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Review

Impact of tumour bed boost integration on acute and late toxicity in patients with breast cancer: A systematic review

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ABSTRACT

The purpose of this systematic review was to summarise the evidence from studies investigating the integration of tumour bed boosts into whole breast irradiation for patients with Stage 0-III breast cancer, with a focus on its impact on acute and late toxicities. A comprehensive systematic electronic search through the Ovid MEDLINE, EMBASE and PubMed databases from January 2000 to January 2015 was conducted. Studies were considered eligible if they investigated the efficacy of hypo- or normofractionated whole breast irradiation with the inclusion of a daily concurrent boost. The primary outcomes of interest were the degree of observed acute and late toxicity following radiotherapy treatment. Methodological quality assessment was performed on all included studies using either the Newcastle–Ottawa Scale or a previously published investigator-derived quality instrument. The search identified 35 articles, of which 17 satisfied our eligibility criteria. Thirteen and eleven studies reported on acute and late toxicities respectively. Grade 3 acute skin toxicity ranged from 1 to 7% whilst moderate to severe fibrosis and telangiectasia were both limited to 9%. Reported toxicity profiles were comparable to historical data at similar time-points. Studies investigating the delivery of concurrent boosts with whole breast radiotherapy courses report safe short to medium-term toxicity profiles and cosmesis rates. Whilst the quality of evidence and length of follow-up supporting these findings is low, sufficient evidence has been generated to consider concurrent boost techniques as an alternative to conventional sequential techniques.

Introduction

Breast cancer is the most common cancer to affect women and the third most commonly diagnosed cancer in Australia [1]. For patients diagnosed with breast cancer, whole breast irradiation (WBI) following local excision of the primary tumour (lumpectomy) is a fundamental part of contemporary multimodality management of breast cancer. This approach, known as breast-conserving therapy (BCT) has shown optimal loco-regional control and equivalent overall and disease-free survival compared to mastectomy alone in early breast cancer [2].

Standard protocol for radiotherapy after breast-conserving surgery (BCS) involves irradiation of the whole breast to 45–50 Gy, often with the addition of a boost dose to the tumour bed of

Abbreviations: WBI, whole breast irradiation; BCS, breast-conserving surgery; BCT, breast-conserving therapy; CB, concurrent boost; RCT, randomised-controlled trial; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; CER, comparative effective research.

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10–16 Gy [3–6]. Whilst the addition of further dose to the tumour bed after WBI has been shown to reduce local failure rates in the range of 20–50% [7], its addition is also associated with negative effects on acute and late toxicities, cosmesis and quality of life [8].

With improvements in radiotherapy planning and treatment technologies, there has been an increase in studies investigating the effect of the integration of the boost dose into the WBI schedule over the last 15 years [9]. Employment of concurrent boost strategies significantly reduce treatment course length and hence are associated with improved patient compliance, quality of life, lowered patient-related costs and increased utilisation of BCT [10,11]. Tumour bed boost integration is also theorised to improve disease control due to the overall increased dose per fraction to the tumour bed. Furthermore, advanced planning and treatment techniques may also reduce acute and long-term radiation sequelae [12].

Despite the evidence suggesting that the use of radiotherapy treatment courses with a concurrent boost has significant clinical benefits, its utilisation amongst various institutions has been less promising [9,13]. Reasons for the lack of uptake have primarily been due to the absence of supporting Level I-II evidence with long-term follow up data [14]. More so, there has been no systematic review (SR) to date that has summarised the overall safety and effectiveness of SIB for the practicing clinician. Therefore, the current study aimed to review all available data focussing on the impact of concurrent boost regimes on clinical outcomes such as toxicity and cosmesis in patients with breast cancer managed with adjuvant radiotherapy.

Materials and methods

Data sources and search strategy

This SR was performed in accordance with the PRISMA guidelines [15]. A structured literature search was performed in Ovid MEDLINE, Ovid EMBASE and PubMed from January 2000 to January 2015 using a series of key words: 'breast tumour', 'breast cancer', 'breast disease', and 'intensity-modulated radiation therapy', 'computer-assisted radiotherapy', and 'simultaneous or concomitant boost therapy'. The selected time frame was chosen to take into account the development and clinical utility of concomitant and simultaneous-integrated boosts. In addition to the automated search strategies, reference lists of related journal articles, key journals, and existing reviews were hand searched for additional studies. No attempt was made to locate unpublished material or to contact authors of unpublished studies.

Study selection criteria and procedures

All published randomised and non-randomised studies involving adult women with breast cancer who underwent BCS and adjuvant RT with a daily concurrent boost were included. Women with distant metastases, previous history of invasive cancer, previous radiotherapy, patients receiving accelerated partial breast radiotherapy, concurrent chemotherapy or those that received treatment without the use of CT data to define target volumes were excluded. In addition, the authors excluded studies that were non-English, not available in full-text or unpublished, narrative or systematic reviews, clinical practice guidelines or commentaries.

The studies retrieved by the initial search underwent a scanned process by a single review author (DH) to exclude irrelevant studies. Two authors (DH; JW) then screened titles and abstracts against the inclusion criteria. Full-text articles were retrieved and reviewed independently in duplicate by the primary author (DH) and another member of the authorship team (RB; CJ; EF; KK) for the purpose of applying inclusion criteria. In all instances, differences of opinion were resolved by discussion among the authors. In the case of multiple reports on the same patient cohort and endpoint/s, only the latest publication was included.

Multiple review authors (DH, RB, CJ, EF, KK) extracted data independently and in duplicate using standardised forms. The standardised forms allowed for the extraction of specific data such as study design, patient demographics, intervention characteristics, and primary and secondary outcomes. Discrepancies were resolved by discussion amongst the authorship team.

Methodological quality

Methodological study quality was assessed using pre-defined criteria (Supplement 1). Cohort studies were evaluated using the Newcastle–Ottawa Scale (NOS), with seven relatable items being identified [16]. Cohort studies assigned 7–8, 5–6, 4 and 0–3 were considered as "very good", "good", "satisfactory" or "unsatisfactory" respectively. Other study designs (e.g. case series) were assessed using a series of criteria described by Chambers et al. [17]. Case series were considered "good", if the study met all criteria, or "satisfactory" or "poor", depending whether the study of interest fulfilled criteria 2, 4, 5, 6 and 7. Two authors (DH; JW) independently reviewed and assessed the methodological quality of the studies in duplicate, with any disagreements resolved by discussion until a consensus was achieved.

Study outcomes and data synthesis

Primary outcomes of interest were acute skin toxicity assessed within 12 weeks following radiation treatment, and late toxicity (induration-fibrosis and telangiectasia) assessed at least 90 days after radiotherapy treatment. Secondary outcomes included long-term cosmesis. To make cosmetic outcomes more comparable across various scales, categories were dichotomised [18,19]. Biologically equivalent doses were also calculated for each fractionation schedule using currently accepted α/β ratios, with no correction for overall treatment time length [20].

Statistical analysis

All data were managed and analysed using Microsoft Excel with summative data presented for categorical variables. Due to the heterogeneity of the included studies, the absence of randomised controlled trials, and inconsistent outcome reporting measures, pooling of the studies in the form of meta-analysis was not possible. Therefore, a narrative approach was adopted in order to synthesise the findings of the included studies.

Results

Results of the search

The initial search strategy identified a total of 2933 studies for potential inclusion. Independent scrutiny of the titles and abstracts identified 35 potentially relevant articles. After applying the selection criteria, 18 studies were excluded for the following reasons: patients having undergone mastectomy [21], patients not receiving a daily concurrent boost [22–26], insufficient reporting of patient characteristics or outcomes of interest [12,27], the absence of CT data to define boost planning target volumes [28,29], combined integrated and sequential boost regimes on the same cohort [30], reported on the same populations as later studies [31–34], did not report on the primary outcomes of interest [35,36] or were inaccessible [37]. Therefore, a total of 17 studies formed the basis of this review [3,4,10,11,38–50]. See Fig. 1 for the PRISMA study flow diagram.