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Objective assessment of oncological & cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery: protocol for a systematic review

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Title:

Objective assessment of oncological & cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery: protocol for a systematic review - registered with PROSPERO (registration number: CRD42017075700)

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Authors' contributions:

RR & RP conceptualised the idea.

JH & RP drafted the manuscript.

JH, RR, AS, OP & RP contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria.

JH, RR, AS, OP & RP read, provided feedback and approved the final manuscript

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Ethics and dissemination: This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

ABSTRACT

Introduction:

Oncoplastic breast surgery allow the excision of larger tumours without compromising cosmetic outcome and can be broadly divided into volume displacement and volume replacement techniques. Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, the evidence is still lacking especially in patients who underwent volume replacement technique. As it is a relatively new technique where newer techniques have been described in literature in the recent years, the summary of evidence from these literature can help clinicians to understand both the oncological & cosmetic outcomes of such procedures.

Methods and analysis:

All original studies including randomised controlled trials, cohort studies, case-control studies and case series involving more than 10 women undergoing partial breast reconstruction using volume replacement technique will be included. Primary outcomes include oncological safety and cosmetic outcomes. This includes overall survival and local recurrence rate in the follow-up period. Secondary outcomes include clinical complications such as flap necrosis, infection, readmission, re-excision and completion mastectomy rates. A comprehensive literature search, eligibility assessment and extraction of data will be conducted by 2 trained teams acting independently. Data will be extracted and stored in a database with standardised extraction fields to facilitate easy and consistent data entry. Heterogeneity will be assessed using the Cochrane tests.

Ethics and dissemination:

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.
Registered with PROSPERO (registration number: CRD42017075700)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The search for studies is limited by language.
- Many of the publications of new techniques are reporting small numbers of patients

INTRODUCTION

Surgery for breast cancer has evolved drastically over the years, from Halsted's radical mastectomy which was standard of care for all women diagnosed with breast cancer right up to 1960s, to the development and acceptance of breast conserving therapy as standard of care in the recent years. Breast conserving therapy refers to breast conserving surgery (BCS) followed by radiotherapy has been found to have equivalent disease-free and overall survival when compared to mastectomy, and hence has become the standard of care for early-stage breast cancer.

The primary aim of BCS is tumour excision to achieve tumour-free resection margins while the secondary aim is to achieve a satisfactory cosmetic outcome. Although many early cancers can be successfully treated by standard lumpectomy, some lesions still remain a challenge for breast surgeon to achieve a good outcome especially with regards to patients with large tumour to breast size ratio. Oncoplastic breast surgery (1-4) combine oncological resection with plastic surgery techniques and allow the excision of larger tumours without compromising cosmetic outcome.

Oncoplastic breast surgery can be broadly divided into 2 fundamentally different techniques: (i) volume displacement using glandular or dermoglandular redistribution of breast tissue into the resection site; (ii) volume replacement using autologous tissues from extra mammary site to compensate the volume loss after tumour resection.

Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, the evidence is still lacking on both short- and long-term outcomes, especially in patients who underwent volume replacement technique. As it is a relatively new technique where newer techniques have been described in literature in the recent years, the summary of evidence from these literature can help clinicians to understand both the oncological & cosmetic outcomes of such procedures.

What have we learnt from prior systematic reviews?

Previous systematic reviews have largely focused on oncoplastic breast surgery as a collective group. Volume replacement techniques have been developing and gaining acceptance, hence we feel there is a need to focus on it as a separate entity, analysing the latest available literature. A summary of published evidence will update the clinical,

oncological and cosmetic outcomes of these procedures. Our study proposes to look at the oncological and aesthetic outcome after volume replacement in patients undergoing oncoplastic breast conserving surgery.

Review	**Databases included & years searched**	**Studies included**	**Key findings**
Losken et al 2014 (5)	PubMed	61 papers	Meta-analysis comparing breast conservation therapy and oncoplastic breast surgery. Length of follow up in the oncoplastic breast surgery group was shorter than breast conservation therapy. Main focus was on age, tumour size and local recurrence. Very little focus on the various techniques available and cosmetic outcomes.
Haloua et al 2013(6)	MEDLINE, EMBASE & Cochrane 2000-2011	12 studies - most are volume displacement techniques	This systematic review reveals that current evidence supporting the efficacy of oncoplastic breast surgery is based on poorly designed and underpowered studies. Given the increasing importance and application of oncoplastic breast surgery, there is a pressing need for robust comparative studies, including both randomized controlled trials and well-designed, multicenter prospective longitudinal studies.

Yiannakopoulou EC et al 2016(7)	Pubmed, Scopus, Google Cholar, Science citation Index 1966-2013	40 studies - only 15 were volume replacement	Study quality was low. The majority of studies were observational studies. The length of follow up was relatively short, long term oncological outcome of oncoplastic surgery for breast cancer is not adequately investigated. Further research efforts should focus on Level I evidence on oncological outcome of oncoplastic surgery

Why is it important to do this systematic review?

However, as volume replacement techniques have been developing and gaining acceptance, we feel the need to focus on it as a separate entity and include the latest literature that is available.

Since the most recent systematic review of oncoplastic breast surgery concluded its search in 2013, there have been over 30 more articles published in regards to partial breast reconstruction using volume replacement technique. A new systematic review is needed to update our understanding of this rapidly evolving area and potentially answer the questions previous studies have failed to.

Objectives

The primary objective of this review is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery. A secondary objective is to review the patient-reported outcomes associated with oncoplastic breast surgery to help refine patient selection for the procedure and to develop an algorithm for identifying patients suitable for volume replacement rather than volume displacement during OBS.

METHODS AND ANALYSIS

This review will be conducted in line with the recommendations specified in the Cochrane Handbook for intervention reviews V.5.1.0. It will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. This protocol has been registered on PROSPERO.

Criteria

To minimize heterogeneity and to address the objectives of the review, studies will be selected according to the criteria outlined below.

Study designs

We will include all randomized controlled trials (RCTs), cohort and case-control studies. Single group cohorts and case series will be included if there are more than 10 patients. Case reports, expert opinions and duplicate studies will be excluded.

Participants

Women undergoing partial breast reconstruction using volume replacement in breast conserving surgery for breast cancer.

Interventions

Partial breast reconstruction using volume replacement in breast conserving surgery. Volume displacement and usage of non-autologous tissue will be excluded.

Outcomes

Primary outcomes include oncological safety and cosmetic outcomes. This includes overall survival and local recurrence rate in the follow-up period. Secondary outcomes include clinical complications such as flap necrosis, infection, readmission, re-excision and completion mastectomy rates.

Search strategy

The following electronic databases will be searched from inception to 31 June 2018: MEDLINE, EMBASE, the Cochrane database and Database of Abstracts of Reviews of Effect (DARE). This will be supplemented by manual search of references lists and the review of "epub ahead of print" articles.

A comprehensive search will be performed using the following search terms: BCS, oncoplastic breast surgery, partial breast reconstruction, partial mastectomy, immediate reconstruction and cosmesis. Additional keywords and further logical combinations of these and related terms will be used to maximize sensitivity. The search will include all study designs but limited to articles published in English.

Studies identified will be listed within a Microsoft Excel database and duplicates excluded. The selection of articles will be conducted by 2 teams who will independently evaluate the titles and abstracts to assess the eligibility in terms of outcome measures and study designs. The authors will be blinded to each other's results during the review process and the findings will then be compared. Discrepancies will be resolved through discussion. The full text of the articles selected will be further assessed for inclusion by 2 review authors. Where required, authors will be contacted in clarify inclusion, data overlap and data.

Once the study has been included, data extraction will be performed independently by two teams of researchers. Discrepancies will then be resolved by consensus.

Data will be extracted into a standardised Microsoft Excel database. The following data will be extracted:

- Author names, countries and year of publication
- Study design and level of evidence
- Conflicts of interest and funding
- Number of participants
- Number of breasts treated
- Age of participants
- Oncological parameters—type of cancer (invasive or in situ), grade, stage, axillary nodal status, hormone receptor status (ER, PR), HER2 status, size of tumour, tumour-nipple distance, solitary or multifocal or multicentric and presence of lymphovascular invasion.
- Adjuvant radiotherapy
- Prior neoadjuvant or adjuvant chemotherapy
- Previous breast surgery
- Technical details—incision used and reconstruction performed
- Median follow-up duration
- Loss to follow-up expressed as a percentage

- Outcomes—primary and secondary as described above

Assessment of risk of bias

We will use the Cochrane Risk of Bias Tool(8) for RCTs and the Cochrane Risk of Bias Assessment Tool ACROBAT-NRSI for non-randomised studies. We will compare study protocols with final papers where possible and key missing information across all study types will be presented.

We will also analyse the funnel plot asymmetry(9) to determine if there is a deficiency of reports of negative study outcomes.

Strategy for data synthesis and statistical analysis

Outcomes of interest will be presented appropriately.

ETHICS AND DISSEMINATION

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

REFERRENCES

1. Clough KB, Lewis JS, Couturaud B, Fitoussi A, Nos C, Falcou MC. Oncoplastic techniques allow extensive resections for breast-conserving therapy of breast carcinomas. Annals of surgery. 2003;237(1):26-34.

2. Rainsbury RM. Surgery insight: Oncoplastic breast-conserving reconstruction--indications, benefits, choices and outcomes. Nat Clin Pract Oncol. 2007;4(11):657-64.

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4. Regano S, Hernanz F, Ortega E, Redondo-Figuero C, Gomez-Fleitas M. Oncoplastic techniques extend breast-conserving surgery to patients with neoadjuvant chemotherapy response unfit for conventional techniques. World journal of surgery. 2009;33(10):2082-6.

5. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. Annals of plastic surgery. 2014;72(2):145-9.

6. Haloua MH, Krekel NM, Winters HA, Rietveld DH, Meijer S, Bloemers FW, et al. A systematic review of oncoplastic breast-conserving surgery: current weaknesses and future prospects. Annals of surgery. 2013;257(4):609-20.

7. Yiannakopoulou EC, Mathelin C. Oncoplastic breast conserving surgery and oncological outcome: Systematic review. Eur J Surg Oncol. 2016;42(5):625-30.

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	breast cancer, oncoplastic, partial breast reconstruction, breast conserving surgery

Title:

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Authors' contributions:

RR & PR conceptualised the idea.
JH & PR drafted the manuscript.
JH, RR, AS, OP & PR contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria.
JH, RR, AS, OP & PR read, provided feedback and approved the final manuscript

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Ethics and dissemination: This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

ABSTRACT

Introduction:

Oncoplastic breast surgery allows the excision of larger tumours without compromising cosmetic outcome and can be broadly divided into volume displacement and volume replacement techniques. Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, evidence is still lacking especially in patients who underwent volume replacement techniques. As it is a relatively new technique which has been described in the literature in the recent years, a summary of evidence from this literature can help clinicians to understand both the oncological & cosmetic outcomes of such procedures.

Methods and analysis:

All original studies including randomised controlled trials, cohort studies, case-control studies and case series involving more than 10 women undergoing partial breast reconstruction using a volume replacement technique will be included. Primary objective is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery. The secondary objective is to review the patient-reported outcomes (PROMs) associated with onocplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery.

A comprehensive literature search, eligibility assessment and extraction of data will be conducted by 2 trained teams acting independently. Data will be extracted and stored in a database with standardised extraction fields to facilitate easy and consistent data entry. Heterogeneity will be assessed using the Cochrane tests.

Ethics and dissemination:

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

Registered with PROSPERO (registration number: CRD42017075700)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first review to specifically focus on volume replacement techniques
- The search for studies is limited by English language.
- Many of the publications of new techniques are reporting small numbers of patients and hence potential lack of high quality studies limiting the ability to conduct a meta-analysis
- It would be difficult to tease out volume displacement and volume replacement techniques
- Potential reporting bias within the existing literature

INTRODUCTION

Surgery for breast cancer has evolved dramatically over the years, from Halsted's radical mastectomy which was standard of care for all women diagnosed with breast cancer right up to the 1960s, to the development and acceptance of breast conserving therapy as standard of care in more recent years. Breast conserving therapy refers to breast conserving surgery (BCS) followed by radiotherapy. BCS has been found to have equivalent disease-free and overall survival when compared to mastectomy, and hence has become the standard of care for early-stage breast cancer.

The primary aim of BCS is tumour excision to achieve tumour-free resection margins while the secondary aim is to achieve a satisfactory cosmetic outcome. Although many early cancers can be successfully treated by standard lumpectomy, some lesions still remain a challenge for breast surgeon to achieve a good outcome especially with regards to patients with large tumour to breast size ratio. Oncoplastic breast surgery(1-4) combine oncological resection with plastic surgery techniques and allow the excision of larger tumours without compromising cosmetic outcome.

Oncoplastic breast surgery can be broadly divided into 2 fundamentally different techniques: (i) volume displacement using glandular or dermoglandular redistribution of breast tissue into the resection site; (ii) volume replacement using autologous tissues from an extra mammary site to compensate for volume loss after tumour resection. Women with small breasts or a large tumour/breast ratio may not be suitable for volume displacement and hence volume replacement serves as an alternative to mastectomy. Examples of volume replacement techniques include the latissimus dorsi miniflap, chest wall perforator flaps, omental flaps etc.

Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, evidence is still lacking on both short- and long-term outcomes, especially in patients following volume replacement. As with any relatively new technique, a summary of evidence from the literature can help clinicians to understand both the oncological & cosmetic outcomes of these novel procedures.

What have we learnt from prior systematic reviews?

Previous systematic reviews have largely focused on oncoplastic breast surgery as a collective group (see Table 1). Volume replacement techniques have been developing and gaining acceptance, and we feel there is a need to focus on these techniques as a separate entity, analysing the latest publications. A summary of published evidence will update the clinical, oncological and cosmetic outcomes of these procedures. Our study proposes to look specifically at the clinical, oncological and aesthetic outcomes patients undergoing volume replacement alongside oncoplastic breast conserving surgery.

Table 1: Prior reviews of volume replacement in patients undergoing oncoplastic breast conserving surgery

Review	Databases included & years searched	Studies included	Key findings
Losken et al 2014 (5)	PubMed	61 papers	Meta-analysis comparing breast conservation therapy and oncoplastic breast surgery. Length of follow up in the oncoplastic breast surgery group was shorter than breast conservation therapy. Main focus was on age, tumour size and local recurrence. Very little focus on the various techniques available and cosmetic outcomes.
Haloua et al 2013(6)	MEDLINE, EMBASE & Cochrane 2000-2011	12 studies - most are volume displacement techniques	This systematic review reveals that current evidence supporting the efficacy of oncoplastic breast surgery is based on poorly designed and underpowered studies. Given the increasing importance and application of oncoplastic breast surgery, there is a pressing need for robust comparative studies, including both randomized controlled trials and well-designed, multicenter prospective longitudinal studies.
Yiannakopoulou EC et al 2016(7)	Pubmed, Scopus, Google Cholar, Science citation Index 1966-2013	40 studies - only 15 were volume replacement	Study quality was low. The majority of studies were observational studies. The length of follow up was relatively short, long term oncological outcome of oncoplastic surgery for breast cancer is not adequately investigated. Further research efforts should focus on Level I

			evidence on oncological outcome of oncoplastic surgery
L. De La Cruz et al 2016(8)	Pubmed 1988-2015	55 studies with broad spectrum of oncoplastic techniques	Systematic review comparing breast conserving surgery using oncoplastic techniques in place of standard lumpectomy. The review only included T1 and T2 breast cancers. The oncoplastic techniques evaluated were mainly volume displacement (>50%) but very little details on surgical technique available.
J.J Yoon et al 2016(9)	Pubmed 1995-2015	41 studies – only 11 were volume replacement	Review comparing post-radiation outcomes of volume replacement and volume displacement. Did not describe the surgical techniques involved.

Why is it important to do this systematic review?

As volume replacement techniques have been developing and gaining acceptance, there is a need to focus on it as a separate entity and to include the latest available literature.

Since the most recent systematic review of oncoplastic breast surgery concluded its search in 2015, there have been over 30 more articles published in regards to partial breast reconstruction using volume replacement technique. A new systematic review is needed to update our understanding of this rapidly evolving area of clinical practice, and to address the questions unanswered by previous studies

OBJECTIVES

The primary objective of this review is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery.
A secondary objective is to review the patient-reported outcomes (PROMs) associated with oncoplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery

METHODS AND ANALYSIS

This review will be conducted in line with the recommendations specified in the Cochrane Handbook for intervention reviews V.5.1.0. It will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. This protocol has been registered on PROSPERO. (Registration number: CRD42017075700)

Inclusion and Exclusion Criteria

To minimize heterogeneity and to address the objectives of the review, studies will be selected according to the criteria outlined below.

Study designs

We will include all randomized controlled trials (RCTs), cohort and case-control studies. Single group cohorts and case series will be included if there are more than 10 patients who underwent volume replacement after oncoplastic breast conserving surgery. Hence, levels of evidence 1-4 as defined by the Oxford Centre for Evidence-Based medicine (10). Case reports, abstracts, expert opinions and duplicate studies will be excluded. Only studies published in English will be included.

Participants

Only women with breast cancer who are undergoing partial breast reconstruction using volume replacement in breast conserving surgery will be included. Males, patients who underwent mastectomy and patients who underwent surgery for benign breast conditions will be excluded.

Interventions

Partial breast reconstruction using volume replacement such as chest wall perforator flaps, latissimus dorsi mini-flaps etc. Volume displacement techniques such as therapeutic mammoplasty and usage of non-autologous tissue will be excluded.

Outcomes

The primary objective of this review is to evaluate the clinical, oncological and cosmetic following volume replacement in patients undergoing oncoplastic breast conserving surgery. Early clinical outcomes include clinical complications such as flap necrosis, infection, re-admission, re-excision and completion mastectomy rates. Later clinical outcomes include correction of symmetry (contralateral augmentaion/reduction), nipple reconstruction, correction of deformity (lipomodelling, scar revision etc), mastectomy for recurrence, and any other procedures. Oncological outcomes include overall survival and local recurrence rate in the follow-up period. Cosmetic outcomes include cosmetic results and cosmetic evaluation method.

A secondary objective is to review the patient-reported outcomes (PROMs) associated with oncoplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery. PROMs include patient satisfaction and quality of life. We would also be looking at parameters, if reported in the published studies, optimising patient selection for these surgical procedures such as age, smoking history, co-morbidity such as diabetes mellitus, tumour size and location, and pre-operative breast/bra size.

Search strategy

The following electronic databases will be searched from January 1990 to 31 December 2017: MEDLINE, EMBASE, the Cochrane database and Database of Abstracts of Reviews of Effect (DARE). This will be supplemented by a manual search of references lists and the review of "epub ahead of print" articles.

A comprehensive search will be performed using the following search terms: breast conserving surgery, oncoplastic breast surgery, oncoplastic breast conserving surgery, partial breast reconstruction, partial mastectomy, immediate reconstruction and volume replacement. Additional keywords such as chest wall perforator flaps, latissimus dorsi mini flap, omental flap and further logical combinations of these and related terms will be used to maximize sensitivity. The search will include all study designs but limited to articles published in English.

Studies identified will be listed within a Microsoft Excel database and duplicates excluded. The selection of articles will be conducted by 2 teams who will independently evaluate the titles and abstracts to assess the eligibility in terms of outcome measures and study designs. The authors will be blinded to each other's results during the review process and the findings will then be compared. Discrepancies will be resolved through discussion. The full text of the articles selected will be further assessed for inclusion by 2 review authors. Where required, authors will be contacted to clarify inclusion, data overlap and data.

Once the study has been included, data extraction will be performed independently by two teams of researchers. Discrepancies will then be resolved by consensus.

Data will be extracted into a standardised Microsoft Excel database. The following data will be extracted:

- Author names, countries and year of publication
- Study design and level of evidence
- Conflicts of interest and funding
- Number of participants

- Number of breasts treated
- Age of participants
- Smoking history
- History of diabetes
- Pre-operative breast/bra size
- Oncological parameters—type of cancer (invasive or *in situ*), grade, stage, axillary nodal status, hormone receptor status (ER, PR), HER2 status, size of tumour including any associated additional foci, location of tumour (which quadrant), tumour-nipple distance, solitary or multifocal or multicentric and presence of lymphovascular invasion.
- Adjuvant radiotherapy
- Prior neoadjuvant or adjuvant chemotherapy
- Previous breast surgery
- Technical details—incision used and reconstruction performed, whether flap included a skin paddle used to reconstruct a skin defect.
- Median follow-up duration
- Loss to follow-up expressed as a percentage
- Primary outcomes as described above
  - Early clinical outcomes including clinical complications such as flap necrosis, infection, re-admission, re-excision and completion mastectomy rates.
  - Later clinical outcomes including correction of symmetry (contralateral augmentaion/reduction), nipple reconstruction, correction of deformity (lipomodelling, scar revision etc), mastectomy for recurrence, any other procedures
  - Oncological outcomes include overall survival and local recurrence rate in the follow-up period.
  - Cosmetic outcomes include cosmetic results, cosmetic evaluation method, patient's satisfaction and quality of life.

Assessment of risk of bias

We will use the Cochrane Risk of Bias Tool(11) for RCTs and the ROBINS-1 tool for non-randomised studies. We will compare study protocols with final papers where possible and key missing information across all study types will be presented.

Strategy for data synthesis and statistical analysis

Outcomes of interest will be presented appropriately. We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention

effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. We are not planning to perform any subgroup analysis.

Patient and Public Involvement

No patients or members of the public were involved in this manuscript.

ETHICS AND DISSEMINATION

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

REFERRENCES

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11. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	breast cancer, oncoplastic, partial breast reconstruction, breast conserving surgery

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Authors' contributions:

RR & PR conceptualised the idea.
JH & PR drafted the manuscript.
JH, RR, AS, OP & PR contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria.
JH, RR, AS, OP & PR read, provided feedback and approved the final manuscript

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ABSTRACT

Introduction:

Oncoplastic breast surgery allows the excision of larger tumours without compromising cosmetic outcome and can be broadly divided into volume displacement and volume replacement techniques. Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, evidence is still lacking especially in patients who underwent volume replacement techniques. As it is a relatively new technique which has been described in the literature in the recent years, a summary of evidence from this literature can help clinicians to understand the clinical, oncological & cosmetic outcomes of such procedures.

Methods and analysis:

All original studies including randomised controlled trials, cohort studies, case-control studies and case series involving more than 10 women undergoing partial breast reconstruction using a volume replacement technique will be included. Primary objective is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery. The secondary objective is to review the patient-reported outcomes (PROMs) associated with onocplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery.

A comprehensive literature search, eligibility assessment and extraction of data will be conducted by 2 trained teams acting independently. Data will be extracted and stored in a database with standardised extraction fields to facilitate easy and consistent data entry. Heterogeneity will be assessed using the Cochrane tests.

Ethics and dissemination:

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

Registered with PROSPERO (registration number: CRD42017075700)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first review to specifically focus on volume replacement techniques
- The search for studies is limited by English language.
- Many of the publications of new techniques are reporting small numbers of patients and hence potential lack of high quality studies limiting the ability to conduct a meta-analysis
- It would be difficult to tease out volume displacement and volume replacement techniques
- Potential reporting bias within the existing literature

INTRODUCTION

Surgery for breast cancer has evolved dramatically over the years, from Halsted's radical mastectomy which was standard of care for all women diagnosed with breast cancer right up to the 1960s, to the development and acceptance of breast conserving therapy as standard of care in more recent years. Breast conserving therapy refers to breast conserving surgery (BCS) followed by radiotherapy. BCS has been found to have equivalent disease-free and overall survival when compared to mastectomy, and hence has become the standard of care for early-stage breast cancer.

The primary aim of BCS is tumour excision to achieve tumour-free resection margins while the secondary aim is to achieve a satisfactory cosmetic outcome. Although many early cancers can be successfully treated by standard lumpectomy, some lesions still remain a challenge for breast surgeon to achieve a good outcome especially with regards to patients with large tumour to breast size ratio. Oncoplastic breast surgery(1-4) combine oncological resection with plastic surgery techniques and allow the excision of larger tumours without compromising cosmetic outcome.

Oncoplastic breast surgery can be broadly divided into 2 fundamentally different techniques: (i) volume displacement using glandular or dermoglandular redistribution of breast tissue into the resection site; (ii) volume replacement using autologous tissues from an extra mammary site to compensate for volume loss after tumour resection. Women with small breasts or a large tumour/breast ratio may not be suitable for volume displacement and hence volume replacement serves as an alternative to mastectomy. Examples of volume replacement techniques include the latissimus dorsi miniflap, chest wall perforator flaps, omental flaps etc.

Although oncoplastic surgery has rapidly gained acceptance and is now widely practiced, evidence is still lacking on both short- and long-term outcomes, especially in patients following volume replacement. As with any relatively new technique, a summary of evidence from the literature can help clinicians to understand the clinical, oncological & cosmetic outcomes of these novel procedures.

What have we learnt from prior systematic reviews?

Previous systematic reviews have largely focused on oncoplastic breast surgery as a collective group (see Table 1). Volume replacement techniques have been developing and gaining acceptance, and we feel there is a need to focus on these techniques as a separate entity, analysing the latest publications. A summary of published evidence will update the clinical, oncological and cosmetic outcomes of these procedures. Our study proposes to look specifically at the clinical, oncological and aesthetic outcomes patients undergoing volume replacement alongside oncoplastic breast conserving surgery.

Table 1: Prior reviews of volume replacement in patients undergoing oncoplastic breast conserving surgery

Review	Databases included & years searched	Studies included	Key findings
Losken et al 2014 (5)	PubMed	61 papers	Meta-analysis comparing breast conservation therapy and oncoplastic breast surgery. Length of follow up in the oncoplastic breast surgery group was shorter than breast conservation therapy. Main focus was on age, tumour size and local recurrence. Very little focus on the various techniques available and cosmetic outcomes.
Haloua et al 2013(6)	MEDLINE, EMBASE & Cochrane 2000-2011	12 studies - most are volume displacement techniques	This systematic review reveals that current evidence supporting the efficacy of oncoplastic breast surgery is based on poorly designed and underpowered studies. Given the increasing importance and application of oncoplastic breast surgery, there is a pressing need for robust comparative studies, including both randomized controlled trials and well-designed, multicenter prospective longitudinal studies.
Yiannakopoulou EC et al 2016(7)	Pubmed, Scopus, Google Cholar, Science citation Index 1966-2013	40 studies - only 15 were volume replacement	Study quality was low. The majority of studies were observational studies. The length of follow up was relatively short, long term oncological outcome of oncoplastic surgery for breast cancer is not adequately investigated. Further research efforts should focus on Level I

			evidence on oncological outcome of oncoplastic surgery
L. De La Cruz et al 2016(8)	Pubmed 1988-2015	55 studies with broad spectrum of oncoplastic techniques	Systematic review comparing breast conserving surgery using oncoplastic techniques in place of standard lumpectomy. The review only included T1 and T2 breast cancers. The oncoplastic techniques evaluated were mainly volume displacement (>50%) but very little details on surgical technique available.
J.J Yoon et al 2016(9)	Pubmed 1995-2015	41 studies – only 11 were volume replacement	Review comparing post-radiation outcomes of volume replacement and volume displacement. Did not describe the surgical techniques involved.

Why is it important to do this systematic review?

As volume replacement techniques have been developing and gaining acceptance, there is a need to focus on it as a separate entity and to include the latest available literature.

Since the most recent systematic review of oncoplastic breast surgery concluded its search in 2015, there have been over 30 more articles published in regards to partial breast reconstruction using volume replacement technique. A new systematic review is needed to update our understanding of this rapidly evolving area of clinical practice, and to address the questions unanswered by previous studies

OBJECTIVES

The primary objective of this review is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery.
A secondary objective is to review the patient-reported outcomes (PROMs) associated with oncoplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery

METHODS AND ANALYSIS

This review will be conducted in line with the recommendations specified in the Cochrane Handbook for intervention reviews V.5.1.0. It will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. This protocol has been registered on PROSPERO. (Registration number: CRD42017075700)

Inclusion and Exclusion Criteria

To minimize heterogeneity and to address the objectives of the review, studies will be selected according to the criteria outlined below.

Study designs

We will include all randomized controlled trials (RCTs), cohort and case-control studies. Single group cohorts and case series will be included if there are more than 10 patients who underwent volume replacement after oncoplastic breast conserving surgery. Hence, levels of evidence 1-4 as defined by the Oxford Centre for Evidence-Based medicine (10). Case reports, abstracts, expert opinions and duplicate studies will be excluded. Only studies published in English will be included.

Participants

Only women with breast cancer who are undergoing partial breast reconstruction using volume replacement in breast conserving surgery will be included. Males, patients who underwent mastectomy and patients who underwent surgery for benign breast conditions will be excluded.

Interventions

Partial breast reconstruction using volume replacement such as chest wall perforator flaps, latissimus dorsi mini-flaps and other volume replacement techniques. Volume displacement techniques such as therapeutic mammoplasty and usage of non-autologous tissue will be excluded.

Outcomes

The primary objective of this review is to evaluate the clinical, oncological and cosmetic following volume replacement in patients undergoing oncoplastic breast conserving surgery. Early clinical outcomes include clinical complications such as flap necrosis, infection, re-admission, re-excision and completion mastectomy rates. Later clinical outcomes include correction of symmetry (contralateral augmentaion/reduction), nipple reconstruction, correction of deformity (lipomodelling, scar revision etc), mastectomy for recurrence, and any other procedures. Oncological outcomes include overall survival and local recurrence rate in the follow-up period. Cosmetic outcomes include cosmetic results and cosmetic evaluation method.

A secondary objective is to review the patient-reported outcomes (PROMs) associated with oncoplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery. PROMs include patient satisfaction and quality of life. We would also be looking at parameters, if reported in the published studies, optimising patient selection for these surgical procedures such as age, smoking history, co-morbidity such as diabetes mellitus, tumour size and location, and pre-operative breast/bra size.

Search strategy

The following electronic databases will be searched from January 1990 to 31 December 2017: MEDLINE, EMBASE, the Cochrane database and Database of Abstracts of Reviews of Effect (DARE). This will be supplemented by a manual search of references lists and the review of "epub ahead of print" articles.

A comprehensive search will be performed using the following search terms: breast conserving surgery, oncoplastic breast surgery, oncoplastic breast conserving surgery, partial breast reconstruction, partial mastectomy, immediate reconstruction and volume replacement. Additional keywords such as chest wall perforator flaps, latissimus dorsi mini flap, omental flap and further logical combinations of these and related terms will be used to maximize sensitivity. The search will include all study designs but limited to articles published in English.

Studies identified will be listed within a Microsoft Excel database and duplicates excluded. The selection of articles will be conducted by 2 teams who will independently evaluate the titles and abstracts to assess the eligibility in terms of outcome measures and study designs. The authors will be blinded to each other's results during the review process and the findings will then be compared. Discrepancies will be resolved through discussion. The full text of the articles selected will be further assessed for inclusion by 2 review authors. Where required, authors will be contacted to clarify inclusion, data overlap and data.

Once the study has been included, data extraction will be performed independently by two teams of researchers. Discrepancies will then be resolved by consensus.

Data will be extracted into a standardised Microsoft Excel database. The following data will be extracted:

- Author names, countries and year of publication
- Study design and level of evidence
- Conflicts of interest and funding
- Number of participants

- Number of breasts treated
- Age of participants
- Smoking history
- History of diabetes
- Pre-operative breast/bra size
- Oncological parameters—type of cancer (invasive or *in situ*), grade, stage, axillary nodal status, hormone receptor status (ER, PR), HER2 status, size of tumour including any associated additional foci, location of tumour (which quadrant), tumour-nipple distance, solitary or multifocal or multicentric and presence of lymphovascular invasion.
- Adjuvant radiotherapy
- Prior neoadjuvant or adjuvant chemotherapy
- Previous breast surgery
- Technical details—incision used and reconstruction performed, whether flap included a skin paddle used to reconstruct a skin defect.
- Median follow-up duration
- Loss to follow-up expressed as a percentage
- Primary outcomes as described above
  - Early clinical outcomes including clinical complications such as flap necrosis, infection, re-admission, re-excision and completion mastectomy rates.
  - Later clinical outcomes including correction of symmetry (contralateral augmentaion/reduction), nipple reconstruction, correction of deformity (lipomodelling, scar revision etc), mastectomy for recurrence, any other procedures
  - Oncological outcomes include overall survival and local recurrence rate in the follow-up period.
  - Cosmetic outcomes include cosmetic results, cosmetic evaluation method, patient's satisfaction and quality of life.

Assessment of risk of bias

We will use the Cochrane Risk of Bias Tool(11) for RCTs and the ROBINS-1 tool for non-randomised studies. We will compare study protocols with final papers where possible and key missing information across all study types will be presented.

Strategy for data synthesis and statistical analysis

Outcomes of interest will be presented appropriately. We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention

effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. We are not planning to perform any subgroup analysis.

Patient and Public Involvement

No patients or members of the public were involved in this manuscript.

ETHICS AND DISSEMINATION

This systematic review requires no ethical approval. It will be published in a peer-review journal and it will also be presented at national & international conferences.

REFERRENCES

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 3, introduction
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	page 1, Title
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	page 1, Authors
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	page 1, Authors' contribution
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	page 1, funding statement
Sponsor	5b	Provide name for the review funder and/or sponsor	page 1, funding statement
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	page 1, funding statement
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3, introduction,
Objectives	7	Provide an explicit statement of the question(s) the review	Page 6, objectives

		will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7, methods and analysis
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 8, search strategy
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 8, search strategy
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 8, search strategy
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 8, search strategy
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 8, search strategy
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and	Page 8, search strategy

		simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 9, strategy for data synthesis
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 9, assessment of risk bias
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 9, strategy for data synthesis and statistical analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 9, strategy for data synthesis and statistical analysis
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9, strategy for data synthesis and statistical analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 9, strategy for data synthesis and statistical analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9, assessment of risk of bias
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7, study designs

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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