

Review article

CORRESPONDENCE

# Utility of synchronous chemo radiotherapy as a viable alternative to sequential chemotherapy and radiotherapy (RT) after breast conserving surgery (BCS)

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## ABSTRACT

Breast cancer (Ca) is a very common cancer and an important reason for malignancy associated deaths around the globe. Treatment typically includes different sequencing and combinations of surgery, radiation therapy (RT) and systemic treatments. Selecting optimal surgical modality for a given patient takes into account several considerations such as patient and tumor characteristics, logistical issues, thorough assessment of expected treatment outcomes with incorporation of various treatment combinations, and patient preferences. From a scientific standpoint, accumulating evidence has demonstrated comparable efficacy of both surgical modalities. While BCS may be increasingly utilized for breast Ca therapy, it may not be adequate for achieving optimal treatment outcomes if used as the sole treatment modality for management. There is accumulating data suggesting a role for RT after BCS to achieve improved treatment outcomes with its incorporation as adjunct therapy. Chemotherapy and RT are delivered in a sequential fashion typically, nevertheless, optimal sequencing of these modalities has been the focus of active investigation. Synchronous use of adjuvant systemic treatment with RT after BCS allows for shortened treatment time without any delay in use of both modalities, and may exploit the biological interplay of both modalities to achieve a potentially greater anti-tumoral effect than that could be achieved by their sequential administration through different mechanisms such as radio sensitization. Vigilance is required for toxicity monitoring during the course of synchronous treatment, nevertheless, contemporary technologies including adaptive RT and breathing adapted RT may improve the toxicity profile of management. Clearly, further investigation is needed to shed light on optimal sequencing of treatment modalities after BCS. Herein, we evaluate the utility of synchronous chemo radiotherapy as a viable alternative to sequential administration after BCS.

## INTRODUCTION

Breast cancer (Ca) is a very common cancer and an important reason for malignancy associated deaths around the globe. Management of breast Ca typically includes different sequencing and combinations of surgery, radiation therapy (RT) and systemic treatments. Surgery as the traditional treatment modality has a long history with evolving concepts and inclusion of operations with a wide spectrum of extents such as extensive radical mastectomies more than a century ago and contemporary skin sparing procedures in the more recent treatment era <sup>[1,2]</sup>. Selecting optimal surgical modality for a given patient takes into account several considerations such as patient and tumor characteristics, logistical issues, thorough assessment of expected treatment outcomes with incorporation of various

treatment combinations, and patient preferences. Breast conserving surgery (BCS) may be utilized instead of mastectomy with potential for improved cosmesis for selected patients, and has gained widespread acceptance and popularity. From a scientific standpoint, accumulating evidence has demonstrated comparable efficacy of both modalities <sup>[3-5]</sup>. Given the comparable outcomes with both modalities, BCS has even supplanted mastectomy in several centers despite utility of mastectomy with a substantiated role in breast Ca management supported by robust data. While BCS has been adopted as a more appealing modality taking into account the patient preferences typically favoring a remainder breast tissue of their own, it is always important to decide on management with a

multidisciplinary team of experts including surgical and clinical oncologists.

While BCS may be increasingly utilized for breast Ca therapy, it may not be adequate for achieving optimal treatment outcomes if used as the sole treatment modality for management. There is accumulating data suggesting a role for RT after BCS to achieve improved treatment outcomes with its incorporation as adjunct therapy [6-8]. Chemotherapy and RT are delivered in a sequential fashion typically; nevertheless, optimal sequencing of these modalities has been the focus of active investigation. Herein, we evaluate the utility of synchronous chemo radiotherapy as a viable alternative to sequential administration after BCS.

### **Literature review on synchronous chemo-radiotherapy as adjuvant treatment after BCS for breast Ca management**

Rationale of synchronous rather than sequential use of systemic treatment with RT may include shortened treatment duration, avoiding any delay in use of both chemotherapy and RT, and exploiting the biological interplay of both modalities to achieve a potentially greater anti-tumoral effect than that could be achieved by their sequential administration through different mechanisms such as radio sensitization.

A recent study assessed synchronous versus sequential chemo radiotherapy for early breast Ca management: The prospective open-label study included 48 United Kingdom centers with the randomization being stratified by center, axillary surgery, chemotherapy, and RT boost. The synchronous RT administration was performed either between the second and third cycles of the CMF regimen or between the fifth and sixth cycles of the anthracycline-CMF regimen. Local recurrence (LR) has been considered as the primary outcome. Baseline characteristics were balanced between the 2 treatment arms receiving RT doses of 40 Gy with hypo-fractionation or 50 Gy with conventional fractionation. Ten year LR rate was 4.6% in synchronous versus 7.1% in the sequential treatment arms at a median follow up duration of 10.2 years. Planned subgroup analysis of the anthracycline-CMF revealed the 10 year LR rates as 3.5% versus 6.7% favoring the synchronous treatment arm. While overall survival and disease free survival were comparable between the 2 treatment arms, dermatological toxicity was higher in the synchronous treatment arm as 24% compared to 15% in the sequential treatment arm. Late toxicity was comparable between the 2 groups except for telangiectasia. This very recent study provides high level and up to date evidence on a critical focus of investigation and suggests significantly decreased LR by use of synchronous chemo

radiotherapy rather than the typically utilized sequential administration [9].

A meta-analysis of adjuvant chemo radiotherapy versus standard chemotherapy followed by RT in operable breast Ca revealed significantly improved locoregional recurrence free survival with concurrent compared to utilization of systemic treatment with RT. No significant difference was found in 5 year overall survival or acute skin toxicity [10].

A study of concurrent chemo radiotherapy revealed that disease free survival after 5 years was 80.4% with concurrent chemo radiotherapy using anthracycline and RT, and 76.4% with concurrent chemo radiotherapy using CMF and RT. The authors concluded that anthracycline based concurrent chemo radiotherapy achieved superior results in adjuvant locoregional breast Ca management [11].

A study assessing concomitant adjuvant chemo radiotherapy with anthracycline based regimens in breast Ca reported that concomitant chemotherapy was not a significant factor in RT interruption [12].

Final results of the phase III ARCOSEIN trial demonstrated comparable 5 year disease free survival, locoregional recurrence free survival, metastasis free survival and overall survival in both treatment arms, however, concurrent chemo radiotherapy achieved superior 5 year locoregional recurrence free survival outcomes for the node positive subgroup of patients. The synchronous use of systemic treatment with RT was found to have potential for serving as an appealing therapeutic option for breast Ca patients with high risk of recurrence [13].

Concurrent chemotherapy and RT after BCS for stage I and stage II breast Ca was evaluated in a feasibility study, which revealed that this treatment approach was not associated with increased toxicity. The authors concluded that this concurrent treatment strategy could serve as a feasible management modality with shortened treatment time and reasonable cosmetic results [14].

Sequencing of RT and chemotherapy after BCS was assessed in a trial which revealed that concurrent administration of CMF chemotherapy and RT was safe [15].

### **CONCLUSIONS AND FUTURE PERSPECTIVES**

Synchronous use of systemic treatment with RT after BCS allows for shortened treatment time without any delay in use of both modalities, and may exploit the biological interplay of both modalities to achieve a potentially greater anti-tumoral effect than that could be achieved by their sequential administration through different mechanisms such as radio-sensitization.

Vigilance is required for toxicity monitoring during the course of synchronous treatment, nevertheless, contemporary technologies including adaptive RT and breathing adapted RT may improve the toxicity profile of management. Clearly, further investigation is needed to shed light on optimal sequencing of treatment modalities after BCS.

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