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ORIGINAL ARTICLE

Evidence based whole breast hypo-fractionated radiation therapy in patients with early breast cancer

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Summary

Purpose: *The aim of the current study was to evaluate the efficacy and tolerability of hypo-fractionated whole breast radiation therapy in patients with early breast cancer.*

Methods: *Searching electronically PubMed and the Cochrane Central Register we made a comprehensive literature review regarding the randomized controlled phase III trials for hypo-fractionated radiation therapy in early breast cancer.*

Results: *The collected and analyzed data showed that a short course of hypo-fractionated radiation therapy in early breast cancer patients is as effective as the conventional long course regarding tumor response as well as long term side effects.*

Conclusion: *More data are needed about the usage and integration of a boost treatment for higher-risk women receiving neo-adjuvant or adjuvant chemotherapy, or the results in special subgroups such as women with large breast size.*

Key words: *early breast cancer, evidence, hypo-fractionation, radiation therapy*

Introduction

Breast cancer represents the most frequently diagnosed malignancy and the leading cause of cancer-related deaths in women, accounting worldwide for 23% of total new cancer cases and 14% of total cancer deaths in 2008 [1]. The diagnosis and treatment of breast cancer has been improved significantly in the past decades, associated with a decrease of mortality rate, though the changes vary widely among countries [2,3]. Among treatments, adjuvant radiotherapy has shown to improve local control and overall survival, with 70% proportional reduction of the risk of recurrence [4] and a 9–12% proportional reduction of the risk of death [5–8]. Despite this established role of radiotherapy, there are considerable disparities in administering radiotherapy that are attributable to various factors such as limited availability of treatment centers, geographical distance, long waiting times, and costs [9–11]. The disparities can further be compounded by the long-lasting schedules required with conventional radiotherapy, since these schedules that were evaluated in clinical trials and were found to be associated with improved survival are based on conventional fractionation of 1.8-2.5 Gy/fraction, delivering treatment over 5 to 7 weeks [5,8,12,13]. Many researchers are vigorously investigating alternative approaches. Intraoperative radiotherapy (IORT) [14,15] or accelerated partial breast irradiation (APBI) [16] provide the shortest schedules. However, IORT and APBI are restricted to selected cases of breast-conserving therapy [17].

This paper focused on the whole breast radiation with a hypo-fractionated schedule. Literature review has shown that using short schedules of whole breast radiation therapy is as effective as

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using long schedules regarding both tumor control as well as toxicity. All available controlled randomized trials providing evidence on hypo-fractionated whole breast radiation therapy are presented in this article.

Methods

Identification of eligible studies

In order to clarify the role of hypo-fractionated radiation therapy in early-stage breast cancer, we searched MEDLINE and the Cochrane Central Register of Randomized Controlled Trials (last search on May 2013) using combinations of terms, such as early breast cancer, carcinoma, radiation therapy, hypo-fractionation, and standard fractionation. We considered all English written meta-analyses and randomized controlled trials, providing evidence about the efficacy and tolerability of hypo-fractionated radiation therapy in patients with early breast cancer, as eligible.

Data extraction

We extracted information from each eligible study. The data recorded included author's name, year of publication, number of patients included in the study, combination(s) of treatment(s) used, doses of radiation therapy, local recurrence rate, overall survival and toxicity profile.

Results

According to selection criteria, 4 prospective phase III randomized trials of hypo-fractionated whole breast irradiation vs conventional fractionation in early-stage breast cancer were fund.

A Canadian study that was conducted several years ago [18], and the long-term results of hypo-fractionated radiation therapy for breast cancer were recently published by Whelan et al. [19]. Between April 1993 and September 1996, a total of 1234 patients underwent randomization, with 612 assigned to standard whole-breast irradiation at a dose of 50 Gy given in 25 fractions over a period of 35 days (control group) and 622 to the accelerated, hypo-fractionated whole-breast irradiation at a dose of 42.5 Gy given in 16 fractions over a period of 22 days (hypo-fractionated-radiation group). The authors reported that the risk of local recurrence at 10 years was 6.7% among the women assigned to the control group and 6.2% among the women assigned to the hypo-fractionated regimen (absolute difference, 0.5 percentage points; 95% confidence interval [CI], −2.5 to 3.5). Moreover, at 10 years, 71.3% of women in the control group and 69.8% of the women in the hypo-fractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, −6.9 to 9.8). Finally, 10 years after treatment the authors concluded that accelerated, hypo-fractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes.

The Standardisation of Breast Radiotherapy (START) Trial A [20] was a randomised trial of radiotherapy hypofractionation for the treatment of early breast cancer. Between 1998 and 2002, 2236 women with early breast cancer (pT1-3a pN0-1 M0) at 17 centres in UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 3 weeks vs 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3.0 Gy over 5 weeks. The protocol-specified principal endpoints were local-regional tumor relapse, defined as reappearance of cancer at irradiated sites, late normal tissue effects, and quality of life. Of the women included in this study 749 were assigned to the 50 Gy group, 750 to the 41.6 Gy group, and 737 to the 39 Gy group. After a median follow up of 5.1 years the rate of local-regional tumor relapse at 5 years was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0.2% after 41.6 Gy and 0.9% after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than after 50 Gy, with an HR for late change in breast appearance (photographic) of 0.69 (95% CI 0.52–0.91, p=0.01). The authors concluded that a lower total dose in a smaller number of fractions could offer similar rates of tumor control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions.

The UK START Trial B [21] was a randomized study comparing the standard 5-week schedule of postoperative radiation therapy to an alternative hypo-fractionated 3-week schedule. Between 1999 and 2001, 2215 women with early breast cancer (pT1-3a pN0-1 M0) from 23 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks. 1105 women were assigned to the 50 Gy group and 1110 to the 40 Gy group. After a median follow up of 6 years the rate of local-regional tumor relapse at 5 years was 2.2% in the 40 Gy group and 3.3% in the 50 Gy group. Photographic

Table 1. Randomized phase III trials for hypo-fractionated whole breast radiation therapy in early breast cancer patients

First author [ref]	*No. of patients*	*Arms of radiation therapy schedules*	*Local recurrence rate %*	*Late toxicity*
Whelan et al. [18,19]	1234	Arm 1: 612 patients received 50 Gy/25 frs Arm 2: 622 patients received 42.5 Gy/16 frs	At 10 years 6.7 in Arm 1 6.2 in Arm 2	At 10 years excellent cosmetic outcome for 71.3% of patients in Arm 1 and 69.8% in Arm 2
START A [20]	2236	Arm 1: 749 patients received 50 Gy/25 frs Arm 2: 750 patients received 41.6 Gy/13 frs Arm 3: 737 patients received 39 Gy/13 frs	At 5 years 3.6 in Arm 1 3.5 in Arm 2 5.2 in Arm 3	At 5 years lower rates of late adverse effects after 39 Gy than with 50 Gy
START B [21]	2215	Arm 1: 1105 patients received 50 Gy/25 frs Arm 2: 1110 patients received 40 Gy/15 frs	At 5 years 3.3 in Arm 1 2.2 in Arm 2	At 5 years lower rates of late adverse effects after 40 Gy than after 50 Gy
Owen et al. [23]	1410	Arm 1: 470 patients received 50 Gy/25 frs Arm 2: 466 patients received 42.9 Gy/13 frs Arm 3: 474 patients received 39 Gy/13 frs	At 10 years 12.1 in Arm 1 9.6 in Arm 2 14.8 in Arm 3	At 10 years excellent cosmetic outcome for 71% of patients in Arm 1, 74 % in Arm 2 and 58% in Arm 3

No: Number, frs: fractions, START: Standardisation of Breast Radiotherapy

and patient self-assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy. The authors concluded that the hypo-fractionated schedule seems to offer rates of local-regional tumor relapse and late adverse effects at least as favorable as the standard schedule.

The group of Royal Marsden Hospital from the Radiotherapy and Oncology Department has examined in a randomized trial the fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer [22]. Between January 1986 and March 1998, 1410 patients with operable invasive breast cancer (T1-3 N0-1 M0) requiring radiotherapy were enrolled into one of three radiotherapy regimens: 50 Gy in 25 fractions vs two dose levels of a test schedule giving 39 or 42.9 Gy in 13 fractions over 5 weeks. The primary endpoint was late change in breast appearance compared to post-surgical appearance scored from annual photographs blinded to treatment allocation. Secondary endpoints included palpable breast induration (fibrosis) and ipsilateral tumor recurrence. The authors concluded that, the fractionation sensitivities of the normal breast tissues were consistent with expectations based on the existing literature. Furthermore, they stated that, if the fractionation sensitivity of breast cancer is comparable, this opens the way for further research into the applications of hypo-fractionation to breast radiotherapy. The same group has recently published the long term results from their randomized trial [23]. They found that after a median follow-up of 9.7 years, for the 838 (95%) patients who survived, the risk of ipsilateral tumor relapse after 10 years was 12.1% in the 50 Gy group, 14.8% in the 39 Gy group, and 9.6% in the 42.9 Gy group. The sensitivity of breast cancer to dose per fraction was estimated to be 4.0 Gy, similar to that estimated for the late adverse effects in healthy tissue from breast radiotherapy. The authors concluded that breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues. The results of randomized phase III trials for hypo-fractionated whole breast radiation therapy are summarised in Table 1.

Discussion

One problem with standard radiation to the whole breast may be the extended 6- to 7-week length of treatment. Delivering postoperative radiation therapy in a shorter period of time could result in greater convenience for patients and therefore greater use of postoperative radiation. Cost is also an increasingly important consideration, both to the individual and to the society as a whole. A typical fractionation schedule for breast radiation of 30-35 fractions is associated with costs to patients that include a daily deductible for each radiation treatment, costs to a personal medical savings account, expenses for travel to

receive radiation, and lost hours of work.

Despite the successful outcomes in four prospective randomized trials [19-22] of whole breast radiation discussed above, there has not been significant adoption of hypo-fractionated whole breast radiation in the United States. This may in part be due to many clinical questions that remain about hypo-fractionated whole breast radiation that are not able to be addressed by the data from the existing randomized trials.

Important questions have been arisen regarding the optimal method of delivering a boost after hypo-fractionated whole breast radiation and if the inclusion criteria of hypo-fractionated whole breast radiation can be widened. The four prospective studies of hypo-fractioned whole breast radiation either did not use a boost, or used it only at the discretion of the treating department policy in a nonrandomized fashion. The randomized trials of hypo-fractionated whole breast radiation treated few women with large breast sizes and included mostly lower-risk patients, so as a result the applicability and safety of hypo-fractionation in women treated with adjuvant systemic chemotherapy is not well known.

In recent times, guidelines recommendations regarding the use of hypo-fractionated whole breast radiation in early-stage breast cancer have been published by the American Society of Radiation Oncology (ASTRO) task force of experts [24]. The task force has stated that hypo-fractionated whole breast radiation was suitable outside of a clinical trial in the following patients: breast cancer patients with pT1–2 tumor size, N0 nodal disease, age greater than 50 years, and patients who do not receive chemotherapy. Regarding the use of a tumor bed boost, the task force concluded that there were "few data to define the indications for and toxicity of a tumor bed boost" in patients treated with hypo-fractionated whole breast radiation. The task force recommended that hypo-fractionated whole breast radiation should not be used when a tumor bed boost was thought to be indicated. When the boost was indicated, there was lack of consensus regarding the appropriateness of hypo-fractionation.

The concern of using hypo-fractionated whole breast radiation when a boost is needed has led to research into methods for integrating the tumor bed boost with hypo-fractionated radiation. Three phase I/II trials [25-27] have been published showing the safety and short-term efficacy of hypo-fractionated whole breast radiation with a concurrent boost for early-stage breast cancer.

Freedman et al. [25] have reported the 5-year results of a phase II study of intensity modulated radiation therapy, hypo-fractionation, and incorporated boost in early breast cancer patients. In this study 75 patients received whole breast radiation therapy to a total dose of 45 Gy in 20 daily fractions of 2.25 Gy each. An incorporated tumor bed boost gave simultaneously to the tumor bed 2.8 Gy per fraction for a total of 56 Gy. There were no exclusion criteria regarding the breast size or if the patient had received or not chemotherapy. There was no grade 3 or higher skin toxicity. After radiation, all grade 2 skin toxicity had resolved by 6 weeks. With a median potential follow-up of over 5 years, the 5-year local recurrence rate was 1.4%.

Between September 2003 and August 2005, 91 patients with stages I or II breast cancer, operated with breast-conserving surgery with negative margins, were treated with accelerated whole-breast intensity modulated radiotherapy, with the patient in prone position by Formenti et al [26]. They delivered 40.5 Gy to whole breast in 15 fractions of 2.7 Gy each with an additional concomitant boost of 0.5 Gy delivered to the tumor bed, for a total dose of 48 Gy to the lumpectomy site. The authors reported that acute skin toxicity was quite modest, mainly restricted to grade 1 to 2 dermatitis in 67% of the patients, and they concluded that accelerated whole breast intensity modulated radiotherapy in the prone position is feasible and permits a drastic reduction in the volume of lung and heart tissue exposed to significant radiation.

Recently, Chadha et al. [27] presented their results regarding accelerated whole breast radiation therapy with concomitant boost in patients with stage TisN0, T1N0, and T2N0 breast cancer. Between October 2004 and December 2010, 160 patients were treated. The whole breast received 40.5 Gy in 2.7-Gy fractions with a concomitant lumpectomy boost of 4.5 Gy in 0.3-Gy fractions. Total dose to the lumpectomy site was 45 Gy in 15 fractions over 19 days. The authors reported that with a median follow-up of 3.5 years (range 1.5-7.8) the 5-year overall survival and disease-free survival rates were 90% and 97%, respectively. Five-year local relapse-free survival was 99%. Acute grade 1 and 2 skin toxicity was observed in 70% and 5% of the patients, respectively. Among patients with ≥2-year follow-up, no toxicity higher than grade 2 on the Late Effects in Normal Tissues-Subjective, Objective, Management, and Analytic scale was observed. Finally, the authors

concluded that the results are encouraging with minimal side effects and excellent local control.

Since the results of the aforementioned phase I/II studies are encouraging, they needed to be validated with well designed ongoing phase III randomized trials.

The IMPORT (Intensity Modulation and Partial Organ) High trial in the United Kingdom opened in 2009. This trial is for women with early-stage breast cancer and an average or above average risk of recurrence. The three-arm trial has a control arm of 40 Gy whole breast radiation in 15 fractions with a sequential boost of 16 Gy in 8 fractions over 4.5 weeks. The two experimental arms both deliver 36 Gy whole breast radiation in 15 fractions (escalated to 40 Gy in a higher-risk partial breast region) and two different dose levels of a concomitant tumor bed boost to 48 Gy or 53 Gy all in the same 15 fractions over 3 weeks.

The Radiation Therapy Oncology Group has opened a phase 3 randomized trial (RTOG 1005) in May 2011 that proposes to establish a whole breast hypo-fractionation schedule with a concurrent boost over 3 weeks that can be applied to a broader patient population than the patients enrolled in the existing whole breast radiation hypo-fractionation studies (having indications for a tumor bed boost, having large breast size, or those requiring chemotherapy). Patient inclusion criteria are defined to include patients at higher than average risk for local recurrence who could most benefit from the addition of a tumor bed boost such as age less than 50 years, node-positive breast cancer, lymphovascular space invasion, presence of an extensive in situ ductal component, close resection margins, focally positive resection margins, and/or non-hormone sensitive breast cancer. The control arm is whole breast radiation, with a standard sequential tumor bed boost using a conventional 2-Gy radiation fraction size. The whole breast radiation fractionation for the control arm can be either conventional 50 Gy in 25 fractions or hypo-fractionated 42.7 Gy in 16 fractions. In the experimental arm, the overall length of treatment is fixed at 3 weeks with a whole breast radiation dose fractionation of 40 Gy in 15 fractions and a concurrent tumor bed boost of a total of 48 Gy. The primary endpoint is non-inferiority of local control, with secondary endpoints examining survival, breast-related symptoms and cosmesis, cost, and radiation physics and biological correlative studies.

Conclusions

The results presented from the prospective randomized trials have shown that hypo-fractionation may be used for whole breast radiation with acceptable toxicity and equivalent local control as conventional fractionation. Nevertheless, for hypo-fractionation to become more widely applied, more data are needed about the use and integration of a boost, treatment of higher-risk women receiving neo-adjuvant or adjuvant chemotherapy, or results in special subgroups such as women with a large breast size. This is the case of the ongoing well designed phase 3 trials such as RTOG 1005, which is studying hypo-fractionated whole breast radiation with a concurrent boost over 3 weeks in such higher-risk patients.

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