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ONCOLOGICAL SAFETY OF ONCOPLASTIC BREAST SURGERY

Thesis

Doctor of Science

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ABBREVIATIONS

ACOSOG	American College of Surgeons Oncology Group
AJCC	American Joint Committee on Cancer
AIC	Akaike information criterion
AICAP	Anterior Intercostal Artery Perforator Flap
ANC	axillary node clearance
ANS	axillary node sampling
ASA	American Society of Anaesthesiologists
BI-RADS	Breast Imaging Reporting and Data System
BCS	breast conservation surgery
BCSS	breast cancer specific survival
BCT	breast conservation treatment
BMI	body mass index
CI	confidence interval
CBC	conventional breast conservation
CDC	Clavien-Dindo classification
CCC19	COVID-19 and Cancer Consortium
CLI	chemiluminescence imaging
cPR	complete pathological response
CRP	C-reactive protein
cT stage	clinical tumour stage
CV	cardio-vascular
CWPF	chest wall perforator flap
DCIS	ductal carcinoma *in situ*
DDFS	distant disease-free survival
DFS	disease-free survival
DIEP flap	deep inferior epigastric perforator flap
DR	delayed reconstruction
DXT	radiotherapy (deep X-ray therapy)
EOBCS	Extreme Oncoplastic Breast Conservation Surgery
EPBVEE	estimated percentage of breast volume excised
ER	oestrogen receptor
GA	general anaesthetic
GIRFT National Report	“Getting It Right First Time” National Report
HER-2	Human Epidermal Growth Factor Receptor 2
HR	hazard ratio
HTN	hypertension
IBR	immediate breast reconstruction
ICAP	Intercostal Artery Perforator Flap
iKnife	Intelligent Knife
IMAP	internal mammary artery perforator
IR	immediate reconstruction
iTOP	immediate techniques of oncoplastic surgery
ITS	invasive tumour size
LA	local anaesthetic
LBCR	local breast cancer recurrence rate
LD	latissimus dorsi
LDm	latissimus dorsi miniflap
LICAP	Lateral Intercostal Artery Perforator Flap
LTAP	Lateral Thoracic Artery Perforator Flap
LMR	lymphocyte-to-monocyte ratio

MCN	Managed Clinical Network
MFMC	multifocal/multicentric cancers
MICAP	Anterior Intercostal Artery Perforator Flap
MMG calc.	mammographic microcalcification
Ms	mastectomy
Mast	mastectomy
MCFAP	medial circumflex femoral artery perforator
MIR	mastectomy with immediate reconstruction
Ms±IR	mastectomy with or without immediate reconstruction
Mx	mastectomy
NACT	neoadjuvant chemotherapy
NHS	National Health Service
NHSBSP	NHS Breast Screening Programme
NICE	National Institute of Clinical Excellence
NLR	neutrophil-to-lymphocyte ratio
NOSCAN	North of Scotland Cancer Network
NPI	Nottingham Prognostic Index
NSM	nipple-sparing mastectomy
NST	no special type
OBC	oncoplastic breast conservation
OBCI	oncoplastic breast conservation Clough level I
OBCII	oncoplastic breast conservation Clough level II
OBCS	oncoplastic breast conservation surgery
OCT	Optical Coherence Tomography
OPBC	Oncoplastic Breast Consortium
ORM	oncoplastic reduction mammoplasty
OS	overall survival
PET	primary endocrine therapy
PLR	platelet-to-lymphocyte ratio
PR	progesterone receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROMS	patient reported outcome measurements
RBCR	regional breast cancer recurrence rate
RCT	randomised control trial
REIMS	Rapid Evaporative Ionization Mass Spectrometry
Resp	respiratory
RRFS	regional recurrence free survival
SBC	standard breast conservation
sBCS	standard breast conservation surgery
SCAN	East of Scotland Cancer Network
SIGN	Scottish Intercollegiate Guideline Network
SNB	sentinel node biopsy
SSM	skin sparing mastectomy
TDAP	thoracodorsal artery perforator
TE flap	thoraco-epigastic flap
TM	therapeutic mammoplasty
Thoraco-epig	thoraco-epigastric flap
UK	United Kingdom
UKCCMP	UK Coronavirus Cancer Monitoring Project
US	ultrasound
VR	volume replacement
WLE	wide local excision
WOSCAN	West of Scotland Cancer Network
WTS	whole tumour size
yp	post-neoadjuvant chemotherapy pathology

1. INTRODUCTION

Breast cancer remains the most frequently diagnosed cancer among women worldwide, affecting 1.5 million women each year. The primary aim of breast conserving surgery (BCS) is achieving oncological safety through complete tumour excision with clear margins. BCS with adjuvant whole breast irradiation is well established as an oncologically safe option in the management of early breast cancer. As surgical techniques have moved away from more radical approaches towards breast conservation and the use neoadjuvant therapy increased, oncoplastic surgery has evolved from BCS.

As with any emerging technique, oncological safety is of prime concern. OBCS has the advantage of allowing for higher volume surgical resection, thereby reducing positive resection margins, and subsequently re-excision and mastectomy rates. This may have the added benefit of preventing delays in adjuvant therapy due to lower rates of positive margins encountered and obviating further surgery.[1] OBCS also has the ability to improve cosmesis and patient satisfaction as compared to mastectomy and standard BCS.

The aim of oncoplastic breast conservation surgery is to prevent major distortion, as delayed correction of major deformity is much more difficult in a breast which was treated with radiotherapy as well. Radiotherapy impairs wound healing properties in tissues via microvascular injury, defective collagen deposition due to fibroblast dysfunction due to upregulation of TGFβ family members. As wound healing problems after radiotherapy are significantly higher, delayed correction or reconstruction of major deformities would expose the patient to unnecessary risks compared to immediate correction before radiotherapy delivered. Further, in case wound healing problems develop after delayed correction, it further impairs the aesthetic outcome which we wanted to correct originally. Nevertheless, the patient needs to be informed during informed consent that there will always be deformity, her breast will “never be the same” again, and the only aim of oncoplastic surgery is to prevent major deformities, which would significantly impair her quality of life very likely. Having said these, there will always be impairment in the quality of life even with oncoplastic surgery, but – hopefully – it will be moderate only compared to non-oncoplastic wide excision caused major deformity.

Importantly, oncoplastic surgery should not be mixed with onco-cosmetic surgery, when the tumour-breast ratio would not indicate the application of oncoplastic techniques as the tumour could have been removed with simple wide local excision resulting in no significant

aesthetic defect. In onco-cosmetic surgery a simple wide excision is combined with aesthetic surgery to improve quality of life, i.e., using breast cancer surgery for aesthetic purposes. It is mainly applied in macromastia when patients always wanted to have smaller breasts, or patients with significant (grade III) ptosis who always wanted to have more “perky” breasts but has not undergone aesthetic breast surgery before. In these cases, breast cancer surgery can improve quality of life via improving breast cosmesis at the time of cancer surgery.

Adequate application of oncoplastic surgery requires experience. There is no way to objectively determine what an individual considers major deformity and how it affects her quality of life. Oncoplastic surgeons are left with their own experience when they advise patients about techniques and the likely outcomes. While there is always a common sense amongst the oncoplastic surgeons in choosing the oncoplastic technique, a thorough and detailed discussion with the patient is an absolute pre-requirement to find out what breast shape and size she thinks is ideal for her. Additionally, these complex decisions are ideally discussed in multiple settings, as patient are unable to concentrate on and balance on quality-of-life issues right after breaking bad news, as well as fully understand and digest specific risks and complications of complex oncoplastic operations. Needless to say that decisions should be backed up by discussions on oncological and oncoplastic multidisciplinary teams.

A great consideration was given how to organise the presentation of the methods, results, and conclusions in this thesis. Ideally the various oncological outcomes are presented in relation to each oncoplastic surgical techniques. Here, however, it would have been difficult and rather confusing due to the heterogeneity and overlap in the oncoplastic techniques. There would have been too many variables in techniques and outcomes to be presented in a didactic manner. Hence, I opted to present these in a way to reflect the natural evolution of the techniques which was paralleled with the recognition of the oncological safety and its measurement. Firstly, oncological safety was audited on unit level when new techniques were introduced, which was followed by regional and national studies when the given technique gained popularity and was applied in many units too. This represents the first step in benchmarking of a unit’s performance, i.e. local results are matched to regional / national results. The second step of benchmarking is when the latter is matched to international data based on systematic reviews or meta-analyses. These two steps benchmarking is the only possible way to audit the quality of a newly applied surgical technique when prospective randomised controlled trials are not feasible.

Therefore, in this thesis, the oncological safety data measured on unit level are presented first, followed by regional and national data that we studied. While the highest level of evidence for the oncological safety in oncoplastic breast surgery is based on the systematic reviews and meta-analyses, these are not based on our original research hence these are not presented separately, but rather included in the introduction as part of literature review. This also helps the reader to familiarise with the most up-to-date results and understand how our own original research contributed to the overall evidence of the oncological safety of oncoplastic surgery.

The studies included in this thesis dating back to the late 2000s. However, mastectomy followed by immediate reconstruction or delayed reconstruction – the latter being introduced even earlier – have been established procedures and their oncological safety have already been investigated widely in the preceding two decades and published extensively. Hence, my thesis is focuses on the oncological safety of oncoplastic breast conservation surgery primarily, which started to gain popularity in the late 2000s and there was hardly any data published on the oncological safety for that at that time.

2. BACKGROUND

2.1. Review of the relevant literature

Breast conservation treatment (BCT) defined as breast conservation surgery (BCS) with whole breast irradiation is the standard of care in the management of early breast cancer. The goal of BCT is tumour free resection margins and good local control. An important secondary goal is a satisfactory cosmetic outcome as this is associated with both patient satisfaction and improved quality of life.[2] Poor cosmetic outcomes can affect up to 40% of patients undergoing BCT.[3] There are many factors influencing the ultimate cosmetic outcome including host factors, adjuvant therapy administered, tumour location in breast however the percentage of breast volume excised is the single most important factor influencing cosmetic outcome.[2] How the breast looks after treatment is important because of the correlation between cosmetic outcome and the patients' anxiety and depression score, body image, sexuality and self-esteem.[4]

In the last decade BCT has evolved to ensure both adequate oncological resection and good cosmetic outcome for patients with larger tumours. Increasing utilisation of neoadjuvant therapy to enable tumour shrinkage and allow BCT is one strategy. Oncoplastic breast conservation surgery (OBCS) with or without neoadjuvant therapy facilitates tumour excision with a wide margin of resection followed by immediate reconstruction of the defect (partial breast reconstruction), thus preserving a natural breast shape in woman and improving cosmetic outcome. Indications for OBCS include: anticipated poor cosmetic outcome with standard BCS (sBCS); large tumour in large breast; an alternative to mastectomy; or prevention of lymphoedema, fibrosis and chronic pain that may be associated with irradiation in large breasted woman.[5] Additionally, as OBCS is increasingly being utilised as an alternative to mastectomy +/- immediate reconstruction, this approach may offer a lower complication rate compared with total mastectomy and reconstruction, particularly if radiotherapy is being given in the adjuvant setting.[6-8] Potential benefits of this approach could be improved patient satisfaction, quality of life, as well as decreased health care costs compared to full breast reconstruction.[9]

OBCS has become widely accepted and adopted into routine clinical practise. Accurate national data on current utilisation and practise of OBCS is limited.[6] A recent study from the MD Anderson Cancer Centre in the USA demonstrated that OBCS had a nearly fourfold increase in the percentage of all breast cancer surgeries performed (from 4 to 15%) between

2007 and 2014. In 2014 OBCS accounted for over 33% of all breast conservation surgeries.[8] It is likely that similar increasing rates of OBCS procedures are being undertaken in Europe and UK. The techniques of OBCS previously required either specialist oncoplastic training for breast surgeons or a combined approach between breast oncological surgeon and plastic surgeons. For this reason, in the UK, an oncoplastic fellowship network was set up in 2005 with eight units in England and two in Scotland (of which the author of this thesis was one of the first fellows) and this has been developed further subsequently. Competency in mammoplasty techniques and involvement in pedicled flaps is now a certificate of completion of training requirement for all general surgeons with a breast sub speciality interest in the UK, subsequently all newly appointed consultant breast surgeons in the UK will be trained in the techniques of mammoplasty.

Despite the widespread adoption of OBCS, there is limited high quality evidence to support the benefits of this approach.[3, 5, 6, 10] OBCS utilises the principles of sBCS however the landmark prospective randomised trials that established the safety and efficacy of BCT mostly included patients with small tumours.[11, 12] Patients who are treated with OBCS often have larger tumours, in studies over half the patients treated with OBCS had T2-T3 cancers.[13-23] The evidence that cancers of these sizes can be safely treated with breast conservation is not robust in the classic prospective randomized trials.[23] Only 599 patients with T2 cancers were randomized into the arm of breast conservation with radiotherapy in three trials published by van Dongen et al, Poggi et al and Fisher at al. although the later one randomized up to 4cm cancer size.[24-26] Interestingly, patients with T1 cancers only were randomized by Veronesi et al and Arriagada.[27, 28] Hence, the classic randomised controlled trials do not provide sufficient evidence that breast conservation is safe in T2 cancers and above. Most published OBCS studies are small, single centre, observational studies reporting (often inconsistent and heterogenous) outcomes. Comparative studies represent a higher level of evidence and currently this is the best available evidence.

2.1.1. Tumour resection margins and re-excision rates

Re-excision rates are of the upmost importance in allowing for accurate assessment of tumour size, margin status, and local recurrence, as well as minimising impact on cosmetic outcome. The evidence base for surgical margins is continuously evolving and there is no universal consensus on what defines a positive margin. In the UK most breast surgeons consider a 1mm minimum clear radial margin for both DCIS and invasive breast cancer.[29] However, the Society

of Surgical Oncology, the American Society for Radiation Oncology & the American Society of Clinical Oncology recently published a consensus statement on margins.[30] This guidance differs from the Association of Breast Surgery (ABS) guidance in that they recommend a 2mm excision margin for DCIS. Involved surgical margins occurs in 20-40% of all standard BCS and one in five BCS patients undergo a re-operation (including re-excision or completion mastectomy).[3, 31]

Previous studies have clearly demonstrated a reduction in re-excision rates in the setting of OBCS as compared to standard BCS or wide local excision (WLE).[32, 33] Despite this, some critics are concerned that tissue rearrangement may inhibit the ability to perform an accurate re-excision. OBCS allows wider oncological resections and although wider negative margins are not associated with lower recurrence rates advocates of OBCS argue that wider resections reduce positive margin rate and results in less re-excisions (or re-operations) compared to standard BCS.[34, 35] Re-excisions have the potential for a delay to adjuvant treatment, surgical complications, and may compromise cosmetic outcome. Additionally, a further operation will cause stress for patients and their families, patient discomfort and increased health care costs. Thirteen comparative studies have compared OBCS with a control group examining rates of positive margin involvement and re-operation rates (**Table 1**).[8, 17, 18, 22, 32, 36-41]

Table 1. Comparative studies analysing resection margin involvement and re-operation.

First Author	Year	No of cases		Margin Definition	Positive (+) margin rate		Re-excision Rate		Mastectomy conversion rate		Conclusion
		OBCS Arm*	Control arm		OBCS arm	Control	OBCS	Control	OBCS	Control	
Kaur et al	2005	30	30	a	3.3% + 13.3% close	3.3% + 33% close	nd	nd	nd	nd	OBCS better
Giacalone et al	2007	31	43	a	10% + 13% close	16.6% + 16.6% close	0%	2.3%	13%	16.2%	OBCS better
Chakravorty et al	2012	150	440	nd	nd	nd	2.7%	13%	3.9%	1.5%	OBCS better
Down et al	2013	37	121	b	5.4%	29%	2.7%	15%	2.7%	14%	OBCS better
Mazouni et al	2013	45	214	b	15.6%	14%	2%	9%	24%	18%	No difference
Gulcelik et al	2013	106	162	nd	8.4%	11%	10.3%	15%	nd	nd	No difference
Tenofsky et al	2014	58	84	nd	nd	nd	5.2%	13.1%	nd	nd	No difference
Losken et al	2014	83	139	f	24%	41%	12%	26%	2%	9%	OBCS better
Crown et al	2015	387	425	e	18%	32%	18%	32%	15%	34%	OBCS better
Mansell et al	2015	119	881**	c	13.4%	13.2%	1.6%	7.7%	11.9%	5.5%	No difference
De Lorenzi et al	2016	454*	908	d	2.9%	2.3%	0%	0%	15.4%	28.6%	No difference
Chauhan et al	2016	33	46	a	0%	11%	0%	4.5%	0%	6.5%	OBCS better
Carter et al	2016	1,177*	9,066**	a	1.0% + 4.8% close	2.1% + 6.2% close	nd	nd	nd	nd	OBCS better

All studies detailed level 2 oncoplastic techniques as described by Clough et al

* OBCS techniques not clearly defined and may include level 1 oncoplastic techniques.

Margin definition: a. negative >2mm between tumour cells and edge, positive (+) tumour cells at cut edge, close <2mm between tumour cells and edge; b. positive if <5 mm clear margin; c. positive if <1mm for invasive and <2mm DCIS; d. no ink on invasive tumour or DCIS; nd. not defined.

** Control group included sBCS and Mastectomy+/- Immediate reconstruction

Not all studies report the positive margin rate and there is clear lack of consensus regarding the definition of positive margins. Additionally, not all studies report the re-excision or mastectomy conversion rate. Only eight of these comparative studies report a statistically significant benefit in terms of negative margins and/ or re-operation rate. The largest of these was a retrospective cohort study which included 1177 patients treated with OBCS.[8] The control arms included patients treated with sBCS (n=3559), mastectomy only (n=3263) and mastectomy plus immediate reconstruction (n=2608). In terms of margin status, patients who underwent OBCS had significantly less positive or close margins (5.8%) compared to sBCS (8.3%, p=0.04), the study did not report on re-excisions or re-operation rates. Chakravorty et al reported significantly less re-excision and mastectomy conversion in OBCS patients (n=150) compared to sBCS (n=440).[32] The remaining comparative studies reporting significantly less

tumour margin involvement and re-excision rates are limited by small patient numbers. Five comparative studies failed to demonstrate a benefit in terms of tumour free margins and re-operations between OBCS and sBCS (**Table 1**).

A recent systematic review collectively evaluated over five thousand patients treated with OBCS in 49 studies reported a weighted average positive margin rate of 10.8%, re-excision rate 6.0% and conversion to mastectomy rate 6.2%.[1] Crown et al. assessed a total of 812 patients undergoing either OBCS or WLE. Of these 18% underwent re-excision in the OBCS cohort, as compared to 32% in the standard WLE group ($p < 0.0001$).[33] Our systematic review in volume replacement oncoplastic conservation demonstrated an 11.3% (0-29.3) positive margin rate.[42] The re-excision rate however was only 7.2% (0-26.7) due to the variability in what was deemed a positive margin. This would suggest that the positive margin rate and subsequent re-operation rate is lower than sBCS. Other systematic reviews have failed to conclude on benefit of tumour free margins and lower re-excision rates in OBCS given the diverse and heterogenous study reporting with variation in the frequency of margin involvement ranging between 0-36% of patients.[3, 5, 10]

In patients with positive margins the subsequent management varied with re-excision rates of 11%-75%, completion mastectomy rates of 8-100%, no further treatment or radiotherapy boost to tumour bed in some studies.[5] It is clear from the current literature that the wider resections resulting from OBCS procedures does not obviate positive tumour margins and that the management of involved margins is not standardised. Oncoplastic volume displacement procedures are the most commonly employed OBCS procedure and this can result in displacement of the mammary tissue and hamper subsequent re-excision of the tumour bed necessitating conversion to mastectomy to ensure oncological safety and adequate tumour excision. However, several papers have demonstrated a reduction in mastectomy rates with the introduction of OBCS. Crown et al. demonstrated in the OBCS cohort 15% required completion mastectomy, as compared to 34% in the WLE cohort ($p < 0.001$), despite the average tumour size in the OBCS group being larger.[33] Our systematic review in volume replacement oncoplastic conservation demonstrated a completion mastectomy rate of only 2.3% (0-10.3).[42]

2.1.2. Complications after oncoplastic surgery

Depending on the technique of OBCS applied, procedures can be complicated and lengthy, and potentially associated with relatively high post-operative complication rates.[16, 43-46] A recent systematic review of OBCS reported post operative complications occurred in 14.3% of patients, including liponecrosis (3.3%), skin necrosis (0.5%), haematoma (2.5%), seroma (1.0%), delayed wound healing (2.2%), nipple necrosis (0.4%) and/ or infection (1.9%)[1]. Most studies comparing OBCS with standard breast conservation surgery (sBCS) have reported no difference in surgical complications between the groups.[37, 47] Carter et al compared complication rates in 9861 patients treated with sBCS, OBCs, Mastectomy only (Mx) and mastectomy plus immediate reconstruction (Mx+IR).[8] OBCS had a lower seroma rate (13%) than sBCS but wound related complications (4.8%) were statistically higher in OBCS. OBCS and sBCS had similar haematoma (2%) and surgical site infection rates (4.5%). Interestingly, compared to Mx+IR, OBCS had significantly lower wound complications, surgical site infections and haematomas. Reporting and classification of surgical complications is highly variable, the Clavien-Dindo classification (CDC) is a validated and simple system used in general and oncological surgery.[48] A modified CDC to evaluate postoperative morbidity in breast cancer patients has been validated and may be a useful tool for standardization of complication reporting in future clinical studies.[49] The international TeaM multicentre prospective cohort study on the outcomes of therapeutic mammaplasty (TM) including 880 patients showed that in total 205 patients (23.3%) developed a complication, but only 25 (2.8%) required reoperation.[50] Further, a subgroup of patients in the TeaM study who underwent TM to avoid mastectomy were identified, and data on demographics, complications, oncology and adjuvant treatment were compared with those of patients undergoing mastectomy with or without IBR in the iBRA-2 study. A total of 2916 patients (TM 376; mastectomy 1532; mastectomy and IBR 1008) were included in the analysis. Patients undergoing TM were more likely to be obese and to have undergone bilateral surgery than those having IBR. However, patients undergoing mastectomy with or without IBR were more likely to experience complications than the TM group (TM: 79, 21%; mastectomy: 570, 37.2%; mastectomy and IBR: 359, 35.6%; $p < 0{\cdot}001$).[51] In our systematic review on volume replacement oncoplastic conservations, we found that overall complications ranged from 0-65.7%, with a mean of 21.1%. Complications described were divided into minor (I-II) and major (III -IV) as per the Clavien-Dindo classification - 17.1% (0-52) and 5.6% (0-13.7) respectively. The majority of these complications were seroma formation (particularly donor site), fat necrosis, haematoma,

and wound infection. These results demonstrate that the majority of VR surgery complications can be managed conservatively.[42]

In order to further investigate the effect of postoperative complications on survival and recurrence after surgery for breast cancer we carried out a systematic review and meta-analysis which included 37,657 patients.[52] Risk of recurrence, 1-year and 5-year recurrence-free survival and overall survival were related to complications, particularly for patients with poor Nottingham Prognostic Index. Five studies failed to demonstrate a relationship between complications and prognosis. Complication was found to significantly affect 5-year recurrence-free survival (HR 1.48 95% CI 1.02-2.14, p = 0.04) but not recurrence (HR 2.39, 95% CI 0.94-6.07, p = 0.07), with a high degree of heterogeneity amongst analysed studies (I2 = 95%).[52] This has been further confirmed by a recent study from the Swedish cancer registry including 57152 patients, which demonstrated that all-cause and breast cancer mortality rates remained higher after a major surgical postoperative complication (OS: HR 1.32, 95% CI: 1.15 to 1.51; BCSS: HR 1.31, 1.04 to 1.65).[53] Interestingly, not only the postoperative complications, but the preoperative circulating systematic inflammatory markers may have a role in the prognosis of breast cancer. Our meta-analysis including 42 studies showed that higher neutrophil-to-lymphocyte ratio (NLR) was associated with worse overall survival (OS) (pooled HR 1.75, 95% CI: 1.52 to 2.00; P < 0.001), disease-free survival (DFS) (HR 1.67, 1.50 to 1.87; P < 0.001), and breast cancer-specific survival (BCSS) (HR 1.89, 1.35 to 2.63; P < 0.001). This effect was also seen with an arithmetically-derived NLR (dNLR). Higher platelet-to-lymphocyte ratio (PLR) was associated with worse OS (HR 1.29, 1.10 to 1.50; P = 0.001) and DFS (HR 1.58, 1.33 to 1.88; P < 0.001). Higher lymphocyte-to-monocyte ratio (LMR) was associated with improved DFS (HR 0.65, 0.51 to 0.82; P < 0.001), and higher C-reactive protein (CRP) level was associated with worse BCSS (HR 1.22, 1.07 to 1.39; P = 0.002) and OS (HR 1.24, 1.14 to 1.35; P = 0.002).[54]

2.1.3. Timely delivery of adjuvant therapy

Radiotherapy is an essential component of breast conservation treatment and delaying radiotherapy beyond 8 weeks has been demonstrated to have a detrimental effect on local recurrence.[55, 56] There is also evidence that delaying chemotherapy beyond 3 months following surgery may have a detrimental outcome in older patients.[57] Current UK guidelines recommend that adjuvant treatment (chemotherapy or radiotherapy) should be commenced as soon as clinically possible within 31 days of completion of surgery.[58]

Tenofsky et al compared OBCS with sBCS and reported a higher rate of non-healing wounds in the OBCS group, although this did not prolong time to radiation therapy in the OBCs.[39] Yoon et al also highlighted that boost after whole breast radiotherapy has been demonstrated to reduce local recurrence. This is of particular importance in this setting as young women are at greater risk of local recurrence and more likely to undergo OBCS.[59] Concern regarding accurate delivery of radiotherapy boost to the tumour bed given the breast parenchymal rearrangement inherent to the majority of OBCS has been raised. No studies have reported cases where the tumour bed could not be localised for boost therapy. Tumour bed marking with clips is under reported in studies, but clips and good communication between oncoplastic breast surgeon and radiotherapist are essential to aid accurate tumour bed boost.[60]

Most studies report that OBCS seems safe in terms of adjuvant chemotherapy delivery and showing no delay in time to adjuvant treatment.[13, 16, 20, 45, 46, 61-64] A few studies however have reported a delay in time to adjuvant therapy.[14, 15, 43, 44] Published data on the oncological safety of mastectomy followed by immediate reconstruction is much more robust than that of OBCS. The evidence for any potential delay of adjuvant chemotherapy after immediate reconstruction, is conflicting.[65-67] Nevertheless, authors agree that even if some delay occurs, it is unlikely to influence prognosis significantly after mastectomy and reconstruction.

2.1.4. Recurrence and survival

The Oxford overview demonstrates that 75% of local recurrences occur within 5 years of surgery and confirmed the observation that for every 4 local recurrences prevented by adjuvant radiotherapy, one breast cancer death was prevented (4:1 ratio) highlighting the importance of local control in terms of patient survival.[68] Rates of breast cancer local recurrence are falling. A 1% annual rate was considered acceptable however reported rates are now less than 0.5% per annum.

Loco-regional recurrence has historically been perceived as a failure of adequate local control, however in the modern era there is increasing recognition that local-regional recurrence is influenced by tumour biology. Meta-analysis has demonstrated that local recurrence after BCT for non-triple negative breast cancer have approximately half the risk of local recurrence compared to triple negative breast cancer, and breast cancer subtype affects the number of locoregional events.[69, 70] Additionally, systemic therapy has a major impact on both local regional recurrence and distant recurrence.[68, 71]

Patients treated with OBCS often have larger breast tumours. T2-T3 tumours comprise over half the OBCS patients treated in many studies.[13-23] Large tumour size is a poor prognostic marker and may be a marker of time in situ or accelerated tumour growth and biological aggressiveness. It remains poorly defined whether OBCS represents an extension of the application of sBCS to larger tumours or whether a mastectomy was turned into conservation surgery with oncoplastic techniques.

There is lack of high-level evidence supporting the oncological safety of OBCS in terms of local recurrence, patient disease free survival (DFS) and breast cancer specific survival (BCSS). Prospective randomized trials are unlikely to ever be undertaken given the complex ethical considerations. The current best available evidence is level 3, observational studies with control groups. To date 8 comparative studies have been published which report on recurrence rates and survival, the ultimate measures of oncological safety (**Table 2**).[8, 18, 23, 32, 38, 40, 41, 72] Only 3 studies included local recurrence rates and survival compared to mastectomy patients and most studies are limited in term of follow up time.

Table 2. Local, Distant Recurrence in OBCS comparative studies

First Author	Year	Study type	No of cases		Surgery control arm	T2 + T3 cancers (%)		Follow up time (years)	Oncological outcome
			OBCS arm	Control arm		OBCS arm	Control arm		
Chakravorty	2012	R	150	440	sBCS	40.7	34.8	2.3	No difference
Mazouni	2013	R	45	214	sBCS	28.9	20.1	3.8	No difference
Gulcelik	2013	P	106	162	quadrantectomy	nd	nd	2.7	No difference
De Lorenzi	2016	R	454*	908	sBCS	44.7	44.7	7.2	No difference
De Lorenzi	2016	R	193*	386	Mx	100	100	7.4	No difference
Chauhan	2016	P	33	46	sBCS	64	56	1.5	No difference
Carter	2016	R	1177*	3559	sBCS	36.3	26	3.4	No difference
				3263	Mx		46.7		OBCS better
				2608	Mx+IR		36.8		Mx+IR better
Mansell	2017	R	104	558	sBCS	53.7	15.4	4.6	sBCS better
				318	Mx+/- IR		56.2		OBCS better

All studies detailed level 2 oncoplastic techniques as described by Clough et al
* OBCS techniques not clearly defined and may include level 1 oncoplastic techniques.
** Control group included sBCS and Mastectomy+/- Immediate reconstruction.

Chakravorty et al reported equivalent safety in a retrospective comparative study that compared OBCS with sBCS.[32] The OBCS group included significantly larger tumours, higher grade and more patients had received neoadjuvant chemotherapy. However, the OBCS also included a significant greater number of patients with non-invasive breast cancer. There was no difference in the adjuvant treatment therapy given and no significant difference in local relapse rates (OBCS 2.7% vs sBCS 2.2%) or distant relapse (1.3% OBCS vs 7.5% sBCS) at median follow up of 28 months. Mazouni et al compared sBCS with OBCS after primary chemotherapy in a retrospective study with median follow up of 46 months.[18] They reported no significant difference in 5-year overall survival (96.2% OBCS vs 94.2% sBCS) or relapse free survival (92.7% OBCS vs 92% sBCS). The groups were equivalent in terms of tumour size, grade, nodal disease however the OBCS had significantly less HER2 positive patients, more ER+ suggesting better breast cancer subtypes. Gulcelik et al performed a prospective study comparing quadrantectomy to therapeutic mammoplasty with a median follow up of 33 months and reported no difference in disease free survival or overall survival.[38] Between the groups there was no significant difference in tumour size, ER status, HER 2 status and adjuvant treatment given. Although the study failed to detail tumour grade and nodal involvement in the two groups.

The largest comparative study is a retrospective single-institution study that included 9861 consecutive patients diagnosed between 2007 and 2014 with a median follow up of 3.4 years.[8] Four groups were included: sBCS (n=3559), OBCS (n=1177), mastectomy only (Mx) (n=3263) and mastectomy plus immediate reconstruction (Mx+IR) (n=2608). Compared to sBCS (n=3559) patients undergoing OBCS (n=1177) had more aggressive disease. There was no difference in the proportion of hormone receptor positive or triple negative patients in the OBCS group however they were significantly: younger in age, had larger tumours, more advanced disease stage, higher tumour grade, higher incidence of multifocality, node positivity, LVI, more HER2 positivity, more adjuvant chemotherapy administered and surprisingly less adjuvant hormonal therapy and adjuvant radiotherapy. Despite the marked differences in the clinicopathological features between sBCS and OBCS groups there was no difference in 3-year overall survival (95.8% OBCS vs 96.8% sBCS) and recurrence free survival (94.6% OBCS vs 96.1% sBCS). Comparing patients undergoing Mx+IR (n=2608) with OBCS, non-invasive breast cancer and stage 0 was statistically more frequent in the Mx+IR group, although there was no difference between Mx+ IR and OBCS in nodal stage or triple negative breast cancer. Ms +IR patients compared to OBCS did have higher grade tumours, higher incidence of multifocality, higher LVI, lower proportion of hormone receptor positivity, and higher number

of HER2 positive tumours. More Mx+ IR patients received adjuvant chemotherapy. Patients undergoing Mx+IR had significantly better 3-year OS (97.7% Mx+IR vs 95.8% OBCS, p=0.0007) and recurrence free survival (96.6% Mx+IR vs 94.6% OBCS, p=0.01). The authors accounted this difference in outcome to the larger proportion of patients with *in situ* or stage 0 disease in the Mx+IR group. The authors did not perform a direct statistical analysis comparing demographics of OBCS to Mx (n=3263), although Mx patients had the most advanced stage disease in the cohort, including 5% with metastatic disease. Unsurprisingly the Mx had the worst patient outcome of all the groups. In multivariate analysis when comparing surgical procedures only Mx was significantly different from OBCS, with a hazard ratio over 2 times that of OBCS for death or recurrence. The authors concluded that OBCS does not disadvantage patients in terms of short-term outcomes when compared to sBCS or Mx. Whilst this is the largest comparative study performed, the follow up period in this study is too short to be truly meaningful in terms of local/ distant recurrence or survival, especially given the heterogenous tumour pathology between the unmatched groups.

A weakness of the above comparative studies is that the control groups are not matched, and it is therefore difficult to make conclusions on oncological safety and patient outcome given the heterogenous tumour pathology. De Lorenzi et al. published two case matched studies comparing OBCS to sBCS and mastectomy respectively for primary invasive breast cancer patients diagnosed in a single institution between 2000 and 2008.[40, 72] In the first study OBCS (n=454) was compared with sBCS (n=908). Age at surgery, year of surgery, and tumour size (including T1-4) were the variables used for matching. In terms of clinicopathological features between the two groups there was no significant differences in tumour histological type, grade, lymph node status, surgical margin involvement, tumour subtype (luminal A, B, ER+/HER+, HER2 enriched and triple negative), presence of perivascular invasion and adjuvant systemic therapy administered. The OBCS group had significantly more patients with multifocal disease. The median follow up was 7.2 years. The overall survival was similar (91.4% OBCS vs 91.3% sBCS at 10 years). The incidence of local recurrence was slightly higher on the OBCS group (3.2% vs 1.8% at 5years; 6.7% vs 4.4% at 10 years) but this was not statistically significant, and regional and distant events were similar between the groups. In the second study, OBCS (n=193) was compared with mastectomy (n=386) in patients with T2 (2-5cm) invasive breast cancers. Over 90% of mastectomy patients had immediate reconstruction performed. Cases were matched using age at surgery, year of surgery, and tumour subtype. In the mastectomy group, tumour multifocality was more frequent and tumours were significantly larger than in the oncoplastic group. For all other clinicopathological features not used in the matching

algorithm the two groups were well balanced. The median follow-up was 7.4 years. There was no significant difference in overall survival 87.3% (OBCS) and 87.1% (Mx) at 10 years. Disease free survival was similar in both groups: 60.9% (OBCS) and 56.3% (Mx) at 10 years. The incidence of local events was slightly higher in the OBCS group (7.3 vs. 3% at 10 years), whereas the incidence of regional events was slightly higher in the mastectomy group. These differences were not statistically significant. The oncoplastic procedures described in both these studies were quite heterogenous involving advancement of glandular flaps which suggests level 1 oncoplastic surgery only. Nevertheless, these 2 retrospective studies which include a large series of patients with matched control groups provide the best available evidence that OBCS is a safe treatment option for early breast cancer patients.

The above is supported by both Losken and Chand who found that therapeutic mammoplasty and volume replacement with mini-LD flaps respectively, had no effect on local recurrence.[73, 74] Yoon et al found assessed 10 papers in their systematic review, where local recurrence ranged from 0-10% at a mean follow-up of 40 months.[59] Our systematic review on volume replacement oncoplastic conservation including a total of 1,729 patients with a mean follow-up of 40.8 months (6-125) showed a loco-regional and distant recurrence of 2.5% (0-8.1) and 3.1% (0-14.6%) at 43.7 and 36.4 months respectively.[42]

In term of survival, 5-year DFS has been found to be 91.7%, OS 93.8%, and cancer-specific survival of 96.1% in previous studies.[75] This is comparable with findings in our systematic review in volume replacement oncoplastic conservation demonstrating an overall survival and disease-free survival were 96.8% (93.3-100) and 92.6% (84.6-100) at 49.8 and 39.0 months respectively, with a mortality rate of 5.9% (0-35.0) at a mean follow-up of 48.9 months.[42]

2.1.5. Aesthetic outcomes after oncoplastic conservation

Systematic review among 25 studies evaluated the cosmetic outcome of OBCS patients (n=1962). OBCS achieved excellent, good, fair or poor outcomes in 55.2%, 31.0%, 9.4% and 4.4% of patients respectively. Most studies report good cosmetic outcome after OBCS in nearly 90% of patients.[3] However: variation in how cosmetic outcome was evaluated, reporting with non-validated assessment tools and timing of evaluation for cosmetic outcome is heterogenous. Evaluation of cosmetic outcome should be performed at least two years post operatively to allow for long term effects of radiation therapy.[76] Patient self-evaluation is a valuable assessment because the subjective experience of the patient is central to assessment of quality

of life, however patients frequently report better scores than professionals.[3, 43, 44] Panel-evaluation is also a reliable alternative. Breast retraction assessment is the only truly objective method of measuring changes in symmetry. Haloua et al suggest a combination of cosmetic assessments will produce the most reliable results.[3]

Clough et al undertook a prospective study (n=101) and evaluated cosmetic outcome using an independent panel format and after a follow up period of 2 years.[14] Favourable cosmetic outcome was reported in 82% of patients. Viega et al performed a prospective study to assess OBCS on patient quality of life and self-esteem (n=45).[77] A matched (BMI, age, demographic and oncological details) control group of sBCS patients (n=42) was used. Validated patient questionnaires were completed at 6 and 12 months. At postoperative 12 months, the OBCS group reported significantly better health status than the control group with regard to physical functioning, health perception, vitality, self-esteem, social functioning, role emotional and mental health. Compared with preoperatively, the OBCS group scores were significantly higher at 12 months postoperative for seven of the eight dimensions of the Short Form-36. They also assessed aesthetic outcome using patient scores and panel assessment with standardized photographs at 6 and 12months post operatively.[19] Patients in both the OBCS and sBCS scored the aesthetic outcome better than physicians. Panelists and patients considered the aesthetic outcomes of the OBCS better than sBCS.

Estimated percentage of breast volume excised (EPBVE) has been shown to have a significant impact on patient satisfaction. By estimating volume through mammograms, subjective cosmetic assessment tools can be used to measure patient satisfaction. In relation to BCS, studies have demonstrated less than 10% EPBVE correlates with majority patients satisfaction (83.5%), as compared to over 10%, where this is significantly reduced (37%).[2] In terms of location in the setting of conventional BCS, Pukancsik et al. demonstrated maximum breast volumes that were resectable without resulting in unacceptable aesthetic and functional outcomes, or decreased quality of life.[78] Percentage volumes were 18-19% in the upper-outer quadrant ($p < 0.0001$), 14-15% in the lower-outer quadrant ($p < 0.0001$), 8-9% in the upper-inner quadrant ($p < 0.0001$), and 9-10% in the lower-inner quadrant ($p < 0.0001$). In the setting of OBCS, patient satisfaction remains high with volume excision of less than 20%.[79] Once 20% of breast volume or more is excised, there is a significant risk of deformity. However, tumours located in the upper inner quadrant and lower pole have been found to more commonly lead to breast deformity, even when volume excised is less than 20%.[80]

Timing of contralateral symmetrising procedures is variable in studies. De Lorenzi et al performed simultaneous contralateral reduction mastopexy in 67% of OBCS undertaken.[40] Advocates of delayed symmetrising procedures argue that poor cosmetic results occur as a result of radiotherapy change in the treated breast.[81]

There is no standardised patient reported outcomes measures (PROMs) currently used routinely in the setting of OBCS, however several tools are in existence. The BREAST-Q is a validated questionnaire-based tool using a Likert scale that assesses physical, psychological and sexual wellbeing, cosmetic appearance, and overall satisfaction. Chand et al. used the BREAST-Q questionnaire to assess breast appearance, physical, emotional, and sexual wellbeing, in patients who underwent either therapeutic mammoplasty or mini-LD flap, with those who underwent mastectomy and immediate autologous reconstruction. Overall satisfaction was high in both groups, with 82% reporting "excellent/very good" (mammoplasty 88%; mini-LD 78%), with therapeutic mammoplasty patients being significantly more satisfied with breast shape ($p < 0.05$), size (< 0.05), and natural feel ($p < 0.01$) as compared to the mini-LD group, however they demonstrated similar scores for physical and emotional wellbeing. 89% felt that OBCS was better than mastectomy. Mean outcome scores for breast appearance, physical and emotional wellbeing persisted beyond 15 years.[73] Kelsall et al. used the validated Hopwood body image scale (BIS) scores of psychosocial function and PROMs for breast appearance and return to function analysis comparing case-matched OBCS with mastectomy and immediate reconstruction. They found overall BIS score ($p = 0.002$), self-rated breast appearance, return to work, and function (all $p < 0.001$) significantly favoured OBCS. This difference was most marked in women with larger breasts.[82]

Patient reported outcome and cosmetic outcome lacked standardisation, however amongst patients the Breast-Q,[73, 83, 84] satisfaction expressed on a scale of 1-10[85] or poor-excellent,[86-88] and the Modified Michigan cosmetic and overall outcomes[89, 90] were most commonly used. In terms of surgeon reported cosmetic outcome, panel assessments[87, 88, 91-94] were most frequently used. Overall, results tended towards good-excellent outcomes as reported by the patient and surgeons.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Oncoplastic approach in breast cancer surgery--a new challenge for the future breast surgeon?
Romics L, Weiler-Mithoff E, Cooke TG, George WD.
Magyar Sebészet. 2008 Feb;61(1):5-11. In Hungarian.

Oncological safety and cosmetic outcomes in oncoplastic breast conservation surgery, a review of the best level of evidence literature. Campbell EJ, **Romics L**.
Breast Cancer. 2017 Aug 4;9:521-530.

Systematic review of partial breast reconstruction with pedicled perforator artery flaps: Clinical, oncological and cosmetic outcomes.
Pujji OJS, Blackhall V, **Romics L**, Vidya R.
European Journal of Surgical Oncology. 2021 Aug;47(8):1883-1890.

A systematic review of oncoplastic volume replacement breast surgery: oncological safety and cosmetic outcome.
Rutherford CL, Barker S, **Romics L.**
Annals of the Royal College of Surgeons of England. 2022 Jan;104(1):5-17.

The effect of postoperative complications on survival and recurrence after surgery for breast cancer: A systematic review and meta-analysis.
Savioli F, Edwards J, McMillan D, Stallard S, Doughty J, **Romics L.**
Critical Reviews in Oncology and Haematology. 2020 Nov;155:103075.

Prognostic role of preoperative circulating systemic inflammatory response markers in primary breast cancer: meta-analysis.
Savioli F, Morrow ES, Dolan RD, **Romics L**, Lannigan A, Edwards J, McMillan DC.
British Journal of Surgery. 2022 Nov 22;109(12):1206-1215.

2.2. Short summary of oncoplastic surgical techniques

In oncoplastic breast conservations the percentage of breast tissue excised has been found to correlate with aesthetic outcome, which is still reported as poor in up to half of the patients.[89,95] OBCS has developed as a mean to address this. OBCS can be classified into volume displacement or volume replacement techniques. Volume displacement involves the filling of a defect through transposition of a glandular or a dermo-glandular flap of breast tissue, and often requires symmetrisation of the contralateral breast. Volume replacement involves the use of autologous tissues to replace volume loss. Breast symmetrisation of the contralateral breast is an integral part of OBCS and should always be considered either in an immediate or a delayed fashion.

Oncoplastic breast conservation rate is steadily increasing nationwide, which is due the robust national training programme in the UK in oncoplastic breast surgery as well as development of diagnostic and localisation techniques in parallel with the increasing use neo-adjuvant systemic therapy. **Figure 1** shows the percentage of oncoplastic breast conservations within all breast conservation surgeries in England based on the GIRFT Programme National Subspecialty (Breast) Report between 2008 and 2018.[96] We found a similar trend in Scotland with increasing number of oncoplastic breast conservations with a similar ratio of just less than 10% oncoplastic of all breast conservation surgeries between 2005 and 2016 based on the Managed Clinical Network (Scotland) data.[75, 97] However, it has been recognised that oncoplastic breast conservations were underreported in both audit, and those are very likely more frequently applied although the exact “real-life” figures are not known.

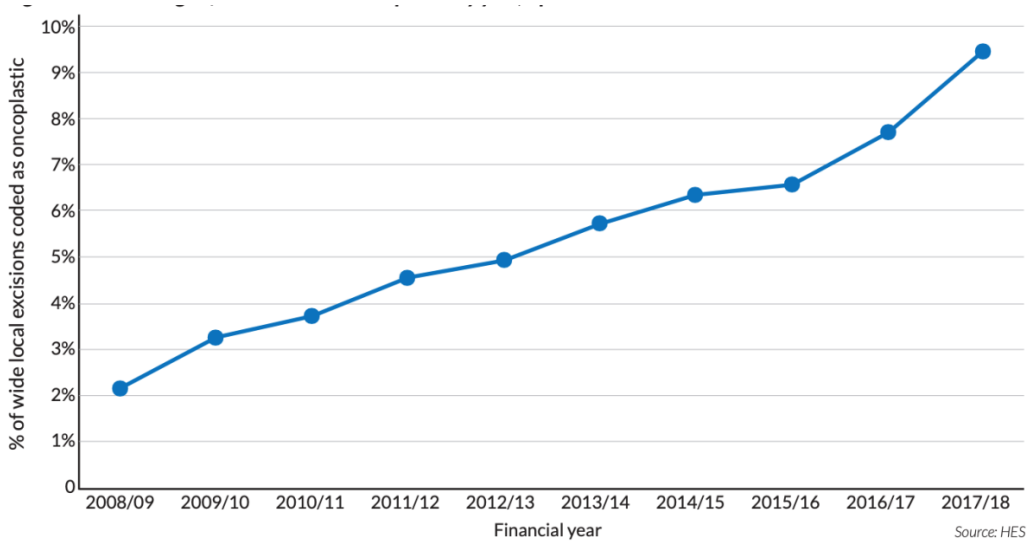


Figure 1. Percentage of Wide Local Excisions coded as oncoplastic by year, April 2008 – March 2018
(GRIFT National Subspecialty Report 2021)

Immediate reconstruction rates were between 25-30% between 2013 and 2018 in England based on the GIRFT report, although it was significantly higher in patients below 50 years of age compared to the older patients[96] (**Figure 2**). Similar figures of immediate reconstruction rates were recorded in Scotland, too. In the West of Scotland, it was 25% in 2019, which was the last year before the COVID pandemic.[98] Importantly, a significant variation from between 15% to 31% were noted in between various breast units in the country. During the years of the pandemic the immediate reconstruction rate dropped down to 10% in 2021 and 15% in 2021.[98]

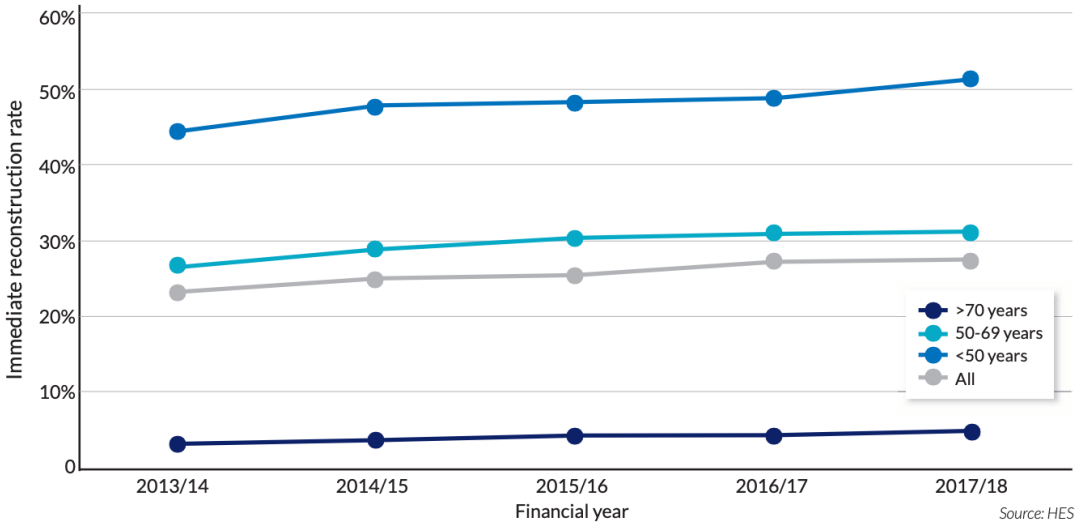


Figure 2. Immediate reconstruction rate by age group, April 2013 – March 2018
(GRIFT National Subspecialty Report 2021)

A significant difference can be observed between oncoplastic breast conservation rates and immediate reconstruction rates in the above figures. While oncoplastic breast conservation surgeries are firmly increasing on the national level, immediate reconstruction rates are steady, perhaps a slight increase can be observed. The reason for this is multifactorial, including increasing application and improved response to neoadjuvant systemic treatment allowing more breast conservation surgery on the expense of less mastectomy,[99] as well as the recognition that breast conservation surgery in multifocal and multicentric breast cancer can be an oncologically safe option based on the recent ACOSOG Z11102 trial.[100]

The firm increase in oncoplastic breast conservation surgery (OBCS) rate is new. **Figure 1** suggests that it reached 5% of all breast conservation surgeries (BCS) in England in 2013. Similarly, Public Health Scotland included OBCS as part of the National Minimum Core Dataset of the Breast Cancer Audit only in 2014, when clinicians noted first time that OBCS rate became significant with 4% of all BCS.[97, 101]

Hence, oncological safety of OBCS is much less established than the oncological safety of breast reconstructions. This thesis, therefore, concentrate on studies and investigations carried out to build evidence for the oncological safety of OBCS primarily, but includes relevant data and studies for breast reconstruction too.

Selection of the surgical technique is multifactorial, it mainly depends on tumour location, breast size and shape, body habitus, comorbidities, available surplus tissue on the donor sites, as well as patient's preference. **Figure 3.** illustrates the decision-making algorithm for selection of oncoplastic breast conservation technique, followed by a short summary of the most commonly applied oncoplastic breast conservation techniques without providing detailed description due to obvious limitations of the text in a thesis.

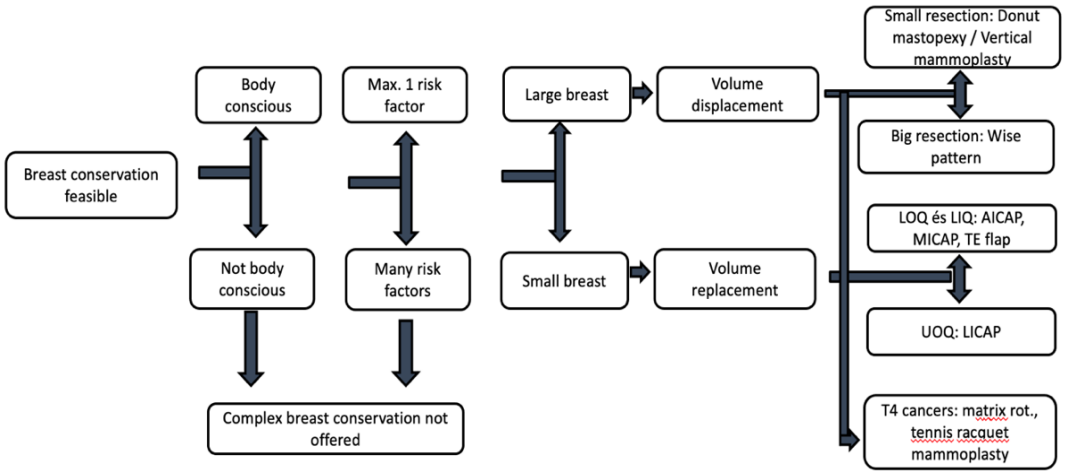


Figure 3. Flowchart illustrating the algorithm for selection of surgical technique for oncoplastic breast conservation

LOQ: lower outer quadrant of the breast, LIQ: lower inner quadrant of the breast, UOQ: upper outer quadrant of the breast, AICAP: anterior intercostal perforator flap, MICAP: medial intercostal perforator flap, LICAP: lateral intercostal perforator flap, TE: thoraco-epigastric flap

The principles of oncoplastic of oncoplastic OBCS is to create a flap that can be used to fill in the tumour excision cavity during re-shaping. During therapeutic mammoplasty either an extended primary pedicle is created or a secondary pedicle (or both) (**Figure 4**). This is a glandular flap created from the remaining breast tissue. In volume replacement OBCS the flap is created from the vicinity of the breast and rotated in the breast to fill in the excision cavity (**Figure 5**). Free flaps (DIEP flap) or implants are used most nowadays to replace the breast after mastectomy (**Figure 6**). (Figure 4, 5, 6 photographs were provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

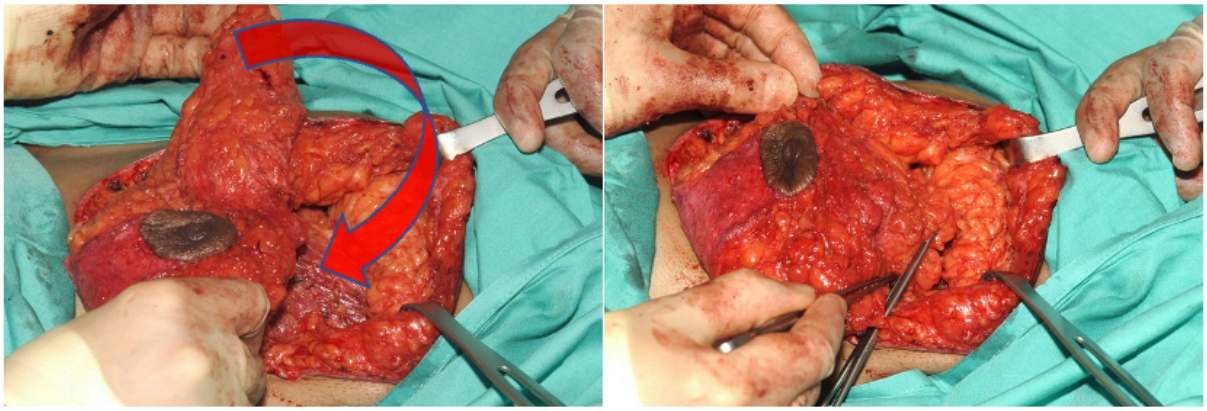


Figure 4. Extended primary pedicle to the nipple is rotated supero-laterally into the excision cavity.

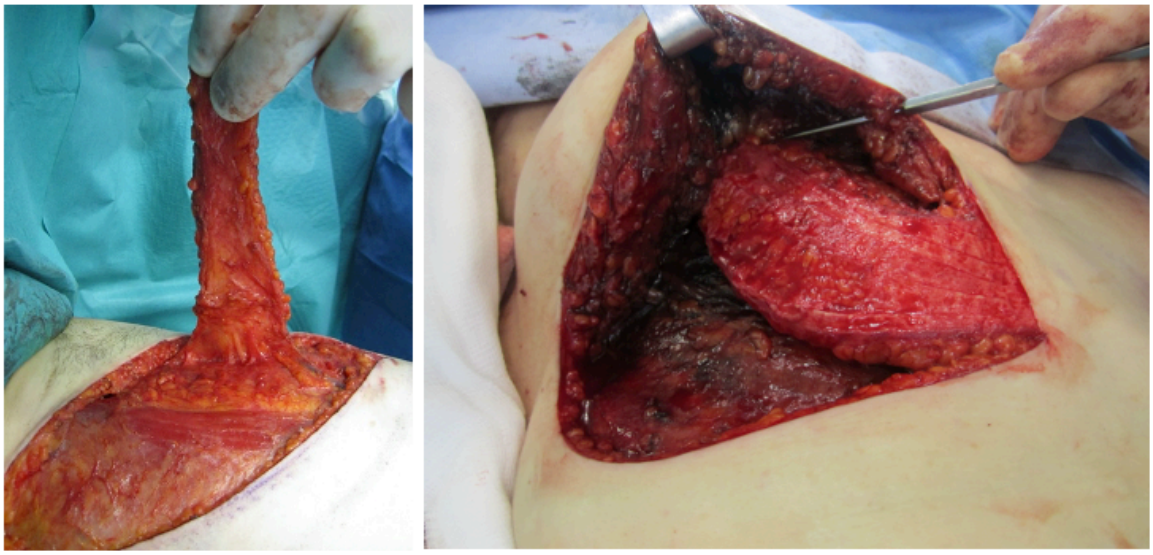


Figure 5. LICAP flap created from the lateral chest wall (LEFT) and thoraco-epigastric flap from the upper abdomen (RIGHT)

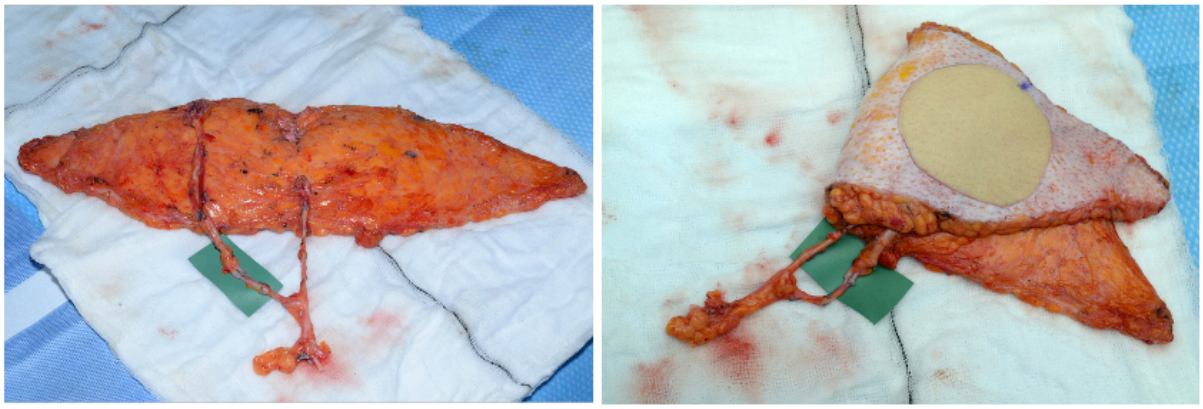


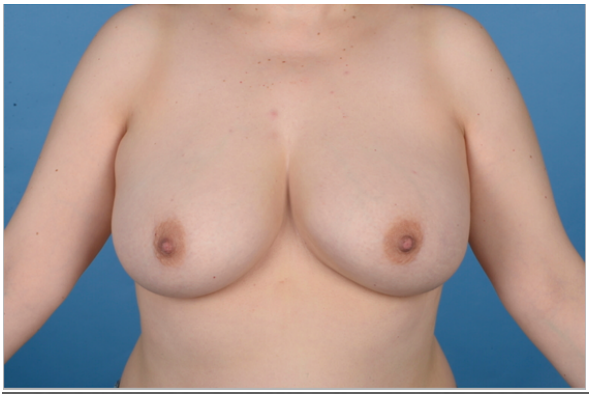
Figure 6. DIEP flap, depicting its blood supply, the deep inferior epigastric perforator artery

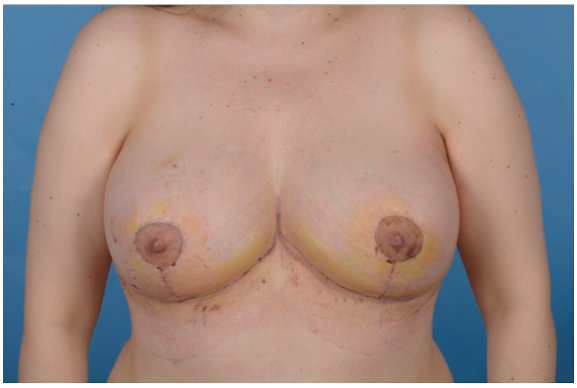
2.2.1. Therapeutic mammoplasty and case presentations

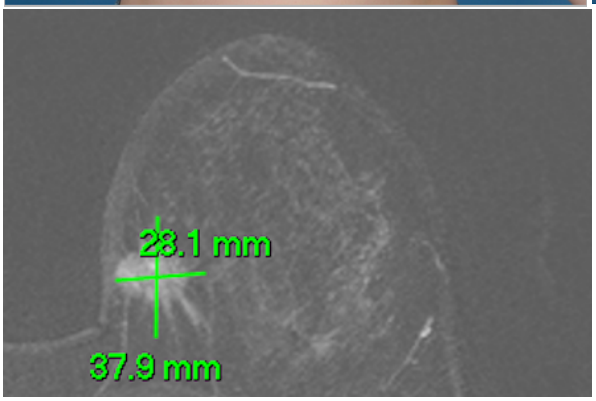
OBCS is defined as level 1 and level 2 techniques.[102] Level 1 oncoplastic techniques does not require specialist plastic surgical techniques and is used to prevent deformities for tumours excisions which are less than 20% of the breast volume and includes simple reshaping without skin excision and may require nipple re-centralizing. Level 2 oncoplastic techniques should be considered when major volume loss is anticipated and are classified as volume displacement and volume replacement techniques. The majority of OBCS level 2 techniques utilise volume displacement techniques, which comprises tumour excision followed by reshaping of the breast parenchyma as well as reduction of the breast skin envelope.[102] This is commonly referred to as therapeutic mammoplasty, this is often accompanied by a reduction of the contralateral breast to improve symmetry. Level 2 OBCS has traditionally been regarded as requiring specialised training in plastic surgical techniques.

A) Therapeutic mammoplasty from "wise pattern" incision

Wise pattern therapeutic mammoplasty is suitable for excision of large tumours in moderate to large breast. Re-shaping after tumour excision can be carried out with either a secondary pedicle created from the remaining breast parenchyma or an extended primary pedicle to the nipple. It usually requires reduction of the contralateral side with a standard breast reduction technique.



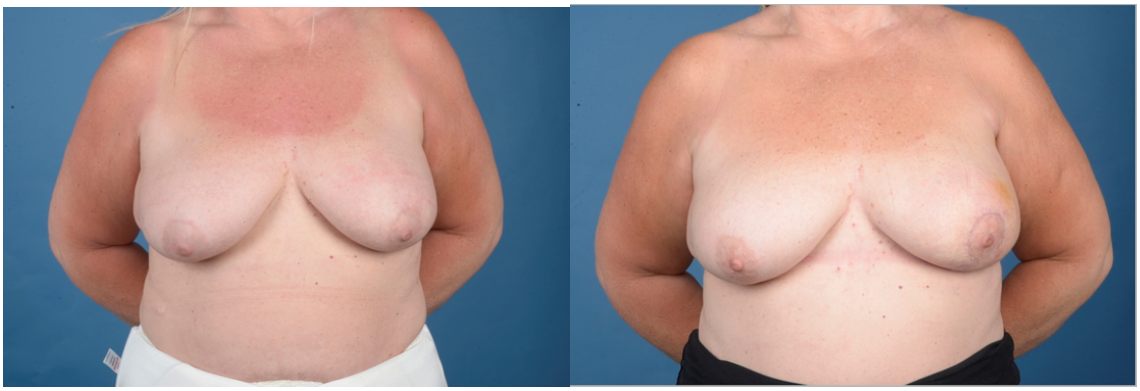


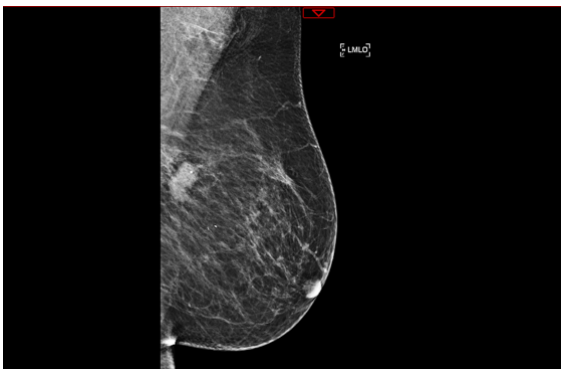


42-year-old patient underwent a left therapeutic mammoplasty, sentinel node biopsy and right symmetrising reduction for a 38x28 mm invasive lobular cancer in the upper inner aspect of the left breast as illustrated on MRI. Her final pathology showed a 40 mm grade 3 pleomorphic invasive lobular cancer with pleomorphic lobular carcinoma in situ which did not increase the whole tumour size. Excision margins were clear. ER7, PR8, HER2 negative, sentinel node 0/1. The right breast reduction was benign. Postoperatively she received adjuvant chemotherapy based on Oncotype DX recurrence score 22 and absolute benefit of chemotherapy 6% improvement in OS at 10 years based on NHS Predict. She also received 2 field radiotherapy with boost in the tumour bed, goserelin with exemestane and bisphosphonate. Top left: preoperative photograph, top right: postoperative photograph, bottom left: breast MRI. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

B) Donut mastopexy (Benelli)

Donut mastopexy or Benelli mammoplasty is applied in smaller and less ptotic breasts when re-shaping is required after excision. The skin envelope is reduced by parallel circumareolar incisions and re-shaping is carried out with a glandular rotation flap after double-layer mobilisation. This technique usually does not require immediate symmetrisation on the contralateral.

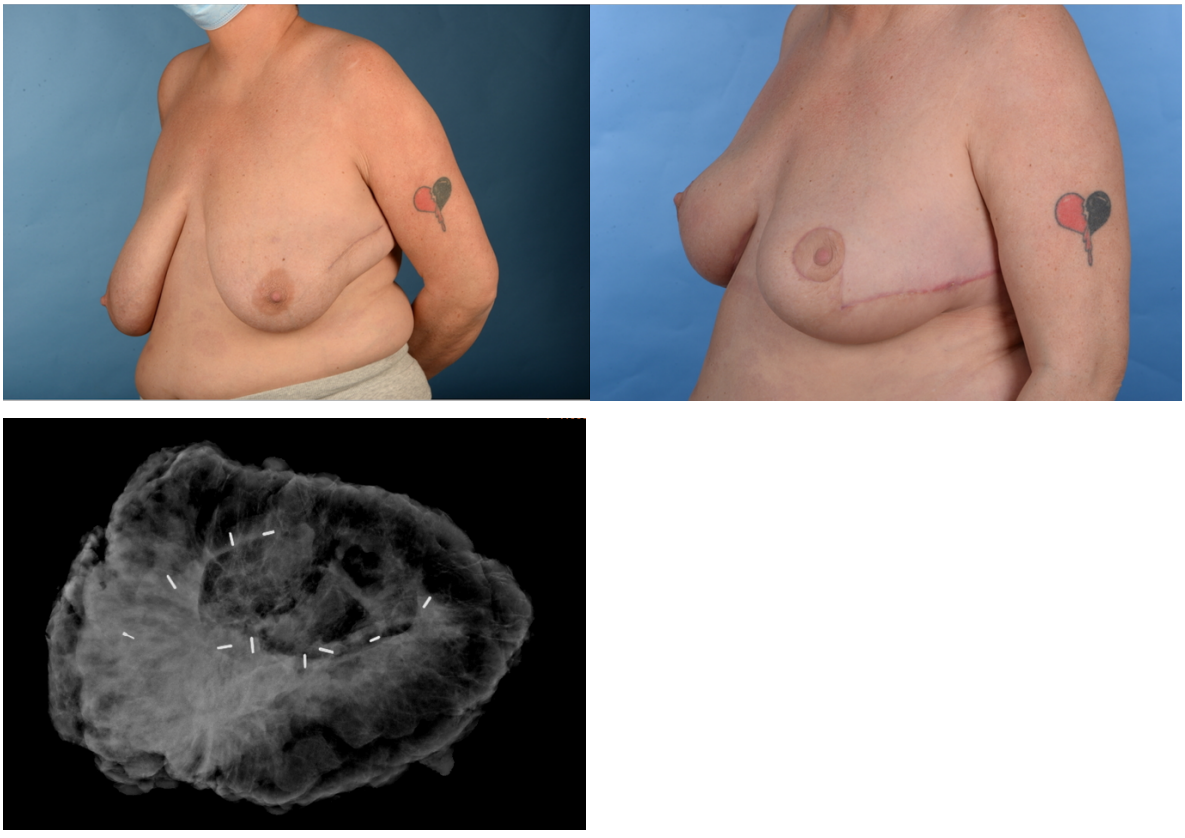




57-year-old patient was diagnosed with a 28 mm cancer in the left breast upper outer quadrant as illustrated on the mammogram. She was treated with a left donut mastopexy and sentinel node biopsy and histology showed 26 mm invasive ductal cancer, grade 3, LVI present, background of DICS but same whole tumour size. Excision margins were clear. 1/4 sentinel nodes with extra capsular invasion and 1 node with isolated tumour cells. ER8, PR7, HER2 negative. Adjuvant treatment was chemotherapy within the OPTIMA trial (TCx4), 3 field radiotherapy, bisphosphonates, and 10-year endocrine treatment. Top left: preoperative photograph, top right: postoperative photograph, bottom left: mammogram. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

C) "Tennis racquet" therapeutic mammoplasty

This technique is suitable for moderate to large breasts when a large area from the upper outer aspect needs to be excised together with the overlying skin. Skin envelope is reduced with the skin removed from the upper outer aspect in continuity with a circumareolar skin reduction. The breast is re-shaped by approximating the parenchyma in the upper outer quadrant and circumareolarly. Contralateral standard reduction is usually required.



50-year-old patient underwent magseed localised wide local excision of a 4 cm polymorphic microcalcification representing DCIS from the upper outer aspect of the left breast, followed circumferential re-excision for multiple involved margins by a colleague. She still had incomplete margins in three radial directions but refused mastectomy and was referred to the author. A wide circumferential re-excision (illustrated by the intraoperative Faxitron image above) with re-shaping using tennis racquet technique was carried out for the occult DCIS, with sentinel node biopsy and contralateral reduction from wise pattern technique. Pathology on the left showed extensive DCIS with a 3 mm ER/PR/HER-2 positive ductal cancer, margins were clear, 0/1 sentinel node. On the right side an occult, incompletely excised DCIS was revealed, which required re-excision from the lower outer quadrant and clear margins were achieved finally. Bilateral 2 field radiotherapy was completed, and the patient currently is on endocrine treatment. Top left: preoperative photograph, top right: postoperative photograph, bottom left: intraoperative Faxitron image. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

2.2.2. Partial breast reconstruction with flaps and case presentations

The term 'volume replacement' was first described in a full paper by Raja, Straker and Rainsbury in 1997.[103] Multiple oncoplastic volume replacement techniques have evolved including latissimus dorsi (LD) flap, thoracodorsal artery perforator (TDAP) flap, lateral/anterior/medial intercostal artery perforator (LICAP/AICAP/MICAP) flap, lateral thoracic artery perforator (LTAP) flap, thoracoepigastric (TE) flap, omental flap, and lateral adipose tissue flap, medial circumflex femoral artery perforator (MCFAP) and internal mammary artery perforator (IMAP) flaps. The aim of these techniques is to fill the excised defect thus eliminating deformity and maintaining breast appearance. The most commonly used oncoplastic volume replacement techniques nowadays are LICAP, MICAP, AICAP, TDAP, and LTAP flaps, and their applications to the various breast quadrants are shown in **Figure 7.**

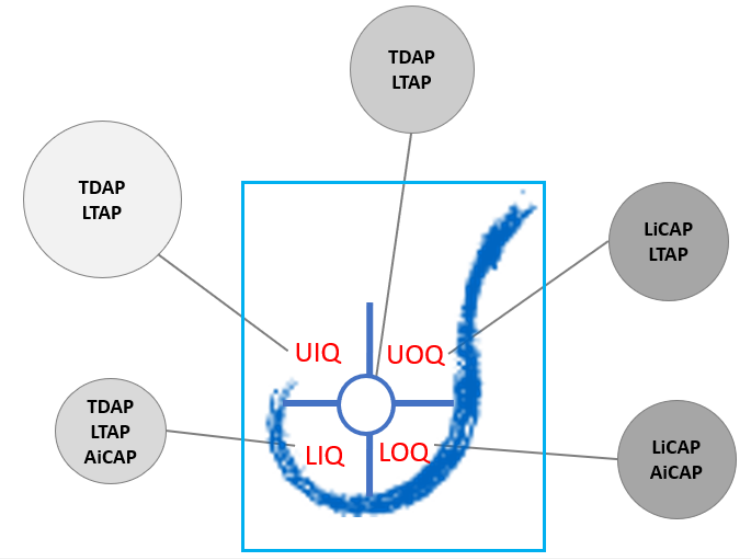
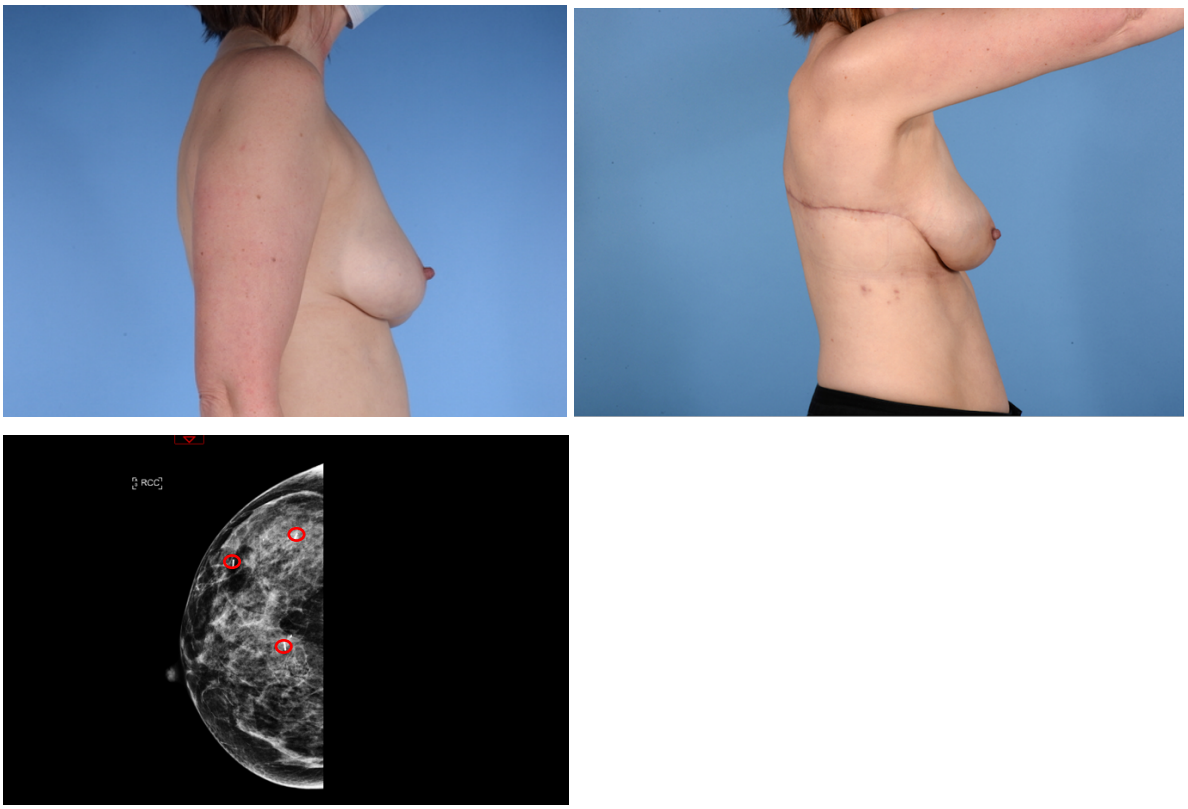


Figure 7. Distribution of flap types across the breast template

LICAP, Lateral Intercostal Artery Perforator Flap; LTAP, Lateral Thoracic Artery Perforator Flap; AICAP, Anterior Intercostal Artery Perforator Flap; TDAP, Thoracodorsal Artery Perforator Flap

D) LICAP flap partial breast reconstruction

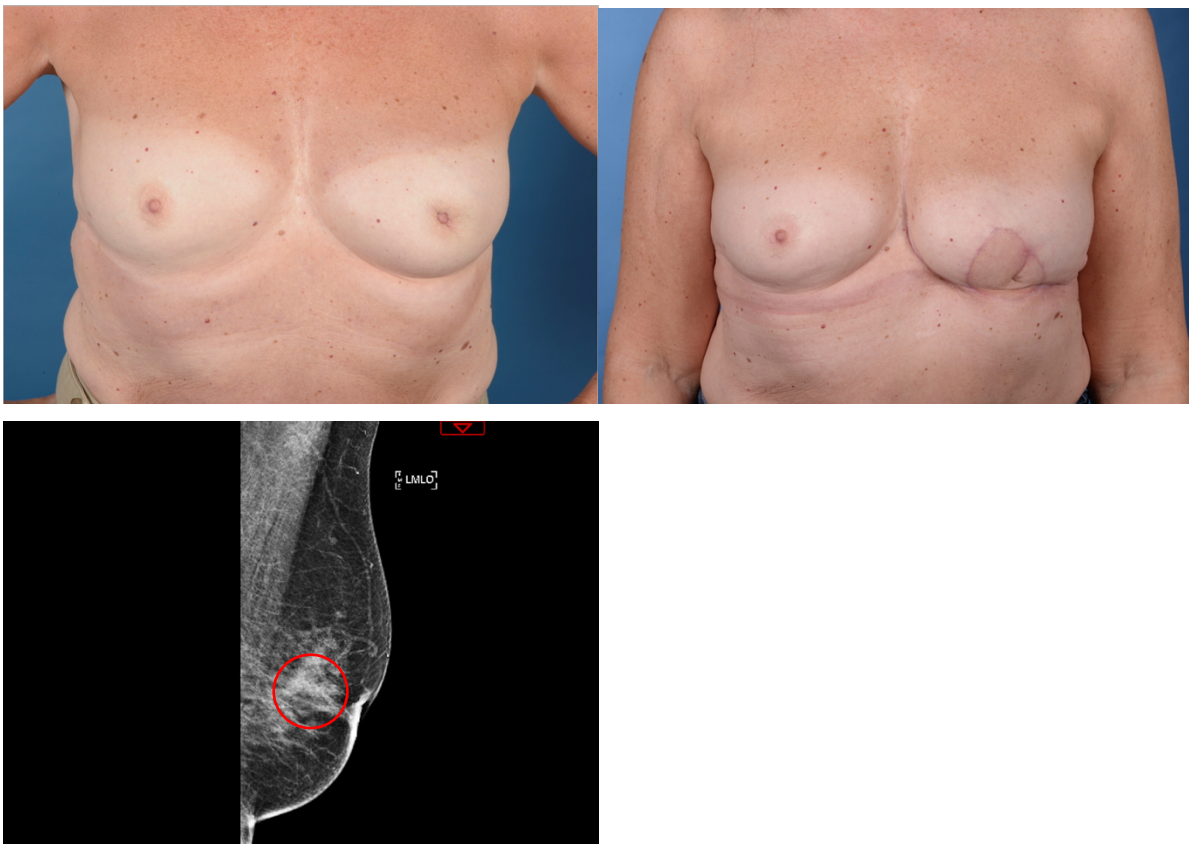
Chest wall perforator flap based on the lateral intercostal artery perforators are most commonly used to replace volume in the lateral to aspect of small, non-ptotic breasts. The flap is harvested from the lateral chest wall from the area below the axilla extending posteriorly – if required – towards the tip of the scapula. The donor site closed with mobilisation of the lateral chest wall and dorsal skin superiorly. It does not require contralateral symmetrisation surgery.



49-year-old patients was diagnosed with multifocal cancer extending over 55 x 36 x 35 mm in the lower outer quadrant of the right breast (3 marking clips indicating biopsy sites encircled in red). She underwent right breast magseed localised oncoplastic wide local excision, sentinel node biopsy and partial reconstruction with LICAP flap. Histology showed multi-focal tubular cancer of the right breast with one 24 mm and two 12 mm foci, all tumours are ER8, PR8 and HER-2 negative. She completed two field radiotherapy and currently on Tamoxifen. Top left: preoperative photograph, top right: postoperative photograph, bottom left: mammogram. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

E) AICAP flap partial breast reconstruction

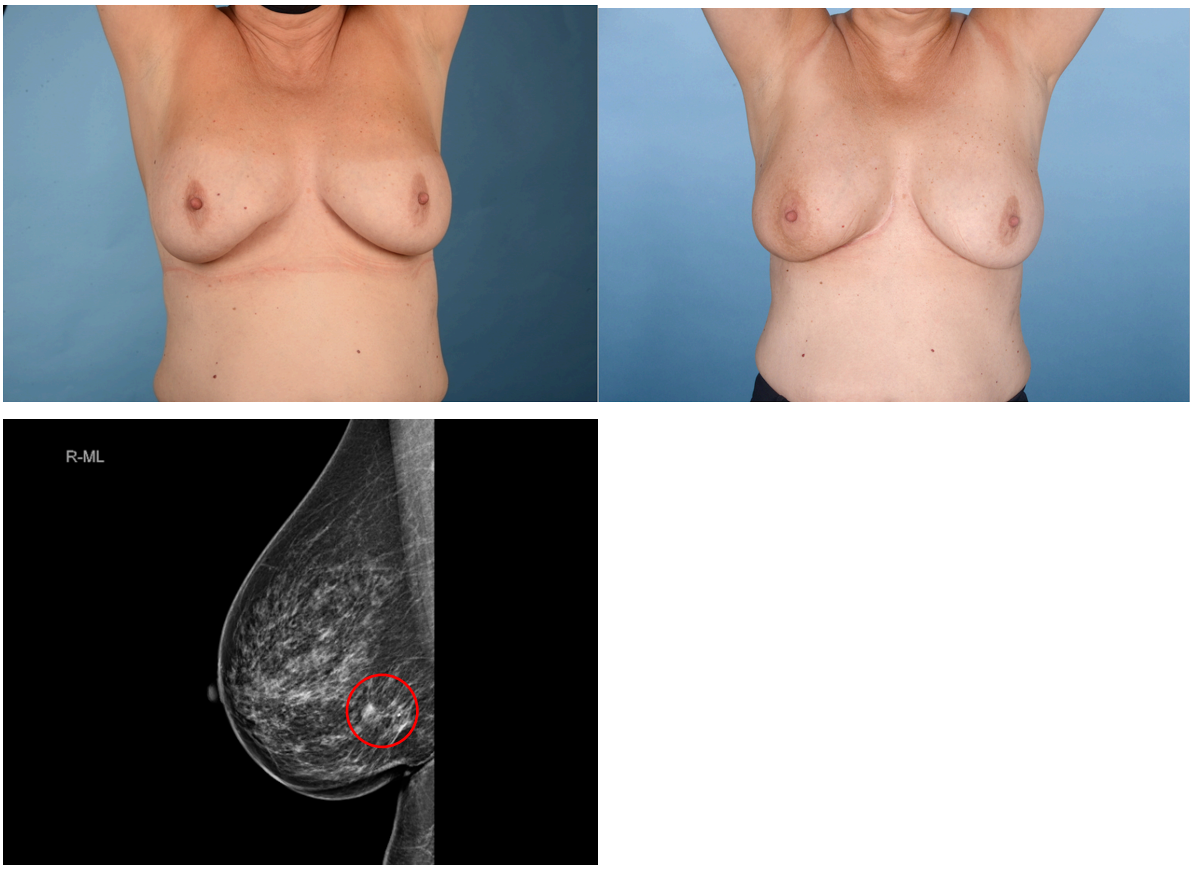
Chest wall perforator flap based on the anterior intercostal artery perforators are most commonly used to replace volume in the lower pole and central aspect of small, non-ptotic breasts. The flap is harvested from beneath the inframammary fold and the donor site closed with mobilisation of the abdominal skin superiorly. It does not require contralateral symmetrisation surgery.



65-year-old patient was diagnosed with a 3cm central tumour behind the left nipple areola complex causing nipple retraction. As the tumour was ER8 PR7 HER-2 negative, and the patient did not want to undergo mastectomy she was offered neoadjuvant endocrine treatment to downstage the cancer, but it failed to achieve clinically significant response after 6 months of letrozole. Hence, oncoplastic wide excision was carried out with removal of the nipple and sentinel node biopsy, and partial reconstruction with AICAP flap. Histology showed a residual 20 mm Grade 2 ductal cancer with high grade DCIS increasing the whole tumour size to 23 mm. No LVI was present and excision margins were clear. 3 out of 4 sentinel nodes were involved, two nodes contained macro-, one node contained micrometastatic disease. Postoperative staging CT was clear, she received adjuvant TC chemotherapy, 4 field radiotherapy, bisphosphonates, adjuvant currently she is on Exemestane which is planned for 5 years altogether followed by adjuvant Tamoxifen for another 5 years. Top left: preoperative photograph, top right: postoperative photograph, bottom left: mammogram. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.

F) MICAP flap partial breast reconstruction

Chest wall perforator flap based on the medial intercostal artery perforators are used to replace volume in the lower inner quadrant of small, non-ptotic breasts. The flap is harvested from beneath the inframammary fold and the donor site closed with mobilisation of the abdominal skin superiorly, quite similarly to the AICAP flap but the base of the MICAP flap is more medial than that of the AICAP. It does not require contralateral symmetrisation surgery.



60-year-old patient was diagnosed with a 25mm cancer in the lower inner quadrant of the right breast (ill-defined mass with marking clip encircled in red). She underwent an oncoplastic wide excision, sentinel node biopsy and partial reconstruction with MICAP flap. Histology showed 28 mm grade 1 invasive ductal cancer. Excision margins were clear. ER8, PR8, HER-2 negative. Postoperatively she received two-field radiotherapy and currently she is on endocrine treatment. Top left: preoperative photograph, top right: postoperative photograph, bottom left: mammogram. (Operated by the author, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

2.2.3. Skin-sparing and nipple sparing mastectomies with reconstructions

Breast reconstruction after mastectomy requires complex decision making. In terms of timing of the reconstruction, immediate reconstruction is preferable than delayed, as better cosmetic outcome can be achieved when the skin envelope is kept during mastectomy (**Figure 8)**. In terms technique of the reconstruction, implant-based reconstruction is unlikely to result in favourable cosmetic outcome in the setting of chest wall radiotherapy, hence it is advised to avoid implant reconstruction in this scenario. Importantly, there is no evidence that reconstructive techniques would influence oncological outcome.

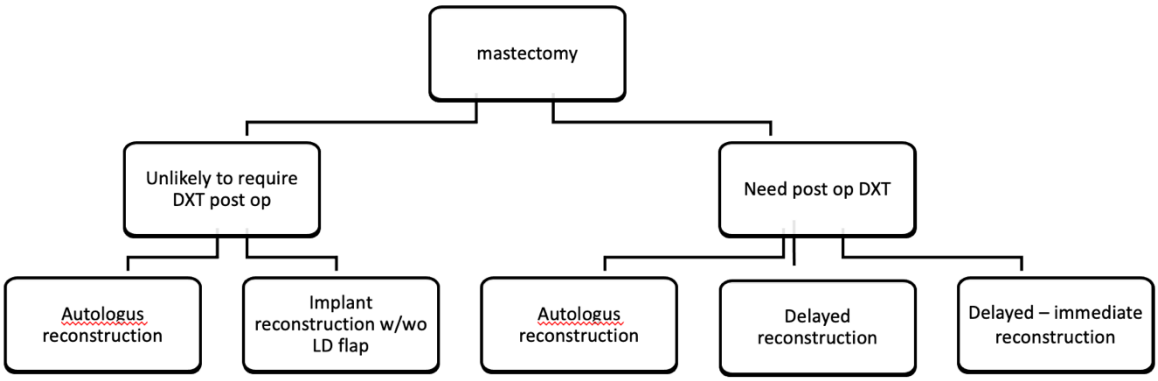
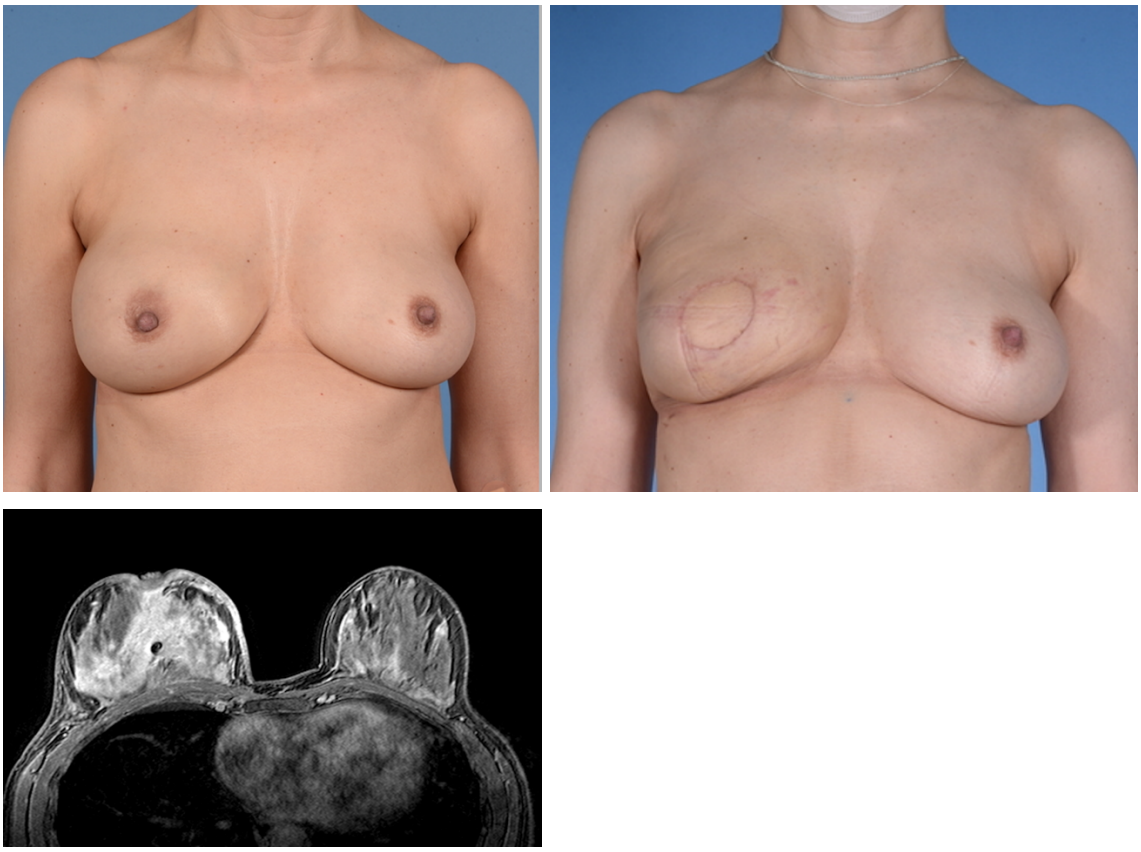


Figure 8. Flowchart illustrating the algorithm for selection of surgical technique for breast reconstruction

G) Skin-sparing mastectomy and immediate autologous reconstruction

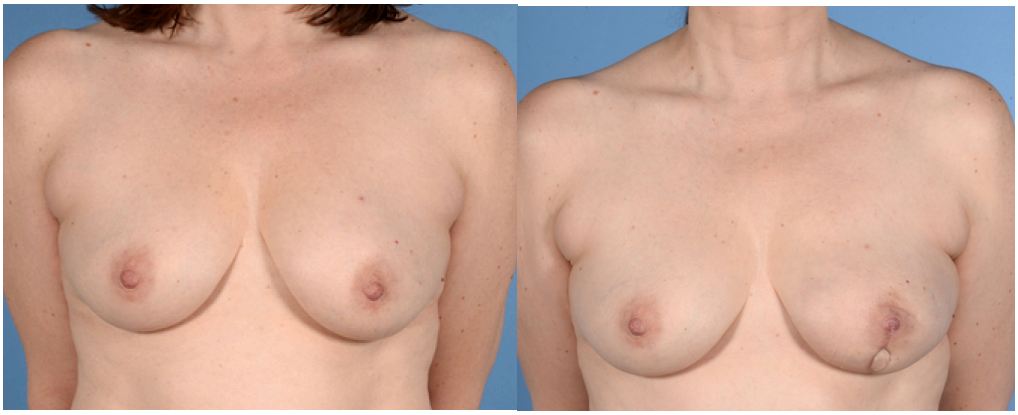
During skin-sparing mastectomy the breast tissue is removed – most commonly – from a circumareolar incision together with the nipple areola complex. The skin envelope is undermined in the mastectomy plane circumferentially, and the breast parenchyma is removed from the chest wall subsequently. Sentinel node biopsy is carried out from a separate axillary incision.

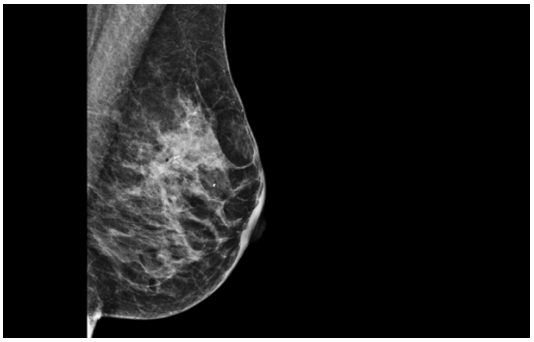


53-year-old patient presented with a large distorting cancer in the right breast of over 12 cm in size (as illustrated on the baseline MRI scan). Biopsies showed invasive ductal cancer, grade 3. ER/PR negative, HER-2 positive. Axillar core biopsy confirmed nodal metastasis. As staging CT scan was clear, she underwent neoadjuvant chemotherapy followed by skin-sparing mastectomy, axillary node clearance and immediate reconstruction with DIEP flap. Histology showed a residual 88mm cancer with extensive LVI, 8 of 12 nodes positive and scarring in 4 nodes. She underwent postoperative 3 field radiotherapy as well as further systemic treatment but a year and a half after her surgery she developed cutaneous recurrence in the skin envelope requiring neo-mastectomy and latissimus dorsi flap cover. The patient currently on Herceptin but not distant metastasis is evident. Top left: preoperative photograph, top right: postoperative photograph, bottom left: breast MRI. (Operated by the author and a plastic surgeon as a joint case, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

H) Nipple-sparing mastectomy and immediate autologous reconstruction

During nipple-sparing mastectomy the breast tissue is removed from a radial incision in the lower aspect of the breast (with the option of splitting the nipple-areola complex if required) or from an incision from the infra-mammary fold. The nipple-areola complex is preserved, but the retroareolar tissue (terminal ducts) should be sent for histology separately to make sure it is free of malignancy. At immediate reconstruction nipple-sparing mastectomy should be the standard surgery, unless radiological or clinical suspicion exists that the nipple is involved, or nipple spare surgically not feasible.





54-year-old patient was referred with screen detected grade 2 invasive lobular carcinoma (ER7 / PR8 / HER-2 negative) in the left breast, with 45mm in size on mammogram, located in the central / superior aspect in a moderate sized breast. She underwent a nipple-sparing mastectomy and sentinel node biopsy and immediate reconstruction with DIEP flap. Histology showed at least 43mm Grade 2 invasive lobular carcinoma, ER7 PR8 HER2-ve. Oncotype DX risk recurrence score of 11 indicated not for adjuvant chemotherapy. She underwent adjuvant radiotherapy to left chest wall and currently on letrozole. Top left: preoperative photograph, top right: postoperative photograph, bottom left: mammogram. (Operated by the author and a plastic surgeon as a joint case, photographs provided by the Medical Illustration Department, NHS Greater Glasgow and Clyde. Patient's informed consent for publication is available upon request.)

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Thoraco-epigastric pedicled flap for partial breast reconstruction
Romics L., Weiler-Mithoff E., Morrow E.
in ***Oncoplastic Breast Surgery Techniques for the General Surgeon*****,** Springer Nature Switzerland, 2020**,** ISBN: 978-3-030-40195-5, 261-280.

Oncoplastic techniques in lateral tumour location
L Romics, P Kelemen
in ***Principles and Practice of Oncoplastic Breast Surgery***, Medicina Publishing, 2019
ISBN: 978-963-226-725-8, 247-257

Omega oncoplastic techniques
P Kelemen, **L Romics**
in ***Principles and Practice of Oncoplastic Breast Surgery***, Medicina Publishing, 2019
ISBN: 978-963-226-725-8, 258-261

Oncoplastic techniques in medial tumour location
P Kelemen, **L Romics**
in ***Principles and Practice of Oncoplastic Breast Surgery***, Medicina Publishing, 2019
ISBN: 978-963-226-725-8, 261-267

Oncoplastic techniques for lower pole tumours
L Romics, P Kelemen
in ***Principles and Practice of Oncoplastic Breast Surgery***, Medicina Publishing, 2019
ISBN: 978-963-226-725-8, 268-273

Oncoplastic approach in breast cancer surgery--a new challenge for the future breast surgeon?
Romics L, Weiler-Mithoff E, Cooke TG, George WD.
Magyar Sebészet. 2008 Feb;61(1):5-11. In Hungarian.

3. OBJECTIVES

3.1. To establish the oncological safety of oncoplastic breast conservation surgery and mastectomy followed by immediate breast reconstruction in the Glasgow breast units

3.1.1. To determine long-term recurrence rates and survival after mastectomy and immediate breast reconstruction and compare with the published literature data of the time

1) To investigate local and distal recurrence in the context of tumour characteristics and stage
2) To show overall and disease-free survival in the whole cohort
3) To investigate local and distal recurrence in the context of adjuvant treatment and reconstructive techniques

3.1.2. To establish a comparative group to oncoplastic breast conservation surgery

1) To compare histological characteristics of patients treated with oncoplastic conservation, wide local excision, and mastectomy
2) To compare adjuvant treatment given after oncoplastic conservation, wide local excision, and mastectomy
3) To compare incomplete excision rate after oncoplastic conservation to wide local excision

3.1.3. To investigate the impact of oncoplastic surgery on the timely commencement of adjuvant treatment

1) To describe tumour characteristics, oncoplastic surgical techniques, postoperative complications, and further surgery in the OBCS group
2) To compare time between first surgery and adjuvant chemotherapy after oncoplastic conservation, wide local excision and mastectomy +/- reconstruction

3.1.4. To study the safety of radiological follow up after oncoplastic breast conservation surgery

1) To compare patient, tumour, and treatment characteristics of OBCS and WLE groups of the study
2) To compare number, indication and outcomes of mammograms, ultrasounds, and biopsies in between the two groups in the first two years of follow up

3.1.5. To determine the long-term recurrence rates and survival after therapeutic mammoplasty and volume-replacement oncoplastic conservation respectively

1) To study recurrence rate in the context of tumour characteristics, stage, oncoplastic surgical technique and adjuvant treatment, and determine incomplete excision rate after therapeutic mammoplasty
2) To study recurrence rates in the context of tumour characteristics, surgical technique, and incomplete excision rates after volume replacement oncoplastic surgery

3.1.6. To compare the oncological outcomes of oncoplastic breast conservation surgery to wide local excision and mastectomy

1) To compare patient, tumour, and treatment characteristics of the three groups
2) To compare 5-year local and distal recurrence rates, as well as disease free, breast cancer-specific and overall survival rates

3.1.7. To study the oncological safety of extreme oncoplasty

1) To analyse patient and tumour characteristics, surgical technique, complications, and adjuvant treatment characteristics of the cohort
2) To investigate incomplete excision rate, 5-year local and distant recurrence as well as cancer-specific and overall survival rates

3.1.8. To investigate the impact of the COVID-19 pandemic on oncoplastic surgery

1) To compare tumour characteristics of patients and surgery applied during hospital lock-down and before the COVID-19 pandemic in the West of Scotland
2) To analyse patients' risk factors and postoperative complications during hospital lock-down
3) To show the overall impact of the pandemic on the management of patients with breast cancer in the West of Scotland

3.2. To invetigate the oncological safety of oncoplastic breast conservation surgery in national and international studies

3.2.1. To compare the indications of oncoplastic breast conservation, wide local excision, and mastectomy in the whole of Scotland

1) To investigate regional differences in the type of breast cancer surgeries in Scotland
2) To compare clinicopathological characteristics, adjuvant and neoadjuvant treatment of patients treated with OBCS, WLE, Mastectomy and Mastectomy with Immediate Reconstruction
3) To compare time to surgery from diagnosis, and time to adjuvant treatment from surgery in between the groups

3.2.2. To compare the width of excision margins after oncoplastic breast conservation versus wide local excision and its impact on recurrence (OPBC-1/iTOP2 study)

1) To compare clinicopathological features of tumours treated with oncoplastic conservation and wide local excision
2) To compare margin width differences and incomplete margin rates in between the two groups
3) To compare local and regional recurrence rates, and disease-free survival in between the two groups

3.2.3. To study the oncological safety of oncoplastic breast conservation surgery in the whole of Scotland – a real life experience

1) To classify breast units as high and low volume oncoplastic units in the context of number of cases and variability of oncoplastic techniques applied
2) To determine the clinicopathologic and treatment characteristics, and incomplete excision rates of patients undergoing oncoplastic breast conservation
3) To investigate relationship between postoperative complications and case-load as well as learning curve and measure 5-year recurrence rates and disease-free survival

3.2.4. To determine the oncological safety of volume replacement oncoplastic surgery using chest wall perforator flaps in the whole of the UK – a real life experience

1) To determine clinicopathological characteristics, oncoplastic surgical techniques applied and postoperative complications in the cohort
2) To measure excision margin width, incomplete excision and conversion to mastectomy rate, as well as short-term recurrence rate

3.2.5. To study if surgery (breast conservation versus mastectomy) is an independent factor that impacts survival rates in Scotland

1) To compare breast cancer-specific and overall survival in patients treated with breast conservation followed by radiotherapy, and mastectomy with or without radiotherapy
2) To study survival rates in multivariate analysis including tumour characteristics, mode of referral and surgical treatment

4. INVESTIGATION OF THE ONCOLOGICAL SAFETY OF ONCOPLASTIC SURGERY IN THE GLASGOW BREAST UNITS

4.1. Long-term oncological safety of skin-sparing mastectomy followed by immediate breast reconstruction

4.1.1. Introduction

Breast reconstruction after mastectomy is an integral part of the complete management of breast cancer. Skin-sparing mastectomy (SSM) followed by immediate breast reconstruction (IBR) has been shown to be superior to simple mastectomy with breast reconstruction in terms of cosmetic results.[104] While in the past the main focus of surgical intervention was to achieve local control of disease, a further objective – patient satisfaction – emerged, and oncological safety and aesthetic outcome have become common goals in breast cancer surgical treatment recently.[105] In parallel, a paradigm shift from radical surgery towards technically demanding and oncologically tailored breast cancer surgery evolved in the last two decades. Therefore, IBR is considered an essential element of the therapeutic armamentarium for breast cancer requiring mastectomy.

Indication and timing of breast reconstructions are largely debated due to the lack of high level of evidence, since prospective randomized controlled trials have not been carried out yet.[106] In addition to this, most of the native breast skin is left intact during SSM in patients undergoing IBR, which may compromise the completeness of mastectomy.[107, 108] Consequently, some authors speculated that SSM and IBR may be oncologically inferior to conventional mastectomy and associated with a higher loco-regional recurrence rate.[109] Local and loco-regional recurrence after mastectomy is generally regarded as a poor prognostic sign, because it is usually – but not always – associated with systemic relapse.[110-112] Nevertheless, loco-regional recurrence is surely a difficult psychological burden for breast cancer patients since it requires further surgical and oncological treatment.[113]

Another concern regarding IBR is whether it delays diagnosis of local or loco-regional recurrence.[114] This is further complicated by the lack of consensus in the radiological follow-up of reconstructed breasts. In addition to these, some authors speculated that complex – and occasionally multiple – reconstructive procedures may potentially delay adjuvant therapy,

because these patients have a relatively higher chance to develop postoperative complications compared to ones treated with mastectomy only.[66, 115, 116] Lastly, adjuvant postmastectomy radiotherapy – which is generally regarded as being deleterious to the reconstructed breast – cannot be reliably predicted before surgical treatment.[117] Therefore, a generally negative attitude with scepticism developed gradually towards SSM combined with IBR, and a fear of potentially worse prognosis.[118]

While there is a general agreement for IBR in cases of in situ disease and early breast cancer, many centres advocate mastectomy with a delayed reconstruction approach after completion of adjuvant treatment in cases of advanced breast cancer.[119-121] Furthermore, it is very difficult to obtain consensus and definitive guidance given the quality of the published data on oncological safety of skin-sparing mastectomy. Most studies are uncontrolled, single institution, retrospective studies with small sample sizes, insufficient follow-up and variation in operative techniques[20] and (neo)adjuvant treatments regimens.[122] Importantly, local and loco-regional recurrence events are uncommon and small differences in oncological outcomes must be interpreted with more than a degree of caution.

Although several recent publications underline the safety of IBR,[118, 123-127] very few demonstrate long-term oncological follow-up data.[128] Importantly, evidence from these studies has a degree of surgical selection-bias since SSM was mostly offered to patients with in situ disease or early breast cancer only. Therefore, a lack of evidence remains in terms of oncological safety in cases of more advanced disease. Furthermore, published follow-up data of patients who underwent SSM address early recurrence almost exclusively and disregard late loco-regional recurrences. Since most of these studies include a three-to-five year follow-up time, the issue of long term oncological safety has yet to be satisfactorily answered.[129]

4.1.2. Aims

In this study we carried out a long-term (10-year period) follow-up of patients who underwent SSM and IBR in the greater Glasgow area. Unusually for the time, an approach to SSM and IBR was adopted in Glasgow; all women requiring mastectomy for in situ or invasive breast cancer were offered SSM and IBR. The primary aim of the study was therefore to determine the incidence of local, loco-regional and distant recurrence rate across the broad spectrum of indications for mastectomy with the intention to determine the long-term oncological safety of SSM.

4.1.3. Methods

A prospectively maintained institutional breast surgery database of the Canniesburn Plastic Surgical Unit, Glasgow Royal Infirmary was searched to identify patients who underwent SSM and IBR between January 1995 and June 2000. A retrospective review of medical records of the identified patients was then carried out to include patients only with indications of ductal carcinoma in situ and invasive breast cancer. Patients with previous ipsilateral or contralateral ductal carcinoma in situ or breast cancer as well as risk reducing mastectomies were excluded. Clinical records for selected patients were analysed for demographic, oncological and treatment characteristics. Details on tumour characteristics were obtained from the pathology reports, whereas surgical, oncological records and radiology reports were analysed for follow-up to determine pattern and timing of recurrence up to February 2009. Length of follow-up was determined as time elapsed from first treatment.

Recurrences and other treatment failures were documented by clinical examination, radiological tests and/or pathological assessment. Local recurrence was defined as histologically proven recurrent tumour occurring within the soft tissues of the ipsilateral anterior chest (skin, subcutaneous tissue, or muscle) within the anatomical borders of sternum medially, the clavicle superiorly, the posterior axillary line laterally and the costal margin inferiorly. Locoregional recurrence included the anatomical area of local recurrence in addition to sites of regional relapse, which meant tumour spread in the internal mammary, supraclavicular, infraclavicular, ipsilateral axillary nodes. All other sites of tumour recurrence were classified as distant metastases. Local, regional, and distant recurrence rates were the primary outcome of interest since those correlates well with the overall oncological safety of SSM, while local and regional relapses characterize the selected surgical technique. For tumour staging The American Joint Committee on Cancer staging system latest edition (Seventh Edition © 2010 AJCC) was used.[130]

SSM was performed in an established manner by experienced breast surgeons as outlined previously by Toth and Lappert, which was the modified original Freeman's procedure.[131, 132] The nipple–areola complex together with the entire breast parenchyma was removed as well as any existing biopsy scar and skin overlying superficial tumours. The remaining healthy breast skin envelope was left behind. Periareolar, tennis racquet-type and Wise-pattern incisions were most applied. An elliptical incision was used in cases of a superficial tumour or a previous biopsy scar, including the nipple–areola complex. When the preoperative diagnosis was invasive cancer SSM was combined with level I or II axillary lymph node dissection (sentinel

lymph node biopsy alone was not used at the time of the study). When ductal carcinoma in situ was the preoperative diagnosis four node axillary sampling was carried out routinely. SSM was followed by IBR by a team of reconstructive plastic surgeons. Various reconstructive methods were applied, depending on standard indications, patient anatomy and ultimately patient choice.

Chemo-, radio- and hormonal therapy were administered according to local evidence-based guidelines of the given time period. In general, radiotherapy was administered to patients with four or more positive lymph nodes or a primary tumour larger than 4 cm in diameter. Chemotherapy was administered to patients at high risk of recurrence. This involved lymph node positive cases, patients with a primary tumour of more than 5 cm in diameter, smaller tumours with higher histological grade and/or negative hormone receptor expression and patients younger than 35 years of age. Patients who had hormone receptor positive tumours also received tamoxifen for 5 years after surgical treatment or completion of chemotherapy. Patients with high-risk breast cancer received aromatase inhibitor, too, according to timely evidence.

Patients were followed up according to the standard protocol of the given time period of the Scottish Intercollegiate Guideline Network (SIGN 29: Breast Cancer in Women, 1998, Scottish Intercollegiate Guideline Network, www.sign.ac.uk). Patients were followed up six monthly by clinical examination by the medical and surgical oncologists alternating. Surveillance mammograms were carried out on the contralateral side on the healthy breast one year after surgery and then two-yearly. The reconstructed breasts were surveyed routinely by thorough clinical examinations only. Abnormal clinical findings were further investigated accordingly by mammogram, ultrasound, CT scan, MRI scan, fine needle aspiration, core and/or excisional biopsy and consequent histological analysis as appropriate.

Statistical calculations were performed using software (Minitab Statistical Software®, Version 15; State College, Pennsylvania, USA) and SPSS® version 18 (SPSS, Chicago, Illinois, USA). Descriptive and univariate statistical analyses were performed. Multivariable analysis was not feasible due to sample size limitations. Survival was calculated from the time of first diagnosis to death. Z-test for two proportions was used to determine associations with recurrence for nodal metastasis, hormone receptor expression, radio-, chemotherapy, Tamoxifen, histological tumour type and reconstructive techniques. In addition, comparisons of locoregional versus distal recurrence or breast cancer versus non-breast cancer related death were calculated by the same test. Chi-square test was applied to calculate associations between recurrence and tumour size, grade and disease stage. Two-sample t-test was used to compare cancer specific survival between groups of patients with locoregional and distant recurrence as

first event. For all analyses, results were considered statistically significant if the p value was .05 or less.

4.1.4. Results

253 consecutive patients who underwent SSM and IBR for invasive breast cancer (n=191) or ductal carcinoma in situ (DCIS) (n=62) were identified and analysed in the study. 35 patients with incomplete follow-up data were excluded from the analysis (invasive cancer (n=27) and DCIS (n=8)). Another 11 patients with invasive cancer were disregarded as these patients were undergoing SSM for recurrent disease following previous lumpectomies. Therefore altogether 207 patients were included and analysed in the study (invasive cancer: n=153; DCIS: n=54) (**Table 3**). The median age of patients was 49 [26-68] years. The median length of follow-up of the whole cohort was 119 months [14-163], while the median follow-up of those who survived was 122 [99-163] months.

Table 3. Tumour characteristics of patients and overall, loco-regional, local, and distant recurrence rates, based on first event of recurrence.

PATIENTS			RECURRENCES							
			Overall		Locoregional		Local		Distant	
	No.	%	No.	%	No.	%	No.	%	No.	%
All patients	**207**	**100**	**39**	**18.8**	**17**	**8.2**	**6**	**2.9**	**22**	**10.6**
Invasive cancer	**153**	**73.9**	**38**	**24.8**	**17**	**11.1**	**6**	**3.9**	**21**	**13.7**
T1	94	45.4	18	19.1	7	7.4	5	5.3	11	11.7
T2	52	25.1	16	30.8	7	13.5	0	0	9	17.3
T3	6	2.9	4	66.7	3	50	1	16.7	1	16.7
T4	1	0.05	0	0	0	0	0	0	0	0
G1	29	14	2	6.9	1	3.4	1	3.4	1	3.4
G2	52	25.1	13	25	3	5.8	2	3.8	10	19.2
G3	72	34.8	23	31.9	13	18	3	4.2	10	13.9
Ductal	136	65.7	34	25	16	11.8	6	4.4	18	13.2
Lobular	12	5.8	3	25	1	8.3	0	0	2	16.7
Tubular	3	1.4	1	33.3	0	0	0	0	1	33.3
Mucoid	1	0.5	0	0	0	0	0	0	0	0
Paget's	1	0.5	0	0	0	0	0	0	0	0
Oestrogen rec +	119	57.5	27	22.7	11	9.2	4	3.4	16	13.4
Oestrogen rec -	34	16.4	11	32.3	6	17.6	2	5.9	5	14.7
Node +	73	35.26	25	34.2	12	16.4	4	5.5	13	17.8
Node -	80	38.6	13	16.2	5	6.2	2	2.5	8	10
DCIS	**54**	**26.1**	**1**	**1.8**	**0**	**0**	**0**	**0**	**1**	**1.8**
Low	6	2.9	0	0	0	0	0	0	0	0
Intermediate	20	9.6	0	0	0	0	0	0	0	0
High	28	13.5	1	3.6	0	0	0	0	1	3.6
Stage of disease										
0	54	26.1	1	1.8	0	0	0	0	1	1.8
IA	57	27.5	10	17.5	4	7	1	1.7	6	10.5
IIA	55	26.6	12	21.8	5	9.1	2	3.6	7	12.7
IIB	28	13.5	9	32.1	4	14.3	2	7.1	5	17.8
IIIA	12	5.8	7	58.3	4	33.3	1	8.3	3	25
IIIB	1	0.5	0	0	0	0	0	0	0	0

Footnote: + receptor expressed or metastasis present

All patients treated with mastectomy underwent IBR unless they were medically unfit, refused reconstruction, or had Stage IV or T4 disease (although the latter two were not absolute contraindications). This approach was uncommon between 1995 and 2000, provided us with a larger proportion of patients with more advanced disease compared to other studies of the same time period. Indication for SSM was invasive cancer in almost three-quarters of our patients (73.9 per cent; 153 of 207), and almost half of our patients were diagnosed with stage II or stage III breast cancer (46.4 per cent; 96 of 207) (**Table 3**). Out of 207 patients analysed 49 patients

(23.6 per cent) had multifocal disease (invasive cancer: 10.6 per cent; 22 of 207 and DCIS: 13 per cent; 27 of 207).

During the 119 months median follow-up period 39 patients were detected with distant and/or locoregional recurrence, therefore the overall recurrence rate was 18.8 per cent (39 of 207) (**Figure 9 and Table 3**).

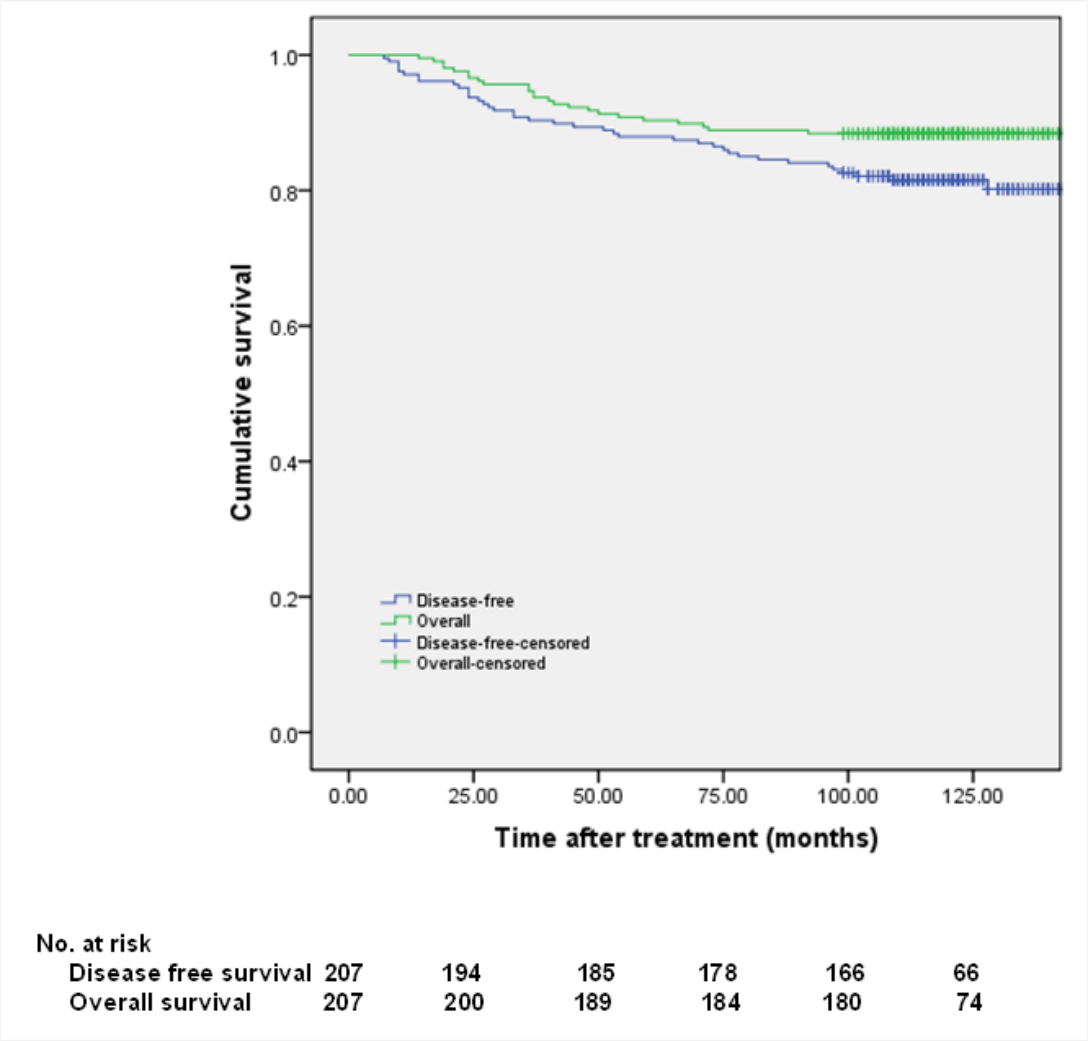


Figure 9. Overall and disease-free survival in patients who underwent skin-sparing mastectomy and immediate breast reconstruction for invasive cancer or DCIS.

17 patients were detected with locoregional recurrence as first event of recurrence, which resulted in an 8.2 per cent locoregional recurrence rate (17 of 207). Of these, true local recurrences were found in six patients only resulting in a 2.9 per cent local recurrence rate (6 of 207). 7 of 17 patients diagnosed with locoregional recurrence developed synchronous or metachronous distant metastasis as well and all of them died since. However, 10 patients with locoregional recurrence who did not develop distant metastases were alive and well at the end of their follow-up. 22 patients developed distant recurrence as first event of detected recurrence,

which resulted in 10.6 per cent (22 of 207) distant recurrence rate (**Table 3**). All distant and/or locoregional recurrences developed in patients with invasive cancer, except one distal recurrence in a patient with high grade DCIS on original pathology. In this sense, recurrence rates calculated for patients with invasive breast cancer only was proportionally higher. In this subgroup overall recurrence rate was 24.8 per cent (38 of 153), locoregional recurrence rate was 11.1 per cent (17 of 153), local recurrence rate was 3.9 per cent (6 of 153) and distant recurrence rate was 13.7 per cent (21 of 153) as first event of recurrence (**Table 3**). Presence of axillary lymph node metastases was statistically significantly associated with higher overall recurrence rate (95 per cent confidence interval: 0.044 to 0.31; P=0.009). Similarly, patients with higher stages (P<0.001) and grade (P=0.031) were statistically more likely to relapse. However, no statistically significant association was found between tumour size, histological type, hormone receptor expression, adjuvant radio-, chemotherapy, tamoxifen and overall tumour recurrence (**Table 3 and 4**).

Table 4. Adjuvant therapy and relevant overall, locoregional, local and distant recurrence rates.

PATIENTS			**RECURRENCES**							
			Overall		**Locoregional**		**Local**		**Distant**	
	No.	%	No.	%	No.	%	No.	%	No.	%
All patients	**207**	**100**	**39**	**18.8**	**17**	**8.2**	**6**	**2.9**	**22**	**10.6**
Radiotherapy +	72	34.8	18	25	5[3]	6.9	1	1.4	13	18
Radiotherapy -	81	39.1	20	24.7	12	14.8	5	6.2	8	9.9
Chemotherapy +	97[1]	48.3	29	29.9	14	14.4	4	4.1	15	15.5
Chemotherapy -	56	51.7	9	16.1	3	5.3	2	3.6	6	10.7
Tamoxifen +	126[2]	60.9	29	23	12	9.5	5	3.9	17	13.5
Tamoxifen -	27	13	9	33.3	5	18.5	1	3.7	4	14.8

Footnote: [1] 3 patients with DCIS received chemotherapy, [2] 4 patients received Zoladex in addition to Tamoxifen, [3] one patient refused radiotherapy, + treatment received, - treatment not received.

As far as breast reconstructive methods, no statistically significant difference was found between free flaps versus pedicled flaps, but patients who underwent autologous tissue reconstruction were more likely to recur compared to ones with implant-based breast (95 per cent confidence interval: 0.226 to 0.021; P=0.018) (**Table 5**).

Table 5. Type of reconstructive surgery and relevant overall, locoregional, local and distant recurrence rates.

PATIENTS			RECURRENCES							
Type of reconstruction			Overall		Locoregional		Local		Distant	
	No.	%	No.	%	No.	%	No.	%	No.	%
All patients	**207**	**100**	**39**	**18.8**	**17**	**8.2**	**6**	**2.9**	**22**	**10.6**
LD	70	33.8	23	32.8	10	14.3	1	1.4	13	18.6
LD with Becker	38	18.3	3	7.9	0	0	0	0	3	7.9
Becker only	54	26	8	14.8	5	9.2	5	9.2	3	5.5
DIEP	29[1]	14	3	10.3	1	3.4	0	0	2	6.9
TRAM	8	3.9	0	0	0	0	0	0	0	0
SIEA	5	2.4	1	20	0	0	0	0	1	20
SGAP	3	1.4	1	33.3	1	33.3	0	0	0	0

Footnote: [1] 5 patients underwent bilateral DIEP reconstructions due to contralateral risk-reduction. LD: latissimus dorsi flap; DIEP: deep inferior epigastric perforator flap; TRAM: free transverse rectus abdominus myocutaneous flap; SIEA: superficial inferior epigastric artery flap; SGAP: superior gluteal artery flap.

This is partially be due to that autologous reconstructive techniques were more frequently applied in patients with higher stages, while implant based methods in lower stages (stage 0: autologous (a): 36 per cent (19 of 54) vs. implant based (i): 65 per cent (35 of 54); stage IA-IIA: a: 61 per cent (68 of 112) vs. i: 39 per cent (44 of 112); stage IIB and above: a: 66 per cent (27 of 41) vs. i: 34 per cent (14 of 41)). Reliable statistical associations between the aforementioned variables and locoregional or local recurrence rates in specific could not have been determined due to the low number of events detected. Median time to first overall recurrence was 36 months [7-128], while median time to first locoregional recurrence was 24 months [7-99] and to distant recurrence was 62 months [10-128]. There were 14 patients with newly diagnosed first recurrence (three with locoregional and 11 with distant metastases) detected later than a 60-month post-surgical follow-up period in this cohort. In terms of timescale of relapses, 48.9 (19 of 39) per cent of first event recurrences occurred beyond 36 months and 35.9 per cent (14 of 39) of recurrences beyond 60 months follow-up time in our cohort. While the latter one increased overall recurrence rate by 6.7 per cent (14 of 207) from 12.1 per cent (25 of 207) to 18.8 per cent (39 of 207), these 14 patients were diagnosed mostly with distant recurrence (n=11) and only three locoregional recurrences were detected later than 60 months follow-up time period.

Altogether 24 patients died during the follow-up of the cohort, and therefore the overall survival rate was 88.4 per cent (24 of 207) (**Figure 9**). 23 of these 24 patients were diagnosed with invasive disease, while the remaining one had high grade DCIS diagnosed on pathology. Since five patients (four with invasive breast cancer and one with DCIS) died due to other

reasons than metastatic breast cancer, cancer-specific survival rate was actually 90.9 per cent (19 of 207). Proportion of patients who died after distant recurrence, as first recurrent event detected, was (54.5 per cent (12 of 22). This was similar to the 41.2 per cent of patients (7 of 17) with locoregional recurrence, as first event and died eventually during the follow-up (95 per cent confidence interval: -0179 to 0.447; P=0.403). Obviously, proportion of cancer related death of patients with recurrence (48.7 per cent; 19 of 39) was statistically significantly higher compared to non-breast cancer related death (2.9 per cent; 5 of 168) (95 per cent confidence interval: 0.298 to 0.616; P<0.001). Importantly, median time of cancer-specific survival of patients who developed distant disease after or with locoregional recurrence was 19 [8-37] months, while the similar figure for patients with distant recurrence only was 39 months [19-92], which is a significant difference (95 per cent confidence interval: -37.54 to -10.18; P=0.002).

4.1.5. Discussion

Local recurrence after mastectomy is likely to be a multifactorial phenomenon with surgical technique, adjuvant treatment and tumour biology all playing a role. There is no doubt that surgical technique plays an important role in minimising local recurrence; by minimising the amount of residual disease and normal breast tissue left under mastectomy flaps. The literature seems to support the theory that it is technically impossible to remove all breast tissue at mastectomy[110, 133] and residual breast tissue is left behind under the skin flaps in more than a fifth of the patients.[108] In SSM, which is often carried out through a more technically challenging approach it has been reported that there may be residual breast tissue in the inframmary fold as well as under the breast skin-envelope in more than half of the patients.[107, 134]

These studies need to be viewed cautiously given the varied techniques and understanding of the ‘mastectomy plane’. It has been reported that the mastectomy plane is achievable when the superficial fascial layer is evident between the subcutaneous fat and breast parenchyma. The often quoted study by Beer et al. claims that there is an absence of this anatomical landmark for flap dissection in more than 40 per cent of the patients [135]. Their study looked at the reduction mammaplasty specimens of less than 100 patients and it seems difficult to be able to extrapolate this more generally. The superficial fascia however is a constant entity with a sound embryological explanation. Indeed, the surgical challenge in skin sparing mastectomy remains to use the best possible technique to meticulously maintain this fascial layer on the breast

parenchyma (thereby removing all breast tissue) yet to avoid disrupting the subcutaneous fat layer when dividing ligaments of Cooper at their anchor points to the dermis (and thus minimising the risk of native skin flap envelope necrosis).

Importantly, it has been suggested that tumour biology and disease stage determines loco-regional recurrence rate rather than the surgical technique applied.[110, 125, 35, 36] Further, it has been demonstrated that local treatment affecting local recurrence rates could avoid about one breast cancer death for every four local recurrences avoided and should reduce 15-year overall mortality.[37] We found that patients who were detected with locoregional recurrence as well as synchronous or metachronous distant metastasis had poorer prognosis compared to ones diagnosed with distant relapse only. This supports the view that patients who relapse locoregionally as well as distally suffer from potentially more aggressive disease than the ones who relapse either locally or distally only. Locoregional recurrence from our data appears to be more a sequel of aggressive tumour biology rather than inadequate or technically poor surgery. Similarly, patients with autologous reconstructions were more likely to relapse, since they were diagnosed with more advanced cancers as opposed to ones who underwent implant-based reconstructions. Hence, recurrence rate is determined primarily by tumour biology but not surgical reconstructive technique

The reported local recurrence rate after SSM is between 2 per cent to 10.4 per cent, which is similar to non-SSM local recurrence rates in the published literature.[109, 110, 125-127, 134, 136-1401] These results, however, should be interpreted with caution, because there is usually no analysable information provided about adjuvant therapy, and local protocols and guidelines can significantly vary by countries and markedly change by time. In addition, patient cohorts are relatively heterogenous ranging from non-invasive disease or low-risk patients only to the whole spectrum of breast cancer patients including even stage III or IV disease.[110] Further, most oncological follow-up after SSM focuses on early relapse only, which occurs mostly in the first two to three years after surgery.[42] While some studies extend follow-up time up to 5 years, it is relatively rare to determine recurrence rate beyond that time period, despite it has been suggested that higher locoregional recurrence rates can be detected with longer follow-up time.[111, 133, 141, 1424] We think that determination of true locoregional and distant recurrence rates are essential to measure oncological safety of SSM reliably. Therefore, studies with longer than 60 months follow-up time were identified from published literature and we found 0-11.1 per cent local and 1.1-12.9 per cent locoregional recurrence rates (**Table 6**).[104, 110-112, 119, 124, 126, 133, 141, 143-1479, 51-53] These recurrence rates are somewhat higher than those of shorter follow-up time.In our opinion, therefore, studies with short (up to 3 years) follow-up time focusing on the

peak of early recurrences do not provide sufficient information to determine the safety of SSM. Follow-up should be at least five years, although extension beyond 60 months is more preferable to provide an adequate estimation of true recurrence rates following SSM.

There were concerns raised that the surgical stress caused by delayed reconstruction may activate dormant breast cancer cells, and recurrence develops after delayed reconstruction making these patients' prognosis poorer. In order to investigate this, in a separate small study 158 patients who underwent delayed breast reconstruction consecutively in the above-mentioned regional plastic surgical unit (Glasgow Royal Infirmary "Canniesburn" plastic surgical department) between 2005 and 2009 were compared to the this – above analysed – 207 patients who underwent immediate reconstruction in the same unit during the same timeframe. We found that delayed breast reconstruction was offered primarily to those with larger, more aggressive, and metastatic tumours. A higher mortality rate was observed in the delayed reconstruction group, but these differences were not adjusted to the differences in tumour stages (delayed reconstruction group: 13.9% compared to immediate: 9.1%). The impaired survival rate after delayed reconstruction was demonstrated by others as well which supports our findings, too. We also found that locoregional recurrence rate was twice as high in the patients who had immediate reconstruction as opposed to delayed reconstruction (8.2% vs. 3.6%). We concluded that while all these data support the previous concerns our study provides preliminary results only and further studies are necessary on the subject. Unfortunately, the equal safety of delayed reconstruction to immediate has still not been proven yet. While delayed reconstructions are seldomly preformed these days the evidence gap still persists.

As far as oncosurgical safety of SSM, some studies do not define or even differentiate local or locoregional recurrence. We feel that this is important if we are to adequately categorise and understand our recurrences [50]. While local recurrence rate mirrors the quality of oncosurgical technique of SSM only, regional recurrence provides information about the quality of axillary surgery. Since axillary procedures are essential part of SSM and IBR – especially in moderate or high-risk breast cancer patients – provision of detailed local and locoregional recurrence rates are essential to measure adequately oncosurgical safety. Unfortunately, almost half of the long-term oncological follow-up studies did not provide clear local and locoregional recurrence rates (8 out of 17) (**Table 6**).[7, 23, 25, 43, 45, 46, 48, 53] In addition, most of these studies did not disclose tumour size or stage either, which makes the evidence even weaker in this respect.[104, 110, 124, 126, 133, 141, 143-1479, 53] Moreover, the data on high risk patients is very difficult to interpret, given that in the 6 studies we found, the subgroups were small and too highly selected for useful interpretation.[25, 43, 46-48, 51]

Table 6. Loco-regional recurrence rates published during long-term (more than 5 years) follow-up period after skin-sparing or subcutaneous mastectomy.

First author	Year	No. of cases	Tumour size	Tumour stage	Mastect. technique	Median follow-up (months)	Recurrence rates (%)	
							Local	Loco-regional
Kroll et al.	1999	114	T1 - T2	n/d	SSM	72	n/d	7
Medina-Franco et al.	2002	176	T1 - T4	I-III	SSM	73	4.5	8.5
Spiegel et al.	2003	221	Tis - n/d	0-II	SSM	118	n/d	4.5
Carlson et al.	2003	565	n/d	0-IV / Recur.	SSM	65	n/d	5.5
Horiguchi et al.	2001	133	n/d	0-IIIA	Subcut. M	66	3.8	n/d
Kroll et al.	1997	104	T1 - T2	n/d	SSM	67	n/d	6.7
Gerber et al.	2009	108	n/d	0-IIIB	SSM	101	11.1	12.9
Petit et al.	2008	518	T1 - T3	I-IIIB	SSM	70	5.2	6.6
Omranipour et al.	2008	95	n/d	I-II / Recur.	SSM	69	0	1.1
Carlson et al.	2007	223	Tis	0	SSM	82	3.3	4.2
Meretoja et al.	2007	197	n/d	0-IIIC / Recur.	SSM	70	5.1	9.7
Woerdeman et al.	2006	85	n/d	0-n/d / Recur.	SSM	73	n/d	2.3
Langstein et al.	2003	1694	T1 - T4	I-IV	SSM	81	1.6	2.3
Murphy et al.	2003	158	n/d	I-IV	n/d	75	1.3	n/d
Noone et al.	1994	306	n/d	I-III	SSM	71	5.2	8.8
Kim et al.	2010	368	n/d	I-IIIA	SSM	67	0.8	n/d
Eriksen et al.	2011	300	T1 - T4	n/d	SSM	144	8.2	16.4
Romics Jr. et al.	2011	253	Tis - T4	0-IIIB	SSM	119	2.9	8.2

Footnote: For tumour staging Seventh Edition 2010 AJCC (American Joint Committee on Cancer) classification was applied. If true local recurrence was not differentiated from regional recurrence) n/d was inserted to local recurrence and the published recurrence rate is entered as loco-regional recurrence. Prophylactic mastectomies were not considered and removed from analysis.

n/d = not disclosed; SS = skin-sparing; Subcut = subcutaneous; M = mastectomy; Recur = recurrent.

4.1.6. Novel findings

1. Our study has clear and detailed oncological follow-up data, of large number of unselected patients and one of the longest median follow-ups in the published literature.[141, 1482]
2. Our cohort, which is based on an oncologically unselected group of patients, had a 2.9 per cent local and 8.2 per cent locoregional recurrence rate.
3. Thus, we believe that offering IBR to all women requiring mastectomy is an oncologically safe approach and, as a result, SSM combined with IBR can be offered for all breast cancer patients who require mastectomy, even for patients with more advanced breast cancer.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Ten-year follow-up of skin-sparing mastectomy followed by immediate breast reconstruction.
Romics L Jr, Chew BK, Weiler-Mithoff E, Doughty JC, Brown IM, Stallard S, Wilson CR, Mallon EA, George WD.
British Journal of Surgery. 2012 Jun;99(6):799-806.

Oncologic safety of skin-sparing mastectomy followed by immediate breast reconstruction: rate and localization of recurrences, and impact of reconstruction techniques
Romics L Jr, Stallard S, Weiler-Mithoff E.
Orvosi Hetilap. 2013 Feb 3;154(5):163-71. Hungarian.

Long-term oncological safety of delayed breast reconstruction compared to a cohort of immediate reconstruction.
Romics L, Weiler-Mithoff E, Mallon E, McLellan D, Dolan R, Mansell J, Ray A
Proceedings of the 12th Congress of the European Society of Plastic, Reconstructive and Aesthetic Surgery – ESPRAS 2014. 99-103. ISBN 978-88-7587-714-9.

4.2. How to benchmark the oncological safety of oncoplastic breast conservation surgery

4.2.1. Introduction

The oncological safety of OBCS is debated owing to the lack of high-level evidence; and prospective randomized trials are unlikely to be ever undertaken given the complex ethical considerations.[3] The current evidence for the oncological safety of OBCS is largely based on single-institution uncontrolled retrospective studies along with a few comparative studies where OBCS outcomes are compared to simple WLE or quadrantectomy.[13-17, 32, 36-38, 43, 44, 46, 149-155] The majority of studies showed similar pathological characteristics in terms of size, grade, subtype, hormone receptor expression and axillary node metastasis,[17, 19, 36, 38, 39] although some demonstrated that larger tumour size, presence of invasive cancer and axillary nodal metastasis were more common following OBCS.[32, 37, 153] In these analyses OBCS was compared with WLE exclusively, but a comparison to mastectomy may have been appropriate, too, since more advanced pathology was demonstrated after OBCS.

At present it is not clear what the best control group is for OBCS. The majority of oncoplastic breast surgeons believe that patients who would have conventionally required mastectomy may now be considered for breast conservation using oncoplastic techniques. While there is little evidence for this hypothesis investigation of this theory is desirable as it would mean that we can provide yet another treatment option for our breast cancer patients keen to keep their breast. In order to give accurate oncological outcomes, it is important to determine if breast cancer pathology in patients treated with OBCS are comparable to patients treated with mastectomy or simple WLE. Hence, it is important to determine if postoperative pathology in patients treated with OBCS are similar to WLE or mastectomy.

4.2.2. Aim

In this study, we compared postoperative histopathological characteristics of OBCS patients with WLE and mastectomy (Ms) with or without immediate reconstruction (IR) in order to determine who OBCS should be compared when oncological safety is measured.

4.2.3. Methods

Details of patients treated with OBCS are recorded prospectively into a standardised institutional database in two of the Glasgow breast units (Victoria Infirmary and Western Infirmary). Patients treated with OBCS between June 2009 and November 2012 were considered for inclusion in the study arm. In the control groups, patients treated with WLE or Ms±IR were identified from the West of Scotland Managed Clinical Networks (Breast Cancer) database. All breast cancer patients who underwent WLE or Ms±IR in the Victoria Infirmary between January 2009 and December 2011 were included in the control arms (this unit gave the majority of patients to the study arm). Each group of patients were consecutive. Clinical records of the patients were analysed for demographic, tumour and treatment characteristics. Patients with previous ipsilateral or contralateral DCIS or breast cancer were excluded.

An oncoplastic breast surgeon, or a breast and a plastic surgeon decided the indication and technique of OBCS, as detailed previously.[152] Oncoplastic technique was determined by patients' anatomy, preferences and tumour location, which resulted in a variety of methods applied. Patients who underwent significant volume excision followed by volume displacement technique accompanied by adequate skin envelope reduction, or true volume replacement technique were included in the OBCS study group (level II oncoplastic techniques as defined by Clough et al).[102] Simple reshaping such as dual plane mobilization without skin reduction was listed under WLE, since this technique is routinely performed for smaller lesions in order to prevent deformity. After simple WLE four quadrant cavity shavings were taken in a routine manner from the tumour bed [156]. Since the tumour bed is significantly larger after OBCS than WLE, cavity shavings were taken less often after oncoplastic excision. Excision margin was considered clear if the closest margin to the excision plane was at least 1 mm with invasive cancer or 2 mm with DCIS. Radiotherapy, chemotherapy and hormone therapy were administered according to evidence-based guidelines of the Beatson West of Scotland Cancer Centre.

The commonly described histopathological characteristics of patients treated with OBCS versus WLE or Ms with or without IR were compared with Chi square and Fisher's exact tests. Median age of the study group patients was compared to the two control groups using Mann-Whitney test. Adjuvant radiotherapy, chemotherapy and endocrine therapy were compared with Fisher's exact test. For all analyses, results were considered statistically significant if the p value was .05 or less. Statistical calculations were performed using SPSS® Statistics version 19.0 (SPSS, Chicago, Illinois, USA).

4.2.4. Results

Altogether 1000 patients' data were analysed. Of those 119 patients were treated with OBCS, 600 patients had WLE and 281 patients underwent Ms±IR. The median age of patients treated with OBCS was 53 (range 24-79) years. Patients who had WLE or Ms±IR were significantly older with a median age of 61 (31-88) ($p<0.001$) and 62 (28-95) ($p<0.001$) years, respectively.

The majority of patients had invasive ductal carcinoma in all three groups (OBCS: 78.1 per cent; WLE: 71.2 per cent; Ms±IR: 72.2 per cent) followed by lobular cancer and other types of invasive carcinomas (**Table 7**).

Table 7. Comparison of histological characteristics of patients treated with OBCS, WLE and Ms.

Characteristics	OBCS (%)	WLE (%)	P value	Mastectomy (%)	P value
Histological type					
DCIS	10 (8.4)	98 (16.3)	=0.03	32 (11.4)	=0.632
Ductal/NST	93 (78.1)	427 (71.2)		203 (72.2)	
Lobular	12 (10.1)	36 (6)		32 (11.4)	
Other	4 (3.4)	39 (6.5)		14 (5)	
Tumour size					
T1	48 (44)	420 (83.7)	<0.001	106 (42.6)	=0.138
T2	58 (53.2)	79 (15.7)		122 (49)	
T3	3 (2.8)	3 (0.6)		21 (8.4)	
Grade[1]					
1	8 (7.3)	97 (19.4)	<0.001	11 (4.6)	=0.497
2	40 (36.7)	274 (54.6)		102 (42.3)	
3	61 (56)	128 (26)		128 (53.1)	
Involved nodes					
0	71 (65.7)	414 (82.5)	<0.001	141 (56.6)	=0.175
1-3	25 (23.2)	71 (14.1)		63 (25.3)	
>3	12 (11.1)	17 (3.4)		45 (21.5)	
ER					
Positive	86 (78.9)	444 (88.4)	=0.007[2]	197 (78.8)	=1[2]
Negative	23 (21.1)	58 (11.5)		52 (21.2)	
PR					
Positive	72 (66)	389 (77.5)	=0.009[2]	161 (64.4)	=0.904[2]
Negative	37 (34)	113 (22.5)		88 (35.6)	
HER-2					
Positive	17 (15.6)	42 (8.4)	=0.058[2]	44 (17.7)	=0.533[2]
Negative	92 (84.4)	460 (91.6)		205 (82.3)	

DCIS – ductal carcinoma *in situ*; NST – no special type; ER – oestrogen receptor; PR – progesterone receptor; HER-2 – Human Epidermal Growth Factor Receptor 2; [1]No grade was given in two patients who had WLE and 8 patients with mastectomy due to complete pathological response after neo-adjuvant chemotherapy. [2]Fisher's exact test. OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction.

The proportion of patients with DCIS was higher in patients treated with WLE (16.3 per cent) compared to patients who underwent OBCS (8.4 per cent) ($p=0.03$), but the latter was not significantly different from Ms±IR (11.4 per cent). While most of the patients were diagnosed

with T1 cancers at histopathology after WLE (83.7 per cent), T2 cancers were the most common after OBCS and Ms±IR. Tumour size, in general, was significantly smaller in patients treated with WLE as opposed to OBCS ($p<0.001$), but it was similar after OBCS and Ms±IR. Tumour grade in patients treated with OBCS and Ms±IR was relatively similar. Although grade 3 cancers were the most prevalent in these groups, grade 2 cancers were the most common in patients who had WLE ($p<0.001$). Likewise, axillary status was similar in patients who had OBCS and Ms±IR, but significantly fewer nodes were involved in patients who had WLE when we compared to OBCS ($p<0.001$). Similar findings were evident in hormone receptor expression, too. While ER and PR expressions were almost identical in patients with OBCS and Ms±IR, they were significantly higher in the WLE group in comparison to OBCS ($p=0.007$ and 0.009, respectively). Lastly, HER-2 expression followed a similar trend being similar in patients who had OBCS and Ms±IR, and lower in patients treated with WLE than OBCS ($p=0.058$). Hence, the same trend was found in all common histological characteristics, namely that patients treated with OBCS were similar to patients treated with Ms±IR, but they were different from patients who underwent WLE (**Table 7**).

The majority of patients undergoing OBCS were treated with volume displacement techniques (103 of 119). Of those, 81 underwent Wise pattern reduction, 16 patients had a Benelli-type “round-block” breast reduction, 3 patients were treated with a “racquet-type” excision, while Lejour, Grisotti and “melon slice” reduction techniques were applied in one patient each. 17 patients had volume replacement oncoplastic conservation with thoracoepigastric flap in 10, breast matrix rotation in 5 and thoracodorsal artery perforator (TDAP) flap in one patient. 51 of the 119 patients underwent simultaneous symmetrisation surgery of their contralateral breast with standard breast reduction techniques.

The rate of incomplete excision margins after OBCS was similar to patients treated with WLE (13.4 per cent vs. 13.2 per cent; $p=0.883$). Of the 16 patients, who had incomplete margins after OBCS, 14 underwent completion mastectomy and two had re-excisions. 8 of the 14 patients who underwent completion mastectomy opted for immediate reconstruction. Completion mastectomy rate after OBCS was significantly higher than that of WLE (11.8 per cent vs. 5.5 per cent; $p=0.023$). Adjuvant radiotherapy was given to similar proportion of patients after OBCS and WLE (**Table 8**).

Table 8. Details of adjuvant radio-, chemo- and endocrine therapy of patients treated with OBCS, WLE and Ms±IR

	Radiotherapy (%)				Chemotherapy (%)		Endocrine therapy (%)	
	all patients	P =	invasive	P =	invasive	P =	invasive	P =
OBCS	118 (99.1)	n/a	109 (100)	n/a	71 (65.1)	n/a	83 (76.1)	n/a
WLE	578 (96.3)	0.153	490 (97.6)	0.138	134 (26.7)	0	454 (90.4)	0.001
Ms±IR	119 (42.3)	0	119 (47.8)	0	135 (54.2)	0.063	214 (85.9)	0.032

P – statistical difference vs. OBCS. OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction.

There was no difference between the numbers of patients who received chemotherapy after OBCS and Ms±IR, but slightly more patients received endocrine therapy after mastectomy than OBCS (**Table 8**). Neoadjuvant chemotherapy was given to 5.5% of patients before OBCS, 1.9% of patients before WLE and 9.6% of patients before mastectomy. Neoadjuvant endocrine therapy rate was 1.8%, 1.6% and 7.5% before OBCS, WLE and Ms±IR, respectively.

4.2.5. Discussion

The evidence base for oncoplastic breast conservation is limited. Most studies are single-centre observational studies with quite small sample sizes. 15 comparative studies have been published which report on results following OBCS (**Table 9**).[17-19, 32, 36, 38, 39, 77, 152, 153, 157-159] Of those, 9 papers reported various aspects of oncological outcomes,[17, 18, 32, 36-39, 152, 153] but recurrence rates and survival – the ultimate measures of oncological safety – were detailed in three comparative studies only.[18, 32, 38] OBCS was compared to standard breast conservation techniques (WLE or quandrantectomy) in almost all studies (**Table 9**).

Table 9. Comparative studies analysing outcomes of OBCS.

First author	Year	No. of cases		Surgery control arm	T2 + T3 cancers (%)		Objectives	Outcomes
		OBCS arm	Control arm		OBCS arm	Control arm		
Chakravorty et al.	2012	150	440	WLE	40.7	34.8	margins	OBCS better
							survival	no difference
Kahn et al.	2013	31	66	WLE	77.4	n/d	time to chemo-therapy	no difference
			56	Ms				
			16	MsIR				
Kaur et al.	2005	30	30	quadrant-ectomy	20	16.7	margins	OBCS better
Giacalone et al.	2006	31	43	quadrant-ectomy	54.9	41.9	margins	OBCS better
Gulcelik et al.	2011	101	52	reduction	n/d	n/d	complicat.	no difference
Veiga et al.	2011	45	45	WLE	71.1	66.7	aesthetic results	OBCS better
Veiga et al.	2010	45	42	WLE	n/d	n/d	quality of life	OBCS better
Down et al.	2013	37	121	WLE	n/d[1]	n/d[1]	margins	OBCS better
							complicat.	no difference
Mazouni et al.	2013	45[2]	214[2]	WLE	28.9[3]	20.1[3]	margins	no difference
							survival	no difference
Lima et al.	2013	36	102	WLE	n/d	n/d	cost of surgery	OBCS more expensive
Gulcelik et al.	2013	106	162	quadrant-ectomy	n/d	n/d	margins	no difference
							survival	no difference
Tenofsky et al.	2014	58	84	WLE	n/d	n/d	margins	no difference
							complicat.	no difference
							time to adj.	no difference
Peled et al.	2014	37[2]	64[2]	MsIR	n/d	n/d	complicat.	OBCS better
Mátrai et al.	2014	60	60	WLE	36.5	21.6	margins	WLE better
							complicat.	no difference
							time to adj.	no difference
Imahiyerobo et al.	2014	64	56	BBR	n/d	n/d	complicat.	no difference
Mansell et al.	2015	119	600	WLE	51.3	13.7	margins	no difference
			281	Ms ± IR		50.9	survival	no difference

[1] The difference between mean tumour sizes of OBCS vs. control patients was significant. [2] Patients received neoadjuvant chemotherapy. [3] Tumour size greater then 3 cm.

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction; complicat. – complications; adj. – adjuvant treatment; BBR – bilateral breast reduction.

Tumour size was similar to standard breast conservation except for three papers.[32, 37] Other pathological characteristics were comparable, too, except for tumour grade, oestrogen receptor expression and axillary metastasis, each in three separate studies.[18, 32, 153] These similarities suggest that OBCS was offered to patients who could have been treated with WLE, but patients with more advanced cancers were not considered suitable for OBCS. Unfortunately, none of the authors reported multifocality, DCIS size or breast volume, which could have explained the application of oncoplastic techniques. In addition, the relatively frequent use of level 1 oncoplastic techniques defined by Clough et al.[102] may have diminished differences in terms of tumour size between OBCS and standard breast conservation groups, since level 1 oncoplastic techniques allow minor corrections of relatively smaller defects only. No reference was available for the level of oncoplastic techniques applied in the comparative studies except for one.[18]

We found striking similarities between OBCS and mastectomy patients' histopathological results, which are in sharp contrast with the relevant published data. In our study, patients treated with OBCS had more advanced tumours compared to those who were treated with WLE. In fact, patients who underwent OBCS had similar tumour size, grade, nodal status and hormone receptor expression to patients who underwent Ms±IR (**Table 7**). This supports the idea that patients conventionally treated with mastectomy can be offered breast conservation by using oncoplastic techniques. More importantly the similarities in pathology of patients treated with OBCS and Ms±IR indicate that patients treated with Ms±IR should be considered as a separate control group. Hence, it is important to involve mastectomy patients in comparative analyses of oncological outcomes following OBCS.

The weakness of our study was that indications for OBCS, WLE and Ms±IR were not recorded prospectively. Hence the argument that OBCS was offered to patients who would have been treated with mastectomy conventionally was based on postoperative tumour characteristics only, but it did not include preoperative tumour size, patients' anatomy and preferences. Similarly, the argument that we offered OBCS with wider indications in contrast with other breast units is supported by the comparison of postoperative pathological characteristics only (**Table 7**). Retrospectively, a reduction in the rate of mastectomies in association with an increase in OBCS could have further supported the above, but a study with an even higher patient number would have required to prove it. A prospective study is awaited to determine whether OBCS can be considered as an alternative to mastectomy in selected patients.

The oncological safety and principles of breast conservation surgery are based on historical prospective randomised controlled trials, which compared the oncological outcome of mastectomy to breast conserving surgery followed by adjuvant radiotherapy.[11, 12, 24, 25, 28, 160] Results from these trials, however, may not be applicable for OBCS as the majority of patients included had small breast tumours while patients who are treated with OBCS often have larger breast tumours hence the requirement for the oncoplastic technique.[17-19, 152] While over half of the patients treated with OBCS had T2-T3 cancers in our as well as several other studies (Table 3),[13-17, 20, 21, 32] the evidence from the classic prospective randomized trials may not fully support that cancers with such sizes can be safely treated with breast conservation.[161] In fact, altogether only 311 patients with pathological T2 cancer size were randomized into the arm of breast conservation with radiotherapy in the trials published by von Dongen et al and Poggi et al.[24, 25] Although 288 patients were followed-up in the same arm of the trial published by Fischer et al, the tumour size was only 2.1 – 4 cm.[26] Further, patients with T1 cancers only were randomized in the trials by Veronesi et al and Arriagada et al.[11, 28] Hence, there is no robust evidence that patients with cancer > 4 cm can be safely treated with breast conservation, and the oncological safety of breast conservation for T3 cancers has not been examined in a randomized controlled trial yet.

In this study we had no intention to analyse recurrence rates, since a less than 5-year follow-up would be entirely meaningless to determine oncological safety. Ultimately, a comparative analysis of local, locoregional and distant recurrence rates in between these three groups of patients will determine if OBCS can be offered for more advanced cancers, too. We are convinced, however, that both WLE and mastectomy patients' recurrence rates need to be involved in the comparison with OBCS, when OBCS is offered for relatively more advanced cancers. From a pragmatic point of view, local recurrence rates of OBCS should be compared to simple WLE, while distant recurrence rates should be related to mastectomy patients, if postoperative histopathological data indicate so.

4.2.6. Novel findings

1. Striking similarities were found between OBCS and mastectomy patients' histopathological results.
2. Patients who underwent OBCS had similar tumour size, grade, nodal status and hormone receptor expression to patients who underwent Ms±IR.

3. This supports the idea that patients conventionally treated with mastectomy can be offered breast conservation by using oncoplastic techniques.
4. It is important to involve mastectomy patients in comparative analyses of oncological outcomes following OBCS.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

How to compare the oncological safety of oncoplastic breast conservation surgery - to wide local excision or mastectomy?
J Mansell, E Weiler-Mithoff, J Martin, A Khan, S Stallard, J C Doughty, **L Romics**.
Breast. 2015 Aug;24(4):497-501.

4.3. Impact of oncoplastic surgery on the timely commencement of adjuvant therapy

4.3.1. Introduction

The evidence for oncological safety of OBCS is relatively vague.[5, 16] Studies focus on recurrence rates and survival data almost exclusively, but the evidence reported is mostly based on single centre retrospective analyses with relatively low patient numbers and no control arms.[13-16, 20, 43, 44, 61-64, 149] However, there is hardly any evidence on immediate postoperative oncological safety of OBCS, which includes timely commencement of adjuvant systemic and / or locoregional treatments.

Depending on the technique of OBCS applied, procedures can be complicated and lengthy, and potentially associated with relatively high postoperative complication rates [16, 43-46]. Some surgeons and oncologists are concerned that OBCS may delay adjuvant systemic and locoregional treatment and compromise prognosis.

4.3.2. Aim

In this study, we analysed the effect of OBCS on the timing of starting adjuvant chemotherapy in breast cancer patients, and compared that with other methods of breast cancer surgery such as simple wide local excision, mastectomy and mastectomy with immediate breast reconstruction.

4.3.3. Methods

Prospectively maintained oncoplastic breast surgical databases of the Victoria and Western Infirmary Glasgow were searched to identify patients who underwent OBCS followed by adjuvant chemotherapy between August 2008 and December 2011. The following objectives were prospectively recorded in these databases: age, risk factors for developing wound healing problems (co-morbidities, BMI and smoking habit), breast (brassiere) size, tumour location, preoperative radiological tumour size, oncoplastic technique and any synchronous or further surgical intervention, pathology, (neo)adjuvant treatment, postoperative complications, locoregional and distant recurrence. Patients treated with neoadjuvant chemotherapy were excluded from the analysis. Clinical records for eligible patients were analyzed for

demographic, oncological and treatment characteristics. Patients of control arms were identified from the Victoria Infirmary Glasgow database of similar time period (December 2009 – September 2011). All patients treated either with wide local excision (WLE), mastectomy (Ms) or mastectomy with immediate reconstruction (MsIR) followed by adjuvant chemotherapy were considered for analysis. Axillary surgery (sentinel node biopsy, four-node sampling, axillary clearance) made no difference in eligibility in any of the groups. Patients in the study as well as the control groups were consecutive.

In order to determine the effect of surgery on starting of adjuvant chemotherapy the time elapsed between multidisciplinary decision on adjuvant treatments (including to offer chemotherapy) and delivery of the first cycle of adjuvant chemotherapy was checked. This time period was determined using the records of the breast multidisciplinary team meetings and the Pharmacy of the Beatson West of Scotland Cancer Centre. Time of multidisciplinary decision was applied in order to standardise initial time point in each patient of the study as well as control groups. Standardisation was necessary because surgical treatment may have involved multiple interventions in all groups of patients, of which the procedures compared (OBCS, WLE, Ms, MsIR) were not necessarily the last surgery in the course of surgical treatment. Hence false delays due to subsequent oncological procedures were avoided, but delays due to surgical complications of any reason were included in the measurement of time to chemotherapy.

Kruskall-Wallis test was used to perform a combined statistical analysis involving the study group and the three control groups. Arms were compared separately to one another using Mann-Whitney U test. For all analyses, results were considered statistically significant if the p value was .05 or less.

Finally, a literature search was carried out to identify studies of breast cancer patients treated with OBCS and determine if any delay to adjuvant therapy was recorded. Articles were identified by searches of MEDLINE and PubMed databases using the terms “oncoplastic” or “therapeutic mammaplasty” and “breast cancer” and “adjuvant” and “treatment” or “therapy” and “chemotherapy” or “radiotherapy”. Studies identified were screened for those that focused on oncologic outcomes after OBCS and references of each article were further scrutinized to include all relevant published data.

4.3.4. Results

169 breast cancer patients were identified from the databases altogether, who received adjuvant chemotherapy after surgical treatment.

Median age of patients treated with OBCS (n=31) was 50 (24-78) years, median BMI was 26 (21-46) and breast (brassiere cup) size was an E (A-JJ) cup. Tumours were located mainly in the upper-outer (n=13) and lower-outer quadrants (n=7) of the breast. Median size of the largest diameter of the radiological abnormalities on preoperative imaging was 30 (17-70) mm. Majority of oncoplastic resections were done with volume displacement techniques (**Table 10**).

Table 10. Oncoplastic breast surgical techniques applied in relation to radiological tumour size and location, body habitus and contralateral symmetrising surgery.

Oncoplastic techniques (n=)		Median size of radiological abnormality (mm)	Location of tumours[1]	Median breast (brassiere cup) size	Median body mass index (BMI)	Contralateral symmetrisation[2] (n=)
All patients	**31**	**30 [15-70]**	**OUQ: 14 UIQ: 4 LOQ: 6 LIQ: 4 C: 3**	**E [A-JJ]**	**26 [21-46]**	**17**
Volume displacement	**25**	**30 [15-70]**	**OUQ: 13 UIQ: 3 LOQ: 3 LIQ: 3 C: 3**	**E [A-JJ]**	**26 [21-46]**	**17**
Wise pattern reduction	16	32.5	OUQ: 8 UIQ: 2 LOQ: 2 LIQ: 3 C: 1	F	26	16
Benelli (round block) reduction	6	26	OUQ: 3 UIQ: 1 C: 2	B	25	0
Lateral excision & nipple recentralisation	3	30	OUQ: 2 LOQ: 1	EE	26	1
Volume replacement	**6**	**24.5 [15-70]**	**OUQ: 1 UIQ: 1 LOQ: 3 LIQ: 1**	**E [B-FF]**	**28.5 [24-31]**	**0**
Breast matrix rotation	3	34	OUQ: 2 LOQ: 1	E	30	0
Thoracoepigastric flap	2	16.5	LOQ: 1 LIQ: 1	CC	27	0
V-Y advancement flap	1	29	UIQ: 1	E	27	0

[1] U: upper; O: outer; I: inner; Q: quadrant; C: central. [2] Contralateral symmetrisation for aesthetic reasons. One further patient with bilateral breast cancer underwent contralateral surgery (skin-sparing mastectomy and immediate autologous reconstruction with extended latissimus dorsi flap).

27 patients had sentinel node biopsy and four patients had axillary clearance carried out at the time of OBCS. One of these four patients underwent previous bilateral sentinel node biopsy due to bilateral breast cancer requiring skin-sparing mastectomy, immediate reconstruction with axillary clearance and contralateral OBCS. Median weight of the resected tissue on pathology was 134 g [22-950] and the median pathological tumour size of the invasive component was 24 mm [10-62] (**Table 11**).

Table 11. Tumour characteristics of patients treated with OBCS.

Tumour type	n=	Tumour size	n=	Tumour grade	n=
Ductal	29	T1	7	G1	0
Lobular	2	T2	21	G2	8
Mucoid[1]	1	T3	3	G3	23

ER / PR expression	n=	HER2 expression	n=	Nodal metastasis	n=	Multi-focality	n=
ER / PR positive	20	HER2 positive	10	Node positive	12	Unifocal	24
ER / PR negative	11	HER2 negative	21	Node negative	19	Multifocal	7[2]

[1] One patient with multifocal cancer also had a mucoid cancer. [2] Three patients had three cancers of these seven multifocal cancers

Ten patients treated with OBCS needed further surgery after their initial oncoplastic resection (**Table 12**). Four patients had incomplete resections margins. Three of them were treated with completion mastectomy and immediate breast reconstruction, and one patient underwent wider excision. Another four patients with metastatic sentinel node(s) underwent axillary clearance as a second operation. Further two patients needed to be taken back to theatre for complications and required debridement and secondary closure for fat necrosis and partial loss of thoracoepigastric flaps.

Table 12. Summary of further surgeries of patients underwent OBCS.

Further surgeries after OBCS	**(n=)**
All patients	**31**
Further surgery needed	**10**
Axillary node clearance	4
SSM, IR followed by chemotherapy	2
SSM, IR, ANC after chemotherapy	1
Debridement and secondary closure, ANC	1
Debridement and secondary closure	1
Wider excision, ANC after chemotherapy	1

SSM: skin-sparing mastectomy, IR: immediate breast reconstruction, ANC: axillary node clearance

In order to investigate if OBCS (n=31) compromises timely commencement of adjuvant chemotherapy breast cancer patients treated as described above were compared to relevant control groups. Control groups of patients treated either with wide local excision (n=66), mastectomy (n=56), or mastectomy with immediate reconstruction (n=16) were chosen consecutively from the same institute. Time between multidisciplinary team decision about adjuvant treatment after surgical treatment and delivery of first cycle of chemotherapy was compared in between the groups. The median time of commencement of adjuvant chemotherapy after OBCS was 29 days [16-58], which is comparable with the time after wide local excision (29.5 days [15-105]; p=0.433), mastectomy (29 days [15-57]; p=0.800) and mastectomy followed by immediate reconstruction (31 days [15-58], p=0.405). The difference between the times after OBCS compared to the times of any of the three control groups were insignificant, which suggest that OBCS does not cause a delay in the commencement of adjuvant chemotherapy. Furthermore, a combined analysis involving all the four groups demonstrated no significant difference in between those, too (p=0.524). This means that none of these four modalities of surgical breast cancer treatment influences adversely the timing of adjuvant chemotherapy when we compare one to the other three groups. Inter-group analysis further confirmed the above showing no significant differences in between the three control groups when compared to one another (WLE vs. Ms: p=0.233; Ms vs. MsIR: p=0.260; WLE vs. MsIR: p=0.663).

4.3.5. Discussion

The oncologic principles applied for OBCS is based on studies comparing outcomes of breast cancer patients treated with traditional conservation surgery plus radiotherapy to mastectomy [11, 12]. Papers published on the oncological safety of OBCS focus on recurrence rates and rarely report data on the effect on timing of adjuvant therapy. **Table 13** summarizes papers which disclose any data on the effect of OBCS on timing of adjuvant therapy.[13-16, 20, 43-46, 61-64]

Table 13. Summary of evidence for delivery of adjuvant chemotherapy after OBCS.

Year	First author	Country / Institution	No. of patients	Tumour size	Adjuvant chemotherapy received No. of patients (% of patients)	Delay in adjuvant therapy	Delayed adjuvant therapy No. of patients (% of patients)
1998	**Nos et al.**	France / Institut Curie Paris	50	Tis – T4	5 (10%)	Yes	3 (6%)
2002	**Losken et al.**	USA / Emory University Hospital	20	Tis - n/d, benign	n/d	No	0
2003	**Clough et al.**	France / Institut Curie Paris	101	T1 – T4	0	Yes	4 (4%)
2003	**Spear et al.**	USA / Georgetown University Hospital	22	n/d	22 (100%)	No	0
2005	**McCulley et al.**	UK / Nottingham City Hospital	50	Tis – n/d	23 (46%)	No	0
2006	**Munhoz et al.**	Brazil / University of Sao Paolo	74	T1 – T2	22 (29.7%)	No	0
2006	**Thornton et al.**	USA / University of Kentucky	6	T1 – T2	0	No	0
2007	**Kronowitz et al.**	USA / M.D. Anderson Cancer Ctr.	41	Tis – T2	18 (44%)	No	0
2007	**Losken et al.**	USA / Emory University Hospital	63	Tis - n/d, benign	n/d	No	0
2007	**Rietjens et al.**	Italy / European Institute of Oncology	148	T1 – T3	89 (60%)	No	0
2010	**Meretoja et al.**	Finnland, Helsinki Univ. Ctr. Hosp.	90	Tis – T3	60 (67%)	Yes	2 (2%)
2010	**Fitoussi et al.**	France / Institut Curie Paris	540	T1 - T3	n/d	Yes	10 (1.9%)
2010	**Song et al.**	USA / Emory University Hospital	28	Tis	n/a	No	0
2012	**Romics Jr. et al.**	UK / Glasgow University Hospitals	31	T1 – T3	31 (100%)	No delay compared to adequate control arms	

n/d – not disclosed, n/a – not applicable

Reported data was hard to interpret since no explanation was given how the time to adjuvant therapy was compared. While two papers reported data on higher patient numbers,[16, 44] only a fraction of patients received adjuvant chemotherapy after OBCS in most studies.[13, 15, 45, 61, 64] Some authors did not even disclose the number of patients when they report on the time of delivery of adjuvant therapy after OBCS.[43, 46, 62] Nevertheless, most of the studies reported no delay,[13, 16, 20, 45, 46, 61-64] while a few showed some delay[14, 15, 43, 44] in time to adjuvant therapy.

Time between surgery and commencement of adjuvant chemotherapy is only one aspect of oncological safety after OBCS. Patients who undergo complex surgery, such as OBCS, may be more susceptible to immunosuppression caused by chemotherapy. This may increase surgery related complication rate, which can lead to an internal delay in between chemotherapy cycles, requiring frequent administration of expensive pegylated granulocyte colony-stimulating factor, or repeat hospital admissions. While the complication rate was 45% in our patients treated with OBCS (oral antibiotics for cellulitis, n=5; delayed wound healing, n=3; prolonged seroma leakage, n=2; postoperative haematoma, n=2; debridement and secondary closure, n=2), it was not significant enough to lead to a delay in the start of adjuvant chemotherapy. However, we did not measure internal delays, overall cost of chemotherapy or hospital readmission rates, which may be influenced by these complications, hence it needs to be elucidated in the future.

4.3.6. Novel findings

1. The evidence for any potential delay of adjuvant chemotherapy after immediate breast reconstruction, however, is conflicting.
2. Even if some delay occurs, it is unlikely to influence the prognosis significantly after mastectomy and reconstruction.
3. Despite the poor evidence in the literature, nothing suggests that OBCS is not safe enough in terms of starting adjuvant therapy on time.
4. Our study provides evidence that OBCS does not lead to a delay in the commencement of adjuvant chemotherapy, when compared to three adequate control groups from the same institution and time periods.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Oncoplastic breast conservation does not lead to a delay in the commencement of adjuvant chemotherapy in breast cancer patients.
Kahn J, Barrett S, Forte C, Stallard S, Weiler-Mithoff E, Doughty JC, **Romics L Jr.**
European Journal of Surgical Oncology. 2013 Aug;39(8):887-91.

4.4. Radiological follow-up of oncoplastic breast conservations surgery

4.4.1. Introduction

Indications and outcomes of breast imaging after OBCS are influenced by the surgical technique as well as the postoperative complication rate.[162, 163] Extensive parenchymal manipulation, old age, high BMI, large tumour size and medical risk factors irreversible within short time increases complication rate up to 27% in OBCS patients.[13, 39, 64, 102, 162, 164]

So far, three studies only reported on imaging results after OBCS.[163, 165, 166] Two studies described imaging results after volume replacement OBCS only.[165, 166] One study showed imaging results after oncoplastic conservation with breast reduction techniques in comparison to standard wide excision.[163] Arguably, OBCS may not be directly comparable to standard surgical techniques, numerous comparative studies have already been published to benchmark emerging evidence of this relatively new technique against well-established standard breast surgery.[167, 168]

4.4.2. Aim

We did a retrospective analysis on postoperative imaging and biopsies, comparing the numbers, indications and outcomes of mammograms, breast ultrasound and MRI scans, and breast biopsies taken in the first two years after OBCS and WLE.

4.4.3. Methods

Patients treated with OBCS consecutively in two breast units (Victoria Infirmary and Western Infirmary in Glasgow) between May 2009 and December 2011 were enrolled in the analysis. Patients treated with standard WLE in the Victoria Infirmary breast unit between February and December 2010 were included in the control arm. Details of patients treated with OBCS are kept in a prospectively maintained institutional standardized database in two of the Glasgow breast units (Victoria Infirmary and Western Infirmary). In the control groups, patients treated with simple WLE were identified from the West of Scotland Managed Clinical Networks (Breast Cancer) database.

Patients were followed up the in the first 24 months of their postoperative period to analyse imaging and biopsies required during this period of time. Number, indication and outcome of these investigations were compared in between the two groups. In terms of follow-up, all patients in both groups were seen in the follow-up clinic for physical examination once a year. Bilateral mammograms were carried out routinely for follow-up. All patients had a bilateral mammogram 12 months after surgery. Majority of patients had their second mammogram 24 months after surgery, apart from a minority of patients in the OBCS group who were treated in the Western Infirmary (n=16), where the surgeons routinely arrange the second postoperative surveillance mammogram 36 months post surgery. The same group of radiologists in the department reported imaging in all patients. All radiology results were categorized according to BI-RADS (Breast Imaging Reporting and Data System) assessment categories published by the American College of Radiology.[169]

Statistical calculations were performed using SPSS® Statistics version 20.0 (SPSS, Chicago, Illinois, USA). For comparisons of overall number of imaging or biopsies the mean number of imaging or biopsies per patient was used, since the median value would be always 2 for mammograms and 0 for ultrasound, MRI and breast biopsies. Mean number of mammograms was adjusted to differences in mammographic follow-up between the two units. Two-tailed Mann-Whitney test was used to calculate statistical difference for median age and mean number of imaging or biopsies. Two-tailed Z-test was used to calculate difference in the proportion of patients who underwent ultrasound scans or biopsies in between the two groups. Differences were considered statistically significant when the p value was less than 0.05.

4.4.4. Results

211 patients were treated either with OBCS (n=83) or WLE (n=128) during the time period mentioned above. 11 patients were excluded from the OBCS and 10 patients from WLE group, because they required completion mastectomy for incomplete margins after breast conservation. A further patient was removed from the OBCS group who had a Grisotti flap for squamous cell carcinoma on her nipple requiring no follow-up imaging. Two further patients were excluded from the WLE group, because both of them died within the 2 years follow-up period (one of them was breast cancer related death). Hence, 71 patients were included in the study from the OBCS group, and 116 patients were involved from the WLE group.

Incomplete margin rate after OBCS was 16% (13/83), while the same was 18% 23/128) after standard WLE. Of these, two patients had to undergo wider excision and 11 patients had completion mastectomy in the OBCS group, while 13 patients had wider excision and 10 patients completion mastectomy in the WLE group.

Patients treated with OBCS were significantly younger than WLE with median age of 54 years (24-79) vs. 61 years (44-88) (p=0). Oncoplastic surgical techniques applied for oncoplastic conservation were mainly volume displacement techniques (n=61), volume replacement was used much less frequently (n=10). Contralateral symmetrisation was carried out in 29 patients (**Table 14**).

Table 14. Surgical techniques and symmetrisation rate in patients treated with OBCS

Classification of oncoplasty	**Surgical techniques**	**Patients**		**Symmetrisation**	
		number	% *	number	% **
Volume Replacement	Benelli	12	17	0	n/a
	Wise pattern	44	62	26	59
	Melon slice	1	1.4	1	100
	Tennis racquet	3	4.2	1	33
	Le Jour	1	1.4	1	100
Volume Displacement	Thoraco-epigastric	6	8.4	0	n/a
	Matrix rotation	3	4.2	0	n/a
	T-DAP	1	1.4	0	n/a

* Percentage of patients altogether. ** Percentage of patients within the given oncoplastic technique. Thoraco-epigastric: thoraco-epigastric flap. T-DAP: thoracodorsal artery perforator flap.

Further two patients were treated with bilateral breast cancers. The first patient had a Benelli type reduction mammoplasty on one side, and a skin-sparing mastectomy and immediate breast reconstruction with extended autologous latissimus dorsi flap on the contralateral side. The second patient was treated with bilateral reduction mammoplasties from Wise pattern incisions. In terms of postoperative complication rates, five patients (7%) required reoperation for complications in the OBCS group (debridement +/- grafting in three patients, re-closure of wound and evacuation of haematoma in one patient each). Three patients required reoperation for complications in the WLE group (2.6%), of these two patients needed evacuation of haematoma and one underwent incision and drainage of an abscess.

Patients treated with OBCS had more advanced malignant disease compared to patients who had standard WLE, which is mirrored by more invasive cancers, larger tumour size, higher tumour grade and more involved axillary nodes in the OBCS group (**Table 15**). Consequently, much more patients received chemotherapy in the OBCS group than in the WLE group (**Table 16**).

Table 15. Common histopathological characteristics of patients treated with OBCS.

Characteristics	OBCS (%)	WLE (%)
Histological type		
DCIS	3 (4.2)	18 (15)
Ductal/NST	60 (84)	86 (74)
Lobular	4 (5.6)	6 (5.2)
Other	4 (5.6)	6 (5.2)
Tumour size [1]		
T_{is}	3 (4.2)	18 (15)
T1	31 (44)	93 (81)
T2	32 (45)	5 (4.3)
T3	4 (5.6)	0
Grade [2]		
1	6 (8.8)	24 (24)
2	25 (37)	54 (55)
3	37 (54)	20 (20)
Involved nodes [2]		
0	43 (63)	85 (87)
1-3	21 (31)	11 (11)
>3	4 (5.9)	2 (2)
ER [2]		
Positive	54 (79)	90 (92)
Negative	14 (21)	8 (8.2)
PR [2]		
Positive	45 (66)	83 (85)
Negative	23 (34)	15 (15)
HER-2 [2]		
Positive	10 (17)	10 (10)
Negative	58 (85)	88 (90)

OBCS: oncoplastic breast conservation surgery; [1] one patient underwent neoadjuvant chemotherapy in each group, and had complete pathological response prior to OBCS; [2] invasive cancers only

Table 16. Adjuvant radio-, chemo- and hormonal therapy in patients treated with OBCS or standard WLE.

	Radiotherapy (%)	Chemotherapy (%) *	Endocrine therapy (%)
	DCIS + invasive ca.	invasive ca. only	invasive ca. only
OBCS	70 (99)	38 (56)	51 (75)
WLE	114 (98)	23 (23)	94 (96)

OBCS: oncoplastic breast conservation surgery; WLE: wide local excision; DCIS: ductal carcinoma *in situ*; ca.: cancer.
*one patient underwent neoadjuvant chemotherapy in each group.

Number of breast ultrasounds per OBCS patients was almost two-folds of the mean number of ultrasounds carried out in the WLE patients (OBCS: 0.394 ultrasound / patient (0-6) vs. WLE: 0.211 ultrasound / patient (0-2); p=0.116). However, the mean number of mammograms (OBCS: 2 mammograms / patient (0-3) vs. WLE: 1.914 (0-3); p=0.327) and breast MRI scans (OBCS: 0.028 / patient (0-2) vs. WLE: 0.069 (0-2); p=0.674) were similar in

the two groups. Finally, total number of imaging per patient was similar, too, in between the two groups (OBCS: 2.186 imaging / patient (0-8) vs. WLE: 2.146 (0-5); p=0.857).

In terms of number of patients who required breast ultrasound, significantly more patients required breast ultrasound in the OBCS group as opposed to the WLE group (OBCS: 20/71 patients vs. WLE: 17/116 patients; p=0.024). Altogether 29 ultrasounds were carried out in 71 patients treated with OBCS. Of those, 15 patients had one ultrasound, four patients required two ultrasound scans, while one patient had six breast ultrasounds. 19 breast ultrasounds were carried out in 116 patients who underwent WLE. In this group 15 patients had one ultrasound scan, and two patients required two ultrasound scans. "Indeterminate" or "suspicious" (BI-RADS category 3 or 4) ultrasound results were detected only in the OBCS group (OBCS: 6/29 ultrasound scans vs. WLE: 0/19 ultrasound scans; p=0.034), while all ultrasound scans were either "normal" or showed only "benign" changes after WLE (BI-RADS category 1 or 2) (**Table 17**).

Table 17. BI-RADS categories of postoperative mammograms, ultrasounds and breast MRI in patients who had OBCS and WLE.

	R1	U1	M1	R2	U2	M2	R3	U3	M3	R4	U4	M4
OBCS	3	1	0	109	22	2	2	5	0	2	1	0
WLE	0	2	0	218	17	6	3	0	1	0	0	0

Number of imaging is presented under various BI-RADS categories. R: mammogram; U: ultrasound; M: breast MRI. There was no BI-RADS category 5 result in any of these imaging modalities. OBCS: oncoplastic breast conserving surgery; WLE: wide local excision.

Common indications for breast ultrasound were lumps felt on clinical examination or suspicion of underlying collection in association with cellulitis and / or leakage through the wound in the OBCS group (**Table 18**).

Table 18. Indications, numbers, outcomes of postoperative ultrasound scans and consequent biopsies in patients treated with various oncoplastic surgical techniques

Indications for US	**US scans (n = number of US scans)**	**Outcome of US scans (n = BI-RADS category reports)**	**Biopsy (n = number of biopsies taken)**	**Patients (n = number of patients)**	**Surgical technique (n = number of cases)**
Lump	16	U4 (1) U3 (3) U2 (11) U1 (1)	4	11	Wise pattern (8) Matrix rotation (1) Thoraco-epig. (1) Le Jour (1)
Collection	8	U2 (8)	0	5	Wise pattern (4) Benelli (1)
Lumpy area	2	U3 (1) U2 (1)	2	2	Wise pattern (2)
Pain	2	U3 (1) U2 (1)	1	2	Benelli (1) Matrix rotation (1)
MMG calc.	1	U2 (1)	0	1	Thoraco-epig. (1)

US: ultrasound. Thoraco-epig.: thoraco-epigastric flap. MMG calc.: mammographic microcalcification.

Similar proportion of patients required breast ultrasound of those who had a volume displacement vs. volume replacement oncoplastic surgery (16/61 vs. 4/10; p=0.36), although there was a trend that patients with volume replacement require more ultrasound scans (**Table 5**). 9 patients underwent immediate symmetrisation surgery of the 20 patients who required breast ultrasound in the OBCS group. Of those, 7 patients required ultrasound on the treated breast, while two patients had ultrasound on the reduced side.

Significantly more patients required breast biopsy from the OBCS group than the WLE group (9/71 vs. 3/116; p=0.006). All of these patients underwent a core biopsy, except one patient who had a punch biopsy of the dermis. Indications for biopsies were a new distinct lump or a lumpy area in the majority of cases, and the biopsy confirmed fat necrosis in most patients (**Table 19**).

Table 19. Indications, numbers, and outcomes of postoperative biopsies in patients treated with oncoplastic or standard breast conserving surgery.

Indications for biopsy	**Patients (n = number of patients)**	**Outcome of biopsy (n = numbers of various histopathology reports)**	**Surgical technique (n = number of cases)**	**Previous imaging (n = BI-RADS category reports)**
Distinct lump	7	Fat necrosis (3) Edge of seroma (1) Fibrosis (1) Foreign body reaction (1) Normal (1)	OBCS - Wise pattern (4) OBCS - Benelli (1) WLE (2)	U4 (1) U3 (3) U2 (2)
Lumpy area	2	Fat necrosis (2)	OBCS - Wise pattern (1) OBCS - Benelli (1)	U2 (2)
MMG calc.	1	Fat necrosis (1)	OBCS - Wise pattern (1)	R4 (1)
Indeterminate US finding	1	Fat necrosis (1)	OBCS - Wise pattern (1)	U3 (1)
Dermatitis	1	Dermal inflammation (1)	WLE (1)	U1 (1)

OBCS: oncoplastic breast conserving surgery; WLE: wide local excision; MMG calc.: mammographic microcalcification; US: ultrasound.

Fat necrosis rate after OBCS was 18% on clinical examination, 15% with ultrasound, and 7% of those was confirmed on pathology (**Table 18 and 19**). One more biopsy was carried out in a patient treated with OBCS from her pelvic bone who underwent investigation for distant metastatic disease. This biopsy was normal, and it was not involved in the calculation.

4.4.5. Discussion

This study showed that OBCS was applied for more advanced malignant disease than standard WLE, which is consistent with our previously published results.[167] More ultrasound scans and biopsies were necessary after OBCS than simple WLE. These investigations were required for benign reasons, e.g. lumps, lumpiness or collections (**Table 18**). Ultrasonographic findings were mostly benign, but indeterminate and suspicious outcomes were also noted after OBCS (**Table 18**). Biopsy results were benign, too, fat necrosis being the most common finding. No local recurrence was diagnosed which is probably due to the relatively short follow-up time.[13,16]

Mammograms are not adversely affected after aesthetic breast reduction, which may imply that surveillance mammograms after OBCS would not be impeded, too.[170] Losken et al. demonstrated that "mammographic stabilisation" is delayed after OBCS compared to WLE, but overall mammographic findings including architectural distortion, cysts, and calcification are similar.[163] Monticciolo et al. showed in a historical study that mammographic findings are predict even after volume replacement with mini-LD flap.[165] Common mammographic changes visible after OBCS include parenchymal redistribution, dermal calcification along the skin

incisions and repositioned nipples, and fibrous bands extending to the nipple-areola complex.[170] Mammographic microcalcification is rarely a confounding factor after OBCS, unless it is followed or accompanied by autologous fat grafting. In those cases microcalcification can occur in 13% of patients, while oil cyst formation – a special form of fat necrosis – develops in up to 90% of patients.[171] In our study, the mean number of mammograms per patients was almost identical in the two groups. Microcalcification was found in two patients who had OBCS, but none after WLE. One of the two cases required biopsy, which showed fat necrosis.

Reduction mammoplasty, however, increases the development of fat necrosis and the incidence of masses requiring further imaging and biopsy ultimately.[172] This may indicate that OBCS – with volume displacement technique in particular – may contribute to the development of breast lumps or lumpy areas that need to be further investigated. In comparative studies of OBCS and WLE, an increased trend towards ultrasound was found after OBCS.[163, 173] Indeed, a significantly higher proportion of patients after OBCS required ultrasound in our study, too. Breast lumps or lumpiness were the indications for ultrasound scans in 62% of patients treated with OBCS (13/21) (**Table 18**). Finally, lumps or lumpy area were the indication for true-cut biopsy in all except one patient (6/7) in the OBCS group (**Table 19**).

Fat necrosis, as complication of OBCS, was reported between 6.3% and 26%.[13, 39, 64, 159, 162, 174] In fact, some suggested that the rate of fat necrosis was higher after OBCS than reduction mammoplasty or lumpectomy.[13, 39] However, the authors did not disclose that fat necrosis was clinical, radiological or pathological diagnosis in their series. In our study, the rate of fat necrosis was between 7% and 18%, depending on the way of diagnosis (**Table 18 and 19**). Clough et al. suggests that fat necrosis rate can be reduced by the integration of glandular density in the careful planning of oncoplastic technique.[102] Low-density breast tissue with a major fatty composition carries a higher risk of fat necrosis after extensive undermining, hence widespread dual plane mobilization should be avoided in these cases.[102]

The limitation of this study is that it reflects the practice of a relatively few surgeons and radiologists in two breast units. In fact, all patients who were treated with standard WLE were from one unit, which gave the majority of OBCS patients, too. In addition, this study reflects the relatively early phase of the learning curve for OBCS techniques, which became part of the routine practice since then. Hence, it is conceivable that in other units where the indications and applications of various OBCS practices developed earlier these differences in postoperative breast ultrasounds and biopsies have diminished earlier.

Indications for further investigation of postoperative lumpiness or distinct lumps in the operated breast may be subjective. While most surgeons would request at least a breast ultrasound scan, a fine needle aspiration or a true-cut biopsy may also be appropriate even if the clinical examination and imaging correlate fully. Surgeons' and radiologists' anxiety level are understandably higher at the initial phase of the learning curve of a new surgical technique. In addition, patients with a recent diagnosis of breast cancer can be very concerned about lumps in their treated breast explicably. It is conceivable that increasing experience and familiarity with postoperative findings after OBCS will decrease our anxiety, and postoperative investigations will be less frequent in the future.

In conclusion, patients treated with OBCS required significantly more ultrasound scans and consequent biopsies. New lumps or lumpiness were the commonest indications, and pathology confirmed fat necrosis in the majority of cases.

4.4.6. Novel findings

1. Reduction mammoplasty increases the development of fat necrosis and the incidence of masses requiring further imaging and biopsy ultimately. This indicate that OBCS – with volume displacement technique in particular – may contribute to the development of breast lumps or lumpy areas that need to be further investigated.
2. Patients treated with OBCS required significantly more ultrasound scans and consequent biopsies. New lumps or lumpiness were the commonest indications, and pathology confirmed fat necrosis in the majority of cases.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Imaging results following oncoplastic and standard breast conserving surgery
R Dolan, M Patel, E Weiler-Mithoff, J Mansell, S Stallard, JC Doughty, **L Romics Jr.**
Breast Care (Basel). 2015 Oct;10(5):325-9.

4.5. Long term oncological safety of therapeutic mammoplasty

4.5.1. Introduction

Majority of oncoplastic breast conservations is carried out with volume displacement techniques, which comprises of tumour excision followed by reshaping of the breast parenchyma as well as an adequate reduction of the breast skin-envelope.[102] This is commonly referred as oncoplastic reduction mammoplasty (ORM), or therapeutic mammaplasty.[164, 175] ORM is frequently accompanied by the reduction of the contralateral breast to improve symmetry.[62]

The evidence for oncological safety of ORM is relatively vague and prospective randomized trials are unlikely to be ever undertaken given the complex ethical considerations.[5, 16] ORM can be applied for large malignancies including those which were conventionally treated with mastectomy with relatively low incomplete excision rate.[22] It has also been demonstrated previously that ORM does not delay adjuvant chemotherapy, which further contributes to the oncological safety of this surgical technique.[168]

The current evidence for local and distal recurrence rates is largely built on single-institutional retrospective studies.[13-16, 20, 32, 38, 43, 44, 46, 61-63, 149-151, 154, 155, 175-178] Majority of these reports are based on relatively short follow-up time between 13 and 54 months.[13-15, 20, 32, 38, 43, 44, 46, 61-63, 150, 151, 154, 155, 175] There are only five studies that report true recurrence rates based on at least five years follow-up after oncoplastic breast conservation.[16, 149, 176-178] Three studies, altogether 299 patients' follow-up time extend beyond six years, which is the current evidence for long-term recurrence rates after breast conservation surgery involving oncoplastic techniques.[16, 177, 178]

4.5.2. Aim

We studied long-term, six-year recurrence rates in patients treated with ORM for invasive and non-invasive breast cancer.

4.5.3. Methods

Details of patients treated with ORM were recorded into a standardised institutional database. The following characteristics were recorded prospectively in the oncoplastic dataset: demographic data (age, BMI, brassiere size, risk factors for breast cancer and breast surgery), preoperative tumour size, pre- and postoperative pathology, surgical, oncological management, surgical complications, time and site of recurrence. The clinical records included in the oncoplastic dataset were analysed for demographic, tumour, treatment characteristics and recurrences. Missing data was retrospectively searched via case records and included in the analysis. Preoperative tumour size was determined as the largest diameter given on any preoperative imaging. Patients with previous ipsilateral or contralateral DCIS or breast cancer were excluded. All patients were diagnosed between August 2005 and September 2010.

An oncoplastic breast surgeon, or a breast and a plastic surgeon together decided the indication and technique of ORM, as detailed previously.[168] Oncoplastic technique was determined by patients' anatomy, preferences and tumour location. All patients were treated with oncoplastic reduction mammoplasty, when a significant volume excision was followed by reshaping of the breast parenchyma with volume displacement technique and accompanied by adequate skin envelope reduction (level II oncoplastic techniques as defined by Clough et al).[102] Simple reshaping such as dual plane mobilization without skin reduction was excluded, since this technique is routinely performed for smaller lesions in order to prevent deformity. Excision margin was considered clear if the closest margin to the excision plane was at least 1 mm with invasive cancer or 2 mm with DCIS. Radiotherapy, chemotherapy and hormone therapy were administered according to evidence-based guidelines of the Beatson West of Scotland Cancer Centre in the given time period.

Surgical, oncological, radiology and pathological reports were analysed for follow-up to determine the pattern and timing of recurrence up to April 2015. Length of follow-up was determined as time elapsed from first treatment. Patients were followed up every 12 months by surveillance mammogram and clinical examination, and abnormal clinical findings were further investigated as appropriate. Recurrences were documented by clinical examination, radiological tests and/or pathological assessment. Local and distant recurrence rates were the primary outcome of interest as these correlate with the overall oncological safety of ORM. The seventh edition of the American Joint Committee on Cancer staging system (2010) was used for tumour staging.[179]

For statistical calculations, two-tailed Mann-Whitney test was used to assess possible associations between preoperative tumour size and applied surgical technique or incomplete excision rates. Fisher's exact test was used to calculate associations between incomplete excision rate and oncoplastic technique. For all analyses, $P < 0.050$ was considered statistically significant. Statistical calculations were performed using SPSS® Statistics version 19.0 (SPSS, Chicago, Illinois, USA).

This study was designed and reported in line with the STROBE criteria.[180]

4.5.4. Results

A total of 65 patients treated with ORM were considered for the study, but six patients were excluded due to early loss of follow-up (shorter than 3 years), and further three patients were excluded for previous contralateral breast cancer. Hence, 56 patients were included in the follow-up finally. Their median age was 54 (range 27 – 79) years. The median length of follow-up was 72 (range 36 – 120) months for the whole cohort. The indication for ORM was invasive cancer in 52 patients and DCIS in four patients. Altogether, almost two-thirds of this cohort was diagnosed with stage II or III breast cancer (32 patients) (**Table 20**). Eight patients had multifocal invasive cancer.

Table 20. Tumour characteristics and overall, local and distant recurrence rates, based on first event of recurrence

PATIENTS		RECURRENCES		
		Overall	Local	Distant
	No.	No.	No.	No.
All patients	**50**	**4**	**1**	**3**
Invasive cancer	**46**	**3**	**0**	**3**
T1 *	16	0	0	0
T2	28	3	0	3
T3	2	0	0	0
G1 *	7	0	0	0
G2	16	1	0	1
G3	23	2	0	2
Ductal	43	2	0	2
Lobular	2	1	0	1
Mixed	1	0	0	0
Hormone rec +ve	33	3	0	3
Hormone rec -ve	13	0	0	0
Her-2 +ve	8	1	0	1
Her-2 -ve	38	2	0	4
Node +ve *	11	2	0	2
Node -ve	35	1	0	1
DCIS	**4**	**1**	**1**	**0**
Stage of disease				
0	4	1	1	0
IA	13	0	0	0
IB	1	0	0	0
IIA	21	1	0	1
IIB	7	0	0	0
IIIA	4	2	0	2

* one patient had a complete pathological response after neo-adjuvant chemotherapy, and tumour size, grade, nodal status was not determined

The majority of patients were treated with ORM from a “Wise” pattern excision, followed by “Benelli”-type round block excision, “melon slice” wedge resection, “Grisotti”-flap and “Lejour” vertical mammoplasty (**Table 21**).

Table 21. Type of oncoplastic surgical techniques in relation to overall, local and distant recurrence.

PATIENTS		RECURRENCES		
Type of ORM		**Overall**	**Local**	**Distant**
	No.	No.	No.	No.
All patients	**50**	**4**	**1**	**3**
Wise pattern	35	1	0	1
Round block	12	2	1	1
Wedge resection	1	0	0	0
Grisotti	1	0	0	0
Lejour	1	1	0	1

ORM – oncoplastic reduction mammaplasty

The average weight of the resected breast tissue was 272 (25 – 1000) grams altogether, which included the tissue resected around the cancer as well as tissue removed with technical – and not oncological – indications. Mean preoperative tumour size was 2.95 (range 1 – 7.7) cm on imaging. There was no significant association in preoperative tumour size and the surgical technique applied, although tumours treated with "Benelli"-type round block excision was somewhat smaller compared to the other techniques (2.67 (range 1.5 – 4.3) vs. 3.05 (range 1 – 7.7) cm; p = 0.46). 31 patients underwent simultaneous contralateral symmetrizing reduction. Sentinel node biopsy was carried out in 19 patients, axillary sampling in 21 patients and upfront axillary clearance in 12 patients. All 50 patients had postoperative radiotherapy (**Table 22**). 30 patients received chemotherapy, three had neoadjuvant chemotherapy with one of them having complete pathological response. Adjuvant hormonal therapy was given to 30 patients, while five patients received trastuzumab (**Table 22**).

Table 22. Adjuvant therapy in relation to recurrence.

PATIENTS		RECURRENCES		
		Overall	**Local**	**Distant**
	No.	No.	No.	No.
All patients	**50**	**4**	**1**	**3**
Radiotherapy +	50	4	1	3
Radiotherapy -	0	0	0	0
Chemotherapy +	30[1]	2	0	2
Chemotherapy -	20[2]	2	1	1
Hormonal ther. +	30	3	1	2
Hormonal ther. -	20[2]	1	0	1
Herceptin +	5	0	0	0
Herceptin -	45[2]	4	1	3

[1] Three patients had neo-adjuvant chemotherapy; [2] four patients were diagnosed with DCIS.

The rate of incomplete excision margins after ORM was 16.1% (9 of 56 patients). Of the nine patients, who had incomplete margins after ORM, six underwent completion mastectomy and three had had a re-excision. Five patients had immediate breast reconstruction after mastectomy using extended autologous latissimus dorsi flap in four patients, and implant in the remaining patient. While incomplete excision rate was not significantly different based on mammoplasty techniques, it appeared relatively higher after "Benelli"-type round block technique (28.6%; 4 of 14) compared to ORM from "Wise" pattern excision (10.5%; 4 of 38; p=0.189). The remaining one patient had a "melon slice" wedge resection prior to her completion mastectomy. Preoperative radiological tumour size was somewhat bigger in patients with incomplete margins after ORM compared to those with clear margins after the first surgery (3.36 (2 – 5.8) cm vs. 2.85 (1 – 7.7) cm; p = 0.658). Similarly, multifocality was not associated with higher incomplete excision rate (1 of 8 multifocal cancers vs. 4 of 44 unifocal cancers).

During the six-year follow-up time recurrence was detected in four patients (8%) (**Table 20, 21, 22**). Only one patient (2%) developed local recurrence, who was diagnosed with DICS. Three patients (6%) developed distant recurrence as the first detected recurrence event (**Table 20**). All distant recurrences developed in patients with invasive cancer (6.52%). The median (range) time to relapse was 53 (48 – 95) months for first distant recurrence. One patient developed a contralateral breast cancer, which was diagnosed at the time when her distant recurrence was diagnosed, too.

Altogether four patients died during the follow-up, and the crude overall survival rate was therefore 92%. Of these, two patients died from metastatic breast cancer, hence the six-year cancer-specific survival rate was 96%. All patients who died during the follow-up were diagnosed with invasive disease.

4.5.5. Discussion

Evidence about oncological safety after oncoplastic breast conservation is vague. There were concerns that oncoplastic conservation delayed adjuvant therapy due to postoperative complications. In this study we found 15.4% postoperative complication rate, which is identical to the figure published in a recent meta-analysis by Losken et al.[181] Majority of these postoperative complications are not so severe to delay adjuvant treatment, which has been confirmed by numerous studies including ours.[14, 16, 43, 168] Further concern arose that ORM displaced surgical clips intended to demarcate tumour bed tissue. This may potentially increase the likelihood of local recurrences developing outside the original tumour quadrant; this fear,

however, has been refuted recently, too.[175, 182] Recurrence rates, in general, are also comparable to standard wide excision in most studies published so far.[16, 43, 61, 150] In fact, in a recent meta-analysis favourable recurrence rates were demonstrated when ORM or volume replacement oncoplastic breast conservation were compared to standard wide excision.[181] However, all these data are based single centre retrospective reviews with relatively short follow-up periods.

The aim of this study was to provide long-term oncological results after oncoplastic conservation surgery. There are only 10 other published studies on recurrence rates after oncoplastic conservation based on at least five-year follow-up (**Table 23**).[14-16, 43, 149, 175-178, 183] In fact, two institutes published five studies altogether, with one institute updated their results twice (**Table 23**). True recurrence rates with at least six-year median follow-up are presented in four papers only published by three institutes.[16, 177, 178, 183]

Table 23. Published local and distal recurrence rates during long-term follow-up (at least 5 years) after oncoplastic reduction mammoplasty.

First author	Country / Institution	No. of cases	Tumour size	Tumour stage	Surgical technique	Median follow-up (months)	Recurrence rates (%)	
							Local	Distant
Nos et al.	France / Institut Curie	50	Tis – T4	0-IIIb	Reduction	60[1]	7[1]	19[1]
Clough et al.	France / Institut Curie	101	Tis – T4	0-IIIb	Reduction	60[2]	9.4[2]	17.2[2]
Rietjens et al.	Italy / European Institute of Oncology	148	Tis – T3	n/d	Reduction + Vol. replac.	74	3	13
Caruso et al.	Italy / Humanitas Centro Catanese	61	T1a – T4	n/d	Reduction	68	1.5	9.8
Fitoussi et al.	France / Institut Curie	540	Tis – T3	0-IIIc	Reduction	60[3]	6.8[3]	12.1[3]
Eaton et al.	USA / Emory University, Atlanta	86	Tis – T4	0 – IIIb	Reduction	60[4]	7-9[4]	9[4]
Bogusevic iuset al.	Lithuania /University of Health Sciences	60	Tis – T4	IIIa-IIIc	Reduction + Vol. replac.	86	10	38.3
Ren et al.	China, Jiangsu Cancer Hospital	91	Tis – T2	n/d	n/d	87[5]	7[5]	9[5]
Rezai et al.	Germany/Düsseldorf Luisenkrankenhaus	944	n/d	n/d	Reduction + Vol. replac.	62	4	5.1
De Lorenzi et al.	Italy / European Institute of Oncology	454	T1 – T4	n/d	Reduction + Vol. replac.	86	6.7[6]	12.7[6]
Romics Jr. et al.	UK / Glasgow University Hospitals	50	Tis – T3	0-IIIa	Reduction	72	2	6

Vol. – volume; replac. – replacement; n/d – not disclosed; [1] actuarial recurrence rates (true median follow-up: 48 months); [2] actuarial recurrence rates (true median follow-up: 46 months); [3] actuarial recurrence rates (true median follow-up: 49 months); [4] actuarial recurrence rates (true median follow-up: 54 months); [5] actuarial recurrence rates (true median follow-up: 83 months); [6] actuarial recurrence rates at 10 years.

In this study, during the six-year follow-up only one patient developed a local recurrence. This low local recurrence rate is due to various factors. Cavity shavings are taken routinely for decades in the Glasgow breast surgical units after wide local excisions which have been shown to reduce local recurrence rates after breast conservation due to more accurate pathological assessment of excision margins.[156, 184] While cavity savings are not taken routinely after oncoplastic breast conservation, it may have played a role in the ones when shavings were taken. Further, completion mastectomy was relatively frequently carried out after incomplete excision in oncoplastic conservation (6 of 9). Due to the difficulties of correctly identifying margins of the tumour bed tissue after the parenchymal reshaping, we feel that further excision may not be oncologically safe if the excision is incomplete after ORM. This may be in contrast with the routine practice of other units, although those treat relatively smaller cancers with oncoplastic surgery.[17, 36, 153, 176]

The indication for ORM in our practice included stage II or III breast cancers in almost two-thirds of the patients (32 of 56), which is consistent with the results of our comparative study on a larger series of patients.[22] Some of the studies with long follow-up are based on patients with similarly staged cancers with the ratio of patients with at least stage II cancers between 71% and 82% (**Table 23**).[14, 15, 178] However, most of the patients of the long follow-up studies have smaller cancers characterized by either a relatively low proportion of patients of having stage II or higher cancers (35-53%) or very small excisions (32g on average) (**Table 21**).[43, 175, 176] In comparison, our 2% local recurrence is similar to the other long-term follow-up studies (1.5 – 10%). Long-term distant recurrence rates (5.1 – 38.3%) are also comparable to the one in our study (6%) (**Table 23**).

While we could not demonstrate statistically significant association between incomplete excision rate and oncoplastic technique, we found that patients who underwent ORM with “Benelli”-type round block technique were almost three times more likely to have incomplete margins (28.6%) than patients who had ORM with the most commonly used “Wise” pattern excision (10.5%). This happened despite round block excision was applied for somewhat smaller tumours on preoperative imaging (mean 2.67 cm vs. 3.05 cm). These data suggest that the “Benelli”-type excision should be applied with relatively more caution and delicate indications. In fact we apply round block excision less frequently now due to the recognition that this technique allows only a limited access to the tumour compared to other techniques, hence this may jeopardize complete excision in the end.

Although this series has one of the longest follow-up periods to date of breast cancer patients treated with oncoplastic conservation surgery, the ability to draw definitive conclusions based on our analysis is limited by relatively small patient numbers. Given the retrospective nature of this study, we were also unable to provide information regarding cosmetic outcome and life quality measures following ORM.

4.5.6. Novel findings

1. We found that patients who underwent ORM with "Benelli"-type round block technique were almost three times more likely to have incomplete margins (28.6%) than patients who had ORM with the most commonly used "Wise" pattern excision (10.5%). These data suggest that the "Benelli"-type excision should be applied with relatively more caution and delicate indications.
2. This study demonstrates low long-term recurrence rates in patients treated with oncoplastic reduction mammoplasty for predominantly stage II-III cancers. Six-year local recurrence rate is 2%, distant recurrence rate is 6%, and cancer-specific survival is 96%. Based on these long-term follow-up data, ORM is an oncologically safe treatment option.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Six-year follow-up of patients treated with oncoplastic reduction mammoplasty: A cohort study.
Kabir SA, Stallard S, Weiler-Mithoff E, Mansell J, Mallon E, Doughty JC, **Romics L Jr. International Journal of Surgery.** 2016 Feb;26:38-42.

4.6. Oncological safety of volume replacement oncoplastic breast conservation surgery

4.6.1. Introduction

OBCS is generally comprised of two techniques, which are volume displacement and volume replacement. The use of volume displacement OBCS has been well established. Similarly, several volume replacement techniques have also been well established, such as the latissimus dorsi (LD) myocutaneous flap,[92, 185, 186] and the LD myosubcutaneous flap or LD mini (LDm) flap.[187-189] Variations of pedicled flaps based on the intercostal artery perforators and thoracodorsal artery perforators have been described and shown to be reliable in immediate BCS reconstruction.[190-192] Additionally, it has been used in combination with other flaps such as the thoracoabdominal advancement flap to achieve desirable results.[193] Similar, the thoracoepigastric flap has also been shown to be another reliable, effective and relatively simple form of volume replacement.[194, 195] OBCS is an effective technique used in patients in whom 10% of the breast volume is excised in medial tumours and 20% in lateral tumours, where outcomes with volume displacement techniques would not achieve an acceptable cosmetic outcome.[196, 197]

The current evidence on the oncological outcomes of other forms of volume replacement oncoplastic conservation largely focusses on latissimus dorsi myocutaneous (LD) or myosubcutaneous (LD-mini) flaps in multiple study designs. As previously established, the likelihood of conducting a prospective randomised controlled trial for oncoplastic breast conservation is highly unlikely due to the ethical considerations[5, 16] and this extends to volume replacement, too. We aim to ascertain the recurrence and complication rates after volume replacement oncoplastic breast conservation in our local population. As with all cancer resections, the primary outcome is oncological safety. We sought to investigate and report our experience in two breast units in Glasgow on volume replacement OBCS.

4.6.2. Aim

The primary outcome of this study was tumour-free margin resection rates, and the secondary outcomes were locoregional and distant recurrence rates as these correlates with the overall oncological safety of volume replacement OPBS. Surgical complication rates were the secondary outcome of interest in this study.

4.6.3. Methods

This study was designed and reported in line with STROBE criteria.[198] Methods for data collection in our centres have previously been described.[22, 168] Details of patients treated with OBCS in two centres within the publicly funded NHS Greater Glasgow and Clyde health trust between November 2010 and October 2015, namely the Victoria Infirmary and Western Infirmary, were prospectively recorded in a standardised institutionalized database. The following characteristics were recorded prospectively in the oncoplastic dataset: demographic data (age, BMI, brassiere size, risk factors for breast cancer and breast surgery), preoperative tumour size, pre- and postoperative pathology, surgical, oncological management, surgical complications, time and site of recurrence. Patients who had undergone volume replacement OBCS were identified. The clinical records included in the oncoplastic dataset were analysed for demographic, tumour, treatment characteristics and recurrences. Missing data was retrospectively searched via case records and included in the analysis. Preoperative tumour size was determined as the largest diameter given on any preoperative imaging. Patients with previous ipsilateral or contralateral DCIS or breast cancer were excluded.

Patients in whom breast cancers were detected either on screening or after a symptomatic presentation were included. The confirmation of cancer diagnosis was with radiological and pathological evidence (core biopsy, axillary biopsy, etc). Treatment plans were decided in a local multidisciplinary meeting consisting of radiologists, pathologists, oncologists, breast surgeons and breast specialist nurses. Oncoplastic technique was mutually decided between patient and oncoplastic breast surgeon or breast surgeon, with or without consultation and surgical co-intervention of a plastic surgeon. Radiotherapy, chemotherapy and hormone therapy were administered according to evidence-based guidelines of the Beatson West of Scotland Cancer Centre in the given time period.

Surgical, oncological, radiological and pathological reports were analysed for follow-up to determine the pattern and timing of recurrence up to April 2016. Length of follow-up was determined as time elapsed from first treatment. Patients were followed up every 12 months by surveillance mammogram and clinical examination, and abnormal clinical findings were further investigated as appropriate. Recurrences were documented by clinical examination, radiological tests and/or pathological assessment.

The primary outcome of this study was tumour-free margin resection rates, and the secondary outcomes were locoregional and distant recurrence rates as these correlates with the overall oncological safety of volume replacement OPBS. We defined tumour-free margins as a

distance of at least one millimetre between cut edge of the specimen and the outer limit of the tumour when the pathology was invasive cancer, and two millimetres for DCIS. This is based on findings that greater distances are not associated with improved outcomes.[34, 199, 200] Surgical complication rates were the secondary outcome of interest in this study.

4.6.4. Results

A total of 208 oncoplastic breast conservation procedures have been carried out in this time period. 30 of 208 (15.9%) patients underwent volume replacement surgery and the remaining underwent volume displacement surgery. The mean age of the former group was 51 (range 24-69). 3 patients had A-cup breasts, 4 patients had B-cup breasts, 4 patients had C-cup breasts, 3 patients had D-cup breasts, 2 patients had E-cup breasts and 2 patients had F-cup breasts. The mean BMI was 28 (range 21-37). 6 patients were current smokers and 2 patients were ex-smokers. Comorbidities in sample population included diabetes in 1 patient (3.3%), immunosuppression in 4 patients (13.3%) and 1 patient (3.3%) was anticoagulated. Baseline characteristics are outlined in **Table 24**.

Table 24. Baseline characteristics and risk factors

Variable		(n, %)
Age (mean, range)		51, 24-69
BMI (mean, range)		27.8, 23.6-36.2
Diabetes	Yes	1
	No	24
	No data	1
Family history	Yes	5
	No	21
Smoking status	Current smoker	6
	Ex-smoker	??2
	Non-smoker	20
HRT	Yes	4
	No	20
	No data	2
Immunosuppression	Yes	0
	No	30
Breast cup size	A	3
	B	4
	C	4
	D	3
	E	2
	F	2
	Larger than F	3
	No data	7

Twice as many patients presented symptomatically than had tumours detected on screening - 20 (66.7%) versus 10 (33.3%). Of these, 11 patients (36.7%) had tumours found in the upper outer quadrant, 4 (13.3%) in the upper inner quadrant, 12 (40.0%) in the lower outer quadrant and 3 (10.0%) in the lower inner quadrant. The mean preoperative tumour size on radiology was 25.4 mm.

Pathological tumour subtypes were ductal in 23 (76.7%), lobular in 5 (16.7%), mixed in 1 (3.3%) and ductal carcinoma-in-situ in 1 (3.3%). 16 patients (53.3%) had grade 3 tumours, 13 patients (43.3%) had grade 2 tumours and 1 patient (3.3%) had a grade 1 tumour. Mean whole tumour size was 25 mm (range 9-45 mm). 4 patients (13.3%) had multifocal tumours. Oestrogen receptor was expressed in 23 tumours (79.3%), progesterone receptor was expressed in 21 tumours (72.4%) and HER-2 receptor was expressed in 4 tumours (13.8%). 8 patients had node positive tumours (27.6%) (**Table 25**).

Table 25. Tumour characteristics

Patients			**Incomplete excisions**	**Recurrences**
				Locoregional
		No.	No.	No.
All patients		26	7	1
Presentation	Screening			
	Symptomatic			
Laterality	Left			
	Right			
Quadrant	Upper outer			
	Upper inner			
	Lower outer			
	Lower inner			
Invasive cancer		25	7	1
T1		8	2	0
T2		21	5	1
T3		0	0	0
Tumour grade	G1	1	0	0
	G2	13	4	0
	G3	16	3	1
Pathological subtype	Ductal	23	3	1
	Lobular	5	4	0
	Mixed	1	0	0
Oestrogen receptor status	Positive	23	7	0
	Negative	7	0	1
Progesterone receptor status	Positive	21	5	0
	Negative	9	2	1
Her-2 receptor status	Positive	4	1	0
	Negative	26	6	1
Nodal status	Positive	8	3	1
	Negative	22	4	0
DCIS		1	0	0
Stage of disease	0	1	0	0
	IA	8	1	0
	IB	1	0	0
	IIA	16	5	0
	IIB	0	0	0
	IIIA	1	0	1
	IIIB	0	0	0
	IIIC	1	1	0

The majority of patients (13 of 30) underwent oncoplastic breast conservation using a thoracoepigastic flap. A total of 8 patients underwent pedicled flap reconstructions – 5 patients received lateral intercostal artery perforator (LICAP) flaps, 2 patients had thoracodorsal artery perforator (TDAP) flaps and 1 patient had a lateral thoracic artery perforator (LTAP) flap. 1 patient underwent crescent flap volume replacement surgery. Of the 8 patients that underwent matrix rotation, 5 were inferior, 1 was supero-medial and 1 was superior matrix rotation. Synchronously, 24 patients underwent sentinel node biopsy, 5 patients underwent axillary node clearance, and 1 patient underwent symmetrising contralateral breast reduction (**Table 26**).

Table 26. Summary of surgical techniques

Patients		**Incomplete excisions**	**Recurrences**	**Recurrences**
			Overall	Local
	No. (%)	No.	No.	No.
All patients		3	0	0
Thoracoepigastric flap	13 (43.3)	0	0	0
Matrix rotation	8 (26.7)	2	1	1
Inferior	5 (16.7)	1	1	1
Supero-medial	1 (3.3)	0	0	0
Superior	1 (3.3)	1	0	0
Lateral intercostals artery perforator (LICAP) flap	5 (16.7)	1	0	0
Thoracodorsal artery perforator (TDAP) flap	2 (6.7)	0	0	0
Lateral thoracic artery perforator (LTAP) flap	1 (3.3)	0	0	0
Crescent flap	1 (3.3)	0	0	0

2 of 30 patients (6.7%) had neoadjuvant chemotherapy. Postoperatively, 14 patients (48.3%) underwent adjuvant chemotherapy, and all 30 patients were treated with adjuvant radiotherapy. 22 patients (82.7%) were treated with hormonal therapy and 4 patients (13.8%) were treated with Herceptin (**Table 27**).

Table 27. Summary of (neo)adjuvant therapies

Patients	No (%)
All patients	**30 (100)**
Neoadjuvant chemotherapy	2 (6.7)
Radiotherapy	30 (100)
Chemotherapy	14 (46.7)
Hormone therapy	22 (73.3)
Herceptin	4 (13.3)

The rate of incomplete excision was 10% (3 patients), which were all subsequently re-excised successfully. From a median follow up time of 48.5 months (range 6-66 months), we have detected no local recurrences, 1 regional recurrence involving the brachial plexus and no distant metastases. Overall, 8 patients (26.7%) encountered some form of complication. Of these, 2 patients had seromas, 2 patients had partial flap failure, 1 patient had a haematoma, 2 patients had fat necrosis and 1 patient had cellulitis. Of these, only 2 patients (6.7%) required surgical intervention. Specifically, the patient with fat necrosis was returned to theatre for a washout, and one of the patients with flap failure required debridement followed by secondary closure.

4.6.5. Discussion

Oncoplastic breast surgery is quickly becoming the preferred option in suitable patients due to its focus on aesthetic results without compromise for oncological safety. Volume replacement can maintain the original shape and size of the breast and achieve a balanced aesthetic result without any contralateral surgery.[80]

The safety of OBCS is becoming increasingly established. However, the evidence for long term outcomes of volume replacement oncoplastic surgery is lacking. The main concern with breast conserving surgery compared with mastectomy is the plausible increased risk of margin positive resections. Volume replacement OPBS circumvents the problem of replacing volume loss by obtaining volume from autologous non-breast tissue in the combination of skin, fat, fascia and/or muscle to match the volume resected. However, compared to volume displacement techniques, there is some concern over the relationship between increased volume and decreased efficacy of adjuvant radiotherapy, and that distortion of tissue planes to complicates re-excision in the case of margin-positive resections and follow up imaging. Several studies, including ours, have already addressed the issue of follow up mammography after volume replacement surgery to not be a major factor due to the radiolucent nature of the tissues.[165]

Our data indicate a margin-free resection rate of 83.3%. This is comparable to a recent systematic review focussing on volume displacement surgery by Haloua et al on oncoplastic breast surgery, which, found margin-free resection rates to vary between 78-93%.[3, 201] It should be noted that definitions of margin-free resection varied between publications. Reviews focussing on volume replacement OBCS have found margin-positive resection rates to range

between 0 and 26.6%.[10] Nevertheless, all 4 patients with margin-positive resections underwent re-resection successfully and have no evidence of recurrence.

In this study, the incidence of locoregional recurrence is 3.3%. We found no incidents of postoperative distant metastasis throughout our follow up period in our patient population. The patient who had the regional recurrence was one of six to have a triple negative tumour and had the highest AJCC stage of our study population, which was IIIA. This is consistent with findings of several previously published studies and reviews on volume replacement OBCS, which report a range from 0 to 8.1% throughout a large variation of follow up periods.[10, 14, 202, 203] In comparison, reviews focussed on volume displacement OBCS found a locoregional recurrence rate to range from 0 to 9.4%.[3, 201]

With a median of 48 months of follow up, no distant recurrences have been found in our study. Multiple previously published studies on volume replacement OBCS have also found a range of distant metastasis or recurrence rates ranging from 0 to 14.6%.[10, 202] Haloua et al, whose review focussed on volume displacement OBCS found distant metastasis rates to be as high as 13%.[3]

As we had previously reported, our centres have implemented taking cavity shavings as a routine part of our tumour resections, which resulted in a significantly lower incomplete excision rate compared to other centres.[22] This may explain the relatively low local and distant recurrence rates in this study.

Concerns arise regarding complications of the donor site is unique to the volume displacement techniques in OCBS, but throughout our period of follow up we have not found any reported cases of donor site morbidities. However, partial flap failure was reported in 2 patients. Both patients underwent wide local excisions with immediate thoracoepigastric flap reconstruction which subsequently had debridement. 5 other complications that did not require surgical intervention were recorded. A study by *Lee et al* found acute complication rates (infection and wound dehiscence) of 5.6% and chronic complication rates (fat necrosis) to be 12.5%.[202] In a systematic review *Haloua et al* on volume displacement OBCS, complication rates were found to be low for delayed wound healing (2 to 16%), abscess (2%), axillary seroma (4%), haematoma (2 to 7%), partial skin necrosis (1 to 68%), fat necrosis (3%) and dehiscence (3 to 4%). In this review, complications requiring surgical intervention ranged from 4 to 9%.[3]

Baseline characteristics and tumour characteristics were not disclosed in many of the studies and reviews referenced in this study. As such, we were unable to make comparisons of the aforementioned characteristics of our patients and relate them with the outcomes in this

study. This study was not designed to evaluate patient perspectives or cosmetic outcomes which are important considerations in oncoplastic breast conservations.

4.6.6. Novel findings

1. Incomplete excision rate of 10% and locoregional recurrence rate of 3.3% indicate that volume replacement oncoplastic breast conservation surgery is an oncologically safe option for partial breast reconstruction in breast cancer patients in the Glasgow breast units.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Oncological outcomes and complications after volume replacement oncoplastic breast conservations - the Glasgow experience.
W Ho, S Stallard, J Doughty, E Mallon, **L Romics**.
Breast Cancer: Basic and Clinical Research 2016 Dec 19;10:223-228.

4.7. Oncological outcomes of oncoplastic breast conservation surgery in comparison to wide local excision and mastectomy

4.7.1. Introduction

The evidence for the oncological safety of OBCS is limited and prospective randomized controlled trials are unlikely to be ever undertaken given the complex ethical implications [3]. Concerns exist regarding the oncological safety of re-excision for incomplete margins; safe delivery of radiotherapy boost and postoperative mammographic surveillance due to the significant rearrangement of the breast parenchyma.[32, 150, 163, 204-206]

The current evidence for the oncological safety of OBCS is largely based on single-institution retrospective series.[13-17, 22, 32, 36-38, 40, 43, 46, 72, 149, 150, 153, 168, 198] In the few comparative studies OBCS is usually compared to simple WLE or quandrantectomy.[17, 18, 22, 32, 36-40, 158, 159, 168, 198, 207] In these studies, recurrence rates are rarely reported. The majority of comparative studies show similar post-operative pathological characteristics of patients treated with OBCS and WLE despite the belief that OBCS is often applied for larger tumours.[17, 19, 36, 38, 39] We previously showed that OBCS is often utilised for relatively large cancers in our unit.[22]

4.7.2. Aim

The primary aim of our study was to compare recurrence rates of patients treated with OBCS to WLE and mastectomy with or without immediate reconstruction (Ms±IR).

4.7.3. Methods

All patients treated with OBCS between June 2009 and August 2012 were considered for the study. Their details were recorded prospectively into a standardised institutional database in two breast units in Glasgow. Consecutive patients treated with WLE or Ms±IR during a similar time period in one unit were identified from the West of Scotland Managed Clinical Networks (Breast Cancer) database. Since the above mentioned oncoplastic database was opened in 2005, an additional 12 patients treated with OBCS consecutively between 2005 and 2008 was also included in the analysis. Hence, all consecutive patients treated with OBCS and entered the database up to August 2012 were included in the analysis. Clinical records of the patients were reviewed for demographic, tumour and treatment variables; and local, contralateral and distant

recurrence events and cause of death were recorded. Patients with previous DCIS or breast cancer were excluded. Follow-up was recorded up to June 2015. Length of follow-up was defined as time from the date of diagnostic biopsy to the end of follow-up or death from any cause.

Oncoplastic technique was determined by the ratio of tumour size to breast, tumour location, patients' anatomy and preferences. Oncoplastic breast surgeons, or breast and plastic surgeons decided together these subjectively. Patients who underwent significant volume excision followed by volume displacement accompanied by adequate skin envelope reduction, or true volume replacement were included in the OBCS study group (level II oncoplastic techniques as defined by Clough et al).[102] Simple reshaping such as dual plane mobilization without skin envelope reduction was listed under WLE. After simple WLE four quadrant cavity shavings were taken in radial directions. Since the tumour bed is significantly larger after OBCS than WLE, cavity shavings were not always taken after oncoplastic excision. Excision margins were considered clear if the distance from the excision plane was at least 1 mm with invasive cancer or 2 mm with DCIS. Adjuvant treatment was decided according to evidence-based guidelines of the Beatson West of Scotland Cancer Centre.

Patients were followed up by annual clinical examination and mammography. Local and contralateral breast recurrence were defined as histologically proven recurrent tumour occurring within the ipsilateral breast or skin envelope. Tumour recurrence at all other sites was classified as distant metastasis in this study and based on histological and/or radiological evidence. Regional recurrence was not included in the analysis because we did not detect any isolated regional metastases during this follow-up.

The commonly described histopathological characteristics of patients treated with OBCS versus WLE or Ms±IR were compared with Chi square and Fisher's exact tests. Adjuvant radiotherapy, chemotherapy and endocrine therapy were compared with Fisher's exact test. Median age and follow-up time of the study group was compared using Mann-Whitney test. Survival and recurrence data of patients who underwent OBCS was compared to patients who had WLE or Ms using Kaplan Meier analysis and Log rank test. For all analyses, results were considered statistically significant if the p value was ≤ 0.05. Statistical calculations were performed using SPSS® Statistics version 19.0 (SPSS, Chicago, Illinois, USA).

4.7.4. Results

Altogether 980 patients' data were analysed with a median age of 61 (range 24-95). Of those 104 patients were treated with OBCS, 558 patients had WLE and 318 patients underwent Ms±IR. The median age of patients treated with OBCS was 54 (24-79) years. Patients who had WLE or Ms±IR were significantly older with a median age of 62 (31-88) ($p<0.001$) and 60 (28-95) ($p<0.001$) years, respectively.

The majority of patients undergoing OBCS were treated with volume displacement techniques (90 of 104). Of those, 78 underwent Wise pattern reduction, 6 patients had a Benelli-type "round-block" breast reduction, 3 patients were treated with a "racquet-type" excision, while Lejour, Grisotti and "melon slice" reduction techniques were applied in one patient each. 14 patients had volume replacement oncoplastic conservation with thoracoepigastric flap in 9, breast matrix rotation in 4 and thoracodorsal artery perforator (TDAP) flap in one patient. 45 of the 104 patients underwent simultaneous symmetrisation surgery of their contralateral breast with standard breast reduction techniques. Axillary clearance was carried out in all node positive patients except one patient in the OBCS group, who received axillary radiotherapy.

The rate of margin involvement after OBCS was similar to patients treated with WLE (14.4 per cent vs. 13.1 per cent; p=0.752). Of the 15 patients, who had positive margins after OBCS, 13 underwent completion mastectomy and two had re-excisions. 8 of the 13 patients who underwent completion mastectomy opted for immediate reconstruction. Completion mastectomy rate after OBCS was significantly higher than that of WLE (12.5 per cent vs. 5.4 per cent; p=0.015). Adjuvant radiotherapy was given to similar proportion of patients after OBCS and WLE (**Table 28**).

Table 28. Details of adjuvant radio-, chemo- and endocrine therapy of patients treated with OBCS, WLE and Ms±IR.

	Radiotherapy (%)				**Chemotherapy (%)**		**Endocrine therapy (%)**	
	all patients	P =	invasive	P =	invasive	P =	invasive	P =
WLE	538 (96.4)	0.786	451 (96.6)	0.596	116 (24.8)	0	425 (91)	< 0.001
OBCS	101 (97.1)	n/a	92 (96.8)	n/a	58 (61)	n/a	74 (77.9)	n/a
Ms±IR	131 (41.2)	0	130 (45.6)	0	160 (56.1)	0.472	240 (84.2)	0.162

P – statistical difference vs. OBCS. OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction.

(Neo)adjuvant chemotherapy and endocrine therapy were given to similar proportion of patients after OBCS and Ms±IR, (**Table 26**). Neoadjuvant endocrine therapy was given in 1.9% (2 patients), 2.7% (15 patients) and 8.8% (28 patients) before OBCS, WLE and Ms±IR, respectively.

The majority of patients had invasive ductal carcinoma in all three groups (OBCS: 79.8 per cent; WLE: 71.5 per cent; Ms±IR: 72 per cent) followed by lobular cancer and other types of invasive carcinomas (**Table 29**).

Table 29. Comparison of histological characteristics of patients treated with OBCS, WLE and Ms.

Characteristics	WLE (%)	OBCS (%)	P value	Mastectomy (%)	P value
Histological type					
DCIS	91 (16.3)	9 (8.7)	< 0.001	33 (10.4)	= 0.708
Ductal/NST	399 (71.5)	83 (79.8)		229 (72.0)	
Lobular	31 (5.6)	8 (7.7)		41 (12.9)	
Other	37 (6.6)	4 (3.8)		15 (4.7)	
Tumour size					
T1	395 (84.6)	44 (46.3)	< 0.001	125 (43.9)	= 0.708
T2	71 (15.2)	48 (50.5)		137 (48.1)	
T3	1 (0.2)	3 (3.2)		23 (8.1)	
Grade[1]					
1	95 (20.3)	7 (7.4)	<0.001	11 (4.0)	= 0.633
2	260 (55.5)	34 (35.8)		118 (42.6)	
3	113 (24.1)	54 (56.8)		148 (53.4)	
Involved nodes					
0	390 (85.7)	65 (69.1)[2]	<0.001	163 (65.7)[3]	=0.369
1-3	63 (13.8)	21 (22.3)		71 (28.6)	
>3	2 (0.4)	8 (8.5)		14 (5.6)	
ER					
Positive	418 (89.5)	76 (80.0)	<0.001	224 (78.6)	= 0.929
Negative	49 (10.5)	19 (20.0)		63 (21.4)	
HER-2					
Positive	36 (7.8)	10 (10.9)	= 0.308	52 (18.3)	= 0.107
Negative	425 (92.2)	82 (89.1)		232 (81.7)	

DCIS – ductal carcinoma *in situ*; NST – no special type; ER – oestrogen receptor; PR – progesterone receptor; HER-2 – Human Epidermal Growth Factor Receptor 2; [1]No grade was given in two patients who had WLE and 8 patients with mastectomy due to complete pathological response after neo-adjuvant chemotherapy. [2]Sentinel node biopsy was carried out in one patient from the OBCS group with diagnosis of DCIS. [3]Patients treated with mastectomy for DCIS were excluded. OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction.

The proportion of patients with DCIS was higher in patients treated with WLE (16.3 per cent) compared to patients who underwent OBCS (8.7 per cent). While most of the patients were diagnosed with T1 cancers at histopathology after WLE (84.6 per cent), T2 cancers were the most common after OBCS and Ms±IR (p<0.001). Median tumour size was similar in OBCS

(21 mm [0-70]) and Ms±IR (24 mm [0-110]; p=0.158), but it was significantly smaller in WLE (13 mm [0-60]; p<0.001). Tumour grade in patients treated with OBCS and Ms±IR was relatively similar being grade 3 the most prevalent in these groups. However, grade 2 cancers were the most common in patients who had WLE (p<0.001). Likewise, axillary status was similar in patients who had OBCS and Ms±IR, but significantly fewer nodes were involved in patients who had WLE when we compared to OBCS (p<0.001). Similar findings were evident in hormone receptor expression, too. While ER expressions were very alike in patients with OBCS and Ms±IR, they were significantly higher in the WLE group in comparison to OBCS (p<0.001). Lastly, HER-2 expression was the highest in patients treated Ms±IR, followed by OBCS and WLE with no statistical difference detected in between the groups (**Table 29**).

Median follow-up time was 56.2 months (range: 2-121 ;IQR 48-67). For patients who were treated with OBCS, WLE and Ms±IR it was 56.8 months (range: 21-121; IQR: 43-67), 57.2 months (range: 3-78; IQR: 49-67) and 54.4 months (range: 2-78; IQR: 48-66), respectively. We found altogether 25 local and 67 distant recurrences during this follow-up time. 84 patients died, but only 49 deaths were directly related to breast cancer.

The 5-year local recurrence rate was 2% after OBCS, which was similar to WLE (3.4 per cent; HR: 1.21 (0.28-5.29)) and Ms±IR (2.6 per cent; 95 per cent CI: 1.19 (0.25-5.62) (p=0.973)) (**Figure 10**).

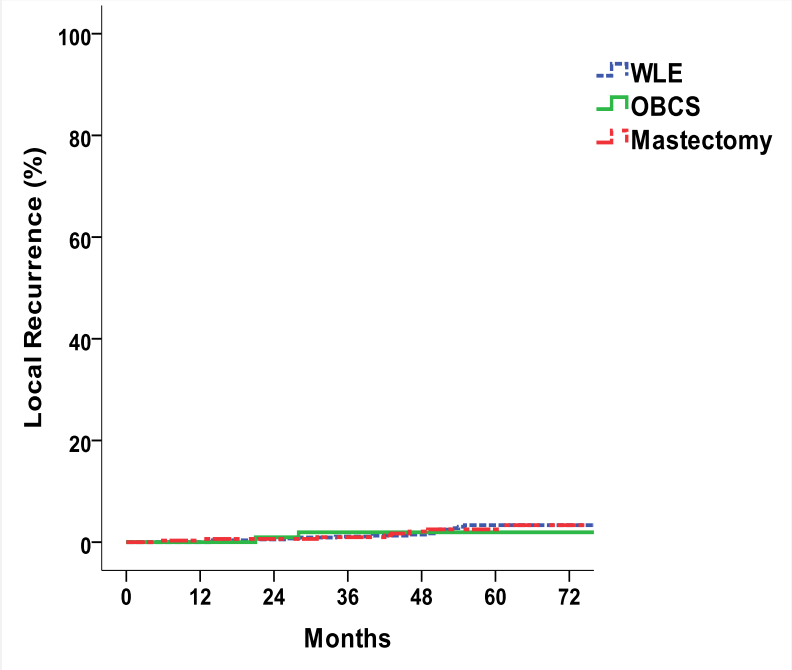


Figure 10. Local recurrence rates of patients treated with OBCS, WLE and Ms with or without IR.

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision.

The 5-year local recurrence rate for patients treated with invasive cancer was 1.1% after OBCS, 2.5% after WLE and 2% after Ms±IR.

The 5-year distant recurrence rate was 7.5 per cent after OBCS, which was lower after WLE (3.3 per cent; 95 per cent CI: 0.53 (0.21-1.33), but significantly higher after Ms±IR (13.1 per cent; 95 per cent CI: 2.28 (0.97-5.38) (p<0.001)) (**Figure 11**). The 5-year distant recurrence rate for patients treated for invasive cancer was 8% after OBCS, 3.9% after WLE and 14.7% after Ms±IR (p<0.001).

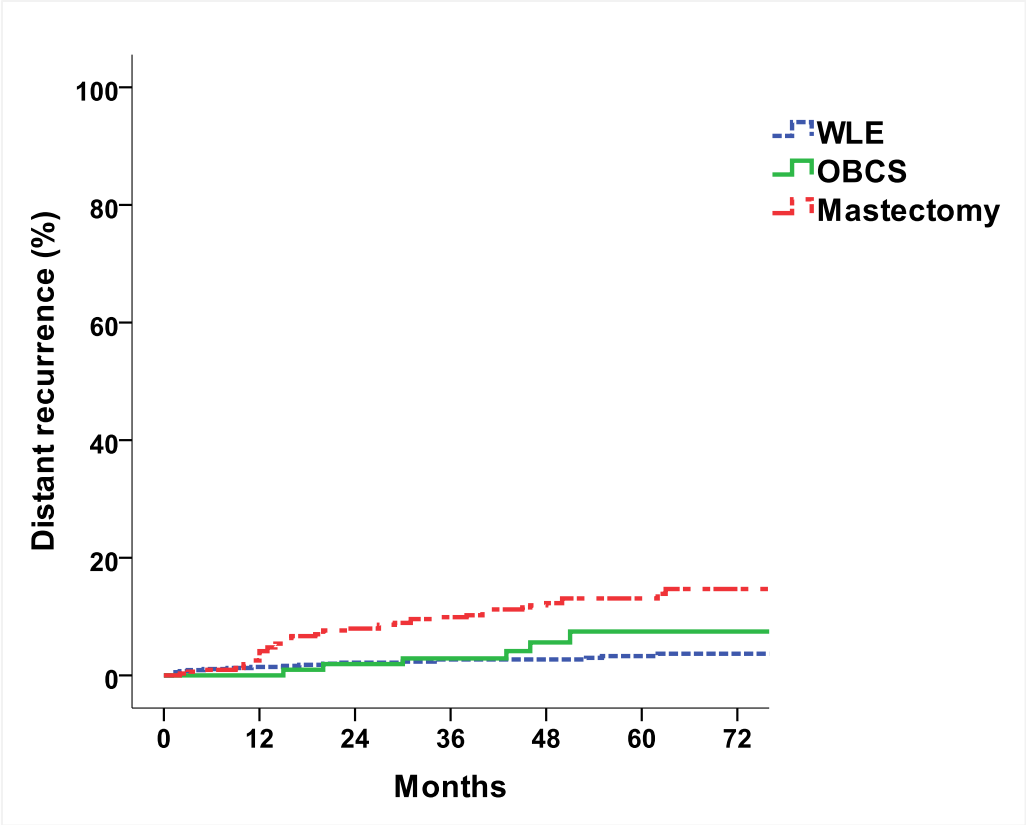
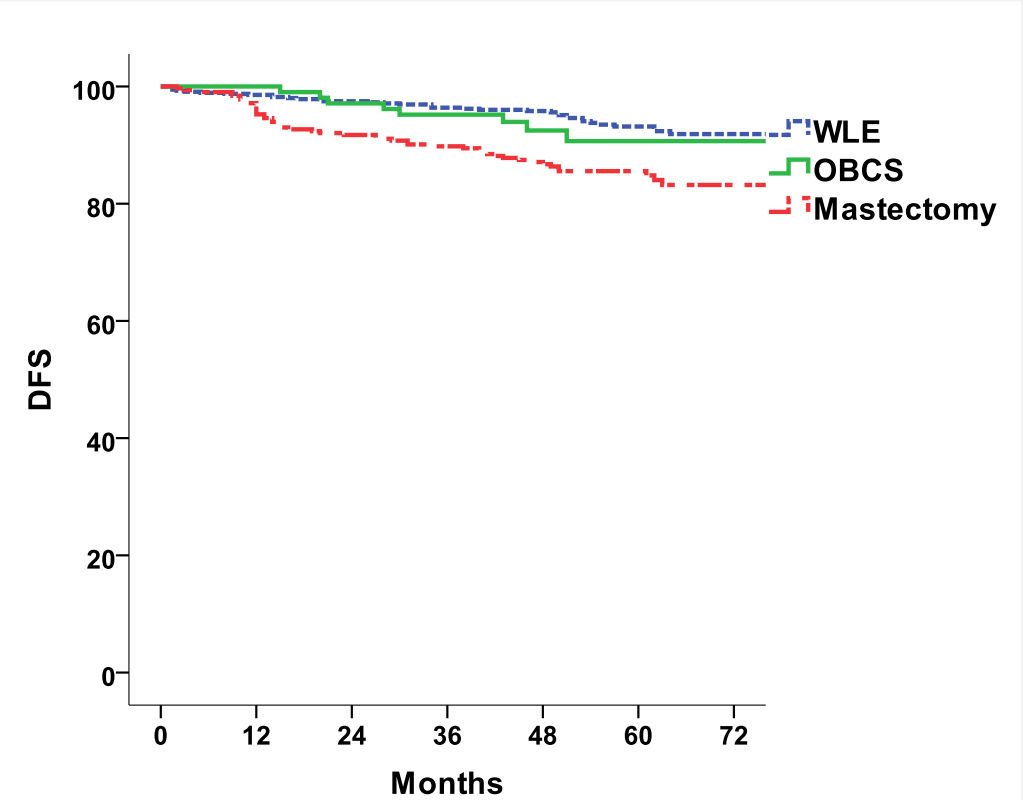


Figure 11. Distant recurrence rates of patients treated with OBCS, WLE and Ms with or without IR.

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision.

Disease free survival at 5 years was better after OBCS (90.7 per cent) and WLE (93.2 per cent; 95 per cent CI: 0.76 (0.36-1.65)) compared to mastectomy (85.6 per cent; 95 per cent CI: 1.86 (0.88-3.94)) (p<0.001) (**Figure 12**).

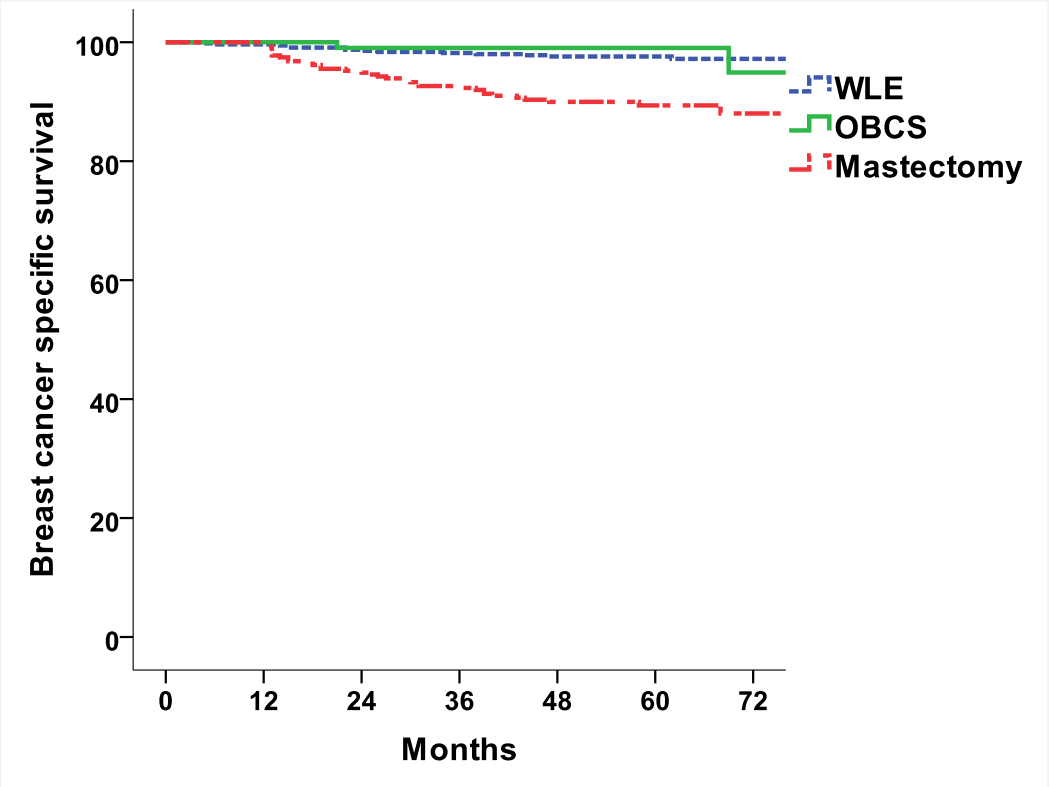


WLE	558	547	536	525	431	245	51
OBCS	104	104	101	91	55	30	20
Mast	318	299	285	276	226	128	16

Figure 12. Disease free survival rates of patients treated with OBCS, WLE and Ms with or without IR

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision.

Breast cancer specific survival was better after OBCS (99 per cent) and WLE (97.6 per cent; 95 per cent CI: 1.26 (0.29-5.56) than after mastectomy (89.4 per cent; 95 per cent CI: 5.5 (1.32-22.91)) ($p<0.001$) (**Figure 13**).

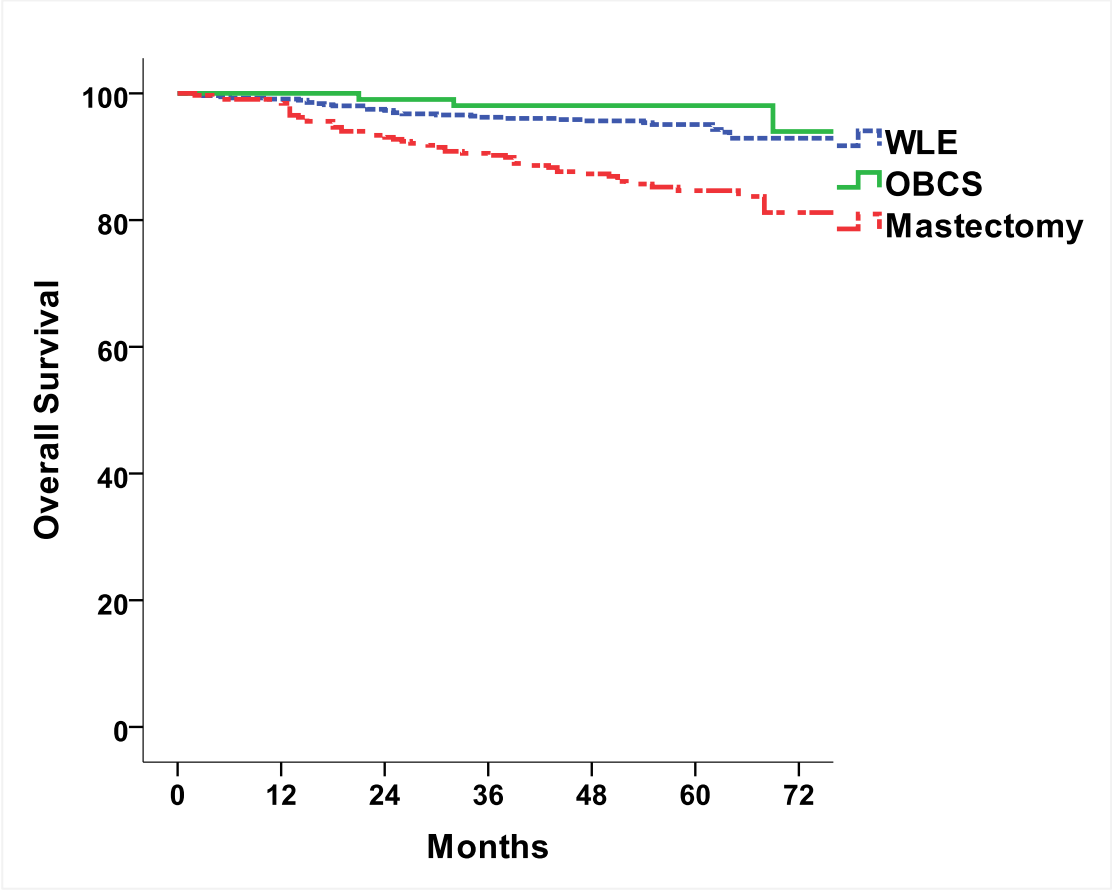


WLE	558	553	542	534	449	267	60
OBCS	104	104	102	96	63	32	21
Mast	318	315	296	285	241	133	21

Figure 13. Breast cancer specific survival of patients treated with OBCS, WLE and Ms with or without IR

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision.

The 5-year overall survival rate of patients treated with OBCS was 98.1 per cent, which was similar to patients having undergone WLE (95.1 per cent; 95 per cent CI: 1.81 (0.56-5.95)), but it was significantly lower after Ms±IR (84.6 per cent; 95 per cent CI: 5.31 (1.65-17.03)) ($p<0.001$) (**Figure 14**).



WLE	558	553	542	534	449	267	60
OBCS	104	104	102	96	63	32	21
Mast	318	315	296	285	241	133	21

Figure 14. Overall survival of patients treated with OBCS, WLE and Ms with or without IR

OBCS – oncoplastic breast conservation surgery; WLE – wide local excision

4.7.5. Discussion

The evidence for oncoplastic breast conservation is mostly based on single-centre observational studies with the oncological outcomes reported.[10] Retrospective comparative studies represent a higher level of evidence and 13 comparative studies have been published which report on the oncological outcomes following OBCS (**Table 30**).[17, 18, 22, 32, 36, 38-40, 47, 72, 153, 157, 168]

Table 30. Comparative studies analysing oncological outcomes of OBCS.

First author	No. of cases		Surgery control arm	T2 + T3 cancers (%)		Follow-up time (months)	Objectives	Outcomes
	OBC arm	Control arm		OBCS arm	Control arm			
Chakravorty et al.	150	440	WLE	40.7	34.8	28	margins	OBCS better
							survival	no difference
Kahn et al.	31	66	WLE	77.4	n/d	n/a	time to chemo-therapy	no difference
		56	Ms					
		16	MsIR					
Kaur et al.	30	30	quadrant-ectomy	20	16.7	n/a	margins	OBCS better
Giacalone et al.	31	43	quadrant-ectomy	54.9	41.9	n/a	margins	OBCS better
Down et al.	37	121	WLE	n/d[1]	n/d[1]	n/a	margins	OBCS better
Mazouni et al.	45[2]	214[2]	WLE	28.9[3]	20.1[3]	46	margins	no difference
							survival	no difference
Gulcelik et al.	106	162	quadrant-ectomy	n/d	n/d	33	margins	no difference
							survival	no difference
Tenofsky et al.	58	84	WLE	n/d	n/d	n/a	margins	no difference
							time to adj.	no difference
Mátrai et al.	60	60	WLE	36.5	21.6	n/a	margins	WLE better
							time to adj.	no difference
Mansell et al.	119	600	WLE	51.3	13.7	n/a	margins	no difference
		281	Ms±IR		50.9			
De Lorenzi	454	908	WLE	44.7	44.7	86	margins	no difference
							survival	no difference
De Lorenzi	193	386	Ms	100	100	89	survival	no difference
Chauhan et al.	33	46	WLE	64	56	18	margins	OBCS better
							survival	OBCS better

[1] The difference between mean tumour sizes of OBCS vs. control patients was significant. [2] Patients received neoadjuvant chemotherapy. [3] Tumour size greater then 3 cm. OBCS – oncoplastic breast conservation surgery; WLE – wide local excision; Ms±IR – mastectomy with or without immediate reconstruction; complicat. – complications; adj. – adjuvant treatment; BBR – bilateral breast reduction; n/d – not disclosed; n/a – not applicable.

Recurrence rates and survival – the ultimate measures of oncological safety – were detailed in six of these studies only. OBCS was compared to WLE in five studies, with pathological characteristics being similar in both groups.[18, 32, 38, 40, 47] There is only one study published so far that compares OBCS to mastectomy, which is a pair-matched comparison of patients who had larger than 2 cm tumour size.[72]

Hence, our study is the only one that compares oncoplastic conservation to wide local excision as well as mastectomy for consecutive patients operated during similar time periods.

We found that the postoperative pathology results after OBCS and Ms±IR were similar (**Table 29**). However, OBCS was significantly different from WLE in that tumour characteristics were more favourable after WLE (**Table 29**). Tumour size was larger than 2 cm in more than half of the patients treated with OBCS or Ms±IR (53.7% vs. 56.2%), but it was only in 15.7% of those treated with WLE. In addition, grade, subtype, nodal involvement and ER expression were all similar between OBCS and Ms±IR patients, but dissimilar to WLE (**Table 29**). Hence, a comparison to Ms±IR is necessary for this group of patients treated with OBCS.

The 5-year distant recurrence rates after OBCS was much higher than WLE, which is explained by the more adverse pathological features seen in patients treated with OBCS (**Table 29**). Therefore, OBCS needs to be compared to patients who underwent surgery for similar tumour pathology which in our cohort were patients who underwent Ms±IR. Distant recurrence rates after mastectomy and OBCS were not significantly different (**Figure 11**). The 5-year local recurrence rates were comparable between the groups. Although the 2 per cent local recurrence rate after OBCS was somewhat lower compared to WLE (3.4 per cent) and Ms±IR (2.6 per cent), the number of events were too low to make a definitive conclusion (**Figure 10**). Whilst oncoplastic surgery has been shown to be oncologically safe based on similar rates of local disease control compared to WLE and Ms±IR, the fact that it is performed on disease of more advanced stage inevitably means that rates of distant metastases are different with long-term disease-free survival rates being intermediate between those of WLE and Ms±IR (**Figure 12**).

While some studies showed a better local control after OBCS possibly due to better resection margins,[14, 17, 32, 36, 37, 47, 178] others implicated less favourable margins after OBCS and slightly higher local recurrence rates.[40, 72, 153] Nevertheless, no studies suggested so far that oncoplastic breast conservation would be oncologically unsafe when recurrence rates were shown (**Table 30**).

Patients in the two control groups are not matched for the OBCS patients, which is one of the weaknesses of this study. Recently, *DeLorenzi* et al. published two case matched studies comparing oncoplastic breast conservation to conservation alone and mastectomy, respectively.[40, 72] While their studies were based on larger cohorts, oncoplastic techniques described were quite heterogeneous involving advancement of glandular flaps in a third of patients suggesting inclusion of level I oncoplastic surgery.[102] Oncoplastic techniques in our study were level II techniques exclusively. In addition, our approach of having the control

groups of consecutive patients over a similar time period from the same unit allowed us to offer a "real-time" estimation of the niche where oncoplastic breast conservation can be offered between wide local excision and mastectomy. We found that approximately one in seven patients treated with breast conservation was offered oncoplastic surgery in our practice, but they were more alike to Ms±IR in terms of tumour biology (**Table 29**). Obviously, the frequency of OBCS is multifactorial and depends on case-mix, co-morbidities, patient's preference and oncoplastic surgical resources. Nevertheless, the indication for oncoplastic surgery should be the tumour biology in the majority of cases.[43, 150, 163, 164] In addition, avoidance of radiotherapy induced toxicity in macromastia, and breast reduction surgery combined with tumour excision for symptomatic macromastia are also reasonable indications for therapeutic mammoplasty.[20, 62, 174, 208, 209] However, when oncoplastic breast conservation surgery is applied frequently for other than therapeutic reasons – which can be referred as oncocosmetic surgery – it can place significant demand on already limited health care resources. Data should be collected about how frequently oncoplastic breast conservation is carried out across the country in order to better define the oncoplastic surgical resource required for a breast unit and possibly to prevent unnecessary procedures.

The principles of breast conservation surgery are based on historical prospective randomised controlled trials.[11, 12, 24, 25, 28, 160] In these trials the majority of patients had small breast tumours while patients treated with OBCS often have larger breast tumours like in our study were over half of the patients treated with OBCS had T2-T3 cancers[13-21, 32] (**Table 29 and 30**). The evidence that cancers with such sizes can be safely treated with breast conservation is not supported by the classic prospective randomized trials.[161] Only 599 patients with T2 cancers were randomized into the arm of breast conservation with radiotherapy in three trials published by *von Dongen* et al, *Poggi* et al and *Fischer* et al, although the latter one randomised up to just 4 cm cancer size.[24-26] Interestingly, patients with T1 cancers only were randomized by *Veronesi* et al and *Arriagada* et al.[11, 28] Hence, the classic randomised controlled trials do not provide sufficient evidence that breast conservation is safe in T2 cancers and above.

The similarities, we found, in the postoperative tumour characteristics between OBCS and mastectomy suggest that oncoplastic conservation may be applied for patients who are routinely treated with mastectomy otherwise (**Table 30**). The potential benefits could be improved patient satisfaction and quality of life, as well as decreased health care costs when compared to full breast reconstruction.[9, 210] Retrospective comparisons of pathology results could provide an estimation of whether a patient who would traditionally be offered a mastectomy could be offered conservation with oncoplastic techniques, thereby extending the

role of breast conservation.[40, 72, 178] Since the indications for oncoplastic conservation is based on preoperative imaging results, patient's anatomy and preference, a prospective study involving all these variables could be informative.

A weakness of this study is that an additional 12 patients were enrolled in the oncoplastic group from a time period preceding the time period of the two control groups. However, extending the time period for the control groups for that initial three years – which was the beginning of the learning curve with low number of OBCS cases – would not have provided additional value for the study. The oncological safety of OBCS can be safely determined involving consecutive WLE and Ms patients from the time period only when OBCS was part of the routine practice, which provided significant excess in terms of patient numbers for the control groups, comparable median follow-up periods and adjuvant treatment variations for all three groups. Involvement of the initial twelve patients in the analysis strengthen the conclusion about oncological safety when it is extended to patients treated at the beginning of the learning curve, too, besides allowing us to measure oncological safety in a comparative way for all consecutive OBCS patients in the prospectively maintained database treated up to August 2012.

Oncoplastic breast conservation should be a quality performance indicator of a breast surgical service, similarly to full breast reconstruction. More evidence needs to be generated to support the oncological safety of oncoplastic breast conservation surgery. This should ideally happen via prospective data collection, or via multicentric retrospective studies preferably in a comparative fashion. In addition, a nationwide audit for oncoplastic breast conservation could significantly contribute to the generation of stronger evidence as this has become a relatively popular and frequently offered treatment option in the UK.

4.7.6. Novel findings

1. Pathology results after oncoplastic breast conservation are similar to mastectomy, but significantly different from WLE.
2. Local recurrence rate after oncoplastic breast conservation is similar to wide local excision and mastectomy.
3. Disease free and cancer specific survival after oncoplastic conservation is comparable to mastectomy.
4. Oncoplastic breast conservation is oncologically safe even when tumour pathology is similar to mastectomy.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Oncoplastic breast conservation surgery is oncologically safe when compared to wide local excision and mastectomy.
Mansell J, Weiler-Mithoff E, Stallard S, Doughty JC, Mallon E, **Romics L**.
Breast. 2017 Apr;32:179-185.

Intraoperative, postoperative and long-term oncosurgical safety of therapeutic mammaplasty.
L Romics, S Barrett, E Weiler-Mithoff, S Stallard.
Orvosi Hetilap 2013 Aug 18;154(33):1291-6. In Hungarian.

4.8. Oncological safety of extreme oncoplasty

4.8.1. Introduction

Extreme oncoplasty, first coined by Silverstein and colleagues, is used to describe a subset of breast conservation surgery (BCS) offered to patients who would otherwise be expected to require mastectomy due to their tumour characteristics.[211] These patients usually fall into two categories: those with cancers of 50mm or above, and those with multifocal/multicentric cancers (MFMC). The change from mastectomy to breast conservation with apparent survival equivalence between these groups, coupled with improved patient satisfaction and cosmesis, suggest that this method may be considered for more advanced or multicentric disease.[11, 211-213] In fact, we offer BCS for potentially poorer prognostic single-tumour patients or in-situ disease but continue to exclude larger or MFMC tumours.[214] The introduction of screening coupled with ultrasonography (US) and magnetic resonance imaging (MRI) has allowed us to identify more sensitively multifocal and multicentric cancers, making diagnosis of these "extreme" cases more common, thus surgical options more valid for debate.[215-217]

Extreme oncoplastic breast conservation surgery (EOBCS) remains a subject of controversy and strong evidence supporting its application is awaited. Study heterogeneity, differences in terminology and classification between multifocal versus multicentric cancers, and variation in outcome measures examined in small studies means that high-powered and standardised research is essential. The current concern is that limitations associated with small studies may tend towards a bias favouring BCS for MFMC cancers due to patient surgical selection bias, favouring patients with better prognostic indicators.[218] Early data from the ACOSOG Z11102 Trial (Alliance) suggests that 67.6% of patients with multiple ipsilateral breast cancer achieve margin-negative excision at first surgery.[219] Finally, de Lorenzi et al. have described the safety in offering Oncoplastic BCS for patients with pT2 cancers in a patient-matched cohort when overall and disease-free survival are examined.[220] However, we again see limitation in the retrospective nature of the data, considering that patients undergoing mastectomy had significantly larger tumours, and were also more likely to be multifocal.[5] Nonetheless, the time to completion of larger studies can anecdotally be supported thanks to this early work, benefitting patients who are currently undergoing treatment. Previous review of outcomes in standard oncoplastic breast surgery in multiple centres across Scotland has shown that practice is comparable to those in high volume centres,[221] suggesting this may translate to extreme OBCS (EOBCS). In addition, recent systematic review suggests that

absolute tumour size may not preclude BCS, based on published mean tumour size and available outcome figures [222]. It is with this in mind that short and long-term outcomes for these patients have been reported [211, 219, 223-226] leading us to examine our own practice within two regional breast units in Glasgow, United Kingdom.

4.8.2. Aim

Recent evidence has suggested that EOBCS may be a valuable resource for patients with MFMC who may avoid the risk associated with mastectomy in favour of the benefits of breast conservation without risking their oncological outcomes. Our study examined the practice of EOBCS in the Glasgow breast units, in the United Kingdom.

4.8.3. Methods

Patients who underwent BCS in 2 breast units in Glasgow (Victoria Infirmary and Western Infirmary in Glasgow) between June 2007 and May 2018 were identified. Patients who had tumours 50mm or greater or were MFMC were considered to have an indication for EOBCS and were therefore included in the analysis. Demographic, histopathologic, and surgical data was collected and analysed retrospectively. Medical records were assessed for additional information as necessary. All data was subject to Caldicott approval, anonymised at the point of collection and collected retrospectively, together with access to local Managed Clinical Network data.

The decision to proceed to EOBCS or mastectomy, and whether contralateral surgery was warranted was at the discretion of the Breast surgeon and plastic surgeon (if performed in conjunction) and according to patient wishes, with input from the multidisciplinary team (MDT), reflecting practice dating back to earlier years within the study, during which immediate symmetrisation and joint operations were less commonly performed. Surgical oncoplastic techniques included a variety of reduction mammoplasty or local flap techniques, together with contralateral breast symmetrisation where indicated following consultation with the patient and according to degree of volume resection. The technique used varied based on pre-operative anatomy, patient preference, tumour location and possibility of volume replacement. The surgical procedures were performed by several breast specialty consultants.

As this was a retrospective study, in accordance with our local guidelines and the Declaration of Helsinki, the need for consent was waived, and patient data was anonymised at the point of collection, each patient assigned a study number (stored confidentially in a secure database), and all analysis based on study number from then onwards. Statistical analysis was performed using Microsoft Excel and IBM Statistical Package for Social Sciences version 24 (SPSS, Chicago, IL, USA).

4.8.4. Results

Reports extracted from our regional (Glasgow) institutional database made within the period June 2007 to May 2018 show a diagnosis of 8580 cases of breast cancer, of whom 4230 had BCS. 304 of these patients had oncoplastic breast surgery. Of these, 50 patients (16%) within this cohort underwent EOBCS for cT3 or MFMC breast cancer and were included in this study. These patients were selected if their radiology or pathology results showed multifocal/multicentric cancer, or in which a single lesion was 50mm or more in size. Results are summarised in **Table 31**.

Table 31. Population and Tumour Characteristics for Study Cohort

All Patients	50 (100%)
Age (range)	55 (35-79)
BMI mean (range)	31.3 (21-44)
Body Mass Index >25	12 (24%)
Body Mass Index >30	22 (44%)
Smoker	8 (16%)
Ex-smoker	9 (16%)
Detection Method	
Screening	22 (64%)
Symptomatic	27 (54%)
Family History Clinic	1 (2%)
Follow up (range) months	56 (1-151)
Tumour Characteristics	
Size on imaging	
• **Unifocal Tumours**	53mm (Median, range 20-90mm)
• **Span of multifocal and multicentric tumours**	2-46mm
Size on Final Pathology	
• **Unifocal Tumours**	42mm (Median, range 8-100mm)
• **Largest size of multifocal and multicentric tumours**	23 (Median, range 10-50mm)
Specimen size (diameter mm)	55 (50-90)
Specimen weight (grams)	243 (85-1400)
Tumour Type	
Ductal carcinoma in situ (DCIS)	7 (14%)
Invasive	43 (86%)
Ductal	38 (76%)
Lobular	3 (6%)
Mixed lobular/ductal	2 (4%)
Invasive Grade	
1	2 (4%)
2	22 (44%)
3	19 (38%)
Oestrogen Receptor positive (ER+)	33 (66%)
Progesterone Receptor positive (PR+)	28 (57%)
Human Epidermal Growth Factor (HER2)+	5 (10%)
Triple Negative (ER/PR/HER2-)	3 (6.1%)
Unifocal	28 (66%)
Multifocal	22 (44%)
Lymphovascular Invasion	14 (28%)
Nodal Status positive	14 (28%)
Positive Margins	9 (18%)
Re-excision	3 (6%)
Mastectomy	6 (12%)
Surgical Technique	
Wise-pattern reduction mammoplasty	39 (78%)
Mastopexy	5 (10%)
Racquet Mammoplasty	1 (2%)
Lateral intercostal Artery Perforator Flap (LICAP)	4 (8%)
Fish-tail mammoplasty	1 (2%)
Melon slice	1 (2%)
Batwing	1 (2%)
Contralateral Symmetrisation	24 (48%)
Thoracodorsal Artery Perforator Flap (TDAP)	1 (2%)
Surgery Characteristics	
<1mm margins for ductal carcinoma in situ (DCIS)	9 (18%)
Re-excision	3 (6%)
Completion Mastectomy	6 (12%)
Adjuvant Therapies	
Chemotherapy	24
Neoadjuvant Chemotherapy	3
Adjuvant Chemotherapy	21

The median age was 55 (range 35-79). Of these, 32 patients were screen-detected, 27 patients were symptomatic, and one was identified via the family history service. 28 patients had cT3 disease on pre-operative imaging, with a median tumour size of 55 (50-90) mm. 22 patients had MFMC cancers, with the largest lesion being less than 50mm in size, but overall radiological abnormality exceeding 50mm in largest diameter within each patient. The mean BMI of the patients was 31.3kg/m^2 (21-44), with 12 patients being considered overweight (BMI 25-30 kg/m^2) and 22 patients being obese (BMI >30 kg/m^2). 8 patients were current smokers, and 9 patients were ex-smokers.

45 patients were treated with volume displacement reduction mammoplasty. Reduction mammoplasties were carried out using a "Wise" pattern incision in 39 patients, Benelli-type reduction was done in two patients, while tennis-racquet, melon slice, batwing and fish-tail mammoplasties were done in one patient each. Immediate contralateral symmetrisation was carried out in 24 patients. 5 patients were treated with volume replacement oncoplastic conservation, of which lateral intercostal artery perforator (LICAP) flap was used in four cases and thoraco-dorsal artery perforator (TDAP) flap in one patient. The median excised specimen weight was 243 (85 – 1400) grams.

43 patients had invasive cancer and seven patients had ductal carcinoma in situ (DCIS) on final postoperative pathology. Of the invasive cancers 38 patients had invasive ductal cancer, 3 patients had invasive lobular cancer, and two patients had mixed ductal / lobular cancer. 22 patients had grade 2, while 19 had grade 3 invasive cancers. 33 patients had ER positive disease, and five patients were HER-2 positive. 14 patients were node positive.

14 (28%) patients developed surgical complications, but only two of them required reoperation for haematoma (**Table 32**). Within the patient who developed complications 5 patients developed haematoma in the breast, 5 had delayed wound healing or skin breakdown, 3 patients developed fat necrosis and 1 patient had cellulitis.

Table 32. Surgical Complication following Extreme Oncoplastic Breast Conservation and interventions required – Major Surgical Complication identifies patients requiring further surgery

Surgical Complication (All)	**14 (28%)**
Major Surgical Complication	
Haematoma	2 (4%)
Minor Surgical Complication	
Haematoma	3 (6%)
Delayed wound healing	5 (10%)
Fat Necrosis	3 (6%)
Cellulitis	1 (2%)
Intervention	
Reoperation/Washout	2 (4%)
Wound expressed (outpatient)	1 (2%)
Aspiration	1 (2%)
Admission for Intravenous antibiotics	1 (2%)

Nine patients had incomplete margins (18%), of which three underwent re-excision and six required completion mastectomy. Those who required mastectomy either had multiple margin involvement, or had multiple previous attempts at breast conservation without successful clearance of margins, or in whom there were concerns in confidently recognising the original tumour bed following re-shaping. 23 patients received adjuvant chemotherapy and all received radiotherapy. Three patients received neoadjuvant treatment with no radiological response prior to surgery. Patients who developed complications did not have a delay in the commencement of their adjuvant therapy.

Median follow-up time of all patients was 62 (6-165) months. 49 patients had a minimum follow-up of 13 months. During this follow-up period 5 patients developed distant metastases, of which one also developed local recurrence diagnosed at the time of metastatic presentation. Overall recurrence was therefore 10%. 4 (8%) patients had died at time of follow up, of which 3 were due to recurrence of disease, with one further patient who died due to metastatic ovarian cancer. All patients with recurrence had tumours >50mm in size rather than a diagnosis of MFMC breast cancer.

4.8.5. Discussion

Extreme oncoplasty must strike a balance between oncological clearance and satisfactory aesthetic outcome. This should not come at the cost of postoperative complications, or survival/disease recurrence disadvantage Historically, guidance has suggested that MFMC cancers, (together with T4 cancers) should be considered a contraindication to BCS, however recent international consensus unanimously voted that oncoplastic surgery should allow the broadening of indication for BCS for larger or multifocal tumours.[213, 227] In this study, we

describe the short-term outcomes for patients who would normally be offered mastectomy due to the clinical size or multifocal/multicentric nature of their breast cancer and demonstrate that EOBCS is oncologically safe.

Our results are comparable to those in the literature. Previous work by Rosenkranz et al. in 2018 suggested that in the case of multiple ipsilateral breast cancers, breast conservation is possible, suggesting rates of 67.6% achievement of negative margins.[219] Despite this, conversion to mastectomy remained low (7.1%). It remains to be seen how these impacts on long term survival and recurrence rates, the results of which are as yet awaited as part of the ACOSOG Z11102 (Alliance) Trial.[219] Koppiker et al. looked at 39 cases of extreme oncoplasty in which routine cavity shaving with frozen section were performed, although follow up is limited to 12 months, and suggested that EOBCS may be an option in patients with larger breasts, particularly when standard BCS may not yield satisfactory results.[95, 226, 228]

Within our study cohort, postoperative complications, although affecting more than a quarter of patients, only required significant intervention in 4%. The variability in standard nomenclature for oncoplastic surgeries, and the "tailored" nature of each procedure make direct comparison difficult.[213] The complication rates for therapeutic mammaplasty in the literature vary greatly amongst a very heterogeneous group of studies, reviews quoting between 10% and 90% risk of complication.[5, 17, 149, 229] Nevertheless, the complication rate here is comparable to the one we reported earlier in a population-based audit in Scotland.[230]

Thanks to EOBCS, 88% patients within this study were spared mastectomy, with margin positivity comparable to other studies which have reported rates from 5%-37.8%.[222, 225, 226, 229, 231] In previous work by Silverstein, the examination of 66 patients with multi-focal/multi-centric cancer or cancers measuring 50mm or above suggests that clear margins could be achieved 83% of the time.[211, 232] Re-excision was required in 9.1% (six) cases, and mastectomy was eventually required in 6.1% (four) cases. In another study clear margins were achieved in 78.3% (n=87) patients, while 37.8% (n=42) and 13.5% (n=15) required re-excision for DCIS or invasive cancer in the margins, respectively.[229] Mean follow up of 24 months suggested 1.5% (n=1) patients developed early recurrence, although long term follow up data is still required.[211]

To reduce the inherent risk associated with advanced, larger tumours, any delay to adjuvant treatment must be avoided.[151] BCS does not impact on commencement of adjuvant therapy, including in the case of larger tumours.[95, 224, 230, 233, 234] This mirrors reports that when compared to BCS and mastectomy (with and without reconstruction) no delays resulted from the use of oncoplastic procedures, although the results are limited by variability in reporting

within the literature.[13, 95, 224] Although not formally assessed as part of this study, we did not identify significant delays to adjuvant treatment in this cohort.

Due to the retrospective nature of our data, cosmetic assessment was not available within our study. However, evidence suggests that satisfactory outcomes are possible in extreme oncoplasty. When viewing cosmetic outcomes, Nebril et al. report significantly greater satisfaction and quality of life in patients undergoing extreme oncoplastic procedures when compared to non-extreme oncoplastic surgery.[222] In a study by Crown et al. 111 patients undergoing extreme oncoplasty were examined and cosmetic outcomes scored and 95% (n=85) patients reported good to excellent cosmesis.[229] Complications were reported in 18 patients (16%), but within those, good cosmesis was reported in 93.3% (n=14) of the 15 who were assessed. Future study should regularly evaluate patient reported outcome measures (PROMs) in order to assess not only feasibility and oncological outcomes but also cosmesis to inform decision-making and patient selection.[5]

Pearce et al. have described the use of Latissimus dorsi (LD) miniflaps and therapeutic mammaplasty in patients in the "extreme" subset.[231] They describe similar practices of frozen section and intra-operative specimen radiology in 90% and 50% of their LD mini-flap and TM cases respectively. Based on their local recurrence rates at mean follow up, predicted recurrence-free 5-year survival was estimated at as 98% for the entire study cohort, with predicted 5-year and 10-year recurrence rates of 1.1% and 16%. The longer follow up, although limited by the size of the cohort, begins to indicate that the long-term outcomes for these patients may prove to be comparable to those undergoing mastectomy.[231]

4.8.6. Novel findings

1. EOBCS should be offered to patients who would usually be exclusively offered mastectomy due to the clinical size or multifocal/multicentric nature of their breast cancer.
2. EOBCS is oncologically safe in short term follow up. Large scale studies are required to confirm these preliminary results, in order to offer EOBCS as a valid option to patients with advanced or multifocal breast cancer.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Extreme Oncoplasty: Breast Conservation in Patients with Large, Multifocal, and Multicentric Breast Cancer.
Savioli F, Seth S, Morrow E, Doughty J, Stallard S, Malyon A, **Romics L.**
Breast Cancer (Dove Med Press). 2021 May 25;13:353-359.

4.9. The impact of COVID-19 pandemic on the frequency of oncoplastic breast conservations in the West of Scotland

4.9.1. Introduction

Patients diagnosed with breast cancer have been facing unprecedented challenges during their treatment since the onset of SARS-CoV-2 (COVID-19) pandemic. Breast cancer specialists have struggled to maintain optimal breast cancer treatment for their patients in the midst of potentially compromised medical resources for cancer therapy while minimising exposure of their patients to COVID-19 infection related risks.[235]

Numerous professional bodies issued valuable recommendations to aid prioritisation of breast cancer care based on tumour biology and cancer stage including recommendations for the surgical treatment of breast cancer in the health care crisis.[236-238] In general, upfront surgery was recommended as a priority led by the biology and potential prognosis therefore, triple-negative and HER-2 positive disease were deemed as priority, while primary endocrine treatment was accepted to temporise surgery in luminal-A tumours.[239]

COVID-19 infection related death has been implicated to be dependent on co-morbidities, age, and anti-cancer treatment including surgery, although the extent of contribution of these factors is confounding due to the limited evidence available.[240-246] Specifically, COVID-19 related risk in patients requiring surgery for breast cancer have been evaluated in three studies only.[241, 247, 248]

4.9.2. Aim

We evaluated the safety of breast cancer surgery during COVID-19 pandemic as well as analysed the change in frequency of oncoplastic breast surgery applied in a prospective observational study in the West of Scotland region during the first eight weeks of the national lockdown in the United Kingdom and compared outcomes to the regional cancer registry data of pre-COVID-19 patients.

4.9.3. Methods

A prospective registry of patients who had surgical treatment for invasive or non-invasive breast cancer in the West of Scotland was created when lockdown was introduced by the Scottish Government on 23 March 2020. Patients entered in the first 8 weeks of the lockdown, between 23 March 2020 and 15 May 2020, were included in the analysis. Three NHS Scotland Health Boards participated in the audit, which was approved by the relevant clinical directors of the health boards.

The following parameters were collected prospectively: age, dates of diagnosis and surgery, perioperative risk factors (BMI, co-morbidities, smoking habit, ASA grade), clinical and pathological tumour size, nodal status, subtype, grade, ER and HER-2 expression, details of neoadjuvant treatment, types of breast and axillary surgery, length of hospital stay, treatment affected by COVID-19 pandemic, COVID-19 infection rates, details of postoperative complications, unplanned hospital readmission or return to operating theatre.

This prospective cohort was compared against a cohort of patients (n=1415) from the same region, who were diagnosed with invasive or non-invasive breast cancer between 1 January 2015 and 31 December 2015. This cohort was identified from the prospectively maintained Managed Clinical Network (MCN) database and Caldicott Guardian approval was gained previously.[249] Comparison was made of clinicopathological factors and surgical treatments between pre-COVID-19 hospital lockdown and the same units during hospital lockdown due to COVID-19 pandemic.

During lockdown all patients were screened for possible COVID-19 infection related symptoms. In cases where COVID-19 infection was clinically suspected patients were asked to self-isolate and surgery was postponed by a minimum of two weeks followed by a re-assessment of the patient. In one Health Board routine preoperative COVID-19 PCR testing was introduced four weeks after the hospital lockdown, which was performed within 72 hours of the date of surgical treatment followed by self-isolation until the time of surgery. The operating hospitals were non-receiving hospitals for patients with diagnosed COVID-19 infections including Ambulatory Care and Diagnostic Centre facility or independent sector hospital procured for NHS cancer surgery. These hospitals do not have a High Dependency Unit so patients requiring emergency surgery, or those deemed as having a high anaesthetic risk were operated on in an acute receiving hospital where patients with diagnosed COVID-19 infection were being treated. Data collection and analysis was performed using Microsoft Excel

365 Software. Statistical significance (considered as p≥0.05) was calculated using Mann-Whitney U test, Chi-Square test and Z-test for two proportions, as appropriate.

4.9.4. Results

179 patients were included in the analysis, all patients underwent surgical treatment for invasive or non-invasive breast cancer in the West of Scotland. Three of the four NHS Scotland Health Boards in the West of Scotland participated in the audit including seven of the eleven breast surgical units of the region. These seven breast units diagnose and treat 61.2% (1415 of 2292) of all newly diagnosed breast cancers in the region yearly based on previous figures of Managed Clinical Network in Scotland (2015), hence this is a representative audit of the region.

189 surgeries were carried out in 180 patients. 5 patients had two oncological surgeries, another 4 patients returned to theatre due to postoperative complications. One patient required emergency surgery to remove an infected implant inserted 10 months earlier, who was excluded from the analysis.

Median age of the patients was 54 years (27-81). Date of diagnosis ranged between 31 July 2019 and 7 May 2020. 42 of the 179 patients were diagnosed during lockdown due to the COVID-19 pandemic. Almost two-thirds of the patients were diagnosed in the symptomatic service (64.8%), which was significantly higher compared to patients diagnosed in the symptomatic service before lockdown in this region (52.9%; p<0.001) (**Table 33**). Breast screening had been stopped in Scotland at the start of lockdown.

Table 33. Comparison of clinicopathological characteristics of patients treated during COVID-19 pandemic caused lockdown and outside of the pandemic in the West of Scotland

		COVID-19 database		MCN database		P value
Clinicopathological characteristics		No. of patients (%)		No. of patients (%)		
Presentation	symptomatic	116	64.8%	749	52.9%	<0.001 CS
	screener	57	31.8%	469	33.1%	
	other	6	3.3%	197	13.9%	
cT[1]	cTis	7	4.2%	132	6.3%	<0.001 CS
	cT1	57	34.1%	685	32.7%	
	cT2	75	44.9%	1121	53.6%	
	cT3-4	28	16.8%	154	7.4%	
cN[2]	cN0	127	75.1%	1125	80.9%	0.099 (NS)
	cN1-3	41	24.9%	265	19.1%	
Tumour subtype[3]	DCIS / LCIS	8	4.7%	116	8.3%	0.057 MW
	Ductal	126	73.7%	988	70.8%	
	Lobular	22	12.7%	152	10.9%	
	Mixed	3	1.7%	16	1.1%	
	Mucinous	2	1.2%	22	1.5%	
	Tubular	2	1.2%	15	1.1%	
	Papillary	2	1.2%	5	0.3%	
	Other	5	2.9%	71	5.1%	
	Inflammatory	1	0.6%	11	0.8%	
(y)pT	yPt0	10	5.9%	N/A	N/A	0.002 CS
	(y)pTis	11	6.5%	116	10.1%	
	(y)pT1	71	42%	619	54.1%	
	(y)pT2	57	33.7%	344	30.1%	
	(y)pT3 – T4	20	11.8%	64	5.6%	
Grade[4]	G1	11	6.8%	96	9.1%	0.107 (NS) CS
	G2	70	43.2%	522	49.5%	
	G3	81	50%	436	41.3%	
ER expression[4]	negative	67	41.3%	217	17%	<0.001
HER-2 expression[4]	positive	38	23.4%	188	14.8%	=0.004
(y)pN[4]	(y)pN0	112	69.1%	711	68.2%	=0.791 (NS)
	(y)pN1	36	22.2%	253	24.2%	
	pN2	8	4.9%	53	5.1%	
	pN3	6	3.7%	26	2.5%	

[1] Data was not available for 12 patients in the COVID database and 717 patients had either cT0, or primary tumour was not assessed in the MCN database. [2] Data was not available for 11 patients in the COVID database and 26 patients lymph nodes were not assessed or recorded in the MCN database. [3] Final pathology is awaiting in 7 patients in the COVID database and primary tumour subtype was not assessable or recorded in 19 patients in the MCN database. [4] Grade not assessable or not applicable in 218 patients in the MCN database. Grade, ER status and HER-2 status were determined in invasive cancer only.

Median preoperative tumour size was 25 mm (5-110). The clinical tumour size was significantly larger in patients undergoing surgery during lockdown with 28 patients (16.8%) having cT3-4 disease compared to patients operated before lockdown (vs. 154 of 1415 patients (7.4%); p<0.001)) (**Table 33**). This trend is reflected in the pathological tumour size with more patients having surgery for pT2 – pT4 disease during the pandemic compared to patients treated before lockdown (45.5% vs. 35.6%; p=0.002). However, the rate of clinically and pathologically node positive disease were similar in patients who underwent surgery during lockdown compared to the pre-lockdown times (cN1-3: 24.9% vs. 19.1%, p=0.099; (y)pN1-3: 30.8% vs. 31.8%, p=0.791). Tumour subtypes and grade were comparable in the two groups with somewhat less patients undergoing surgery for DCIS and more patients undergoing

surgery with G3 disease during the COVID-19 pandemic (p=0.057 and p=0.107, respectively). However, a sharp difference between ER- and HER-2 expression were found in between the two groups with significantly more patients having ER negative and HER-2 positive disease in the COVID-19 group compared to patients operated before the pandemic (ER negative: 41.3% vs 17%, p<0.001; and HER-2 positive: 23.4% vs. 14.8%, p=0.004) (**Table 33**).

105 (58.6%) patients had breast conservation surgery (BCS) during lockdown, of which 24 (13.4%) patients underwent level II oncoplastic breast conservation surgery comprising of 22.8% oncoplastic surgical rate of all BCSs (**Table 34**).

Table 34. Comparison of breast cancer surgeries during COVID-19 pandemic caused hospital lock down and outside of the pandemic in the West of Scotland.

		COVID database				MCN database		
Surgical technique								
Breast surgery		No. of cases	Per cent	Details of operations	No. of cases	No. of cases[4]	Per cent	p value
OBCS	**Therapeutic mammoplasty[1]**	13	7.7%	TM + ANC	2	41	3.5%	<0.0001
				TM + SLNB	4			
				TM + sym. red + SLNB	7			
	LICAP flap reconstruction	6	3.5%	LICAP + SLNB	5			
				LICAP + ANC	1			
	AICAP flap reconstruction	2	1.2%	AICAP + SLNB	1			
				AICAP + ANC	1			
	Round block excision	3	1.8%	Round bl. + SLNB	2			
				Round bl.	1			
Wide local excision		81	47.9%	WLE + SLNB	63	730	61.6%	
				WLE +ANC	9			
				WLE	9			
Mastectomy		64	37.9%	Mx[2] + ANC	27	314	26.5%	
				Mx + sampling	1			
				Mx only	5			
				Mx + SLNB	31			
Mastectomy and IBR		0	0		0	100	8.4%	
Re-excisions[3]		13	N/A	Re-exc.	12	N/A	N/A	
				Re-exc. + ANC	1			
Axillary surgery								=0.05
Sentinel lymph node biopsy		113	72.4%			851	79.4%	
Axillary clearance		41	26.3%			203	18.9%	
Sampling		1	0.6%			16	14.9%	
Excision of lymph node		1	0.6%			1	0.01%	

[1] In 7 patients contralateral symmetrising reduction was carried out simultaneously. [2] In one patient bilateral mastectomy was carried out. LICAP = lateral intercostal perforator flap. [3] In 7 patients the WLE was carried out before the hospital lock down, while in another patients both the wide and the re-excision were done during lock down. [4] In the breast 220 patients and in the axilla 344 patients did not receive any / require surgery or refused treatment or data not recorded. TM = therapeutic mammoplasty with breast reduction technique from "wise" patter incision. ANC = axillary node clearance. SLNB = sentinel node biopsy. Sym. red. = symmetrising reduction. Round bl. = round block technique. LICAP = lateral intercostal perforator flap. AICAP = anterior intercostal perforator flap. In 2 cases axillary surgery was carried out only. In 28 cases no axillary surgery was carried out.

While BCS rate was higher in patients operated before the COVID-19 pandemic (65%), only 5.6% of the patients were treated with oncoplastic surgery of all patients treated with BCS (**Table 34**). There was no immediate reconstruction carried out during lockdown and no significant difference was found in terms of axillary surgical procedures between the two groups of patients. Length of hospital stay during lockdown was less than 24 hours in 166 cases (90.2%), and of these day-case surgery was carried out in 65 cases (35.3%). Significantly higher proportion of patients received neo-adjuvant chemotherapy in the COVID-19 group compared to the patients treated before the pandemic (30.1% vs. 10.4%; p<0.001).

For perioperative risk factors BMI, co-morbidities, recent smoking habit, and COVID-19 infection was analysed (**Table 35**).

Table 35. Risk factors and postoperative complications in patients operated during COVID-19 pandemic caused hospital lock down in the West of Scotland.

	No. of patients (%)	Details of risk factors	No. of patients
Risk factors			
Co-morbidities[1]	93 (53.1%)	Respiratory only (asthma, COPD, bronchiectasis)	7
		CV only (HTN, DVT, AF, mitral regurg, IHD, CVA, MVR)	31
		Endocrine (DM, hypo, hyperthyr)	4
		Musculo-skeletal (OA, RA)	3
		Morbid obesity	6
		Other (aneamia, chronic pain, Guillan-Barré sy, epilepsy, MS, PBC, depression, SLE, previous malignancy)	11
		GI (GORD)	6
		Combined Resp + CV	6
		Combined Resp + other	2
		Combined CV + morb obesity	1
		Combined CV + GI	2
		Combined CV + morb obesity + endocrine	1
		Combined CV + other	2
		Combined CV + GI + endocrine	1
		Combined CV + GI + endocrine + morb obese	1
		Combined CV + GI + other	1
		Combined endocrine + other	3
		Combined Resp + CV + other	1
Obesity[2]	57 (35%)	Obese	23
		Severe obese	24
		Morbidly	10
Current Smoker[3]	27 (15.7%)		
ASA II and above[4]	124 (69.3%)	ASA II	114
		ASA III	10
Complications			
Clavien-Dindo I	8 (4.5%)	Repeated of aspirations of seroma	1
		Infection treated with oral antibiotics	6
		Delayed wound healing	1
Clavien-Dindo II	2 (1.1%)	Postoperative hypoxia	1
		Postoperative delirium	1
Clavien-Dindo III	4 (2.2%)	Evacuation haematoma	2
		Washout of infected seroma	2

[1] No data available for 4 patients. [2] No data available for BMI in 16 patients. [3] No data available in 7 patients. [4] No data available on 9 patients. CV = cardio-vascular. HTN = hypertension. Resp = respiratory.

The median BMI of the patients was 26.3 (15-48), with 128 patients (71.5%) being at least overweight, of which 57 (35%) suffered from various degree of obesity (**Table 35**). 93 patients (51.2%) had co-morbidity, of which 29 patients (16.2%) had at least two co-morbidities documented. 27 patients (15.7%) were current smokers. Similar data for co-morbidities are not available in the MCN database, hence a direct comparison could not have been carried out.

Altogether 14 patients (7.8%) developed postoperative complications, of which 6 patients (3.3%) had major complication requiring in-hospital treatment. 4 patients returned to theatre for complications including evacuation of haematoma and washout of infected seroma (**Table 35**). Two of these four cases were carried out in an acute receiving hospital with patients treated with COVID-19 infection. A further two patients required transfer to the acute receiving hospital. One of them developed postoperative hypoxia, while the other patient had delirium. Of the elective cases, four patients with significant co-morbidities were operated on in acute receiving site (one unilateral therapeutic mammoplasty and three mastectomies).

Patient management was affected by COVID-19 pandemic in 78 patients (43.6%) overall (**Table 36**).

Table 36. Impact of COVID-19 pandemic and consequent hospital lock down on the overall management of patients.

Impact of COVID-19 pandemic on patients' management	No. of patients	% of all patients
IBR not carried out	28	15.6%
Contralateral reduction not carried out	3	1.7%
Change to LA from GA	1	0.5%
NAC not completed	19	10.6%
NAC not completed + Contralateral reduction not carried out	2	1.1%
NAC not completed + IBR not carried out	7	3.9%
NAC not offered	7	3.9%
NAC not offered + IBR not carried out	5	2.8%
PET due to COVID-19 lockdown, surgery delayed	5	2.8%
PET due to presumed COVID-19 infection, surgery delayed	1	0.5%

LA = local anaesthetic. GA = general anaesthetic. IBR = immediate breast reconstruction. NAC = neo-adjuvant chemotherapy. PET = primary endocrine therapy.

40 patients would have been suitable for immediate postmastectomy breast reconstruction, which comprised of 62.5% of all patients treated with mastectomy during COVID-19 lockdown. Of the six patients who had unilateral therapeutic mammoplasty through a "Wise" pattern incision, five would have had immediate contralateral symmetrisation outside the pandemic. 28 patients had their neo-adjuvant chemotherapy interrupted due the pandemic, which comprised of 51.8% of all patients having surgery after neo-adjuvant chemotherapy during the pandemic. Conversely, 12 patients went straight to surgery who would have been

offered neoadjuvant chemotherapy outside COVID-19. In 14 patients (7.8%) both the surgical and adjuvant treatments were affected by the pandemic (**Table 36**).

COVID-19 infection was suspected in five patients altogether. In two patients the preoperative imaging raised suspicion of COVID-19 infection, and surgery was delayed by two weeks but patients were not tested. In further three patients postoperative COVID-19 infection was suspected. These three patients all subsequently tested negative, although one of them required transfer to an acute receiving hospital due to hypoxia. There was one patient who tested positive on routine preoperative COVID-19 testing, whose surgery was also delayed. There was no mortality and no peri-operative COVID-19 infection related morbidity detected in this cohort of patients.

4.9.5. Discussion

Our study of 179 patients undergoing breast cancer surgery in the West of Scotland region during the COVID-19 pandemic demonstrates that selected surgery for breast cancer surgery can be safely delivered. Initial data suggested that cancer patients receiving anti-cancer treatment have a higher mortality rate if they develop COVID-19 infection. A retrospective analysis by Zhan et al. of 28 patients from Wuhan, China showed a 28.6% mortality rate, and having the last anti-cancer treatment within 14 days of the infection significantly increased the risk of mortality from COVID-19 infection.[246] Similarly, a nationwide analysis by Liang et al. showing similar data based on the extraction of data from 18 cancer patients from 1590 patient with COVID-19 infection.[250] However more recent data by Lee et al. from the UK Coronavirus Cancer Monitoring Project (UKCCMP), which involved 800 cancer patients with COVID-19 infection, demonstrated no significant effect on mortality for patients who received chemo-, immuno-, hormonal, or radiotherapy within 4 weeks of the infection.[242] Vaugnat et al. claimed the same analysing a population of 59 patients with COVID-19 infection from the 15600 patients actively treated with breast cancer at the Institut Curie Hospitals.[244] In fact, age (>70), male gender and severe comorbidities were independently associated with mortality from COVID-19 infection.[242, 244]

Early data of patients with COVID-19 infection undergoing elective general surgery suggested a significantly increased mortality rate up to 20.5% based on the analysis of 34 patients in Wuhan, China.[243] This preliminary finding was confirmed by a large scale international cohort study (COVIDsurg collective) including 294 patients with preoperatively confirmed COVID-19 infection from a cohort of 1128 undergoing surgery.[240] In adjusted

analyses, 30-day mortality was associated with male gender, age (>70), ASA grade 3-5, malignancy, emergency and / or major surgery.[240] The COVID-19 and Cancer Consortium (CCC19) database including 928 patients with COVID-19 infection undergoing active anti-cancer treatment revealed that 30-day all-cause mortality is independently associated with age, male gender, and the number of comorbidities among others, but not with the type of anti-cancer therapy or recent surgery.[241]

There is hardly any evidence however on the safety of breast cancer surgery during COVID-19 pandemic available as the number of patients who had breast cancer surgery were either single figures (Wuhan study, COVIDsurg collective) or the breast cancer specific anti-cancer treatment (CCC19 database: 191 breast cancers, UKCCMP study: 102 breast cancers) were not provided.[240-243]

In terms of surgical techniques more oncoplastic breast conservations were carried out in comparison to our pre-COVID-19 practice due to immediate breast reconstruction not being offered after mastectomy (**Table 34**). Oncoplastic breast conservation surgery has been shown as a safe alternative to mastectomy and immediate breast reconstruction in selected patients based on the combined data of iBRA-2 and TeaM studies of 2916 patients.[51] Further, the Scottish audits of oncoplastic breast conservations indicate that oncoplastic surgery can widen the indications for breast conservation, and provide good oncological outcome with low complication rates in our hands, hence it can be a reasonable alternative to mastectomy with immediate reconstruction.[75, 95, 97, 251] One unit in Italy did offer immediate breast reconstruction even during the peak of the COVID-19 pandemic as it is indicated by Fragetti et al. who reported 15 nipple-sparing mastectomies with immediate reconstruction done in 13 patients, although reconstructive techniques were not disclosed.[248] In our study the higher rate of oncoplastic breast conservation surgery was partly a consequence of declined immediate breast reconstruction due to COVID-19 risks as opposed to an elective planned argument, although it also reflects practice changes over a period of five years. Nevertheless, a very careful approach, within a framework of close collaboration between breast and reconstructive surgeons, is required to carefully select patients and reconstructive techniques to allow re-starting of immediate breast reconstructions when appropriate.[236, 252]

In terms of COVID-19-related risk in patients undergoing treatment for breast cancer we found six patients of the 179 who had suspected or proven COVID-19 infection perioperatively. Corsi et al. reported on 63 patients who underwent breast cancer surgery over a five-week period in one of the breast units in Pavia (Lombardy, Italy), with one patient only being diagnosed with COVID-19 infection.[253] Similarly, Fragetti et al. reported on 85 patients, who

had breast cancer surgery in a four-week time period with three patients being diagnosed with COVID-19 infection preoperatively and further three patients required to have two-week delay in surgery due to suspected infection.[248] These figures imply that we need to carefully select our patients and avoid operating – if possible – on those with relatively high COVID-19 mortality risk. The above mentioned three large prospective cohort studies (UKCCMP, CC19, COVIDSurg) had similar outcomes in terms of risk factors for COVID-19 related death, hence surgery should be carried out with extreme caution in patients with multiple co-morbidities in particular those who are elderly.[240-242]

There is some weakness of this paper which mainly relates to the control group of patients from the MCN database. Breast surgical practice has undoubtedly changed in the last 5 years hence a more recent cohort would have been more ideal. Due to time pressure arising from the relative urge of these results during lockdown this was not available in the MCN database at the time when the manuscript was written. Further, we did not have co-morbidity data in the MCN database so we could not make a comparison which would have been an important point of the study. Nevertheless, this study provides the strongest evidence about safety of breast cancer surgery in lockdown due to COVID-19 infection and may provide reassurance in the future if lockdown happens again.

In conclusion, we have demonstrated that in a population in whom over 50% have co-morbidities surgery for breast cancer can be safely provided during COVID-19 pandemic in selected patients.

4.9.6. Novel findings

1. Tumour size was significantly larger in patients undergoing surgery during hospital lockdown than before as well as ER negative and HER-2 positive rate was significantly higher during lockdown.
2. While breast conservation rate was lower during lockdown, level II oncoplastic conservation rate was significantly higher in order to reduce mastectomy rate during the COVID-19 pandemic.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

A prospective cohort study of the safety of breast cancer surgery during COVID-19 pandemic in the West of Scotland.
Romics L, Doughty J, Stallard S, Mansell J, Blackhall V, Lannigan A, Elgammal S, Reid J, McGuigan MC, Savioli F, Tovey S, Murphy D, Reid I, Malyon A, McIlhenny J, Wilson C.
Breast. 2021 Feb; 55:1-6.

5. INVESTIGATION OF THE ONCOLOGICAL SAFETY OF ONCOPLASTIC SURGERY IN NATIONAL AND INTERNATIONAL STUDIES

5.1. Comparative analysis of indications for oncoplastic conservation, wide local excision, and mastectomy in Scotland

5.1.1. Introduction

To date, practice and outcomes of oncoplastic breast conservation (OBC) have primarily been reported in the form of single institution case series with a significant proportion of those being retrospective studies with small patient numbers.[22, 23, 32, 38, 40, 44, 46, 175, 198, 234, 254-256] So far only one single national audit on OBC practice has been published despite the global application of the technique.[75]

Traditionally, breast cancer national audits on surgical outcomes classify breast surgeries as breast conservation, mastectomy and mastectomy with immediate reconstruction.[257, 258] As oncoplastic breast conservation (OBC) represent a further treatment option, it is important to collect robust comparative nationwide data.

Existing comparative studies of OBC generally compare outcomes to those in SBC.[18, 23, 32, 39, 40, 95, 168, 259] While a few comparative studies with mastectomy have also been published, the role of OBC is not fully defined in terms of whether it is equivalent to SBC, but rather an alternative to mastectomy, or whether it occupies its own niche somewhere between the two.[22, 23, 72, 82, 168]

5.1.2. Aim

We carried out a population-based prospective audit of current OBC practice in comparison to SBC, mastectomy and mastectomy with immediate reconstruction (MIR) based on the cancer registry database of the National Managed Clinical Network in Scotland. We have focused on comparative analysis of tumour and patient characteristics, adjuvant and neoadjuvant treatments, time to surgery from diagnosis and time to adjuvant treatment from surgery.

5.1.3. Methods

All patients diagnosed with breast cancer in Scotland over a two year period (between 01/01/2014 and 31/12/2015) were identified from prospectively maintained databases within the National Managed Clinical Networks / Cancer Networks of the 3 Scottish regions covering the whole of Scotland (WOSCAN: West of Scotland Cancer Network, SCAN: East of Scotland Cancer Network and NOSCAN: North of Scotland Cancer Network.[260] Since 2014, therapeutic mammoplasty (OBC) has been coded separately as final surgical treatment within the National Minimal Core Dataset to Support the Introduction of Breast Quality Performance Indicators (Information Services Division of NHS National Services Scotland).[261] Therefore, from this database we were able to identify patients who had undergone OBC, SBC, mastectomy, or MIR as their final definitive surgery in whole Scotland. From the same database, data was collected for each patient regarding patient age at diagnosis, tumour pathology, neoadjuvant treatment and adjuvant treatment including the dates on which this was commenced. Patients who had any other kind of procedure or who received non-operative treatment only were excluded. Approval for access to this data was granted by the Public Benefit and Privacy Panel for Health and Social care in Scotland. Caldicott guardian approval was gained for the study from the relevant Cancer Networks.

Patient and tumour characteristics were compared between the four groups. Pearson Chi square was used to compare categorical variables. Z-test was used to compare 2 population proportions. Mann-Whitney test was used to compare two medians. All tests were two sided. All analysis was carried out using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY).

5.1.4. Results

8075 patients were included in the study. The median age at diagnosis was 61.6 years (23-97). 217 (2.7%) patients had OBC as their definitive surgical procedure. 5241 (64.9%) had SBC, 710 (8.8%) had MIR and 1907 (23.6%) had mastectomy alone. Of all patients who underwent conservation surgery, OBC comprised 4.0% of these operations. When rates were analysed between the three geographical regions of Cancer Networks in Scotland, WOSCAN patients had the highest rates of OBC within the breast conservation group (WOSCAN: 120/2484, 4.8%; SCAN: 60/1695, 3.5%; NOSCAN: 37/1279, 2.9%; p=0.0032). However, overall, SCAN had the highest rate of breast conservation from the three regions (SCAN: 1695/2229, 76.0%; NOSCAN: 1279/1983, 64.5%; WOSCAN: 2484/3863, 64.3%; p<0.0001) **(Table 37).**

Table 37. Regional differences in type of breast cancer surgeries in Scotland

	WOSCAN n (%)	SCAN n (%)	NOSCAN n (%)	Totals n (%)
OBC	120 (3.1)	60 (2.7)	37 (1.9)	217 (2.7)
SBC	2364 (61.2)	1635 (73.4)	1242 (62.6)	5241 (64.9)
Mastectomy	1018 (26.4)	362 (16.2)	527 (26.6)	1907 (23.6)
MIR	361 (9.3)	172 (7.7)	177 (8.9)	710 (8.8)
	3863	2229	1983	8075

OBC: oncoplastic breast conservation; SBC: standard breast conservation; MIR: Mastectomy with immediate reconstruction SCAN: East of Scotland Cancer Network; NOSCAN: North of Scotland Cancer Network; WOSCAN: West of Scotland Cancer Network.

The median age of OBC patients was between that of SBC and mastectomy patients (OBC: 55 years (29-81) vs. SBC: 62 years (23-97), or vs. mastectomy: 70 years (25-96), both $p<0.0001$) and MIR patients (50 years (24-78), $p<0.0001$) **(Table 38**).

Table 38. Clinicopathological characteristics of patients in each surgical group

	OBC n (%)	SBC n (%)	Mastectomy n (%)	MIR n (%)	p value OBC v SBC	P value OBC v mastect.	P value OBC v MIR
Age					<0.0001	<0.0001	<0.0001
≤50years	66 (30.4)	882 (16.8)	319 (16.7)	361 (50.8)			
51-69 y≥≥ears	127 (58.5)	3130 (59.7)	802 (42.1)	325 (45.8)			
≥70 years	24 (11.1)	1229 (23.4)	786 (41.2)	24 (3.4)			
Mode of referral					0.074	<0.0001	<0.0001
Screening service	92 (42.4)	2468 (47.1)	387 (20.3)	175 (24.7)			
Other screening (eg. review/FH clinic)	4 (1.8)	189 (3.6)	127 (6.7)	66 (9.3)			
Symptomatic	119 (54.8)	2569 (49.0)	1380 (72.4)	464 (65.4)			
Other	2 (0.9)	15 (0.3)	13 (0.7)	4 (0.6			
Tumour type					0.015	<0.0001	0.078
DCIS	29 (13.4)	524 (10.0)	107 (5.6)	114 (16.1)			
Ductal/NST	153 (70.5)	3814 (72.8)	1308 (68.6)	437 (61.5)			
Lobular	27 (12.4)	426 (8.1)	339 (17.8)	101 (14.2)			
Mucin/Medul/Tubul	5 (2.3)	231 (4.4)	46 (2.4)	21 (3.0)			
Mixed/other invasive	2 (0.9)	175 (3.3)	102 (5.3)	34 (4.8)			
Other	1 (0.5)	67 (1.3)	5 (0.3)	3 (0.4)			
cT stage					<0.0001	<0.0001	0.121
cT0	0 (0)	64 (1.3)	12 (0.7)	13 (2.0)			
cTis	35 (18.8)	553 (11.6)	134 (7.8)	136 (21.2)			
cT1	61 (32.8)	2887 (60.4)	501 (29.1)	215 (33.4)			
cT2	76 (40.9)	1177 (24.6)	733 (42.6)	212 (33.0)			
cT3	8 (4.3)	42 (0.9)	179 (10.4)	47 (7.3)			
cT4	6 (3.2)	60 (1.3)	163 (9.5)	20 (3.1)			
ITS					<0.0001	<0.0001	0.030
≤20mm	94 (51.9)	3272 (72.5)	581 (33.5)	265 (47.7)			
21-50mm	76 (42.0)	1201 (26.6)	899 (51.8)	216 (38.9)			
>50mm	11 (6.1)	42 (0.9)	255 (14.7)	74 (13.3)			
WTS					<0.0001	<0.0001	<0.0001
≤20mm	69 (33.0)	3295 (65.1)	390 (21.2)	166 (24.8)			
21-50mm	113 (54.1)	1690 (33.4)	1032 (56.2)	314 (46.9)			
>50mm	27 (12.9)	79 (1.6)	414 (22.5)	189 (28.3)			
Grade					0.030	0.008	0.645
I	17 (9.2)	745 (16.2)	87 (5.0)	50 (8.9)			
II	97 (52.7)	2344 (51.1)	836 (47.7)	318 (56.6)			
III	70 (38.0)	1502 (32.7)	831 (47.4)	194 (34.5)			
ER status					0.042	0.323	0.232
Negative	40 (20.2)	716 (14.9)	423 (23.3)	104 (16.5)			
Positive	158 (79.8)	4087 (85.1)	1391 (76.7)	526 (83.5)			
HER2 status					0.003	0.144	0.197
Positive	34 (18.3)	509 (11.1)	338 (19.0)	102 (17.4)			
Negative	151 (81.2)	4083 (88.8)	1437 (80.9)	484 (82.6)			
Inconclusive	1 (0.5)	5 (0.1)	1 (0.1)	0 (0)			
Nodal status					0.211	<0.0001	0.006
Negative	141 (74.2)	3609 (78.0)	947 (51.4)	431 (63.5)			
Positive	49 (25.8)	1015 (22.0)	897 (48.6)	248 (36.5)			

OBC: oncoplastic breast conservation; SBC: standard breast conservation; mastect.: mastectomy; MIR: mastectomy with immediate reconstruction; Mucin: mucinous; Medul: medullary; Tubul: tubulary; cT stage: clinical tumour stage; ITS: invasive tumour size; WTS: whole tumour size; ER: oestrogen receptor

OBC patients were more likely to present through screening than patients in either of the other two groups (both p<0.0001) (**Table 38).** OBC patients had a higher proportion of lobular cancers and DCIS compared to SBC patients (p=0.015), and had more DCIS but fewer lobular cancers compared to mastectomy patients (p<0.0001). Interestingly, tumour subtypes were similar between OBC and MIR patients (**Table 38)**. OBC patients had higher clinical T (cT) stage (p<0.001) and larger pathological tumour size compared to SBC patients (median invasive tumour size (ITS) OBC: 20mm (1-90) v SBC: 15mm (0-95), p<0.001; median whole tumour size (WTS) OBC: 25mm (1-120) v SBC: 17mm (0-123), p<0.001) (**Table 38)**. Conversely, OBC patients had lower cT stage (p<0.001) and smaller pathological tumour size compared to mastectomy (median ITS mastectomy: 27mm (0-190), p<0.001; median WTS mastectomy: 33mm (0-190), p<0.001). cT stage was similar in patients treated with OBC and MIR (p=0.121), but ITS and WTS was, again, smaller in OBC in comparison to MIR patients (median ITS MIR: 21mm (0-180), p=0.030; median WTS MIR: 35mm (1-246), p<0.001) **(Table 38)**. Tumour grade of patients treated with OBC was between the SBC and mastectomy groups, with more high-grade tumours in the SBC group (p=0.030) and more lower grade cancers compared to the mastectomy group (p=0.008) **(Table 38)**. There were more ER negative (p=0.042) and HER-2 positive (p=0.003) patients in the OBC group than in the SBC group and fewer node positive cases in OBC patients when compared to mastectomy (p<0.001) or MIR patients (p=0.006) **(Table 38)**.

Time to first surgery from diagnosis was significantly longer for patients treated with OBC compared to SBC (median 43 days (11-133) vs 29 days (4-176); p<0.0001) or mastectomy (32 (4-178); p<0.0001), but it was shorter than MIR (51 days (8-175); p<0.0001) **(Table 39)**. Similarly, time to final surgery was longer when patients were treated with OBC compared to SBC (median 49 days (11-133) vs 33 days (4-176); p<0.0001) or mastectomy (34.5 (4-178); p<0.0001), but it was shorter than MIR (59 days (11-175); p=0.0001) **(Table 39)**.

Table 39. Time to surgery from diagnosis by type of surgery

	OBC n (%)	SBC n (%)	Mastectomy n (%)	MIR n (%)	p OBC v SBC	p OBC v mastect	p OBC v MIR
Time to first breast surgery from diagnosis					<0.0001	<0.0001	0.007
1-30 days	18 (16.4)	1731 (52.5)	520 (46.4)	58 (16.5)			
31-60 days	70 (63.6)	1397 (42.4)	516 (46.0)	167 (47.6)			
61-90 days	16 (14.5)	131 (4.0)	60 (5.4)	107 (30.5)			
90 days	6 (5.5)	37 (1.1)	25 (2.2)	19 (5.4)			
Time to final breast surgery from diagnosis					<0.0001	<0.0001	0.002
1-30 days	14 (12.7)	1478 (44.5)	448 (39.8)	27 (7.6)			
31-60 days	57 (51.8)	1428 (42.9)	483 (42.9)	139 (38.9)			
61-90 days	29 (26.4)	315 (9.5)	123 (10.9)	106 (29.7)			
90 days	10 (9.1)	104 (3.1)	72 (6.4)	85 (23.8)			

OBC: oncoplastic breast conservation; SBC: standard breast conservation; mastect.: mastectomy; MIR: mastectomy with immediate reconstruction. Patients with neodjuvant treatment, M1 stage and time over 6 months to surgery from diagnosis were excluded.

Neoadjuvant chemotherapy rate in patients treated with OBC was significantly higher when compared to SBC (15.3% v 7.3%, p<0.001) (**Table 40**). Similarly, the neoadjuvant hormonal treatment rate before OBC was significantly higher than for SBC (10.2% v 4.6%, p<0.001) (**Table 40**). Neoadjuvant chemo- and hormonal treatment rates were comparable between OBC, mastectomy and MIR patients. A significantly higher rate of OBC patients in comparison to SBC received adjuvant chemotherapy (34.1% v 21.5%, p<0.001), radiotherapy (96.8% v 91.4%, p=0.005), hormonal treatment (54.6% v 65.3%, p=0.001) and trastuzumab (13.9% v 6.8%, p<0.001) (**Table 40**). Adjuvant treatment rates of OBC, mastectomy and MIR patients were comparable except for radiotherapy, as expected.

Table 40. Adjuvant and neoadjuvant treatment by type of surgery

	OBC n (%)	SBC n (%)	Mastectomy n (%)	MIR n (%)	p OBC v SBC	P OBC v mastec.	P OBC v MIR
Neoadjuvant chemotherapy					<0.0001	0.181	0.247
Yes	33 (15.3)	381 (7.3)	228 (12.2)	140 (20.0)			
No/NA	183 (84.7)	4811 (92.7)	1636 (87.8)	560 (80.0)			
Neoadjuvant hormonal treatment					<0.0001	0.088	0.277
Yes	22 (10.2)	241 (4.6)	123 (6.6)	44 (6.3)			
No/NA	194 (89.8)	4951 (95.4)	1741 (93.4)	656 (93.7)			
Adjuvant chemotherapy					<0.0001	0.462	0.941
Yes	72 (34.1)	1072 (21.5)	583 (31.6)	237 (34.4)			
No/NA	139 (65.9)	3918 (78.5)	1260 (68.4)	452 (65.6)			
Adjuvant radiotherapy					0.005	<0.0001	<0.0001
Yes	209 (96.8)	4744 (91.4)	852 (45.7)	264 (37.7)			
No/NA	7 (3.2)	448 (8.6)	1012 (54.3)	436 (62.3)			
Adjuvant hormonal treatment					0.001	0.111	0.641
Yes	118 (54.6)	3391 (65.3)	1123 (60.2)	395 (56.4)			
No/NA	98 (45.4)	1801 (34.7)	741 (39.8)	305 (43.6)			
Adjuvant trastuzumab treatment					<0.0001	0.233	0.536
Yes	30 (13.9)	351 (6.8)	208 (11.2)	86 (12.3)			
No/NA	186 (86.1)	4841 (93.2)	1656 (88.8)	614 (87.7)			

OBC: oncoplastic breast conservation; SBC: standard breast conservation; MIR: mastectomy with immediate reconstruction. Patients with M1 stage were excluded.

1859 patients received adjuvant chemotherapy (67 OBC, 1034 SBC, 555 mastectomy and 203 MIR) (**Table 41**). The median time to adjuvant chemotherapy from final surgery for OBC patients was 42 days (26-161), which was similar to the other cohorts (SBC: 40 days (11-407); mastectomy: 43 days (9-171); MIR: 44 days (23-247)). In particular, a similar proportion of patients in each group started adjuvant chemotherapy within 31 days (OBC: 14.9% v. SBC: 22.1%, p=0.171; mastectomy: 16.2%, p=0.787; MIR: 10.8%, p=0.386) (**Table 41**). 4200 patients received adjuvant radiotherapy but no adjuvant chemotherapy (129 OBC, 3474 SBC, 469 mastectomy and 128 MIR). There was no significant difference in median time from final surgery to adjuvant radiotherapy when OBC was compared to the other three groups (OBC: 51 days (35-125), SBC: 50 days (10-447), mastectomy: 55 days (26-428), MIR: 56 days (33-122)) (**Table 41**).

Table 41. Time from cancer surgery to start of adjuvant chemotherapy and radiotherapy by type of surgery

Time from surgery to adjuvant chemotherapy	OBC n (%)	SBC n (%)	Mastectomy n (%)	MIR n (%)	p value OBC v SBC	p value OBC v mastect	p value OBC v MIR
0-31 days	10 (14.9)	225 (21.9)	87 (15.8)	22 (10.8)	0.585	0.673	0.217
32-60 days	50 (74.6)	691 (67.3)	378 (68.5)	138 (68.0)			
61-90 days	6 (9.0)	96 (9.3)	78 (14.1)	40 (19.7)			
>90 days	1 (1.5)	15 (1.5)	9 (1.6)	3 (1.5)			
Altogether	67	1027	552	203			

Time from surgery to adjuvant radiotherapy	OBC n (%)	SBC n (%)	Mastectomy n (%)	MIR n (%)	p value OBC v SBC	p value OBC v mastect.	p value OBC v MIR
0-31 days	0	27 (0.8)	3 (0.7)	0	0.088	0.626	0.747
32-60 days	81 (62.8)	2394 (69.5)	273 (60.9)	75 (58.6)			
61-90 days	41 (31.8)	786 (22.8)	137 (30.6)	44 (34.4)			
>90 days	7 (5.4)	239 (6.9)	35 (7.8)	9 (7.0)			
Total	129	3446	448	128			

OBC: oncoplastic breast conservation; SBCS: standard breast conservation; mastect: mastectomy; MIR: mastectomy with immediate reconstruction. M1 patients excluded were excluded. Patients who received adjuvant chemotherapy were excluded when time to adjuvant radiotherapy compared.

5.1.5. Discussion

This study has found that, despite increasing experience with OBC, these operations only made up 2.7% of operations for breast cancer and 4% of breast conserving operations in Scotland in 2014 and 2015. There were, however, significant regional differences in the country in OBC rates ranging from 2.9% to 4.8% of breast conserving cases **(Table 37)**. The rate of OBCS in our study is markedly below that reported by large, tertiary referral centres, e.g. the MD Anderson Cancer Centre which has reported an increase from 4% of breast cancer operations in 2007 to 15% in 2014, making up 33% of breast conservation operations[8]. However, uniquely we describe here a real-life population scenario in this audit which has not been previously studied. It is likely that, as all newly appointed breast surgeons in the UK are now required to be competent in mammoplastic techniques as a condition of their completion of training, this rate will rise over the coming decade in Scotland. Further, we have shown previously that the absolute numbers of OBCs are increasing in Scotland, and more frequent application of OBC surgery may result in a reduction in mastectomy rate.[75] Therefore, we are following up our

current 2014-2015 dataset in the subsequent years and relevant national data request from the Information Services Division / NHS National Services Scotland is underway

The average tumour size in the OBC cohort of our study (median ITS 20mm, median WTS 25mm) is comparable to the initial results of the UK-wide TeaM study that reported a median ITS of 19mm and median WTS 24mm in OBC patients[50] (**Table 38**). The finding that tumour size occupies a middle ground between SBC patients and mastectomy patients is not particularly surprising given that one of the main aims of OBC surgery is to conserve the breast with acceptable aesthetic outcome in cases which previously would have required mastectomy. However, these findings are not entirely consistent with the existing literature. A number of studies have found tumour size to be similar to those who undergo SBC [17-19, 36] and we previously found tumour characteristics to be similar to mastectomy patients in breast units in Glasgow.[22, 23] Other studies have reported larger tumours in OBC patients compared to SBC but did not compare to mastectomy.[32, 37, 262-264]

Further differences found in pathology include tumour grade, which was between SBC and mastectomy for patients treated with OBC, more ER negative and HER-2 positive patients in the OBC group than in the SBC and fewer node positive cases in OBC patients when compared to mastectomy or MIR patients (**Table 38**). The difference in age between the groups probably reflects differences in the extensiveness of the surgery with OBC being more extensive than SBC or mastectomy, but less of an undertaking than post-mastectomy breast reconstruction. More OBC patients received neoadjuvant chemo-, hormonal therapy as well as adjuvant chemo-, radio-, hormonal therapy and trastuzumab than patients treated with SBC (**Table 40**). These differences mirror the findings of previously published single centre results but confirm them with a national database.[22, 23, 32, 40]

Time to first and final surgery from diagnosis was significantly longer for patients treated with OBC compared to SBC and mastectomy, but it was shorter than MIR (**Table 39**). The differences probably represent mainly logistical issues such as availability of plastic or oncoplastic surgeons and relatively longer theatre time, but other factors such as regional differences, facilities and socioeconomic factors may also play a role.[265] It is unknown whether the eleven- or fourteen-day delay in surgery when OBC is compared to mastectomy or SBC would affect prognosis, although *Eriksson* et al. recently suggested that a three week delay confers a 1.26-fold increased hazard rate of death, which was strongest in women with the largest tumours.[266] Hence, further studies are required to investigate the potential adverse effect on prognosis of delays in surgery in OBC patients.

This national audit suggests that OBC is a standalone option for the surgical treatment of breast cancer in Scotland, based on the differences found from SBC, mastectomy and MIR. OBC and MIR both improve aesthetic outcome for patients after breast conservation or mastectomy.[267, 268] We and others demonstrated that OBC offers suitable women the option to avoid MIR while providing faster recovery.[22, 23, 82] *Kelsall* et al showed in a case-matched study that better psychosocial and self-rated satisfaction with breast appearance could be achieved with OBC compared to MIR, regardless of the need for radiotherapy.[82] *Chand* et al demonstrated that patients report long-lasting satisfaction after OBC and outcomes compare very favourably with those reported following MIR.[73] Therefore, OBC rate could be regarded as a performance indicator similarly to MIR rate in large national audits.[257, 258]

Our study did not demonstrate a difference between the surgical groups in terms of time to adjuvant therapy. Although there was a suggestion that OBC patients are less likely to start adjuvant therapy within the first 31 days of surgery this slight difference between the two breast conservation groups had disappeared by 60 days (**Table 41)**. The question of whether OBC does genuinely lead to a delay in adjuvant therapy is a matter of debate. A few studies have reported a delay to adjuvant therapy in OBC.[14, 15, 43, 44, 269] However, the majority of studies – including ours – report no statistical delay to adjuvant treatment.[13, 16, 20, 39, 45, 46, 168] The studies which did show a delay are in the main older studies and it may be that, as experience with these techniques has increased, outcomes have improved. Many of the studies, both those reporting a delay and those who did not, are often limited by small patient numbers and, where there is no comparison arm, use variable definitions of 'delay'. Nevertheless, this is the only population-based study which shows no significant difference in the start of adjuvant treatment in patients treated with OBC compared with SBC, mastectomy and MIR. The trend that patients treated with OBC, or MIR start their adjuvant chemotherapy later in comparison to SBC or mastectomy patient requires follow-up in the datasets of the subsequent years.

The limitations of our study are primarily related to the data available within the prospectively collected MCN databases. We do not know details of the surgical technique used, incomplete excision rate in conservation surgery, postoperative complication rates, recurrence rates or patient reported outcomes. However, to our knowledge this is the first prospective national audit of oncoplastic breast conserving surgery, providing a 'real world' view of the current use of OBC in a comparatively large number of patients, with comparison groups from the three other major surgical treatment groups.

5.1.6. Novel findings

1. This national audit demonstrates that OBC occupies its own niche between SBC, mastectomy and MIR in the surgical treatment of breast cancer in Scotland.
2. OBC should be recorded separately from SBC, mastectomy and MIR in the national breast cancer registries.
3. OBC rate could be regarded as a performance indicator similarly to MIR rate in breast cancer surgery.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Oncoplastic breast conservation occupies a niche between standard breast conservation and mastectomy - A population-based prospective audit in Scotland.
Morrow ES, Stallard S, Doughty J, Malyon A, Barber M, Dixon JM, **Romics L**.
European Journal of Surgical Oncology. 2019 Oct;45(10):1806-1811.

5.2. Excision margins of oncoplastic breast conservation surgery compared to wide local excision in an international multicentric study

5.2.1. Introduction

Immediate techniques of oncoplastic surgery (iTOP)[270, 271] include immediate breast reconstruction after nipple/skin sparing mastectomy (IBR) and parenchymal flaps aimed to repair defects after breast conserving surgery, known as oncoplastic breast conservation (OBC). OBC procedures may be divided into small (Clough level I, Tübingen 3,4) or extended (Clough level II, Tübingen 5,6)[102, 272] resections with removal of less or more than 20% of the breast tissue.[273, 274, 78] Compared to conventional breast conservation (CBC), OBC allows resection of larger tumors and achievement of better cosmesis[275, 276] without delaying adjuvant therapies.[32, 276, 277] Additionally, retrospective studies have shown that, compared to CBC, OBC significantly reduces the rate of positive margins resulting in lower re-operation rates.[276, 278] A recent large population-based study has also shown that the use of OBC reduces the number of mastectomies.[279]

Currently international guidelines on breast conserving surgery recommend "no tumor on ink" as a safe resection margin in order to achieve optimal local control (i.e. a recurrence rate below 1%/year).[280-282] These recommendations are based on a large meta-analysis demonstrating higher local recurrence rates in patients with tumors touching the inked margin.[35, 283] However, the question about the optimal margin width following breast conservation remains open. *Vicini et al* meta-analysis including more than 55,000 women showed that a resection margin ≥ 2 mm[284] was associated with a 56% reduction in ipsilateral breast cancer recurrence, similar as for DCIS,[30, 285] suggesting that larger margins may further reduce the risk of local relapse. We therefore hypothesized that extended OBC resections (Clough level II[102] or Tübingen level 5 and 6[272]) may improve local recurrence rates, in high-risk tumors, by increasing resection free margins (≥ 2 mm) as compared to CBC and OBC level I.

5.2.2. Aim

We investigated if oncoplastic breast conservation with large resection volumes (OBCII; Clough level II/Tübingen 5-6) improve local recurrence rates compared to conventional breast conservation or low volume oncoplastic procedures (OBCI; Clough level I/Tübingen 3-4). Since this hypothesis cannot be tested in a randomized controlled trial, the oncoplastic breast consortium (OPBC)[286] gathered to answer this question using data collected at its members' network of international breast cancer centers.

5.2.3. Methods

We performed a retrospective review of prospectively collected consecutive patients treated at 15 institutions, members of the OPBC network, between 01/2010 and 12/2013. In case of missing data, patient charts were reviewed manually. Cases with ≥ 1 exclusion criteria, those with no definitive tumor biology and those lost to follow up were excluded (n=197). The trial was first approved by the local Ethic authorities from the Medical University Vienna (1468/2018) and thereafter by all local Ethic authorities. Case report form (CRF)-related data were anonymized by the local sites and sent to the Medical University Vienna.

Inclusion criteria:

1. Women aged ≥ 18 years, who had surgery between 1st January 2010 and 31st December 2013 with regular documented follow up visits at least once a year
2. Histologically verified primary unilateral breast cancer
3. High-risk invasive cancer defined as having at least one of the following criteria:
    a. Human epidermal growth factor receptor 2 (HER2) positive or triple negative (immunohistochemistry)
    b. genomic high-risk (PAM50, Endopredict, Mammaprint or Oncotype DX)
    c. If endocrine positive and HER2 negative, KI67 ≥ 30% or tumor grade G3
    d. Lymph node positive disease of any tumor biology
4. High-risk in situ cancer defined as high grade (DCIS G3, DIN III)
5. Having received breast conservation, re-excision due to unclear margins (R1/Rx) was allowed at any time

Exclusion criteria:

1. Stage IV breast cancer
2. Omission of adjuvant breast radiotherapy when recommended
3. Ipsilateral breast recurrence defined as an in-breast recurrence of a previous breast cancer operated within the last 5 years
4. Pathogenic BRCA mutation (if genetic testing was available)
5. Positive margins defined as tumor touching the inked margin (R1) without re-excision
6. Mastectomy

1.1. Surgical Groups:

1.2. Two different surgical groups according to the Hoffmann Wallwiener Tübingen classification[272], as recommended by the OPBC[274]

CBC/OBCI Conventional breast conservation Tübingen 1 and 2 (no oncoplastic)
Low Volume Oncoplastic breast conservation Tübingen 3 and 4 (<20% resection volume)

OBCII High Volume Oncoplastic breast conservation Tübingen 5 and 6 (>20% resection volume)

As Tübingen 3 and 4 are usually level I Clough resections such as Batwing, Doughnut or local intraparenchymal flaps without extensive resections we combined the Tübingen 1-4 with the conventional breast conservation group (CBC/OBCI). Tübingen level 5 and 6 or Clough level II are usually oncologic resections combined with extensive breast reduction mastopexies such as the inverse-T Eren technique or Hall Findlay technique[287, 288] and are grouped as oncoplastic breast conservation (OBCII).

1.3. Oncologic Endpoints:

1. Local breast cancer recurrence rate (= LBCR) including ipsilateral in-breast cancer events, invasive and non-invasive
2. Regional breast cancer recurrence rate (=RBCR) defined as regional lymph node recurrence within the ipsilateral axilla
3. Disease-free survival (= DFS) including local, regional (ipsilateral axilla Level I-III) and distant invasive breast cancer events
4. Overall survival = OS (event is death from any cause)

1.4. Perioperative Endpoint:

1. Number of re-excisions due to positive or unclear margins (R1/Rx)
2. Resection free margins in mm comparing <1mm/x with 1-3mm and above 3mm
3. Women with a pathologic complete response were included into the RX group

1.5. Statistical analysis:

Categorical variables are presented as counts and percentages and continuous ones as medians with first and third quartiles. Depending on the scale and distribution either Chi-square test, t-test or Mann-Whitney test was applied to compare CBC/OBC I versus OBC II groups. Kaplan-Meier curves were used to depict survival after surgery. Cox regression was applied to model the effect of type of surgery [CBC/OBC I versus OBC II] and survival. The proportional hazards assumption was evaluated using plots of scaled Schoenfeld residuals versus (rank of) time. Because of non-proportional hazards, weighted Cox regression was applied which estimates an average hazard ratio.[289] For oncological outcomes, the competing risk of death was considered in the statistical models. We used cumulative incidence functions to depict the three oncologic outcomes in the two types of surgery. We applied the Fine & Gray model to estimate the subdistribution hazard, and additionally we estimated the cause-specific (death-censored) Cox regression model. Following the recommendation of Wolbers et al,[290] for the purposes of prognosis and medical decision–making, the subdistribution hazard is of primary interest as it quantifies the absolute risks of the event of interest. The cause–specific hazard directly models the effect of the covariate on event rates among people at risk and are of interest for etiological research questions. All statistical models were adjusted by the following known risk factors and potential confounders: age, tumor biology, tumor size, nodal status and invasive versus non-invasive cancer as well as systemic treatment. For LBCR additional models were estimated with the added confounders ‘margin in mm’ and ‘reoperation due to R1’. A robust sandwich covariance matrix estimate was used to account for the intracluster dependence of this multi-center study. Two-sided p-values smaller 0.05 were used to declare statistical significance. SAS 9.4 and R 4.0.2 was used for statistical analysis.

5.2.4. Results

We included 3,177 patients from 15 different institutions, from 8 different countries (Austria n=660, Brazil n=54, Germany n=837, Hungary n=50, Lithuania n=284, Sweden n=313, Switzerland n=637, United Kingdom n=242). Thirty percent of patients were treated with OBC, 297 (9.3%) with OBC II while 663 (20.9%) with OBC I, while 2,217 (69.8%) received CBC. Four institutions included 75% of all OBCII, five institutions had less than 5% of OBCII cases and 4 centers had none.

The great majority of patients (92.3%) had invasive cancer while the remaining had high-grade DCIS. Twenty seven percent were aged ≤ 50 years and 19% were aged > 70 years. Sixteen percent of patients underwent neoadjuvant chemotherapy. Tumor size was ≥ 2 cm in 40% of cases. Node positivity was confirmed on final pathology in 50% of cases. A minority of patients (6.6%) had invasive lobular breast cancer cases and 9% were Luminal A tumors (all these patients were nodal positive), while 41% were Luminal B, 27% were HER2+ and 21% were triple negative. Compared to the CBC/OBCI group, patients treated with OBCII were more likely to have larger tumors and to be node positive. Tumor size before neoadjuvant therapy was, however, similar in both groups. Tumor biology also differed among surgical groups, HER2+ were more frequent in the OBCII group while triple negative tumors were more likely in the CBC/OBCI group (**Table 42 and 43**).

Table 42. Clinicopathological features

	CBC/OBCI		OBCII		
	n	*%*	*n*	*%*	*p-value*
ALL	2880	**91**	297	**9**	
Age	2880	**58 [49-68]**	297	**54 [46-63]**	**<0.001**
Invasiv cancer	2673	**93**	260	**88**	**0.0012**
Lobular Histology	189	**6**	21	**7**	0.2089
NAC	441	**16**	65	**25**	**0.0032**
Tumor size (mm)*	379	**30 [40-62]**	41	**30 [43-70]**	0.5380
cT1/2*	363	**86**	34	**77**	0.2755
Radiotherapy	2652	**92**	293	**98**	**<0.001**
Radiotherapy boost	2033	**70**	197	**66**	0.1264
Endocrine Therapy	1927	**67**	196	**66**	0.7494
Chemomotherapy	1752	**61**	186	**63**	0.5464

Categorical variables are presented as counts (%) and continuous ones as medians (IQR)
Statistically significant values are indicated in bold
*Refers to patients treated with neoadjuvant chemotherapy only
CBC, conventional breast conservation (Tübingen 1-2);
OBCI, oncoplastic breast conservation level I (Clough level I/Tübingen 3-4);
OBCII, oncoplastic breast conservation (Clough level II/Tübingen 5-6);
NAC, neoadjuvant chemotherapy

Table 43. Clinicopathological features

	CBC/OBCI		OBCII		
	n	*%*	*n*	*%*	*p-value*
ALL	2880	**91**	297	**9**	
Pathological T stage					
pTis	231	**8**	34	**12**	**0.002**
pT1	1367	**50**	103	**37**	
pT2	1014	**37**	119	**43**	
pT3/4	106	**4**	18	**6**	
Pathological N stage					
pN0	1357	**49**	103	**36**	**<0.001**
pN1	1173	**42**	163	**58**	
pN2/3	241	**9**	16	**6**	
Subtype					
Luminal A	272	**10**	18	**6**	**<0.001**
Luminal B	1209	**43**	104	**36**	
Luminal HER2+	505	**18**	80	**27**	
Non Luminal HER2+	232	**8**	40	**14**	
Triple negative	611	**22**	50	**17**	

Categorical variables are presented as counts (%)
Statistically significant values are indicated in bold

Margin width differed in the two groups (17% had a margin < 1mm in CBC/OBCI versus 6% in OBCII p =0.001) (**Figure 15**) as did the number of re-resections due to positive margins (tumor on ink) after the first surgical attempt (11% in CBC/OBCI versus 7% in OBCII; p=0.025) (**Figure 16**).

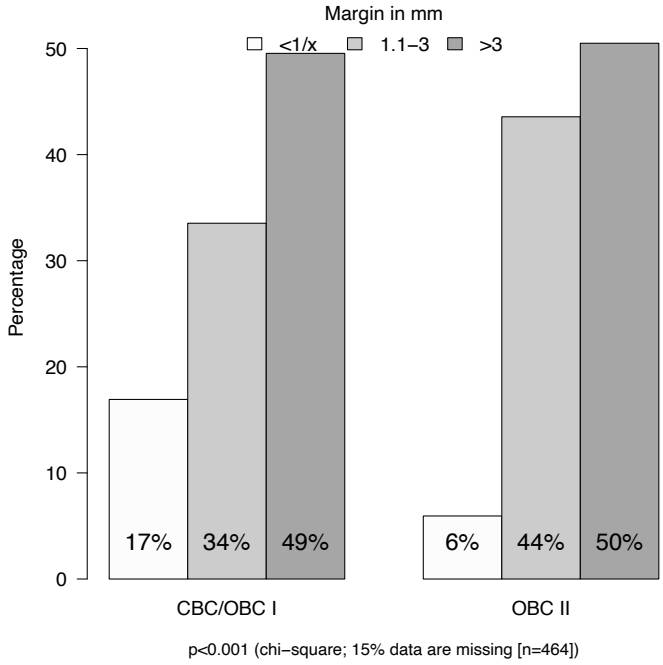


Figure 15. Margin status by type of surgery

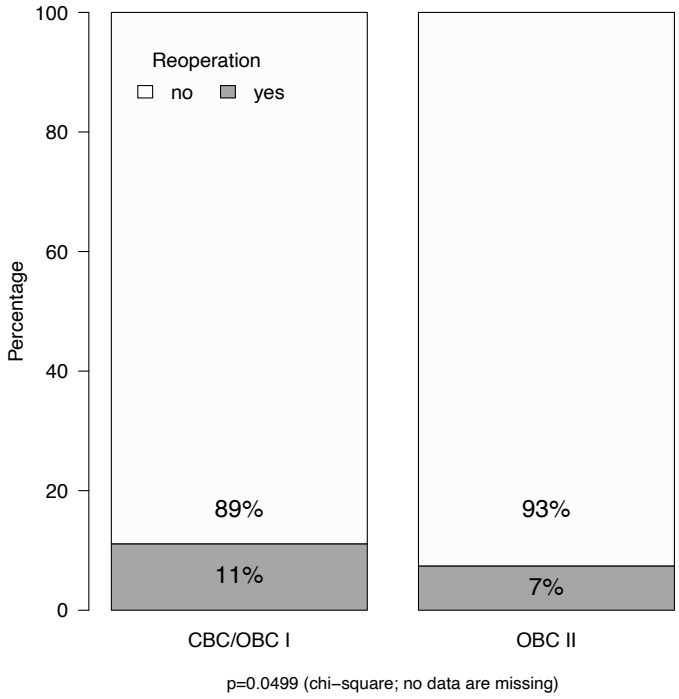
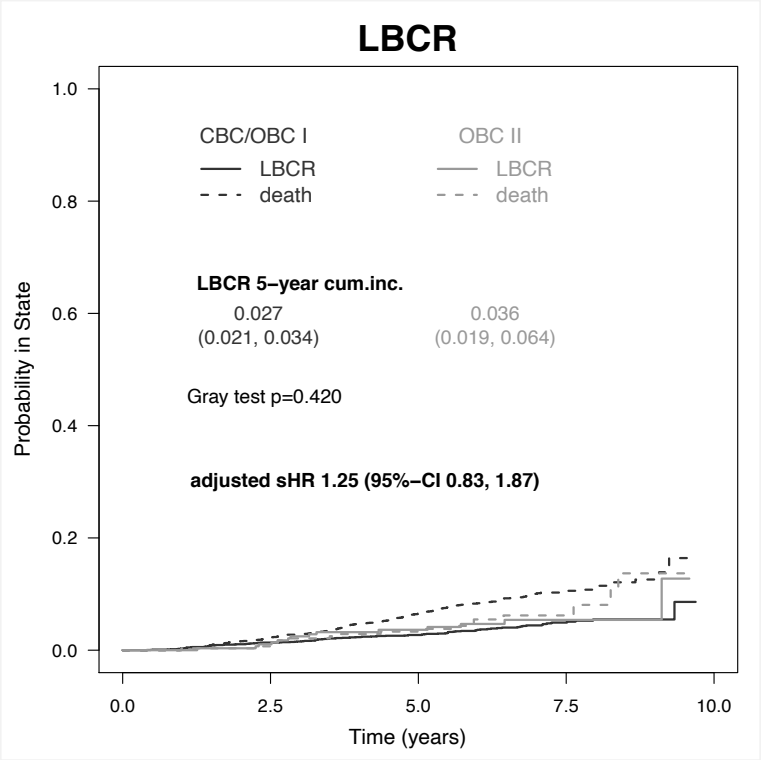
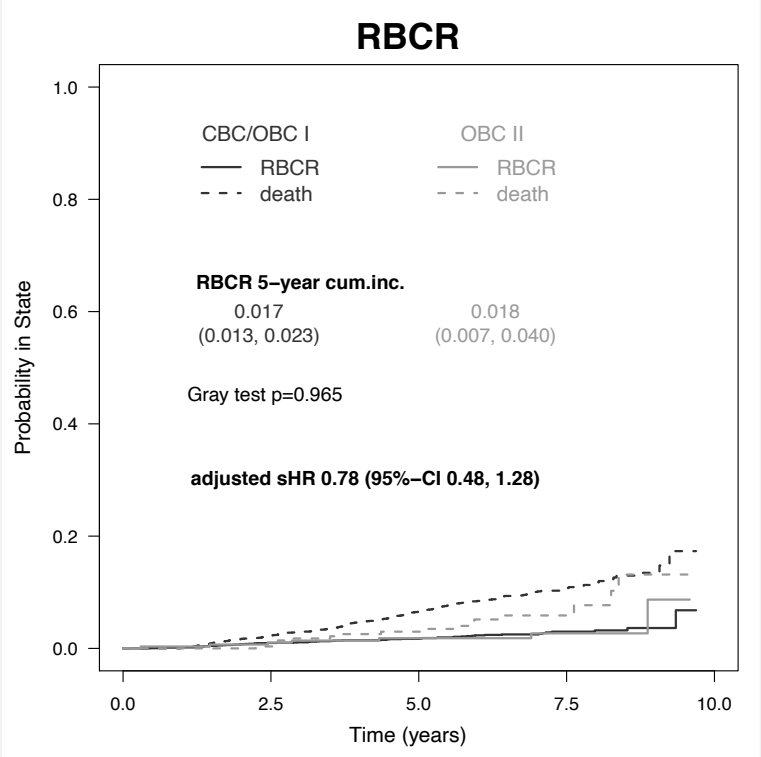


Figure 16. Re-excision rates by type of surgery

At a median follow-up of 74.5 months (IQR 60.32; 89.56), 3.6% (n=121) had a local recurrence, 2.2% (n=74) had a regional recurrence and 9.3% (n=314) had a distant recurrence. Three hundred twenty-one (9.5%) patients died during the study period. Unadjusted Kaplan Meier curves shows no significant differences in all oncologic outcomes for OBCII versus CBC/OBCI. All oncological outcomes did not differ between the two groups (**Figure 17**).


LBCR
CBC/OBC I
LBCR
death
OBC II
LBCR
death
LBCR 5−year cum.inc.
0.027
(0.021, 0.034)
0.036
(0.019, 0.064)
Gray test p=0.420
adjusted sHR 1.25 (95%−CI 0.83, 1.87)
Probability in State
Time (years)


RBCR
CBC/OBC I
RBCR
death
OBC II
RBCR
death
RBCR 5−year cum.inc.
0.017
(0.013, 0.023)
0.018
(0.007, 0.040)
Gray test p=0.965
adjusted sHR 0.78 (95%−CI 0.48, 1.28)
Probability in State
Time (years)

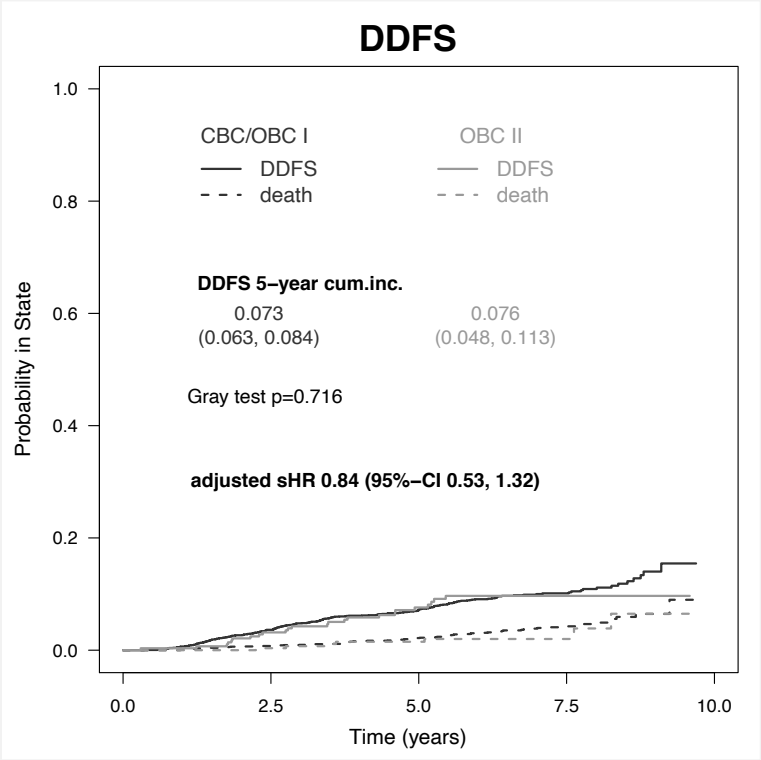


Figure 17. Cumulative incidence plot of LBCR, RBCR and DDFS by type of surgery

The 5-year LBCR was 2.7% in the CBC/OBCI group and 3.6% in the OBCII group (p=0.420). The 5-year distant event rate was 7.3% in the CBC/OBCI groups and 7.6% in the OBCII group (p=0.716) while the 5-year regional recurrence rates were 1.7% and 1.8% (p=0.965). Multivariable Cox regression analysis for DDFS, RRFS and OS showed that OBCII did not independently influence any of these endpoints (**Table 44**).

Table 44. Multivariable associations for oncological outcomes

	n (n events) [0]	cause-specific hazard		subdistribution hazard	
		univariate model	multivariable model [1]	univariate model	multivariable model [1]
LBCR	2834 (97)	1.23 (0.67, 2.07), p=0.470	1.33 (0.67, 2.39), p=0.380	1.26 (0.89, 1.78), p=0.194	1.40 (0.96, 2.05), p=0.080
RBCR	3175 (72)	0.989 (0.41, 2.01), p=0.978	0.731 (0.27, 1.59) p=0.473	1.01 (0.62, 1.66), p=0.473	0.78 (0.48, 1.27) p=0.33
DDFS	2872 (253)	1.00 (0.58, 1.37) p =0.699	0.84 (0.52, 1.31) p =0.441	0.92 (0.61, 1.39) p =0.710	0.84 (0.56, 1.27) p=0.429
LBCR[2]	2561 (78)		1.19 (0.53, 2.66), p=0.677 [2]		1.25 (0.83, 1.87), p=0.292 [2]

All models were corrected for the intracluster correlation of breast center
[0] Sample size of multivariable model
[1] adjusted for subtype, pT, pN, invasive versus non-invasive and neoadjuvant therapy vs adjuvant
[2] additionally adjusted for margin width (mm) and Reoperation due to R1
LBCR: local breast cancer recurrence rate, RBCR: regional breast cancer recurrence rate,
DDFS: distant disease-free survival

Furthermore, a subgroup analysis in women without neoadjuvant treatment and tumors < 2cm (n=1,521) revealed a LBCR of 3.7% in CBC/OBCI compared with 7.3% in OBCII. An exploratory analysis of women without neoadjuvant treatment and a final pathological tumor size ≥ 2cm (n= 1,134) showed a similar LBCR comparing OBCII techniques with CBC/OBCI (2.8% versus 3.4%).

5.2.5. Discussion

This retrospective multicenter analysis of 3,177 high-risk breast cancer patients treated in 15 different institutions demonstrated no significant improvement in local recurrence free survival by large volume oncoplastic surgery compared with conventional breast conservation or low volume oncoplastic surgery. Large volume oncoplastic surgery, however, significantly increased the margin distance from cancer cells and significantly reduced the number of necessary re-resection due to R1 resections at the first surgical attempt.

The demonstration that oncoplastic surgery increases resection free margins and reduces re-operation rates in our analysis is in line with several other retrospective data.[95, 276, 278] This is especially true when using OBCII in breasts with Cup C or larger. The larger resections, however, are accompanied by a significant increased risk, up to 30%, in postoperative morbidity.[270] In a prospective non randomized controlled trial (iTOP1) we were able to demonstrated that OBC, performed for large breast tumors, results in similar breast self-esteem scores and similar quality of life compared with CBC [291, 292], demonstrating that increased morbidity rate does not influence long term quality of life. However morbidity depends on the extent of oncoplastic surgery, with higher morbidity rates with oncoplastic level II, according to the Clough classification,[102] and other authors have reported no significant increase in clinical relevant morbidity in large retrospective analyses.[293]

Our study, however, failed to demonstrate that large oncoplastic resections in high-risk invasive breast cancer patients improves LBCR due to increased resection margins. This is in line with the large retrospective analysis by *Houssami et al*[35,283] demonstrating no influence of margin width on local control. In this respect the definition of "no tumor on ink" for an optimal R0 resection remains true[280] even in larger and high-risk tumors. However, in our study this was not true for women with high grade DCIS, where a margin >3mm was associated with a 10-fold reduction in LBCR (1.4% versus 14.6% n=164).

There is ongoing debate and limited data regarding optimal resection margins after neoadjuvant chemotherapy.[282, 294, 295] In our study we found no significant difference regarding local recurrence in women with and without neoadjuvant chemotherapy (4.9% versus 3.4%; n=1920). Moreover, OBCII with larger resection margins did not further improve local recurrence risk after neoadjuvant therapy. Thus, our data support the current evidence[296-299] that "no tumor on ink" is an appropriate margin width also in patients receiving neoadjuvant chemotherapy.

Landmark trials investigating the safety of breast conserving surgery only included smaller tumors (up to 2cm in size)[11, 300] while larger tumors were less frequently studied.[24, 28, 301] Moreover, tumor biology was unknown in these trials, thus, there is a lack of robust data supporting the use of breast conservation for high-risk pT2/3 tumors. In our study of 3,177 women, 35% of patients had a tumor larger than 2cm on final pathology and the great majority had an aggressive subtype (Luminal B, HER2+ or triple negative tumors). The small percentage of luminal A tumors included in our study were node positive. The overall local recurrence rate, at 74 months of follow up, after breast conservation and radiotherapy was 3.6%, the regional recurrence rate was 2.2%, 9.5% developed a distant relapse and 9.3% deceased during the study period and there was no difference comparing large resections with OBCII compared with CBC/OBCI neither in tumors <2cm nor above 2cm suggesting that breast conservation in high-risk breast cancer and large tumors is safe.

Limitations of this study are its retrospective nature and the low number of local in-breast events (n=121 compared with the expected n=230). Additionally, differences in demographic data between two surgical groups also limited the analyses on oncological outcome. The statistical testing for superiority gives no answer on the question of non-inferiority for one of the two groups. However, with an increased number of events and included women we strongly argue that the results of the statistical analysis will not change.

Strength of the study are the large sample size, the multicentric, international, design and the COX regression analysis with adjustment for several important oncologic parameters. The included patients were treated in 8 different countries outside clinical trials, making our results highly generalizable to the real-world scenario.

In conclusion, our study shows that oncoplastic level II resection in high-risk breast cancer patients increases margin width but does not influence local recurrence rates. The number of resections due to R1 margins, however, were significantly reduced by oncoplastic level II techniques. Our data support the use of breast conservation techniques for women with

tumors ≥ 2cm irrespectively of tumor biology and receipt of neoadjuvant chemotherapy as long as “no tumor on ink” margins are obtained in order to achieve optimal local and distant control.

5.2.6. Novel findings

1. Large resection volumes in oncoplastic surgery increases the distance from cancer cells to the margin of the specimen and reduces re-operation rates significantly.
2. OBCII allows for resection of larger tumors, however margins larger than “no tumor on ink” do not improve local control.
3. Using OBCII larger tumors are resected with a similar local, regional or distant recurrence free as well as overall survival rate compared with CBC/OBCI.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Retrospective, Multicenter Analysis Comparing Conventional with Oncoplastic Breast Conserving Surgery: Oncological and Surgical Outcomes in Women with High-Risk Breast Cancer from the OPBC-01/iTOP2 Study.
Fitzal F, Bolliger M, Dunkler D, Geroldinger A, Gambone L, Heil J, Riedel F, de Boniface J, Andre C, Matrai Z, Pukancsik D, Paulinelli RR, Ostapenko V, Burneckis A, Ostapenko A, Ostapenko E, Meani F, Harder Y, Bonollo M, Alberti ASM, Tausch C, Papassotiropoulos B, Helfgott R, Heck D, Fehrer HJ, Acko M, Schrenk P, Trapp EK, Gunda PT, Clara P, Montagna G, Ritter M, Blohmer JU, Steffen S, **Romics L**, Morrow E, Lorenz K, Fehr M, Weber WP.
Annals of Surgical Oncology 2022 Feb;29(2):1061-1070.

5.3. Oncological safety of oncoplastic breast conservation surgery in Scotland

5.3.1. Introduction

Current evidence is largely based on single-institution retrospective series.[8, 13, 23, 32, 37, 40, 43, 72, 168, 198, 255, 256, 267] Systematic literature reviews, meta-analyses and reviews further strengthen the evidence base but numbers in many series are small.[1, 3, 5, 10, 80, 95, 164, 181, 197, 302] The majority of data reflect the practice of high-volume, mainly tertiary referral centres with few data outside of such units. Due to the lack of robust data outside of the previously mentioned larger units, the published outcomes of OBC do not mirror the results of the majority of patients who are treated outside of these centres. OBC is a rapidly developing field in breast cancer surgery, so it is vital to gain "real-life" data.

Oncoplastic breast conserving surgery practice has been studied in each breast unit from a geographically well-defined area in order to get "real-life" experience in OBC practice and outcomes. In Scotland, all patients treated with oncoplastic breast conservation were analysed with regards to indications, oncoplastic surgical techniques, incomplete excision rate, complication rate, (neo)adjuvant treatment and recurrence rate.

5.3.2. Aim

Current evidence for oncoplastic breast conservation (OBC) is based on single institutional series. Therefore, we carried out a population-based audit of OBC reflecting "real-life" practice in Scotland.

5.3.3. Methods

A predefined database was filled in retrospectively from all breast units who practise oncoplastic breast conservation in Scotland. The following characteristics were collected: age, date of diagnosis and surgery, presentation, oncoplastic surgical technique, immediate contralateral symmetrisation, tumour type, invasive tumour size, whole tumour size, grade, ER and HER-2 expression, lymph node status, multifocality, excision margins, neoadjuvant systemic treatment, adjuvant chemo-, radio-, hormonal, and anti-HER-2 treatment, postoperative complication, date and site of recurrence, date and cause of death, date of last

follow-up, presence of plastic surgeon at the operation. Units were asked to enter patients treated with OBC consecutively. Patients who needed completion mastectomy or who had distant metastasis at presentation were excluded.

Oncoplastic technique was determined by the ratio of tumour size to breast size, tumour location, and patients' anatomy and preferences. This was decided subjectively by oncoplastic breast surgeons, or breast and plastic surgeons together. Only patients who underwent significant volume excision followed by volume displacement accompanied by adequate skin envelope reduction, or true volume replacement were included (level II oncoplastic techniques as defined by Clough et al.).[102] Patients treated with simple reshaping such as dual plane mobilization without skin envelope reduction were not included in the study.

Units were classified as high and low volume units based on the number of OBC done per year. A high volume unit was defined as one which reported at least 100 patients having OBC over two consecutive years.

Joint operations were defined as OBC carried out by a breast (general) and a plastic surgeon together. When a breast surgeon operated together with another breast surgeon, a breast surgical trainee or an oncoplastic fellow, this did not count as a joint procedure.

Incomplete margins were determined by local guidelines of the time. Since 2016, a 1 mm clear margin was considered to be satisfactory for invasive and *in-situ* disease, while 1 or 2 mm clear margin was required previously in some of the Units in Scotland.[303] Overall survival was defined as the time from the date of surgery to the date of death due to any cause, while cancer specific survival is defined as death due to breast cancer. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of the first relapse or the date of death due to any cause. DFS events were defined as any ipsilateral or contralateral breast recurrence (invasive or non-invasive), regional or distant metastases. Patients who were alive or diseased were censored at the time of last follow-up.

Complications were classified as major or minor. A major complication was considered when readmission or prolonged hospital admission was required for subsequent treatments, that were mainly further surgery for complications and / or intravenous antibiotic administration. All other subsequent treatment not requiring inpatient care was classified as a minor complication.

Chi-square and Mann-Whitney U tests were used for comparison of categorical variables. For comparison between case-load of units or case numbers of time periods ANOVA test was used. For correlation between the case load of units and the number of oncoplastic techniques offered Spearman's rho test was used. A P-value equal to or less than 0.05 was considered statistically significant.

5.3.4. Results

589 patients were included in the analysis. The median age was 56 years [range 21-86]. Almost two-thirds of the patients were from the symptomatic service (273 (62.7%); one third from breast screening: 159 (36.5%), and the remainder from follow-up or family history clinics between September 2005 and March 2017. The number of patients treated with OBC in a unit ranged between 4 and 145 (**Table 45**). 11 of 17 units practising oncoplastic breast conservation contributed to the study. The 6 remaining units are relatively small units and they do not practise OBC.

Table 45. Number of patients treated with oncoplastic breast conservation in each unit with time periods over which they were carried out.

Units	Number of patients	Time period
Western General Hospital Edinburgh	145	April 2005 – August 2015
Victoria Infirmary Glasgow	144	September 2005 – March 2017
Ninewells Hospital Dundee	111	January 2013 – October 2016
Western Infirmary Glasgow	78	July 2005 – October 2016
University Hospital Crosshouse	36	June 2005 – December 2015
Aberdeen Royal Infirmary	31	January 2014 – May 2016
Forth Valley Royal Hospital	13	September 2014 – November 2015
Stobhill Hospital Glasgow	12	March 2006 – March 2014
Glasgow Royal Infirmary	9	July 2005 – April 2010
Wishaw General Hospital	6	August 2015 – December 2015
Royal Alexandra Hospital Paisley	4	August 2015 – October 2015

Of these, high volume units performed a mean of 19.3 cases per year [17,3 – 26,5] vs. low volume units doing 11.1 cases per year [7 .7– 14.4] (p=0.012) (**Table 46**). Between 2005 and 2010 the number of patients treated with OBC in Scotland increased yearly. In 2005 - 2010 a mean of 20 patients per year [5-42] were treated with OBC. This trend plateaued after 2011 when no further increase was observed (2011 – 2016: mean of 76 patients per year [51-121] (p=0.002)).

Table 46. Case load of oncoplastic breast conservation in high and low volume units in Scotland with mean cases per year.

Units	Number of patients	Time period reported	Mean number of OBC cases per year
HIGH VOLUME UNITS			
Ninewells Hospital Dundee	106	4 years	26.5 cases / year
Western General Hospital Edinburgh	142	8 years	17.7 cases / year
Victoria Infirmary Glasgow	138	8 years	17.2 cases / year
TOTAL	386	20 years	19.3 cases / year
LOW VOLUME UNITS			
Aberdeen Royal Infirmary	29	2 years	1.4.5 cases / year
Western Infirmary Glasgow	76	6 years	12.7 cases / year
University Hospital Crosshouse	31	4 years	7.7 cases / year
Forth Valley Royal Hospital	13	1 year and 3 months	10.4 cases / year
Stobhill Hospital Glasgow	12	1 year and 3 months	9.6 cases / year
TOTAL	161	14 years and 6 months	11.1 cases / year

23 different oncoplastic surgical techniques were used (**Table 47**). The number of oncoplastic techniques performed in a unit was associated with case-load: high volume units used a wider range of surgical techniques (8 – 14 different oncoplastic techniques per unit) compared to low volume units (3 – 6 different techniques) (p=0.004) (**Table 48**). Oncoplastic reduction techniques (volume displacement) were used in 515 patients (91.3%), compared to volume replacement oncoplastic technique in 49 patients (8.7%) (**Table 47**).

Table 47. Oncoplastic surgical techniques used, with frequencies.

Oncoplastic technique	Number of patients	Percentage
Wise pattern reduction	375	66.5%
Round block	34	6.1%
LICAP / TDAP / LTAP	28	5%
Regnault B-plasty	25	4.4%
Grisotti flap	24	4.3%
Vertical Lejour mammoplasty	23	4.1%
Matrix rotation / J mammoplasty	15	2.7%
Thoraco-epigastric flap	14	2.5%
Lateral / medial mammoplasty	11	2%
Tennis racquet-type excision	8	1.4%
Melon slice reduction	5	0.9%
Crescent flap	3	0.5%
Batwing mammoplasty	3	0.5%
VY lateral advancement	2	0.4%
V - mammoplasty	1	0.2%
Skin pouch mammoplasty	1	0.2%
S - mammoplasty	1	0.2%
Rotational advancement flap	1	0.2%
Local flap (other)	1	0.2%
Unknown	25	-

Table 48. Relationship between the number of different oncoplastic techniques used in each unit and total OBC case-load.

Units	Number of oncoplastic techniques	Number of patients
HIGH VOLUME UNITS		
Ninewells Hospital Dundee	12	111
Western General Hospital Edinburgh	8	145
Victoria Infirmary Glasgow	14	144
LOW VOLUME UNITS		
Aberdeen Royal Infirmary	5	31
Western Infirmary Glasgow	5	78
University Hospital Crosshouse	6	36
Forth Valley Royal Hospital	3	13
Stobhill Hospital Glasgow	3	12

Immediate symmetrisation was carried out in 336 patients (57%). The immediate symmetrisation rate in patients treated with oncoplastic reduction mammoplasty was 61.7% (327 of 530 patients). The joint operation rate was 66.3% (389 patients). Immediate contralateral symmetrisation rate was significantly higher when the procedure was carried out as a joint operation (70.7% vs. not joint operations: 29.8%; $p<0.001$).

The median invasive tumour size was 21 mm [0-120] and the median whole tumour size was 26 mm [1-200]. Although there was a trend that the median whole tumour size was larger in patients who were operated on in high volume units (28 mm [1-180]) when compared to patients treated in low volume units (25 mm [7-200]), this difference was not significant (p=0.164). Details of tumour characteristics are summarized in **Table 49**.

Table 49. Tumour characteristics of all patients who underwent OBC surgery in Scotland with breakdown of those who had at least 5 years follow-up.

	All patients		Patients[1] with 5-year follow-up	
HISTOLOGICAL TYPE	**n=**	**(%)**	**n=**	**(%)**
Ductal	413	(70.2%)	182	(70.3%)
Lobular	53	(9%)	25	(9.6%)
Mixed ductal and lobular	6	(1%)	2	(0.8%)
Mixed ductal and papillary	1	(0.2%)	-	
Tubular	7	(1.2%)	4	(1.5%)
Mucinous	6	(1%)	4	(1.5%)
Metaplastic	2	(0.3%)	1	(0.4%)
Not determined (CPR)	5	(0.8%)	1	(0.4%)
DCIS	78	(13.2%)	36	(13.9%)
Paget's disease	2	(0.3%)	2	(0.8%)
Papillary carcinoma	1	(0.2%)	1	(0.4%)
LCIS	3	(0.5%)	1	(0.4%)
Hamartoma	1	(0.2%)	n/a	
Phylloides	8	(1.3%)	n/a	
Diabetic mastopathy	1	(0.2%)	n/a	
Basal cell carcinoma	1	(0.2%)	n/a	
Osteosarcoma	1	(0.2%)	n/a	
TOTAL	589	(100%)	259	(100%)
PATHOLOGICAL T STAGE				
T_{is}	83	(14.4%)	39	(15%)
- [ypT0]	13	(2.2%) [13]	5	(1.9%) [5]
T1a [ypT1a]	18	(3.2%) [6]	17	(6.6%) [4]
T1b [ypT1b]	47	(8.1%) [10]	28	(10.9%) [4]
T1c [ypT1c]	142	(24.6%) [30]	33	(12.7%) [11]
T2 [ypT2]	225	(39%) [66]	110	(42.5%) [33]
T3 [ypT3]	27	(4.7%) [10]	14	(5.4%) [10]
Incomplete data	22	(3.8%) [17]	13	(5%) [5]
TOTAL	577	(100%) [152]	259	(100%) [72]
TUMOUR GRADE[2]				
Grade 1	50	(10.1%)	26	(11.9%)
Grade 2	243	(49.2%)	105	(48.2%)
Grade 3	197	(39.9%)	83	(38.1%)
Incomplete/ not determined	4	(0.8%)	4	(1.8%)
TOTAL	494	(100%)	218	(100%)
HORMONE EXPRESSION[3]				
ER positive	437	(83.4%)	200	(84.4%)
ER negative	83	(15.8%)	37	(15.6%)
Incomplete data	4	(0.8%)	-	
TOTAL	524	(100%)	237	(100%)
HER-2 EXPRESSION[2]				
HER-2 positive	85	(17.2%)	32	(14.7%)
HER-2 negative	401	(81.2%)	181	(83%)
Incomplete/ not determined	8	(1.6%)	5	(2.3%)
TOTAL	494	(100%)	218	(100%)
NODAL METASTASIS[2]				
Node positive	136	(27.5%)	58	(26.6%)
Node negative	353	(71.4%)	157	(72%)
Incomplete	5	(1%)	3	(1.4%)
TOTAL	494	(100%)	218	(100%)
FOCALITY				
Multifocal	117	(20.3%)	46	(17.8%)
Unifocal	440	(76.2%)	208	(80.3%)
Incomplete / not determined	20	(3.5%)	5	(1.9%)
TOTAL	577	(100%)	259	(100%)

[1] with (non)invasive breast carcinoma; CPR = complete pathological response,

[ ] = number of patients received neo-adjuvant systemic treatment,

[2] invasive cancers only,

[3] hormone receptor expression was determined for 30 and 19 patients with DCIS, respectively;

n/a = not applicable

The neodjuvant systemic treatment rate was 28.6% (142 of 496 patients with invasive carcinoma). Of those, 68 patients received neoadjuvant chemotherapy (13.7%) and 74 patients had neoadjuvant hormonal treatment (14.9%). 208 patients received adjuvant chemotherapy, 419 patients received (neo)adjuvant hormonal treatment including 10 patients with DCIS, and anti-HER-2 treatment was given to 71 patients. Adjuvant radiotherapy was given to all patients when clinically indicated except eight patients with invasive ductal, four patients with DCIS, one patient with invasive lobular and one patient with Paget's disease.

The incomplete excision rate was 10.4% (60 of 578) and was significantly higher in invasive lobular carcinoma (18.86%; 10 of 53) when compared to invasive ductal carcinoma (9.2%; 38 of 413; p=0.029). Incomplete excision rate after DCIS was similar to invasive ductal carcinoma (8.97%; 7 of 78). After neoadjuvant chemotherapy incomplete excision rate was significantly lower (2.94%; 2 of 68 vs. no neoadjuvant treatment: 9.89%; 35 of 354; p=0.031) than when no neoadjuvant treatment was used. When the whole tumour size was larger than the invasive component, incomplete excision rate was higher compared to those cases when whole tumour size was the same as the invasive tumour size, but this difference was not significant (14.96%; 19 of 127 vs. 10.33%; 28 of 271; p=0.092). Case load did not influence incomplete excision rate (high volume: 9.77%; 39 of 399 vs. low volume: 10.65%; 18 of 169). Similarly, incomplete excision rate was almost identical when OBC was performed as a joint case with a plastic surgeon (10.05%; 39 of 388 vs. 10.66%; 21 of 197).

145 of 510 patients developed complications, giving an overall complication rate of 28.4%. 47 patients had major complications (9.2%) and 98 patients had minor complications (19.2%) (**Table 50**).

Table 50. Rates of major and minor complications in 510 patients who underwent OBC surgery

	Number of patients	Percentage of patients
All complications	145	28.4%
MAJOR COMPLICATIONS		
Infection	16	3.1%
Haematoma	10	2%
Delayed wound healing	7	1.3%
Skin necrosis	5	1%
Fat necrosis	5	1%
Nipple necrosis	2	0.4%
Flap insertion delayed	1	0.2%
Pulmonary embolism	1	0.2%
TOTAL	47	9.2%
MINOR COMPLICATIONS		
Infection	27	5.3%
Delayed wound healing	21	4.1%
Haematoma	18	3.5%
Skin necrosis	16	3.2%
Fat necrosis	11	2.1%
Nipple necrosis	5	1%
TOTAL	98	19.2%

79 patients had incomplete data

Overall complication rate was significantly lower after neoadjuvant chemotherapy (15.9%; 11 of 69) compared to patients who did not receive neoadjuvant chemotherapy (27.9%; 127 of 455 patients) (p=0.035). Case load had no influence on complication rates (high volume units: 24.2%; 98 of 401 vs. low volume units: 24.7%; 42 of 170). When complication rate was analysed by date of surgery, it was significantly higher in the third of the patients who were operated earlier, between July 2005 and July 2012 (37.2%; 73 of 196) compared to the third of patients operated on between July 2012 and February 2015 (23.9%; 40 of 167; p=0.006) or the third of patients operated on most recently, between February 2015 and April 2017 (21.8%; 32 of 147; p=0.002).

Median follow-up time for all patients was 30 months [1-129]. Of those, 259 patients diagnosed with (non)invasive carcinoma had a median follow-up time of 5 years [35-124]. Of these 7 patients (2.7%) developed isolated local recurrence. 5-year local recurrence rate after DCIS was higher than after pure invasive ductal carcinoma (DCIS: 8.3%; 3 of 36 vs. ductal: 1.6%; 3 of 181; p=0.026). 5-year disease-free survival was 91.7%, overall survival was 93.8%, and cancer-specific survival was 96.1%. 5-year DFS was somewhat lower in patients who had major postoperative complication compared to patients with minor or no complication, but this was not significant (86.11%; 5 of 36 vs. 92.1%; 16 of 204; p=0.236).

5.3.5. Discussion

Evidence for OBC is largely based on single centre retrospective series [1]. Breast centres that publish their experience on OBC are usually high-volume units, tertiary referral centres, which are the most experienced units in complex breast surgery.[8, 13, 32, 40, 43, 175, 176, 255] It is well established that the outcomes of surgical breast cancer treatment in centres with significantly higher hospital volume are superior.[304-306] However, only a minority of patients are treated in such units overall. It is conceivable that the outcome results in the published meta-analyses on OBC are skewed, as those are predominantly based on data from centres of excellence.[1, 3, 10, 181] As the majority of patients are treated outside of these units, it is important to acquire outcome results reflecting the "real-life" scenario. Hence, we carried out a population-based audit of practice and outcomes of OBC involving all breast units in Scotland.

Individual breast units in Scotland were carrying out between 8 – 26 OBC operations per year, with an average between 11 cases (low volume units) to 19 cases (high volume units) yearly. This is comparable to data published by Clough et al., who found that 13.9% of breast conserving surgeries were OBC in France, based on a representative survey including 33 nationally renowned breast surgeons.[307] However the numbers of OBC procedures performed yearly were much higher in the previously mentioned leading units worldwide in comparison to breast units in Scotland. It ranged from 32 to 147 cases per year, and it was particularly high in the European Institute of Oncology, MD Anderson Cancer Center and the Division of Surgical Oncology, Emory University.[8, 40, 175, 176, 255]

A variety of oncoplastic techniques were used in the Scottish units for OBC. The vast majority of patients were treated with oncoplastic reduction techniques (91.3%), while only a small number had volume replacement surgery (8.7%). Others published similarly low rates of volume replacement amongst all OBC. *Rezai* et al. applied volume replacement in 5.1% of 1035 patients treated with OBC.[176] *De La Cruz* et al. reported on 6011 patients in a meta-analysis and found that 9.5% of patients were treated with volume replacement.[1] *De Lorenzi* et al. applied volume replacement in 10.3% of 454 OBC patients.[40] Amongst oncoplastic reduction techniques Wise pattern reduction was the most frequently applied technique (66.5%) followed by round block excision (6.1%) in Scotland. This trend was similar to other published series, although the dominance of Wise pattern reduction ranged from 35.4% to 87%.[1, 14, 32] Similarly, immediate symmetrisation rate, which was 61.7% in Scotland, varied significantly in the published literature. *Rietjens* et al. performed contralateral symmetrisation in all cases in a

series of 148 patients, while *Fitoussi* et al. reported only 46.1% immediate symmetrisation rate in a series of 540 patients.[16, 43]

Median whole tumour size of 26 mm and invasive tumour size of 21 mm in the Scottish series was comparable to results of others. *Clough* et al. published exactly the same tumour size in a series of 350 OBC patients, while *Fitoussi* et al. published 29.1 mm median tumour size in their series.[43, 255] *McIntosh* et al. reported a mean tumour size ranging between 15 and 32.5 mm in a meta-analysis containing 1702 patients.[5] *De La Cruz* et al. reported 23 mm, while *Losken* et al. reported 27 mm in two meta-analyses, respectively.[1, 181] However, many of the above studies report on invasive tumour size only.[1, 5, 43, 181]

Overall incomplete excision rate of 10.4% in the Scottish series was similar to the figures published elsewhere.[1, 43, 176, 181, 255] However, our study did not include patients who required completion mastectomy after failed OBC. Previous studies from our unit indicated a completion mastectomy rate between 0 - 13.2% of patients treated with OBC indicating a relatively high completion mastectomy rate after initially failed OBC.[22, 23, 198, 256, 308] Although these figures cannot be projected to the practice of the whole country, it is conceivable that true incomplete margin rate after OBC is somewhat higher in Scotland. Interestingly, many of the large retrospective series do not report on completion mastectomy rates either.[8, 40, 72, 255] Others report a completion mastectomy rate between 1 – 9.4% of patients treated with OBC.[16, 32, 43, 61, 176] We found a higher incomplete excision rate after OBC for invasive lobular carcinoma compared to ductal (18.86% vs. 9.2%: p=0.029), which is similar to findings published elsewhere.[255]

Complications are generally poorly defined in the majority of publications, with no definitions or classification provided in the methods.[1, 5, 8, 43, 175, 176] We classified complications as major or minor complications based on the necessity of hospital admission. In our series 9.2% of the patients had major complication, although there was a significant decrease in complication rates noted as units gained experience in OBC techniques. The overall complication rate of 28.4% is higher compared to large series of single institutions or complication rates reported in meta-analyses.[1, 3, 8, 40, 43, 176, 255] This can be explained by the multi-centre nature of our series with initially less experience in OBC techniques. Interestingly, we found a significantly lower overall complication rate after neo-adjuvant chemotherapy (15.9%) despite others reporting no difference in complication rates after neo-adjuvant chemotherapy followed by OBC or mastectomy.[255, 309]

The 2.7% 5-year local recurrence rate and 91.7% DFS in this study is at the lower end of single institutional studies or meta-analyses reporting on recurrence rates after OBC.[1, 3, 5, 8, 10, 40, 43, 176, 181, 255] Interestingly, we found a trend towards a lower DFS in patients with major complications compared to patients who had no complication (86.1% vs. 92.1%). It has been suggested previously that postoperative complications after postmastectomy breast reconstruction worsen prognosis although this has not been demonstrated after OBC as yet.[148, 310]

Our study has a few limitations. We did not determine whether the relatively higher complication rate delayed adjuvant therapy or not, although the low recurrence rates suggest that it had no significant effect overall. Similarly, complications may have had an impact on cosmetic outcome, which was not evaluated either. The time period of patients treated with OBC were not identical in the various units in this study, which more or less reflects the different learning curve for oncoplastic techniques and practices across the country.

5.3.6. Novel findings

1. This is the first nationwide "real-life" data on the oncological outcomes of OBC.
2. This study demonstrated that measured outcomes of OBC in a population-based multicentre setting in Scotland are not inferior to large volume single centre series.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

A population-based audit of surgical practice and outcomes of oncoplastic breast conservations in Scotland - An analysis of 589 patients.
Romics L, Macaskill EJ, Fernandez T, Simpson L, Morrow E, Pitsinis V, Tovey S, Barber M, Masannat Y, Stallard S, Weiler-Mithoff E, Malyon A, Mansell J, Campbell EJ, Doughty J, Dixon JM.
European Journal of Surgical Oncology. 2018 Jul;44(7):939-944.

5.4. Oncological safety of volume replacement oncoplastic surgery using chest wall perforator flaps in the United Kingdom

5.4.1. Introduction

Oncoplastic breast conserving surgery (BCS) enables resection of large tumours which would otherwise require mastectomy with or without immediate breast reconstruction.[1] Whilst ensuring complete oncological resection, patients receiving oncoplastic BCS also achieve optimal aesthetic outcome. Oncoplastic BCS techniques are well established and can be broadly categorised into volume displacement and replacement techniques. Volume displacement combines oncological resection with mastopexy and/or reduction mammoplasty.[311] An increasingly utilised volume replacement technique includes chest wall perforator flaps (CWPF), which enable partial breast reconstruction.

CWPF are pedicled flaps raised on perforating vessels around and outside the breast border. Individual flaps are names after the parent vessel that each perforator arises according to well-published anatomical landmarks.[190, 312] The named flaps are: MiCAP (Medial intercostal artery perforator), AiCAP (Anterior intercostal artery perforator), LiCAP (Lateral intercostal artery perforator), LTAP (Lateral Thoracic artery perforator) and TDAP (Thoraco-Dorsal artery perforator). Individual case series have shown that CWPF can be utilised to reduce mastectomy rates by replacing 20-50% volume loss during oncological resection.[313, 314]

Although the use of CWPF in partial breast reconstruction has been described since the early years of the millennium,[190, 315] its wider adoption has been more recent. Therefore, the current literature is limited to small case series with limited clinical outcomes.[312, 316-319] A recent systematic review (published with the co-authorship of author of this thesis) of 11 studies with 432 cases[320] showed 12.3% overall complication rates (haematoma 1.9%, seroma 2.1%, fat necrosis 2.4%, infection 2.1%, and flap necrosis 2.1%). One local and six distant recurrences were noted at a median follow-up of 21months.

5.4.2. Aim

We conducted a retrospective UK multicentre cohort study (PartBreCon study) with the aim of collating a larger pooled clinical dataset to be analysed to provide real-world experience data on patient demographics, tumour characteristics, surgical techniques utilised, and surgical outcome including complication and re-excision rates.

5.4.3. Methods

This is a UK multicentre retrospective cohort study which aims to describe and evaluate the surgical outcome of patients undergoing CWPF partial breast reconstruction following breast-conserving surgery for early breast cancer.

Main Outcomes and Measures:

A) Demographics and Tumour characteristics
   1. Patient demographics: age, BMI, comorbidities
   2. Preoperative tumour characteristics

B) Treatment characteristics
   1. Surgical: operative data, including flap types and distribution
   2. Oncological: systemic therapies (adjuvant and neoadjuvant), radiotherapy

C) Primary outcome: Surgical
   1. Complications
   2. Oncological clearance: Re-excision rates, Conversion to mastectomy

D) Secondary outcomes
   1. Revisional surgery
   2. Surveillance
   3. Oncological: Recurrence and Mortality

Study design, Setting, Participants and Exposure:

Centres in the UK known to perform CWPF reconstructions based on publications were invited to participate in the study. Centres which volunteered were required to have performed a minimum of 10 CWPF to enable demonstration of experience beyond the early learning phase. Patients at each centre were offered all possible options (simple wide local excision, therapeutic mammaplasty, mastectomy with or without immediate whole breast reconstruction) in keeping with UK Oncoplastic guidelines.[321]

Inclusion criteria:

- Patients undergoing CWPF flap for primary breast cancer between March 2011-March 2021
- Delayed correction of breast deformity following previous breast conservation
- Each centre is to have performed at least 10 CWPFs
- Exclusion criteria:
- CWPFs not used for partial breast reconstruction (such as resurfacing for recurrence)

Surgical Technique:

Each CWPF was performed either by an oncoplastic breast surgeon alone, or jointly with a plastic surgeon and in accordance with the published anatomical landmarks and operative steps.[190, 312, 322, 323] In a single stage procedure, once the cancer resection was completed, the CWPF was raised either as a turnover flap (folded 180º), a pendulum type flap based on longer pedicles (TDAP/LTAP) or as a propeller flap to reconstruct the tumour excision defect. If the flap is based on LTA,[316] a flimsy vessel, authors suggest that it would be wise to approach the LTA during simultaneous axillary node clearance with caution. However, an alternative vessel should be pre-planned in the event of an accidental injury.

A drain was used based on individual intra-operative circumstances (e.g., simultaneous axillary node clearance). In general, if a drain was sited this was placed across the donor site of the flap and the breast cavity. Alternatively, patients underwent a 'two-stage' approach where there was an anticipated concern with regards to achieving clear margin status (e.g., due to DCIS or invasive lobular cancer). This latter approach involved initial cancer resection with filling of the resection cavity with water/saline. Patients then returned few weeks later for a second procedure to perform partial breast reconstruction using CWPFs.[314]

Prior to UK Association of Breast Surgery consensus for 1mm tumour margin in 2015,[324] individual centre's policy varied (largely between 2 mm and 5 mm) and hence margin distance could not be analysed this retrospective study. Hence, presented data includes each centre's stated margin status i.e., positive, or clear.

Data management:

Each centre lead received local clinical governance authority approval to retrospectively collect data. At study planning phase, lead collaborators from each centre agreed on variables that needed to be collected from medical records and data was then entered into Microsoft™ Excel sheet. Participating units securely stored a local spreadsheet linking the study identification number with patient identifiers for cross-checking data, as may be necessary, in accordance with Caldicott's principles (2013). No identifiable patient data was centrally submitted or stored.

Statistical methods:

Data were analysed using the statistical software R™ (version 4.1.1). Descriptive statistics for each variable included counts and percentages of categorical data, whereas median and inter-quartile range (IQR) were calculated for continuous data. Statistical significance was determined using standard Wald tests and the default method in the R™. We performed Shapiro-Wilk test for normality on the distribution of cases (13-107) across 15 centres.

Multivariable logistic regression was performed for possible predictors of postoperative complications: age, comorbidities, smoking within three months,[325] largest tumour size on imaging at diagnosis (mm), tumour position, tumour type, flap type, stage (single or two stages), specimen weight (g), axillary surgery, margins, and postoperative complications. A separate sensitivity analysis was performed, including BMI[325] in the best-fit models. The analysis commenced using all variables and continued using backward elimination or forward selection as appropriate, removing, or selecting variables aiming for the model with the best Akaike information criterion (AIC). The AIC was selected as it is a criterion that deals both with the risk of overfitting (by penalizing the number of variables selected) and underfitting by performing a trade-off between the goodness of fit of the model and its simplicity. Also, the model selected by leave-one-out cross-validation is asymptotically equivalent to the model selected by AIC. AIC is primarily used in cases where the goal is prediction. The study is reported in line with the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) guidelines.

5.4.4. Results

A) Demographics and Tumour characteristics

1. Patient demographics

A total of 507 patients underwent partial reconstruction using CWPFs over 10 years (March 2011-March 2021) across 15 centres in the UK, with a median follow-up period of 23 (1-101) months. In the first five years (2011-15), there were 73 procedures (14.4%), and in the latter half (2015-2021), there were 434 procedures (85.6%).

The median patient age was 54 years (IQR: 48-62 years). 39% (n=198) of the study cohort was diagnosed with screen-detected breast cancer (UK NHS 3-yearly screening mammograms age 50-70) and the remaining 61% (n=309) diagnosed in symptomatic breast clinic. The median BMI (kg/m^2) was 25.4(IQR: 22.5-29). Available breast/bra-cup size data revealed: A-13%, B-38%, C-23%, and D-14%, while the larger D+ cups represented 12%. Other aesthetic data

variables that are usually included during oncoplastic assessment [326] such as ptosis and skin quality, were not available for all patients and thus were not included in our analysis due to inadequate data.

Approximately 11.5% (n=58) of patients smoked within previous 3 months, and 27% (n=137) had comorbidities, including 4.3% (n=22) with diabetes. Other comorbidities included hypertension, asthma, cardiac conditions, haematological disorders, CKD, COPD, CVA, connective tissue diseases, DVT/PE, significant autoimmune or neuromuscular disease, or morbid obesity.

2. Preoperative tumour characteristics

The median (IQR) largest tumour size was 26 mm (IQR: 18-35), based on the maximum size on any imaging modality (mammogram, tomogram, ultrasound, or MRI). **Table 51** shows the preoperative tumour characteristics.

Table 51. Preoperative Tumour Characteristics

Variable	N	Percent
Tumour type	497	
NST	328	66%
ILC	63	12.7%
Mixed/others	37	7.4%
Benign*	6	1.2%
DCIS	63	12.7%
Tumour position	458	
UOQ	235	51.3%
UIQ	15	3.3%
LOQ	107	23.4%
LIQ	50	10.9%
Central	19	4.1%
Others**	29	6.3%
Multicentric	3	0.7%

* Benign (phyllodes 3; 1 each of papilloma, recurrent papillomatosis, and giant cell sarcoma).
** Other locations e.g., upper central quadrant
NST, not otherwise specified; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma in situ; UOQ, upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant.

B) Treatment characteristics

1. Surgical: operative data, including flap types and distribution

86% (n=435) of operations were performed by oncoplastic breast surgeons, and 14% (n=71) jointly with plastic surgeons. 65.9% (n=220) were turnover CWPF flap, 32.6% (n=109) were propeller flap and the remaining 1.5% (n=5) were croissant flap (n=4) or V-Y advancement flap (n=1). **Table 52** shows operation and flap types.

Table 52. Operation and Flap types

Variable	N	Percent
Flap	505	
LICAP	273	54.1%
LTAP	22	4.4%
AICAP/MICAP	99	19.6%
TDAP	11	2.2%
LICAP+LTAP	100	19.8%
Stages of Surgery	506	
Single	373	73.7%
Two	125	24.7%
Delayed	8	1.6%
Axillary surgery	487	
None (In-situ disease)	43	8.8%
SNB	359	73.7%
ANC/ANS	71	14.6%
ANC following SNB	14	2.9%

LICAP, lateral intercostal artery perforator flap;
LTAP, lateral thoracic artery perforator flap;
AICAP/MICAP, anterior/medial intercostal artery perforator flap;
TDAP, thoracodorsal artery perforator flap;
SNB, sentinel node biopsy;
ANC/ANS, axillary node clearance/sampling.

17.5% underwent axillary node clearance for positive nodes at diagnosis (14.6%). Two-stage surgery was performed in 24.7% (n=125) due to: DCIS 17.6% (n=22), invasive lobular cancer 10.4% (n=13), multifocal invasive cancer 16% (n=20), invasive ductal cancer 56% (n=70). The proportion of patients undergoing two-stage surgery decreased from 32% to 18% from first to second half of the study. 1.6% (n=8) of flaps, were utilised in the delayed correction of breast deformity following BCS with defects possibly associated with post-RT shrinkage.

2. Oncological: systemic therapies (adjuvant and neoadjuvant), radiotherapy

44.7% (n=218) received chemotherapy (neoadjuvant, 13.2%; adjuvant, 31.5%); of adjuvant, 12.5% (n,49) received anti-HER2 treatment. Multigene array analysis was used to support the decisions regarding chemotherapy use in 14.6% (71/486).

96.1% received adjuvant radiotherapy (RT), and no flap loss was attributable to RT. The reason for the omission of RT in the remaining 3.9% (n=19) included patient refusal or participation in RT de-escalation trials evaluating the exclusion of RT in low-risk diseases (multidisciplinary team decisions). 30.9% received boost RT. Nine patients from 3 centres had their boost RT method recorded; hence, this needs to be discussed further. None of the patients received neoadjuvant radiotherapy.

Only ten patients (2%) received neoadjuvant hormonal therapy, whereas 75.3% of the women received adjuvant endocrine therapy.

C) Primary outcome: Surgical

The median length of hospital stay was 2 days; two days were next-day discharge after an overnight stay (for calculation, two different dates). 40% (182/453) of patients were discharged on the same day (not a 23-hour stay). Drains were used in 37% (176/477) with a median duration of 2 days (**Figure 18).**

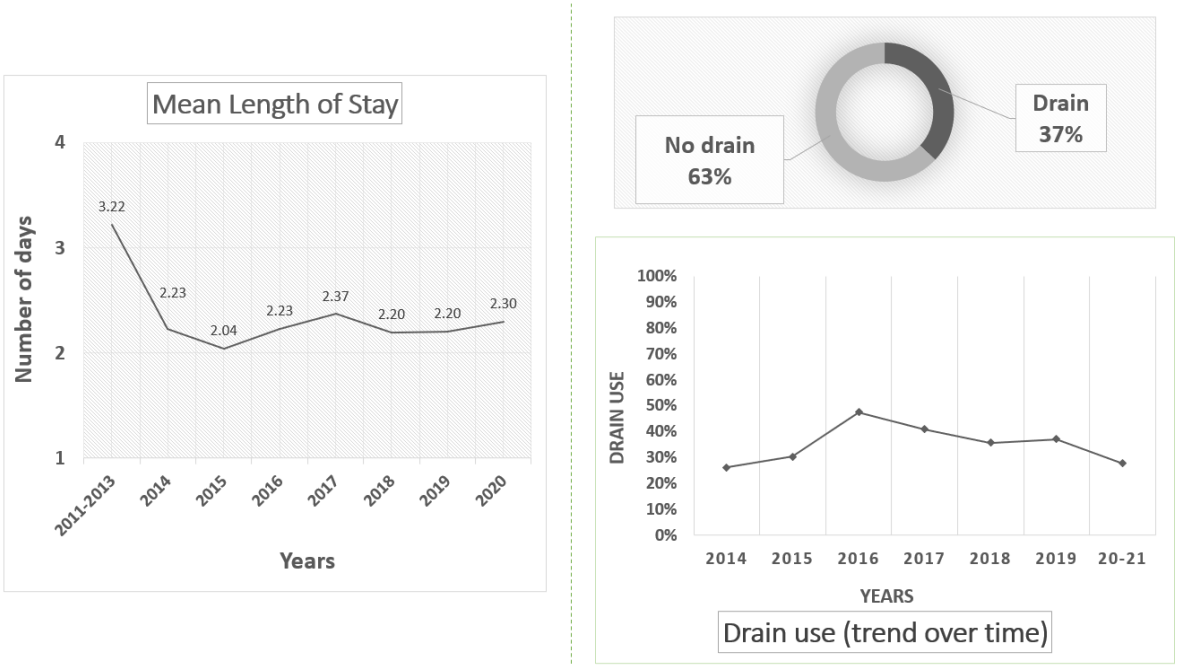


Figure 18. Trend over time of length of stay and drain use

1. Complications

Overall 16.2% (n=82) patients experienced a complication; 12.8% (n=65) were classed as Clavien-Dindo I-II, and 2.6% (n=13), III-IV. Between 2011-2016, overall complications (excluding seroma) were 13% (11/86) and in the latter half between 2016-2021, 12% (50/421). Complications included haematoma (4.3%, n=22), wound infection (4.3%, n=22), delayed wound healing (2.8%, n=14), Flap loss (0.8%, n=4; partial (n=3) and total (n=1)). Two minor flap losses were managed conservatively, the other two debrided with primary closure, and the single major was left open and healed by secondary intention.

Complications resulted in patient readmission in 2.6% (13 cases): infection (n=7), haematoma (n=12), fat necrosis (n=5), delayed wound healing (n=4), and flap loss (n=2). Unplanned return to theatre was in 2.6% (n=13): for infection (n=5), haematoma (n=10), fat necrosis (n=4), delayed wound healing (n=3), and flap loss (n=2).

There were no significant associations between postoperative complications and comorbidities (p=0.42) or smoking status (p=0.35). Flap type (propeller vs turnover; p=0.66), tumour position (inner vs outer quadrants; p=0.07), and single vs two-stage procedures showed no significant association with complication rates (p=0.62).

In the multivariable analysis, the largest tumour size (on any imaging modality) was not statistically significant in the full model or the AIC selection method. Neither usual patient risk factors [comorbidities (RR, 1.06; 95% CI, 0.44–2.47; p=0.902). and smoking (RR, 1.84; 95% CI, 0.47–6.29; p=0.359). nor procedure-specific risk factors (flap type [propeller vs turnover; (RR, 1.26; 95% CI, 0.43–3.61; p=0.666), tumour position (e.g., inner vs outer; (RR, 0.283; 95% CI, 0.07–1.13; p=0.071)), single or two stages (RR, 1.502; 95% CI, 0.30–6.66; p=0.601) were significantly associated with complications in this dataset. The only significant factor associated with a lack of complications was the absence of axillary surgery (RR, 52.212; 95% CI, 3.10–1270.02; p=0.009).

2. Oncological clearance: Re-excision rates, Conversion to mastectomy

Figure 19 and table 53 show the postoperative tumour characteristics. In DCIS with available grades (50), the majority were high-grade (high-grade, 84%; intermediate-grade, 16%; low-grade, none recorded).

	Median	IQR
Largest preoperative tumor size (mm)	26	18-35
Invasive tumor size (mm)	18	9-26 (11 pCR)
Whole tumor size (mm)	26	18-37 (11 pCR)
Specimen weight	62	40-92
Closest margin distance after first surgery (mm)	2	1-5

Tumor grade	
G1	11%
G2	51%
G3	38%

	Positive	Negative
ER	87%	13%
PR	71%	29%
HER2	15%	85%

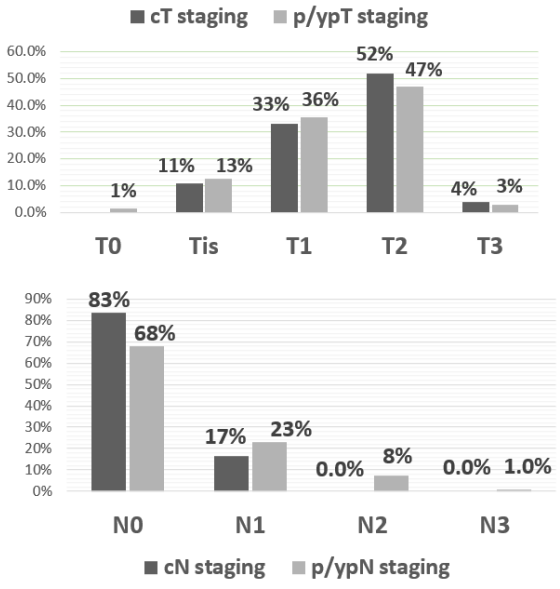


Figure 19. Postoperative tumour data

G-Grade, Bloom-Richardson (Elston-Ellis modification), ER-oestrogen receptor, PR-progesterone receptor, T-Tumour, N-Node, c-Clinical, p-pathological (postoperatively), yp-post-neoadjuvant chemotherapy pathology

Table 53. Postoperative tumour characteristics

Postoperative tumour characteristics	Numbers & percentages
Grade (invasive tumour)	
1	52/430 (12.1%)
2	236/430 (54.9%)
3	142/430 (33%)
ER positive	371/425 (87.3%)
PR positive	206/289 (71.3%)
HER2 positive	55/350 (15.7%)
Grade (DCIS)	
1	0/50 (0%)
2	8/50 (16%)
3	42/50 (84%)
Clinical T staging	
cTis	54/489 (11%)
cT1	160/489 (32.7%)
cT2	254/489 (51.9%)
cT3	21/489 (4.3%)
Pathological T staging	
p/ypT0	8/492 (1.6%)
p/ypTis	65/492 (13.2%)
p/ypT1	178/492 (36.2%)
p/ypT2	228/492 (46.3%)
p/ypT3	13/492 (2.6%)
Clinical N staging	
cN0	358/426 (84%)
cN1	68/426 (16%)
Pathological N staging	
p/ypN0	302/441 (68.5%)
p/ypN1	103/441 (23.4%)
p/ypN2	33/441 (7.5%
p/ypN3	3/441 (0.7%)
Focality	
Unifocal	391/494 (79.1%)
Multifocal/Multicentric	103/494 (20.9%)
Margins	
Clear	415/503 (82.5%)
Involved	88/503 (17.5%)
Re-excision	
Yes	79/503 (15.7%)
No	422/503 (84.3%)
Mastectomy	
Yes	9/507 (1.8%)
No	498/507 (98.2%)

DCIS, Ductal Carcinoma In Situ; ER, Oestrogen Receptor; PR, Progesterone Receptor; HER2, Human Epidermal Receptor 2

Figure 20 shows tumour margin data and surgical re-operation rates. Clear margins were achieved in 82.5% (n=415/503). Of the 17.5% (88/503) involved margins, and 15.7% (n=79) underwent re-excision. Of these 7.4% (n=37/502) – which is 47% of all re-excisions – underwent re-excision during the planned second stage of a 2-stage surgery. Four patients who had re-excisions received neoadjuvant systemic treatment. Completions mastectomy rate was 1.8% (n=9) due to multiple involved margins.

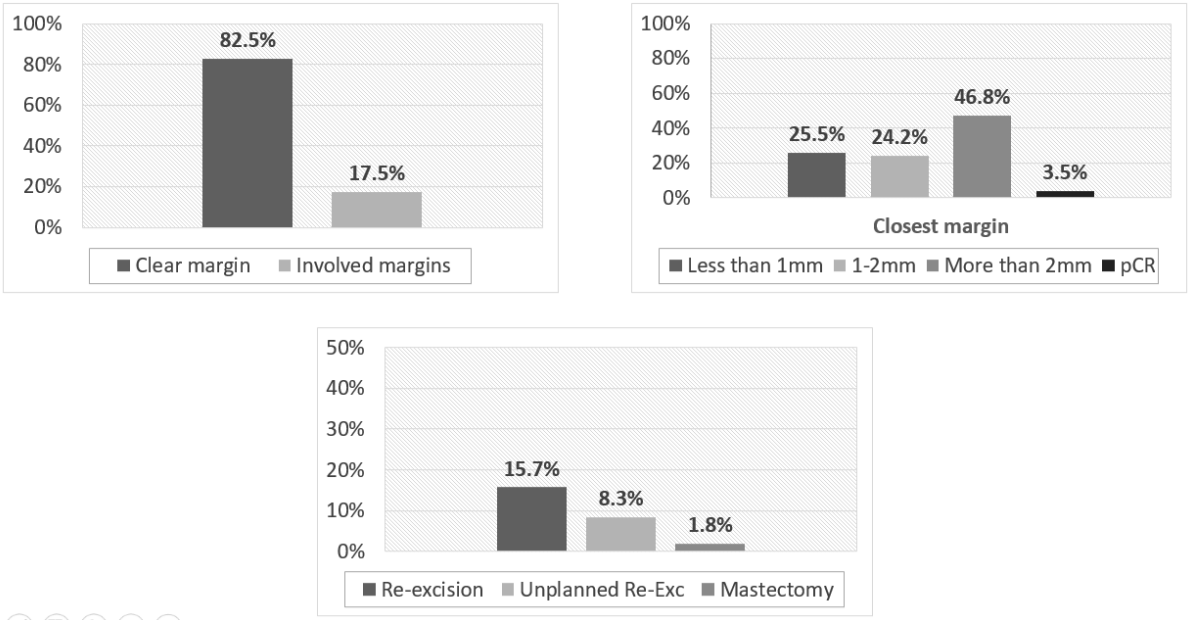


Figure 20. Tumour margin data and surgical re-operation rates

D) Secondary outcomes

1. Revisional surgery

Six patients (1.2%) required a contralateral symmetrising procedure, while 2.6% required corrective procedures, including lipomodelling and/or scar revision.

2. Surveillance

Fourteen patients (2.9%) underwent recall biopsy either due to symptoms or findings during mammographic surveillance.

3. Oncological: Recurrence and Mortality

Recurrence rates at a median follow-up of 23 months (IQR; 11-39)months: local, 1% (5/504); regional/nodal, 0.6% (3/503); and distant, 3.2% (16/495). There were 8 (2.0%) mortality recorded during median follow-up period of 23 months, of which breast cancer-specific mortality was 0.8%.

5.4.5. Discussion

In our study cohort, 85% CWPF surgeries were performed in the last 5 years including the Covid-afflicted year 2020, clearly confirming the increasing use of this innovative oncoplastic procedure. While the CWPF volume increased, confidence in the technique was also evident by the decreasing use of drains and length of stay observed within the latter part of our dataset.

In our study cohort, drains were mostly used in cases of larger tumour resection, TDAP flaps (aimed at donor site drainage) or axillary node clearance. Furthermore, overall complications decreased from 26.9% in the first 5 years to 15.2% in the latter 5 years suggestive of a learning-curve as well as learning-surge in this technique assisted by shared learning through several hands-on courses and colleague-to-colleague mentoring.

The median patient age was 54 years. In this dataset, 41 patients (8%) were over 70 years old, demonstrating that CWPFs may be incorporated amongst the range of surgical options irrespective of patient age.

The median largest tumour size was 26 mm, and the median specimen weight was 62 grams, reflective of the majority of our patient cohort being a B or C cup. Margins were clear in 82.5% of tumours during the first cancer resection surgery. These tumours were relatively larger excisions in at least half the women in the A-B bra-cup range that otherwise would cause deformities. A single-centre series [327] sought to understand excision volumes in a variety of breast operations. It compared tumour and specimen 3-dimensions measurements i.e., radial (medial-lateral and superior-inferior) and antero-posterior dimension in mammaplasty (n-31) versus flaps (n-29). Although antero-posterior tumour dimension in flap was significantly lower than mammaplasty (flap, 13.6 mm vs mammaplasty, 19.3 mm; p=0.036), radial tumour dimensions were non-significantly different between the two. This supports the fact that flaps help achieve similar radial margin clearances as in mammaplasty (better than simple wide local excisions), assuming skin-to-fascia cylindrical excisions.

Margins were involved in 17.5% (n=88) of cases, and of these, 79 (15.7%) underwent re-excision and the remaining (1.8%) completion mastectomy. Of the 79 who underwent re-excision, 47% were at pre-planned second stage in patients undergoing 2-stage reconstruction. It needs to be taken into the account that the UK Association of Breast Surgery guideline on margin policy[324] recommended 1mm margin clearance in 2015. Therefore, some patients in the study (pre-2015 cohort) were more likely to undergo margin re-excision even if the 1mm margin clearance had been achieved. Earlier surgical practice had advocated for margin clearance of at least 2 mm for invasive disease (and 5 mm for DCIS in some practices).

Most flap reconstructions (n=414; 85%) were performed in T1-2 tumours (tumour stages included in all breast-conserving versus mastectomy trials). Thus, most excised tumours were in the evidence-robust category. Only 4.1% (21/507) were in the T3 category, perhaps due to patient preference, or due to discrepancy between imaging and pathology tumour sizes, or there may have been a postoperative increase in size such as more DCIS (38%, 8 cases of the T3 tumours had DCIS on postoperative specimens, increasing the whole tumour size compared to

invasive tumour size). MRI is increasingly used for preoperative assessment of the extent of DCIS to enable more BCS. A systematic review revealed that MRI is a more accurate predictor of actual tumour size than conventional imaging; however, it does not appear to translate to improved surgical outcomes, such as mastectomy or re-excision rates. In addition, there is a lack of data in the oncoplastic setting[328] though it can complement surgical planning for complex oncoplastic scenarios.

The median BMI of 25.4 kg/m^2 and available breast size (50% in A-B cup range) suggest case-selection for lower BMI with higher tumour: breast volume ratio. Although, therapeutic mammaplasty (displacement technique) cannot be strictly compared to partial breast reconstruction, it is worth noting that in the UK TeAM study[329] the median BMI was 28.3. Only 22.7% of the patients in this study had a BMI of ≤25 (classed as normal). Although not a rule, this suggests inherently higher odds of increased breast volume owing to the overall higher body weight fitting with the displacement technique.

The study cohort included 11.7% smokers, 4.3% diabetics, and 27.1% with other comorbidities. The rates of major and minor complications were 1.8% (n=1) and 16.3% (n=9) in current smokers, and 3.5% (n=15) and 12.5% (n=53) in ex/non-smokers, respectively. Owing to the non-comparable numbers, it was not possible to perform a meaningful statistical comparison between the outcomes of smokers and non-smokers. Since CWPF is a pedicled flap, it may be assumed that perfusion-related complications may be no worse than other pedicled flaps, such as the LD flap (in addition to donor site wound healing issues in smokers). Although it may be extrapolated that pedicle-based reconstruction, for example, LD or TRAM, will have fewer complications than vascular anastomosis-based reconstruction, the evidence thus far has not confirmed this.[330] This could be partly due to the magnitude of these pedicled procedures or finer techniques, which would have improved over time.

The overall complication rate in this study (16.2%) was similar to the recent systematic review of flaps (n=432) (in which the author of this thesis is a co-author, too)[320] and systematic review of oncoplastic reduction mammoplasty (n=1324)[331] that reported 13.2% complications (wound dehiscence, 4.6%; fat necrosis, 4.3%; wound infection, 2.8%; partial/total nipple necrosis, 0.9%; seroma, 0.6%). Therefore, it can be extrapolated that CWPF complication rates are no inferior to mammaplasty. Although in some patients, both CWPF or therapeutic mammaplasty may be valid oncoplastic BCS options, in a large majority of patients, these are two surgical techniques are different in their applications with different patient profiles that cannot be strictly compared.

A recent meta-analysis[332] demonstrated a lower seroma rate with oncoplastic surgery than with standard BCS (13.4% vs. 18.0%; p=0.002) and higher wound-related issues (4.8% vs. 1.4%; p=0.0001). The lower rate of seroma/haematoma in our series (8.8%) may be explained by the plug effect of replacement with the perforator flap in the resection cavity; and patient factors: lower BMI, smaller breasts, and less contralateral symmetrisation compared to other oncoplastic techniques. It should be noted that most systematic reviews on oncoplastic surgery include volume-displacement techniques only.

Recently, a retrospective cohort study of 109 procedures[333] reported a significantly lower overall complication rate and less need for additional oncoplastic breast surgery compared to mastectomy and immediate total breast reconstruction. A meta-analysis[334] comparing oncoplastic breast surgery and standard BCS revealed a significantly lower re-excision rate in the BCS plus OPS group (RR, 0.66; 95% CI, 0.48–0.90; p=0.009); however, pooled data from nine studies showed that the total relapse rate was similar in the two groups (RR, 1.07; 95% CI, 0.88–1.30; p=0.525).

Only 1.2% of patients (n = 6) required symmetrisation surgery and 2.6% (n = 13) required lipomodelling and/or scar revision, which is in keeping with literature.[320, 335] This alone may be the most advantageous characteristic as opposed to any option that does not replace defects confirming applicability of CWPF in small-sized non-ptotic or mildly ptotic breasts.

An analysis of the UK breast screening NHSBSP audit 2019/2020 report[336] shows that the mastectomy rate among women with tumour size between 35-50 mm was 42-51%, whereas it was as high as 74-77% for those with a tumour size >50 mm. Hence, this multicentre collaborative cohort data buttresses the available body of evidence on the safety and reproducibility of partial breast reconstruction techniques in situations where mastectomy would otherwise be the only available surgical option.

Radiotherapy is an integral component of BCS, and tumour bed boost radiotherapy is often used to minimise the risk of local recurrence.[337] In our study, most patients (96.1%) received adjuvant radiotherapy (RT) and the data were limited with regards to radiotherapy boost components. Since planning of integrated boost is increasingly complex, discussion with radiation oncologists is recommended when commencing CWPF in a new unit.[338]

Our study is limited by medium-term follow-up, however, shorter follow-ups are not uncommon in oncoplastic breast surgery due to the recency of these procedures as noted in the systematic reviews of both flaps[320] and mammaplasty[331] with similar reported recurrence rates. Radiotherapy can affect the short-and long-term aesthetic outcomes intended to be achieved by oncoplastic surgery by affecting the breast in multiple ways: the breast as a whole, breast skin

and parenchyma.[339] Our dataset was limited by the objective and patient-reported outcome data. This highlights the importance of establishing a practical evaluation process using available patient-reported outcome measurement tools.

5.4.6. Novel findings

1. This study, which is the world's largest cohort study on partial breast reconstruction using chest wall perforator flaps, showed that outcomes after partial breast reconstruction with chest wall perforator-based flaps are excellent, with low complication and revisional surgery rates.
2. Locoregional recurrence rates at 'medium' term follow up are low and thus appears to be a safe alternative to mastectomy in higher tumour: breast volume ratio and hence facilitating increased rates of breast conservation.
3. Confidence in the technique was also evident by a decrease in overall complications from 26.9% in the first 5 years to 15.2% in the latter 5 years suggestive of a learning-curve as well as learning-surge in this technique assisted by shared learning through several hands-on courses and colleague-to-colleague mentoring.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

'PartBreCon' study. A UK multicentre retrospective cohort study to assess outcomes following PARTial BREast reCONstruction with chest wall perforator flaps.
Agrawal A, **Romics L,** Thekkinkattil D, Soliman M, Kaushik M, Barmpounakis P, Mortimer C, Courtney CA, Goyal A, Garreffa E, Carmichael A, Lane RA, Rutherford C, Kim B, Achuthan R, Pitsinis V, Goh S, Ray B, Grover K, Vidya R, Murphy J.
Breast 2023 Jul; 71:82-88

Systematic review of partial breast reconstruction with pedicled perforator artery flaps: Clinical, oncological and cosmetic outcomes.
Pujji OJS, Blackhall V, **Romics L**, Vidya R.
European Journal of Surgical Oncology. 2021 Aug;47(8):1883-1890.

5.5. Breast cancer related survival and overall survival in patients treated with breast conservation versus mastectomy in Scotland

5.5.1. Introduction

Since the publication of key trials confirming the oncological equivalence of breast-conserving surgery followed by adjuvant radiotherapy and mastectomy, BCS is recommended for patients with early breast cancer.[11, 12] In the last decade, there have been a few studies published which suggested that breast conservation followed by radiotherapy may provide a superior survival compared to mastectomy.[340-342] Recently, a population-based study has reported improved overall survival after BCS with RT over Mx without RT.[343] Mastectomy has subsequently been questioned as an equally valid surgical alternative.

5.5.2. Aim

There has been recent observational evidence to support that breast conserving therapy is associated with improved survival compared with mastectomy. We evaluated the survival following breast conserving therapy and mastectomy in the West of Scotland population.

5.5.3. Methods

This is a cohort study using data from a prospective national database. All patients diagnosed with Stage I-III invasive breast cancer who underwent surgery in the West of Scotland population from 2010-2018 were included. Patients were grouped by locoregional treatment: Breast conserving surgery with radiotherapy (BCS + DXT), mastectomy alone (Mx) and mastectomy with radiotherapy (Mx + DXT). Overall Survival (OS) and Breast cancer specific survival (BCSS) was performed using the Kaplan-Meier and Cox Regression analysis.

5.5.4. Results

Of 12,650 women, 7990 (63.2%) underwent BCS + DXT, 2111 (16.7%) underwent Mx and 2549 (20.2%) underwent Mx + DXT. Median follow up was 63 months. There were a total of 1729 deaths of which 899 (52.0%) were breast cancer related. 5-year OS and 5-year BCSS were

88.4% (95% CI, 88.1-88.7) and 93.3% (95% CI, 93.1-93.5) respectively (**Figure 21 and 22**). Following adjustment for co-variates including screen detection OS and BCSS were significantly worse for both Mx (HR 1.70 (95% CI 1.49-1.94) and HR 1.75 (95% CI 1.42-2.15)) and Mx + DXT (HR 1.33 (95% CI 1.16-1.52) and HR 1.57 (95% CI 1.32-1.86)) compared with BCS + DXT (**Table 54 and 55**).

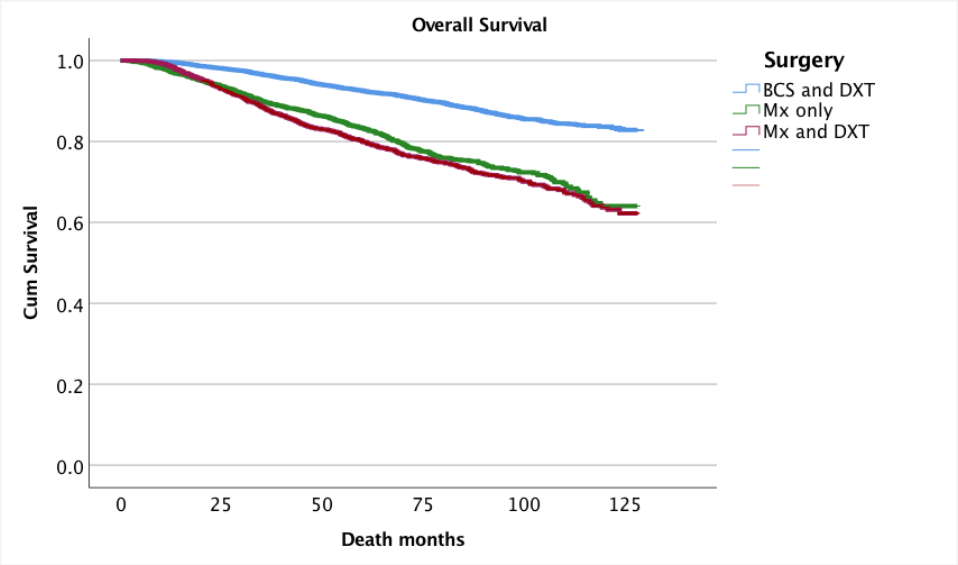


Figure 21. Overall survival for patients treated with BCS and DXT, Mx only and Mx and DXT

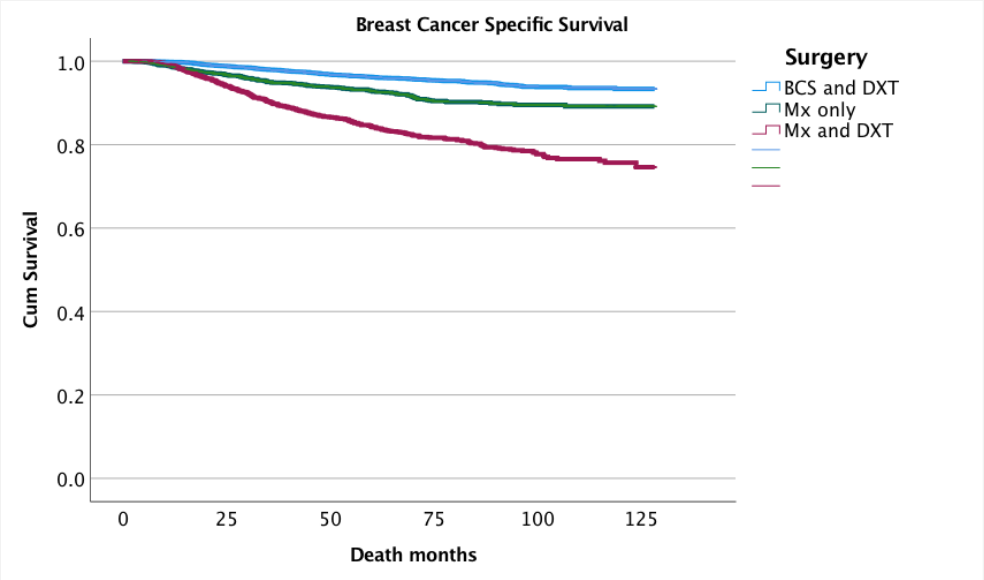


Figure 22. Breast cancer specific survival for patients treated with BCS and DXT, Mx only and Mx and DXT

Table 54. Multivariate analysis of overall survival for patients treated with BCS and DXT, Mx only and Mx and DXT

Characteristic	No.	Hazard Ratio (95% CI)	P value
Age (yrs)			
<50	2368	1.40 (1.20-1.63)	<0.001
50-70	7214	3.33 (2.87-3.86)	<0.001
>70	2434		
Referral			
GP	6979	0.66 (0.56-0.77)	<0.001
Screening	4129	1.08 (0.91-1.28)	0.372
Other	908		
Stage			
I	6135	1.29 (1.14-1.45)	<0.001
II	5167	2.08 (1.73-2.49)	<0.001
III	714		
Grade			
1	1433	1.23 (0.98-1.54)	0.081
2	5629	1.71 (1.35-2.15)	<0.001
3	4954		
LN status			
Negative	7926	1.76 (1.57-1.98)	<0.001
Positive	4090		
Receptor Profile			
ER+ HER2-	8876	1.02 (0.89-1.19)	0.749
HER2+	1692	2.40 (2.10-2.73)	<0.001
TN	1448		
Surgery			
BCS + DXT	7617	1.70 (1.49-1.94)	<0.001
Mastectomy	1948	1.33 (1.16-1.52)	<0.001
Mastectomy + DXT	2451		

Table 55. Multivariate analysis of breast cancer specific survival for patients treated with BCS and DXT, Mx only and Mx and DXT

Characteristic	No.	Hazard Ratio (95% CI)	P value
Age (yrs)			
<50	2368	1.04 (0.87-1.25)	0.631
50-70	7214	1.55 (1.29-1.87)	<0.001
>70	2434		
Referral			
GP	6979	0.54 (0.43-0.69)	<0.001
Screening	4129	1.11 (0.87-1.41)	0.396
Other	908		
Stage			
I	6135	1.60 (1.33-1.92)	<0.001
II	5167	2.85 (2.24-3.63)	<0.001
III	714		
Grade			
1	1433	3.82 (1.96-7.45)	<0.001
2	5629	7.68 (3.95-14.94)	<0.001
3	4954		
LN status			
Negative	7926	2.90 (2.45-3.44)	<0.001
Positive	4090		
Receptor Profile			
ER+ HER2-	8876	0.96 (0.79-1.18)	0.713
HER2+	1692	3.12 (2.65-3.68)	<0.001
TN	1448		
Surgery	7617	1.75 (1.42-2.15)	<0.001
BCS + DXT	1948	1.57 (1.32-1.86)	<0.001
Mastectomy	2451		
Mastectomy + DXT			

5.5.5. Discussion

The findings of this study confirm the superiority of BCS with RT over Mx with an overall and breast cancer–specific relative survival gain. This association resisted adjustment for tumour biology and status, way of referral and age. Because there was no inferior survival for BCS, this report gives no support to advocate Mx in women without specific risk factors, such as a strong family history or gene mutations.

While the previously mentioned studies deliver evidence encouraging the use of BCS, it remains unclear why such survival differences would exist. Theories of a negative effect of larger surgery on recurrence rates and survival through the systemic release of growth factors and inflammatory effects have not been sufficiently corroborated, so Mx in itself may not be an

independent factor for worse survival. Selection mechanisms and unmeasured confounders may also be suspected.

Complications impacting survival can be a plausible mechanism behind superior survival after breast conservation. In our systematic review and meta-analysis including 37657 patients we identified five studies, in which a relationship between wound complications, infection and pyrexia and recurrence or recurrence-free survival was found.[52] Risk of recurrence, 1-year and 5-year recurrence-free survival and overall survival were related to complications, particularly for patients with poor Nottingham Prognostic Index. Five studies failed to demonstrate a relationship between complications and prognosis. Complication was found to significantly affect 5-year recurrence-free survival (HR 1.48 95% CI 1.02-2.14, p = 0.04) but not recurrence (HR 2.39, 95%CI 0.94-6.07, p = 0.07), with a high degree of heterogeneity amongst analysed studies (I2 = 95%). In another recent meta-analysis we carried out we found evidence that elevated circulating inflammatory response markers adversely impact prognosis including higher neutrophil-to-lymphocyte ratio, higher platelet-to-lymphocyte ratio, higher lymphocyte-to-monocyte ratio, and higher C-reactive protein levels.[54]

We have investigated whether a single dose of amoxicillin–clavulanic acid would reduce wound infection at 30 days postoperatively in breast cancer surgery (PAUS trial) in a randomised double-blind parallel-group multicentre superiority trial. In this trial participants were randomised to either a single bolus of 1.2 g intravenous amoxicillin–clavulanic acid or no antibiotic.[344] The primary outcome was the incidence of wound infection at 30 days postoperatively. 438 received prophylactic antibiotic and 433 served as controls. 71 (16.2%) patients in the intervention group developed a wound infection by 30 days, while there were 83 (19.2%) infections in the control group, which was not statistically significant (OR 0.82, 95% c.i. 0.58 to 1.15; P=0.250). The risk of infection increased for every 5 kg/m^2 of BMI (OR 1.29, 95 per cent c.i. 1.10 to 1.52; P=0.003). Patients who were preoperative carriers of Staphylococcus aureus had an increased risk of postoperative wound infection; however, there was no benefit of preoperative antibiotics for patients with either a high BMI or who were carriers of S. aureus. The above findings are particularly interesting when antimicrobial resistance to common pathogens has been a growing concern in recent decades. Antimicrobial resistance poses a worldwide threat of ‘a post-antibiotic era’, when antibiotics would be unavailable to treat common illnesses. Hence, developing severe infections may further worsen clinical prognosis in breast cancer (and other solid tumours) as a result of antibiotic resistance due to unnecessary overuse of antibiotics.

Boniface et al. investigated the impact of major complications on survival in a Swedish database involving 57152 women and found that major surgical postoperative complications are associated with inferior survival, especially after mastectomy.[53] Major surgical postoperative complications were more common after mastectomy with or without immediate reconstruction (7.3 and 4.3% respectively) than after breast-conserving surgery (2.3%). They demonstrated that all-cause and breast cancer mortality rates remained higher after a major surgical postoperative complication (OS: HR 1.32, 95 per cent c.i. 1.15 to 1.51; BCSS: HR 1.31, 1.04 to 1.65). After stratification for type of breast surgery, this association remained significant only for women who had mastectomy without reconstruction (OS: HR 1.41, 1.20 to 1.66; BCSS: HR 1.36, 1.03 to 1.79).

A population-based UK study (data from the national iBRA-2 (a prospective data collection on outcomes of mastectomy with or without reconstruction) and TeaM (a prospective data collection of therapeutic mammoplasty outcomes) studies were combined) including a total of 2916 patients (TM: 376; mastectomy 1532; mastectomy and IBR: 1008) showed that patients undergoing mastectomy with or without IBR were more likely to experience complications than the TM group (TM: 79, 21%; mastectomy: 37.2%; mastectomy and IBR: 35.6%; $P < 0{\cdot}001$).[51]

The above data indirectly suggests that patients should be conserved at all cost, as both simple wide excision as well as therapeutic mammoplasty carry lower complication rates compared to mastectomy and mastectomy with immediate reconstruction, and they provide better prognosis as well, partially due to their lower complication rate.

In conclusion, in our observational cohort study BCS + DXT has improved survival compared with Mx with or without DXT after adjustment for other proven prognostic factors. Careful consideration of this data along with other studies should be given when discussing surgical options with breast cancer patients.

5.5.6. Novel findings

1. In this observational cohort study BCS + DXT has improved survival compared with Mx with or without DXT after adjustment for other proven prognostic factors.
2. In the context of the above findings the role of oncoplastic breast conservation surgery is even more important as it looks that breast conservation itself improves prognosis. Hence, patients routinely treated with mastectomy will need to be thoroughly assessed and determine the suitability for oncoplastic breast conservation surgery by an oncoplastic breast surgeon or by a plastic and general surgeon together. Mastectomy should be offered to patients only who are not suitable for breast conservation even with complex oncoplastic techniques.
3. Mastectomy should not be offered to patients as an option who can be treated with breast conservation surgery as mastectomy would impair prognosis.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Survival following breast conserving therapy vs. mastectomy in the West of Scotland
L. Magill, J. Campbell, C.R. Wilson, **L. Romics**, J.C. Doughty, J. Mansell
Association of Breast Surgery Annual Conference 2023
Abstract published in European Journal of Surgical Oncology, 2023 May; 49(5):e221

Prognostic role of preoperative circulating systemic inflammatory response markers in primary breast cancer: meta-analysis.
Savioli F, Morrow ES, Dolan RD, **Romics L**, Lannigan A, Edwards J, McMillan DC.
British Journal of Surgery. 2022 Nov 22;109(12):1206-1215.

The effect of postoperative complications on survival and recurrence after surgery for breast cancer: A systematic review and meta-analysis.
Savioli F, Edwards J, McMillan D, Stallard S, Doughty J, **Romics L.**
***Critical Reviews in Oncology and Hematology*.** 2020 Nov;155:103075.

Antibiotic prophylaxis in breast cancer surgery (PAUS trial): randomised clinical double-blind parallel-group multicentre superiority trial.
Stallard S, Savioli F, McConnachie A, Norrie J, Dudman K, Morrow ES, **Romics L**.
British Journal of Surgery. 2022 Nov 22;109(12):1224-1231.

6. SUMMARY

Oncoplastic breast surgery developed as a result of a paradigm shift when aesthetic outcome became an important factor for patients in addition to longer survival after breast cancer treatment due to improved prognosis seen from the early 1990's. Oncoplastic breast surgery started with breast reconstruction after mastectomy in a delayed setting initially, followed by immediate breast reconstruction in the 2000's. These were the first two steps in the development of oncoplastic breast surgery. The third step in oncoplastic breast surgery emerged when aesthetic breast reduction surgical techniques were applied along the oncological principles in order to improve the cosmetic outcome of breast conserving surgery. This technique is called therapeutic mammoplasty. In parallel with therapeutic mammoplasties another technique emerged, which is called partial breast reconstructive techniques using locally available flaps. This third step – which is the rise of oncoplastic breast conservations – dates back to the early 2010's. The ultimate step in oncoplastic surgery comprises conversion of mastectomy into breast conservation surgery with the joint help of complex oncoplastic techniques and ever more effective neoadjuvant treatments.

The above-described evolution of breast surgery resulted finally in a new subspecialty surgeon called the "oncoplastic breast surgeon" which arose from the "general surgeon with interest in breast" on one hand and the "plastic surgeon with interest in breast" on the other hand. Nowadays there are numerous oncoplastic surgical fellowships exist worldwide for either general or plastic surgeons who can be trained to oncoplastic breast surgeons. However, the author was one of the first formal oncoplastic breast surgical fellow in 2006 and 2007 in the UK oncoplastic fellowship training programme in the Glasgow breast and plastic surgical units.

It is important to note that the above detailed progress in breast surgery was demanded and driven by the patients due their increased survival, and not by the oncological surgeons. Initially, partial or full breast reconstructive surgeries were not considered as part of the oncological treatment. In parallel, concerns were raised in the surgical and oncological community upon realisation that these operations increase surgical stress on the patients, and may carry higher complication rate, delay adjuvant treatment, increase incomplete excision rate, and, in turn, oncoplastic surgery impairs prognosis via higher recurrence and lower cancer-specific survival rates in comparison to non-oncoplastic breast cancer surgery. These concerns were addressed and investigated in this thesis thoroughly.

The above-described shift in the surgical treatment of breast cancer is not based on prospective randomised trials due to obvious ethical considerations because patients cannot be randomised between reconstructive and non-reconstructive surgery, and, in fact, the single trial in the UK which attempted to investigate certain aspects of oncoplastic breast surgery failed to recruit (MIAMI Trial). As the concern about oncological safety cannot be investigated in a prospective randomised format, we had to look into alternatives such as retrospective and – lately – prospective audits based on single centre oncoplastic databases, and then followed by regional, national and international audits in order to generate evidence that the surgery we offer to our breast cancer patients – and once again demanded by the patients to be treated with oncoplastic surgery – is oncologically safe.

The author of this thesis started to investigate the oncological safety of oncoplastic surgery in the early 2010's. In those years a shift from delayed to immediate full breast reconstructions took place as well as the dawn of oncoplastic conservations was observed. Hence, this thesis mainly focuses on studies investigating the oncological safety of oncoplastic breast conservations besides the initial studies looking at the oncological safety of immediate reconstructions.

Breast reconstructions after mastectomy have a longer history and their oncological safety have been investigated quite thoroughly by the early 2010's, although all those studies focused on patients with DCIS or stage I cancer due to a fear of offering immediate reconstruction to patients with more advanced disease. The generally accepted concept was to offer delayed reconstruction only for patients with stage II-III cancer after some time of their oncological surgery in almost all the breast units. The timely evidence was poor as it was based mostly on short-term follow-up data from highly selected patients Hence, we investigated the oncological safety of immediate breast reconstructions in a so-called "all-comer" patient population (including more advanced disease), which was a relatively unique approach in those days, with long-term follow-up in a regional (West of Scotland) breast reconstructive service serving a population of approximately 2.5 million people. The results below were published in the *British Journal of Surgery* (Ten-year follow-up of skin-sparing mastectomy followed by immediate breast reconstruction. *Romics L Jr*, Chew BK, Weiler-Mithoff E, Doughty JC, Brown IM, Stallard S, Wilson CR, Mallon EA, George WD. *British Journal of Surgery*. 2012; 99(6):799-806).

Follow-up data from 253 consecutive patients with immediate reconstruction operated between 1995 and 2000 were reviewed retrospectively and after exclusions 207 were included for analysis. We found that offering immediate reconstruction to all women requiring

mastectomy resulted in a large proportion of patients with advanced disease. During a median follow-up of 119 months, 17 (8.2%) locoregional, six (2.9%) local and 22 (10.6%) distant recurrences were detected; the overall recurrence rate was 39 (18.8%). Overall recurrence rate was associated with axillary lymph node metastasis (P = 0.009), higher stage (P < 0.001) and higher tumour grade (P = 0.031). The 10-year breast cancer-specific survival rate was 90.8 per cent (19 of 207 women died from recurrence). As we included large number of unselected patients with one of the longest median follow-up times in the published literature of those days, we concluded that offering immediate reconstruction to all women requiring mastectomy is an oncologically safe approach and, as a result, skin-sparing mastectomy combined with immediate reconstruction can be offered for all breast cancer patients who require mastectomy, even for patients with more advanced breast cancer.

At the dawn of oncoplastic breast conservations we believed that the only impact of incorporation of plastic surgical techniques in cancer resection is the better aesthetic outcome. Soon after, however, we started to suspect that by using oncoplastic techniques in our breast units in Glasgow we are able to offer breast conservation for larger, more advance tumours than in the past when we used non-oncoplastic techniques only. This was in contrast to a few other publications from elsewhere in the UK or internationally, which showed similarities in clinicopathological characteristics between oncoplastic breast conservations and standard wide local excisions. Hence, we compared tumour and treatment characteristics of patients treated consecutively with oncoplastic conservations to standard wide local excisions and mastectomy ± immediate reconstruction in the Glasgow breast units between 2009 and 2012. 1000 patients' data were analysed (oncoplastic conservation = 119; wide excision = 600; mastectomy ± reconstruction = 281), and these results were published in the *Breast* (How to compare the oncological safety of oncoplastic breast conservation surgery - to wide local excision or mastectomy? J Mansell, E Weiler-Mithoff, J Martin, A Khan, S Stallard, J C Doughty, *L Romics*. *Breast***.** 2015 Aug;24(4):497-501).

We found that the tumour size was significantly bigger after oncoplastic conservation than wide local excision (p < 0.001), but similar to mastectomy ± reconstruction (p = 0.138). Tumour grade was higher after oncoplastic conservation than wide local excision (p < 0.001), but similar to mastectomy ± reconstruction (p = 0.497). More axillary nodes were involved in patients with oncoplastic conservation than wide local excision (p < 0.001), but comparable to mastectomy ± reconstruction (p = 0.175). ER and PR expressions were lower after oncoplastic conservation compared to wide local excision (p = 0.007, p = 0.009), but identical to mastectomy ± reconstruction (p = 1, p = 0.904 respectively). Differences in application of

systemic (neo)adjuvant therapy followed the above trend. We were surprised finding so striking similarities between oncoplastic conservation and mastectomy patients' clinicopathological results, which were in sharp contrast with previously published data. We concluded that in our practice in the Glasgow units, the oncological outcomes following oncoplastic conservation should be compared to mastectomy rather than wide local excision (although wide excision group would also need to be included to benchmark incomplete excision rates). This study also suggested first that we can convert mastectomy to conservation using oncoplastic techniques in the routine practice due to the similarities in the clinicopathological characteristics of patients treated with oncoplastic conservation and mastectomy. This finding carries huge significance as almost a decade later we realised that patients treated with breast conservation have better prognosis when compared to mastectomy, which is demonstrated later this thesis.

One of the concerns for oncological safety in relation to oncoplastic conservation was that it may delay the commencement of adjuvant treatment, in particular adjuvant chemotherapy. Hence, we investigated if whether oncoplastic conservation led to a delay when compared to simple wide local excision, mastectomy, or mastectomy with immediate reconstruction in the Glasgow breast units. The time between multidisciplinary team decision to offer chemotherapy and delivery of first cycle of chemotherapy was measured and compared among the four groups of patients. The findings of this study were published in the *European Journal of Surgical Oncology* (Oncoplastic breast conservation does not lead to a delay in the commencement of adjuvant chemotherapy in breast cancer patients. Kahn J, Barrett S, Forte C, Stallard S, Weiler-Mithoff E, Doughty JC, *Romics L Jr. European Journal of Surgical Oncology.* 2013;39(8):887-91).

We found that the time to chemotherapy of breast cancer patients (n = 169) treated between 2008 and 2011 with oncoplastic conservation (n = 31) were 29 [16-58] days, while it was 29.5 [15-105] days after wide local excision (n = 66), 29 [15-57] days after mastectomy (n = 56) and 31 [15-58] days after mastectomy with reconstruction (n = 16). A combined analysis involving all four groups demonstrated no statistically significant difference (p = 0.524). Similarly, inter-group analysis revealed no significant differences in between patients treated with oncoplastic conservation compared to any of the three control groups (oncoplastic conservation to wide local excision: p = 0.433; oncoplastic conservation to mastectomy: p = 0.800; oncoplastic conservation to mastectomy and reconstruction: p = 0.405). We concluded that oncoplastic conservation seemed as safe as wide local excision, mastectomy or mastectomy and reconstruction in terms of delivery of adjuvant chemotherapy. However, we needed to acknowledge that the timely evidence for any potential delay of adjuvant chemotherapy after

immediate breast reconstruction, however, was conflicting. Having said this, even if some delay occurred, it was unlikely to influence the prognosis significantly after mastectomy and reconstruction.

By the mid 2010's we had long enough follow-up data on oncoplastic breast conservation to look at recurrence rates in the Glasgow breast units, which is the ultimate measure of oncological safety. A series of patients treated exclusively with therapeutic mammoplasty (n=65) was reviewed who were treated between 2005 and 2010 (Six-year follow-up of patients treated with oncoplastic reduction mammoplasty: A cohort study. Kabir SA, Stallard S, Weiler-Mithoff E, Mansell J, Mallon E, Doughty JC, *Romics L Jr. International Journal of Surgery.* 2016;26:38-42). Majority of patients had relatively advanced cancer with a mean preoperative tumour size of 2.95 cm on imaging and almost two-thirds of them had stage II - III cancers, which required large resections with the average weight of the tissue resected being 272g. The mean preoperative tumour size was 2.95 cm on imaging. 64% of patients had stage II - III cancers. We found an acceptable incomplete excision rate with 16.1% and completion mastectomy rate of 10.7%. Needless to say, that this series included patients at the very beginning of the learning curve and as more experience was gained during the years both incomplete excision and completion mastectomy rates significantly decreased. We found 2% local and 6% distant recurrence rates during a median follow-up of 72 months, with breast cancer-specific survival rate of 96%. Similarly, we found reassuring results when we analysed our initial series of patients treated exclusively with volume replacement surgery (n=30) using LICAP, TDAP, LTAP, crescent flap, and matrix rotation techniques (Oncological outcomes and complications after volume replacement oncoplastic breast conservations - the Glasgow experience. W Ho, S Stallard, J Doughty, E Mallon, *L Romics. Breast Cancer: Basic and Clinical Research* 2016;10:223-228). In this series the mean preoperative tumour size was 25.4 mm, and the rate of incomplete excision was 10%. During a median follow-up time of 48.5 months one regional recurrence was detected but no local recurrence. While these are relatively small series and much larger series have been published later, it was very important to show at the start of the oncoplastic conservation era that oncoplastic conservations are safe oncologically and recurrence and incomplete excision rates are not different from conventional wide local excision or mastectomy in the Glasgow breast units.

The oncological safety of oncoplastic breast conservation surgery (OBCS) needs to be put in context of other surgical treatment options and correlate it with the oncological outcomes after WLE and mastectomy. Previously we demonstrated that the clinicopathological characteristics of patients we were treating with OBCS in Glasgow are closer to mastectomy

than WLE. Hence, we compared the OBCS oncological outcomes to mastectomy, and – due to the similar "nature" of OBCS and WLE being both breast conservation surgery – to simple wide local excision, too. 980 patients' data were analysed, who were all treated between 2009 and 2012 (OBCS: n = 104; WLE: n = 558; Ms ± IR: n = 318) and the results were published in the *Breast* (Oncoplastic breast conservation surgery is oncologically safe when compared to wide local excision and mastectomy. Mansell J, Weiler-Mithoff E, Stallard S, Doughty JC, Mallon E, *Romics L. Breast.* 2017 Apr;32:179-185). Tumour size, grade, nodal status, ER, and PR expression were similar in patients treated with OBCS and Ms ± IR, but more adverse compared with patients treated with WLE ($p < 0.001$). 5-year local recurrence rates were similar in all three groups (WLE: 3.4 per cent, OBCS: 2 per cent, Ms ± IR: 2.6 per cent; log rank = 0.973), while distant recurrence rates were higher after Ms ± IR and OBCS (Ms ± IR:13.1 per cent, OBCS:7.5 per cent, WLE:3.3 per cent; log rank: $p < 0.001$). These results proved on one hand that OBCS is oncologically safe in terms of providing local control. On the other hand, it also demonstrated that the distant recurrence rate after OBCS is lower compared to mastectomy despite the similar clinicopathological and treatment characteristics. In hindsight, this was likely due to the fact that breast conservation provides better prognosis than mastectomy, which we were not aware at the time of this study but discuss later in the thesis.

As the oncoplastic techniques became the part of the everyday practice we were keen to find how far we can increase the indication of breast conservation without risking the oncological outcomes. Extreme Oncoplastic Breast Conservation Surgery (EOBCS) is offered in selected patients with multifocal or multicentric breast cancer (MFMC), or with single focus of at least 5 cm (cT3) radiological tumour size. In the Glasgow breast units, we prospectively collected a database of 50 patients treated with EOBCS between 2007 and 2018 (Extreme Oncoplasty: Breast Conservation in Patients with Large, Multifocal, and Multicentric Breast Cancer. Savioli F, Seth S, Morrow E, Doughty J, Stallard S, Malyon A, *Romics L. Breast Cancer.* 2021;13:353-359. Median tumour size was 55mm (50-90) and multifocal / multicentric disease was identified in 22 (44%) patients. 9 patients (18%) were found to have positive margins and underwent a second procedure, with 6 (12%) proceeding to mastectomy. Five-year disease-free survival rate was 91.5%, while cancer-specific survival was 95.7%. Undoubtedly, large scale studies are required to confirm these preliminary results, although this small study suggested that in well selected patients EOBCS is a valid option to conserve the breast and could be considered in patients who are routinely treated with mastectomy otherwise.

The COVID-19 pandemic brought up unprecedented circumstances. The surgical options for breast cancer treatment were substantially guarded during lockdown. Most important changes included the abandonment of neo-adjuvant chemotherapy and immediate breast reconstruction, and frequent use of neo-adjuvant endocrine treatment to time surgery in suitable patients. Hence the clinicopathological spectrum of patients undergoing breast cancer surgery significantly changed compared to the pre-pandemic time, and we evaluated its impact on oncoplastic breast conservation surgery. A prospective cohort study of patients having breast cancer surgery was carried out in the West of Scotland region during the first eight weeks of the hospital lockdown in the UK (188 operations in 179 patients) and outcomes were compared to the regional cancer registry data of pre-COVID-19 patients of the same units (n = 1415) (A prospective cohort study of the safety of breast cancer surgery during COVID-19 pandemic in the West of Scotland. *Romics L*, Doughty J, Stallard S, Mansell J, Blackhall V, Lannigan A, Elgammal S, Reid J, McGuigan MC, Savioli F, Tovey S, Murphy D, Reid I, Malyon A, McIlhenny J, Wilson C. *Breast.* 2021 Feb; 55:1-6). We found that tumour size was significantly larger in patients undergoing surgery during hospital lockdown than before (cT3-4: 16.8% vs. 7.4%; $p < 0.001$; pT2 - pT4: 45.5% vs. 35.6%; $p = 0.002$). ER negative and HER-2 positive rate was significantly higher during lockdown (ER negative: 41.3% vs. 17%, $p < 0.001$; HER-2 positive: 23.4% vs. 14.8%; $p = 0.004$). Importantly, although breast conservation rate was lower during lockdown (58.6% vs. 65%; $p < 0.001$), level II oncoplastic conservation was significantly higher in order to reduce the relatively high mastectomy rate during lockdown. (22.8% vs. 5.6%; $p < 0.001$). This regional data – which showed a four-time rise in the application of OBCS – suggested that proper application of OBCS techniques can reduce mastectomy rates effectively – even during a COVID-19 pandemic.

Towards the second half of 2010's OBCS became the part of routine practice in the UK breast units. This was mainly due to the decade-long oncoplastic fellowship training network. which resulted in oncoplastic breast surgical consultants from the very beginning of their career. Hence, opportunities arose to collect firmer evidence on national level this time on the oncological safety of OBCS.

We have previously demonstrated that the clinicopathological characteristics of patients treated with OBCS in Glasgow is similar to mastectomy patients rather than simple wide local excision. This however is not necessarily the case on the national level and previous comparative studies showed no significant difference between OBCS and WLE. Hence, we carried out a population-based prospective audit of the OBCS practice in Scotland. All patients diagnosed with breast cancer in the whole of Scotland between 01/01/2014 and 31/12/2015

were prospectively recorded within the National Managed Clinical Networks databases. Patients treated with OBCS were compared to patients who had standard breast conservation (SBC), mastectomy and mastectomy with immediate reconstruction (MIR). 8075 patients were included (OBC:217(2.7%); SBC:5241(64.9%); mastectomy:1907(23.6%); MIR:710(8.8%)) and we published our results in the *European Journal of Surgical Oncology* (Oncoplastic breast conservation occupies a niche between standard breast conservation and mastectomy - A population-based prospective audit in Scotland. Morrow ES, Stallard S, Doughty J, Malyon A, Barber M, Dixon JM, Romics L. *European Journal of Surgical Oncology.* 2019;45(10):1806-1811).

We found that OBCS patients were younger than SBC or mastectomy, but older than MIR ($p < 0.0001$). OBC patients were between SBC and mastectomy patients in terms of clinical and pathological tumour size (all $p < 0.001$), rates of lobular cancers (v. SBC: $p = 0.015$ and v. mastectomy: $p < 0.001$), high-grade tumours (v. SBC: $p = 0.030$ and v. mastectomy: $p = 0.008$), ER negative (v. SBC: $p = 0.042$) and HER-2 positive (v. SBC: $p = 0.003$) tumours, and nodal metastasis (v. mastectomy: $p < 0.001$). More OBCS patients received (neo)adjuvant chemo- and hormonal therapy ($p \leq 0.001$), adjuvant radiotherapy ($p = 0.005$), trastuzumab ($p < 0.001$) than SBC. More OBCS patients presented through screening (v. mastectomy/MIR: $p < 0.0001$). Time to surgery from diagnosis was longer for OBC than SBC/mastectomy ($p < 0.0001$), but shorter than MIR ($p = 0.007$). This national audit demonstrated that OBCS occupies its own niche between SBC, mastectomy and MIR in the surgical treatment of breast cancer in Scotland. Hence, we suggested that OBCS should be recorded separately in breast cancer registries as a standalone surgical treatment, which is different from standard conservation (i.e. WLE) or mastectomy with or without reconstruction. Furthermore, these data suggests that OBCS rate could be a quality performance indicator in the national registries, similar to immediate breast reconstruction rate.

Excision margin is a key element in local control in breast conservation surgery. Some suggested that margins ≥2 mm after breast-conserving surgery may improve local control in invasive breast cancer, hence, by allowing large resection volumes, OBCS may achieve better local control than conventional breast conserving surgery. We investigated this in an international multicentric retrospective study. Data of consecutively treated 3,177 patients were included with high-risk breast cancer from 15 centres, all patients were operated between January 2010 and December 2013. Of these 297 were OBCS. We published our results in a multi-author paper (over 30 authors): Retrospective Multicenter Analysis Comparing Conventional with Oncoplastic Breast-Conserving Surgery: Oncological and Surgical

Outcomes in Women with High-Risk Breast Cancer from the OPBC-01/iTOP2 Study. *Annals of Surgical Oncology*. 2022;29(2):1061-1070. We found that WLE patients had significantly smaller tumours and smaller resection margins compared with OBCS (pT1: 50% vs. 37%, p = 0.002; proportion with margin <1 mm: 17% vs. 6%, p < 0.001), as well as incomplete excision rate was higher after WLE, too (11% vs. 7%, p = 0.049). However, univariate and multivariable regression analysis adjusted for tumour biology, tumour size, radiotherapy, and systemic treatment demonstrated no differences in local, regional, or distant recurrence-free or overall survival between the two groups. Nevertheless, this large-scale study showed that OBCS increases the distance from cancer cells to the margin of the specimen and reduces re-excision rates significantly. Additionally, we showed that applying OBCS larger tumours are resected with similar local, regional and distant recurrence-free as well as overall survival rates as standard breast conservation surgery.

As OBCS became the part of routine practice in all breast units, the ultimate evidence of oncological safety is to measure it in a "real-life" setting, i.e. in all breast units in a defined area serving the population of a large geographical region or the whole of a country. Evidence emerging from such studies is superior to single centre large volume units, as the outcomes of large volume units tend to be superior, hence it is skewed due to their broader experience. It is important to make sure that everyone who gets treated in a country has good quality of care and not only those who have the privilege to get access to large volume units. Hence, we carried out a population-based audit of OBCS practice and outcomes in Scotland using a predefined database of patients treated with OBCS, which was completed retrospectively in all breast units in Scotland. 589 patients were included from 11 units. Patients were diagnosed between September 2005 and March 2017, and we published our results in the *European Journal of Surgical Oncology* (A population-based audit of surgical practice and outcomes of oncoplastic breast conservations in Scotland - An analysis of 589 patients. Romics L, Macaskill EJ, Fernandez T, Simpson L, Morrow E, Pitsinis V, Tovey S, Barber M, Masannat Y, Stallard S, Weiler-Mithoff E, Malyon A, Mansell J, Campbell EJ, Doughty J, Dixon JM. *European Journal of Surgical Oncology*. 2018;44(7):939-944).

We found that high volume units performed a mean of 19.3 OBCSs per year vs. low volume units who did 11.1 (p = 0.012). 23 different oncoplastic surgical techniques were used. High volume units offered a wider range of techniques (8-14) than low volume units (3-6) (p = 0.004). OBCS was carried out as a joint operation involving a breast and a plastic surgeon in 389 patients. Immediate contralateral symmetrisation rate was significantly higher when OBCS was performed as a joint operation (70.7% vs. not joint operations: 29.8%; p < 0.001). The

incomplete excision rate was 10.4% and it was significantly higher after surgery for invasive lobular carcinoma (18.9%; p = 0.0292) but was significantly lower after neoadjuvant chemotherapy (3%; p = 0.031). 9.2% of patients developed major complications requiring hospital admission. Overall, the complication rate was significantly lower after neoadjuvant chemotherapy (p = 0.035). The 5-year local recurrence rate was 2.7%, which was higher after OBCS for DCIS (8.3%) than invasive ductal cancer (1.6%; p = 0.026). 5-year disease-free survival was 91.7%, overall survival was 93.8%, and cancer-specific survival was 96.1%. This study was the first nationwide "real-life" data on the oncological outcomes of OBCS in those years. As the study demonstrated that measured outcomes of OBCS in a population-based multi-centre setting can be comparable to the outcomes of large volume single centre series we felt reassured that the service we provide in OBCS has a good quality on the national level in Scotland. The findings of this nationwide retrospective study was confirmed prospectively in a UK nationwide study later, the "TeaM" study, which had similar outcomes strengthening the relevant evidence further.

A unique subgroup of OBCS is volume replacement oncoplastic surgery as it applied much less frequently than volume displacement techniques. Various volume replacement techniques were applied at the start of the OBCS ear including LD mini-flap, thoraco-epigastric flap or matrix rotation. More recently, chest wall perforator flaps (CWPF) such as lateral intercostal perforator (LICAP), medial intercostal perforator (MICAP), anterior intercostal perforator (AICAP), thoraco-dorsal artery perforator (TDAP) and lateral thoracal artery perforator (LTAP) flaps replaced the previous techniques. However, there was not much evidence on the oncological safety of these. Hence, we carried out a retrospective cohort study in the whole of the UK aiming to ascertain immediate (30-days) and medium-term (follow-up duration) surgical outcomes for CWPF, which, were caried out between March 2011 – March 2021. UK centres known to perform CWPF partial breast reconstructions were invited to participate in the study if a minimum of 10 cases were performed. Results were published in the *Breast* ('PartBreCon' study. A UK multicentre retrospective cohort study to assess outcomes following PARTial BREast reCONstruction with chest wall perforator flaps. Agrawal A, *Romics L*, Thekkinkattil D, Soliman M, Kaushik M, Barmpounakis P, Mortimer C, Courtney CA, Goyal A, Garreffa E, Carmichael A, Lane RA, Rutherford C, Kim B, Achuthan R, Pitsinis V, Goh S, Ray B, Grover K, Vidya R, Murphy J. *Breast* 2023;71:82-88).

Across 15 centres, 507 patients were included with a median age of 54 years (IQR;48-62), and median body mass index (BMI, Kg/m^2) = 25.4 (IQR; 22.5-29). Median tumour size was 26mm (IQR; 18-35), and median specimen weight was 62 grams (IQR; 40-92). Flap types

included LICAP (54.1%, n=273), MICAP/AICAP (19.6%, n=99), combined LICAP-LTAP (19.8%, n=100) and TDAP (2.2%, n=11). 30-days complication rates were 12%: haematoma rate was 4.3% (n=22), wound infection rate was also 4.3% (n=22), delayed wound healing developed in 2.8% (n=14) and overall flap loss rate was 0.6% (n=3; 1 full flap loss), which lead to readmissions in 2.6% (n=13) and re-operations also in 2.6% (n=13). Growing confidence in the technique was also evident by a decrease in overall complications from 26.9% in the first 5 years to 15.2% in the later 5 years suggestive of a learning-curve as well as learning-surge in this technique assisted by shared learning through several hands-on courses and colleague-to-colleague mentoring. Incomplete excision rate was 17.5% (n=88), which lead to re-excision in 15.7% (n=79) and completion mastectomy in 1.8% (n=9). Of the re-excisions, 7.3% (n=37) were planned to have the flap reconstruction as two-stage operation, hence had re-excision at the time of the planned second stage. At a median follow-up period of 23 months (IQR; 11-39), 1.2% of patients (n=6) contralateral symmetrising surgery was carried out, and we observed local recurrence in 1%, regional/nodal recurrence in 0.6% and distant recurrence in 3.2%. We concluded that this large multicentre cohort study, which is the world's largest cohort study on partial breast reconstruction using chest wall perforator flaps, showed acceptable and relatively low complication rates and margin re-excision rates. Furthermore, locoregional recurrence rates at short-term follow up are low and – although its value is limited – CWPFs appear to be a safe alternative to mastectomy in higher tumour: breast volume ratio and hence facilitating increased rates of breast conservation. No doubt that further studies are required for long-term oncological outcomes. As all retrospective studies have their own limitations, we have recently launched the prospective UK-wide data collection of CWPFs called PartBRECON-Pro.

There has been recent observational evidence to support that breast conserving therapy is associated with improved survival compared with mastectomy. Recently, a population-based study reported improved overall survival after breast conservation with radiotherapy over mastectomy without radiotherapy, which subsequently questioned mastectomy as an equally valid surgical alternative to breast conservation. Hence, we evaluated the survival following breast conserving therapy and mastectomy in the West of Scotland population (Survival following breast conserving therapy vs. mastectomy in the West of Scotland. L. Magill, J. Campbell, C.R. Wilson, *L. Romics*, J.C. Doughty, J. Mansell. Abstract published in *European Journal of Surgical Oncology,* 2023; 49(5):e221). In this cohort study we used data from a prospectively collected national database. All patients diagnosed with Stage I-III invasive breast cancer who underwent surgery in the West of Scotland population from 2010-2018 were included. Patients were grouped by locoregional treatment: Breast conserving surgery with

radiotherapy (BCS + DXT), mastectomy alone (Mx) and mastectomy with radiotherapy (Mx + DXT). Overall Survival (OS) and Breast cancer specific survival (BCSS) was performed using the Kaplan-Meier and Cox Regression analysis. Of 12,650 women, 7990 (63.2%) underwent breast conservation surgery (BCS) + radiotherapy (DXT), 2111 (16.7%) underwent mastectomy (Mx) and 2549 (20.2%) underwent Mx + DXT. Median follow up was 63 months. There were a total of 1729 deaths of which 899 (52.0%) were breast cancer related. 5-year OS and 5-year BCSS were 88.4% (95% CI, 88.1-88.7) and 93.3% (95% CI, 93.1-93.5) respectively. Following adjustment for co-variates including screen detection OS and BCSS were significantly worse for both Mx (HR 1.70 (95% CI 1.49-1.94) and HR 1.75 (95% CI 1.42-2.15)) and Mx + DXT (HR 1.33 (95% CI 1.16-1.52) and HR 1.57 (95% CI 1.32-1.86)) compared with BCS + DXT. We concluded that in this observational cohort study BCS + DXT has improved survival compared with Mx with or without DXT after adjustment for other proven prognostic factors. We claim that mastectomy should not be offered to patients as an option who can be treated with breast conservation surgery as mastectomy would impair prognosis. These findings are consistent with internationally published data by others based on national breast cancer databases of other countries.

In the context of the above findings the role of oncoplastic breast conservation surgery is even more important as it looks that breast conservation itself improves prognosis. Hence, patients routinely treated with mastectomy will need to be thoroughly assessed and determine the suitability for oncoplastic breast conservation surgery by an oncoplastic breast surgeon or jointly by a plastic and general (breast) surgeon. Mastectomy should be offered to patients only who are not suitable for breast conservation even with complex oncoplastic techniques. The above data suggests that applying oncoplastic breast conservation instead of mastectomy seems to improve the prognosis of breast cancer, hence OBCS should be the part of routine practice in all breast units.

7. FUTURE OF ONCOPLASTIC SURGERY

Oncoplastic breast surgery is a continuously evolving field. Development is driven by various factors including increasing patient expectations, dedication of surgical oncologists and oncoplastic breast surgeons as well as technological innovations. The progress in oncoplastic surgery aims at even better tumour control locally in parallel with superior aesthetic outcome. These, in turn, may result in longer survival with improved quality of life.

The following topics illustrate some of the areas we can expect major development in the near future. The topics were chosen and based on publications the author participated in or carried out; therefore, this chapter does not aim to provide a comprehensive review of the matter but rather serves as a taster for the future we envisage. Further, a short closing chapter about the future would leave the reader with the right impression how rapidly progressing field is oncoplastic breast surgery.

7.1. Reduction of incomplete excision rate in oncoplastic breast conservation surgery

Oncoplastic breast surgery has advanced the limits of conventional BCS, and permits excision of larger tumours, with correction of lumpectomy defects. Presently, the average rate of reoperations following failed BCS is approximately 18% for invasive disease; higher rates have been identified for ductal carcinoma in situ (DCIS), resulting in cost inefficiencies, delays to adjuvant therapy, and inferior cosmesis.

Technology offers exciting solutions to improving precision in BCS and OBCS, by better identification of the index lesion and/or helping to visualize satellite lesions. Despite its modest diagnostic accuracy, immediate evaluation of the resection specimen with three-dimensional (3D) digital specimen radiography is common.[345] Systems offering intraoperative 3D tomosynthesis (such as MozartVR ; Kubtec Medical Imaging (Connecticut, USA)), with advantages over two-dimensional planar views, have already been developed, and early studies have suggested encouraging results. In future, high-dimensional, 3D specimen images will likely be captured using miniaturized specimen CT imaging or micro-CT and/or portable MRI scanners.[346, 347]

Even more exciting is the potential to obtain functional information regarding cellular activity that goes beyond morphological imaging. Luminescence imaging (CLI) detects light emitted from PET agents, making it a promising candidate for functional specimen assessment.[348]

Innovative handheld probes are being developed that can be applied to the edge of the resected specimen to determine margin status based on differences in tissue bioimpedance, the electrical impedance of tissue measured in relation to an applied electric field. For example, Margin ProbeVR (Dilon Technologies = (Virginia, USA)) is a commercially available system that uses radiofrequency spectroscopy to detect electrical signatures of cancer at the resection margin. There are emerging data from RCTs to suggest that its use can reduce re-excision rates by approximately 50% besides a large, randomised trial being underway (NCT02774785).[349, 350] Similarly, ClearEdgeTM (LsBioPath (California, USA)), which uses bioimpedance spectroscopy sensitive to cancer-related changes in dielectric properties, has been evaluated in a phase II cohort study with demonstrable high diagnostic accuracy for in vivo margin assessment.[351]

Confocal microscopy provides real-time highly magnified surface-level images allowing intraoperative non-invasive histopathological examination of the breast margin [352]. Commercial confocal systems such as HistologVR (Samantree) enable wide-field ultrafast imaging with subcellular resolution of the entire resection surface for immediate review. Optical coherence tomography (OCT) measures the speed and reflection of infrared light waves to produce high-resolution non-invasive images of tissue microstructure. Recent clinical feasibility studies of OCT have reported encouraging diagnostic accuracy (86–96%).[353]

Rapid evaporative ionization mass spectrometry (REIMS) of the diathermy plume has been shown to accurately (over 90 per cent) and rapidly (about 1.8 s) characterize breast tissue type based on differences in chemical composition between healthy breast (upregulation of triglycerides) and breast cancers (upregulation of phospholipids).[354] The diagnostic accuracy of the REIMS based intelligent knife (iKnife) in vivo is under investigation in a clinical feasibility trial in the UK (REI-EXCISE trial).

7.2. Breast conservation surgery in multifocal and muticentric breast cancer

Multifocal multicentric breast cancer has traditionally been considered a contraindication to breast conserving surgery because of concerns regarding locoregional control and risk of disease recurrence. However, the evidence supporting this practice is limited. Increasingly, many breast surgeons are advocating breast conservation in selected cases. Oncoplastic techniques are now widely accepted and allow breast conserving surgery for tumours that have a high tumour to breast size ratio. However, it is important to evaluate the oncological safety of extending these surgical practices to patients with multifocal multicentric breast cancer.

There has been debate in the literature about the impact of multifocality and multicentricity on prognosis and outcomes. A recent meta-analysis of 22 studies including 67,557 women reported multifocal disease in 9.5% of patients and showed a trend towards worse prognosis for multifocal breast cancer (although without statistical significance on many occasions).[355] Multivariate analysis showed significantly worse overall survival (hazard ratio, HR, 1.65; P = 0.02) and a non-significant association with disease-free survival (HR 1.96; P = 0.07). However, there was significant interstudy heterogeneity for both overall and disease-free survival data and, on excluding the studies with significant heterogeneity, the overall survival rate was similar (HR 1.07; P = 0.31). Univariate analysis showed poorer disease-free, overall and disease-specific survival rates and locoregional recurrence over 5 years, but the 10-year data reached significance only for disease-specific survival and locoregional recurrence. There was also considerable heterogeneity between the studies, which rendered the conclusions weak.[355]

Another important paper by the BRENDA Study Group retrospectively analysed breast cancer data from 17 centres comparing multifocal multicentric breast cancer with unifocal disease. It examined outcomes, mortality and the impact of adhering to treatment guidelines.[356] Of 8935 patients with breast cancer, 15.6% had multifocal breast cancer and a further 5.2% had multicentric disease. The Nottingham prognostic index for multifocal multicentric breast cancer was higher than for unifocal disease, implying a worse prognosis with a significantly higher percentage of node-positive disease, younger patients and higher-grade tumours. However, on correcting for stage and nodal status, the prognosis did not differ between patient groups who had surgery and adjuvant treatment adherent to the guidelines. Additionally, the MINDACT study (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) looked at 3090 patients at clinically low risk, of whom 238 had multifocal

disease, and showed that multifocal tumours were more likely to have a higher genomic risk profile compared with unifocal disease. However, the study failed to show any significant association between tumour multifocality and disease-free survival.[357]

Does surgery change the prognosis in multifocal multicentric breast cancer, and is mastectomy really the oncologically safer option? The influential 1999 study, when the team from the Marie Curie Cancer Centre in Paris reported comparable five-year survival and recurrence rates for patients with multifocal multicentric breast cancer treated with either breast conserving surgery or mastectomy.[358] This was a case–control study with 56 patients in the breast conserving surgery arm matched with 132 in the mastectomy arm. In 2003, *Kaplan et al* reported a prospective small cohort of 55 patients with multifocal multicentric breast cancer, 36 of whom had breast conserving surgery and 19 mastectomy, with no significant difference in the five-year recurrence rate or overall survival.[359] In 2009, *Gentilini et al* followed 476 patients with multifocal multicentric disease treated with breast conserving surgery for a median of 73 months, reporting a 5-year local recurrence rate of 5.1%.[360] This study also demonstrated better cosmetic outcomes and lower recurrence rates for breast conserving surgery compared with mastectomy.

Larger studies such as the BRENDA study assessed survival outcomes in multifocal (n = 1398) and multicentric (n = 464) breast cancer compared with unifocal disease (n = 7073) showing no difference in overall and disease-free survival for patients who had breast conserving surgery and mastectomy. Similar results were reported from the MD Anderson Cancer Centre in a cohort of 3924 patients, of whom 924 had multifocal and 247 had multicentric disease.[361] Here, the presence of multifocal multicentric disease was associated with poor prognostic factors such as advanced disease and locoregional spread, which themselves impact on prognosis and survival. However, multicentricity and multifocality alone were not independent factors for either breast cancer recurrence or survival. The same group also looked at locoregional control in a separate paper where breast conserving surgery was performed on 256 of the 673 patients with multifocal (not multicentric) cancer and concluded that breast conserving surgery is a safe option with patients with multifocal breast cancer.[362] This is further supported by yet another study of 706 patients receiving neoadjuvant chemotherapy, where 97 patients with multifocal multicentric breast cancer had no significant differences in recurrence-free or overall survival when compared with unifocal disease, regardless of they had breast conserving surgery or a mastectomy. Importantly, there were no in-breast recurrences in patients with multifocal disease treated with breast conserving surgery.[299] A recent meta-analysis including 17 comparative studies and 7 case series totalling

3537 women undergoing breast conserving surgery demonstrated a locoregional recurrence rate of 2–23% following breast conserving surgery in multifocal multicentric breast cancer at a median follow-up of 59.5 months (range 56-81 months) with equivalent rates to mastectomy (risk ratio 0.94, 95% confidence interval 0.65–1.36).[221]

The ACOSOG Z11102 (Alliance) trial is a single-arm, prospective trial evaluated the effect of BCT when combined with whole breast radiation therapy on the local recurrence rate in patients over 40 years of age with multifocal multicentric breast cancer. The study enrolled 270 patients, 204 of which were deemed evaluable, with the primary end point of a 5-year local recurrence rate for BCT, which was defined as less than 8%.[363] Initial results from the trial were presented at the 2022 San Antonio Breast Cancer Symposium, which demonstrated that the estimated 5-year local recurrence rate was 3.1%, which was deemed clinically acceptable. Importantly, recent data from the same study showed that breast conservation followed by whole breast radiotherapy plus boost to each tumour bed was feasible in the majority of patients with multiple ipsilateral breast cancer. Increasing radiation boost volume was associated with increased incidence of acute dermatitis but was not associated with worse overall cosmesis.[100]

With the best evidence currently available indicating that multifocal multicentric breast cancer has a similar prognosis to unifocal cancers and equipped with over 30 years' experience in breast conserving surgery in the management of unifocal cancers, there remains valid consideration for a conservative approach in multifocal multicentric breast cancer. In particular, there is no evidence that surgical approach affects prognosis, provided that tumours are completely excised. Recently, the MINIM survey evaluated the management of MFMCBC in a large international cohort of experienced breast surgeons. This survey clearly showed that the international breast surgical community is largely supportive of the use of BCS in multifocal and, to a lesser extent, multicentric breast cancer.[364]

7.3. Latest developments in non-autologous reconstructive surgery

The introduction of biological and synthetic meshes has revolutionized implant-based reconstructions and allows single-stage direct-to-implant reconstruction. Biological meshes can be derived from a number of dermal and non-dermal sources, but acellular dermal matrices (ADMs) are the most commonly used.[365] ADMs may be subdivided into human-derived types and xenografts of porcine or bovine origin. ADMs have recently become significantly more user-friendly, including shaped, perforated, and bilateral versions. Their use has become an attractive but expensive option. Synthetic meshes are mass-synthesized polymers, which may be multifilament or monofilament. These may be more cost-effective than biological meshes, but comparative evidence is lacking. The TiLOOP Bra is a permanent titanium-coated polypropylene mesh, which has been shown to have a major complication rate of 13.4 per cent.[366] Polyglactin is an absorbable mesh with a low infection rate (2.7%), but well controlled studies to evaluate outcomes after use of these meshes have been infrequent to date.[367]

Traditionally ADMs/meshes have been used for lower-pole coverage in subpectoral breast reconstruction. They are increasingly being used in prepectoral implant-based procedures where mesh is used to cover the implant. Prepectoral reconstruction has the advantage of leaving the pectoralis muscle undisturbed, reducing breast animation and postoperative pain, although evidence is sparse. There is currently limited high-quality evidence to suggest which meshes should be recommended for use in implant-based reconstruction or whether prepectoral or subpectoral techniques offer better outcomes for patients. A number of RCTs comparing techniques are under way to address these issues. The best available data from the UK multicentre iBRA (implant breast reconstruction evaluation) study, including over 2000 patients, has suggested no differences in short-term complications in implant reconstruction with or without mesh, or between prepectoral or subpectoral techniques [368]. The iBRA study recently reported short-term outcomes after implant-based reconstruction, where the majority of patients had either a biological (1133, 54%) or synthetic (243, 12%) mesh. The rate of implant loss at 3 months was 9 (95% c.i. 8 to 10) per cent, indicating that further work is required to reduce the complication rate associated with this reconstructive technique.[369]

The underlying premise for tissue engineering technology is use of an absorbable biological matrix that is impregnated with autografted lipocytes from the patient's abdomen or other fatty area. This may be used to fill a defect after BCS or whole-breast reconstruction. Microtubular structures throughout the matrix provide influx of blood and bionutrients to

potentially increase lipocyte viability compared with that of fat grafting alone, although trials to date have been confined to animal models. Researchers in Australia are developing bioabsorbable 3D-printed scaffolds, based on MRI reconstruction of the contralateral breast, that dissolve over 2–3 years as the fatty breast tissue regenerates. Scientists in the USA are working with TeVido BioDevices to create 3D bioprinted breast implants for nipple–areola complex reconstruction and bespoke volumetric replacement of lumpectomy defects.

SELECTED LIST OF MY PUBLICATIONS RELEVANT TO THIS CHAPTER

Innovations for the future of breast surgery.
Vidya R, Leff DR, Green M, McIntosh SA, St John E, Kirwan CC, **Romics L**, Cutress RI, Potter S, Carmichael A, Subramanian A, O'Connell R, Fairbrother P, Fenlon D, Benson J, Holcombe C.
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Masannat YA, Agrawal A, Maraqa L, Fuller M, Down SK, Tang S, Pang D, Kontos M, **Romics L**, Heys SD.
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* marking publications prior to PhD thesis

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8.1.1. Original research

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European Journal of Surgical Oncology. 2019 Oct;45(10):1806-1811.

A population-based audit of surgical practice and outcomes of oncoplastic breast conservations in Scotland - An analysis of 589 patients.

Romics L, Macaskill EJ, Fernandez T, Simpson L, Morrow E, Pitsinis V, Tovey S, Barber M, Masannat Y, Stallard S, Weiler-Mithoff E, Malyon A, Mansell J, Campbell EJ, Doughty J, Dixon JM.
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Oncoplastic breast conservation surgery is oncologically safe when compared to wide local excision and mastectomy.
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Breast. 2017 Apr;32:179-185. PMID: 28214785

Oncological outcomes and complications after volume replacement oncoplastic breast conservations - the Glasgow experience.
W Ho, S Stallard, J Doughty, E Mallon, **L Romics**.
Breast Cancer: Basic and Clinical Research 2016 Dec 19;10:223-228.

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Kabir SA, Stallard S, Weiler-Mithoff E, Mansell J, Mallon E, Doughty JC, **Romics L Jr.**
International Journal of Surgery. 2016 Feb;26:38-42.

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R Dolan, M Patel, E Weiler-Mithoff, J Mansell, S Stallard, JC Doughty, **L Romics Jr**.
Breast Care (Basel). 2015 Oct;10(5):325-9.

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J Mansell, E Weiler-Mithoff, J Martin, A Khan, S Stallard, J C Doughty, **L Romics**.
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Kahn J, Barrett S, Forte C, Stallard S, Weiler-Mithoff E, Doughty JC, **Romics L Jr**.
European Journal of Surgical Oncology. 2013 Aug;39(8):887-91.

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A systematic review of oncoplastic volume replacement breast surgery: oncological safety and cosmetic outcome.
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Masannat YA, Agrawal A, Maraqa L, Fuller M, Down SK, Tang S, Pang D, Kontos M, **Romics L**, Heys SD.
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Pujji O, Blackhall V, **Romics L**, Vidya R
in ***Pedicled Flaps in Partial Breast Reconstruction***, Springer Nature Switzerland, 2023, ISBN 978-3-031-08482-9
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Oncological outcomes and safety of oncoplastic breast conservation
Romics L., Campbell EJ
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Thoraco-epigastric pedicled flap for partial breast reconstruction
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in ***Oncoplastic Breast Surgery Techniques for the General Surgeon*****,** Springer Nature Switzerland, 2020**,** ISBN: 978-3-030-40195-5, 261-280.
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Omega oncoplastic techniques
P Kelemen, **L Romics**
in ***Principles and Practice of Oncoplastic Breast Surgery***, Medicina Publishing, 2019
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Oncoplastic techniques in medial tumour location
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in „**Az emlőrák korszerű sebészete"**, Medicina, Hungary, 2015, ISBN: 978-9-632-26545-2
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„Mediális onkoplasztikus technikák"
Kelemen P., **Romics L**.
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Romics L, Weiler-Mithoff E, Mallon E, McLellan D, Dolan R, Mansell J, Ray A
Proceedings of the 12th Congress of the European Society of Plastic, Reconstructive and Aesthetic Surgery – ESPRAS 2014. 99-103. ISBN 978-88-7587-714-9.

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Breast Cancer (Dove Med Press). 2019 May 8;11:179-188.

The presentation, management and outcome of inflammatory breast cancer cases in the UK: Data from a multi-centre retrospective review.
Copson E, Shaaban AM, Maishman T, Moseley PM, McKenzie H, Bradbury J, Borley A, Brzezinska M, Chan SYT, Ching J, Cutress RI, Danial I, Dall B, Kerin M, Lowery AJ, Macpherson IR, **Romics L**, Sawyer E, Sharmat N, Sircar T, Vidya R, Pan Y, Rea D, Jones L, Eccles DM, Berditchevski F.
Breast. 2018 Sep 15;42:133-141.

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Morrow E, Lannigan A, Doughty J, Litherland J, Mansell J, Stallard S, Mallon E, **Romics L.**
British Journal of Surgery. 2018 Jul;105(8):987-995.

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British Journal of Surgery 2009 Jun;96(6):602-7.

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Journal of Leukocyte Biology 2007; 82(4):906-14.

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Journal of Immunology 2006 Aug; 177(4): 2592-2600.

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Hepato-Gastroenterology 2007 Mar;54(74):590-4.

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Evidence based use of enteral nutrition in acute pancreatitis.
A Oláh, **L Romics Jr.**
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