

Postmastectomy Hypo Fractionated Radiotherapy: May be a Breakthrough in Breast Cancer Management

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Abstract

Hypo fractionated schedules deliver greater than 2 Gy of radiation per fraction while reducing the total cumulative dose through reducing the number of treatment sessions. In breast cancer, radiotherapy is indicated for all patients after breast conservative surgery and for patients after mastectomy if indicated. Radio biologically, this approach appears to be as effective and safe as the conventional regimen in both experimental and clinical studies, based on the LQ model, when the α/β ratio of the tumor is similar to that of the surrounding normal tissue, the hypo fractionated regimen may be equally or potentially more effective than that of the conventional one. Conventional fractionated radiotherapy has been challenged by patient's compliance, travelling, unplanned interruption and others compared to hypo fractionated regimen which would be more appealing and convenient to the patients, and financially, this treatment schedule is useful in reducing the radiotherapy costs. It is thought that if these schedules found to have an equivalent loco regional control, survival and cosmesis to standard conventional schedules, it would be a revolutionary breakthrough in the future for breast cancer management as if these schedules are established, it will be a major breakthrough as it will decrease the waiting list and the number of hospital visits in several cancer centers especially in the developing countries.

Keywords: Hypo Fractionation; Breast Cancer; Post Mastectomy Radiotherapy

Introduction

In breast cancer, radiotherapy is offered to all patients after breast conservative surgery and if indicated for patients after mastectomy [1]. Most patients in several randomized trials received conventional fractionated radiotherapy which consisting of 50GY in 25 fractions over 5 to 6 weeks but hypo fractionated radiotherapy uses a smaller number of fractions and doses per fraction above 2 Gy [2,3]. Radio biologically, breast cancer tissue is appeared to be sensitive to fraction size as that of normal tissue, so, larger fractions might be safely delivered with better therapeutic results [3]. Therefore, this schedule leads to decrease in treatment time from 5 weeks or more to 3 weeks or less with nearly the same local control and cosmetic rate, also, it has more convenient and financial advantages as it has lower costs due to fewer travels to treatment centers compared to conventional radiotherapy[4]. Although post mastectomy hypo fractionated radiotherapy trials reported a high rate of quite devastating late radiation morbidity including severe fibrosis, plexopathy, and rib fractures, retrospective data indicated that the use of hypo fractionated radiotherapy in 13-16 fractions using 2.5-3.3 Gy per fractions to decreased total doses of 39-43 Gy is not associated with high radiation-induced acute and late toxicity and seemed to result in local recurrence rates as low as those achieved with conventionally fractionated radiotherapy in the adjuvant setting [5,6].

Radiobiological Aspects

The studies on cell kinetic parameters of human breast cancer showed that a larger-than-average potential doubling time (10.4 days) can be an indication towards hypo fractionation. Also, the estimated α/β ratios of 4 Gy support this suggestion [3]. Malignant tissues as well as normal tissues vary in their responses to radiotherapy fraction size, which known as radiation sensitivity which is distinctive in early and late responding normal tissues, the alpha/ beta ratio, offers a reliable way of describing these differences [1]. The lower the α/β (in Gy), the greater the effect of changes of fraction size on both normal and malignant tissues of. It is thought that normal breast tissues are sensitive to fraction size with α/β of 5Gy or less, so changes in fraction size will cause relatively large changes in radiotherapy effects on these tissues known as late responding effect which need months or years to cause late effects as fibrosis and skin atrophy [7].

It is proposed by Ellis, when the radiotherapy schedule is changed from 50 GY in 25 fractions to a 15 fractions delivered over the same overall treatment time results in increased acute skin reactions, but not matching to late effects as fibrosis and telangiectasia that more sensitive than acute effects to hypo fractionation schedule. So, according to Ellis formula, α/β of 3.0 Gy for late responding tissue,

a 15 fractions of 3.0 Gy regimen reproducing the same effects of 25 fractions of 2.0 Gy needs a decrease in total dose from 50 to 42.8 Gy in fractions of 2.85 Gy, it is estimated that 45 Gy in 15 fractions is equal to 54 Gy in 27 fractions, or to 56.3 Gy as assumed by Ellis formula. So, by using Ellis formula to estimate biologically effective doses for late effects may result in overdose to the tissues, however these effects are dose limiting [8-10].

Efficacy of hypo fractionation in breast cancer

Over the last decades, several randomized controlled trials were conducted to compare hypo fractionated radiotherapy to conventional regimen, although the most of these studies had been conducted in cases underwent breast conservative surgery, post mastectomy hypo fractionated radiotherapy schedule was concerned, there are prospective controlled studies have provided data analyzing different post mastectomy hypo fractionated regimens.

Safety of hypo fractionation in breast cancer

The results of numerous randomized trials conducted to compare conventional fractionated radiotherapy (50 Gy/25 fractions in 5 weeks) for patients with breast cancer to that hypo fractionated radiotherapy in which a reduction total dose by about ten percent (39-42.9 Gy/13-16 fractions in 3-5 weeks) indicate that hypo fractionated radiotherapy can be safely used in most breast cancer patients [5,10,11]. Fears that hypo fractionated radiotherapy could result in an unacceptable high rate of late radiation-induced toxicity were not confirmed in most of these trials as The late toxicities in the START trials may not have been assessed with the optimal methods, but can be considered as sufficient to exclude that relevant toxicities were not present as well as a detailed evaluation of these studies indicates that not all tested hypo fractionated regimens are equally suitable for clinical use, however 39 Gy in 13 fractions appeared to be associated with less acute and late toxicity compared to conventional fractionated regimen, also it is noted that slightly increased ipsilateral breast cancer recurrences was observed in both START trials [12-15]. Budach et al. reported in his review that none of the patients in the hypo fractionated trials received neoadjuvant chemotherapy and the use of hypo fractionated radiotherapy after neo adjuvant chemotherapy is safe for the patients or not, is formally unknown, so, it is not generally recommended in this situation.

Also, they reported that as there were no change in tumor and normal tissue sensitivity an induced by chemotherapy was observed in both experimental clinical data indicating that hypo fractionated radiotherapy is probably safe in this clinical setting and they recommended for further and well documented clinical studies to confirm the safety of hypo fractionation after neoadjuvant chemotherapy [12]. Regarding cardio-pulmonary toxicity, the low volumes and doses applied with tangential techniques after mastectomy used in hypo fractionation trials there were no any evidence of more frequent heart toxicity in the hypo fractionated trials.

In most recent study conducted by Khan et al and published in journal of clinical oncology, which was a phase II prospective

study offered one of the shortest courses of post mastectomy hypo fractionated radiotherapy delivered in eleven fractions to the chest wall and regional nodes with fifteen fractions inclusive of a boost, they demonstrated low toxicity and high local control with this regimen but they finally reported that these are more robustly tested and described in breast cancer than in any other human malignancy and still, they do not believe these shorter schedules should be used routinely off study, particularly among women with breast reconstruction [16].

Future directions

The future endeavors include several studies to evaluate the role of hypo fractionated radiotherapy in breast cancer are currently in progress the, FAST trial compares two doses (5.7 and 6.0 Gy/ 5F) over five weeks with a control dose of 50 Gy/25F, also, a regimen of thirty Gy in five fractions delivered in fifteen days to the whole breast using 3DCRT reported very mild acute reactions and satisfactory 2 year outcome in terms of changes in breast indurations and appearance compared to the matched sample of patients treated to 50 Gy in 25 fractions [17]. AllianceA221505, a randomized phase III trial of post mastectomy hypo fractionated radiotherapy in which it will test the safety of a shorter course schedule (42.56 Gy in 16 fractions) compared to conventional fractionation, all women in this trial will have breast reconstruction or intent for ultimate reconstruction. The primary end point of this trial is reconstruction complication rate and secondary end points will include lymph edema, toxicities including brachial plexopathy, recurrence-free survival, and end points for health costs/economics [16].

Conclusion

In conclusion, post mastectomy hypo fractionated radiotherapy using schedules shorter than that of conventional ones has been shown to be effective and safe for most patients with breast cancer in need for adjuvant radiotherapy. It is thought that If these schedules found to have equivalent loco regional control, survival and cosmeses to standard conventional schedules, it would be a revolutionary breakthrough in the future for breast cancer management as if these schedules are established, it will be a major breakthrough as it will decrease the waiting list and the number of hospital visits in several cancer centers especially in the developing countries.

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