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Oncoplastic Breast Surgery

Surgical Strategy, Oncological
and Patient-reported Outcome

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Oncoplastic Breast Surgery

Surgical Strategy, Oncological and Patient-reported Outcome

Michael Rose



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DOCTORAL DISSERTATION

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Title and subtitle Oncoplastic Breast Surgery - Surgical Strategy, Oncological and Patient-reported Outcome		
<p>Abstract</p> <p>Oncoplastic breast surgery (OBS) is an evolving discipline in the surgical treatment of breast cancer and OBS is striving for improvement of the outcome after breast-conserving surgery (BCS). The aims of this thesis are to present and evaluate a strategy for implementation of (OBS) in a daily clinical setting including the broad spectrum of breast cancer patients in an unselected population, to present a novel replacement technique for immediate partial breast reconstruction, and to evaluate the oncological and patient-reported outcome of OBS compared with conventional BCS.</p> <p>Study I: OBS was performed on 72 patients, two of whom with bilateral breast cancer, thus 74 breast cancers were treated. Careful preoperative evaluation revealed the possibility of reconstruction with volume reduction, volume displacement or volume replacement techniques. The preoperative plan was technically feasible in all but one case. The study showed that it was feasible to implement OBS in clinical practice with the presented strategy.</p> <p>Study II: The aim of the study was to describe the technique and evaluate the results of a tunnelled lateral fasciocutaneous flap with a skin island in immediate partial breast reconstruction in OBS. Fifteen patients with a mean age of 53.5 (38-65) years were operated. The study indicated that this technique can be a useful tool in OBS.</p> <p>Study III: The aim of this study was to compare the oncologic outcome after OBS to the outcome after conventional BCS in patients with invasive breast cancer. In all, 197 patients treated with OBS were compared to 1399 patients treated with conventional BCS. The end points were non-radical primary tumour excision, time to initiation of adjuvant therapy, disease-free survival and survival. Identification of patients was carried out using the DBCG registry and the Danish Cause of Death registry. In conclusion, when comparing OBS to conventional BCS, a lower risk of non-radical primary tumour excision was found for patients treated with OBS, but no other significant differences in oncologic outcome were found. These results indicate that OBS is a safe procedure.</p> <p>Study IV: The aim of the study was to evaluate the possible benefits of OBS, as compared with conventional BCS, with regard to health-related quality of life (HRQoL), using patient-reported outcome measures (PROMs). Patients treated with OBS (n=200) and conventional BCS (n=1304) were included. Patients were sent a survey including the Breast-QTM BCT postoperative module and a study-specific questionnaire (SSQ). The study indicated better outcomes of HRQoL for breast cancer patients treated with OBS as compared with conventional BCS.</p>		
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Oncoplastic Breast Surgery

Surgical Strategy, Oncological and Patient-reported Outcome

Michael Rose



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To breast cancer patients

“There is a crack in everything
That's how the light gets in.”

Leonard Cohen

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List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

Paper I: Surgical strategy, methods of reconstruction, surgical margins and postoperative complications in oncoplastic breast surgery. Rose M, Manjer J, Ringberg A, Svensson H. *Eur J Plast Surg.* 2014; 37: 205–214.
Open Access and distributed under the Creative Commons Attribution 4.0 International Licence.

Paper II: Tunnelled lateral fasciocutaneous thoracodorsal flap with a skin island in breast reconstruction in oncoplastic breast surgery. Rose M, Svensson H. *J Plast Surg Hand Surg.* 2012; 46: 404–409.
Reprinted by permission of the publisher Taylor & Francis Group.

Paper III: Oncoplastic breast surgery compared to conventional breast-conserving surgery with regard to oncological outcome. Michael Rose, Henry Svensson, Jürgen Handler, Ute Hoyer, Anita Ringberg, Jonas Manjer. *Clinical Breast Cancer*, 2019; 19: 423-32
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Paper IV: Patient-reported outcome after oncoplastic breast surgery compared to conventional breast-conserving surgery. Michael Rose, Henry Svensson, Jürgen Handler, Ute Hoyer, Anita Ringberg, Jonas Manjer. *Breast Cancer Research and Treatment*, 2020;00:00-00 (in press).
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Thesis at a glance

Studies on oncoplastic breast surgery (OBS) and conventional breast-conserving surgery (BCS)

Paper	Aims	Patients and methods	Main results
I	<p>To present and evaluate the strategy in the surgical planning of OBS in terms of different reconstruction methods related to tumour size, tumour location and size of the breast.</p> <p>Furthermore, to present and evaluate the results of surgical radicality in terms of resection margins, surgery due to insufficient resection margins, late positive sentinel nodes, i.e. positive sentinel node in final microscopical examination, and early postoperative complications.</p>	<p>Seventy-two patients with 74 primary (two bilateral) breast cancers were treated with level II OBS from January 2008 to December 2010.</p> <p>Data were collected through an approved research database.</p> <p>Surgery was performed at three Danish hospitals.</p>	<p>In 73 of 74 resections, the tumour was resected with free margins based on peroperative macroscopic evaluation. In 10 cases (14 %), peroperative macroscopic evaluation was corrected after postoperative histological evaluation. In seven cases (10 %), free margins were achieved by re-resection, whereas three cases (4 %) required a mastectomy. Nine patients (12.3%) had surgery due to postoperative haematomas. Delay of adjuvant therapy occurred in four patients (6 %) due to wound healing problems.</p>
II	<p>To describe a novel technique, a technique using a tunnelled lateral fasciocutaneous flap with a skin island, and evaluate the results of immediate partial breast reconstruction with this technique.</p>	<p>Fifteen patients, mainly with small breast (<250 cc), from a subpopulation of an OBS cohort, had a partial mastectomy and were immediately reconstructed with a tunnelled lateral fasciocutaneous flap with a skin island from January 2008 to January 2011.</p>	<p>In all cases, macroscopic free margins were achieved. In four patients the resections were microscopically too narrow and a re-resection was performed. No mastectomy was needed. No patients had necrosis, but one patient had a postoperative haematoma. No patients had any delay in the adjuvant therapy.</p>
III	<p>To investigate if there are differences in the oncological outcome between (OBS) and conventional (BCS).</p>	<p>Patients treated for invasive primary breast cancer from 2008 to 2013 were included. An OBS cohort (n=197) was compared with a conventional BCS cohort (n=1399). Data were retrieved from the DBCG registry. Data was evaluated by uni- and multivariate logistic regression and Cox Proportional Hazards analyses.</p>	<p>We found a statistically significant lower risk of non-radical primary tumour excision for patients treated with OBS, including levels I and II, compared with conventional BCS. Regarding time to initiation of the first mode of adjuvant therapy, disease-free survival, and survival, we found no statistically significant differences.</p>
IV	<p>To investigate if there are differences in patient-reported outcome among breast cancer patients between patients operated with OBS and conventional BCS.</p>	<p>In 2016, patients treated with either OBS or conventional BCS were sent the Breast-Q postoperative module and a study-specific questionnaire (SSQ) yielding 96 evaluable replies from the OBS cohort and 631 from the BCS cohort. The OBS and BCS cohorts were compared using uni- and multi-variate logistic regression analyses for the scores for each domain in the Breast-Q BCT module, yielding odds ratios (OR) with 95% confidence intervals.</p>	<p>There was a statistically significant better outcome, above vs. below the median, considering the HRQoL domain "Psychosocial Well-being" for patients treated with OBS as compared with BCS. (OR=2.15: 1.25-3.69). No statistically significant differences were found for the domains "Physical Well-being" with the adjusted OR (0.83: 0.50-1.39), "Satisfaction with Breast" (0.95: 0.57-1.59) or "Sexual Well-being" (1.42: 0.78-2.58).</p>

Abbreviations

AFT	Autologous Fat Transplantation
ALND	Axillary Lymph Node Dissection
BCS	Breast-Conserving Surgery
BCT	Breast-Conserving Treatment
BMI	Body Mass Index
CI	Confidence Interval
DAR	Danish Cause of Death Register
DBCG	Danish Breast Cancer Cooperative Group
DCIS	Ductal Carcinoma In Situ
DIEP-flap	Deep Inferior Epigastric Perforator – flap
ER-receptor	Estrogen-Receptor
FISH	Fluorescence In Situ Hybridisation
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICAP-flap	Intercostal Artery Perforator flap
IHC	Immunohistochemistry
MAPI	Messaging Application Program Interface
MDT	Multi-disciplinary Team
ms-LD-flap	Muscle-sparing Latissimus Dorsi flap
NAC	Nipple Areola Complex
NHG	Nottingham Histological Grade
OBS	Oncoplastic Breast Surgery
OPEN	Open Patient data Explorative Network
OUH	Odense University Hospital
OR	Odds Ratio
PrG-receptor	Progesterone-receptor
PRO	Patient-reported Outcome
PROM	Patient-reported Outcome Measure
REDCap	Research Electronic Data Capture
RKKP	Regionernes Kliniske Kvalitetsudviklingsprogram
SN	Sentinel Node
SNB	Sentinel Node Biopsy
SPSS	Statistical Package for the Social Sciences
SSQ	Study-specific Questionnaire
TAP flap	Thoracodorsal Artery Perforator flap
TNM	Tumour, Node, Metastases
TRAM flap	Transverse Rectus Abdominis Myocutaneous flap

Danish summary

Brystkræft er den hyppigste kræftform blandt kvinder og udgør omkring 25% af alle kræfttilfælde blandt kvinder. Hver niende kvinde i Danmark vil i løbet af deres liv blive diagnosticeret med brystkræft. Brystkræft er sjældent hos yngre kvinder, mens antallet af kvinder, der får brystkræft, stiger med alderen og når et maksimum omkring 65-75 års alderen. Omkring 4700 kvinder fik i 2016 brystkræft i Danmark og 87% af disse kvinder vil stadig være i live efter 5 år, mens 67000 kvinder vil leve med en tidligere brystkræft diagnose. Heldigvis er antallet af kvinder, der får brystkræft faldende. I perioden 2012 til 2016 er der sket et fald på ca. 1% i antallet af kvinder pr. år der får brystkræft og et fald i dødeligheden på ca. 3,5% pr. år. Konsekvensen af denne udvikling er at flere kvinder vil leve med en tidligere brystkræftdiagnose – og vil leve længere. Det betyder, at det funktionelle og æstetiske resultat af brystkræftbehandlingen bliver stadig mere væsentlig.

Den kirurgiske behandling af brystkræft er enten mastektomi, hvor hele brystet bortopereres, eller brystbevarende kirurgi, hvor kun kræftknuden fjernes. Behandlingen med begge disse behandlingsformer har den samme dokumenterede effekt på tilbagekomst og død af sygdommen. Omkring 70% af patienterne med brystkræft behandles med brystbevarende kirurgi og ca. 30% af disse kvinder ender med et utilfredsstillende funktionelt og æstetisk resultat af den kirurgiske behandling.

Onkoplastisk brystkirurgi er gennem de sidste årtier udviklet med det mål at forbedre det funktionelle og æstetiske resultat af den kirurgiske brystkræftbehandling. I onkoplastisk brystkirurgi anvendes teknikker kendt fra den rekonstruktive og æstetiske plastikkirurgi i den brystbevarende kirurgi. Når disse teknikker anvendes i den brystbevarende kirurgi er det muligt, at rekonstruere brystet når kræftknuden er bortopereret, så resultatet bliver et normalt formet bryst med et funktionelt og æstetisk acceptabelt resultat. På trods af at implementeringen af onkoplastisk brystkirurgi påbegyndtes for mere end 10 år siden i Danmark, er onkoplastisk brystkirurgi ikke fuldt implementeret i alle brystkirurgiske klinikker i landet.

Målet med denne afhandling er at præsentere en strategi for implementeringen af onkoplastisk brystkirurgi i daglig klinisk praksis i klinikker der er engageret i den kirurgiske behandling af brystkræft. Endvidere er det målet at evaluere resultaterne med onkoplastisk brystkirurgi med tanke på om behandlingen kan gennemføres som skitseret i strategien, og at undersøge den onkologiske sikkerhed af behandlingen samt

hvordan patienter oplever resultatet og deres livskvalitet efter behandlingen. I afhandlingen indgår 4 studier.

I det første studie præsenteres en strategi for implementationen af onkoplastisk brystkirurgi. I dette studie indgår 72 patienter (74 kræftknuder), der er opereret med onkoplastisk brystkirurgi som et samarbejde mellem plastikkirurger og brystkirurger i perioden 2008 til 2010. Alle patienter var registreret i en forskningsdatabase. Patienterne der blev behandlet med onkoplastisk brystkirurgi var udvalgt fra en bred gruppe af brystkræftpatienter. Patienterne blev opdelt i 4 grupper efter størrelsen af brystet og hvor i brystet kræftknuden var lokaliseret. De kirurgiske teknikker for rekonstruktion af brystet efter bortoperation af kræftknuden inkluderede teknikker, hvor størrelsen af brystet blev reduceret (volumen reduktion), teknikker hvor brystvævet blev re-arrangeret eller forskudt indenfor brystet (volumen displacement) og teknikker hvor defekten i brystet efter fjernelse af kræftknuden blev erstattet af væv hentet udenfor brystet (volumen replacement). Næsten $\frac{3}{4}$ af patienterne blev også opereret på det andet bryst for at opnå symmetri med det rekonstruerede bryst. Studiet viste at den kirurgiske teknik, der blev valgt til rekonstruktion af brystet afhang af, hvilken af de 4 grupper patienterne var placeret i. Med andre ord præsenteres en strategi, for hvordan forskellige patienter kan rekonstrueres, når de er fundet egnede til onkoplastisk brystkirurgi. Behandlingen blev gennemført som planlagt forud for operationen i alle 74 tilfælde undtaget hos en patient, hvor det ikke var muligt at fjerne hele kræftknuden uden at fjerne hele brystet. Der var ingen stigning i antallet af komplikationer til den kirurgiske behandling og ingen indikationer af at den adjuverende behandling blev forsinket sammenlignet med konventionel brystbevarende kirurgi. Sammenfattende indikerer dette studie, at implementeringen af onkoplastisk brystkirurgi i daglig klinisk praksis er mulig med den præsenterede strategi uden at svække sikkerheden af behandlingen.

I det andet studie præsenteres en ny kirurgisk teknik – brugen af en tunnelleret fasciocutan lap med en hudø – til umiddelbar brystrekonstruktion i onkoplastisk brystkirurgi. Ved denne teknik rekrutteres væv fra brystvæggen som flyttes gennem en tunnel lavet i brystet til defekten i brystet efter bortoperation af kræftknuden. Lappen består af subkutant fedt og hud og erstatter både fylden (volumen) af kræftknuden og huden, der eventuelt blev fjernet sammen med kræftknuden. Der indgik 15 patienter i studiet med små ($<250 \text{ cm}^3$) eller mellem store bryster ($250\text{-}500 \text{ cm}^3$). Disse patienter var en del af patienterne i forskningsdatabase, som også indgik i det første studie, og blev opereret i perioden 2008 – 2011. Ingen af patienterne blev opereret på det modsidige bryst for at opnå symmetri, da dette ikke var nødvendigt, fordi der blev anvendt en kirurgisk replacement teknik. Alle operationer blev gennemført som planlagt. Dog måtte 4 patienter re-opereres pga. at kræftknuden ikke var fjernet i sundt væv ved første operation. Brystvorte komplekset blev hos 3 patienter bortopereret sammen med kræftknuden og erstattet af en hudø. Fraset en enkelt komplikation, en blodansamling, var der ingen komplikationer til kirurgien. I studiet konkluderes det, at

denne kirurgiske teknik er meget brugbar og sikker, og en mulig teknik til brystrekonstruktion i onkoplastisk brystkirurgi.

Målet med det tredje studie var at evaluere den onkologiske sikkerhed ved onkoplastisk brystkirurgi sammenlignet med konventionel brystbevarende kirurgi. Som nævnt ovenfor er målet med onkoplastisk brystkirurgi, at forbedre det funktionelle og æstetiske resultat af konventionel brystbevarende kirurgi. Imidlertid er det meget væsentligt at dokumentere, at den onkologiske sikkerhed ikke svækkes ved implementeringen af onkoplastisk brystkirurgi. Den onkologiske sikkerhed kan måles gennem for eksempel at undersøge, hvor ofte der ved operationen tages tilstrækkeligt væv væk, for at man kan være sikker på, at kræftknoten er fjernet eller ved at undersøge risikoen for tilbagefald af sygdommen. Kun få studier er tidligere udgivet, hvor den onkologiske sikkerhed undersøges ved at sammenligne onkoplastisk brystkirurgi med konventionel brystbevarende kirurgi. I dette studie indgik 197 patienter med brystkræft opereret med onkoplastisk brystkirurgi. Langt de fleste af disse patienter blev opereret i det sydlige Jylland. Disse patienter blev sammenlignet med 1399 patienter behandlet med konventionel brystbevarende kirurgi fra en anden geografisk region i Danmark, Region Nordjylland. Alle data blev hentet fra DBCG's register, som er et dansk national brystkræft register, og alle patienter blev opereret i perioden 2008 til 2013. Til evaluering af den onkologiske sikkerhed undersøgte vi fire emner. Var der forskelle i antallet af patienter, der ikke fik bortopereret kræftknoten med frie rande (i sundt væv), om der var forsinkelse i påbegyndelsen af adjuverende behandling (kemo- og stråleterapi), om der var forskelle i antallet af patienter, der overlevede uden tilbagekomst af sygdommen, og om der var forskelle i overlevelse. Data for patienter, diagnose og kræftknode karakteristika blev hentet fra DBCG's register og Dødsårsagsregisteret. Data for patienter opereret med henholdsvis onkoplastisk brystkirurgi og brystbevarende kirurgi viste, at patienter opereret med onkoplastisk kirurgi havde mere fremskreden brystkræft end patienter behandlet med konventionel brystbevarende kirurgi. Resultaterne viste en signifikant lavere risiko for ikke-radikal fjernelse af kræftknoten for patienter behandlet med onkoplastisk kirurgi sammenlignet med patienter opereret med konventionel brystbevarende kirurgi. Der fandtes ingen signifikante forskelle med hensyn til tidspunkt for påbegyndelse af adjuverende behandling, sygdom-fri overlevelse eller overlevelse. Sammenfattende indikerer resultaterne af dette studie, at onkoplastisk brystkirurgi er en onkologisk sikker behandling.

Da målet for onkoplastisk brystkirurgi er at forbedre resultatet af brystbevarende kirurgi, er det væsentligt at dokumentere om resultaterne faktisk var en forbedring, set fra patientens synspunkt. I det fjerde og sidste studie i afhandlingen undersøges de patient-rapporterede resultater af onkoplastisk brystkirurgi sammenlignet med konventionel brystbevarende kirurgi. Til måling af dette anvendte vi det validerede spørgeskema Breast-Q™ BCT og et studie-specifikt spørgeskema. I studiet indgik de samme patienter som i det tredje studie, og i alt fik 1504 patienter i 2016 tilsendt

spørgeskemaerne enten som et brev digitalt via E-post eller som almindeligt brev. Der kom 96 svar fra patienter opereret med onkoplastisk kirurgi og 631 svar fra patienter opereret med konventionel brystbevarende kirurgi, i alt 727 svar. Resultaterne viste statistisk signifikant bedre resultater for "Psychosocial Well-being" for patienter behandlet med onkoplastisk brystkirurgi. Der var ingen signifikante forskelle for "Satisfaction with Breast" eller "Sexual Well Being". Endvidere fandtes ingen forskelle for "Physical Well Being" trods mere omfattende kirurgi for patienter behandlet med onkoplastisk brystkirurgi, hvor der ofte blev opereret på begge bryster for at opnå bedre symmetri. Sammenfattende indikerer resultaterne af dette studie, at patienterne rapporterer en bedre livskvalitet efter behandling med onkoplastisk brystkirurgi.

Opsummerende viste resultaterne af studierne i afhandlingen, at implementering af onkoplastisk brystkirurgi i daglig klinisk praksis er gennemførlig uden at kompromittere den onkologiske sikkerhed og indikerer, at onkoplastisk brystkirurgi øger patienttilfredsheden med behandlingen sammenlignet med konventionel brystbevarende kirurgi

Swedish summary

Bröstcancer är den vanligaste cancerformen bland kvinnor och den utgör ca 25% av all cancer i denna grupp. Var nionde kvinna i Danmark kommer att diagnosticeras med bröstcancer under sin livstid. Bröstcancer är ovanligt bland unga kvinnor, men blir vanligare med åldern för att nå en topp i 65-75 års åldern. Cirka 4700 kvinnor fick bröstcancer i Danmark 2016 men 87% av dessa kommer fortfarande att vara i livet efter 5 år. Samtidigt finns det 67000 kvinnor som tidigare har haft en bröstcancer. Mellan 2012 och 2016 minskade antalet nya bröstcancerfall med ca 1% per år och antalet som dog av bröstcancer minskade med hela 3,5% per år. Som en följd av detta kommer det att finnas allt fler kvinnor som lever vidare efter en bröstcancerdiagnos. Detta har gjort att man allt mer har börjat betona betydelsen av ett bra funktionellt och estetiskt resultat efter behandlingen för bröstcancer.

Den kirurgiska behandlingen vid bröstcancer består antingen av mastektomi, att man tar bort hela bröstet, eller av bröstbevarande kirurgi där man bara tar bort tumören och en marginal omkring denna. Dessa behandlingar är lika bra om man jämför överlevnaden efter behandling. Ungefär 70% av alla behandlas med bröstbevarande kirurgi men man vet att ca. 30% upplever ett dåligt funktionellt eller estetiskt resultat.

Onkoplastikkirurgi för bröst (oncoplastic breast surgery - OBS) har utvecklats under senare år med syfte att förbättra det funktionella och estetiska resultatet efter bröstkirurgi. OBS innebär att man använder tekniker hämtade från rekonstruktiv och estetisk bröstkirurgi. Dessa tekniker gör att det är möjligt att återskapa form och storlek på bröstet samtidigt med canceroperationen. Tekniken började införas i Danmark för mer än 10 år sedan men trots det så är den inte fullt ut implementerad i hela landet.

Denna avhandling har flera syften. Det övergripande målet är att presentera ett koncept för införandet av OBS vid bröstcancerbehandling. Specifika mål är att utvärdera om behandlingen går att införa enligt det föreslagna konceptet, om den onkologisk säkerhet påverkas och hur patienterna upplever behandlingen. Avhandlingen innehåller fyra studier.

I den första studien introduceras ett möjligt koncept för införandet av OBS. I studien ingår 72 patienter som opererades med tekniken mellan 2008 och 2010. Patienterna behandlades vid tre sjukhus i Danmark. Alla patienter delades in i fyra grupper beroende på hur stor tumören var och var i bröstet den satt. OBS inkluderar olika typer av tekniker. Vissa minskar storleken på bröstet (volyne reduction), andra flyttar på

bröstvädnad inom bröstet (volume displacement) och slutligen finns tekniker som ersätter den bortopererade vädnaden med material som hämtas utanför bröstet (volume replacement). Nästan $\frac{3}{4}$ av alla patienter blev också opererade i det andra bröstet för att förbättra symmetrin. Studien visade att den valda tekniken väl överensstämmer med den ideala grundat på vilken av de fyra grupperna patienten tillhör. Alla patienter blev förutom en opererad så som man planerat före operation. Den enda där det inte kunde genomföras var en patient där man var tvungen att ta bort hela bröstet för att säkert kunna få med hela tumören. Inget stöd fanns för att OBS, jämfört med tidigare studier, ökade antalet komplikationer eller ledde till en fördröjning av den efterföljande adjuvanta behandlingen. Sammantaget visade denna studie att det är möjligt att introducera ett standardiserat koncept för OBS, samt att OBS är ett kirurgiskt säkert koncept.

I den andra studien presenteras en ny teknik inom OBS – en ”tunnelerad fasciokutan lambå med en hudö”. Tekniken innebär att vädnad från ryggen på patienten frias från underlaget och att man skapar en lambå, en vädnadssträng. Denna lambå träs sedan bakom huden och bröstet så att den når defekten i bröstet som skapas då man tar bort en tumör. Lambån består av både underhuds fett och hud och kan användas för att ersätta vädnad på ett annat ställe än där den ursprungligen satt. Det ingick 15 patienter i studien med antingen ”små” bröst (mindre än 250 ml) eller ”mellanstora” bröst (250-500 ml). Dessa patienter hade hämtats från den grupp som ingick i den första studien och de hade opererats mellan 2008 och 2011. Ingen av patienterna behövde opereras på det andra bröstet eftersom tekniken eftersträvade att just ersätta vädnad som man var tvungen att ta bort och därmed kan man minska risken för skillnader mellan brösten. Alla operationerna kunde genomföras som planerat men efter slutlig bedömning av preparaten så behövde fyra patienter opereras igen eftersom tumören inte var avlägsnad med en tillräcklig marginal. Hos tre av patienterna opererades bröstvårtan bort och denna kunde ersättas med en hudö. Endast en patient fick en komplikation, en blödning. Sammantaget kan man betrakta denna OBS-teknik som genomförbar och säker.

Syftet med den tredje studien är att jämföra onkologisk säkerhet för OBS jämfört med konventionell bröstbevarande kirurgi. Som nämnts ovan så är syftet med OBS att förbättra det funktionella och estetiska resultatet efter bröstcancerkirurgi. Det är emellertid mycket viktigt att säkerställa att den onkologiska säkerheten inte påverkas. Den onkologiska säkerheten kan mätas t.ex. genom att undersöka hur ofta kirurgen tar bort tillräckligt mycket vädnad för att man skall vara säker på att hela tumören är borta (radikal operation) eller genom att studera återfallsrisk. I denna studie ingick 197 patienter opererade med OBS mellan 2008 och 2013 och det var en utvidgning av den grupp som analyserades i arbete ett och två. Dessa patienter hade i huvudsak opererats i södra Jylland. Denna grupp jämfördes med alla patienter i norra Jylland som opererats under samma tid, totalt 1399 patienter. Vi undersökte den onkologiska säkerheten genom att mäta fyra olika utfall. Det första var att undersöka om tumören var borttagen

med tillräcklig marginal, det andra var att se om den adjuvanta behandlingen (cytostatika eller strålning) fördröjts, det tredje måttet var återfallsrisk och det fjärde överlevnad. All data hämtades från den Danska Bröstcancergruppen (DBCG) vilken driver ett nationellt behandlingsregister. Studien visade att OBS-patienter hade relativt sett mer avancerade tumörer. Analyserna visade också att OBS-gruppen hade en mindre risk för en icke-radikal operation. Det sågs ingen skillnad mellan grupperna vad gällde tidpunkt för adjuvant behandling, återfallsrisk eller överlevnad. Sammantaget stöder studien antagandet att OBS är en onkologiskt säker teknik.

Målet med OBS är att förbättra resultaten efter bröstbevarande kirurgi. Då är det ytterst väsentligt att undersöka hur patienterna själva upplever resultatet. Det fjärde arbetet undersöker om det finns skillnader i patientupplevt resultat mellan OBS-patienter och patienter opererade med konventionell bröstbevarandekirurgi. Studien undersökte de patienter som identifierats i studie tre. Det mätinstrument som användes var ett validerat frågeformulär: Breast-Q. Dessutom ingick en studiespecifik enkät. Totalt sändes formulären till 1504 patienter och det besvarades av 727 kvinnor. Analyserna visade att OBS-patienterna hade ett statistiskt säkert högre ”psykosocialt välmående” än jämförelsegruppen. Det sågs ingen skillnad mellan grupperna vad gällde ”tillfredsställelse med bröstet” eller ”sexuellt välmående”. Vidare sågs det inte heller någon skillnad vad gällde ”fysiskt välmående”; detta även om OBS tekniken i många fall innebär större operativa ingrepp. Sammantaget stöder denna studie antagandet att OBS-kirurgi kan öka livskvalitén efter bröstkirurgi.

Slutsatsen av avhandlingen är att OBS kan introduceras som en säker teknik vid behandling av bröstcancer och att den kan förbättra livskvalitén.

English summary

Breast cancer is the most common cancer among women and accounts for about 25% of all female cancers in Denmark, and every ninth woman will be diagnosed with breast cancer during her life. Breast cancer is rare in young women, but the number of women with breast cancer increases with age with a maximum at 65-75 years of age. In 2016, around 4700 women in Denmark were diagnosed with breast cancer, and 87% of these will still be alive after five years. About 67000 women in the country are living after breast cancer treatment. Fortunately, the number of women diagnosed with breast cancer has decreased in the last decade. Since 2012 we have seen an annual decrease of about 1% of new patients diagnosed with breast cancer and an annual decrease in mortality of about 3.5%. The consequence of this development is that still more women will be alive after the diagnosis of breast cancer - and will live longer. This means, that the functional and aesthetic outcome of treatment becomes increasingly important.

Surgical treatment of breast cancer is either mastectomy, where the breast is totally removed, or breast-conserving surgery (BCS), where only the tumour is removed. These two treatment options have the same documented effect on disease recurrence and survival. Today, about 70% of breast cancer patients are treated with BCS and up to 30% of these patients may end up with an unacceptable functional and aesthetic result of surgery.

With the aim of achieving better outcomes of the surgical treatment of breast cancer, oncoplastic breast surgery (OBS) has been developed in the last few decades. In OBS the techniques used in reconstructive and aesthetical plastic surgery have been applied to BCS. When these techniques are used in BCS it may be possible to reconstruct a larger number of breasts, after removal of the tumour, into normally shaped breasts with an acceptable functional and aesthetic result. Although, the implementation of OBS was initiated more than 10 years ago in Denmark, it has still not been fully implemented in all departments throughout the country.

The aims of this thesis were to present a strategy for implementation of OBS in daily clinical practice in departments engaged in the surgical treatment of breast cancer, to evaluate the results of OBS with regard to feasibility of implementation, oncological safety of treatment, and to evaluate how breast cancer patients perceived satisfaction with treatment and quality of life after treatment. This thesis consists of four studies.

In the first study a strategy for implementation of OBS was presented. The study included 72 patients (74 tumours) operated with OBS in a collaboration between plastic and reconstructive surgeons and breast surgeons in the period 2008 to 2010. All patients were registered in a research database. Patients treated with OBS were selected from the wide population of all breast cancer patients. The patients were categorised into four groups depending on the size of the breast and the location of the tumour in the breast. The surgical techniques for reconstruction of the breast after removal of the tumour included techniques where the volume of the breast was reduced (volume reduction), where the breast tissue was rearranged within the breast after tumour removal (volume displacement), and where the defect in the breast after tumour removal was replaced by tissue recruited from outside the breast (volume replacement). Nearly $\frac{3}{4}$ of the patients also had an operation on the opposite breast to achieve symmetry. It was shown that the surgical technique chosen for reconstruction of the breast – the surgical strategy – depended on which of four groups the patient had been categorised into. In other words, we presented a strategy for how to choose the reconstruction technique in different cases of breast cancer selected for OBS. Surgery was performed as preoperatively planned on all 74 breasts except one, where it was not possible to remove the tumour without resection of the whole breast. We did not find an increase in complications of surgery or indications of delay of adjuvant therapy compared with BCS. In summary, this study indicated that implementation of OBS in daily clinical practice is feasible with the presented strategy without an increase in complications and without impairing the safety of the treatment with regard to timely administration of adjuvant therapy.

In the second study we introduced a novel surgical technique using a tunnelled fasciocutaneous thoracodorsal flap with a skin island for immediate partial breast reconstruction in OBS. Using this flap, tissue is recruited from the thoracic wall and transposed through a tunnel in the breast, filling the defect after tumour resection. The flap is constituted of subcutaneous fat and skin and replaces both the volume removed by tumour resection and, if necessary, skin resected along with the tumour. This study included 15 patients, with small or medium-sized breasts, a subpopulation of the patients in the research database also used in the first study operated in the period 2008 to 2011. Using this replacement technique none of the patients needed surgery in the other breast to achieve symmetry. All surgeries were performed as planned, although re-resection due to non-radical surgery was performed in four patients. In three patients the nipple areola complex (NAC) was removed along with the tumour and replaced with a skin island. There was only one complication to surgery, a haematoma at the site of reconstruction. In conclusion, we find this technique very useful and safe as an option in partial breast reconstruction in OBS.

The aim of the third study was to evaluate the oncological safety of OBS compared with conventional BCS. As mentioned above, the aim of OBS is to improve the functional and aesthetic results of conventional BCS. However, it is very important to

document that oncological safety is not impaired by OBS. Only a few studies on this subject have previously been published comparing the oncological outcome of OBS with conventional BCS. In this study we identified 197 patients from the DBCG registry (a nationwide registry for breast cancer in Denmark) with newly diagnosed breast cancer treated with OBS that had been registered in the research database. These patients were compared with 1399 patients treated with conventional BCS, also identified in the DBCG registry, from another geographical region in Denmark, Region North. All patients were operated in the period 2008 to 2013. For evaluation of oncological safety we examined four items: non-radical tumour resection, delay in administration of adjuvant therapy (chemotherapy and radiotherapy), recurrent disease (disease-free-survival) and survival. Data for patient, tumour, and treatment characteristics were retrieved from the DBCG registry and the Danish Cause of Death registry for all patients. Data for OBS and conventional BCS, respectively, showed that patients treated with OBS had more advanced breast cancers than patients treated with conventional BCS. The results showed a lower risk for non-radical surgery for patients treated with OBS. We found no significant statistical differences with regard to time to administration of adjuvant therapy, disease-free-survival or survival. In conclusion, this study indicated that OBS is as oncologically safe as conventional BCS.

As the aim of OBS is to improve the outcome of BCS it is important to document if the outcome of OBS, from the patient's point of view, actually is an improvement. In the fourth study we evaluated the patient-reported outcome (PRO) of OBS compared with conventional BCS. For evaluation the validated questionnaire Breast-Q™ BCT module and a study-specific questionnaire (SSQ) were used. In 2016, the same patients from the OBS research database and from Region North, who were included in the third study (1504 patients in all), were sent the questionnaires either by E-post (a secure public digital platform) or by ordinary mail. Ninety-six replies were received from OBS patients and 631 replies from patients treated with conventional BCS, 727 replies in all. The results showed a statistically significant better outcome of "Psychosocial Well-being" for patients treated with OBS compared with conventional BCS. No statistical differences were shown for "Satisfaction with Breast" or "Sexual Well-being". Furthermore, no differences were shown for "Physical Well-being", despite more comprehensive surgery for patients treated with OBS, where surgery of both breasts was often performed to achieve better symmetry. In conclusion, the results of this study indicated better PRO for OBS concerning psychosocial well-being.

In summary, the results of the studies in this thesis showed that implementation of OBS in daily clinical practice is feasible without compromising the oncological safety of the treatment of breast cancer, and indicate that OBS improves the PRO compared with conventional BCS.

Introduction

The subject of this thesis is oncoplastic breast surgery (OBS). In brief, OBS is a discipline in which techniques known from reconstructive and aesthetical plastic surgery are applied to breast conserving surgery (BCS) in an effort to achieve better functional and aesthetical outcomes in the surgical treatment of primary breast cancer ¹⁻³.

The motivation for the studies included in the thesis arose from the daily clinical work at the Department of Surgery, Hospital of South Jutland, Denmark, in the Plastic Surgery and Breast Surgery sections. At the Department of Surgery, we, as plastic surgeons, work closely with the breast surgeons. Formerly, this the cooperation was limited to surgery for congenital defects such as tuberous breast or aplasia of the breasts, and total reconstruction after mastectomy, either as primary or secondary reconstruction, while treatment of primary breast cancer with BCS or mastectomy was performed solely by breast surgeons. Inspired by the early research results presented at conferences and in literature – especially the work of McCulley and MacMillan ^{4, 5} - combined with our experience with the results of BCS, we saw a potential for improving the surgical outcome of surgery for breast cancer for our patients. The experience was that BCS in many cases led to poor results for our patients - in the literature up to 30% ^{6, 7}.

As a result of this we agreed to develop a strategy for implementation of OBS in the daily clinical practice for treatment of breast cancer patients. The goal was to develop a surgical strategy and a setup in the clinic to include the broad spectrum of breast cancer patients that receive surgical treatment at the department. This meant that we had to schedule consultations where breast surgeons and plastic surgeons were able to see possible candidates for OBS. After referral to the breast unit all patients were first seen in a consultation with the breast surgeon. When the breast surgeon's judgement was that a patient would not have an acceptable outcome of BCS, a common consultation was scheduled the same day or within a few days – very often on an ad hoc basis as time is short in the treatment of breast cancer.

The result of this setup was that we as plastic surgeons were presented with very different cases with very different reconstructive problems. Breasts vary in size from small to large, as do tumours, and the tumours can be located anywhere in the breast – and can even be multifocal or bilateral. In the effort to solve these different reconstructive tasks we had to include our experience with a wide range of techniques

from reconstructive and aesthetical breast surgery. If we concluded that OBS was a feasible option, and the patient accepted the plan for surgery, surgery was scheduled and carried out with both a breast surgeon and a plastic surgeon working together as a team. Although surgery was performed by both breast and plastic surgeons in the same surgical procedure, we had a clear agreement on responsibilities – the breast surgeon was responsible for the oncological surgery while the plastic surgeon was responsible for the reconstructive surgery. Through the first years we learned a lot – both breast and plastic surgeons – and the strategy developed as a result of this experience. This meant that we included more patients and more difficult cases, as well as patients who otherwise would have been recommended for mastectomy, and new surgical techniques were included and improved. Over time, the breast surgeons took decisions on and performed minor reconstructive procedures themselves, while we as plastic surgeons participated in reconstructions when needed.

Although it was our opinion that our approach to OBS worked and our results were promising with regard to aesthetical and functional outcome after the first years, it was obvious that two very important issues had to be evaluated. The first issue, and the most important one, was whether OBS led to impairment of the oncological safety of treatment of breast cancer compared with conventional BCS. The second issue was how the patients perceived the results of the treatment: did they benefit from the more extensive surgery and how did that influence their HRQoL?

The aims of the studies included in the thesis are to present a strategy or a guideline, which could possibly inspire other clinicians to implement OBS in daily clinical practice and as a second aim, to present a novel surgical technique using a tunnelled fasciocutaneous thoracodorsal flap with a skin island, as a supplementary tool for reconstruction of defects after partial mastectomy. Furthermore, it was very important to evaluate the oncological and HRQoL outcomes of OBS compared with conventional BCS.

Breast cancer

Epidemiology

Breast cancer is the most frequently occurring cancer among woman in Denmark. Every ninth woman will be diagnosed with breast cancer during her life span, and breast cancer accounts for 25% of all female cancers ⁸.

The incidence of breast cancer in Denmark, i.e. new cases per year, increased until approximately 2010, when a fall was registered, and the incidence has continued to fall since then ⁹. In 2016, the incidence in Denmark was 4694 (mean for the period 2012-2016). The incidence of breast cancer is strongly correlated to age. Breast cancer is rare before the age of 30 years in Denmark. The incidence reaches its maximum at the age of 65-75 years and declines gradually to the age of 85+ years. Over the last 10 years there has been an estimated annual age-standardised change per year in incidence of minus 1.1% ⁹.

In 2016, 1120 women in Denmark died per year due to breast cancer (total mortality as a mean for the period 2012-2016) and the estimated age-standardised annual change was minus 3.4% ⁹. In 2012 to 2016 the one-year relative survival (%), i.e. the probability of patient survival in the absence of other causes of death, was 97% (CI 95%; 96-97) and the five-year relative survival was 87% (CI 95%; 86-88). The prevalence of breast cancer in Denmark, i.e. women living with the breast cancer diagnosis, was 66300 in 2016. The consequence of these figures is that the prevalence of breast cancer in Denmark at present is increasing ⁹.

Diagnosis

The diagnosis of breast cancer in Denmark is based upon three items, according to the national guidelines provided by DBCG, called the “Triple-diagnostic principle”: clinical examination, diagnostic imaging (e.g. mammography and ultrasound) and cytological and histological examination of tissue samples ¹⁰.

Suspicion of breast cancer occurs mainly either because of clinical symptoms, such as detection of a palpable tumour in the breast, retraction of the nipple or skin, secretion of fluid or blood from the nipple, or as a result of screening mammography. When a suspicion has been raised the patient is then referred, usually by a general practitioner, to a breast unit or to a department of radiology for a clinical mammography ¹⁰.

When a breast cancer diagnosis is established, the decision on the treatment recommendation of the individual patient, based on the results of the triple-diagnostic procedure, is taken at the Multi Disciplinary Team (MDT) conference, according to national guidelines ¹¹. Specialists in breast surgery, pathology, oncology and radiology participate in the MDT team.

Prognostic factors

Age and menopausal status

The prognosis of breast cancer is correlated to age at diagnosis ¹². Patients diagnosed with breast cancer when aged under 40 and more than 80 years have a poorer prognosis than patients when aged between 40 to 80 years. It is well known that menopausal status is closely associated with age, and as such, is also covariate with prognosis ¹³.

Multifocality

Most breast cancers are uni-focal tumours but some tumours are multifocal or multicentric ¹⁴. Multifocal tumours are defined as those with more than one focus of invasive tumours separated by carcinoma in situ or normal breast tissue in the same quadrant, whereas multicentric tumours have two or more focuses in more than one quadrant. Multicentricity are associated with an increased risk of metastases, which indicates a poor prognosis ^{14, 15}.

Vascular invasion

Invasion of tumour cells in blood vessels is seen as tumour growth progresses in breast cancer. Vascular invasion is documented to be a prognostic factor as vascular invasion predicts a poorer prognosis ¹⁶.

Histopathology

Invasive breast cancer is defined as malignant tumours cells penetrating the basal membrane originating from the ducts or lobules in the mammary gland. With 75-80% the invasive ductal carcinoma, or invasive ductal carcinoma of no special type (NST), is the most common histological type followed by invasive lobular carcinoma with approximately 10-15% ^{10, 17}. Mucinous, tubular and medullary tumours represent approximately 5%. The prognosis of breast cancer is associated with histopathology of the tumour, where invasive ductal cancers have a better prognosis compared with

lobular cancers¹⁸. Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ represent another histopathological type of breast tumour. These tumours are non-invasive but might develop into invasive carcinomas^{19, 20}. The prognoses of DCIS tumours are indexed according to the Van Nuys Prognostic Index, based on tumour size, margin width and pathological classification from 1 – 9. A high index corresponds to a higher recurrence rate.

Histological grade

During the study, breast tumours were classified according to The Nottingham Histological Grade (NHG) system^{21,22}. The grading is based on microscopic examination of tissue samples, where tubule formation, nuclear pleomorphism and mitotic activity are graded and expressed as a sum as NHG 1 to NHG 3. A high NHG grade corresponds to lower differentiation and is associated with a poorer prognosis^{18, 23}.

Biomarkers

Immunohistochemical (IHC) analysis for estrogen receptors (ER) and progesterone receptors (PgR) is routinely performed¹⁰. Approximately 80% of the tumours are ER-positive (> 1% of the cells in the tumours have the receptor in the cell nucleus) and ER is a strong predictive factor in breast cancer and can be targeted by hormone therapy²⁴. ER- and PgR-positive tumours are predictors for a long-lasting effect of hormone therapy²⁵. Human epidermal growth factor receptor 2 (HER2) is a tyrosin kinase receptor located in the cell membrane and can be overexpressed in breast cancer, i.e. HER2 positive, which is found in approximately 20 % of tumours¹⁰. HER2-positive tumours are associated with poorer prognosis and will benefit from immunotherapy (trastuzumab), hence HER2 is a strong prognostic and predictive factor²⁶. Also, analysis for the human epidermal growth factor (HER2) is routinely performed (with IHC and FISH). The biomarker Ki-67 is a marker for the speed of cell divisions and cell proliferation, and is a prognostic but not a predictive factor as high levels of Ki67 are associated with poorer prognosis²⁷. Data for ER, PgR and HER2 are included in the DBCG registry for the study period and in the studies in this thesis. The Ki-67 index was not included in the DBCG registry throughout the entire study period and due to this it was not included in the studies.

TNM-classification

The TNM-classification system is an international recognised one in which the cancer is staged with regard to the size of the tumour, nodal involvement and metastases²². The TNM staging is strongly correlated to the prognosis of breast cancer, where a higher stage indicates a poorer prognosis for the individual patient, and it is used when deciding on the recommended treatment^{18, 28}.

Treatment of breast cancer

The DBCG provides national guidelines for the treatment of breast cancer in Denmark, and these guidelines are followed by all certified departments involved ¹⁰.

Surgery

Recommended surgical treatment depends on stage, the tumour size and location, and the breast size as well as a broader evaluation of the patient with regard to age and comorbidity.

Sentinel node surgery

A sentinel node biopsy (SNB) is nearly always performed as a part of the staging of breast cancer ¹⁰. The SNB is usually performed as the first part of the surgical procedure, but can be performed as an independent procedure prior to BCS or mastectomy, e.g. if a primary autologous total reconstruction is planned. The SNB was during the study period examined by frozen sections. In the case of malignant cells in the SN, i.e. a positive SN, an axillary clearance was also performed within the same surgical procedure. If no malignancy was found, i.e. a negative SN, no further surgery was performed ¹⁰. A positive SN is correlated to a poorer prognosis ²⁹.

Axillary lymph node dissection

Axillary lymph node dissection (ALND), i.e. surgical removal of the axillary lymph nodes, was recommended during the period when metastases to axillary lymph nodes were diagnosed ¹⁰. The purpose of axillary dissection is staging and regional disease control. Metastases to the axillary lymph nodes can be diagnosed by SNB either as micro- (0.2 - 2 mm), macro-metastases (>2 mm) or cell clusters (ITC, isolated tumour cells <0.2 mm), or by other diagnostic tools such as PET-CT scans, MR scans, ultrasound, excision or needle biopsies and even clinical examination. In 2019 ALND was only performed when macro-metastases were diagnosed by SNB¹⁰. Axillary dissection is usually performed in the same surgical procedure as BCS or mastectomy. However, axillary dissection can be performed later in cases of late positive SNB, diagnosed in the final histopathological examination. Surgery is usually performed through a separate incision in the axilla, i.e. a different incision than the incision for partial mastectomy or mastectomy. According to the national guidelines by DBCG in Denmark, an axillary dissection ought to include at least 10 lymph nodes¹⁰.

Mastectomy

Mastectomy is the surgical procedure where the whole mammary gland is removed ³⁰. In Denmark approximately 30% of patients with breast cancer were treated with mastectomy in 2016 ¹⁰. Mastectomy is recommended in cases where it can be foreseen that the outcome after BCS will leave the patient with an unacceptable aesthetical

outcome. This can be the scenario when the tumour is large, multifocal or located in an unfortunate position with regard to BCS. Mastectomy is also recommended in cases with recurrent local disease and in most cases with local advanced disease with involvement of the skin. Mastectomy can be performed in a procedure where the mammary gland along with an appropriate amount of skin is resected for adaption to the thoracic wall for closure or as a subcutaneous mastectomy³¹ where the skin overlying the mammary gland is preserved.

Conventional breast-conserving surgery

In breast-conserving surgery the tumour is removed by a partial mastectomy, with the intention of not leaving any cancer cells in the breast. BCS can be performed if an acceptable functional and aesthetic outcome is anticipated – and accepted by the patient. In Denmark approximately 70 % of patients (2016) with breast cancer are operated with BCS¹⁰. In BCS it is essential that the tumour is removed with free margins. During the study period (2008-2013) a radical excision was defined as ≥ 2 mm from carcinoma to excision line for both invasive and carcinoma in situ. Since 2013 “no tumour on ink”, i.e. no tumour cells at the resection surface coloured by ink at the final histopathological examination, is accepted as demonstrating free margins^{10, 32}. Whether the resection margin is sufficient is determined peroperatively by the pathologist by macroscopic examination. If the microscopical examination with frozen section peroperative shows that the resection margins are too narrow, an immediate re-resection is performed. The ensuing defect in the breast after the resection is then closed by suture with no further adaption of the breast. A final histopathological examination is always performed. In cases where this examination shows tumour cells at the resection margin, i.e. there is a positive margin, a secondary re-resection or a mastectomy is recommended¹⁰.

Breast reconstruction

Breast reconstruction is the surgical reconstruction of the breast after either complete or partial mastectomy. Breast reconstruction can be performed as an immediate or delayed procedure, and with regard to surgical techniques, with the use of implants or by transfer of autologous tissue to the breast - or combinations of implant and tissue transfer.

An immediate reconstruction is performed in the same surgical procedure as the mastectomy or BCS, while a delayed reconstruction is performed in a later surgical procedure. Breast reconstruction after mastectomy can be performed as either an immediate or delayed procedure. Breast reconstruction after partial mastectomy is performed as an immediate procedure.

In autologous total reconstructions the breast is reconstructed using tissue flaps transferred from outside the breast. The flap most often used for breast reconstruction

is the deep inferior epigastric perforator flap (DIEP) flap, recruited from the abdomen, which is transferred to the breast with a microsurgical technique³³. With the use of this flap it is possible to recruit enough tissue to reconstruct the breast without the use of an implant. Another flap for breast reconstruction is the muscle-sparing latissimus dorsi flap (ms-LD flap), which is a pedicled flap harvested from the back³⁴. Reconstruction with ms-LD flaps is usually combined with an implant as it is not possible to recruit enough tissue to reconstruct the breast volume with the flap alone. In cases where patients have had adjuvant radiotherapy autologous reconstructions are highly preferred due to fibrosis caused by radiation³⁵.

Partial immediate autologous breast reconstruction, i.e. OBS, is reconstruction of the breast when a partial defect in the breast caused by partial mastectomy is present. The reconstruction is carried out by the use of internal tissue transfer, e.g. tissue recruited from inside the breast, or by the use of external tissue transfer by local flaps from outside the breast.

Reconstructions with implants are either one- or two-stage reconstructions. In an immediate reconstruction the mastectomy may be performed as a subcutaneous mastectomy³¹, with or without resection of the NAC, immediately followed by a reconstruction with an implant, usually placed under the pectoral muscle³⁶. In a delayed reconstruction either a one- or a two-stage procedure is needed. Delayed one-stage breast reconstruction is performed by implantation of an expandable implant designed for one-stage reconstruction³⁷. In a two-stage reconstruction an expandable implant is implanted, which, after expansion of the overlying tissue over several weeks, is replaced in a second surgical procedure by a permanent implant³⁸. Delayed total reconstruction with an implant is not recommended when the patient has had adjuvant radiotherapy due to the increased risk of fibrosis with capsular contracture³⁵.

As a new technique for breast reconstruction, autologous fat transplantation (AFT), has been developed. This is a tool for corrections of sequelae after oncological or reconstructive surgery and even for total breast reconstructions³⁹⁻⁴¹.

Reconstruction of the NAC is often performed as the final part of the breast reconstruction. Several techniques for reconstruction of the nipple as well as the areola are available⁴²⁻⁴⁴.

Adjuvant therapy

Adjuvant therapy includes several modalities: radiotherapy, chemotherapy, hormonal therapy and immunotherapy. Specific treatment guidelines are provided by DBCG for all modalities and are continuously updated¹⁰. In selected cases with large or multifocal tumours, and HER2 positive or high grade tumours, neoadjuvant chemotherapy is recommended for down-staging of the tumour prior to surgery^{8, 10}. Whether

postoperative adjuvant chemotherapy is indicated depends on the results of histopathology examination, TNM-classification and analysis of biomarkers, age and comorbidity independently of the surgical treatment (BCS or mastectomy). Patients treated with BCS are recommended to undergo postoperative adjuvant radiotherapy in all cases regardless of the results of these parameters. Only patients who have had a mastectomy with macro-metastases in regional lymph nodes, with tumours > 5 cm or non-radical surgery, are recommended to have postoperative adjuvant radiotherapy ¹⁰. The indication of treatment with hormonal therapy and immunotherapy depends on the analysis of the biomarkers ER and HER2 according to the national guidelines ¹⁰.

Follow-up

Patients are scheduled for follow-up according to the Danish national guidelines ¹⁰. Follow-up visits at department of oncology or breast surgery were usually planned for every three months during the first year postoperatively, every sixth months from two to five years, and once every year from six to ten years postoperatively. Patients treated with BCS (including OBS) are recommended to have a mammography 18 months postoperatively. After this first postoperative mammography patients are referred to the screening programme, having a mammography every second year. Later events such as recurrence of disease either as local or disseminated disease, a second contra lateral breast cancer or death are registered in the DBCG registry ¹⁰.

Oncoplastic Breast Surgery

In reconstructive plastic surgery, the main task is to repair defects of various kinds. These may be congenital, such as cleft lip and palate defects, or acquired following trauma or ablative surgery. One such example is surgery to the breast due to cancer. The goal of reconstruction is then to restore function with the best possible aesthetic outcome. From a plastic surgical point of view the defect caused by partial mastectomy is a classical reconstructive problem. Partial mastectomy leaves the breast with a defect and a problem to solve: how to restore the breast with an acceptable aesthetic and functional outcome.

In OBS, resection of the tumour is immediately followed by reconstruction of the breast. The goal of this combined procedure is to achieve local control of the disease and at the same time an acceptable aesthetic and functional outcome. Studies have shown that these goals are achieved in the short term^{3, 4, 7, 45, 46} although studies on long-term outcomes are few^{47, 48}. The surgical strategy chosen for the individual patient depends on the size and location of the tumour in the breast, the size of the breast, and possible donor sites^{2, 46}. Furthermore, the patient's acceptance of the preoperative plan including possible surgery to the contralateral breast to achieve better symmetry has to be obtained. The patient also has to be informed of the possibility of mastectomy in case it is not possible to achieve free margins with a partial mastectomy.

With this approach to breast-conserving surgery, OBS has evolved in the last few decades. OBS applies techniques from reconstructive and aesthetic plastic surgery to conventional BCS with the aim of improving the outcome of BCS. With this evolution the indications for BCS have also expanded with the result that more women with breast cancer can avoid mastectomy and still achieve an acceptable aesthetical and functional outcome^{49, 50}.

The reconstructive problem to solve – if possible - is determined by several factors. The volume and shape of the breast(s) are not equal from woman to woman, but vary widely from small breasts to very large breasts. Furthermore, the breasts are not always symmetrical. The size of tumours varies from patient to patient within a range of a few mms to several cm in diameter. The shape can be round or highly irregular, the tumours can be unifocal or multifocal, and can be located anywhere in the mammary gland. Regardless of these factors, the essential goal for BCS is to achieve radical resection of the tumour within acceptable margins, according to national guidelines, to provide the safest possible oncological outcome.

This means that the location and relative size of the defect, after resection of the tumour, varies from woman to woman, leaving very different reconstructive problems to be solved taking the remaining breast into consideration ^{5, 51}. This can be illustrated by the differences in the problems between cases where, for example, a small tumour is located in the lower part of a large breast compared to a case where a tumour of the same absolute size is located in the upper lateral part of a small breast. This calls for different reconstructive approaches and techniques to achieve acceptable aesthetic and functional outcomes. The first case could be operated with a reduction mammoplasty, possibly in combination with a contralateral mastopexy to achieve symmetry ⁴. The second case could be reconstructed with a replacement technique with use of a perforator flap from the thoracic wall, thus leaving no need for contralateral surgery ^{52, 53}. However, not all defects after radical tumour resection are possible to reconstruct with an acceptable outcome. In these cases, mastectomy and maybe immediate or delayed total breast reconstruction with implants or autologous tissue are still the best options for surgical treatment ^{33, 34, 36, 38}.

Definition of OBS

Over the last few decades several different approaches to OBS have been described involving a number of surgical techniques for reconstruction of various defects in the breast leading to different concepts for implementation of OBS in breast cancer surgery ^{2, 4, 46, 54-56}.

Different definitions of OBS have been introduced but so far there has been no agreement on a common international definition of OBS. Recently Chatterjee et al. published the American Society of Breast Surgeons' consensus definition and classification system of OBS ¹. Their definition and classification is widely inspired by the work of Clough et al. ^{2, 51}. Chatterjee et al. define OBS as "A form of breast conservation surgery that includes oncologic resection with a partial mastectomy, ipsilateral reconstruction using volume displacement, or volume replacement techniques with possible contralateral symmetry surgery when appropriate" ¹.

Chatterjee et al. also propose a classification system in which they classify OBS at levels I and II based on the needed resection volume as a percentage of the total breast volume ¹. Furthermore, they include the surgical skills and techniques required for levels I and level II in the categorisation. When up to 20% of the total breast volume has to be resected to achieve free margins, level I OBS is usually sufficient. The techniques used in level I OBS are, in their classification system, local tissue rearrangement, mastopexy and doughnut mastopexy. Level I OBS can be performed by most breast surgeons without experience of reconstructive techniques ^{1, 2}. When the partial mastectomy constitutes 20 – 50% of total breast volume they classify OBS as level II. The proposed technique for partial immediate reconstruction in level II is reduction mammoplasty,

possibly including a free nipple graft and circum vertical mastopexy. A third category called “Volume replacement” is proposed when the partial mastectomy includes more than 50% of the total breast volume. For possible reconstructive techniques in this scenario, local and regional flap reconstruction such as thoracodorsal artery perforator flaps (TAP flaps) are listed as well as implant-based reconstructions. Level II requires experience with reconstructive techniques from plastic surgery ¹.

However, the proposed cut-offs in volume at 20% for level I surgery and 50% for level II surgery, and the corresponding surgical techniques recommended, should not be regarded as hard cut-offs. The definition and categorisation rather have to be regarded as guidelines ¹. The specific reconstruction option that is chosen for the individual patient depends on the size of the breast, the size and location of the tumour – and the patient’s wishes.

In this thesis we have defined OBS levels I and II as described below.

Surgical strategies in OBS

Level I OBS

The surgical techniques used in level I OBS include simple partial mastectomy, possibly with expanded skin incision lines, and closure of the ensuing defect by minor mobilisation of adjacent skin, subcutaneous and mammary tissue with or without recentralisation of the NAC. Examples of these techniques are donut ^{57, 58}, racket ⁵⁹ and batwing ⁶⁰ techniques. These techniques are most often used in cases where the defect after partial mastectomy in relation to the remaining breast is small (<20%) ¹. Furthermore, the tumour has to be located in a suitable position in the breast. Surgery for level I OBS can be performed by most breast surgeons and does not require skills or experience from reconstructive or aesthetical plastic surgery.

Level II OBS

Surgery for level II OBS includes three main categories of surgical techniques: the volume reduction technique or therapeutic mammoplasty ⁴, displacement techniques⁵ and replacement techniques ^{34, 52, 61, 62}. These surgical techniques all require acquired surgical skills and experience with methods used in reconstructive and aesthetical plastic surgery as they include techniques used in breast reduction surgery, mastopexy and flap procedures. Patients operated with mastectomy followed by an immediate autologous or implant reconstruction were not included in our definition of level II.

Volume reduction techniques

For women with large or even medium-sized breasts, volume reduction for immediate reconstruction is an easy and safe technique^{4, 5}. The technique is applicable in patients where the size of the breast and the location of the tumour allow a reduction mammoplasty including the tumour, leaving a sufficient amount of breast tissue to reshape the breast after tumour removal, i.e. a therapeutic mammoplasty⁴. Different surgical techniques for reduction mammoplasties exist⁶³. The volume reduction technique is typically, but not all ways, used in cases where the tumour is located in the lower part of the breast within the limits of the incision lines used for breast reduction⁵. Patients with breast cancer operated with the volume reduction technique will have a smaller, but naturally shaped breast. If needed, reduction mammoplasty of the contralateral breast to achieve appropriate symmetry may be performed.

Volume displacement techniques

The principle used in the displacement technique is to fill the defect after resection of the tumour, i.e. after partial mastectomy, wherever it is located in the breast, with breast tissue recruited from within the breast^{5, 64, 65}. The use of displacement techniques also implies that the volume of the breast is large enough to allow a reduction of the breast that equals, at a minimum, the volume of the partial mastectomy. An example of reconstruction with displacement technique is reconstruction of a central defect following resection of a tumour including the NAC using a flap from the lower part of the breast. The NAC can be reconstructed as an immediate reconstruction using a flap with a skin island^{42, 44, 53}. There are numerous ways of designing immediate reconstruction with displacement techniques depending on the surgeon's skills and experience^{5, 51}. How to design the reconstruction depends on the size of the breast and the location and size of the ensuing defect after tumour resection. These reconstructions include wide skin incisions, mobilisation of breast tissue and often flap surgery with random flaps. These reconstructions are used with medium to large breasts. As these techniques also result in a smaller breast than preoperatively, a contralateral reduction mammoplasty is usually performed in the same procedure to achieve symmetry.

Volume replacement techniques

For women with small breasts, conventional BCS usually leads to a considerable and mutilating deformity of the breast, which adjuvant radiation therapy might further aggravate^{48, 66}. The relation between the size of the breast and the tumour in women with small breasts also means that it is not possible to reconstruct the breast after tumour resection using volume reduction or volume displacement techniques with an acceptable aesthetic outcome. To reconstruct such defects, it is necessary to replace volume with external flaps, i.e. to recruit tissue from outside the breast to fill the defect. Different flaps for this purpose are available depending on the location and the volume of the defect. For smaller defects, random flaps^{53, 62} or perforator flaps⁵², e.g. ICAP-

flaps ⁶⁷ or TAP flaps ⁶⁸, with or without skin are often suitable. When more tissue is needed for the larger defects, the muscle sparing ms-LD flap may be a versatile option ³⁴. Also, in these reconstructions using flaps the NAC can be reconstructed if needed in the same surgical procedure ^{42, 44}. The replacement technique can also be used for women with medium-sized breasts, who do not consent to an operation on the contralateral breast to achieve better symmetry.

Oncological outcomes of the treatment of breast cancer

To evaluate if the oncological outcomes of OBS compared with conventional BCS, primary radical excision and timing of adjuvant therapy were chosen as the first two endpoints. The outcome of these two endpoints could affect the outcome of disease-free survival, the third end-point, and survival, the fourth end-point, which are the most essential outcomes. It is reasonable to assume that the evaluation of these endpoints can give a fair indication of the oncological safety of OBS compared with conventional BCS.

Primary radical excision

Radical excision is essential in the surgical treatment of breast cancer. In consequence, a non-radical primary excision has to be followed by secondary surgery with re-excision to achieve free margins according to the national guidelines. In our study, radical excision was defined as ≥ 2 mm from invasive carcinoma to excision line and ≥ 2 mm from ductal carcinoma in situ if ductal carcinoma in situ was also present. However, during the last six months of the study period “no tumour on ink” was accepted as demonstrating free margins for invasive carcinoma and remains so¹⁰.

In cases where the size of the tumour in relation to the size of the breast is small, tumour excision can often be performed with sufficient margins without applying oncoplastic techniques^{1, 2, 51}. However, in breasts where the size of the tumour in relation to the size of the breast is large, tumour excision may compromise the aesthetic outcome^{4, 46, 66, 69}. This is also true in cases where a small tumour is, for instance, located in an upper medial quadrant of the breast. 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 tumour excision by minimising the excision margins in an effort to get the best possible result regarding aesthetical and functional outcome. Because of this it is substantially to evaluate the outcome of OBS compared with conventional BCS with regard to primary radical excisions.

Timing of adjuvant therapy

It is generally agreed that, to have the best effect, adjuvant chemotherapy ought to be initiated within a maximum of 12 weeks after surgery⁷⁰⁻⁷². Other results have confirmed that this is true for radiotherapy as well⁷³. Furthermore, studies show that the time to initiation of adjuvant chemo- and radiotherapy has an impact on disease-free survival and survival⁷¹⁻⁷³.

OBS includes more extensive surgical procedures than conventional BCS and in some patients even contralateral surgery to achieve better symmetry. More extensive surgery can lead to an increase in the rate of complications. Due to this fact, it is a concern that complications, e.g. haematomas, infections, delayed wound healing and necrosis of flaps, could be a reason for delay of adjuvant therapy in OBS as administration of radiotherapy as well as chemotherapy requires a well healed breast^{69, 74}.

In this study we regarded administration of the first mode of adjuvant therapy as delayed if initiated after more than four weeks. In our study III we investigated whether there were any statistically significant differences in time to initiating administration of adjuvant therapy comparing OBS with conventional BCS.

Disease-free survival

Disease-free survival, i.e. survival with absence of recurrent disease, has improved over the last decades as a result of screening mammography, better surgery and the development of adjuvant therapy¹⁰. The oncological safety of conventional BCS has proved to be as high as that of mastectomy^{75, 76}. To evaluate the oncological outcome of OBS compared with conventional BCS, we consider evaluation of disease-free survival important. Data for recurrent disease was retrieved from the DBCG registry.

Survival

A decrease in mortality following treatment of breast cancer has also been reported in the few last decades⁹. To evaluate the oncological outcome of OBS compared with conventional BCS mortality is an essential subject. In our study, we evaluate mortality expressed in terms of cancer as the underlying cause of death, breast cancer as the underlying or multiple cause of death, and overall cause of death.

Patient-reported outcome

Previous evaluations of surgical treatment, including breast surgery, have mainly focused on clinical outcomes such as duration of hospital stay, number of surgical complications, e.g. haematomas, wound healing, infections etc., evaluation of postoperative pain, and, of course, cancer recurrence and mortality, but these clinical outcomes can no longer stand alone^{77, 78}. Studies of functional and aesthetic outcomes in reconstructive and especially aesthetical breast surgery have also been performed to get an indication of patient satisfaction with the results of treatment^{47, 79-82}.

During the last few decades an increasing interest in measuring and evaluating the patient perception of results of treatment, i.e. PRO, has evolved with a focus on satisfaction and HRQoL⁸³. This is true for aesthetical and reconstructive breast surgery, but this also applies to services in other specialities, e.g. bariatric and body-contouring surgery after massive weight loss^{84, 85}. PROM data is increasingly used in decision-making in healthcare. Data is used with regard to treatment of the individual patient, in research and healthcare policy, and makes it important that PROMs provide scientifically sound measurements^{77, 86, 87}. The use of PROMs that are not properly developed or validated could lead to use of data that do not reflect reality, i.e. that are imprecise or biased, and this can lead to undesirable decisions and strategies for clinical practice⁸⁸.

For the measurement of PRO in OBS we chose the Breast-Q BCT postoperative module⁸³.

Breast-QTM - a Patient-Reported Outcome Measure (PROM)

The Breast-QTM is a disease-specific validated questionnaire for evaluating PRO developed by the Memorial Sloan Kettering Cancer Institute, New York, USA, and the University of British Columbia, Toronto, Canada^{77, 78, 89, 90}.

The Breast-Q is a part of the q-portfolio⁸³. The Breast-QTM questionnaires, at present including five modules (augmentation, reduction, reconstruction, BCT and mastectomy), have been developed based on literature reviews, patient interviews, focus

groups and expert panels ⁸⁹. The questionnaires were tested and re-tested among patients and scales (scoring) constructed by use of Rasch measurement methods and psychometric analysis ⁹⁰. The linguistically validated Danish version of the Breast-Q[™] BCT postoperative module (2016) includes 10 domains. The domains represent two overall categories: satisfaction and HRQoL ⁸⁹. Each domain can be used independently of the other domains. Four domains concern the patient-reported outcome of treatment, “Satisfaction with breast”, “Psychosocial Well-Being”, “Sexual Well-Being” and “Physical Well-Being”, and four domains concern satisfaction with the breast surgeon and oncologist and their information prior to treatment. Finally, two domains regarding satisfaction with medical staff other than the breast surgeon are included. Each domain, or subscale, consists of a varying number of items. Permission to use the Danish version of the Breast-Q BCT postoperative module was granted by the MAPI Research Trust Institute ⁹¹. Data from the Breast-Q[™] BCT postoperative module was transformed into scores ranging from 0 to 100 for each domain according to the guidelines for the Breast-Q BCT postoperative module with higher scores representing more favourable outcomes.

Aims

The overall aim of the studies is to present a strategy for implementation of OBS and to evaluate the strategy with regard to feasibility, oncological safety and patient-reported outcome.

The specific aims for the studies were:

Paper I: To present and evaluate a possible strategy in the planning of OBS in terms of different reconstruction methods related to tumour size, tumour location and size of the breast. The result of surgical radicality, surgery due to insufficient resection margins, late positive sentinel nodes and early postoperative complications was also evaluated.

Paper II: To introduce and evaluate a novel technique, using a tunnelled lateral fasciocutaneous flap with a skin island, for use in OBS when tissue replacement is indicated.

Paper III: To investigate if there are differences in the oncological outcome between OBS and conventional BCS with regard to resection margins, timely administration of adjuvant therapy, disease-free survival and survival.

Paper IV: To investigate if there are differences in patient-reported outcome with regard to “Satisfaction with Breast”, “Psychosocial Well-being”, Physical Well-being” and “Sexual Well-being” among breast cancer patients between patients operated with either OBS or conventional BCS.

Patients and methods studies I – IV

This thesis is based on a study-population of patients treated with OBS for early breast cancer and DCIS registered in a local research database. Patients in the study-population were recruited in the Southern Region of Denmark and from a private hospital in Copenhagen from 2008 to 2013. In order to avoid a potential selection bias due to different indications for surgical technique, we did not compare OBS patients to the other patients treated with conventional BCS from the same geographical area. Instead, we chose all patients treated with conventional BCS in the Northern Region of Denmark, the BCS North cohort, in the same period of time as controls in papers III and IV. OBS was not performed in Region North as a routine procedure during the study period. In order to identify potential regional differences in routines e.g. adjuvant treatment, in paper III, we also collected information for all patients treated with BCS in the Southern Region of Denmark. To retrieve comparable data for the oncological (III) and patient-reported outcome study (IV) the studies were designed to use data from the national DBCG registry for both the study cohort and the control cohort.

Patients and databases

Research database

Patients were consecutively registered from the 1 January 2008 until 31 December 2013 in a research database when treated with techniques used in OBS (Figure 1). Patients registered in the database were diagnosed with primary invasive breast cancer, DCIS, sequelae after previous breast cancer surgery or with benign diseases, e.g. giant adenomas⁹². Data on diagnosis, type of surgery, time of surgery, age as well as pre-, per- and postoperative data were recorded, including follow-up visits. All patients had been operated with surgical techniques used in reconstructive and aesthetical plastic surgery for OBS. Surgery was performed at the Hospital of Southwest Jutland, Esbjerg, at the Hospital of South Jutland, Aabenraa, and at the Private Hospital, Hamlet, Copenhagen. In total, 236 patients were registered (Figure 1). The research database was approved by the Danish Data Protection Agency⁹³. Data for patients in the research database, who were also identified in the DBCG registry¹⁰, were retrieved from

the DBCG registry by permission from the Danish Clinical Registries (RKKP), the Danish National Board of Health ⁹⁴.

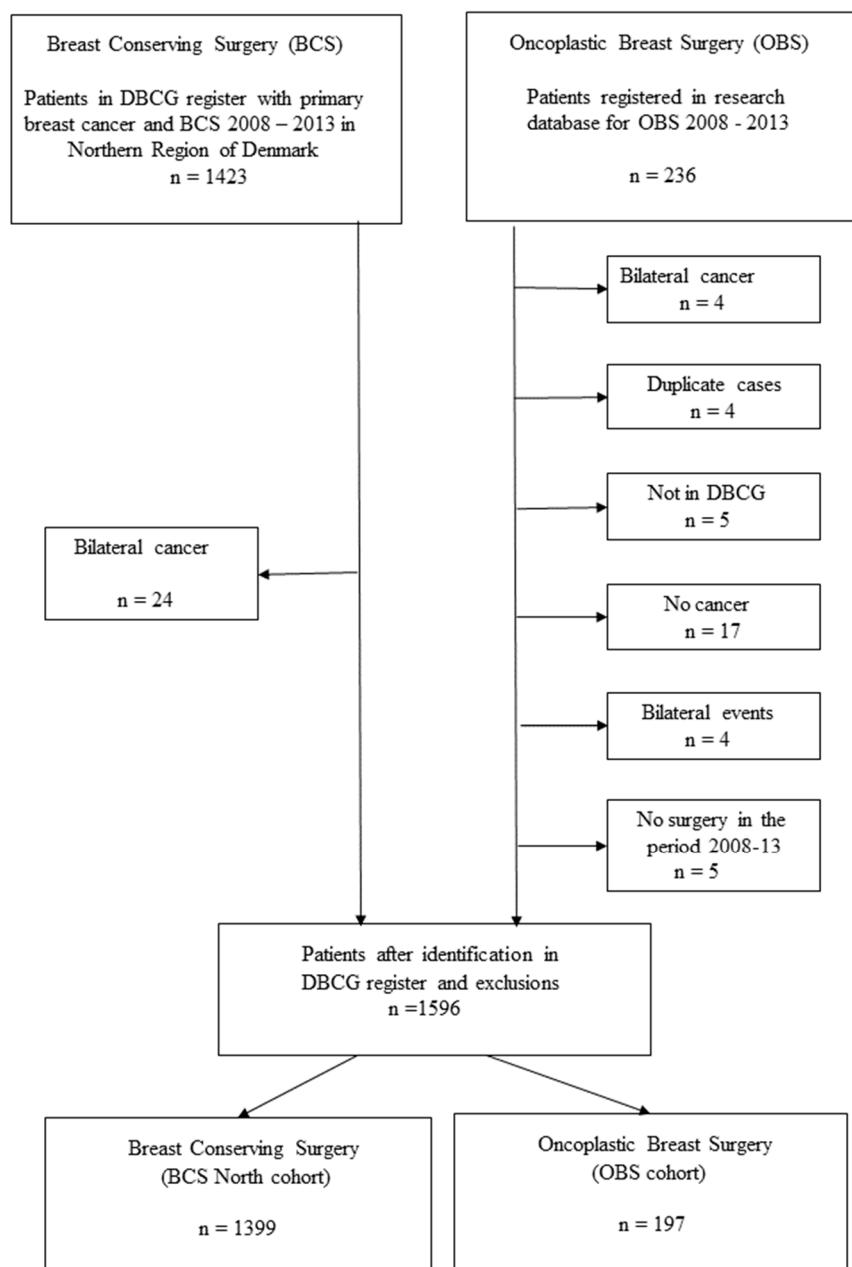


Figure 1. Breast Conserving Surgery (BCS) and Oncoplastic Breast Surgery (OBS) cohorts.

Danish Breast Cancer Cooperative Group registry

The DBCG registry, 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 in Denmark¹⁰. Data recorded include date of diagnosis, tumour characteristics, surgical treatment, oncological adjuvant therapy and information on recurrent disease and death. The use of oncoplastic surgical techniques has been registered since 1 July 2010. Data on postoperative complications are not registered in the DBCG registry.

Patients in the research database, the BCS North and the BCS South cohorts were identified in the DBCG registry by permission from the Danish Clinical Registries, the Danish National Board of Health⁹⁴. The BCS North cohort, including all patients with primary invasive breast cancer treated with BCS in the Region of Northern Denmark from 1 January 2008 to 31 December 2013, was identified as a consecutive population-based cohort in the national DBCG registry (n=1423, figure 1). The BCS South cohort, which included all patients treated with BCS in the Region of Southern Denmark from 1 January 2008 to 31 December 2013, were similarly identified in the DBCG registry (n=3662). Only data regarding time of surgery, administration of and time to initiation of adjuvant therapy were collected for the BCS South cohort. The studies in papers III and IV used data collected between 1 January 2008 and 3 January 2017.

Study-specific Questionnaire (SSQ)

Using an SSQ we collected data on patient characteristics regarding body mass index (BMI), chest circumference, bra-size, menopausal status, smoking habits, marital status, living arrangements and education. These characteristics could possibly influence the outcomes of satisfaction and HRQoL evaluated by the Breast-Q postoperative module. These data were included in the analyses in paper IV as potential confounding factors along with predictive factors retrieved from the DBCG registry.

Study populations

Patients - paper I

Patients with invasive breast cancer were included from the research database between January 2008 and December 2010. OBS was performed on 72 patients with a total of 74 primary tumours (two cases with bilateral breast cancer). Breast size was categorised as small, medium or large which correlates to a clinical norm where a small breast is up to 250 cc, a medium one is 250–500 cc and a large one is 500 cc or more. For descriptive reasons, tumour location was categorised in zones I–IX as described by

McCulley and Macmillan (Figure 2) ⁵. A categorisation of the patients was made as guidance for planning and evaluation of the reconstruction based on breast size and tumour location into four groups. Groups I to III included medium to large breasts with tumours located in the lower part, the mid or upper part, and the central part of the breast, respectively. Group IV included small breasts with all possible tumour locations. Patients in group I were treated with volume reduction techniques, patients in groups II and III were treated mainly with displacement techniques while patients in group IV were treated with replacement techniques.

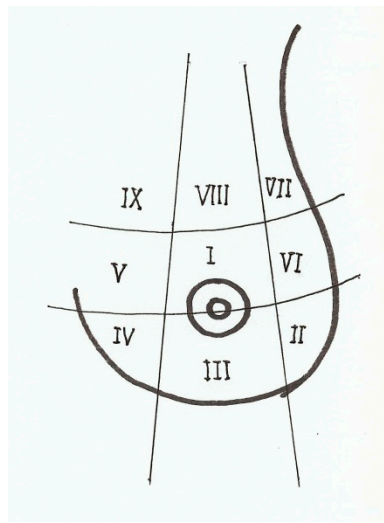


Figure 2. Illustration of the distribution of zones in the breast described by McCulley and MacMillan.

For all patients, volume reduction, volume displacement or volume replacement techniques were used for immediate reconstructions, thus, all operations represented what was later defined as level II OBS ^{1 2 51}. Forty-four patients were operated at the Hospital of Southern Denmark, Esbjerg, twenty-three patients at Aleris-hamlet Privathospitaler, Copenhagen, and five patients at the Hospital of Southern Denmark, Aabenraa.

Patients – paper II

A subpopulation of 15 patients operated with OBS and whose breasts were reconstructed with the tunnelled fasciocutaneous thoracodorsal flap with skin island, a replacement technique, were identified in the research database in the period January 2008 to January 2011. Thirteen patients had small breasts (<250 cc) where no contralateral surgery was needed to achieve symmetry, while two patients with

medium-sized breasts (250-500 cc), who did not want to have contralateral surgery, were operated with this technique. Data were collected consecutively for all patients preoperatively and also postoperatively at follow-up visits. All patients were seen at follow-up visits after three months, 10 after one year, and 6 after two years by a plastic surgeon. Patients were operated at the Department of Surgery, Section of Plastic Surgery, Hospital of Southwest Jutland, and at the Department of Plastic and Breast Surgery, Privathospitalet Hamlet, Copenhagen, in the period from January 2008 to January 2011.

Patients – paper III

OBS cohort

Patients treated with OBS were consecutively registered in the research database at the Hospital of Southwest Jutland, which was approved by the Danish Data Protection Agency ⁹³, and 236 patients were registered. In all, 197 patients with primary invasive breast cancer registered in the research database remained in the OBS cohort after exclusion due to the reasons shown in figure 1. These patients underwent surgery in the Region of Southern Denmark at the Hospital of Southwest Jutland, Esbjerg, between 1 January 2008 and 31 December 2013 or at the Hospital of South Jutland, Aabenraa, from 1 October 2010 to 31 December 2013. Patients from Privathospitalet Hamlet, Copenhagen, in the period 1 January 2008 to 31 December 2010 were also included.

BCS North and BCS South cohorts

Patients in the BCS North cohort (n=1423) were identified in the DBCG registry ¹⁰ and treated for invasive breast cancer in the period 1 January 2008 to 31 December 2013 from a dataset retrieved in January 2014 (figure 1). After exclusion of 24 patients with bilateral cancer, 1399 patients remained in the BCS North cohort. Furthermore, 3662 patients were included in the BCS South cohort. These patients had surgery in the Northern and Southern Regions of Denmark, respectively, in the period 1 January 2008 to 31 December 2013.

Patients – paper IV

All patients diagnosed with primary invasive breast cancer treated with BCS in the Region of Northern Denmark from 1 January 2008 to 31 December 2013, in the BCS North cohort, were identified as a consecutive population-based cohort in the national DBCG registry ¹⁰ (n=1423) in a dataset retrieved in January 2014 (Figure 3). Patients treated with OBS were consecutively registered in the research database, approved by the Danish Data Protection Agency ⁹³ at the Hospital of Southwest Jutland, and 236 patients were registered. At the time of the survey in March 2016, patients not

registered with breast cancer (17) and double entries to the database (n=6) were excluded as well as patients who at the time of survey had died (n=132) according to data from the Danish Cause of Death register⁹⁵. In all, 1504 patients were sent the survey, which resulted in 764 patient replies (figure 3).

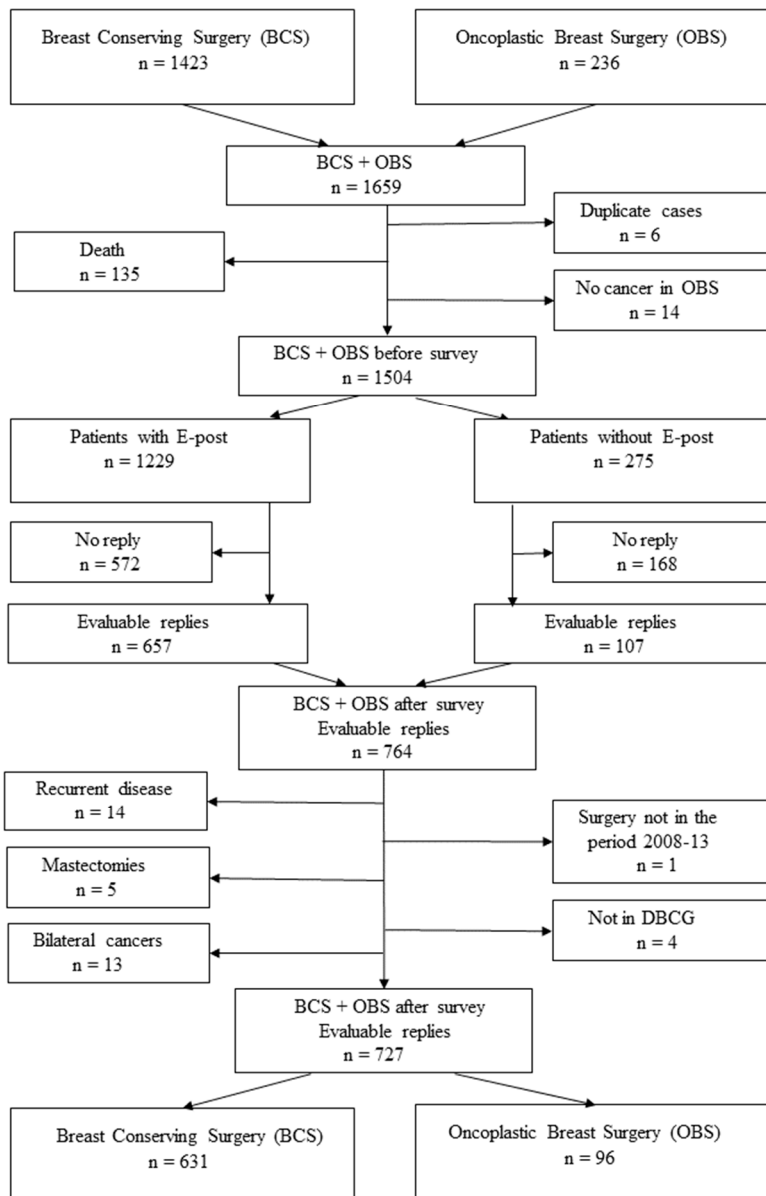


Figure 3. Breast Conserving Surgery (BCS) and Oncoplastic Breast Surgery (OBS) cohorts.

Based on a second DBCG registry¹⁰ dataset retrieved in 2017, patients were excluded (n=37) if at the time of the survey they had experienced recurrence of the disease, a secondary mastectomy, were registered with bilateral cancer, did not have surgery in the period 2008 to 2013 or if they were not registered in the DBCG registry¹⁰. The final study-population included 727 patients in all, with 631 and 96 evaluable replies in the BCS and the OBS cohorts, respectively (figure 3).

Patients in the BCS cohort underwent surgery in the Northern region of Denmark. Patients in the OBS cohort underwent surgery in the Region of Southern Denmark at the Hospital of Southwest Jutland, Esbjerg, (1 January 2008 - 31 December 2013; n = 40), at the Hospital of South Jutland, Aabenraa (1 October 2010 - 31 December 2013; n = 48), or at Privathospitalet Hamlet, Copenhagen (1 January 2008 - 31 December 2010; n = 8).

Among the patients in the OBS cohort, 32 had level I surgery. Sixty-four patients had level II surgery and 32 of them had contralateral surgery for symmetry. The mean follow-up time among all 727 patients was 60.8 months (range 26-100).

Statistical methods

Data were analysed using IBM–SPSS Statistics version 24.0, IBM Corp., US.

Statistical methods paper III

The OBS and the BCS North cohorts were compared regarding factors that might affect the studied endpoints, i.e., patient, diagnostics and tumour characteristics. The risk of non-radical primary tumour excision was compared between the OBS and BCS North cohort, including all patients in an intention to treat design, i.e. including patients who later underwent a mastectomy. A logistic regressions analysis yielded odds ratios (ORs) with 95% confidence intervals. The most important prognostic factors (Table 1) were selected à priori and included in a second multivariate model.

Table 1. Prognostic factors.

Factor	Category	BCS North* n = 1399	OBS** n = 197	Total n = 1596
Column percent				
Age	<50 year	13.9	22.3	14.9
	≥50 year - <65 year	51.3	53.8	51.6
	≥65 year	34.9	23.9	33.5
Nottingham histological 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
Tumour (T) classification (mm)	T1 ≤20	81.7	60.4	79.1
	T2 21-50	17.5	37.1	19.9
	T3 >50	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

* BCS North = Breast Conserving Surgery North cohort, **OBS = Oncoplastic Breast Surgery cohort.

Data in the analyses for initiation of chemotherapy and radiotherapy only included values from 14 days postoperatively until 180 days postoperatively. Adjuvant therapy initiated earlier was regarded as neo-adjuvant therapy, and adjuvant therapy initiated later was probably not directed toward the primary tumour or the values were regarded, as due to incorrect registration. In these analyses patients who had a mastectomy as a secondary surgical procedure were excluded, i.e. these were per protocol analyses. This was because a secondary mastectomy would probably greatly affect the 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 (HRs) with 95% confidence intervals. In a second model, prognostic factors (Table 1) were included as co-variables together with factors that might delay adjuvant therapy, i.e. a non-radical excision, specimen size and axillary dissection (data shown in paper III). The HRs can be regarded as a measure of the difference between groups in the probability of having started adjuvant therapy at a given point in time. Eventually, all selected patients in this sub-analysis received adjuvant therapy.

Disease-free survival, defined as survival without recurrent disease, breast cancer cause of death, multiple and breast cancer cause of death and overall mortality were also analysed using a Cox Proportional Hazards analysis. The same prognostic factors (Table 1) were chosen as co-variables in these analyses. In these analyses, patients who had a mastectomy were included, i.e. these were intention to treat analyses, but sensitivity analyses were also performed excluding these patients, i.e. per protocol analyses (data shown in paper III).

Additional sensitivity analyses were performed for time to initiation of adjuvant therapy, disease-free survival and survival excluding patients in the BCS North cohort who were registered in the DBCG registry as having had OBS (n=51). Furthermore, additional sensitivity analyses were performed excluding patients who had undergone a Level I oncoplastic procedure for the endpoints of non-radical primary tumour excision, adjuvant therapy, disease-free survival and survival.

Statistical methods paper IV

The OBS and BCS cohorts were compared using univariate logistic regression analyses for the scores of each domain in the Breast-Q BCT postoperative module. In the OBS cohort, separate analyses were conducted for all patients and for those patients who had undergone level II oncoplastic procedures. The scores in the Breast-Q domains (0-100) for the BCS cohort were transformed from a linear variable into a binary variable by the median score used for the cut-off value for each domain as the dependent variable, i.e. scores lower than the median score were considered less favourable and higher scores as more favourable. The risk of a better outcome was compared between the OBS and BCS cohorts by the logistic regression analysis and yielded OR with 95% confidence intervals. Factors that might affect the patient-reported outcome, i.e. patient, tumour and treatment characteristics, were selected *a priori* and included in a second multivariate logistic regression model (Tables 2 and 3). We performed sensitivity analyses excluding patients treated with OBS registered in the DBCG registry from 1 July 2010 to 31 December 2013 in the BCS cohort (n = 24). We also compared responders (n = 727) to non-responders (n=683) in order to check for potential selection bias. This analysis included age at surgery and the same tumour characteristics and treatment factors as used in the analyses of responding patients.

Table 2. Patient characteristics.

Factors	Category	BCS n = 631	OBS n = 96	Total n = 727
Column percent*				
Age at surgery (year)	<50	15.5	25.0	16.8
	≥50 - <65	56.6	52.1	56.0
	≥65	27.9	22.9	27.2
Menopausal status	Pre-menopausal	23.6	34.4	25.0
	Post-menopausal	73.9	63.5	72.5
Bra size	A	8.7	13.5	9.4
	B	31.2	26.0	30.5
	C	26.1	24.0	25.9
	D	18.5	16.7	18.3
	E	4.1	6.3	4.4
	≥F	5.1	8.3	5.5
	Missing	6.2	5.2	6.1
Chest circumference (cm)	≤82	20.9	21.9	21.0
	83 - 87	20.0	25.0	20.6
	88 - 92	13.8	15.6	14.0
	93 - 97	8.4	7.3	8.3
	≥98	15.1	10.4	14.4
	Missing	21.9	19.8	21.6
BMI	< 25	36.8	41.7	37.4
	25.0 – 29.9	35.3	39.6	35.9
	≥ 30	17.6	16.7	17.5
	Missing	10.3	2.1	9.2
Smoking prior to surgery	Never-smoker	40.6	57.3	42.8
	Ever-Smoker	53.3	42.7	53.6
Smoking at surgery	Non-smoker	77.7	86.5	78.8
	Smoker	19.5	13.5	18.7
Marital status	Single	7.9	11.5	8.4
	Married	68.3	69.8	68.5
	Separated	0.6	1.0	0.7
	Divorced	9.2	10.4	9.4
	Widow	13.3	7.3	12.5
Living arrangement	Living alone	23.6	18.8	23.0
	Cohabiting	69.6	77.1	70.6
	Others	3.2	1.0	2.9
Education (year)	Primary school	20.8	12.5	20.6
	Secondary school	10.0	12.5	10.3
	Higher educ* (2-3)	32.3	22.9	31.1
	Higher educ* (3-5)	31.9	37.5	32.6
	Higher educ* (5-6)	4.3	7.3	4.7

Column percent does not always add up to 100% as missing data are only shown if >5%. Educ* = education.

Table 3. Tumour characteristics and treatment factors.

Factors	Category	BCS n = 631	OBS n = 96	Total n = 727
Column percent*				
Tumour size (mm)	T1 ≤ 20	84.0	62.5	81.2
	T2 21 – 50	15.7	34.4	18.2
	T3 ≥ 50	0.3	0.0	0.3
Specimen volume (cc)	< 50	20.0	15.6	19.4
	50 - 99	30.7	26.0	30.1
	100 - 199	33.0	32.3	32.9
	≥ 200	14.9	21.9	15.8
Tumour location	Upper lateral	37.9	40.6	38.2
	Upper medial	14.6	8.3	13.8
	Lower lateral	8.9	9.4	8.9
	Lower medial	7.0	6.3	6.9
	Central	6.2	15.6	7.4
	Overlapping regions	23.8	19.8	23.2
Axillary dissection	No	66.2	52.1	64.4
	Yes	33.8	44.8	35.2
Radiotherapy	No	4.4	2.1	4.1
	Yes	95.6	97.9	95.9
Chemotherapy	No	58.6	49.0	57.4
	Yes	41.4	51.0	42.6
Endocrine therapy	No	42.3	34.4	41.3
	Yes	57.7	65.6	58.7
Immune therapy	No	91.1	89.6	90.9
	Yes	8.9	10.4	9.1

Column percent does not always add up to 100 as missing data are not shown.

Ethics

The studies were submitted to The Regional Committee on Health Research Ethics for Southern Denmark. Studies I and II were regarded as studies evaluating the quality of clinical practice, while papers III and IV were regarded as primary register studies. None of these needed approval by the Regional Committee on Health Research Ethics for Southern Denmark. Studies III and IV were also submitted for evaluation to the Regional Ethical Review Board in Lund, Sweden, as the research was conducted at Lund University, Sweden, but their approval was not required (Dnr.2014/882). The research database identifying OBS patients was approved by the Danish Data Protection Agency⁹³.

Results

Paper I

A strategy for implementation of OBS in daily clinical practice was presented. The mean age of the 72 patients included was 53 years (range 31-69 years). Two patients had bilateral tumours, so the total number of cancers was 74. Surgery was performed as planned preoperatively on all but one patient, who had a mastectomy due to an unexpected spread of the tumour. Invasive ductal carcinomas comprised 87 % of tumours, while 3 % were invasive lobular carcinomas, 6 % were mixed types and 4 % were DCIS. The mean tumour size was 21 mm, ranging from 6 to 50 mm. In Table 4 tumour resections with immediate partial breast reconstruction in relation to tumour location (zones) and size of the breast (small, medium and large), weight of specimen, methods of reconstruction and contralateral surgery group I–IV are shown. A summary of complications to surgery and secondary surgery caused by complications and disease control is shown in Tables 5 and 6.

Table 4. Tumour resections with immediate partial breast reconstruction in relation to tumour location (zones) and size of the breast (small, medium and large), weight of resection (grammes), methods of reconstruction and contralateral surgery group I–IV

Group (Breast size, zone)	No	Tumour resection weight mean (range)	Reconstruction method	No	Contralateral surgery
I (medium - large, II–IV)	17	367 g (41–1630)	Superior flaps	17	17/17 (100 %)
II (medium - large, V–IX)	25	138 g (27–463)	Inferior flaps	16	22/25 (88 %)
			Superior flaps	4	
			Lateral flaps	1	
			Rotation flap	1	
			Tunnelled LT flap ^a	2	
			TAP flap	1	
III (medium - large, I)	14	83 g (27–124)	Inferior flaps	13	14/14 (100 %)
			Superior flap	1	
IV (small breasts, I–IX)	17	55 g (20–127)	Tunnelled LT flap ^a	13	1/17 (6 %)
			LD flap ^c	3	
			Rotation flap+LT ^b	1	
Total (groups I–IV, I–IX)	73	157 (20–1630)		73	54/73 (74 %)*

Tunnelled LT flap^a: tunnelled lateral fasciocutan thoracodorsal flap with skin island. LT^b: lateral thoracodorsal flap. LD^c: muscle-sparing latissimus dorsi flap. *For one of 72 patients (two patients had bilateral cancer = 74 tumours) mastectomy was required instead of oncoplastic surgery because of non-radical partial mastectomy.

Table 5. Causes of secondary surgery in general anaesthesia.

Complication	Site of complication	No	Percent
Haematoma	Reconstruction	4	(5.4 %)
	Contralateral breast	3	(4.1 %)
	Axilla	2	(2.7 %)
Disease control			
Re-resections		7	(9.5 %)
ALND* due to late positive SN		9	(12.3 %)
Mastectomy		3	(4.1 %)
Reoperations total		28	(38.3 %)

ALND: axillary lymph node dissection. n=73. One patient had haematoma on both the reconstructed and contralateral breast after reduction mammoplasty, as well as a third haematoma after re-resection because of insufficient resection margins.

Table 6: Complications observed after oncoplastic surgery.

Site of complication	Haematoma	Necrosis	Seroma	Delayed wound healing	Infection	Total
Reconstructed breast (n=73)	4	1	0	3	0	8
Donor site (n=20)	0	0	0	0	0	0
Contralateral breast (n=53)	3	0	0	2	0	5
Axilla (n=45)	2	0	1	0	1	4
Total	9	1	1	5	1	n.a.

One patient had a haematoma on both the reconstructed and contralateral breast after reduction mammoplasty, whereas another patient experienced delayed wound healing (more than four weeks) on both breasts. n.a.: not applicable.

Paper II

Fifteen patients, ranging in age from 38 to 65 years (mean 53.5), were included. For three patients, the tumour was located in the upper lateral part of the breast; for seven patients, in the mid-lateral part of the breast; for two patients, in the medial upper part of the breast; and for three patients in the central part of the breast. In three patients, partial mastectomy included the NAC. All tumours were invasive ductal carcinomas and measured 14–37 mm (mean 22.7) and the weight of the lumpectomy ranged from 20 to 108 g (mean 54.5). In 11 patients (73%) SNB was positive, and all of them had ALND.

In all 15 cases the resections margins were per-operatively macroscopically approved by the pathologist. However, in four patients (27%) the resection margins were considered to be too narrow in the final routine histopathological evaluation and in these four patients a re-resection was performed in a second procedure. No secondary mastectomies had to be performed because of insufficient resections.

In the early postoperative period one patient had haematoma in the breast related to the reconstruction, and the haematoma was surgically evacuated. Otherwise, no early complications occurred. Consequently, no patients had complications leading to any delay in the adjuvant therapy. At the follow-up visits after three months and one year, one patient reported intermittent pain at the donor site; however, no specific therapy had so far been needed. Otherwise, no late surgical complications occurred. One patient, however, had recurrence of the tumour with disseminated disease and died 19 months postoperatively.

Paper III

The end points in this paper were: risk of non-radical surgery at the time of partial mastectomy, time to initiation of first adjuvant therapy, disease-free survival and mortality.

The median age of the OBS cohort was 57 years (range 31-80) and of the BCS North cohort 61 years (range 24-93). Patients in the OBS cohort, as compared to the BCS North, had tumours with a higher average histological grade, their tumours more often occurred with vascular invasion, they had a larger number of multifocal tumours, they had larger tumours and more often positive lymph nodes as well as tumours with negative ER and HER2 receptor status (Table 1).

Risk of non-radical surgery at the time of partial mastectomy

The adjusted OR for OBS patients, as compared to BCS North patients, for non-radical primary tumour excision was 0.50 (0.29-0.84), thus showing a statistically significant lower risk of non-radical resection of the tumour in the OBS cohort (Table 7).

Table 7. Odds ratio (OR) for non-radical surgery at the time of lumpectomy.

Cohort	All*	Radical	Non-radical	OR	OR*
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		

All* = Data for 42 of 1596 patients were missing. OR = Odds Ratio. OR* = Odds Ratio adjusted for age, Nottingham histological grade, vascular invasion, tumour focality, T- and N-status, ER status and HER2- status.

Table 8. Days from surgery to initiation of radiotherapy and chemotherapy as first adjuvant therapy in Region of North Denmark (BCS North), OBS population (OBS) and Region of South Denmark (BCS South) in the period 1 January 2008 to 31 December 2014 per protocol i.e. without mastectomies.

First adjuvant therapy	Cohort	Patients				Days					Hazard Ratio	
		All	Treated	%	Mean	SD	Median	Min	Max	Range	HR	HR*
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	n.a.	n.a.
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	n.a.	n.a.

HR* = Adjusted for vascular invasion, age, Nottingham histological grade, estrogen receptor status and HER2-status, tumour focality, T- and N-classification, axillary dissection, primary radical resection and lumpectomy size. Not applicable = n.a.

Time to initiation of first adjuvant therapy

Adjuvant chemotherapy

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 8). We found an unadjusted HR at 1.21 (0.96-1.52) and an adjusted HR of 1.14 (0.89-1.45). The HR refers to the risk (chance) at any given time point of having received adjuvant therapy i.e. a high HR means a lower risk of late initiation. Thus, there was no statistically significant difference between the OBS cohort and the BCS North cohort in time to initiation of chemotherapy.

Adjuvant radiotherapy

In the OBS cohort, 43.2% were treated with radiotherapy as the 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 8). The adjusted hazard ratio was 0.91 (0.71-1.16), thus, no statistical differences in time to initiation of radio therapy were found.

Disease-free survival

Concerning disease-free survival, i.e. survival without recurrent disease, the median follow-up time for the OBS cohort was 4.1 years (range 0.0-8.9) and for the BCS North cohort 5.6 years (range 0.0-9.0). Disease-free survival was lower in the OBS cohort compared to the BCS North cohort. We found a hazard ratio of 1.88 (1.00-3.54), but the adjusted HR was attenuated, at 1.23 (0.61-2.47) showing no statistical differences in disease-free survival between the OBS and BCS North cohorts (Table 9).

Table 9. Disease-free survival measured as the hazard ratio (HR) for recurrence of breast cancer in the period from 1 January 2008 to 3 January 2017.

Cohort	All	Recurrences	Recurrences (%)	Recurrences/ 10.000 year	HR	HR*
BCS North	1399	51	3.7	66.5	1.00	1.00
OBS	197	12	6.1	135.6	1.88 (1.00-3.54)	1.23 (0.61-2.47)
Total	1596	63	4.0	73.7		

*Adjusted for age, vascular invasion, Nottingham histological grade, ER status and HER2-receptor status, tumour focality, T- and N-classification. BCS North = BCS North cohort, OBS = OBS cohort.

Survival

Concerning overall mortality, the median follow-up time was 4.4 years (range 0.0 – 8.9) for the OBS cohort and 5.7 years (range 0.1-9.0) for the BCS North cohort. The median follow-up time for cause-specific mortality was 2.6 years (range 0.7-6.9), and 3.9 years (range 0.0-7.0), respectively. The adjusted risk (HR) of breast cancer as the underlying cause of death in OBS patients as compared to BCS patients was 1.46 (0.52-4.09) (Table 10). Corresponding HR's for breast cancer as the underlying or multiple cause of death was 0.90 (0.34-2.37), and regarding overall mortality it was 0.90 (0.51-1.60). This means that no significant differences between OBS and conventional BCS were revealed.

Table 10. Survival measured as hazard ratio (HR) 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 1 January 2008 to 3 January 2017 for Breast Conserving Surgery in Region North of Denmark (BCS North) and Oncoplastic Breast Surgery (OBS). Including patients who had a secondary mastectomy i.e. an intention to treat analysis.

Cause of death	Cohort	All n = 1596	Death	Mortality/ 10000 year	HR	HR*
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		

* Adjusted for age, vascular invasion, Nottingham histological grade, tumour focality, T- and N-classification, ER status and HER2-receptor status.

Paper IV

The final study population included a total of 727 patients with 631 and 96 evaluable replies in the BCS and the OBS cohorts, respectively (Figure 3). The total response rate for evaluable replies was 48.3% (727/1504), while the response rates for the BCS and OBS cohorts were 48.4% (631/1304) and 48.0% (96/200), respectively. The mean follow-up time among all 727 patients was 60.8 months (range 26-100). Among

patients in the OBS cohort, 32 had level I surgery. Sixty-four patients had level II surgery and 32 of them had contralateral surgery for symmetry.

Patient, tumour and treatment characteristics are shown in Tables 2 and 3 and indicate that the patients in the OBS cohort had more advanced cancers than those in the BCS cohort. Comparing the responder cohort to the non-responder cohort showed only minor differences between the two cohorts, which indicates that the responder cohort was representative for the survey population (Table 11.)

Table 11. Patient and tumour characteristics and treatment factors for the responder and non-responder cohorts.

Covariates	Category	OBS		BCS	
		Responders n = 96	Non-responders n = 71	Responders n = 631	Non-responders n = 612
Column percent*					
Age at surgery (years)	< 50	25.0	18.3	15.5	12.7
	≥ 50 - < 65	52.1	52.1	56.6	50.0
	≥ 65	22.9	29.6	27.9	37.3
Tumour size (mm)	T1 ≤ 20	62.5	63.4	84.0	82.2
	T2 21 – 50	34.4	33.8	15.7	17.3
	T3 ≥ 50	0.0	0.0	0.3	0.3
Specimen size (cm3)	< 50	15.6	12.7	20.0	20.9
	50 - 99	26.0	32.4	30.7	27.8
	100 - 199	32.3	26.8	33.0	30.9
	≥ 200	21.9	25.4	14.9	17.5
Tumour location	Upper lateral	40.6	32.4	37.9	41.0
	Upper medial	8.3	12.7	14.6	11.4
	Lower lateral	9.4	11.3	8.9	10.8
	Lower medial	6.3	12.7	7.0	6.2
	Central	15.6	7.0	6.2	5.4
	> 1 region	19.8	22.5	23.8	22.1
ALND*	No	52.1	59.2	66.2	64.1
	Yes	44.8	39.4	33.8	35.8
Radiotherapy	No	2.1	5.6	4.4	4.2
	Yes	97.9	94.4	95.6	95.8
Chemotherapy	No	49.0	56.3	58.6	69.4
	Yes	51.0	43.1	41.4	30.6
Endocrine therapy	No	34.4	35.2	42.3	40.8
	Yes	65.6	64.8	57.7	59.2
Immune therapy	No	89.6	90.1	91.1	94.3
	Yes	10.4	9.9	8.9	5.7

ALND*: Axillary lymph node dissection. Column percent does not always add up to 100 as missing data is not shown. Patients in the Responder cohort (n = 764) and Non-responder cohort (n = 1504-764 = 740) were excluded (Responder cohort (n = 37) and Non-responder cohort (n = 57)) if the patients were not registered in the DBCG-registry, did not have surgery in the study period, did not have breast cancer, had bilateral cancers or a secondary breast cancer (bilateral event) or if they had a recurrent disease or had undergone a mastectomy before the survey (figure 1). * Axillary dissection.

The risk of a better outcome was compared between the OBS and BCS cohorts by the logistic regression analysis, yielding odds ratios (OR) with 95% confidence intervals. OR's and adjusted OR's for scores in the Breast-Q modules "Psychosocial Well-being", "Physical Well-being", "Satisfaction with Breasts" and "Sexual Well-being" for BCS and OBS levels I+II and BCS and OBS level II are shown in Table 12. We found that patients treated with OBS had a better "Psychosocial Well-being" with the adjusted OR at 2.15 (1.25-3.69) which was even strengthened for OBS level II alone with the adjusted OR at 2.67 (1.37-5.20). However, no significant differences were found for the domains "Physical Well-being", "Satisfaction with Breast" or "Sexual Well-being".

Table 12. Odds ratios for a high score in Breast-Q modules "Psychosocial Well-being", "Physical Well-being", "Sexual Well-being" and "Satisfaction with Breasts" for BSC and OBS levels I+II and BCS and OBS level II.

Domain	Cohort	All	Below median	Above median	OR	OR*
Psychosocial Well-being Median = 82	BCS	627	311	316	1.00	1.00
	OBS level I+II	95	38	57	1.48 (0.95-2.29)	2.15 (1.25-3.69)
	BCS	627	311	316	1.00	1.00
	OBS level II	63	23	40	1.71 (1.00-2.96)	2.67 (1.37-5.20)
Physical Well-being Median = 78	BCS	623	277	346	1.00	1.00
	OBS level I+II	95	50	45	0.72 (0.47-1.11)	0.83 (0.50-1.39)
	BCS	623	277	346	1.00	1.00
	OBS level II	63	32	31	0.78 (0.46-1.30)	0.94 (0.50-1.74)
Satisfaction with Breast Median = 74	BCS	626	308	318	1.00	1.00
	OBS level I+II	95	48	47	0.94 (0.61-1.45)	0.95 (0.57-1.59)
	BCS	626	308	318	1.00	1.00
	OBS level II	63	29	34	1.13 (0.67-1.90)	1.25 (0.67-2.33)
Sexual Well-being Median = 58	BCS	431	205	226	1.00	1.00
	OBS level I+II	75	33	42	1.15 (0.71-1.89)	1.42 (0.78-2.58)
	BCS	431	205	226	1.00	1.00
	OBS level II	50	21	29	1.25 (0.69-2.27)	1.86 (0.90-3.83)

*Adjusted for age, follow-up time, menopausal status, T-classification, lumpectomy size, tumour location, bra size, chest measurement, BMI, radiotherapy, chemotherapy, endocrine therapy, immunotherapy, axillary clearance, smoking, marital status, living arrangement and education.

Discussion

The aim of this thesis was to describe and evaluate the strategy for implementation of OBS. OBS was implemented in a collaboration between breast surgeons and plastic and reconstructive surgeons in a daily clinical setting and applied to a broad, unselected population of breast cancer patients. The results show in summary, that implementation of OBS in the daily clinical setting is feasible without impairing the oncological outcome of the treatment of breast cancer and indicate that OBS improves the HRQoL in regard to psychosocial well-being compared with conventional BCS, despite involving more extensive surgery.

Implementation of oncoplastic breast surgery

The surgical aims of OBS are to achieve radical cancer surgery as well as a good aesthetic and functional outcome and thereby improve the outcome of surgical treatment of breast cancer ^{3, 82, 96}.

In paper I we present a strategy for implementation of OBS designed to meet those aims, along with an evaluation of the strategy and results of surgery ⁴⁶.

The purpose of the first study was to present and evaluate the strategy for implementation of OBS with regard to the feasibility of a surgical strategy designed to include a wide range of patients with variations in breast size, tumour size, and location of tumour, and to evaluate the postoperative outcomes of surgery. The OBS cohort in paper I included 72 patients with small to large breasts, and tumours of various sizes and locations within the breast, thus reflecting the general variations in breast cancer patients. We found the study cohort were compatible with patients in previous studies regarding tumour type, location and size ^{2, 4, 5, 49, 50, 97-99}. In one of their first studies, McCulley and MacMillan ⁵ evaluate 50 patients with tumours located in all quadrants where tumour resection was followed by immediate reconstruction using volume reduction and displacement techniques, while Meretoja et al ⁴⁹ in 2010 evaluated 90 patients operated for OBS, mainly reduction mammoplasties, although they also included some patients with DCIS.

Various methods of reconstruction were used in the study in paper I, including volume reduction, volume displacement and volume replacement techniques, demonstrating

that surgeons performing oncoplastic breast surgery require knowledge of and experience with many reconstructive techniques^{2, 4, 5, 34, 44, 46, 50, 53, 62, 64, 68, 97, 100, 101}.

An obvious concern is that OBS with immediate partial reconstruction involving internal or external flaps and possibly bilateral surgery could be followed by an increase in postoperative complications compared with unilateral conventional BCS. An increase in postoperative complications could lead to delay in administration of adjuvant therapy, possibly impairing the prognosis^{69, 102}.

On evaluating the postoperative results in study I we noted haematomas requiring surgery in 12 % of cases, of which 5 % were located in the reconstructed breast, 4 % in the contralateral breast and 3 % in the axilla. No flap necrosis was observed. These results are consistent with previously reported rates of early postoperative complications for OBS^{4, 65, 99, 100, 103}. In a recent study by Crown et al. evaluating postoperative complications for 273 BCS patients compared with 288 OBS patients, they found complication rates of 17.9% and 8%, respectively, i.e. considerably lower complication rates for OBS¹⁰⁴.

With regard to the timely administration of adjuvant therapy in study I, four patients (6%) had a delay in their adjuvant therapy due to postoperative complications (wound healing problems)⁴⁶. A delay was considered to have occurred when adjuvant therapy was administered later than four weeks postoperatively. Such delays have also been reported in previous studies,^{49, 99, 105}. In the study by Meretoja et al.⁴⁹ 2% of patients experienced a delay in adjuvant treatment due to postoperative complications and in the review by McIntosh⁹⁹ of studies on therapeutic mammoplasties they found a delay in adjuvant treatment in five studies of between 1.9% and 6% of patients.

Although recognising that our sample in study I was small, our results indicate that complications after OBS have little negative impact on the timely administration of adjuvant therapy. In our study evaluating oncological outcomes for OBS compared with conventional BCS (paper III), we did not find any statistically significant differences between the OBS and BCS cohorts with regard to delay in administration of adjuvant therapy¹⁰⁶.

Furthermore, in paper I, we noted that we had positive resection margins in ten of our patients (14 %) for which seven (10 %) required re-resection and three (4 %) required mastectomy. This result is equal to or better than figures reported in previous studies^{2, 4, 49, 98, 99, 107, 108}. Mertoja et al.⁴⁹ found that 16.2% of 90 patients treated with OBS had positive resection margins, while Clough et al.² reported positive margins in 13.%. The favourable results are supported by our findings in study III where OBS was accompanied 10% positive margins, which was statistically a significantly better outcome for primary radical resection compared with conventional BCS (Table 7)¹⁰⁶.

Another aspect of OBS is whether to perform contralateral surgery for better symmetry in the same procedure as a partial mastectomy and immediate reconstruction, or if it is preferable to perform this in a later procedure. This is debated as postoperative radiation therapy can cause subsequent shrinkage due to fibrosis or chronic oedema leading to an increase in breast volume causing asymmetry months after surgery^{3, 105, 109}. We chose to perform contralateral surgery in the same procedure as partial mastectomy, where partial reconstruction was carried out with volume reduction or displacement techniques. During our observation period of more than two years on average, reported in paper I, a supplemental corrective procedure due to asymmetry had to be carried out just for one patient. This supports the use of immediate contralateral surgery and the findings are consistent with previous studies^{2, 4, 5, 49}.

In study I, a total of 946 women had surgery due to breast cancer. Of these patients, 53.8% (n=509) had conventional BCS, 38.6% (n=365) mastectomy, and 7.6% (n=72) OBS. All of the latter had OBS level II. Although the study does not include level I OBS, the low percentage of patients operated with OBS indicates that it is definitely not the case that all patients that would be suitable for OBS are presented with this option. This view is supported by Urban et al.⁷ and Baildam⁶ who reported that up to 30 % of patients treated using BCS experience deformities that require complementary surgery. This is also indicated in the recent study by Crown¹⁰⁴. If more women were presented with the option of OBS, complementary surgery after conventional BCS could be reduced to a minimum.

A limitation of study I is that, at the time of initiation in 2008, i.e. when OBS patients were included in the research database, there was no international consensus regarding the definition of OBS^{1, 2, 51}. This means that it was not possible to categorise our patients and the surgical techniques used based on an existing consensus definition, making it difficult to compare the results to other studies. However, the reconstructive techniques included in the study were later defined as level II OBS¹. Thus patients treated with level I OBS were not included in study I.

In summary, with surgery performed as planned in 73 of 74 operations we found implementation of OBS in a daily clinical setting both feasible and safe. With the presented surgical strategy we found no increase in non-radical primary surgery or postoperative complications, nor any delay in administration of adjuvant therapy. However, the results in study I indicate that far from all patients suitable for OBS are considered for this treatment.

Introducing a modified replacement technique for partial breast reconstruction

In our study (paper II) we introduced the use of a tunnelled fasciocutan thoracodorsal flap with a skin island as a modified replacement technique for partial breast reconstruction ¹¹⁰⁻¹¹². The technique was used for women with small breasts where the tumour was located in the lateral or central parts of the breast and where skin, and sometimes the NAC, overlying the tumour were resected.

Immediate reconstruction after partial mastectomy in women with small breasts (<250 cc) represents a challenge as not enough tissue is left for reconstruction with volume reduction or volume displacement techniques to reach an acceptable aesthetic outcome. The alternative to unfavourable results after partial mastectomy followed by radiotherapy in these women has so far been mastectomy with or without immediate or delayed total reconstruction. To reconstruct these defects, OBS with replacement techniques by use of external flaps thus constitutes an interesting avenue of refinement in BCS ¹¹³.

The technique shows a low postoperative complication rate with only one haematoma requiring surgery compared with previous studies ^{101, 114}. Munhoz et al. ¹¹⁴ found in their study, including 34 patients with immediate partial breast reconstructions with a lateral thoracodorsal fasciocutaneous flap, complications in 11.8% connected to the flap, and overall complications affecting 38.2% of patients, while Kijima et al. ¹⁰¹ found complications affecting 18.8% of patients with skin necrosis. A low complication rate is important so that the adjuvant therapy can be instituted without delay, which actually was achieved in our series of patients. Regarding radical surgery, we had four re-resections due to positive resection margins (27%), which is higher than expected, but no mastectomies ¹⁰². Repositioning the flap after re-resection did not impair the final outcome regarding the breast configuration. Despite adequate margins and early adjuvant therapy within a few weeks, one patient died due to disseminated disease after 19 months. There were no signs of local recurrence and presumably the patient already had disseminated micro metastases from the start.

However, the study has a limitation. The study sample was small with only 15 patients: 13 patients with small breasts and two patients with medium-sized breasts, selected as a subpopulation of level II OBS patients. A larger sample might have shown a different outcome.

Although we find this flap very useful it is important, when considering reconstruction using this flap, to ensure that the volume of the flap matches the volume of the excised specimen. If it is anticipated that the volume of the flap will be too small, another method of reconstruction should be considered to prevent an unacceptable outcome. In such cases, reconstruction with a TAP flap ^{52, 68}, a ms-LD flap ³⁴ or even a microvascular free flap might be alternatives.

Oncological outcomes of OBS compared with conventional BCS

In summary, we found a statistically significant lower risk of non-radical primary tumour excision for patients treated with OBS, including levels I and II compared with conventional BCS (paper III). Regarding the time to initiation of the 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. Thus, our results indicate that OBS is an oncologically safe procedure.

Previous studies have documented that the oncological safety of BCT equals that of mastectomy^{75, 76, 115, 116}. Many studies address indications for OBS, surgical techniques, and complication rates^{2, 4, 44, 46, 53, 103, 117, 118}, but few studies have evaluated the safety of OBS with regard to earl^{47, 69, 102, 119-121}, and especially long-term, oncologic outcomes^{47, 48, 66, 118, 122}.

Radical primary excision

In cases where the size of the tumour in relation to the size of the breast is small, tumour excision can often be performed with sufficient margins without applying oncoplastic techniques^{2, 46, 100}. In our study (paper III), the rates for non-radical primary tumour excision were lower for OBS (10%) compared to conventional BCS patients (16.0%). The definition of what is regarded as radical excision in BCS is often missing in published articles^{32, 123}, and the widths for appropriate negative margins are debated. Najafi et al.¹²⁴ 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 et al.¹⁰² in their review including 55 studies found positive excision margins in 10.8% of patients. Regarding positive resection margins for conventional BCS, Lovrics et al. reported a rate of 26% in a study including 489 patients¹²⁵. Compared with conventional BCS, we found a statistically significant lower risk for non-radical primary tumour excision for patients treated with OBS. This result is in line with several previous studies, suggesting that applying oncoplastic surgery does not compromise primary excision margins^{102, 107, 126}.

Timing of adjuvant therapy

It is a concern that more extensive surgery could lead to delay in the initiation of adjuvant therapy, thereby possibly impairing the oncologic outcome^{2, 69, 107}. Few studies have addressed the possible delay of initiation of adjuvant therapy after OBS. In the recent study by Klit A. et al.⁷⁴, delay following OBS, specifically compared with conventional BCS and mastectomy, was investigated showing there was no delay in the initiation of adjuvant chemotherapy for patients treated with OBS. Studies by Kahn et

al.¹²⁷ and Dogan et al.¹²⁸ showed no delay in initiation of chemotherapy after OBS, while Hillberg et al.⁶⁹ found 8.2% of 150 included patients experienced a delay in the initiation of radiotherapy due to postoperative complications. A study by Clough et al.² 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 should be initiated within a maximum of 12 weeks after surgery⁷⁰⁻⁷². Other results support that this is also true for radiotherapy⁷³. Furthermore, studies confirm that the time to initiation of adjuvant chemo- and radiotherapy has an impact on disease-free survival and survival⁷¹⁻⁷³, although Barbieri et al.¹²⁹ and more recently van Maaren et al.¹³⁰ found that a delay in the administration of radiotherapy did not increase the risk for local relapse. These studies indicate that OBS does not lead to a delay in initiating adjuvant therapy.

Our results showed no significant differences in time to initiation of the first mode of adjuvant therapy - either chemotherapy or radiotherapy. Our results thus support the results of previous studies. To ensure that these results were not reflecting regional differences in time to initiation of adjuvant therapy, we also investigated the time to adjuvant therapy in the BCS South cohort. We found differences in time to initiation of adjuvant therapy when comparing the OBS cohort to the BCS South cohort, with a shorter time to chemotherapy, but a longer time to radiotherapy. However, our interpretation is that these differences in time may be due to logistic reasons in the planning of treatment in the region rather than reasons caused by surgery alone or complications of surgery.

Disease-free survival

Although OBS has been increasingly implemented in the last two decades as an option for BCT, only a few studies have addressed disease-free survival and survival. With recurrence rates at 3.65% for conventional BCS, our observations are in line with results published in other studies¹⁰².

Recurrence rates for patients treated with OBS have been reported to vary from 1.8% to 16%^{47, 48, 117, 118, 123}, and in a review by De la Cruz et al.¹⁰², rates were 6.0% for local recurrence and 11.9% for distance recurrence with an observation period of more than five years. The percentage of recurrences in breast cancer patients treated with OBS in our study was 6.1% at a median follow-up of 4.1 (0.0-8.9) years, which is compatible with previously reported results^{102, 118}. Although the crude HR seems to reveal differences in recurrence, the adjusted analyses led to a marked attenuation of the risk. This was probably due to comparatively disadvantageous prognostic factors in OBS patients, such as tumours of higher grade, the presence of vascular invasion, larger tumours, and a more advanced nodal status. In summary, we did not find significant differences in disease-free survival between patients treated with OBS or conventional BCS. Our results are thus compatible with the results of Carter et al.¹¹⁸.

Survival

There are few studies addressing survival for patients treated with OBS^{102, 118, 123}. The overall survival, with a mean follow-up time of 50.5 months, for patients treated with OBS was reported to be 95% in a review including 6011 patients¹⁰², and another study showed no significant differences in overall survival when comparing OBS with conventional BCS¹¹⁸. Our results are in line with these results, showing no statistically significant differences between OBS and BCS patients with regard to mortality (paper III)¹⁰⁶.

Patient-reported outcomes of OBS compared with conventional BCS

In this study, we evaluated the patient-reported outcome of OBS compared with BCS using the Breast-QTM BCT postoperative module. We found that patients treated with OBS had a better outcome for the domain “Psychosocial Well-being”. However, no significant differences were found for the domains “Physical Well-being”, “Satisfaction with Breast” or “Sexual Well-being”.

The quality of the health care services provided needs attention. Consequently, there is now an increasing demand to evaluate how patients perceive the results of treatment, i.e. PRO¹³¹⁻¹³³. In study IV we took advantage of Breast-QTM, which can be used as a standardised and validated instrument for evaluation of HRQoL in patients operated for breast cancer^{90, 134-136}. The Breast-QTM BCT pre- and postoperative modules were introduced in 2015. One year later, O’Connell et al.¹³¹ published their initial experience with the full BCT postoperative module including 200 patients, thus establishing a benchmark for future research. However, few studies have addressed the HRQoL outcome of conventional BCS^{90, 131, 132} and OBS¹³⁷ or both. Compared with previous studies, patients included in the OBS cohort in study IV represent the full spectrum of OBS, i.e. levels I and II surgery. The sample is therefore not restricted to one surgical procedure such as the therapeutic mastoplasmy technique¹³⁷.

In the domain “Psychosocial Well-being” we found a median score of 82, similar to the results of O’Connell¹³¹ and Dahlbäck¹³⁸ using Breast-QTM for evaluation of the outcome of BCT, while Langendiik¹³⁹ found a mean score of 70.1 and Vesprini¹³² of 73.5. In our study we found a statistically significant better outcome for the OBS cohort, including levels I and II surgery, compared with the conventional BCS cohort. The differences were strengthened by including only level II surgery from the OBS cohort.

In their analyses of the domain “Physical Well-being”, Langendijk¹³⁹ and Vesprini¹³² found mean scores of 71.2 and 74, respectively. A slightly higher score of 75 was reported by O’Connell¹³¹. The median score of 78 in our study (paper IV) reflects a low grade of physical discomfort and there was no statistically significant difference

between the OBS and BCS cohorts. A lower score for the OBS cohort might have been expected, particularly in cases of level II surgery as this surgery is more extensive and often involves the contralateral breast. However, the results indicated the opposite since there was a slight difference in the figures, indicating better outcomes for OBS compared with BCS.

In the analysis of the domain “Satisfaction with Breast” Vesprini ¹³² and Langendijk ¹³⁹ found mean scores of 59.3 and 65.7, respectively, while Dahlbäck ¹³⁸ and O’Connell ¹³¹ found median scores of 66 and 68, respectively. Hence, our median score of 74 in the present studies is higher than those reported previously and indicates a higher degree of satisfaction with the breast. High scores generally imply that possible differences are more difficult to detect and, consequently, we found no difference between OBS and BCS. However, when only level II surgery was considered, a tendency toward a better outcome in the OBS group was noted.

The domain “Sexual Well-being” had a markedly lower median score of 58 and, furthermore, the response rate was low at 69.6%. This pattern has also been seen in similar studies and it seems to be a general issue for this domain ^{131, 132, 139}. Therefore, the results must be interpreted with caution. We found no difference between the OBS and BCS cohorts. However, when only level II surgery was considered, a slight tendency toward a better outcome in the OBS group was noted.

In summary, the results show that patients treated with OBS reported statistically better psychosocial health than those treated with conventional BCS. Patients treated with OBS also scored slightly higher for the domains “Satisfaction with breasts” and “Sexual Well-being”, particularly when the analyses only included level II OBS, although the difference was not statistically significant. Notably, the results in the domain “Physical Well-being” showed no significant differences despite the fact that patients treated with OBS had more extensive and often bilateral surgery.

Methodological issues and limitations with regard to oncological and patient-reported outcome studies

A methodological issue to be considered is the definition of OBS. In studies published in the last few decades, the definition of OBS has varied, making it difficult to compare the outcome results from different studies ^{1 51 56}. When we initiated registration of patients treated with OBS in the research database there was no clear definition of OBS. What we defined as OBS was immediate partial reconstruction with the use of the surgical techniques of volume reduction ⁴, volume displacement ⁶⁵ and volume replacement ^{52, 62, 63}. This was what we later defined as level II OBS. In studies III and IV, we have based our definition on the one proposed by Clough et al. ⁵¹ which is

widely accepted. In the publication of 2019 by Chatterjee et al.¹, a consensus definition and classifications system, developed by the American Society of Breast Surgeons, was presented which was strongly influenced by Clough's definition⁵¹. By using a widely accepted definition of OBS we hope that the results from the present studies may be used for comparison with future studies.

Regarding paper IV, another methodological issue to be considered is the PROM instrument chosen. The Breast-QTM BCT module is now widely accepted since it is a validated PROM instrument. Hence, we chose the Breast-QTM BCT postoperative module for the evaluation of patient-reported outcomes comparing OBS with conventional BCS^{134, 135, 140}.

Papers III and IV do have some limitations due to their designs. Implementing OBS in the treatment of breast cancer includes patients in the OBS cohort who, without the availability of OBS, would have been treated with mastectomy. This may have led to relatively more advanced tumours in the OBS group. However, we included tumour size and specimen size in different models, and we believe that this has reduced a potential selection bias.

In order to avoid another form of selection bias, we did not compare patients treated with OBS to patients treated with conventional BCS from the same geographic area. This would have led to potential confounding due to 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 paper III we found differences between the two geographical areas regarding time to initiation of adjuvant therapy. We found differences in time to initiation of adjuvant therapy comparing the OBS cohort to the BCS South cohort, with a shorter time to chemotherapy but a longer time to radiotherapy as the first mode of adjuvant therapy expressed by median and mean days. It is our interpretation that this difference was due to logistic reasons rather than patient and tumour characteristics or the results of surgical treatment.

In an effort to avoid misclassification of confounding factors, i.e. differences in classification of data, all patients included in the studies were identified in the DBCG registry, and all data were selected from the same registry, except for data collected by the Breast-Q and the SSQ. Because the classification and registration of data in the DBCG registry were performed according to national guidelines, we believe that data for the cohorts are reliable and comparable. This is supported by a recent study by Cronin-Fenton et al. where the authors conclude that DBCG data are valid for epidemiological studies of breast cancer treatment¹⁴¹.

In paper III we have several end points, and the risk of a type I error, i.e. a rejection of a true null hypothesis (false positive results), must be considered in the statistical

analyses. However, the results of all the 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 the results in the analyses of disease-free survival and all survival analyses was very limited. Hence, it is possible that non-significant differences in the analyses on recurrent disease and survival are due to poor statistical power. Concerning recurrent disease and survival, larger studies with longer follow-up are needed.

In paper IV, the response rate and non-responders may be an issue. Response rates in other surveys are reported to be between 31% ¹³² and 76% ¹³⁸. With a total response rate in our study of 48.3 % for evaluable replies (OBS cohort 48.4%, BCS cohort 48.0%) we find our response rate acceptable. The analysis comparing patients in the responder and the non-responder cohorts showed only minor differences, that is, the responder cohort is considered representative of the survey cohort, showing no selection bias.

Conclusions

Paper I:

It is feasible and safe to implement OBS in daily clinical practice based on a thoroughly planned strategy for immediate partial breast reconstruction with a wide range of variations in tumour size, tumour locations and breast size.

Paper II:

The tunnelled lateral fasciocutaneous flap with a skin island is a versatile and safe procedure in immediate partial breast reconstruction in patients with small or medium-sized breasts, provided the tumour is located in the lateral or central parts of the breast.

Paper III:

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

Paper IV

The study indicates better outcomes of HRQoL for breast cancer patients treated with OBS as compared with patients treated with conventional BCS. There was no increase in physical discomfort among OBS patients, despite their more extensive surgery.

Future perspectives and considerations

Since the early start of the implementation of OBS in Denmark at our clinic and a few others, OBS has now become recognised as a valuable concept for expansion of conventional BCS. OBS is now regarded as an integral part of breast cancer surgery by the Danish National Board of Health¹¹. In the guidelines of the National Board of Health for Plastic and Reconstructive Surgery, have appointed seven centres to perform OBS, while guidelines by the National Board of Health for Breast Surgery have appointed eight centres¹¹. These centres are distributed with at least one centre in each of the five Danish Health care regions. In 2010 a guideline for OBS was introduced by DBCG and in July 2010 DBCG included the registration of OBS surgery in its registry. Special coding for the different types of operations in OBS has been developed which in turn is linked to the DRG classification system and thereby to charges. The DRG charges aim to reflect the use of resources for each type of surgical procedure with the intention to correlate this to the financial reimbursement for the operations provided in OBS.

However, many women in Denmark are still not offered OBS as an option for the treatment of breast cancer although they would have benefited from it. This is due to several issues.

One issue is the selection of patients for OBS. Although “we are all surgeons”, e.g. breast and plastic surgeons, we are trained differently and have different competence profiles and approaches^{142, 143}. Compared with plastic surgeons, breast surgeons may have difficulty evaluating whether patients will – or will not - benefit from OBS i.e. achieve better outcomes after partial mastectomy with or without OBS. Furthermore, breast surgeons have less training in recognising the different possibilities for reconstruction after partial mastectomy. On the other hand, plastic surgeons are usually not as familiar as breast surgeons with the oncological aspects related to the treatment including adjuvant therapy. This means it is important that all patients are seen by surgeons, with competences in both plastic surgery and oncological breast surgery at the time surgery is planned. A primary evaluation by a breast surgeon alone renders a risk that too few patients will be considered for OBS.

Another issue is the organisation of the surgical treatment of breast cancer in Denmark. As mentioned above, treatment of breast cancer requiring primary reconstruction including OBS is limited by the National Board of Health¹¹ to eight breast surgery

centres in Denmark. However, in all, 12 centres treat breast cancer (2018). This means that patients diagnosed with breast cancer at a centre where OBS is not possible should be referred to a centre where it is an option – or should await a consultation with a plastic surgeon. This requires that breast surgeons understand the options of OBS and primary reconstruction as alternatives to conventional partial mastectomy and mastectomy. This underlines the importance of continued education of all surgeons involved in the treatment of breast cancer in all centres.

A third issue is information given to patients. Most women know, even before a personal diagnosis of a breast cancer, that the treatment of breast cancer is surgery and that it is usually followed by radio-therapy and chemotherapy. They know that surgery may mean either mastectomy or BCS. However, most women do not know about OBS. The diagnosis of breast cancer always comes as a surprise – to many as a shock – followed immediately by a wish for treatment to “get rid of” the cancer. The elucidation and diagnosis of breast cancer must be finished within two weeks from referral, while treatment of breast cancer must be initiated within two weeks of diagnosis, and three weeks if assistance from a plastic surgeon is needed, according to the Danish national guidelines ¹¹. This is a hard period for the patient, and to examine different surgical treatment options by themselves is hardly realistic. This is certainly not the time when the patients’ first thoughts are about the aesthetical and functional outcomes. As a consequence of this, patients do not know about – and do not ask for – OBS as an option for surgical treatment. This underlines the importance of information given to newly diagnosed patients – and women in general.

An important topic for future research is the cost-effectiveness of OBS. At first glance the impression is that OBS is very resource- and time-consuming, both in the out-patient setting and in the operating theatre, often requiring two surgeons. Furthermore, the number of days in hospital and other costs of care may seem to be higher compared with conventional BCS. However, the costs for corrective procedures and later secondary reconstructive surgeries and expenses related to impaired HRQoL may offset these differences in expenses, even to the advantage of OBS.

In conclusion, it is crucial to advocate continued education of breast and plastic surgeons, even closer cooperation between breast and plastic surgeons engaged in the surgical treatment of breast cancer, better organisation of treatment of breast cancer with full and appropriate implementation of OBS ¹⁴⁴, more and better information will be given to patients— and women in general— and continued research to ensure our patients receive the maximum benefit.

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