

## RESEARCH ARTICLE

# Comparison of Conventional and Hypofractionated Radiotherapy in Breast Cancer Patients in Terms of 5-Year Survival, Locoregional Recurrence, Late Skin Complications and Cosmetic Results

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### Abstract

**Background:** Adjuvant radiation therapy is commonly administered following breast-conserving surgery for breast cancer patients. Hypofractionated radiotherapy can significantly reduce the waiting time for radiotherapy, working load on machines, patient visits to radiotherapy departments and medical costs. **Material/Methods:** Fifty-two patients with operable breast cancer (pT1-3pN0M0) who underwent breast conservation surgery in Tehran Cancer Institute during January 2011 to January 2012, were randomly assigned to undergo radiotherapy in two arms (hypofractionated radiotherapy arm with 30 patients, dose 42.5 Gy in 16 fractions; and conventional radiotherapy arm with 22 patients, dose 50 Gy in 25 fractions). We compared these two groups in terms of overall survival, locoregional control, late skin complications and cosmetic results. **Results:** At a median follow-up of 52.4 months (range: 0–64 months), the follow-up rate was 82.6%. Overall, after 60 months, there was no detectable significant differences between groups regarding cosmetic results ( $p = 0.857$ ), locoregional control or survival. **Conclusions:** The results confirm that hypofractionated radiotherapy with a subsequent boost is as effective as conventional radiotherapy, is well-tolerated and can be used as an alternative treatment method following breast conservation surgery.

**Keywords:** Breast cancer- hypofractionated radiotherapy- late skin toxicity- survival

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### Introduction

Breast cancer is one of the most common cancers affecting women worldwide and a primary cause of cancer-related death in women (Hutchinson, 2010). The choice of therapy depends on the tumor characteristics (Bride et al., 2013). If diagnosed at an early stage, breast conservation surgery can often be performed. Following surgery, patients often receive adjuvant radiation therapy. Previous studies have shown that breast-conserving surgery in conjunction with irradiation has an outcome similar to those of radical operations such as a full mastectomy (Keating et al., 2011).

After breast-conserving surgery, radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about one-sixth (Early Breast Cancer Trialists' Collaborative Group, 2011). To date, an optimal fractionation schedule for breast irradiation has not been universally accepted, although many studies have examined the benefits and

drawbacks of various treatment regimens (Tortorelli et al., 2013; Alford et al., 2013; Chadha et al., 2013; Kim et al., 2011). The current standard for radiation treatment involves whole-breast tangential irradiation (45-50 Gy in 25-28 fractions with 1/8-2 Gy/Fr) with a subsequent boost (10-16 Gy in 5-8 fractions) to the tumor bed, typically occurring over the course of 6–7 weeks. This regimen has been proven to decrease locoregional recurrence (Bartelink et al., 2007), but has drawbacks such as lengthy treatment time and high medical cost.

It has been reported (Khan et al., 2010; Yarnold et al., 2010) that breast cancer has a low a/b ratio (4 for breast adenocarcinoma and 3 for normal breast tissue); therefore, a shorter regimen of radiotherapy (40-44 Gy in 15-16 fractions with 2/5-2/7 Gy/Fr) could theoretically be effective without significantly increasing the adverse effects (Owen et al., 2006; MacLeod et al., 2010; Jones et al., 2000; Marcu, 2010; Qi et al., 2011). Hypofractionated radiotherapy can significantly reduce the waiting time for radiotherapy, working load on machines, patient visits to

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radiotherapy departments and medical costs.

The present study follows a previous trial by Hashemi et al. that compared two groups (hypofractionated radiotherapy arm and conventional radiotherapy arm) of patients in terms of early skin complications and cosmetic outcomes. We continued to evaluate the overall survival, locoregional control, late skin complications and cosmetic results in the two groups.

## Material and Methods

This study follows a previous randomized controlled trial by Hashemi et al. that compared two groups (hypofractionated radiotherapy arm and conventional radiotherapy arm) of patients in terms of early skin complications and cosmetic outcomes. The present study examined these patients with a prolonged follow-up to evaluate overall survival, locoregional control, late skin complications and cosmetic results. Based on the previous study design, 52 patients with operable breast cancer (pT1-3pN0M0) who underwent breast conservation surgery in the Radiation Oncology Department of the Cancer Institute at Imam Hospital, Tehran, Iran were enrolled in this study from January 2011 to May 2012.

The patients had been randomly divided into a hypofractionated short-course radiotherapy group (dose: 42.5 Gy in 16 fractions and a subsequent electron boost; 10 Gy in 5 fractions) and a conventional treatment group (dose: 50 Gy in 25 fractions with subsequent electron boost; 10 Gy in 5 fractions) using the sealed envelope method and a random number table. Written informed consent was obtained from all patients and the Ethics Committee of Tehran University of Medical sciences approved the study protocol. During the study, there were three cobalt and one linear accelerator in the department. Fifty patients were treated with cobalt-60 and 2D radiation treatment; however 2 patients in the conventional group were treated with linac and 3DCRT.

### Inclusion criteria

The inclusion criteria of the present study were having undergone breast-conserving surgery with free margins, stage (pT1-3N0-1M0), being above 18 years of age, the distance from midline to midaxillary line of less than 25 cm (for prevention of tissue dose inhomogeneity), no need for lymph node treatment.

### Exclusion criteria

The exclusion criteria were a poor cosmetic result after surgery, a history of previous radiotherapy in the chest wall, inflammatory breast cancer and indications of lymph node treatment, a history of connective tissue disease or cardiovascular problems.

### Follow-up and endpoint outcomes

Patients were followed until January 2016 at a rate of every 3 months for the first 2 years and every 6 months thereafter. Follow-up was performed immediately after completion of radiation therapy and at 6 weeks, 6 months and 12 months post-therapy as part of the previous study, and at 24 months and 60 months specifically for the present study. The initial cosmetic breast condition were scored based on surgical scarring, breast size difference, nipple, nipple retraction, and the areola (acceptable = 0; no significant difference = 1). The patients were put into four categories based on their scores: excellent (0-1), good (2), fair (3) and weak (4-5). At each follow-up visit, factors affecting appearance (such as onset of radiotherapy), fibrosis and telangiectasia as late skin toxicity, and local and distant recurrence were investigated. The study's primary endpoint was locoregional recurrence. Secondary endpoints included late skin toxicity and cosmetic outcome. Locoregional was defined as the area of the breast and the supraclavicular lymph drainage area within the radiation field; definite diagnosis of locoregional recurrence was confirmed by both clinical and imaging examinations.

### Statistical analysis

The sample size was determined to be 52 patients based on the power of the study (90%), confidence interval (95%) and the samples sizes in similar studies. Kaplan-Meier analysis was used to calculate survival rate and locoregional recurrence. Log-rank tests were performed to compare differences between groups. Data for toxicity and cosmetic outcomes within the two groups were compared and analyzed using the chi-square test. All statistical analyses were performed using SPSS 16.0 (SPSS; USA). The values were considered significant at  $p < 0.05$ .

## Results

A total of 52 patients met the inclusion criteria and were enrolled in the study between January 2011 and

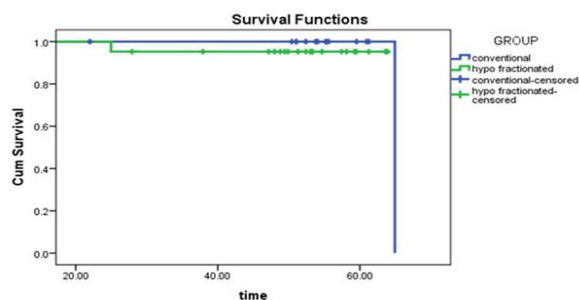


Figure 1. 5-Year Progression Free survival Curve, (Conventional Group=1 , Hypofractionated Group=2)

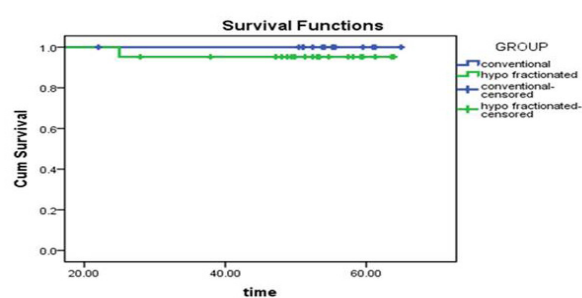


Figure 2. The 5-Year Overall Survival Curve, (Conventional Group=1 , Hypofractionated Group=2)

Table 1. Characteristics of Patients in Both Groups

Group		Conventional Fractionated group=CF	Hypofractionated group=HF
Characteristics			
Age	Mean age	47.1	49.3
	Ranges	37.0-64.0	37.0-80.0
Histopathology	IDC	19.0	30.0
	ILC	1.0	0.0
	DCIS	2.0	0.0
Grading	1	2.0	7.0
	2	17.0	15.0
	3	3.0	8.0
Tumor size	T1	8.0	15.0
	T2	14.0	13.0
	T3	0.0	2.0
Hormone receptores	ER, PR Positive	15.0	24.0
	ER, PR Negative	7.0	6.0
	HER-2 Positive	8.0	7.0
	HER-2 Negative	14.0	23.0
Treatment	Surgery alone	0.0	1.0
	Surgey and Chemotherapy	22.0	29.0

May 2012 (hypofractionated group, n = 30; conventional group, n = 22). Fifty patients were treated with cobalt-60 and 2D radiation treatment; however 2 other patients (in the conventional group) were treated with linac and 3DCRT. Table 1 lists the clinical characteristics of the patients. There were no statistically significant differences between groups in terms of age distribution, histologic grading, tumor staging, hormone receptors and treatment characteristics.

At a median follow-up of 52.4 months (range: 0–64 months), the follow-up rate was 82.6%. There was no locoregional recurrence in either group and the local recurrence-free survival rate was 100%. There was one metastatic recurrence in each group. The recurrence in the hypofractionated group presented as bone metastasis at 6 months after treatment. The patient succumbed to brain metastasis at 24 months after completion of radiation treatment. In the conventional group, the recurrence presented as distant lung metastasis at 17 months after completion of radiation treatment. The patient is currently alive and has undergone chemotherapy. Although the endpoint of the study was local recurrence as zero in both groups, the difference between groups in terms of distant metastasis was also not statistically significant ( $p = 0.811$ ). Figure 1 shows the progression-free survival rate for both groups. Figure 2 shows that the 5-year overall survival rate was 100% for the conventional group and 95.2% for the hypofractionated group, which was not significantly different between groups ( $p = 0.391$ ).

At 60 months post-treatment, the number of adverse late skin reactions were 3 cases of breast fibrosis in the hypofractionated group and 2 cases in the conventional group ( $p = 0.768$ ) and 3 cases of telangiectasia in the hypofractionated group and 2 cases in the conventional group ( $p = 0.768$ ). At 60 months post-treatment, the patients in both groups had experienced good overall

results and similar cosmetic results and no significant difference was detected ( $p = 0.694$ ). Overall, there were no significant differences for any of the categories (late skin complications, cosmetic outcomes, recurrence and survival) between groups.

## Discussion

The present study evaluated differences between two arms of treatment for early-stage breast cancer. In the first arm, patients receiving conventional radiotherapy at a dosage of 50 Gy in 25 fractions with subsequent electron boost at a dosage of 10 Gy in 5 fractions. In the second arm, patients received hypofractionated radiotherapy at a of dosage 42.5 Gy in 16 fractions and a subsequent electron boost at a dosage of 10 Gy in 5 fractions. The dosages used in both arms of this study were equal in terms of radiobiology. There were no significant differences between regimens for any of the outcomes examined of late skin toxicity ( $p = 0.768$ ), cosmetic outcome ( $p = 0.694$ ), recurrence ( $p = 0.811$ ) and survival ( $p = 0.391$ ). This indicates that a hypofractionated radiotherapy schedule with a subsequent boost is as effective as conventional radiotherapy and can be used as an alternative method following breast conservation surgery.

Several randomized clinical trials have been done for comparison of the two treatment regimens. Whelan et al.(2010) studied a clinical cancer group in Ontario and found that early-stage breast cancer patients could benefit from hypofractionated radiotherapy. They found that hypofractionated radiotherapy (42.5 Gy in 16 fractions over 22 days) was not inferior to conventional radiotherapy (50 Gy in 25 fractions over 35 days) in terms of early skin toxicity, lo-cal recurrence within 10 years, or cosmetic outcome. At the same time, subgroup analysis showed that hypofractionated radiotherapy had

a lower efficiency in high-histological grade patients (locoregional recurrence over 10 years was 15.6% in the hypofractionated radiotherapy arm and 4.7% in conventional radiotherapy arm ( $p = 0.01$ ). It should be noted that a boost of radiotherapy to the tumor bed was not used for the patients in their study.

The issue of local control was investigated by the British Columbia Cancer Center (Herbert et al., 2012). In 2012, 1335 breast cancer patients with grade 3 disease (T1–T2, N0, M0) were studied. Of them, 252 patients underwent conventional fractionation of 45–50 Gy in 25 fractions and 1083 patients received a hypofractionated schedule of 42.5–44 Gy in 16 fractions. The 10-year cumulative incidence of local relapse was 6.9% in the hypofractionated group and 6.2% in the conventionally fractionated group ( $p = 0.99$ ). These results show that there were no significant differences between the hypofractionated schedule and conventional fractionation in terms of local recurrence, even for histologic grade 3 breast tumors.

Similar findings have been reported in two large trials; START A and START B. (Haviland et al., 2013)

The START Trialists' Group compared long-term local relapse rates between hypofractionated radiotherapy and conventionally fractionated schedules. These studies showed that hypofractionated radiotherapy and conventional treatment method produced similar results.

Although studies related to using a boost of radiotherapy as sequential to or concomitant with the hypofractionated regimen are few in number, some large trials show the efficacy of boost radiotherapy in reducing of local recurrence (Bartelink et al., 2007; Romestaing et al., 1997). In the present study, based on ASTRO recommendations, a boost radiation treatment for the tumor bed was implemented as described above (Smith et al., 2011).

An important and relatively long-term study in this field was done by Bartelink et al., (2007). They found a significant difference ( $p < .0001$ ) in local recurrence at the 10-year follow-ups between groups with or without the concomitant boost of radiotherapy (10.2% versus 6.2%). Bartelink et al. also showed a significant increase in fibrosis in the boost group, but there was no significant difference for overall survival between groups.

Yarnold et al. (2005) found that a concomitant boost of 14 Gy to the tumor bed increased the risk of late toxicity such as breast hardening and telangiectasia. It has been reported (Lievens, 2010; Suh et al., 2005; Hoopes et al., 2012) that patients prefer hypofractionated radiotherapy, in part because the cost of treatment is significantly lower on these shortened schedules. Taken together, the acceptable cosmetic outcomes, acceptable local control, good survival rates, patient preference, savings in cost and resources indicate that hypo-fractionated radiotherapy is an acceptable alternative treatment.

#### Limitations

This study had a number of limitations. These include 2D radiotherapy planning and treatment by the cobalt 60 machine because of limited availability at the time, the

short follow-up period and the limited number of patients enrolled. More studies using new modern radiotherapy techniques and larger sample sizes should be performed to evaluate the outcomes of hypofractionated radiotherapy.

Then results of the present study show that a hypofractionated radiotherapy schedule with a subsequent boost is as effective as conventional radiotherapy, is well-tolerated and can be used as an alternative treatment method following breast conservation surgery.

#### Conflict of interests

All authors declare that they have no conflicts of interest.

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