Oncoplastic Breast Surgery Compared to Conventional Breast-Conserving Surgery With Regard to Oncologic Outcome

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Abstract

The oncologic outcome of oncoplastic breast surgery (OBS; 197 patients) was compared to conventional breast-conserving surgery (BCS; 1399 patients) with regard to primary radical excision, time to adjuvant treatment, disease-free survival, and overall survival. There was a lower risk for nonradical primary tumor excision in patients undergoing OBS versus conventional BCS. No other statistically significant differences were found. These results indicate that OBS is a safe procedure.

Introduction: Oncoplastic breast surgery (OBS) has been implemented with increasing frequency in the treatment of breast cancer. The aim of this study was to compare the oncologic outcome after OBS to the outcome after conventional breast-conserving surgery (BCS) in patients with invasive breast cancer. **Patients and Methods:** In all, 197 patients treated with OBS were compared to 1399 patients treated with conventional BCS from 2008 to 2013. We evaluated nonradical primary tumor excision, time to initiation of adjuvant therapy, disease-free survival (risk of recurrent disease), and survival (cause specific and overall). Identification of patients and follow-up were made using the Danish Breast Cancer Cooperative Group registry and the Danish Cause of Death registry. Multivariate logistic regression and the Cox proportional hazard analysis were used to obtain odds ratios and hazard ratios with 95% confidence intervals (CI). **Results:** There was a lower risk for nonradical primary tumor excision for patients undergoing OBS versus conventional BCS (adjusted odds ratio:95% CI, 0.50:0.29-0.84). No significant differences were found with regard to a delay in initiation of adjuvant chemotherapy (adjusted hazard ratio:95% CI, 1.14:0.89-1.45) or radiotherapy (0.91:0.71-1.16), disease-free survival (1.23:0.61-2.47), breast cancer as cause of death (1.46:0.52-4.09), breast cancer as underlying or multiple cause of death (0.90:0.34-2.37), or overall survival (0.90:0.51-1.60). **Conclusion:** We found no significant differences in oncologic outcome comparing OBS to conventional BCS. However, a lower risk of nonradical primary tumor excision was found for patients treated with OBS. These results indicate that OBS is a safe procedure.

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Introduction

Breast-conserving surgery (BCS) combined with adjuvant radiotherapy—that is, breast-conserving therapy (BCT)—has been shown to be equally safe as mastectomy regarding oncologic outcome.[1-3] BCS has technically developed, and so-called oncoplastic breast surgery (OBS) has been implemented over the last decades.[4-11] However, the oncologic safety related to OBS is not clear.[6,12-17]

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The aim of OBS is to improve the aesthetic and functional outcomes of OBS, factors that have been shown to influence health-related quality of life.[9,18-20] In addition to this, OBS may expand the indications for BCS, as larger tumors and tumors with technically more challenging locations do not have to undergo mastectomy.[4,5,12,20-22] The surgical procedures in OBS, including level I and II,[23,24] imply more extensive surgery than conventional BCS, eg, wider incisions, extended tissue mobilization, and even flap reconstruction.[4,5,7,8,25] Studies on complications have shown no or only small increases in complication rates in OBS compared to conventional BCS.[4,5,14,26,27] Still, more extensive surgery could potentially lead to delay in the initiation of adjuvant therapy and by this possibly compromise the oncologic outcome, survival affected and poorer prognosis.[14,21,28]

Few studies have evaluated the oncologic outcome after OBS compared to BCS.[13,17,29] The results of these studies indicate oncologic outcomes comparable with conventional BCS. However, many of these studies included a small number of patients, and further studies investigating the safety of the oncologic outcome are still needed.

In this study, we evaluated early and longtime oncologic outcome after OBS for 197 patients, compared to 1399 patients treated with conventional BCS. The cohorts were population based and included consecutive patients treated from 2008 to 2013 at selected centers in Denmark. Baseline information was prospectively collected at the time of surgery, and follow-up was performed using the National Danish Breast Cancer Cooperative Group (DBCG) registry[30] and the Danish Cause of Death Registry.[31] The aim of this study was to compare OBS with conventional BCS with regards to oncologic safety as measured by radical tumor excision at the primary operation and time to initiation of the first adjuvant therapy. An additional aim was to compare disease-free survival (risk of recurrent disease), cause-specific survival, and overall survival.

Patients and Methods

Patients

Patients treated for invasive primary breast cancer with BCS from 2008 to 2013 were included. The OBS cohort (n = 197) was mainly recruited from the southern region of Denmark. In order to avoid a potential selection bias due to different indications for surgical technique, we did not compare OBS patients to the rest of BCS patients from the same geographical area. Instead, we chose all BCS patients in the northern region of Denmark, an area where OBS was not implemented as a routine procedure during the study period. We identified 1399 BCS patients in this area (BCS North cohort). In order to compare potential regional differences, we also collected information on adjuvant therapy for all BCS patients in the southern region of Denmark, the BCS South cohort (n = 3662).

By permission from the Danish Clinical Registries, Danish National Board of Health,[32] data for patients in the OBS cohort, the BCS North cohort, and the BCS South cohort were identified in the DBCG registry.[30] All Danish residents are given a unique identification number, a CPR number, that facilitates record linkage.

OBS Cohort

Patients. Patients treated with OBS were consecutively registered in a research database. These patients underwent surgery in the Region of Southern Denmark at the Hospital of Southwest Jutland, Esbjerg, between January 1, 2008, and December 31, 2013, or at the Hospital of South Jutland, Åbenrå, from October 1, 2010, to December 31, 2013. Patients were also included from a private hospital, Privathospitalet Hamlet, Copenhagen, Denmark, in the period January 1, 2008, to December 31, 2010. The research database had been approved by the Danish Data Protection Agency,[33] and in all, 236 patients were registered (Figure 1). Patients in the research database who were identified in the DBCG registry[30] were included in the OBS cohort. Patients in the database were excluded when they had no breast cancer diagnosis (n = 17), no data in the DBCG registry (n = 5), surgery performed outside the study period (n = 5), or duplicate entries in the database (n = 4). Patients with bilateral cancers at the time of surgery (n = 4) or a second breast cancer in the follow-up period, ie, a bilateral event (n = 4), were also excluded. In all, 197 patients from the research database remained in the OBS cohort (Hospital of Southwest Jutland, n = 86; Hospital of South Jutland, n = 91; and Privathospitalet Hamlet, n = 20), as shown in Figure 1.

Surgery and Adjuvant Therapy. Patients in the OBS cohort were operated with either level I or level II OBS. In this study, we defined level I OBS (n = 63) to include, besides tumor resection, closure of cavity and skin, which represent conventional BCS, additional skin incisions, mobilization and adaption of glandular tissue, and often reorientation of the nipple–areola complex. We defined level II OBS (n = 134) to include more advanced and complex surgical procedures, such as volume reduction or therapeutic mammoplasty (n = 38), or displacement (n = 48) and replacement (n = 48) techniques. The latter include perforator-based flaps but also muscle-sparing latissimus dorsi flaps. Furthermore, level II OBS often include contralateral surgery (n = 75) to achieve symmetry to the reconstructed breast, ie, a reduction mammoplasty or a mastopexy, in the same surgical procedure. Level II OBS procedures require experience with techniques from reconstructive and aesthetic plastic surgery. However, patients operated with a mastectomy followed by an immediate autologous or implant reconstruction were not included in the study as oncoplastic procedures.

Fourteen of the 197 patients had a mastectomy after the primary oncoplastic procedure. Adjuvant chemotherapy was administered at 4 departments of oncology and radiotherapy at 3 departments, 2 in Denmark and 1 in Germany.

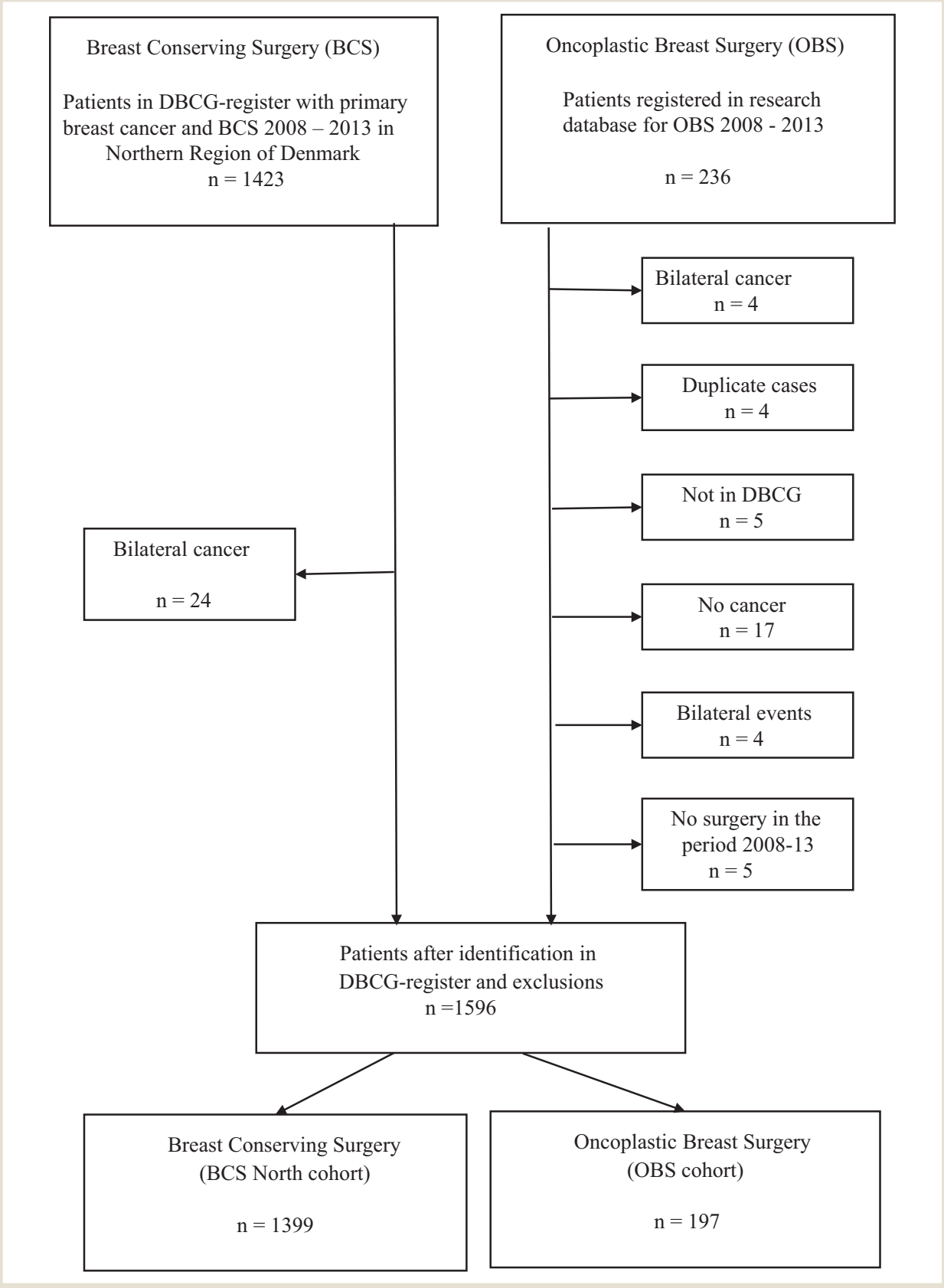
BCS North Denmark Cohort

All patients treated with BCS in the Region of Northern Denmark from January 1, 2008, to December 31, 2013, were identified as a consecutive population-based cohort in the national DBCG registry[30] (n = 1423). Patients who had bilateral cancers at the time of surgery (n = 24) were excluded, resulting in 1399 patients in the BCS North cohort (Figure 1). Among them, 14 patients had a mastectomy resulting from the primary breast-conserving procedure. Adjuvant chemotherapy and radiotherapy were provided at a single department of oncology.

BCS South Denmark Cohort

All patients treated with BCS in the Region of Southern Denmark from January 1, 2008, to December 31, 2013, were similarly identified in the DBCG registry[30] (n = 3662). Only data

Figure 1 Breast-Conserving Surgery (BCS) and Oncoplastic Breast Surgery (OBS) Cohorts



regarding time of surgery as well as administration of and time to initiation of adjuvant therapy were collected. Adjuvant chemotherapy and radiotherapy for the BCS South cohort were administered at the same departments as for the OBS cohort.

DBCG Registry

The DBCG registry,[30] a nationwide registry established in 1976, is a clinical database receiving data from all departments of radiology, surgery, pathology, and oncology involved in the diagnosis and treatment of breast cancer. Data include date of diagnosis, tumor characteristics, surgical treatment, oncologic adjuvant therapy, and information on recurrent disease and death. The use of oncoplastic surgical techniques has been registered since July 1, 2010. Data for postoperative complications are not registered in DBCG. The present study used information collected between January 1, 2008, and January 3, 2017.

Treatment of Breast Cancer in Denmark

Patients in all parts of Denmark with breast cancer are treated according to national guidelines issued by the DBCG.[30] The recommended surgical treatment for conventional BCS implies radical surgery with excision of the tumor and in most cases, with no preoperative known axillary metastases, sentinel node diagnostics. During the study period, proof of axillary metastases (detected clinically, by image diagnostics or the sentinel node examination) led to a recommendation of axillary clearance.

Adjuvant therapy for breast cancer consist of 4 modalities: chemo-, radio-, endocrine-, and immunotherapy, with chemotherapy always initiated as the first mode of adjuvant therapy if indicated, then followed by radiotherapy and endocrine therapy. According to the DBCG guidelines,[34] indication for treatment as well as extent and dose of postoperative adjuvant therapy are dependent on age, menopausal status, resections margins, tumor size, tumor focality, eventual metastatic disease, Nottingham histologic grade, assessment by the tumor, node, metastasis classification system, and estrogen receptor and HER2 status.

Patient, Diagnostic, and Tumor Characteristics

Several factors may influence oncologic safety and prognosis. The present analyses used information on age at time of surgery and tumor-related factors such as Nottingham histologic grade, vascular invasion, tumor focality, tumor (T) and node (N) classification, estrogen receptor status, and HER2 status. Factors used in additional analyses included histologic type, progesterone status, menopausal status, specimen size, mode of detection (screening yes/no), sentinel node status, and whether an axillary clearance had been performed. All of this information was collected from the DBCG registry. Data from a parallel patient-reported outcome study including the OBS and the BCS North cohorts was used to calculate body mass index.

End Point Definition and Follow-up

Data on radical excision was collected from the DBCG registry. A radical excision was defined as $\geq$ 2 mm from carcinoma to excision line, and $\geq$ 2 mm from ductal carcinoma-in-situ if ductal carcinoma-in-situ was diagnosed. In the last 6 months of the study period, no ink on tumor was accepted as radical for invasive carcinoma if a radiotherapy boost was provided.[34] However, this was not registered in the DBCG registry.[30] Information on days from surgery to initiation of adjuvant chemo- and/or radiotherapy was available from the DBCG registry[30] including data from January 1, 2008, to January 3, 2017.

Recurrent disease, as locoregional or distant metastatic disease, was registered in the DBCG registry[30] as the event "recidiv," and data were retrieved for the period January 1, 2008, to January 3, 2017. Data for overall mortality during the same period were also obtained from the DBCG registry.[30] Information on mortality due to breast cancer and breast cancer as underlying or multiple cause of death was available through record linkage with the Danish Cause of Death Registry[31] up until December 31, 2014.

Statistical Analysis

The OBS and BCS North cohorts were compared regarding factors that may affect studied end points, ie, patient, diagnostic and tumor characteristics. The risk of nonradical primary tumor excision was compared between the OBS and BCS North cohorts, including all patients in an intention-to-treat design (ie, including patients who later underwent a mastectomy). A logistic regressions analysis yielded odds ratios (OR) with 95% confidence intervals (CIs). The most important prognostic factors (Table 1) were selected a priori and were included in a second multivariate model.

Data in the analyses for initiation of chemotherapy and radiotherapy included only values from 14 days after surgery until 180 days after surgery, as adjuvant therapy initiated earlier was regarded as neoadjuvant therapy and adjuvant therapy initiated later was probably not provided directed toward the primary tumor or as incorrect registration. In these analyses, patients who had a mastectomy as a secondary surgical procedure were excluded as a per-protocol analysis. This was chosen because a secondary mastectomy will probably heavily affect time to and also indications for adjuvant treatment. However, sensitivity analyses including patients who had a mastectomy were also performed. Time to initiation of adjuvant therapy was compared between OBS and BCS North patients using a Kaplan-Meier analysis including a log-rank test. Following this, a Cox proportional hazards analysis was used to calculate hazard ratios (HR) with 95% CIs. In a second model, prognostic factors (Table 1) were included as covariates together with factors that may delay adjuvant therapy, ie, a nonradical excision, lumpectomy size, and axillary clearance. The HRs can be regarded as a measure on the difference between groups in the probability of having started adjuvant therapy at a given point in time. Eventually, all selected patients in this subanalysis will receive adjuvant therapy.

Disease-free survival, defined as survival without recurrent disease, and survival with regard to breast cancer cause of death, multiple and breast cancer cause of death, and overall mortality were also analyzed by Cox proportional hazards analysis. The same prognostic factors (Table 1) were chosen as covariates in these analyses. In these analyses, patients who had a mastectomy were included in, ie, intention-to-treat analyses, but sensitivity analyses were also performed excluding these patients, ie, per-protocol analyses.

Additional sensitivity analyses were performed for time to initiation of adjuvant therapy, disease-free survival, and survival excluding patients in the BCS North cohort registered in the

Table 1 Prognostic Factors

Factor	Category	BCS North (N = 1399) (%)	OBS (N = 197) (%)	Total (N = 1596) (%)
Age	< 50 y	13.9	22.3	14.9
	≥ 50 y to < 65 y	51.3	53.8	51.6
	≥ 65 y	34.9	23.9	33.5
Nottingham histologic grade	I	29.6	24.9	29.0
	II	36.2	42.1	36.9
	III	21.2	26.9	21.9
	Missing	13.0	6.1	12.2
Vascular invasion	No	88.1	76.1	86.6
	Yes	9.6	18.8	10.8
	Missing	2.3	5.1	2.6
Focality	Unifocal	94.6	92.9	94.4
	Multifocal (≥2)	2.1	5.6	2.5
	Missing	3.4	1.5	3.1
Tumor (T) classification	T1 ≤ 20 mm	81.7	60.4	79.1
	T2 21-50 mm	17.5	37.1	19.9
	T3 > 50 mm	0.4	0.0	0.4
	Missing	0.4	2.5	0.6
Node (N) classification	N0	66.1	51.3	64.3
	N1	25.9	37.6	27.3
	N2	4.9	4.6	4.9
	N3	1.9	4.6	2.3
	Missing	1.1	2.0	1.3
Estrogen receptor status	Negative	13.4	14.7	13.6
	Positive	86.1	83.8	85.8
	Missing	0.5	1.5	0.6
HER2 status	Negative	75.5	85.8	76.8
	Positive	8.6	11.2	8.9
	Missing	15.9	3.0	14.3

Abbreviations: BCS North = Breast-Conserving Surgery North cohort; OBS = Oncoplastic Breast Surgery cohort.

DBCG registry[30] as treated with OBS (n = 51). Further, additional sensitivity analyses were performed excluding patients who had a level I oncoplastic procedure for nonradical primary tumor excision, adjuvant therapy, disease-free survival, and survival. Data were analyzed by SPSS Statistics 24.0 software (IBM, Armonk, NY).

Ethics

The study was approved by the regional committees on health research ethics for Southern Denmark. The study was submitted for evaluation to the regional ethical review board in Lund, Sweden, because the research was also conducted at Lund University, but their approval was not required (2014/882).

Results

Study Cohort Characteristics

Median age for the OBS cohort was 57 years (range, 31-80 years) and for the BCS North cohort was 61 years (range, 24-93 years). Patients in the OBS cohort, compared to the BCS North cohort, had on average tumors with a higher histologic grade, tumors more often had vascular invasion, a larger number of multifocal tumors were present, tumors were larger, and patients more often had positive lymph nodes as well as tumors with negative HER2 receptor status (Table 1). Supplemental Table 1 in the online version shows that patients in the OBS cohort, compared to the BCS North cohort, were more often premenopausal, had a larger resection at surgery, and had been diagnosed by screening to a larger extent.

Table 2 OR for Nonradical Surgery at Time of Lumpectomy

Cohort	All[a]	Radical	Nonradical	OR	aOR[b]
BCS North	1364	1146	218 (16.0%)	1.00	1.00
OBS	190	171	19 (10.0%)	0.58 (0.36-0.96)	0.50 (0.29-0.84)
Total	1554	1317	237		

Abbreviations: aOR = adjusted odds ratio; BCS North = Breast-Conserving Surgery North cohort; OBS = Oncoplastic Breast Surgery cohort; OR = odds ratio.
[a]Data for 42 of 1596 patients were missing.
[b]Adjusted for age, Nottingham histologic grade, vascular invasion, tumor focality, T and N status, estrogen receptor status, and HER2 status.

Table 3 Days From Surgery to Initiation of Radiotherapy and Chemotherapy as First Adjuvant Therapy by Region

First Adjuvant Therapy	Cohort	Patients			Days					HR (95% CI) for:	
		No. Total	No. Treated	%	Mean	SD	Median	Min	Max	Range	HR	aHR[a]
Chemotherapy	BCS North	1385	477	34.4	40.9	13.6	38.0	16	179	163	1.00	1.00
	OBS	183	88	48.1	36.7	21.7	30.0	15	171	156	1.21 (0.96-1.52)	1.14 (0.89-1.45)
	BCS South	3662	1314	35.9	36.5	17.0	33.0	15	171	156	NA	NA
Radiotherapy	BCS North	1385	712	51.4	53.9	28.0	44.0	16	180	164	1.00	1.00
	OBS	183	79	43.2	60.6	38.0	48.0	17	175	158	0.85 (0.68-1.08)	0.91 (0.71-1.16)
	BCS South	3662	2130	58.2	49.4	21.6	43.0	15	180	165	NA	NA

During period January 1, 2008, to December 31, 2014, per protocol (ie, without mastectomy).
Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; BCS South = Breast-Conserving Surgery South cohort; CI = confidence interval; HR = hazard ratio; NA = not applicable; OBS = Oncoplastic Breast Surgery cohort; SD = standard deviation.
[a]Adjusted for vascular invasion, age, Nottingham histologic grade, estrogen receptor status, HER2 status, tumor focality, T and N classification, axillary dissection, primary radical resection, and lumpectomy size.

Tumors in the OBS cohort more frequently had micrometastases and locoregional macrometastases, and hence a higher percentage of patients were operated with an axillary clearance. Patients in the OBS cohort were also more likely to receive all types of adjuvant therapy (Supplemental Table 2 in the online version).

Risk of Nonradical Surgery at Time of Lumpectomy

Data on surgical radicality were available for 1554 of 1596 patients (Table 2). In total, 237 patients had surgery with nonradical primary tumor excision at the time of lumpectomy, 10.0% in the OBS cohort and 16.0% in the BCS North cohort. The adjusted OR for OBS patients compared to BCS North patients for nonradical primary tumor excision was 0.50 (95% CI, 0.29-0.84). These results were similar excluding patients in the BCS North cohort registered as treated with OBS (adjusted OR:95% CI, 0.50:0.29-0.85). However, the results of the sensitivity analysis excluding patients operated with level I oncoplastic procedures in the OBS cohort showed an adjusted OR (95% CI) of 0.58 (0.31-1.06).

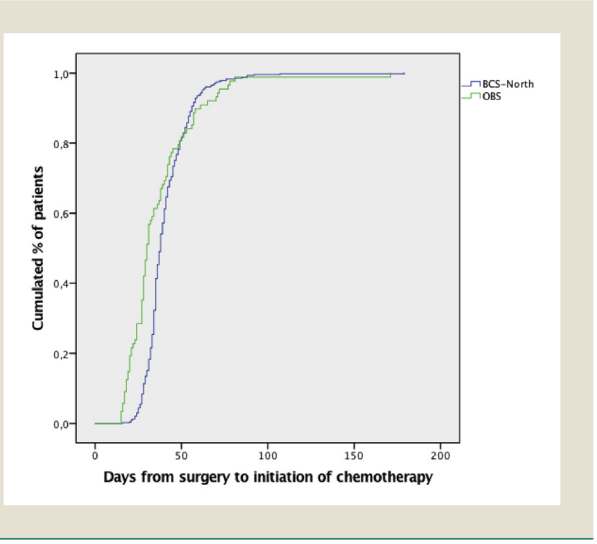
Time to Initiation of First Adjuvant Therapy

In the OBS cohort, 48.1% were treated with chemotherapy as the first mode of adjuvant therapy, initiated after a median time of 30.0 days, while in the BCS North cohort, 34.4% were treated after a median time of 38.0 days after surgery (Table 3). The Kaplan-Meier plot in Figure 2 shows days to initiation of chemotherapy as the first mode of adjuvant therapy. The curve for patients in the OBS cohort raises faster than the curve for BCS North cohort, ie, more patients at a given point of time had initiated therapy, indicating patients treated with OBS receive adjuvant chemotherapy earlier than the BCS North cohort. The result of the log-rank test showed $P = .078$. The HR refers to the risk (chance) at any given time point to have received adjuvant therapy, ie, a high HR means a lower risk of late initiation. We found an adjusted HR (95% CI) of 1.14 (0.89-1.45) (Table 3). That is, there was no statistically significant difference between the OBS cohort and the BCS North cohort in time to initiation of chemotherapy. Comparing the OBS cohort and the BCS South cohort showed virtually the same mean time, and a similar median time, to initiation of chemotherapy (Table 3).

In the OBS cohort, 43.2% were treated with radiotherapy as first adjuvant therapy, with a median time to initiation of 48.0 days, while in the BCS North cohort, 51.4% were treated with a median time to initiation of therapy of 44.0 days (Table 3). The Kaplan-Meier plot shows a slightly later start for OBS patients compared to patients in the BCS North cohort (Figure 3). The result of the log-rank test showed $P = .077$. This corresponded to an adjusted HR (95% CI) of 0.91 (0.71-1.16). When comparing time to initiation of radiotherapy, we found a mean time of 60.6 days and a median time of 48.0 days for the OBS cohort compared to a mean time of 49.4 days and a median time of 43.0 days for the BCS South cohort. Sensitivity analyses including patients who had a secondary mastectomy, ie, an intention-to-treat analysis, did not alter the results for chemotherapy or radiotherapy (Supplemental Table 3 in the online version).

In the same way, the results were similar when excluding patients registered in the DBCG registry for surgery with oncoplastic techniques in the BCS North cohort, as well as results when excluding patients operated with level I oncoplastic procedures in the OBS cohort.

Figure 2 Days From Surgery to Initiation of Chemotherapy as First Adjuvant Therapy by Cohort. Cohorts Include BCS North Cohort and OBS Cohort for Period January 1, 2008, to December 31, 2014. Log-rank $P = .078$



Abbreviations: BCS = breast-conserving surgery; OBS = oncoplastic breast surgery.

Disease-free Survival and Mortality

Concerning disease-free survival, ie, survival without recurrent disease, the median (range) follow-up time for the OBS cohort was 4.1 (0.0-8.9) years and for the BCS North cohort 5.6 (0.0-9.0) years. In the OBS cohort, 12 recurrences were found (6.09%), and in the BCS North cohort 51 (3.65%), as shown in Supplemental Table 4 in the online version. Disease-free survival was lower in the OBS cohort compared to the BCS North cohort (Supplemental Figure 1 and Supplemental Table 5 in the online version). This difference corresponded to an HR (95% CI) of 1.88 (1.00-3.54), but the adjusted HR was attenuated (1.23:0.61-2.47).

Concerning overall mortality, the median (range) follow-up time was 4.4 (0.0-8.9) years for the OBS cohort and 5.7 (0.1-9.0) years for the BCS North cohort. The median (range) follow-up time for cause-specific mortality was 2.6 (0.7-6.9) years, and 3.9 (0.0-7.0) years, respectively. The adjusted risk (95% CI) of breast cancer as the underlying cause of death in OBS patients compared to BCS patients was 1.46 (0.52-4.09) (Supplemental Table 6 and Supplemental Figure 2 in the online version). Corresponding HRs (95% CIs) for breast cancer as underlying or multiple cause of death was 0.90 (0.34-2.37), and regarding overall mortality was 0.90 (0.51-1.60).

All results were similar when excluding patients in the BCS North cohort coded for surgery including oncoplastic technique, when excluding patients operated with level I oncoplastic procedures in the OBS cohort, and also when excluding patients who had mastectomy as a secondary procedure (Supplemental Tables 5 and 7 in the online version).

Discussion

We found a statistically significantly lower risk of nonradical primary tumor excision for patients treated with OBS, including level I and II, compared to conventional BCS. Regarding time to initiation of first mode of adjuvant therapy, disease-free survival, or survival, we found no statistically significant differences. Sensitivity analyses including only level II OBS did not alter these results. By this, our results indicate that OBS is an oncologically safe procedure.

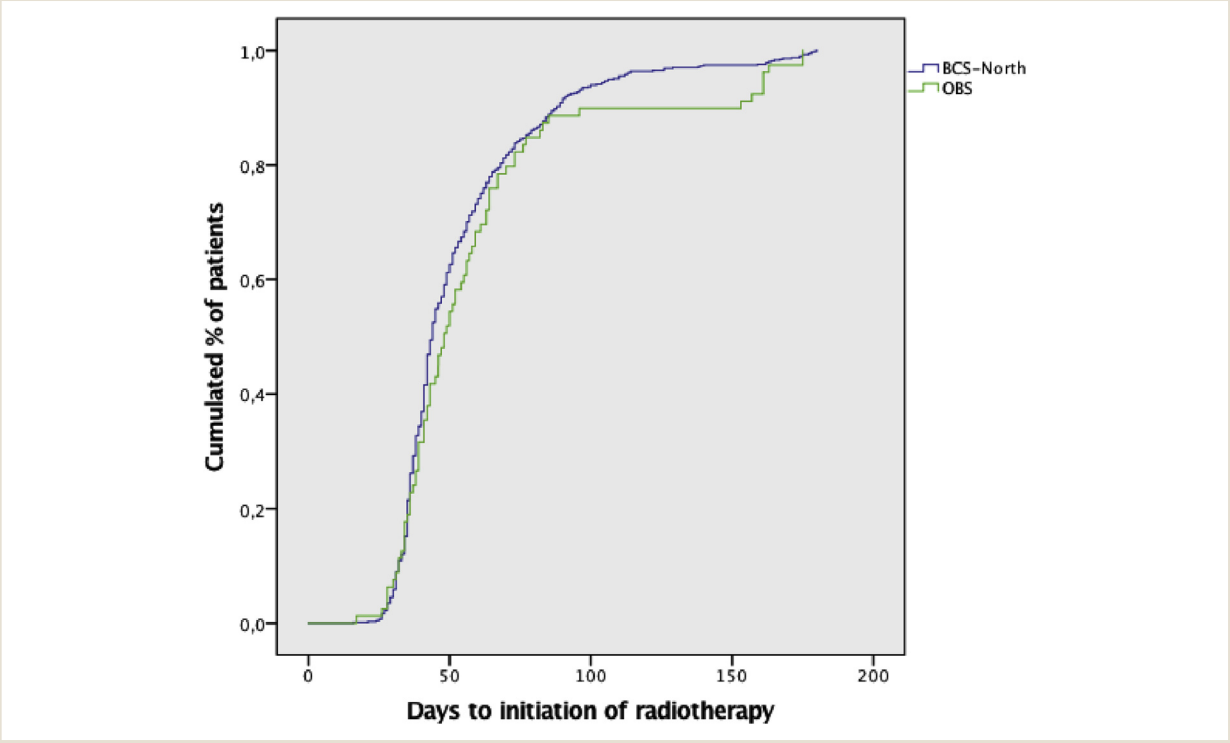
Former studies have documented that the oncologic safety of BCT equals that of mastectomy.[1-3] Recently a large population study even supported a better oncologic outcome for BCT compared to mastectomy.[35] Many studies address indications for OBS, surgical techniques, and complications rates,[4-7,10,11,27,29,36] but few have evaluated the safety of oncoplastic surgery procedures with regard to early,[6,13,16,20,21,25-28,37-40] and especially long-time, oncologic outcomes.[6,12,14-16,19,33,35-37,39]

In cases where the size of the tumor in relation to the size of the breast is small, tumor excision can often be done with sufficient margins without applying oncoplastic techniques.[4,5,22] However, in breasts where the size of the tumor in relation to the size of the breast is large, or even in cases where a small tumor is, for instance, located in an upper medial quadrant of the breast, tumor excision may compromise the aesthetic outcome.[5,7,16,21] In these cases, even when OBS is used, the reconstruction is still technically challenging. With this in mind, one could argue that the surgeons performing OBS could have a tendency to compromise the radicality of the tumor excision by minimizing the excision margins in an effort to get the best possible result regarding cosmetic and functional outcome. In our study, the rates for nonradical primary tumor excision were lower for OBS (10%) compared to BCS patients (16.0%). Studies on OBS have reported varying rates for nonradical primary tumor excision,[4-6,12,13,25,34,35,37,39] although the definition of what is regarded as radical excision is often missing,[15] and the widths for appropriate negative margins are controversial.[41] Najafi et al[13] reported results from 10 studies in 2015 with positive excision margins varying from 3.0% to 22.2% for patients operated with OBS, while De la Cruz[38] in a review including 55 studies found positive excision margins in 10.8%. Compared to conventional BCS, we found a statistically significantly lower risk for nonradical primary tumor excision for patients treated with OBS. This result is in line with several previous studies,[27,38,42] suggesting that applying oncoplastic surgery does not compromise sufficient primary excision margins.

Although studies on complication rates have been published showing no or only small increases in early complication rates for patients treated with OBS,[14,21,29,36,38] it is a concern that more extensive surgery could lead to delay in the initiation of adjuvant therapy, thereby possibly impairing the oncologic outcome.[4,21,27] Few studies have addressed the possible delay of initiation of adjuvant therapy after OBS. Studies by Kahn et al[40] and Dogan et al[28] showed no delay in initiation of chemotherapy after OBS, while Hillberg et al[21] found 8.2% of 150 included patients to have a delay in the initiation of radiotherapy due to postoperative complications. A study by Clough et al[4] reported that surgical postoperative complications after OBS had a negative impact by delaying adjuvant therapy in 1.7% of 175 patients.

It is generally agreed that to have the best effect, adjuvant chemotherapy ought to be initiated within a maximum of 12 weeks after surgery.[43-45] Other results have supported that this counts for radiotherapy as well.[46] Furthermore, studies support

Figure 3 Days From Surgery to Initiation of Radiotherapy as First Adjuvant Therapy by Cohort. Cohorts Include BCS North Cohort and OBS Cohort for Period January 1, 2008, to December 31, 2014. Log-rank $P = .077$



Abbreviations: BCS = breast-conserving surgery; OBS = oncoplastic breast surgery.

that time to initiation of adjuvant chemo- and radiotherapy has an impact on disease-free survival and survival,[44-46] although Barbieri et al[47] and more recently van Maaren et al[48] found that a delay in administration of radiotherapy did not increase the risk for local relapse. Our results showed no significant differences in time to initiation of first mode of adjuvant therapy—neither as chemotherapy nor radiotherapy. For chemotherapy, our results showed mean and median time to initiation well below 12 weeks, and the mean ± 2 standard deviation for the OBS group was 80.1 days.

To ensure that these results were not reflecting regional differences in time to initiation of adjuvant therapy, we also investigated time to adjuvant therapy in the BCS South cohort. The OBS cohort was mainly treated in the southern region of Denmark, while patients in the BCS North cohort were exclusively treated in the northern region of Denmark. We found differences in time to initiation of adjuvant therapy comparing the OBS cohort to the BCS South cohort indicating a shorter time to chemotherapy, but a longer time to radiotherapy as the first mode of adjuvant therapy expressed by median and mean days. Our interpretation is that these differences in time to initiation of adjuvant radiotherapy comparing the OBS cohort and the BCS South cohort may be due to logistic reasons in planning of treatment in the region rather than reasons caused by surgery alone or complications of surgery. If the differences in time to initiation of radiotherapy, with longer time to initiation of radiotherapy for the OBS cohort, were caused by complications of surgery, it would have been expected to observe a longer time to initiation for chemotherapy as well, but this was not the case. On the contrary: the median time to initiation of adjuvant chemotherapy was shorter in OBS patients compared to BCS South patients (30 days vs. 33 days).

Although OBS has been increasingly implemented in the last 2 decades as an option for BCT, only few studies address disease-free survival and survival.[12,15,29,36-39,49] Furthermore, comparison of the available studies is difficult as a result of different designs and varying follow-up times. With recurrence rates at 3.65% for BCS, equal to 66.5 recurrences per 10,000 years, our observations are in line with results published in other studies.[38] Recurrence rates for patients treated with OBS have been reported varying from 1.8% to 16%,[12,15,29,36,37,49] and in a review by De La Cruz et al,[38] it was found to be 11.9%. The percentage of recurrences in breast cancer patients treated with OBS in our study are 6.09% at a median (range) follow-up of 4.1 (0.0-8.9) years, which is comparable to previously reported results.[36,38] Although the crude HR seems to reveal differences in recurrence, the adjusted analyses lead to a marked attenuation of the risk. This is probably due to comparatively unfavorable prognostic factors in OBS patients, such as tumors of higher grade, presence of vascular invasion, larger tumors, and a more advanced nodal status. In conclusion, we did not find significant differences in disease-free survival between patients treated with OBS or BCS, and our results are thus comparable to the results by Carter et al.[36]

Studies addressing survival are few for patients treated with OBS.[15,36,38,39] The overall survival, with a mean follow-up time of 50.5 months, for patients treated with OBS is reported to be 95% in a review including 6011 patients,[38] and another study showed no significant differences in overall survival comparing OBS to BCS.[36] Our results are in line with these results, showing no statistically significant differences between OBS and BCS patients with regard to mortality.

The present study has some limitations due to its design. Implementing OBS in the treatment of breast cancer includes patients in the OBS cohort who without OBS would have been treated with mastectomy. This may have led to relatively more advanced tumors in the OBS group. However, we included tumor size and lumpectomy size in different models, and we expect that this has diminished as a potential selection bias.

In order to avoid another form of selection bias, we did not compare OBS patients to the rest of the BCS patients from the same geographic area. This would have led to a potential confounding by indication bias, as the indication for OBS surgery may affect oncologic safety. However, comparing OBS patients from one geographic area with BCS patients from another area can introduce a bias related to systematic differences between the areas, and not primarily between OBS and BCS patients. In our analysis, the risk of such differences was probably highest regarding time to initiation of adjuvant therapy. For chemotherapy, the time to initiation was slightly longer in the BCS North cohort compared to the BCS South cohort (mean 40.9 days vs. 36.6 days). However, the time was virtually the same in the OBS cohort compared to the BCS south cohort (mean 36.7 vs. 36.6 days). We conclude that it is not likely that the analysis of time to initiation of chemotherapy was affected by any strong systematic differences between the northern and the southern regions of Denmark. Concerning radiotherapy, there was a slightly longer time to initiation in the OBS group compared to both the BCS North and the BCS South cohorts. The mean time was longer in the north, but median time was very similar in the north and the south (53.9 vs. 49.4 days).

There may also be some misclassification in the BCS North group, ie, some patients may actually have been treated with OBS. We only had information from 2010 and onward in the DBCG registry, but this information suggests that only a tiny number of patients underwent OBS in the reference population. Moreover, sensitivity analyses excluding patients registered in the DBCG registry as treated with OBS in the BCS North cohort did not alter these results. Furthermore, the oncoplastic procedures used in the north region at the time, according to the available data in the DBCG register, was mainly level I OBS, ie, less extensive procedures, closer to conventional BCS.

In an effort to avoid misclassification of confounding factors, ie, differences in classification of data, all patients included in the study were identified in the DBCG registry, and all data were selected from the same registry, as were data for follow-up. Because the classification and registration of data in the DBCG registry are performed according to national guidelines, we believe that data for the cohorts are comparable. As we have several end points in this study, the risk of a type I error must be considered in the statistical analyses. However, the results of all different analyses support that there are no significant differences in the oncologic outcome. Finally, it must be kept in mind that the statistical power of results in the analyses of disease-free survival and all survival analyses was limited. Hence, it is possible that nonsignificant differences in the analyses on recurrent disease and survival is due to poor statistical power. Concerning recurrent disease and survival, larger studies with longer follow-up are needed.

Conclusion

The present study found a lower risk of nonradical primary tumor excision for patients treated with OBS compared to conventional BCS. The results showed no statistically significant differences in oncologic safety regarding time to initiation of first mode of adjuvant therapy, disease-free survival, or survival. By this, the results of this study support the oncologic safety of OBS.

Clinical Practice Points

- BCT has been shown to be equally safe as mastectomy regarding oncologic outcome.
- BCS has technically developed and so-called OBS has been implemented over the last decades.
- The surgical procedures in OBS imply more extensive surgery than conventional BCS, eg, wider incisions, extended tissue mobilization, and even flap reconstruction. This may increase the risk of complications and thus a delay in the initiation of adjuvant therapy. This has raised the concern that OBS may affect survival.
- In our study, we found a significant lower risk of nonradical primary tumor resection in OBS patients compared to BCT patients, but no statistically significant differences between groups regarding time to initiation of adjuvant therapy, disease-free survival, or survival.
- The results of the present study support further implementation of OBS as an oncologically safe option for BCS.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.05.016.

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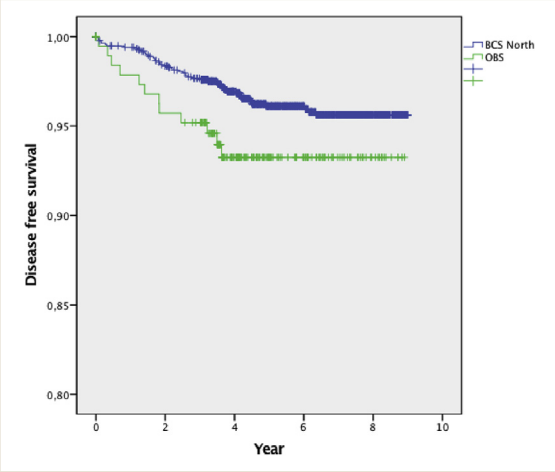
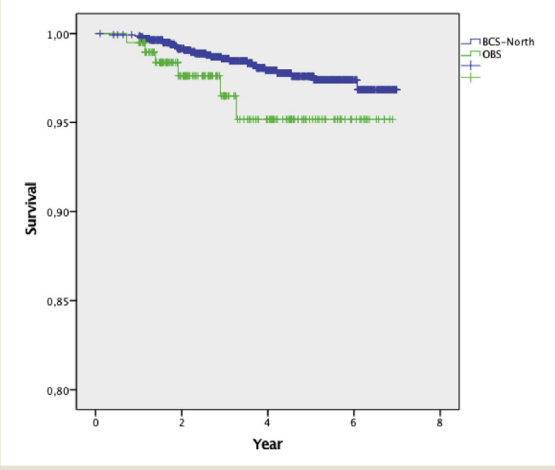
Supplemental Data

Supplemental Figure 1 Disease-Free Survival Among BCS North Cohort and OBS Cohort From January 1, 2008, to January 3, 2017, Disease Free Survival in Cumulated Percentage



Abbreviations: BCS = breast-conserving surgery; OBS = oncoplastic breast surgery.

Supplemental Figure 2 Survival Due to Breast Cancer as Underlying Cause of Death Among BCS North Cohort and OBS Cohort from January 1, 2008, to December 31, 2014, Survival in Cumulated Percentage



Abbreviations: BCS = breast-conserving surgery; OBS = oncoplastic breast surgery.

Supplemental Table 1 Additional Patient, Tumor, and Treatment Factors

Factor	Category	BCS North (N = 1399) (%)	OBS (N = 197) (%)	Total (N = 1596) (%)
BMI	< 18.5 kg/m^2	0.5	0.0	0.4
	18.5-24.9 kg/m^2	16.4	20.3	16.9
	25-29.9 kg/m^2	16.3	19.8	16.7
	30-39.9 kg/m^2	7.7	9.1	7.9
	> 40 kg/m^2	0.6	0.0	0.5
	Missing	58.5	50.8	57.5
Histologic type	Invasive ductal	81.6	86.8	82.2
	Invasive lobular	7.2	7.1	7.2
	Other	10.4	5.6	9.8
	Missing	0.8	0.5	0.8
Progesterone status	Negative	16.5	14.2	16.2
	Positive	35.0	40.1	35.6
	Missing	48.5	45.7	48.2
Menopause status	Before menopause	20.2	32.5	21.7
	After menopause	77.6	66.5	76.3
	Missing	2.1	1.0	2.0
Specimen size	< 50 cm^3	19.9	14.2	19.2
	50-99 cm^3	28.8	26.9	28.6
	100-199 cm^3	31.5	30.5	31.3
	≥ 200 cm^3	17.4	23.4	18.2
	Missing	2.4	5.1	2.8
Cancer found by screening	No	30.3	49.7	32.7
	Yes	39.6	34.5	39.0
	Missing	30.1	15.7	28.3
Sentinel node macrometastases (>2 mm)	No metastases	75.3	59.4	73.4
	Metastases	16.3	23.9	17.2
	Missing	8.4	16.8	9.4
Sentinel node micrometastases (≤2 mm)	No metastasis	80.3	71.1	79.2
	Metastasis	11.1	9.6	10.9
	Missing	8.6	19.3	9.9
Axillary dissection	No	63.8	51.8	62.3
	Yes	35.8	46.2	37.1
	Missing	0.4	2.0	0.6

Abbreviations: BCS North = Breast-Conserving Surgery North cohort; BMI = body mass index; OBS = Oncoplastic Breast Surgery cohort.

Supplemental Table 2 Adjuvant Therapy for Patients in BCS North and OBS Cohorts

Therapy	Therapy Receipt	BCS North (n = 1399) (%)	OBS (N = 197) (%)	Total (N = 1596) (%)
Chemotherapy	No	65.0	51.3	63.3
	Yes	35.0	48.7	36.7
Radiotherapy	No	15.4	11.7	14.9
	Yes	84.6	88.3	85.1
Endocrine therapy	No	43.8	38.1	43.1
	Yes	56.2	61.9	56.9
Immunotherapy	No	93.0	91.4	92.8
	Yes	7.0	8.6	7.2

Abbreviations: BCS North = Breast-Conserving Surgery North cohort; OBS = Oncoplastic Breast Surgery cohort.

Supplemental Table 3 Days From Surgery to Initiation of Chemotherapy and Radiotherapy as First Adjuvant Therapy by Region

First Adjuvant Therapy	Cohort	Patients			Days						HR (95% CI) for:	
		All	Treated	%	Mean	SD	Median	Min	Max	Range	HR	aHR[a]
Chemotherapy	BCS North	1399	481	34.4	41.1	13.8	38.0	16	179	163	1.00	1.00
	OBS	197	95	48.2	36.9	21.6	30.0	15	171	156	1.21 (0.97-1.52)	1.22 (0.96-1.56)
	BCS South	3662	1314	35.9	36.5	17.5	33.0	15	171	174	NA	NA
Radiotherapy	BCS North	1399	714	51.0	54.0	28.1	44.0	16	180	164	1.00	1.00
	OBS	197	82	41.6	62.6	39.6	49.5	17	175	158	0.82 (0.65-1.03)	0.90 (0.71-1.12)
	BCS South	3662	2130	58.2	49.4	21.6	43.0	15	180	165	NA	NA

For period January 1, 2008, to December 31, 2014 (intension to treat; ie, mastectomies included).
Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; BCS South = Breast-Conserving Surgery South cohort; CI = confidence interval; HR = hazard ratio; NA = not applicable; OBS = Oncoplastic Breast Surgery cohort; OR = odds ratio; SD = standard deviation.
[a]Adjusted for vascular invasion, age, Nottingham histologic grade, estrogen receptor status, and HER2 receptor status, tumor focality, T and N classification, axillary dissection, primary radical resection, and lumpectomy size.

Supplemental Table 4 Disease-Free Survival for Recurrence of Breast Cancer During January 1, 2008, to January 3, 2017

Cohort	All	Recurrence			HR (95% CI) for:	
		N	%	Per 10,000 Years	HR	aHR[a]
BCS North	1399	51	3.65	66.5	1.00	1.00
OBS	197	12	6.09	135.6	1.88 (1.00-3.54)	1.23 (0.61-2.47)
Total	1596	63	3.95	73.7		

Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; CI = confidence interval; HR = hazard ratio; OBS = Oncoplastic Breast Surgery cohort.
[a]Adjusted for age, vascular invasion, Nottingham histologic grade, estrogen receptor status, and HER2 receptor status, tumor focality, and T and N classification.

Supplemental Table 5 Disease-Free Survival for Recurrence of Breast Cancer During January 1, 2008, to January 3, 2017, per Study Protocol

Cohort	N	No. With Recurrence	Recurrence		HR (95% CI) for:	
			% in Study Period	Per 10,000 Year	HR	aHR[a]
BCS North	1385	50	3.61	66.0	1.00	1.00
OBS	183	11	6.01	133.7	1.88 (1.00-3.54)	1.39 (0.69-2.84)
Total	1568	61	3.89	72.6		

Study protocol did not permit mastectomy. Recurrence percentage is for study period.
Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; CI = confidence interval; HR = hazard ratio; OBS = Oncoplastic Breast Surgery cohort.
[a]Adjusted for age, vascular invasion, Nottingham histologic grade, estrogen receptor status and HER2-receptor status, tumor focality, T- and N-classification.

Supplemental Table 6 Survival for Death Due to Breast Cancer as Underlying Cause of Death, 2008-2014, for BCS North and OBS

Cause of Death	Cohort	All (N = 1596)	No. of Deaths	Mortality per 10,000 Year	HR (95% CI) for:	
					HR	aHR[a]
Breast cancer as underlying cause of death	BCS North	1399	26	47.3	1.00	1.00
	OBS	197	6	100.1	2.18 (0.90-5.32)	1.46 (0.52-4.09)
	Total	1596	32	52.5		
Breast cancer as underlying or multiple cause of death	BCS North	1399	38	69.1	1.00	1.00
	OBS	197	6	100.1	1.48 (0.63-3.51)	0.90 (0.34-2.37)
	Total	1596	44	72.2		
Overall cause of death	BCS North	1399	130	162.3	1.00	1.00
	OBS	197	16	167.9	1.04 (0.62-1.75)	0.90 (0.51-1.60)
	Total	1596	146	162.9		

Shown are survival for death due to breast cancer as underlying cause of death and breast cancer as underlying or multiple causes 2008-2014, and HRs for overall mortality, January a, 2008, to January 3, 2017, for BCS North and OBS cohorts. Data include patients who underwent secondary mastectomy (ie, intention-to-treat analysis).
Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; CI = confidence interval; HR = hazard ratio; OBS = Oncoplastic Breast Surgery cohort.
[a]Adjusted for age, vascular invasion, Nottingham histologic grade, tumor focality, T and N classification, estrogen receptor status, and HER2 receptor status.

Supplemental Table 7 Survival for Death Due to Breast Cancer as Underlying Cause of Death, 2008-2014, for BCS North and OBS

Cause of Death	Cohort	All	Death	Mortality (%)	Mortality per 10,000 Year	HR (95% CI) for:	
						HR	aHR[a]
Breast cancer as underlying cause of death	BCS North	1385	26	1.88	47.8	1.00	1.00
	OBS	183	5	2.73	88.9	1.91 (0.73-4.97)	1.45 (0.49-4.28)
	Total	1568	31	1.98	51.7		
Breast cancer as underlying or multiple cause of death	BCS North	1385	38	2.74	69.9	1.00	1.00
	OBS	183	5	2.73	88.9	1.30 (0.51-3.30)	0.84 (0.30-2.35)
	Total	1568	43	2.74	71.7		
Over all cause of death	BCS North	1383	129	9.33	162.7	1.00	1.00
	OBS	182	15	8.24	168.4	1.04 (0.61-1.78)	0.95 (0.53-1.70)
	Total	1565	144	9.20	163.3		

Data are for January 1, 2008, to January 3, 2017, per protocol (ie, without mastectomy).
Abbreviations: aHR = adjusted hazard ratio; BCS North = Breast-Conserving Surgery North cohort; CI = confidence interval; HR = hazard ratio; OBS = Oncoplastic Breast Surgery cohort.
[a]Adjusted for age, vascular invasion, Nottingham histologic grade, tumor focality, T and N classification, estrogen receptor status, and HER2 receptor status.