 (90.3)	201 (83.4)	181 (84.2)	
Missing	20	2	0	
Smallest peripheral margin (mm)*	9 (0.1–62)	7 (0.1–55)	10 (0.1–45)	0.002#

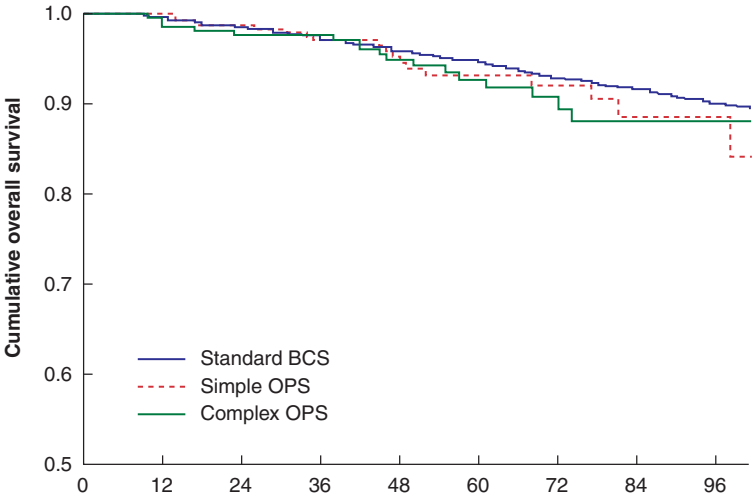
Values in parentheses are percentages unless indicated otherwise; *values are median (range). Each tumour represents one case. Percentages may not sum to 100.0 due to rounding. †Based on histopathological assessment of specimen; neoadjuvant cases excluded. ‡Pretreatment clinical stage for neoadjuvant cases and histopathological tumour size for primary surgery. §Values derived from pretreatment core needle biopsy in neoadjuvant cases and from histopathological assessment of specimen in primary surgery. BCS, breast-conserving surgery; OPS, oncoplastic breast-conserving surgery; ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. ¶χ^2 or Fisher's exact test, except #Kruskal–Wallis test.



No. at risk					
Standard BCS	3697	3684	2639	1519	510
Simple OPS	242	241	125	52	16
Complex OPS	212	210	124	63	17

Fig. 3 Kaplan–Meier survival analysis of local recurrence-free survival according to surgical technique

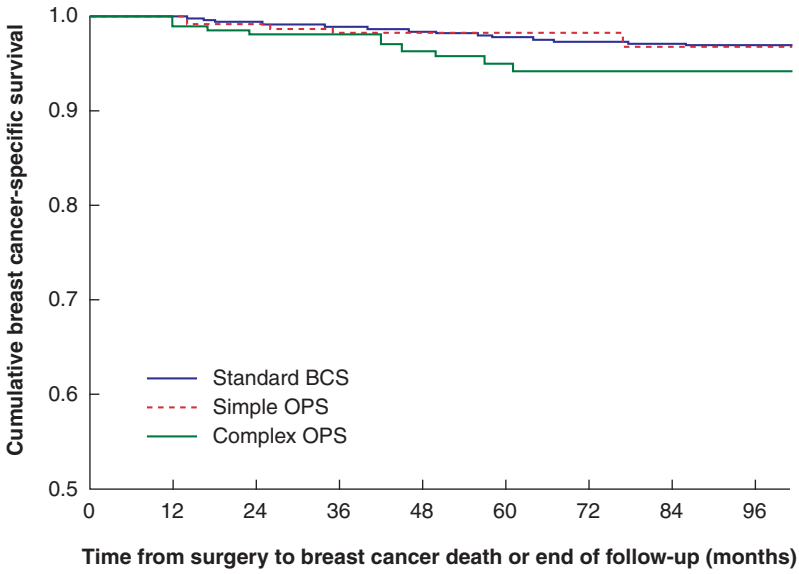
BCS, breast-conserving surgery; OPS, oncoplastic BCS. P=0.484 (log rank test).



No. at risk					
Standard BCS	3719	3662	2895	1740	747
Simple OPS	243	240	143	70	22
Complex OPS	215	210	152	68	27

Fig. 4 Kaplan–Meier survival analysis of overall survival according to surgical technique

BCS, breast-conserving surgery; OPS, oncoplastic BCS. P=0.350 (log rank test).



No. at risk					
Standard BCS	3719	3697	2976	1828	803
Simple OPS	243	241	149	73	25
Complex OPS	215	211	153	71	28

Fig. 5 Kaplan–Meier survival analysis of breast cancer-specific survival according to surgical technique

BCS, breast-conserving surgery; OPS, oncoplastic BCS. *P*=0.056 (log rank test).

on only four events, oncoplastic surgery was not associated with increased rates of local recurrence (simple OPS *versus* standard BCS: HR 0.32, 95 per cent c.i. 0.04 to 2.29; complex OPS *versus* standard BCS: HR 1.02, 0.32 to 3.24; $P=0.522$). Higher tumour grade and hormone receptor-negative tumour subtype were associated with an increased risk of local recurrence. The unadjusted significant effect of receiving chemotherapy was lost when adjusting for tumour subtype (adjusted HR 1.03, 95 per cent c.i. 0.53 to 1.99). The same effect was seen when endocrine therapy was adjusted for tumour subtype (adjusted HR 0.24, 0.04 to 1.28). When adjusting radiation dose for age, considering that boost is given predominantly to patients in younger age groups, standard fractionation, but not boost, remained significantly associated with the risk of local recurrence (adjusted HR 1.90, 1.03 to 3.51).

For the secondary endpoint of OS, OPS was not associated with overall mortality rates (simple OPS *versus* standard BCS: adjusted HR 1.57, 95 per cent c.i. 0.89 to 2.77; complex OPS *versus* standard BCS: adjusted HR 1.12, 0.57 to 2.21; $P=0.314$) (*Table 3*). However, high tumour grade and higher age were independently associated with poorer OS, whereas positive nodal stage and greater tumour size, though significantly worsening OS in univariable analysis, did not retain a significant independent association after adjustment. Worsened breast cancer-specific survival was independently associated with positive nodal stage (adjusted HR 2.35, 1.36 to 4.04) and high tumour grade (adjusted HR 5.73, 1.58 to 20.77), but not with the type of surgical technique used.

Discussion

The main finding of this large cohort study is that the use of oncoplastic techniques did not increase the risk of local recurrence or death. This result was found, despite the fact that patients undergoing OPS had larger tumours, more nodal involvement, and more adverse tumour biology. Furthermore, the use of OPS had increased significantly over time.

Historically, BCS was mostly confined to smaller tumours. Thus, the key randomized trials of the 1970s and 1980s showing the oncological equivalence of BCS—given that whole-breast irradiation was applied—to mastectomy allowed inclusion of tumours up to 4 cm[20] and up to 2 cm[12] respectively. In reality, tumour sizes were still smaller than that, considering that 58 per cent of node-negative cases in the National Surgical Adjuvant Breast Project B-06 trial[21] had tumours of 2 cm or less, and about 45 per cent of patients in the Milan trial[12] had tumours of less than 1 cm in size. Even in one of the largest modern cohort studies by van Maaren *et al.*[3], median tumour size in BCS was barely 15 mm, with a maximum reported size of 20 mm. T1 tumours comprised a large proportion of the tumours in the present study as well, even though 75 per cent of the smallest tumours were excluded. Whether such findings can be translated safely to larger tumours in current breast cancer populations is thus an ongoing debate.

The use of oncoplastic techniques in BCS allows for the excision of larger tissue volumes and therefore of larger tumours. Accordingly, tumour sizes in OPS are closer to those seen in patients undergoing mastectomy than in those having standard BCS[13,22], which in addition increases the likelihood of nodal metastasis. Interestingly, even in the work of Mansell and colleagues[22], the proportion of T3 tumours was exceedingly small, only 2.7 per cent. The single-centre study by Carter *et al.*[23] reached a total of 112 T3–4 cases treated by BCS or OPS, thus amounting to 2.4 per cent of the total BCS cohort of 4736 patients. The proportion of T3–4 tumours was even smaller, only 0.4 per cent, in the single-centre study of Niinikoski and co-workers[24] from Helsinki, which compared 1189 BCS with 611 OPS cases. One of the few studies reporting on tumours larger than 5 cm referred to this type of mastectomy-sparing surgery as ‘extreme

Table 2 Univariable Cox regression analysis with ipsilateral local recurrence as the endpoint

	No. of cases (n=4178*)	No. of local recurrences (n=61)	Univariable HR	P
Age (years)				0.484
<41	188	5	1.96 (0.74, 5.17)	
41–50	701	12	1.21 (0.60, 2.45)	
51–65	1648	22	0.94 (0.52, 1.71)	
>65	1615	22	1.00 (reference)	
Missing	26	0		
Invasive tumour category*				0.304
T1	2913	39	1.00 (reference)	
T2–3	1239	22	1.31 (0.78, 2.22)	
Missing	26	0		
Histological subtype				0.742
Ductal	3312	51	1.00 (reference)	
Lobular	443	6	0.89 (0.38, 2.07)	
Other	381	4	0.68 (0.25, 1.88)	
Missing	42	0		
Tumour multifocality				0.552
Yes	331	6	1.29 (0.56, 3.00)	
No	3787	55	1.00 (reference)	
Missing	60	0		
Node category				0.106
Negative	3050	39	1.00 (reference)	
Positive	1096	22	1.54 (0.91, 2.60)	
Missing	32	0		
Nottingham histological grade				<0.001
1	739	5	1.00 (reference)	
2	2014	14	1.06 (0.38, 2.96)	
3	1144	33	4.37 (1.71, 11.20)	
Missing	281	9		
Tumour surrogate subtype†				<0.001
ER/PR+ HER2−	3232	28	1.00 (reference)	
ER/PR+ HER2+	334	5	1.82 (0.70, 4.71)	
ER/PR− HER2+	128	4	3.75 (1.31, 10.69)	
ER/PR− HER2−	361	19	6.66 (3.72, 11.93)	
Missing	123	5		
Chemotherapy				0.028
Yes	1867	36	1.77 (1.06, 2.96)	
No	2237	25	1.00 (reference)	
Missing	74	0		
Endocrine therapy				<0.001
Yes	3627	36	1.00 (reference)	
No	503	25	5.54 (3.25, 9.02)	
Missing	48	0		
Anti-HER2 therapy				0.405
Yes	432	8	1.37 (0.65, 2.89)	
No	3699	52	1.00 (reference)	
Missing	47	1		
Type of surgery				0.522
Standard BCS	3698	57	1.00 (reference)	
Simple OPS	242	1	0.32 (0.04, 2.29)	
Complex OPS	212	3	1.02 (0.32, 3.24)	
Missing	26	0		
Closest peripheral margin (mm)‡			0.98 (0.94, 1.02)	0.429
≥2	3176	49	1.00 (reference)	
<2	515	6	0.78 (0.33, 1.82)	0.569
Missing	487	6		
Radiation dose and fractionation				0.030
Hypofractionation	1819	16	1.00 (reference)	
Standard fractionation	1482	29	1.91 (1.04, 3.52)	
Hypofractionation + boost	387	3	0.87 (0.25, 2.98)	
Standard fractionation + boost	431	12	2.74 (1.30, 5.81)	
Missing	59	1		

Values in parentheses are 95 per cent confidence intervals. Each tumour represents one case. *Pretreatment cT category for neoadjuvant cases and histopathological tumour size for primary surgery. †Values derived from pretreatment core needle biopsy in neoadjuvant cases and from histopathological assessment of specimen in primary surgery. ‡Continuous variable. HR, hazard ratio; ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast-conserving surgery; OPS, oncoplastic breast-conserving surgery.

Table 3 Univariable and multivariable Cox regression analysis with all-cause death as the endpoint, including only cases with no missing information for all co-variables in both models

	No. of cases (n=3320)	No. of deaths (n=207)	Univariable HR	*P*	Multivariable HR	*P*
Age (years)				<0.001		0.001
<41	129	5	0.40 (0.16, 0.98)		0.71 (0.20, 2.57)	
41–50	530	18	0.36 (0.22, 0.59)		0.70 (0.28, 1.73)	
51–65	1330	70	0.56 (0.41, 0.75)		0.52 (0.38, 0.72)	
>65	1331	114	1.00 (reference)		1.00 (reference)	
Invasive tumour category*				0.011		0.062
T1	2452	135	1.00 (reference)		1.00 (reference)	
T2–3	868	72	1.45 (1.09, 1.92)		1.34 (0.98, 1.82)	
Histological subtype				0.690		0.452
Ductal	2651	168	1.00 (reference)		1.00 (reference)	
Lobular	375	19	0.82 (0.51, 1.31)		0.74 (0.45, 1.22)	
Other	294	20	1.04 (0.65, 1.65)		1.07 (0.66, 1.73)	
Tumour multifocality				0.951		0.986
Yes	258	15	0.98 (0.58, 1.66)		1.00 (0.59, 1.71)	
No	3062	192	1.00 (reference)		1.00 (reference)	
Node category				0.011		0.075
Negative	2536	141	1.00 (reference)		1.00 (reference)	
Positive	784	66	1.46 (1.09, 1.96)		1.45 (0.96, 2.19)	
Nottingham histological grade				0.003		0.035
1	634	28	1.00 (reference)		1.00 (reference)	
2	1716	98	1.38 (0.90, 2.10)		1.36 (0.88, 2.10)	
3	970	81	1.97 (1.28, 3.03)		1.94 (1.16, 3.24)	
Tumour surrogate subtype†				<0.001		0.696
ER/PR+ HER2−	2742	162	1.00 (reference)		1.00 (reference)	
ER/PR+ HER2+	242	9	0.64 (0.32, 1.24)		0.76 (0.26, 2.22)	
ER/PR− HER2+	87	4	0.77 (0.28, 2.07)		0.42 (0.07, 2.44)	
ER/PR− HER2−	249	32	2.32 (1.59, 3.39)		0.98 (0.31, 3.17)	
Chemotherapy				0.479		0.417
Yes	1400	92	1.10 (0.84, 1.45)		0.85 (0.58, 1.25)	
No	1920	115	1.00 (reference)		1.00 (reference)	
Endocrine therapy				<0.001		0.183
Yes	2973	169	1.00 (reference)		1.00 (reference)	
No	347	38	2.01 (1.41, 2.85)		2.15 (0.70, 6.66)	
Anti-HER2 therapy				0.067		0.557
Yes	295	11	0.57 (0.31, 1.04)		0.72 (0.23, 2.19)	
No	3025	196	1.00 (reference)		1.00 (reference)	
Type of surgery				0.508		0.289
Standard BCS	2991	185	1.00 (reference)		1.00 (reference)	
Simple OPS	184	13	1.39 (0.79, 2.44)		1.57 (0.89, 2.77)	
Complex OPS	145	9	1.10 (0.75, 2.16)		1.12 (0.57, 2.21)	
Closest peripheral margin (mm)				0.387		0.258
≥2	2865	184	1.00 (reference)		1.00 (reference)	
<2	455	23	0.83 (0.53, 1.27)		1.29 (0.83, 2.01)	
Radiation dose and fractionation				0.003		0.140
Hypofractionation	1549	100	1.00 (reference)		1.00 (reference)	
Standard fractionation	1165	89	0.95 (0.72, 1.27)		0.84 (0.61, 1.16)	
Hypofractionation + boost	304	5	0.24 (0.10, 0.60)		0.25 (0.07, 0.87)	
Standard fractionation + boost	302	13	0.52 (0.29, 0.92)		0.41 (0.14, 1.19)	
Regional node irradiation				0.043		0.492
Yes	464	39	1.43 (1.01, 2.03)		1.20 (0.71, 2.02)	
No	2856	168	1.00 (reference)			

Values in parentheses are 95 per cent confidence intervals. Each patient represents one case: bilateral cancers generate one case only, with the analysed laterality selected at random. *Pretreatment cT category for neoadjuvant cases and histopathological tumour size for primary surgery. †Values derived from pretreatment core needle biopsy in neoadjuvant cases and from histopathological assessment of specimen in primary surgery. HR, hazard ratio; ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast-conserving surgery; OPS, oncoplastic breast-conserving surgery.

oncoplasty'[25]; the follow-up of 24 months was short, and in only 1 of 66 cases was local recurrence observed. Dedicating an entire study only to patients with large tumours, Mazor and colleagues[26] reported no differences in OS between the use of breast conservation *versus* mastectomy for 37 268 cT3 and/or pT3 tumours; however, no data on local recurrence were presented. Thus, there is mounting evidence that the use of breast conservation may be safe even in patients with large tumours previously thought to require a mastectomy. In the present study, only 51 patients (1.2 per cent) with T3 tumours were identified in the entire cohort, a very low proportion but similar to that in the above-mentioned studies. As all included patients were operated on by BCS, this may indicate that mastectomy rates in patients with large tumours are still rather high, and

warrants a subsequent comparative analysis with patients undergoing mastectomy.

There is international consensus that 'no tumour on ink' is an acceptable resection margin in invasive breast cancer[27,28], even though a recent meta-analysis[29] suggested that a 2-mm margin may be more favourable. It has been proposed[10] that oncoplastic techniques allow for larger resection margins, but this was only partly confirmed in the present analysis; the largest median peripheral margins were found in the complex OPS group, but the smallest median margins were found in the simple OPS group. The present study found no advantage for resection margins wider than 2 mm. Of note, the present authors could not report on the percentage of re-excision in patients with positive margins, as BCS as the final surgical strategy and free margins were part of the selection criteria. In the meta-analysis by Losken *et al.*[9], however, positive margins were significantly less common in OPS than in standard BCS.

It is an interesting notion that local recurrence rates seem to be declining, most probably due to improved systemic treatments and earlier detection, improved preoperative imaging, and more precise identification of high-risk patients. It is important to point out, however, that the proportion of small tumours was high, even in the present study, potentially explaining the low recurrence rates. In a recent analysis[2] of a prospective Swedish cohort, the 13-year local recurrence rate after BCS with whole-breast irradiation was only 9.5 per cent, equal to the outcome after mastectomy without irradiation. It appears that the observation of an increased risk of local recurrence after BCS compared with mastectomy, as described in earlier trials[12], may not hold true today, and as the absolute numbers of local recurrences are decreasing more focus should be on patient-reported outcomes after breast cancer surgery. Here, the benefit of oncoplastic approaches to BCS in terms of an improved quality of life and higher satisfaction with the aesthetic outcome is well documented[9].

The present study found no increased risk of local recurrence for OPS compared with standard BCS. Even though there was a trend towards a lower breast cancer-specific survival rate in the complex OPS group, this could be explained more by the number of advanced tumours in this group than by the type of surgery.

The results of the present study are potentially limited by the relatively short median follow-up of 5 years after surgery, as well as the low numbers of local recurrence and death in the analysed groups. However, the study is strengthened by the high level of data quality and completeness from the well validated NKBC, and the addition of a thorough medical chart review of all included cases, ensuring a high case capture rate with complete and detailed exposure and outcome information.

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