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Review Article

Evaluation of Additional Sequential Boost Radiotherapy (RT) After Whole Breast Irradiation (WBI) for Patients with Early Breast Cancer (Ca)

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Abstract

Breast cancer (Ca) comprises the most common cancer in females and constitutes a leading cause of cancer related deaths around the globe. Contemporary treatment protocols established by incorporation of accumulating high level evidence suggest multimodality therapy for patients suffering from breast Ca with combinations of surgery, radiotherapy (RT) and systemic treatment. Surgical options for management of breast cancer typically include breast conserving surgery (BCS) or mastectomy. In current treatment practice, BCS is used as a viable surgical modality for breast Ca management. RT after BCS has been widely adopted for management of the vast majority of patients with breast Ca particularly to achieve improved local control as suggested by collaborative group studies and metaanalyses. Although alternative dose-fractionation schemes may be considered for management of some patients, current widely accepted practice includes the use of conventionally fractionated RT after BCS for breast Ca. Whole breast irradiation (WBI) constitutes a widely recognized breast Ca RT approach which is typically used to deliver a total dose of 45 to 50 Gy over 5 to 6 weeks in daily fractions of 1.8 to 2 Gy. Hypofractionated RT schemes have also been widely accepted as a viable alternative to conventional fractionation with satisfactory treatment outcomes. A typical location for local recurrences of breast Ca includes the primary tumor site within the tumor bed or its vicinity, which justifies the delivery of additional boost dose focused on this area to improve local control rates particularly for patients with high-risk characteristics including younger age, large tumor size, higher grade, extensive intraductal component, close or positive surgical margins. Herein, we assess the utility of delivering an additional sequential boost RT after WBI for patients with early breast Ca in light of the literature.

Introduction

Breast cancer (Ca) comprises the most common cancer in females and constitutes a leading cause of cancer related deaths around the globe [1,2]. Contemporary treatment protocols established by incorporation of accumulating high level evidence suggest multimodality therapy for patients suffering from breast Ca with combinations of surgery, Radiotherapy (RT) and systemic treatment. Nevertheless, there remain controversies for certain conditions such as the role of postmastectomy RT for subgroups of patients with T3N0 tumors or T1-T2 tumors with 1 to 3 positive axillary lymph nodes, and for patients receiving neoadjuvant chemotherapy before mastectomy [3-9]. Another potential focus of consideration is the role of adjuvant RT for elderly patients deemed at lower risk of recurrence with respect to hormonal receptor status, axillary nodal status, tumor size, grade, lymphovascular invasion, and surgical margin status [10-12]. These considerations primarily stem from a motivation for omission of RT when there is no substantial benefit to improve the therapeutic ratio. Sparing of highly selected subgroups of patients from RT may have potential implications for improved

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quality of life due to elimination of radiation induced adverse effects. Also, cumulative costs of treatment may be reduced along with the RT facility workloads. Hypofractionated RT schemes have gained widespread popularity given the patient and treatment facility convenience along with shorter treatment courses offering satisfactory therapeutic outcomes. Herein, we focus on another critical aspect of multidisciplinary breast Ca management. We assess the utility of delivering an additional sequential boost RT after Whole Breast Irradiation (WBI) for patients with early breast Ca in light of the recent advances and existing literature.

Breast Conserving Surgery (BCS) as an alternative to mastectomy

Surgical options for management of breast cancer typically include BCS or mastectomy. Several factors may have a role in selection of either BCS or mastectomy for a given patient such as patient and treatment characteristics, considerations regarding cosmesis, adverse effects, tumor control and patient preferences. Regarding the outcomes of management with these 2 surgical modalities, BCS and mastectomy were found to achieve comparable efficacy as supported by high level evidence from randomized trials [13-15]. Also, there have been some other studies focusing on favorable aspects of management with BCS [16-18]. In current treatment practice, BCS is used as a viable surgical modality for breast Ca management.

Utilization of RT after BCS

There has been thorough consideration for omission of RT after BCS in selected subgoups of highly selected patients with favorable characteristics regarding the hormonal receptor status, axillary nodal status, tumor size, grade, lymphovascular invasion, and surgical margin status [10-12,19-21]. Nevertheless, RT after BCS has been widely adopted for management of the vast majority of patients with breast Ca particularly to achieve improved local control as suggested by collaborative group studies and metaanalyses [22-25].

Dose and fractionation for RT after BCS

Utility of Accelerated Partial Breast Irradiation (APBI) and hypofractionated RT schedules for breast Ca management has been investigated [26-33]. Although these alternative dose-fractionation schemes may be considered for management of some patients, current widely accepted practice includes the use of conventionally fractionated RT after BCS for breast Ca. Whole Breast Irradiation (WBI) constitutes a widely recognized breast Ca RT approach which is typically used to deliver a total dose of 45 to 50 Gy over 5 to 6 weeks in daily fractions of 1.8 to 2 Gy. Nevertheless, hypofractionated RT schemes have also been widely accepted as a viable alternative to conventional fractionation with satisfactory treatment outcomes and widespread adoption. Rationale of hypofractionation stems from the moderately low alpha/beta ratio of breast tumors together with other potential favorable features of hypofractionated regimens including patient and treatment facility convenience.

Role of an additional boost dose after WBI: review of evidence

A typical location for local recurrences of breast Ca includes the primary tumor site within the tumor bed or its vicinity, which justifies the delivery of additional boost dose focused on this area to improve local control rates particularly for patients with high-risk characteristics including younger age, large tumor size, higher grade, extensive intraductal component, close or positive surgical margins [34-52].

Results of a randomized French trial conducted between 1986 and 1992 including 1024 patients with early breast Ca revealed that an additional boost dose of 10 Gy delivered after WBI significantly reduced the risk of early local recurrence without serious deterioration in cosmetic outcomes [37].

European Organisation for Research and Treatment of Cancer (EORTC) has assessed the utility of delivering a 16 Gy boost dose directed at the tumor bed after WBI in a phase III randomized trial conducted between 1989 and 1996 [44]. Randomization of 5569 patients was achieved. The results at 20 year follow-up revealed that the risk of Ipsilateral Breast Tumor Recurrence (IBTR) was decreased by incorporation of the boost in management with the largest absolute benefit for younger patients [44,48].

A study focusing on a subgroup of the EORTC boost vs no boost trial by Jones et al. revealed that young age and high grade invasive ductal cancer were significant risk factors for local recurrence while margin status did not have significant influence [45]. The boost dose of 16 Gy had a significant effect on reduction of the negative influence of high grade invasive Ca and young age [45].

The recent Cochrane review of 5 randomize controlled trials suggested improved local control rates by use of an additional boost dose to the tumor bed with worsened cosmetic outcomes when assessed by a panel [50].

IBTR may serve as a predictor of prognosis for breast Ca. A study by Komoike et al. reported a correlation between IBTR and subsequent development of distant metastases for patients with early breast Ca [53].

From the opponent standpoint, unfavorable aspects of delivering an additional boost dose may include increased treatment cost and workload, fibrosis, and worse cosmetic results which may have a negative effect on patient satisfaction, psychology and quality of life [39,44,54-57].

In the recent American Society for Radiation Oncology (ASTRO) evidence based guideline, delivery of an additional boost dose to the tumor bed is suggested for patients ≤ 50 years of age with any grade Ca [58].

Recent advances and future perspectives

Recent years have witnessed substantial advances in radiation oncology including Image Guided Radiation Therapy (IGRT), Adaptive Radiation Therapy (ART), Intensity Modulated Radiation Therapy (IMRT) and Breathing Adapted Radiation Therapy (BART), with encouraging potential to further improve treatment outcomes [59-67]. In the context of systemic dissemination, radiosurgical applications in the

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forms of Stereotactic Radiosurgery (SRS), Hypofractionated Stereotactic Radiation Therapy (HFSRT), and Stereotactic Body Radiation Therapy (SBRT) offer safe and effective management of intracranial and extracranial dissemination [68-92].

Conclusion

There is growing body of evidence supporting the use of an additional boost dose to the tumor bed for patients receiving WBI after BCS. Rationale for delivery of the additional boost dose includes eradication of microscopic tumor cells located most likely at the tumor bed or in close vicinity to improve local control. A critical unfavorable aspect of additional boost dose may include impaired cosmesis, however, this may be partly accounted for by incorporation of contemporary RT rechniques with improved normal tissue sparing capability.

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