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Oncological Outcomes of Different Radiotherapy Strategies for Early Breast Cancer: A Systematic Review and Meta-Analysis Protocol

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Corresponding author:
Tsair-Fwu Lee

tflee@nkust.edu.tw

Author Affiliation:
National Kaohsiung University of Science and Technology.

Lee, TF; Chiu, CF; Kuan, YS; Hsieh, YW; Wu, YA; Wang, CC; Cheng, CY; Hu, YC; Lin, YW; Chao, PJ.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 5 January 2026 and was last updated on 5 January 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review and meta-analysis is to evaluate the oncological outcomes of different radiotherapy strategies in patients with early breast cancer. Specifically, among adult patients diagnosed with early-stage breast cancer (Population), this review aims to compare various radiotherapy approaches, including intraoperative radiotherapy (IORT) and external beam radiotherapy (EBRT) (Intervention), against alternative radiotherapy strategies or standard radiotherapy protocols (Comparator). Eligible studies will include randomized controlled trials and observational studies reporting long-term oncological outcomes (Study design). The primary outcomes of interest are overall survival and cancer-specific survival, while secondary outcomes include local recurrence, ipsilateral breast tumor recurrence, and other relevant recurrence-related endpoints, assessed over short- and long-term follow-up periods (Outcomes).The objective of this systematic review and meta-analysis is to evaluate the oncological outcomes of different radiotherapy strategies in patients with early breast cancer. Specifically, among adult patients diagnosed with early-stage breast cancer, this review aims to compare various radiotherapy approaches, including intraoperative radiotherapy (IORT) and external beam radiotherapy (EBRT), against alternative radiotherapy strategies or standard radiotherapy protocols. Eligible studies will include randomized controlled trials and observational studies reporting long-term oncological outcomes. The primary outcomes of interest are overall survival and cancer-specific survival, while secondary outcomes include local recurrence, ipsilateral breast tumor recurrence, and other recurrence-related endpoints, assessed over short- and long-term follow-up periods.

Condition being studied Early breast cancer refers to breast carcinoma diagnosed at an early stage, typically confined to the breast with or without limited regional lymph node involvement and without evidence of distant metastasis. Patients with early breast cancer are commonly

treated with breast-conserving surgery or mastectomy, followed by adjuvant radiotherapy to reduce the risk of local recurrence and improve long-term survival. Various radiotherapy strategies, including external beam radiotherapy and intraoperative radiotherapy, have been developed to optimize oncological outcomes while minimizing treatment-related toxicity and burden. Given the increasing use of different radiotherapy approaches in clinical practice, understanding their comparative effectiveness in terms of survival and recurrence outcomes is essential for evidence-based treatment planning in early breast cancer.

METHODS

Participant or population The population addressed in this systematic review consists of adult patients diagnosed with early-stage breast cancer. Eligible participants include patients with histologically confirmed breast carcinoma, such as ductal carcinoma or lobular carcinoma, who were treated in the early stages of the disease without evidence of distant metastasis at diagnosis. Studies enrolling patients undergoing breast-conserving surgery or mastectomy followed by adjuvant radiotherapy were considered. The review focuses on patients receiving radiotherapy as part of their primary treatment, including those treated with intraoperative radiotherapy or external beam radiotherapy. No restrictions are imposed on patient age, hormone receptor status, or lymph node involvement, provided the study population is clearly defined as early breast cancer and relevant oncological outcomes are reported.

Intervention The interventions evaluated in this systematic review include different radiotherapy strategies administered to patients with early breast cancer as part of their primary or adjuvant treatment. The main intervention of interest is intraoperative radiotherapy (IORT), defined as the delivery of a single fraction of radiation to the tumor bed during surgery. Various IORT techniques are considered eligible, including electron-based and X-ray–based intraoperative radiotherapy, as well as targeted intraoperative radiotherapy approaches. Studies in which IORT was delivered as the sole radiotherapy modality or as a component of accelerated partial breast irradiation are included. The review aims to assess the oncological outcomes associated with these radiotherapy strategies in comparison with alternative radiotherapy approaches.

Comparator The comparator in this systematic review consists of conventional external beam radiotherapy (EBRT) administered to patients with early breast cancer as part of standard postoperative or adjuvant treatment. Eligible comparator interventions include whole-breast irradiation or other forms of external beam radiotherapy delivered using conventional or advanced techniques, such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or volumetric modulated arc therapy. Studies in which EBRT was delivered according to standard fractionation or hypofractionated schedules are considered eligible. The review compares oncological outcomes between patients treated with intraoperative radiotherapy–based strategies and those receiving EBRT as the primary radiotherapy approach.

Study designs to be included This systematic review and meta-analysis will include randomized controlled trials, cohort studies, and case–control studies that evaluate oncological outcomes of different radiotherapy strategies in patients with early breast cancer. Only original clinical studies reporting comparative data between radiotherapy approaches and providing extractable survival or recurrence outcomes will be considered eligible.

Eligibility criteria In addition to the eligibility criteria defined in the PICOS framework, studies must meet the following criteria to be included in this review. Eligible studies are required to report at least one relevant oncological outcome, such as overall survival, cancer-specific survival, or recurrence-related endpoints, with sufficient statistical information to allow data extraction or synthesis. Studies with incomplete reporting of individual patient data may still be included if time-to-event information is available in the form of Kaplan–Meier survival curves, enabling reconstruction of individual patient data using established methods. A minimum follow-up duration of at least three years is required to ensure assessment of long-term oncological outcomes. Full-text articles published in peer-reviewed journals must be available.

Studies will be excluded if they do not report relevant survival or recurrence outcomes, lack extractable quantitative data even after Kaplan–Meier–based reconstruction, or involve overlapping or duplicate patient populations. Non-original studies, including review articles, meta-analyses, conference abstracts, editorials, and case reports, will be excluded. Studies focusing on populations other than early breast cancer or evaluating radiotherapy strategies outside the scope of this review will also be excluded.

Information sources A comprehensive literature search will be conducted using multiple electronic databases to identify relevant studies. The primary information sources will include PubMed, Web of Science, Embase, Scopus, and the Cochrane Library. These databases will be searched for studies published within the predefined time frame relevant to the review question. Reference lists of eligible articles and relevant reviews will also be manually screened to identify additional studies that may not have been captured through the electronic database search.

When necessary, corresponding authors of eligible studies may be contacted to clarify study details or obtain additional information required for data extraction. No formal trial registries or grey literature databases will be systematically searched. Only full-text articles published in peer-reviewed journals will be considered for inclusion.

Main outcome(s) The primary outcomes of this systematic review and meta-analysis are long-term oncological outcomes in patients with early breast cancer receiving different radiotherapy strategies. The main outcome measures include overall survival (OS) and cancer-specific survival, including breast cancer–specific survival (BCSS) or cancer-specific survival (CSS), as reported in the original studies. Survival outcomes will be assessed at multiple clinically relevant time points, including 5-year, 10-year, and, when available, 15-year follow-up.

Time-to-event outcomes will primarily be synthesized using hazard ratios (HRs) with corresponding 95% confidence intervals. When HRs are not directly reported, they will be estimated from published Kaplan–Meier curves using established reconstruction methods. For studies reporting dichotomous survival outcomes at fixed time points, risk ratios (RRs) will be calculated and synthesized as appropriate.

These primary outcomes are selected to reflect both overall mortality and cancer-related mortality, providing a comprehensive assessment of the long-term effectiveness of different radiotherapy strategies in early breast cancer.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included studies will be assessed using validated tools appropriate to each study design. Randomized controlled trials will be evaluated using the Cochrane Risk of Bias tool (ROB 2.0), which assesses bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Observational studies, including cohort and case–control studies, will be assessed using the Newcastle–Ottawa Scale (NOS), which evaluates study quality based on selection of participants, comparability of study groups, and ascertainment of outcomes or exposures.

Quality assessment will be performed independently by two reviewers, with discrepancies resolved through discussion or consultation with a third reviewer when necessary. The results of the risk-of-bias assessment will be summarized descriptively and considered in the interpretation of the pooled findings.

Strategy of data synthesis Quantitative data synthesis will be performed when sufficient clinically and methodologically comparable studies are available. Time-to-event outcomes, including overall survival and cancer-specific survival, will be primarily synthesized using hazard ratios (HRs) with corresponding 95% confidence intervals. When HRs are not directly reported, they will be estimated from published Kaplan–Meier survival curves through reconstruction of individual patient data using established methods. For dichotomous outcomes reported at specific time points, risk ratios (RRs) with 95% confidence intervals will be calculated.

Pooled effect estimates will be calculated using random-effects models to account for between-study heterogeneity. Statistical heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. When appropriate, fixed-effect models may be applied for sensitivity analyses. Forest plots will be generated to visualize pooled estimates, and funnel plots will be used to explore potential publication bias when a sufficient number of studies are available.

All statistical analyses will be conducted using standard meta-analytic software, and results will be presented in accordance with established guidelines for systematic reviews and meta-analyses.

Subgroup analysis When sufficient data are available, subgroup analyses will be conducted to explore potential sources of heterogeneity and to assess whether oncological outcomes differ across clinically relevant subgroups. Planned subgroup analyses include stratification by study design (randomized controlled trials versus observational studies), radiotherapy strategy (different intraoperative radiotherapy techniques versus

external beam radiotherapy), and length of follow-up. Additional subgroup analyses may be performed based on patient or tumor characteristics reported consistently across studies, such as tumor stage or nodal status.

Subgroup-specific pooled estimates will be calculated using the same analytical approach as the primary analysis, and differences between subgroups will be interpreted cautiously, considering potential confounding and limited statistical power. Subgroup analyses will be considered exploratory in nature and will be used to generate hypotheses rather than to draw definitive conclusions.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness of the primary findings. These analyses will include repeating the meta-analyses after sequential exclusion of individual studies to evaluate the influence of any single study on the pooled estimates. Additional sensitivity analyses will be conducted by restricting the analyses to studies with higher methodological quality, as assessed by established risk-of-bias tools, and by excluding studies with potential overlap in patient populations.

Further sensitivity analyses may be conducted by applying alternative statistical models, such as fixed-effect models, and by excluding studies in which effect estimates were derived from reconstructed individual patient data based on Kaplan–Meier curves. The consistency of results across these sensitivity analyses will be examined to determine the stability of the findings and to identify potential sources of heterogeneity.

Country(ies) involved The study is being conducted by authors affiliated with institutions in Taiwan, with potential inclusion of published studies from multiple countries as part of the systematic review.

Keywords Early breast cancer; radiotherapy; intraoperative radiotherapy; external beam radiotherapy; meta-analysis; survival outcomes.

Dissemination plans The findings of this review will be disseminated through publication in a peer-reviewed journal.

Contributions of each author

Author 1 - Tsair-Fwu Lee.
Email: tflee@nkust.edu.tw
Author 2 - Chiu-Feng Chiu.
Author 3 - Ya-Shin Kuan.
Author 4 - Yang-Wei Hsieh.
Author 5 - Yi-An Wu.
Author 6 - Chen-Cheng Wang.
Author 7 - Chih-Yu Cheng.
Author 8 - Yu-Chang Hu.
Author 9 - Yu-Wei Lin.
Author 10 - Pei-Ju Chao.