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Method Article

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Abstract

Introduction: Today mastectomy and breast reconstruction are often coupled for women with breast cancer, where mastectomy has the chance to remove the tumour and reconstruction improves the aesthetic appearance. While rates of post-mastectomy immediate breast reconstruction (IBR) are on the rise, there remains fears of local recurrence (LR).\textsuperscript{1,2}

Purpose: This systematic review aims to compare long-term LR rates in a group of patients with mastectomy and IBR (Mast + IBR) to a group of patients with mastectomy without IBR (Mast – IBR).

Methods: The online databases Medline, Embase, and Web of Science will be searched for relevant articles. Articles published between January 2000 to December 2020 that report LR rates for groups patients who underwent mastectomy for stage I or II breast cancer with or without IBR with stage will be included. The risk of bias will be assessed using the Johanna Briggs Institute scale for observational studies. A fixed-effects meta-regression model will calculate the pooled odds ratio with a 95\% confidence interval, adjusted for age and follow-up time.

Implications: Moreover, this review will synthesis the literature surrounding the study factors, patient factors, reconstructive factors, and outcome factors associated with LR. Finally, the findings will be used to develop clinical recommendations for breast cancer reconstruction.

Ethics and dissemination: Ethics approval is not required. The systematic review will be submitted for publication in a peer-reviewed journal.

Introduction

Background: The World Health Organization estimates that there are 7.8 million women alive with breast cancer, making it the most prevalent cancer in the world.\textsuperscript{3} In 2020, over 2.3 million women were diagnosed with breast cancer, resulting in 685,000 deaths.\textsuperscript{3} Breast cancer occurs in every country to post-pubescent women of any age, with increasing rates with increasing age.\textsuperscript{3}

Historically, the primary mode of treatment was mastectomy, involving removal of the affected breast tissue. Recent advances in conservative mastectomy involve tumor removal coupled with remodelling and reconstruction to improve aesthetic outcomes. Variants include skin-sparing mastectomy (SSM), involving the removal of the glands but leaving the breast skin to create a pocket available for reconstruction efforts, and nipple-sparing mastectomy (NSM), where the nipple-areola complex is preserved.\textsuperscript{4}

Reconstruction often provides improved aesthetic outcomes, leading to higher psychosocial wellbeing and post-operative satisfaction. Autologous reconstruction involves using the patient’s tissues for reconstruction; variants including latissimus dorsi transverse rectus abdominis myocutaneous transport the tissue while keeping the blood supply in-tact, whereas both the deep inferior epigastric perforated and
superficial inferior epigastric artery flap transfer tissue without removing any muscle. Prosthetic silicone or saline implants may also be used for reconstruction. The decision-making depends on a discussion with the surgeon about the donor tissue, patient lifestyle, risk tolerance, and need for radiation therapy. The vast majority of patients prefer prosthetic reconstruction, reflecting the simplicity of implant-based operation, shorter recovery time, and limited access to surgeons who can perform autologous reconstruction.

Reconstruction at the time of mastectomy, called immediate breast reconstruction (IBR), is the most common reconstruction type as it combines surgery and recovery procedures at one time. One estimate suggests that 40% of women undergo reconstruction, resulting in 106,000 reconstructive surgeries performed in 2017 in the United States. Another study estimates that immediate breast reconstruction is performed in 14% of cases in the United States.

One barrier to IBR is the concern of local recurrence (LR), which in this context, refers to recurrent cancer in the breast. A recent systematic review conducted by Bargon et al., comparing IBR and delayed breast reconstruction showed comparable rates of LR, concluding that oncological concern should not be a barrier between different reconstruction timing. While Joo et al., 2021 evaluated the pattern and location of LR following reconstruction, finding that the skin and subcutaneous tissue were the most common sites of LR in the same quadrant as the primary lesion.

Additionally, Blanckaert et al. found that NSM and reconstruction have comparable survival rates and recurrence rates to conventional mastectomy alone. Similarly, Gerber et al. found skin-sparing mastectomy with intraoperative frozen section of the nipple-areola complex can conserve the nipple-areola complex without increasing the risk of LR in 2003. A broader systematic review of LR rates post mastectomy with or without reconstruction has not been conducted since 2007 by Barnsley et al., although it does not specifically investigate IBR.

An observational study McCarthy et al. found no difference in the incidence of locoregional recurrence for patients undergoing immediate, tissue expander reconstruction compared to those without reconstruction. Meanwhile, Huang et al. also found that there were no differences in incidence of LR between patients with or without transverse rectus abdominis musculocutaneous flap reconstruction. Similarly, Shen et al. found similar levels of incidence of recurrence for patients with no reconstruction, immediate reconstruction and delayed reconstruction.

There are many risk factors for recurrence of breast cancer. They can be grouped as patient, treatment, and tumour related factors. Patient related factors include elevated body mass index, advanced age, and young age. Rough textured implants have raised concerns about both implant related anaplastic large cell lymphoma's as well as local primary recurrence. Leaving the skin immediately overlying the initial tumor and the needle track site of a core needle biopsy have been implicated in LR. Furthermore, radiation increases risk of complications, including infection, skin necrosis, and loss of reconstruction for
both autologous and prosthetic.\textsuperscript{5} Therefore, those receiving radiation, may see stronger benefits when delayed reconstruction is performed.\textsuperscript{5} Tumor related factors such as human epidermal growth factor receptor 2 (HER-2) positive, triple negative, estrogen receptor (ER) and progesterone receptor (PR) negative, size of tumour, tumour grade, tumour located on inner quadrant, lymphovascular invasion close/ positive margins and more advanced disease are known to increase recurrence risks.\textsuperscript{15,19–21}

The lack of clear conclusions in the literature regarding IBR complicates clinical decision-making and patient education. Conducting a systematic review and meta-analysis may provide valuable insights into this extensively debated issue. This review aims to explore the impact of IBR on LR incidence and examine the patient, tumour, and reconstructive factors linked to LR.

\textit{Reporting:} For high standards of reporting, this systematic review follows the protocol recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol for this systematic review will be registered and made available on Open Science Framework and Protocol Exchange.

\textit{Research Question:} The systematic review will provide a comprehensive analysis of the incidence of local recurrence and factors associated with local recurrence. To investigate the association between mastectomy, immediate breast reconstruction, and LR, this systematic review will investigate two research questions:

1. What is the incidence of breast cancer local recurrence in patients who have undergone mastectomy and immediate breast reconstruction (Mast + IBR) as compared to those who have had mastectomy but not had immediate breast reconstruction (Mast – IBR)?

2. What are factors associated with local recurrence in patients who have undergone mastectomy and immediate breast reconstruction (Mast + IBR) as compared to those who have not had immediate breast reconstruction (Mast – IBR)?

This systematic review will provide updated evidence on the risk of LR associated with immediate breast reconstruction, including any study factors, patient factors, and reconstruction factors.

We will investigate the relationship between study factors, patient factors, tumour factors, reconstructive factors, and outcome factors. Specifically, if data allows, we will attempt to elucidate relationships between these factors with the incidence of LR.

\section*{Reagents}

\section*{Equipment}
Procedure

Framework: The research question and objective will follow the population, intervention, comparison, outcome, time, and study design (PICOTS) Framework in Table 1 in the Appendix.

The population of interest is adult patients (≥ 18 years) who have a diagnosis of breast cancer (stage I or stage II) and have undergone mastectomy of any kind; however, we will not target the population of patients who have undergone prophylactic mastectomy as these patients do not have a diagnosis of breast cancer. We will not restrict the study population according to sex/gender and geographic location.

The intervention of interest is patients who have mastectomy and immediate breast reconstruction (Mast + IBR), while the comparison group is patients who have had mastectomy but have not had immediate breast reconstruction (Mast – IBR). The outcome of interest is the incidence of LR.

We are primarily looking for studies with a median follow up time of at least one year as one year is the minimum time required for LR to be detected. We are looking for records published between 2000 and 2020 to avoid detection, surgical, and even publication issues associated with the COVID-19 pandemic.

Additionally, we are looking for records that are observational cohort, case-control, and cross-sectional studies; both prospective and retrospective study designs will be accepted.

Search for Existing Reviews and Protocols: We have searched Prospective Register of Systematic Reviews (PROSPERO) for similar systematic reviews already registered. We did not identify any registered systematic reviews protocols.

To search for existing systematic reviews, Epistemonikos, MEDLINE/PubMed, and the Cochrane Library were searched for the two key concepts (local recurrence and breast reconstruction). We identified one systematic review by Barnsley et al. in 2007 for which we will provide an update and respond to their needs to provide more evidence to evaluate this issue. As IBR is becoming more common in recent years, it is important to provide an update with a larger sample and to contextualize these findings with other reviews in reconstructive breast surgery.

In addition, our systematic review will add to discussion to provide more clarity on the decision to choose or not to choose IBR. Specifically, we will investigate risk factors surrounding patient, tumor, and reconstructive factors that are associated with LR in patients who have underwent mastectomy and IBR.

Search for Articles: We will search several databases for potentially relevant records as well as records from the grey literature. We will search for published journal articles, conference abstracts, and consult expert networks. Additionally, the references of all included articles will be hand-searched for additional potential articles using Citation Chaser.

To identify published articles, the following databases will be searched: MEDLINE (Ovid), Embase (Ovid), and Web of Science. To identify any conference abstracts, the following databases will be searched:
MEDLINE (Ovid), Embase (Ovid), and Europe PubMed Central.

To identify reports to be screened from the grey literature, the following expert networks will be searched: BC breast reconstruction network, BC surgical oncology breast tumour group, and Breast Cancer Outcomes Unit from BC Cancer Agency.

**Search Terms:** The concepts included in our search strategy reflect our PICOTS framework. To search for terms related to the population, we will search terms related to breast cancer, including breast cancer, breast neoplasm, breast tumour, ductal carcinoma, and breast tumour.

We will also search terms related to mammoplasty and immediate breast reconstruction, including mammoplasty, autografts, transplantation, autologous, tissue transplantation, adipose tissue, free tissue flaps, and other variants.

To search for terms related to the outcome, we will search for terms related to LR, disease-free survival, recurrence, recurring neoplasms, recurring cancers, and recurring tumours.

We will limit our search to human adult patients and the search was limited to the period 2000 – 2020. **Tables 2, 3, and 4** display the search terms used for MEDLINE (Ovid), Embase (Ovid), and Web of Science, respectively.

**Screening Strategy:** Once the files are uploaded to Covidence, the software will automatically remove duplicates. Any remaining duplicates will be manually marked as duplicates by the reviewers (MC, DL, and DT). To do so, we will use identifying information including the title, authors, year, publication date, journal name, and abstract content. If there are multiple reports of the same study, these will be marked and manually merged in a later phase.

We will use Covidence to screen for studies according to the inclusion and exclusion criteria. The reviewers will use a two-staged approach consisting of title and abstract screening, followed by the full-text screening.

To begin, two reviewers (MC and DL) will conduct a small pilot review of five records and compare results. Any discrepancies will be resolved by discussion to reach an agreement is reached. Then a complete screening will occur.

All identified records will be screened independently by the reviewers (MC and DL) using the inclusion and exclusion criteria below. Any disagreements will be recorded and discussed until a resolution is reached. If a resolution cannot be reached, a third reviewer (DT) will make a final decision. For any record that has been excluded, we will record a list of reasons for their exclusion.

**Inclusion Criteria:** For a record to be marked as “Included”, it must meet all the inclusion criteria and meet none of the exclusion criteria. If a record meets any of the exclusion criteria, it will be marked as “Excluded.”
The inclusion criteria are designed to be comprehensive as described in the list below. Eligible studies include all the following criteria:

- Records written in English.
- Records of any geographical location will be included.
- Records must report about observational cohort studies, case-control, and cross-sectional studies. These may be prospective or retrospective observational studies.
- Studies conducted on human patients.
- Studies must exclusively include adult patients (≥ 18 years).
- Studies with patients of all genders/sexes will be included.
- Studies with a minimum median follow-up time of 1 year.
- Studies specifically reporting on patients with a diagnosis of early-stage breast cancer (stage I or II).
- Studies that report on patients who underwent a mastectomy.
- Studies that compare patients that underwent mastectomy and immediate breast reconstruction (Mast + IBR) to patients that underwent only mastectomy without immediate breast reconstruction (Mast - IBR).
- Studies that report comparable demographic factors (e.g., median age) between groups that underwent mastectomy and immediate breast reconstruction (Mast + IBR) to patients that underwent only mastectomy without immediate breast reconstruction (Mast - IBR).
- Studies that report LR incidence for both patient who underwent immediate breast reconstruction (Mast + IBR), and for patients who did not undergo immediate breast reconstruction (Mast - IBR).

**Exclusion Criteria:** As multiple reasons for excluding a record may exist, we will follow an exclusion flow chart for standardization as described in the Appendix.

The exclusion criteria are designed to be comprehensive as described in the list below. Ineligible studies include any of the following criteria:

- Records not written in English.
- Records that are review articles, case reports, case series, editorials, letters, and commentaries.
- Studies not conducted on humans patients.
- Studies not exclusively conducted on adults (≥ 18 years).
- Studies with a minimum median follow-up time of 1 year.
- Studies reporting patients without a breast cancer diagnosis (i.e., undergoing a mastectomy of prophylactic care).
- Studies reporting only on patients treated with partial mastectomy or completion mastectomy.
- Studies that do not compare patients that underwent mastectomy and immediate breast reconstruction (Mast + IBR) to patients that underwent only mastectomy without immediate breast reconstruction (Mast − IBR).
- Studies that do not report comparable demographic factors (e.g., median age) between groups that underwent mastectomy and immediate breast reconstruction (Mast + IBR) to patients that underwent only mastectomy without immediate breast reconstruction (Mast − IBR).
- Studies that do not report LR incidence for both patient who underwent immediate breast reconstruction (Mast + IBR), and for patients who did not undergo immediate breast reconstruction (Mast − IBR).

Assessment of Risk of Bias: On each record marked as Included in the screening phase, we will perform a risk of bias assessment. We perform the risk of bias assessment on Covidence using the Johanna Briggs Institute (JBI) critical appraisal tool for cohort, case-control, and cross-sectional studies.

Two reviewers (MC and KW) with a small pilot assessment with three records and compare results. Any discrepancies will be resolved by discussion to reach a standardized agreement. Then a complete screening will occur.

For each question on the risk of bias assessment, we will respond with Yes, No, Unclear, or Not Applicable. Two reviewers (MC and KW) will independently review the records. If there is any disagreement, the reviewers will discuss until a resolution is reached. If the two reviewers are unable to agree on a resolution, a third reviewer (KI) will make the final decision.

Data Collection: During the data extraction process, the data will be compiled on a pre-determined template on Excel. The data extraction form is found on Table 5.

To begin, two reviewers (MC and KW) will conduct a small pilot review of two records and compare results. Any discrepancies will be resolved by discussion to reach a standardized agreement. Then a complete data extraction initiative will occur.

Data will be extracted independently by the reviewers (MC and KW). Any discrepancies will be recorded and discussed until a resolution is reached. If a resolution cannot be reached, a third reviewer (KI) will
make a final decision.

The data collected from data extraction will be presented in a Summary of Included Studies table in our final manuscript.

*Multiple Data Sources for Included Studies*: As data for one study may be found across multiple reports (published article, protocol, trial registry, author contact, etc.), we will compile all data on one collection form. In the event of conflicting information among the reports, we will prioritize in order: author contact, published article, protocol, trial registry, and any other report.

If the data described within a single report are inconsistent among different sections of the report (e.g., abstract, body text, tables, and figures), we will contact the study authors and inquire about the correct data. If we do not receive a response, we will use the data that is most frequently reported across the sources.

*Contacting Report Authors*: For any issues, we will attempt to contact the record authors. We will attempt to contact the corresponding author three times by email. We will record each attempt to contact the authors as well as any responses that we receive from them. We will acknowledge any attempts to contact the authors in the limitations section of our review manuscript.

*Data Cleaning*: As we expect that there may be competing outcomes to detecting LR, we intend to analyze the impact of other outcomes for their impact on the results. These competing outcomes include death (all cause mortality, breast cancer specific mortality, LR specific mortality) and time to follow up.

We expect there may be unit-of-analysis issues as some studies may report the number of LR per breast, whereas some studies may report the number of LR events per patient. We intend to conduct the analysis at the level of the patient because we intend to investigate the association of patient factors (eg. HER-2 status, age) with the LR.

If sufficient data is available, we will also draw correlations between various factors collected in the data extraction phase with the occurrence of LR. If data permits, the review will comment on geographical origin of the data, noting any limitations or gaps in the field.

*Meta-Analysis*: If there is sufficient data, the meta-analyses will be performed on RevMan and on R.

For each included study, we will use LR rates in the Mast + IBR and the Mast – IBR groups to calculate the crude odds ratio (OR) with its 95% confidence interval (CI). With each included study, we will calculate the pooled crude OR with the 95% CI. For the crude meta-analysis, a forest plot will be constructed with a Mantel-Haenszel fixed-effect model. Heterogeneity between studies will be assessed using $I^2$ statistic and a p-value.

We will also enlist the support of a statistician, who intends to perform an adjusted meta-analysis using R that accounts for the competing outcome of death, age as a confounder, and follow up time as a confounder. We will report any limitations or gaps in the field.
**Sensitivity Analysis:** We will perform a sensitivity analysis on RevMan by checking the individual impact of each included record on the crude pooled OR. We will then draw inferences about the impact of each included study on the results. We will report the completed sensitivity analysis in a supplementary file.

**Subgroup Analysis:** If there is sufficient data, we will perform a subgroup analysis according to estrogen receptor, progesterone receptor, HER-2 receptor, cancer stage (stage I or II), post-mastectomy radiation therapy, stage, size, and laterality (unilateral and bilateral).

**Assessment of Heterogeneity:** We will create a funnel plot on RevMan to investigate the heterogeneity. Additionally, we will use the funnel plot and forest plot to visually inspect the heterogeneity.

Then, we will assess the heterogeneity of treatment effects between trials using the $\chi^2$ test with a significance level of p-value < 0.1. We will use the $I^2$ statistic to estimate the proportion of total variation across studies that is beyond chance ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity). We will also use $\tau^2$ statistic to estimate the between-study variation.

If we have more than 10 included studies and the funnel plots are not clearly asymmetric, we will also use prediction intervals of the outcomes to express the amount of heterogeneity.

**Handling Missing Data:** To address records with missing data, we will first attempt to find the missing data in the supplementary information. If we can perform simple calculations, we will do so. For example, we may convert years of follow-up to months of follow-up or calculate the HER-2 positive status when given the HER-2 negative status.

If we are unable to locate or calculate the data, we will attempt to contact the record authors according to the protocol outlined earlier. If we are still unable to locate the data, we will not attempt to impute the data and we will exclude this value from the analysis.

If there are several studies where we cannot retrieve missing data, we will use the Outcome Reporting Bias In Trials (ORBIT) method to classify the reasons for missing results. The records will be classified according to if the reason for missing data, including likely due to results, or unlikely due to results. We will make this assessment according to the p-value, direction of the result, and magnitude of the result.

**Implications:** This systematic review has clinical implications that may impact clinician and patient decisions in considering mastectomy and/or immediate breast reconstructive surgery. Therefore, we will provide both a statistical and clinical interpretation. Our statistical interpretation will depend on the statistical results of our meta-analysis. The clinical interpretation will be performed by an expert (KI), which will provide a holistic understanding of the rates of LR given several patient, tumour, and reconstructive factors.

Additionally, we will provide an interpretation of the correlation between the factors and interpret the competing outcomes (death, follow-up time, and LR). This will reduce the bias in the relationship between Mast + IBR with LR, compared to Mast − IBR.
Grading the Certainty of Evidence: We will assess the quality of the outcome presented in this review by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The certainty of evidence will be ranked according to the eight domains: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effects, dose-response, opposing plausible residual bias, and confounding.

We will begin with high certainty, and then upgrade based on low certainty of evidence, or downgrade based on low certainty of evidence. The reasons for upgrading include large effects, dose response, and plausible confounding. While the reasons for downgrading include risk of bias, limitations in the design, unexplained heterogeneity, inconsistency of results, indirectness of evidence, imprecision of results, and high probably of publication bias. For any record that we downgrade, we will describe the reasons in the text.

The outcome will be ranked will range from very low (⊕⊝⊝⊝), low (⊕⊕⊝⊝), moderate (⊕⊕⊕⊝), and high (⊕⊕⊕⊕) certainty of evidence. The overall ranking will be provided for the review and will be presented in a figure. A template of the table will be displayed in Table 6.

Two reviewers (MC and KW) will independently perform the grading. If there is any disagreement, the results will be compared and discussed until an agreement is reached. If no agreement is reached, a third reviewer (KI) will deliver the final decision.

Summary of Findings Table: We will produce a Summary of Findings table that will include a brief description of the population type, intervention, comparison, outcome, time, and study design. It will describe both the groups (Mast + IBR, and Mast – IBR), the outcomes, the effect measure, number of patients, the certainty of evidence, and any associated comments. A template for the summary of findings table is found on Table 7 in the Appendix.

Limitations: We expect that several limitations of this review could exist. First, we have limited our search to records published in the English language, which may limit the global discussion on breast cancer reconstruction. By restricting to a period before the COVID-19 pandemic, we have avoided the bias in surgical patterns, but it does not represent the changes in the current landscape.

This review is limited in its scope as it only investigated LR following IBR, while recurrence may occur in other regions or may follow other forms of breast reconstruction or there may be other consequences associated with IBR. Therefore, this review does not fully estimate the full range of outcomes following breast reconstruction.

The review is limited to the availability of data in the literature, which is subject to reporting biases. There may be reporting bias towards studies that have significant findings of LR. In addition, there may be reporting issues with a sensitive population as there may be issues with loss to follow up. Additionally, our results may reflect clinician bias in offering immediate breast reconstruction to patients of a
particular background; for example, they may be younger, have certain lifestyle factors, comorbidities, or have a certain post-mastectomy radiation therapy treatment status.

**Troubleshooting**

See Table 7 in Appendix.

**Time Taken**

See Table 8 in Appendix.

**Anticipated Results**

*Anticipated Results of Screening:* Based on our preliminary screening, we anticipate roughly unique 2,000 papers, where 10 – 20 papers will meet our inclusion criteria.

*Anticipated Results of Meta-Analysis:* Based on our clinical experience, we expect that younger age is associated with IBR use, and follow-up time is associated with LR. Based on our preliminary literature review and clinical experience, we expect that LR is not associated with IBR when adjusting for age and follow-up time.

**References**


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Conflicts of Interest: Dr. Kathryn Isaac is the holder of the Dr. Patricia Clugston Chair in Breast Reconstruction Surgery at the University of British Columbia and would like to acknowledge the support of Vancouver General Hospital & University of British Columbia Hospital Foundation's donors and partners who made this Chair possible. All other authors have no conflicts of interest to declare.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix.docx