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Hypofractionated Radiotherapy in Breast Cancer Patient after Breast Conservative Surgery: Review Article

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ABSTRACT

Background: The radiation therapy's duration reduction would be advantageous for women who had early breast cancer and received breast conserving surgery. Multiple studies have found that hypofractionated radiotherapy have equal efficacy as regards local and distant control as with conventional fractionation.

Objective: This article aimed to throw the light on the effect of hypofractionated radiotherapy on breast cancer patients who received breast conservative surgery.

Material and methods: We searched Google Scholar, Science Direct, PubMed and other online databases for Breast cancer, Radiotherapy, Hypo fractionation. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2001 to 2020 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: The hypo-fractionated strategy has decreased incidence of acute radiation toxicities more than conventional radiotherapy. Hypofractionation radiotherapy is also less expensive plus more practical, particularly in busy oncology centers. There are significant benefits as regards patient attendance and regularity on daily fraction. Additionally, it has the possibility to improve the radiation oncology departments' efficiency worldwide, thus increasing access to radiation therapy. This can only occur if the shorter therapy is as safe and effective as standard radiation treatment.

Keywords: Breast cancer, Radiotherapy, Hypofractionation.

INTRODUCTION

The most cancer predominant form in women and the most probable reason of cancer-related mortality worldwide is breast cancer (BC) [(1)].

The application of adjuvant radiation therapy (RT) has been demonstrated to enhance locoregional control and overall survival (OS) in a patient population that underwent surgery, particularly breast conservation surgery (BCS). As evidenced by the Early Breast Cancer Trialists' Collaborative Group meta-analysis, adjuvant whole-breast radiation therapy (WBRT) led to enhanced locoregional control of BC death in both node-negative and node-positive individuals in comparison with observation [(2)].

High-risk patients who exhibit subclinical illness subsequent to surgery are administered adjuvant RT to sterilize the peripheral lymphatics, chest walls, and breasts. In doing so, the probability of locoregional recurrence is reduced, and both BC-specific survival and OS are enhanced [(3)].

For the majority of women who undergo breast-conserving surgery, we suggest WBRT as a conservation strategy, as opposed to surgery alone. In addition, this is pertinent to women who underwent neoadjuvant therapy, regardless of whether they achieved a full therapeutic response [(4)].

A technique known as hypofractionation enables the reduction of the RT treatment duration. This method allows for the administration of the dose in a reduced number of fractions, as it necessitates fraction doses that exceed 2 Gy, in contrast to conventional RT. The total dose is typically reduced as a result of these schemes [(5)].

A linear quadratic formula [(6)] can be employed to estimate the various RT schedules biological effects. This equation is based on tissue end point-specific constant known as the α/β ratio, the treatment interval, the treatments number, and the daily dose. This prompted a scientific, incremental examination of the interrelations between the total dose delivered, dose per fraction, and the duration of adjuvant RT delivery in these trials. The potential effects of these variables include acute and chronic toxicity and the probability of tumor control [(5)].

The α/β ratio is low (e.g., 3 Gy) for late normal tissue complications, whereas it is elevated (e.g., 10 Gy) for tumor elimination. Consequently, by administering external beam RT the optimal therapeutic ratio should be achieved in a significant fractions number, including approximately 20–30 fractions of small (≈2 Gy) dose fractions. To illustrate this concept, consider the cell killing linear-quadratic model [(7)].

If the overall radiation dose is sufficiently decreased, shorter RT sessions are equally successful as longer RT programs for women with in situ or invasive BC. As a result, it has been proposed that short fractionation should be regarded as the novel model for the early-stage BC treatment following BCS [(8)]. The benefits of shorter RT courses include an enhanced quality of life, increased convenience, and a reduction in the resource requirements for treatment delivery [(9)].

Several clinical trials were carried out in North America and the United Kingdom to examine the hypofractionation role in BC. These trials was both well-designed and elegant. Radiobiological concerns that were prevalent at that time included the potential

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for the late effects to exacerbate the damage to normal tissues due to the higher doses per fraction and a reduced likelihood of tumor control as a result of the lower total doses. In addition, the toxicity profiles can be impacted by the irradiated tissue volume [10].

RT is highly involved in the BC management. New radiation technologies, such as 3-dimensional conformal therapy, intensity-modulated RT, and brachytherapy, have the potential to broaden the hypofractionation's application scope [11]. 7

Time to start radiation

There is insufficient data to determine the optimal timing for the administration of RT in comparison with systemic therapy. The order in which RT and systemic therapy are administered is determined by institutional norms of practice. Considering the type of systemic therapy that is being implemented is a reasonable approach. Is there a benefit to administering RT immediately after surgery in patients who are candidates for adjuvant chemotherapy? A study has not shown this. RT is typically administered subsequent to chemotherapy for this reason [12].

Conversely, clinical data retrospective examination suggested that BC may be significantly more susceptible to fluctuations in RT dose per fraction than most other cancers. Consequently, strategies for hypofractionation were implemented in a multitude of trials [13].

Second-generation schedules that employ hypofractionated methodologies reduce the total therapy duration to 2–4 weeks in comparison with conventional WBI. All of these methodologies are intended to increase the treatment dose (2.66 Gy/fraction). One of the earliest second-generation trials was conducted by the Ontario Oncology Group. This trial randomized 1234 patients with node-negative BC who had undergone BCS to either standard WBI (n = 612) or hypofractionated WBI (n = 622, 42.5 Gy/16 fractions in 3 weeks). With the primary outcome being local recurrence, the study was conducted utilizing a non-inferiority strategy. The prevalence of excellent/good cosmetic results and the toxicity profile were comparable at the 10-year mark, and there was little variation in local recurrence [14].

A total of four meticulously executed, randomized trials were conducted to assess the long-term outcomes of 7,095 cases. These trials compared a 25-fraction schedule to 13–16 fraction RT regimens. Breast Radiotherapy Standardization (START) was the result of a 10-year follow-up. Similar local control, survival, cosmetic outcome, and normal tissue toxicity were attained by 39 Gy in 13 daily fractions over 5 weeks, 42.5 Gy in 16 daily fractions over 3.5 weeks, and 50 Gy in 25 daily fractions, as demonstrated by the Canadian trial [15].

Additionally, cases who were selected for receiving 40 Gy in 15 daily fractions encountered significantly fewer locoregional recurrences and fatalities than those who underwent 50 Gy in 25 daily fractions [16].

ULTRAHYPOFRACTIONATION

Two comprehensive randomized controlled trials, FAST and FAST-Forward, were recently published. These trials evaluated 5-fraction regimens for adjuvant WBRT. These regimens are referred to as "ultra-hypofractionation" as a result of the reduced fraction number and the large fraction size of 5.2 to 5.6 Gy. 915 women aged 50 years or older with T1-2N0 BC were randomized to one of three adjuvant regimens in the FAST trial: 50 Gy/25 fractions over 5 weeks, 30 Gy/5 fractions once weekly over 5 weeks, or 28.5 Gy/5 fractions once weekly over 5 weeks. Treatment duration was sustained at five weeks in accordance with START. Furthermore, the dose per fraction increased, while the fractionation’s total number decreased. The initial the FAST trial endpoints were changes in breast form at 2 and 5 years. In 2011 the initial findings were available, and a median follow-up of 37.3 months was conducted. There were only 10 local recurrences observed over a 10-year period, and there was minimal evidence of any significant outcomes on normal tissue. The 30 Gy regimen demonstrated a normal tissue effects higher rate in comparison with conventional WBI. On the other hand, the 28.5 Gy arm did not exhibit any significant difference in normal tissue effects at 5 years, and the incidences of moderate/marked normal tissue effects were comparable [17].

In comparison with 50 Gy in 25 fractions, a greater number of moderate or significant changes in photographic breast appearance were observed with 30 Gy in 5 fractions. Conversely, there was no discernible distinction between 28.5 and 50 Gy. Similar patterns were observed for late effects, including breast atrophy, telangiectasia, duration, and edema as well as for a composite endpoint of any moderate or marked negative consequences. The yields produced by 28.5 Gy and 50 Gy are comparable, whereas 30 Gy is inferior, as indicated by these results. A subset of patients were evaluated solely for acute adverse events. In contrast, the standard arm exhibited a higher incidence of acute skin reactions that were more severe than those in both experimental arms. Conversely, these reactions were uncommon. A highly accelerated adjuvant RT regimen that consisted of five fractions that were administered within a single week was employed by the Fast Forward method. The standard regimen, which was moderately accelerated, was contrasted with this regimen over a three-week period [18].

The investigation encompassed 4096 women who were diagnosed with pT1-3N0-1 BC and had undergone mastectomy or BCS. A total of three arms were developed to randomly assign patients to hypofractionated WBI. A non-inferiority design is necessary to accomplish the initial endpoint of ipsilateral breast tumor recurrence. The following fractions must be administered over a five-day period:

40 Gy/15, 27 Gy/5, or 26 Gy/5. The experimental arm, which received a higher dosage of 27 Gy, exhibited a significantly higher chance of nearly every reported late normal tissue effect, as evidenced by longitudinal analyses, in contrast to the standard Arm. According to the FAST trial there is insignificant differences in the OS at five years, recurrence risk, or disease-free survival. The standard arm did not demonstrate insignificant differences in the majority of marked or moderate normal tissue effects in the lower dose experimental arm (26 Gy). Nevertheless, the cases number who stated moderate or severe adverse events during the subsequent period was significantly higher among those who received 27 Gy. The treatment arms did not exhibit any obvious distinctions, and the prevalence of ischemic heart disease and symptomatic lung fibrosis were negligible [(19)].

CONCLUSION

The hypo-fractionated strategy has decreased incidence of acute radiation toxicities more than conventional radiotherapy. Hypofractionation radiotherapy is also less expensive plus more practical, particularly in busy oncology centers. There are significant benefits as regards patient attendance and regularity on daily fraction. Additionally, it has the possibility to improve the radiation oncology departments' efficiency worldwide, thus increasing access to radiation therapy. This can only occur if the shorter therapy is as safe and effective as standard radiation treatment.

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Conflict of interest: Improving radiation-induced toxicities with favorable outcomes.

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