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## Original Article

# The Effect of Waiting Times for Postoperative Radiotherapy on Outcomes for Women Receiving Partial Mastectomy for Breast Cancer: a Systematic Review and Meta-Analysis<sup>☆</sup>

S. Gupta<sup>\*†</sup>, W.D. King<sup>‡</sup>, M. Korzeniowski<sup>§</sup>, D.L. Wallace<sup>\*</sup>, W.J. Mackillop<sup>\*‡§</sup><sup>\*</sup> Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Kingston, Ontario, Canada<sup>†</sup> Department of Medicine, University of Toronto, Toronto, Ontario, Canada<sup>‡</sup> Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada<sup>§</sup> Department of Oncology, Queen's University, Kingston, Ontario, Canada

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## Abstract

**Aims:** To determine the effect of delay in postoperative radiotherapy on local recurrence and overall survival in women receiving partial mastectomy for breast cancer.

**Materials and methods:** This was a systematic review and meta-analysis of published literature. Relevant reports were identified from MEDLINE, EMBASE and the Cochrane Register of Controlled Trials in all languages from 1975 to April 2015, in addition to the abstracts from the annual meetings of major radiotherapy conferences from 2000 to 2011. Reference lists were hand searched to find additional relevant reports and OvidSP's 'Find Citing' function was used to find studies citing papers identified in the primary search. Studies were included if they met the following criteria: (i) all patients received partial mastectomy and radiotherapy, (ii) a delay from surgery to radiotherapy was reported and (iii) one or more of local control/failure and/or survival were reported. Observational studies and randomised controlled trials were included. Studies including patients with *in situ* disease were excluded. Studies were classified as high quality if they adequately controlled for factors known to be associated with the outcomes of interest. Study quality was independently assessed by three authors. Initial disagreements about three studies were resolved by consensus. Only high-quality studies were included in the primary analysis. Delay was modelled as a continuous variable and the relative risk of local recurrence and the relative risk of death are reported per month of delay. The study results were combined using a fixed-effects model.

**Results:** Thirty-four relevant publications including 79 616 patients were identified in the systematic review. Ten high-quality publications reported on local recurrence (13 291 patients) and four high-quality studies reported on overall survival (2207 patients). The relative risk of local recurrence per month of delay was 1.08 (95% confidence interval 1.02–1.14). The relative risk of death per month of delay was 0.99 (95% confidence interval 0.94–1.05).

**Conclusions:** Delays in post-lumpectomy radiotherapy are associated with a significant increase in the risk of local recurrence. We recommend that waiting times for radiotherapy should be kept as short as reasonably achievable.

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**Key words:** Breast cancer; radiotherapy; waiting times

## Introduction

Breast cancer is one of the most common malignancies in the UK and around the world, with most cases detected at an early stage [1]. Multiple randomised trials and meta-analyses have shown that breast conservation therapy (BCT), consisting of partial mastectomy followed by post-operative radiotherapy, provides long-term survival equivalent to that of total mastectomy in women with early breast cancer [2]. Although mastectomy alone remains an

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Author for correspondence: W.J. Mackillop, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, 10 Stuart Street, Level 2, Kingston, Ontario K7L 3N6, Canada. Tel: +1-613-533-6000x78509; Fax: +1-613-533-6794.

E-mail address: [william.mackillop@krcc.on.ca](mailto:william.mackillop@krcc.on.ca) (W.J. Mackillop).

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option, BCT is now used in the management of most patients with stage I and II breast cancer [3].

The clinical trials that originally showed the efficacy of BCT stipulated a maximum interval of 8 weeks between surgery and the start of postoperative radiotherapy, and there is therefore no level 1 evidence that radiotherapy is effective unless it is started within those timelines. In routine practice, however, patients with breast cancer often wait longer than this to start radiotherapy [4]. Concerted efforts to reduce waiting times for radiation have been made in the UK since the publication in 1998 of a national audit showing that 28% of all patients, and 39% of women receiving BCT, were starting treatment later than recommended in consensus guidelines [5]. The Cancer Reform Strategy of 2007 subsequently set a target of 31 days after a patient is 'fit to treat' postoperatively as the maximum acceptable delay for radiation, which would typically be 7–8 weeks from surgery [6]. However, a 2012 audit of screen-detected breast cancers in the UK showed that only 57% of women started radiation treatment within 60 days, which is well short of the mark [7].

There are strong radiobiological reasons to suspect that a delay in starting radiotherapy may decrease the probability of local control, and that long waiting lists for radiotherapy may compromise clinical outcomes [8,9]. For ethical reasons, the effects of a delay in radiotherapy have not been studied directly in randomised trials [9], and observational studies therefore represent the only source of clinical information about the effect of a delay in radiotherapy on outcomes. Over the last 30 years, widespread waiting lists, caused by a shortage of treatment resources, have provided many institutions with the opportunity to compare outcomes among groups of patients who have waited longer or shorter times to start radiotherapy. A large number of publications have described the effects of a delay in radiotherapy in different clinical situations [10]. Many of these focussed on patients with breast cancer because, in times when radiotherapy has been in short supply, this group of patients has often been exposed to particularly long delays [11,12]. However, many of the individual studies that have compared outcomes in patients who waited a longer or shorter time for radiotherapy have had insufficient statistical power to detect the relatively small effects that would be predicted based on radiobiological models [8–10]. In this type of situation, a meta-analysis may be useful in distilling the results of collective clinical experience [10].

A previous meta-analysis of studies of delay in postoperative radiotherapy for breast cancer published in 2008 showed a small but significant association between waiting time for radiotherapy and the risk of local recurrence [10]. At that time, the relative risk of local recurrence was reported as 1.11 (95% confidence interval 1.04–1.19) per month of delay, but more recently published individual studies have not shown a statistically significant increase in the risk of local recurrence with delays of up to 16 weeks in the initiation of post-lumpectomy radiotherapy [13,14]. The issue of whether a delay in radiotherapy is harmful in this situation has therefore remained controversial. Long waits for radiotherapy for breast cancer have caused great public concern in some jurisdictions. In Canada this culminated in a class-action

lawsuit in the province of Quebec on behalf of women who waited longer than 8 weeks for treatment [15]. The lawsuit was eventually settled out-of-court for \$5.4 million (Canadian) for those who waited longer than 12 weeks [16]. We are not aware of any similar lawsuits against the providers of radiotherapy in the UK, but delays in cancer treatment are a matter of great public concern and there are frequent news reports of failure to meet the UK's waiting time targets [17]. The policy implications of even a modest decrease in the effectiveness of BCT with longer waiting times might be very important due to the high societal burden of breast cancer.

Given the ongoing controversy regarding the effect of a delay on the effectiveness of post-lumpectomy radiotherapy, the potentially important policy implications of this issue and the publication of additional relevant information since the last meta-analysis, we carried out an updated systematic review of the literature and synthesised the currently available evidence linking waiting times for radiotherapy to outcomes in women with breast cancer undergoing BCT. Our primary objective was to determine the relationship between waiting time for radiotherapy and the risk of local recurrence.

## Materials and Methods

### Search Strategy

We used OvidSP to search the indexed MEDLINE and EMBASE databases and the Cochrane Register of Controlled Trials from 1975 to April 2015 with the key words and Medical Subject Headings (MeSH) listed in Table 1. The literature search was conducted by one investigator (SG). Relevant studies citing papers from the primary search were identified using OvidSP's 'Find Citing' function. Further relevant reports were identified by searching the reference lists of the papers identified in the primary search. Studies published in abstract form at the annual meetings of the Canadian Association of Radiation Oncology, American Society for Radiation Oncology and European Society of Therapeutic Radiology and Oncology from 2000 to 2011 were also included. Foreign language publications were included if sufficient clinical information was provided in a translated abstract.

### Inclusion Criteria

Studies were included if they met the following criteria: (i) all patients received partial mastectomy and radiotherapy, (ii) a delay from surgery to radiotherapy was reported and (iii) one or more of local control/failure and/or survival were reported. Studies including patients with *in situ* disease were excluded from the analysis. When some or all of the patients included in one publication were also included in another publication, the following principles were used to decide which report(s) to include in the analysis. More recent reports of the same case series from the same institution were preferred. However, where there was only a minor degree of overlap between the study populations in two separate publications, we included both

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