

Systematic Review

# Side Effects Associated with the Use of Intensity-Modulated Radiation Therapy in Breast Cancer Patients Undergoing Adjuvant Radiation Therapy: A Systematic Review and Meta-Analysis

Katherine E. Jensen, MRT(T), BA, MSc (candidate)<sup>ab\*</sup>, Lesley J.J. Soril, MSc<sup>a</sup>,  
Henry T. Stelfox, MD, PhD<sup>ac</sup>, Fiona M. Clement, PhD<sup>a</sup>, Yongtao Lin, MLIS<sup>d</sup> and  
Deborah A. Marshall, PhD<sup>a</sup>

<sup>a</sup> Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>b</sup> Department of Radiation Oncology, Central Alberta Cancer Center, Alberta Health Services, Red Deer, Alberta, Canada

<sup>c</sup> Department of Critical Care Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>d</sup> Tom Baker Cancer Centre, Alberta Health Services, Calgary, Alberta, Canada

## ABSTRACT

**Purpose:** The purpose of the study was to establish the efficacy and safety of breast intensity-modulated radiation therapy (IMRT) compared with non-IMRT standard wedge radiation therapy (RT) for the treatment of adjuvant breast cancer.

**Methods:** A systematic review and meta-analysis were completed using STATA and a random effects model. A total of 1,499 citations were identified from the literature search. Of those, 1,475 were excluded based on abstract review. Full texts of 24 remaining articles were reviewed and 11 articles were included in the final analysis. Side effects were analysed as the primary outcomes of interest. We calculated individual odds ratios and 95% confidence intervals for 17 classifications of side effects reported. The data for eight classifications of side effects were then pooled for meta-analyses to obtain more precise estimates of the relationships between adjuvant RT and a particular side effect.

**Results:** The pooled analyses revealed potential protective associations between adjuvant IMRT and two acute side effects: dermatitis and moist desquamation. The remaining pooled estimates suggest that the odds of developing edema, hyperpigmentation, fat necrosis, pain, induration were no worse, nor better among those treated with IMRT compared with those treated with non-IMRT standard wedge RT.

**Conclusion:** The pooled estimates from this meta-analysis are in line with the existing evidence. When the outcome of interest is reduction of the acute side effects: dermatitis and moist desquamation IMRT is a viable treatment option for women undergoing external beam RT after breast-conserving surgery.

## RÉSUMÉ

**But :** Les auteurs souhaitent établir l'efficacité et la sécurité de la radiothérapie conformationnelle avec modulation d'intensité (RCMI) en comparaison de la radiothérapie (RT) non RCMI standard avec filtre en coin pour le traitement du cancer du sein avec adjuvant.

**Méthodologie :** Un examen systématique et une méta-analyse ont été effectuées à l'aide de STATA et d'un modèle d'effets aléatoires. Au total, 1 499 citations ont été recensées dans la recherche documentaire. De celles-ci, 1 475 ont été exclues à partir de l'examen du résumé. Le texte complet des 24 articles restants a été examiné et 11 articles ont été retenus pour l'analyse finale. Les effets secondaires ont été analysés comme résultat d'intérêt primaire. Nous avons calculé le rapport de cotes (odds ratio-OR) et l'intervalle de confiance à 95% (IC 95%) pour 17 classifications d'effets secondaires signalés. Les données pour huit des classifications d'effets secondaire ont ensuite été regroupées pour la méta-analyse afin d'obtenir une estimation plus précise du lien entre la radiothérapie adjuvante et un effet secondaire en particulier.

**Résultats :** Les analyses regroupées révèlent des associations protectives potentielles entre la RCMI adjuvante et deux effets secondaires aigus, la dermatite et la desquamation humide. Les estimations regroupées restantes suggèrent que les chances de développer de l'œdème, l'hyperpigmentation, la stéatonecrose, la douleur ou l'induration n'étaient pas plus élevées chez les patients traités par RCMI en comparaison de celles traitées par RT non RCMI standard avec filtre en coin.

\* Corresponding author: Katherine E. Jensen, MRT (T), BA, MSc (candidate), Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, and Central Alberta Cancer Centre, Department of Radiation Oncology, 3942-50a Avenue, Red Deer, Alberta T4N 4E7, Canada.

E-mail address: [katherine.jensen@ahs.ca](mailto:katherine.jensen@ahs.ca) (K.E. Jensen).

**Conclusion :** Les estimations regroupées de notre méta analyse correspondent aux données probantes existantes. Lorsque le résultat d'intérêt est à réduction des effets secondaires aigus: dermatite et desquamation

humide, la RCMI est une option de traitement viable pour les femmes qui reçoivent une radiothérapie à faisceau externe après une chirurgie conservatrice du sein.

*Keywords:* IMRT breast; standard wedge breast radiotherapy; breast cancer; side effects

## Introduction

Postoperative radiation therapy (RT) is one of the standard adjuvant treatments used in the prevention of locoregional primary breast cancer failure after lumpectomy or mastectomy [1]. As such, postoperative or adjuvant RT is highly effective at decreasing local breast cancer recurrence and facilitating overall increases in patient survival rates [2]. However, adjuvant RT is also known to induce acute, delayed, and often permanent side effects to the breast tissue and surrounding organs [3–9].

Intensity-modulated radiation therapy (IMRT) improves dose homogeneity by decreasing hot spots and dose to normal tissues and provides intensity-modulated beams that may be adjusted to various levels for a given source position and beam direction [9, 10]. Thus, IMRT is reported to provide superior radiation distributions compared with non-IMRT standard wedge RT [9]. The advantage of breast IMRT over non-IMRT standard wedge RT is suggested to be the reduced frequency and severity of invoked side effects [3, 9]. At the time this research was undertaken, the authors were not aware of any previously published results that provide pooled estimates for the association between breast IMRT and reported side effects compared with non-IMRT standard wedge RT [9]. The authors believe that this dearth of synthesized evidence may be an important obstacle limiting widespread adoption of IMRT technology for the adjuvant treatment of early stage breast cancer after breast-conserving surgery [11].

Therefore, the objective of this study was to conduct a systematic review and meta-analysis of the current literature on the use of IMRT for adjuvant RT for early stage breast cancer patients to determine both the safety and clinical effectiveness of IMRT, in comparison to non-IMRT wedge RT. The authors' intention was to summarize the evidence so that policy makers can better judge the risk, benefits, and associated harms of breast IMRT vs. non-IMRT standard wedge RT.

## Methods

### *Search Strategy*

The study was conducted according to the prespecified protocol that was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the proposal for reporting Meta-analysis of Observational Studies in Epidemiology [12, 13]. The search strategy was developed in consultation with an information scientist. MEDLINE, PubMed, EMBASE, the Cochrane Central Registry of Controlled Trials, the Cumulative Index to Nursing and Allied Health, the Cochrane Database of Systematic Reviews, and the Health Technology Assessment

Database were searched up to and including the date of October 30, 2013. An updated search was conducted to include publication dates to February 2015. The terms “breast neoplasm\*,” “breast cancer\*,” “breast carcinoma\*,” “breast tumor\*, tumour\*” were combined using the Boolean operator “And” with the terms “radiotherapy, intensity-modulated,” “radiotherapy,” and “intensity-modulated therapy.”

The reference lists of pertinent systematic reviews and evidence synthesis publications were handsearched to identify other relevant articles that may not have been identified from the original search. Clinical trials registries were searched to identify ongoing or unpublished trials.

The numerous side effects reported among the included studies were identified by physician assessment and graded based on either the National Cancer Institute (NCI) Common Terminology Criteria for adverse events (NCI CTCAE v3.0), or the Radiation Therapy Oncology Group scale [14]. Pooled analyses were based on side effects that were most frequently reported by studies.

### *Selection of Literature*

All abstracts were screened in duplicate and reviewed independently. Abstracts proceeded to full-text review if they were available in the English language, reported original data, included postsurgical  $\geq 18$  years of age breast cancer patients (Stages I–IV) receiving adjuvant radiotherapy, and reported IMRT as the intervention non-IMRT standard wedge RT as the comparator. Abstracts were excluded if they did not meet the previously mentioned criteria. Abstracts selected for inclusion by either reviewer proceeded to the full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review by two reviewers. The reviewers included only randomized controlled trials (RCTs), quasi-experimental studies, and cohort (retrospective or prospective) studies making every effort to restrict this review to studies of higher quality evidence based on their design. Any disagreement between reviewers was resolved through discussion and consensus a kappa statistic was calculated to determine reviewer agreement.

### *Data Extraction*

The data were extracted in duplicate using standardized data extractions forms based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist standards for reporting systematic reviews and meta-analyses [12]. For all studies, details of the IMRT and standard tangential

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