



## Protocols

# Protocol for a Systematic Review Assessing Surgery versus Primary Endocrine Therapy in Operable Breast Cancer. Prep for Pandemic



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## ABSTRACT

**Introduction:** In COVID-19 pandemic epicenters cancer care was severely impacted. All elective and semi-elective procedures, as well as select urgent cases, were postponed in order to preserve resources and protect patients and staff from SARS-CoV-2 exposure. Structured decision making for breast cancer treatment resulted in deferment of surgery with initiation of endocrine therapy. Moreover, the waitlist for elective breast cancer procedures after mitigation is a challenge for prioritization.

**Objective and significance:** We aim to summarize the current body of evidence, comparatively evaluate oncological outcomes of surgery versus primary endocrine therapy (PET), and determine whether PET is a viable long-term alternative to surgery in the context of crisis management strategy for early, operable hormone receptor positive (HRP) breast cancer. PET could potentially be an acceptable bridging or maintenance therapy in select patients during pandemic crisis or for those choosing to forgo surgery in the treatment of breast cancer.

**Methods and analysis:** The database search includes PubMed, EMBASE, and MEDLINE (via Ovid). This systematic review includes women 18 years or older undergoing one of two interventions for HRP breast cancer: surgery (with or without endocrine therapy post-surgery) or solely PET. Studies comparing one of the two interventions of interest to a non-relevant intervention and studies reporting only descriptive data will not be included in the quantitative synthesis of data. After selection of eligible studies based on title and abstract, these studies will be further screened through full text articles by two independent reviewers, with a third as an arbitrator. Eligible studies will be critically appraised at the study level for methodological quality. Cochrane methodology will be utilized for meta-analysis.

**Ethics and dissemination:** This study does not require an institutional review board approval given its summary design nature. Findings of this systematic review will be published in a peer-reviewed journal.

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## 1. Introduction

The standard of care for breast cancer in women of all ages has been surgery since the 1970s [1]. Since primary endocrine therapy (PET) was first described and assessed in pilot cohort studies [2,3], multiple clinical studies as well as summary design studies performed in the last three decades have found PET alone to be inferior to surgery for the long term local control of breast cancer in hormone receptor unselected patients [4,5]. On the other hand, a Cochrane meta-analysis did not find any survival benefit associated with either treatment when surgery alone was compared to PET [HR (95%CI) = 0.98 (0.81, 1.20; p = 0.85)] [4]. Overall survival

was found to be better following surgery with endocrine therapy in hormone receptor unselected patients as compared to PET [HR (95%CI) = 0.86 (0.73, 1.00; p = 0.06)]. However, the only clinical trial comparing these two interventions in hormone receptor positive (HRP) patients did not find a significant difference in overall survival (p = 0.68) [6].

The rationale behind the search for an alternative for upfront surgery in older patients with early stage breast cancer stems from the risks associated with anesthesia and surgery in addition to the fact that older patients are generally more likely to have hormone receptor positive breast cancers as compared to younger patients [7]. Furthermore, advances in endocrine therapy for breast cancer have kept alive the question as to whether PET is a viable alternative to surgery in select patients. We seek to revisit this question due to the significant changes in healthcare policy and clinical practice pertaining to breast cancer care amidst the COVID-19 pandemic. During the pandemic, difficult decisions were made to offer

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the safest care to ensure optimal patient outcomes. Recommendations for prioritization for management of breast cancer in pandemic epicenters deferred surgery to preserve resources and minimize exposure risks to patients and staff. Furthermore, as elective surgeries have restarted, the prioritization in scheduling surgery of patients with breast cancer after the mitigation is challenging.

## 2. Objectives and significance

We propose a systematic review comparatively evaluating the outcomes of patients treated with surgery to those treated with PET only (selective estrogen receptor modulators, aromatase inhibitors, luteinizing hormone releasing hormone agonist). PET could potentially indefinitely delay or eliminate breast cancer surgery in early stage disease not only in crisis management strategy should a second Coronavirus surge occur, but also in selected patients for whom surgery is not a viable option. A preliminary search of PROSPERO, MEDLINE, and the Cochrane Database of Systematic Reviews was conducted and no current or proposed systematic reviews on the topic were identified. We aim to summarize the current body of evidence, comparatively evaluate oncological outcomes of surgery alone and PET alone, and determine whether PET without surgery is a viable alternative to surgery in the context of crisis management strategy. In this regard, we will seek providing responses to the following questions:

- 1) What are the characteristics of the population undergoing PET alone for the treatment of breast cancer?
- 2) What are the main oncological outcomes reported in studies comparing surgery versus PET alone for the treatment of breast cancer?
- 3) How is failure of nonoperative management, local progression, and local recurrence in patients undergoing PET defined?
- 4) Is PET alone comparable to surgery in terms of mid- and long-term oncological outcomes, including local progression rate and disease-free survival?
- 5) What is an acceptable duration for PET alone in patients with breast cancer, who are candidates for surgery?

## 3. Methods

The proposed systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [9]. This protocol was developed prospectively and complies with the PRISMA for Systematic Review Protocols (PRISMA-P) guidelines [10,11].

### 3.1. Research question

The research question is formulated within the PICOT(S) Framework as follows:

- (P) Participants: women older than 18 years undergoing surgery or PET for HRP breast cancer
- (I) Intervention: surgery with or without endocrine therapy
- (C) Comparator: primary endocrine therapy
- (O) Outcomes: local recurrence rate, distant recurrence rate, progression of disease, overall survival, and disease-free survival.
- (T) Timing: mid- and long-term
- (S) Setting: In- and outpatient

### 3.2. Eligibility criteria

We will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies for inclusion in this systematic review. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. However, we will not consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Studies published in English from 1980 onward will be included.

### 3.3. Search strategy

An initial limited search of PubMed was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to identify records of interest in PubMed (Supplement 1). Moving forward, the search strategy including all identified keywords and index terms, will be adapted for each included data source. The sensitivity of the search strategy will be tested by reviewing the references of the included studies.

### 3.4. Data sources

The databases to be searched include PubMed, EMBASE, and MEDLINE (via Ovid). In addition, ClinicalTrials.gov will be searched for any ongoing studies. Sources of unpublished studies and gray literature to be searched include medRxiv.org.

### 3.5. Study selection

Following the search, all identified records will be collated and uploaded into Zotero 5.0 (Center for History and New Media at George Mason University, VA, USA) and duplicates removed. Identified records will be screened using a cascade system. Screening through titles and abstracts will be undertaken by three independent reviewers (SR, AR, and MG). Potentially relevant papers will be screened through full text articles by three independent reviewers (SR, AR, and MG). Reasons for exclusion of full text papers that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any discrepancies arising during screening and study selection between the reviewers will be resolved through discussion with the senior author (MC). The results of the search will be reported in the final review and presented in a PRISMA flow diagram [8].

### 3.6. Assessment of methodological quality

Eligible studies will be critically appraised for methodological quality at the study level by three independent reviewers (SR, AR, and MG) using the Cochrane Tool of Risk of Bias Assessment [12]. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements or discordance that arise between the reviewers will be resolved through discussion with the senior author (MC). The results of critical appraisal will be reported in risk of bias summary and graph.

### 3.7. Data extraction

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possi-

ble). Studies with lower level of evidence will be excluded during the sensitivity analysis of the findings.

Data will be extracted from studies included in the review by two independent reviewers (SR and AR) and cross-checked by the third reviewer (MG). The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective (Supplement 2).

### 3.8. Data synthesis

Effect sizes will be expressed as either odds ratios (for dichotomous data) or weighted mean differences (for continuous data) and their 95% confidence intervals. Statistical among-study heterogeneity will be assessed using Chi squared and  $I^2$  tests.  $I^2 > 75\%$  will be considered high/substantial heterogeneity. The decision on using fixed or random-effects model of meta-analysis will be made following data extraction depending on the extent of clinical heterogeneity between the study intervention. Sensitivity analyses will be conducted to test decisions made by sequential excluding of studies with highest risk of bias. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated using RevMan (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) to assess publication bias if there are 10 or more studies included in a meta-analysis. Egger's test for funnel plot asymmetry will be performed where appropriate.

## 4. Ethics and dissemination

This study does not require an institutional review board approval given its summary design nature. Findings of this systematic review will be published in a peer-reviewed journal.

## 5. Limitations

We anticipate that this review will be subject to several limitations. First of all, this systematic review will project the setting of a randomized controlled trial to the setting of a pandemic epicenter, thereby not adjusting for such factors as limited resources, burnout among healthcare providers, etc. Another limitation may be a heterogeneity in the definitions of local progression, failure of non-operative management, and local recurrence.

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### Ethical approval

Not applicable.

### Consent

Not applicable.

### Author contributions

Sacha Roberts: Conception and design, Methodology, Writing, Critical review and approval. Aram Rojas: Methodology, Critical

review and approval. Mahir Gachabayov: Conception and design, Methodology, Writing, Critical review and approval. Maria Castaldi: Conception and design, Methodology, Writing, Critical review and approval.

### Registration of research studies

Not applicable.

### Guarantor

Maria Castaldi.

### Systematic review registration number

PROSPERO does not currently accept registrations for scoping reviews, literature reviews or mapping reviews.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.isjp.2020.10.003>.

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