Accelerated Hypofractionated Whole Breast Radiotherapy for Early Breast Cancer; ARandomized Phase III Clinical Trial

Sare Hosseini[1], Mehri Shahabadi[1], Roham Salek[1], Azar Fanipakdel[1], Leila Ghofraniha[2], Fereshteh Ghaderi[3], Seyed Alireza Javadinia[4]

[1] Cancer Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Department of Cardiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[4] Cellular and Molecular Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran

Abstract- To compare the cosmetic outcome and acute cutaneous, cardiac, and pulmonary toxicity profile of accelerated hypofractionated and conventional whole breast radiotherapy (WBRT).This was a blocked randomized, clinical trial on women with early-stage node-negative invasive breast cancer after breast conservation surgery (BCS) with clear margins randomly assigned to receive WBRT either at a conventional dose of 50.0 grays (Gy) in 25 fractions (the conventional group) or at a dose of 42.5 Gy in 16 fractions (the hypofractionated group). Boost irradiation was permitted in both groups. Data were analyzed by SPSS V21.0 using Mann–Whitney U, independent-samples t- and Chi-Square/Fisher's exact tests at the level of $P \le 0.05$.The median follows up was 16 months. Forty-one patients in the conventional WBRT arm and 45 patients in the hypofractionated WBRT group were enrolled. No significant difference was observed in terms of left and right ventricle systolic dysfunction and diastolic dysfunction. Pulmonary function tests after 6 and 12 months follow up, were comparable in both groups ($P=0.2$). Skin toxicity during and after treatment was acceptable in both groups. Breast size change in the conventional and the hypofractionated WBRT groups was 14.3% and 7.1%, respectively ($P=0.6$). Excellent or good cosmetic outcome was similar in both groups.The results of our study support the use of accelerated hypofractionated WBRT in women with invasive breast cancer less than five cm and node-negative after breast-conserving surgery, which provides a more convenient shorter course of radiotherapy with a comparable cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile.

Introduction

Adjuvant whole breast radiotherapy in patients with breast cancer who underwent breast-conserving surgery is the standard of care, which leads to a reduction in the rate of local recurrence and improvement in overall survival (1). Conventionally, the prescribed dose for whole breast radiotherapy was considered 50 Gray (Gy) that was commonly delivered in 25 fractions over a period of five weeks given as two-Gy fraction per day followed by an additionally ten Gy boost to tumor bed (as five two-Gy fractions per day) (2). This relatively long radiotherapy course has disadvantages, including patient discomfort, especially in elderly, increased direct or indirect health care costs, and higher workload of radiotherapy facilities (3). In recent years, the pattern of presentation of breast cancer has been changed to the earlier stages which provides this unique opportunity to deliver adjuvant radiation therapy after breast-conserving surgery at a larger daily dose (hypofractionation) over a shorter time (accelerated therapy) with radiobiology and efficacy equivalent to the conventional regimens (4-6). Previous studies confirmedthe safety of these accelerated hypofractionated radiotherapy courses; however, some investigators have questionedthese approaches (7-9). This study aimed to compare the cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile of

Corresponding Author: R. Salek

Cancer Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran

Tel: +98 513 8426936, Fax: +98 513 8426936, E-mail address: SalekR@mums.ac.ir

accelerated hypofractionated and conventional whole breast radiotherapy (WBRT).

Materials and Methods

Study population

The study was conducted in two academic centers for radiotherapy in the northeast of Iran (Omid Education hospital and Emam Reza Education hospital, both affiliated to Mashhad University of Medical Sciences). The study included patients with histologically confirmed early breast cancer (pT1-2N0M0) after breast-conserving surgery and axillary assessment (by sentinel lymph nodes biopsy or axillary lymph nodes dissections) with negative margins. Key exclusion criteria consisted of age ≥70 years old, pregnancy, history of ischemic heart disease, cardiac ejection fraction (EF) $\leq50\%$, history of collagen vascular disease (scleroderma and lupus symptoms), history of chest wall irradiation, and pathologic margin involvement. Also, patients with any abnormalities in their baseline pulmonary/cardiac function tests were excluded from the relevant analysis.

Study design

In this randomized, phase III study, patients have been randomized to hypofractionated whole breast radiotherapy (WBRT) or conventional WBRT. Randomization was done by randomized blocked lists. The study was approved by the Ethical Committee, and informed consent was obtained from all enrolled patients. Patients were randomly assigned 1:1 to two arms including hypofractionated WBRT arm which patients received accelerated hypofractionated whole-breast irradiation at a dose of 42.5 Gy given in 16 fractions over a period of 22 days; and, conventional WBRT arm which patients were treated with whole-breast radiotherapy at a dose of 50 Gy given in 25 fractions. Boost irradiation of the tumor bed was permitted based on the experience of clinicians and the guidelines of our center. If boost were considered, it was delivered by electrons to the tumor bed with a dose of ten Gy (given as four to five two- two-point-five Gy fractions per day). Whole breast radiation was delivered daily from Saturday through Wednesday by means of two opposed tangential fields. No additional attempt was made to treat the regional lymph nodes. All treatments were performed using the Elekta Compact™ single energy (6 MV) linear accelerator and the Precise Treatment System ™ -Elekta multi-energy (6-15MV) linear accelerator.

Follow-up and outcomes

The follow-up process was designed based on equipment available in our center. At the baseline, patients were assessed for cosmetic outcomes, pulmonary function tests, and cardiac function tests by physical examination, tissue Doppler echocardiography, and spirometry, respectively. During radiotherapy, patients were visited weekly, and after its completion, all patients were seen within one month, then after every three months for two years. At each visit, a history was taken, and physical examination was performed. Subacute toxic effects of radiation on pulmonary and cardiac function were assessed within 6 months after randomization using the same method (as baseline evaluations). Late toxic effects of radiation on pulmonary function tests were assessed one year after randomization by spirometry. Skin toxicities were assessed during radiotherapy, within one month after radiotherapy, and at one and then two years after randomization. Cosmetic outcomes and size of breasts were assessed two years after randomization.

The primary endpoint was cosmetic outcome two years after radiotherapy. Secondary outcomes were acute, sub-acute, and late toxic effects of radiation on cardiac function, pulmonary function, and skin toxicity and cosmetic outcome.

Cardiac function was assessed by tissue Doppler and strain echocardiography using Philips iE33 xMATRIX Echocardiography. Diastolic variables included E/A (E/A$\leq$one, E/A=one- two, and E/A>two were considered normal/grade I dysfunction, grade II dysfunction, and grade III dysfunction) and E/Em (E/Em$\geq$ eight were considered as an abnormal test). Systolic variables consisted of EF (EF$\geq$50% was considered normal), S_m (Decreased levels indicate abnormalities), and $S_{velocity}$ (Decreased levels indicate abnormalities).

Pulmonary function was assessed by spirometry using MIR Spirolab™ New. In this purpose, forced vital capacity (FVC), maximal (mid-) expiratory flow (MMEF), and Tiffeneau-Pinelli index (FEV1/FVC ratio) were evaluated.

Acute radiation dermatitis grading scale and late radiation morbidity grading scale based on National Cancer Institute Common Toxicity Criteria (NCI-CTC) version two.0 (V2.0) were used for assessment of cutaneous toxicity of radiotherapy. Cosmetic outcomes were assessed by the modified Harvard Harris cosmetic scale as excellent, good, fair, and poor outcomes.

Ethical approval and consent to participate

Institutional review board approval was obtained

from the Ethical Committee of Mashhad University of Medical Sciences. All procedures performed in this study involving human participants were approved by the Ethics Committees of Mashhad University of Medical Sciences (reference number: 920067/1/860) and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial was registered in the Iranian Registry of Clinical Trials (Clinical Trial registration number: IRCT2014102519675N1). Written informed consent about the researchable use of the clinical data was obtained from each participant patient. All patient data were anonymous and de-identified prior to analysis.

Statistical methods

Data were analyzed by Statistical Package for the Social Sciences (SPSS) V21.0. The Kolmogorov-Smirnov test (K-S test) was applied to test for a normal distribution. Based on results of K-S test, the Mann–Whitney U test was used for comparison of age, duration of radiotherapy and the lungs V20 Gy (the percent of the lung receiving 20 Gy) between two groups. Also, to compare the heart V25 Gy (the percent of the heart receiving 25 Gy) between studies groups, the independent-samples t-test was applied. For comparing nominal variables, the Chi-Square and or Fisher's Exact were used. Groups were compared with the use of 95% confidence intervals for the difference between proportions. The level of significance was considered $P \leq 0.05$.

Results

Patient population

Between June 2013 and May 2017, 86 patients were randomly assigned to hypofractionated WBRT (n=45) or conventional WBRT arms (n=41). The Consolidated Standards of Reporting Trials (CONSORT) diagram summarizes patient status (Figure 1). Both groups were similar in terms of age, tumor pathologic size, tumor grade, hormonal receptor status, HER2/neu status, and

chemotherapy treatment regimens. Table 1 summarizes the data on demographic and baseline disease characteristics.

Treatment characteristics

In both groups, most patients received a boost to tumor bed (hypofractionated WBRT: 86.7% vs. conventional WBRT: 97.5%, P=0.1). As expected, the duration of radiotherapy was significantly shorter in the hypofractionated group (28.6±3.9 vs. 42.5±4.2 days, P=0.0001). The lungs V20 Gy was 16.5±4.3% in the hypofractionated group and 16.17±4.7% in the conventional group (P=0.5). The heart V25 Gy were similar in hypofractionated and conventional WBRT groups (10.9±4.3% and 10.3±4.8%, respectively P=0.6). The mean dose to the heart in the hypofractionated and conventional was 7.1±2.5 Gy and 7.1±5.7 Gy, respectively.

Toxic effects of radiation and cosmetic outcome

For assessment of cardiac function, only patients with left-side tumors were enrolled for analysis. Tissue Doppler and strain echocardiography revealed considerable abnormalities in the cardiac function of patients after WBRT, although there is no statistical difference between both groups. Furthermore, all EFs were reported in the normal range. Results of spirometry in the assessment of pulmonary function showed that restrictive lung disorder occurred just in one patient of the conventional group after radiotherapy. No symptomatic cardiac dysfunction or pulmonary disorder was reported in patients of both groups. Table 2 compares the data on echocardiographic, spirometric changes, and skin toxicity after radiotherapy.

Cosmetic Outcome, Assessed According to the modified Harvard Harris cosmetic scale showed that at two years, 58.6% of women in the control group as compared with 56.7% of women in the hypofractionated-WBRT group, had an excellent or good cosmetic outcome. Table 3 shows the cosmetic outcome and breast size change at two years.
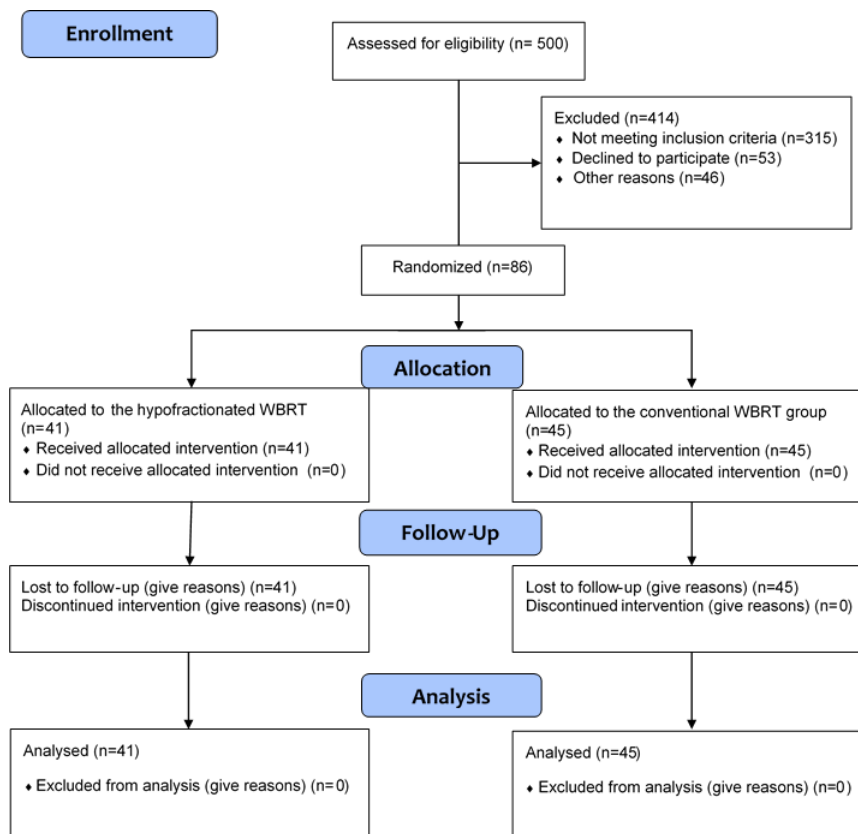
Figure 1. CONSORT diagram showing patients enrolment in the study; in the hypofractionated WBRT group, 9 patients were excluded due to abnormal baseline spirometry results, and one patient was excluded due to chronic obstructive pulmonary disease (COPD) pattern on 2en spirometry from analysis of lung toxicities profile. In the conventional WBRT group, 5 patients had abnormal baseline spirometry results, and 2 patients had COPD pattern on 2en spirometry, and all of them were excluded from the analysis of lung toxicities profile

Table 1. Patient and tumor characteristics per treatment group

Variables		hypofractionated WBRT n=45 Frequency (%)	conventional WBRT n=41 Frequency (%)	P
Age (years)†	45≥	23 (51.1)	20 (48.8)	p=0.7
	45<	22 (48.9)	21 (51.2)	
Side†	left	25 (55.6)	23 (56.1)	p=0.9
	right	20 (44.4)	18 (43.9)	
T (pathologic)†	T1	20 (44.4)	11 (26.8)	p=0.08
	T2	25 (55.6)	30 (73.2)	
Grading†	I	4 (8.9)	9 (22)	p=0.1
	II	32 (71.1)	22 (53.7)	
	III	9 (20)	10 (24.4)	
ERstatus †	Negative	10 (23.3)	8 (17.5)	p=0.5
	Positive	33 (76.7)	33 (82.5)	
PR status †	Negative	13 (30.2)	12 (27.5)	p=0.7
	Positive	30 (69.8)	29 (72.5)	
HER2 status†	Negative	36 (83.7)	36 (87.5)	p=0.6
	Positive	7 (16.3)	5 (12.5)	
Treatment regimen†	ADR-based	34 (75.6)	32 (77.5)	p=0.8
	others	11 (24.4)	9 (22.5)	

ADR: Doxorubicin, ER: The estrogen receptor, HER2: human epidermal growth factor receptor 2, PR: Progesterone receptor. †Chi-Square test revealed no significant difference

Table 2. Cardiac function, pulmonary function, and skin toxicity after radiotherapy

Variables		hypofractionated WBRT Frequency (%)	conventional WBRT Frequency (%)	P
Cardiac function				
Right ventricular systolic dysfunction 6 months after RT†		7 (36.8)	8 (47.1)	P=0.5
Left ventricular systolic dysfunction 6 months after RT†		10 (50)	6 (35.3)	P=0.3
Decreased ejection fraction 6 months after RT#*		5 (25)	4 (23.5)	P=0.6
Diastolic dysfunction based on E/E$_m$ 6 months after RT†		10 (52.6)	7 (41.2)	P=0.4
Diastolic dysfunction based on E/A 6 months after RT†		9 (45)	8 (47.1)	P=0.9
Pulmonary function				
Restrictive lung disorder 6 months after RT#		0 (0)	1 (4.5)	P=0.3
Restrictive lung disorder 12 months after RT#		0 (0)	1 (10)	P=0.2
Skin toxicity				
During RT	Desquamation (grade≥II)†	5 (11.1)	9 (22)	P=0.1
	Erythema (grade=II)†	5 (11.1)	11 (26.8)	P=0.06
	Ulcer#	0 (0)	1 (2.4)	P=0.4
	Edema†	21 (46.7)	14 (34.1)	P=0.2
After one yr	Edema†	21 (46.7)	25 (62.5)	P=0.1
After two yrs	Fibrosis (grade≥II)#	2 (5)	3 (8.6)	P=0.6
	Pigmentation†	9 (32.1)	13 (52)	P=0.1
	Telangiectasia#	2 (5.9)	2 (7.4)	P=0.8

RT: Radiotherapy, yr: year †Chi-Square test revealed no significant difference, #Fisher's Exact test revealed no significant difference, * All EFs were reported in the normal range

Table 3. The cosmetic outcome and breast size change at 2 years

Variables		hypofractionated WBRT Frequency (%)	conventional WBRT Frequency (%)	P
breast size change#	No	26 (92.9)	18 (85.7)	p=0.6
	Yes	2 (7.1)	3 (14.3)	
cosmetic outcome†	Excellent	17 (56.7)	17 (58.6)	p=0.8
	Good	13 (43.3)	12 (41.4)	

Fisher's Exact test revealed no significant difference#Chi-Square test revealed no significant difference, †

Discussion

This was a randomized phase III clinical trial for evaluation of cosmetic outcome and safety of accelerated hypofractionated whole-breast radiotherapy for early breast cancer. This study aimed to compare the cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile of hypofractionated and conventional WBRT. We found that accelerated, hypofractionated whole-breast radiotherapy in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes is the valuable delivering method of adjuvant radiotherapy which provide a shorter course of radiotherapy with a comparable cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile.

In the present study, the cosmetic outcome in both groups was comparable; meanwhile, cutaneous toxicity in hypofractionated and conventional WBRT groups are similar either during radiotherapy or after it. In a study by Cante *et al.*, that was conducted on 463 women with early breast cancer, patients received hypofractionated whole-breast radiotherapy with a dose of 45 Gy in 20 fractions with a concomitant daily boost. Similarly, they reported a good or excellent cosmetic outcome in the hypofractionated group (10). In a retrospective analysis of 162 women who undergone hypofractionated whole-breast radiotherapy at a dose of 42.4 Gy in 16 fractions, also, the cosmetic results were similar to the results of the present study (11). Recently, Ciammella et al. reported toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy and their predictive clinical and dosimetric factors. In their

study, patients in the hypofractionated group received 40.05Gy/2.67Gy with an additional 9 Gy boost to the tumor bed sequentially. They showed that the incidence of acute and subacute toxicity of hypofractionated groups was negligible, and up to 95% of patients had excellent cosmetic outcome (7). Consistent with studies of Pinnarò *et al.*, and Zygogianni *et al.*, (5,12), the results of the present study provide a strong skin safety profile for delivering a higher dose per fractions during hypofractionated WBRT (vs. conventional 2 Gy per fractions). Albeit, in the present study, the frequency of acute skin toxicity was higher in the conventional group. A possible explanation for these findings is that the short course of treatment in the hypofractionated group prevents the expression of side effects of radiotherapy on the skin. In this context, Amouzegar Hashemi *et al.*, observed that the skin toxicity of patients in the hypofractionated group was slightly higher within three weeks after the treatment completion (13).

Unexpectedly, we found a considerable abnormality in cardiac function of patients after WBRT on Tissue Doppler and strain echocardiography, although there is no statistical difference between both groups in term of the heart V25, systolic dysfunction, and diastolic dysfunction neither there is no report on cardiac events in these patients. Interestingly, the ejection fractions (that measured conventionally as the main parameter of cardiac function) were reported normal in all patients. Recently, Erven *et al.,* assessed the cardiac function of patients with breast cancer after radiotherapy using Tissue Doppler and strain echocardiography, as emerging real time ultrasound techniques that provide a measure of wall motion of heart; and showed a significant reduction on the systolic function (14). Also, they reported that unlike conventional echocardiography, Tissue Doppler and strain could find out the subclinical cardiac dysfunctions (15). A clinical trial on short-course radiotherapy with simultaneous integrated boost for stage I-II breast cancer by Van Parijs *et al.*, concluded that accelerated method of WBRT is not accompanied by increased long term cardiac toxicity (9). Also, Haviland *et al.*, reported the 10-year follow-up results of The UK Standardisation of Breast Radiotherapy (START) trials on hypofractionated radiotherapy for treatment of early breast cancer and showed that long term risk of ischemic heart disease is comparable between conventional and hypofractionated radiotherapy (16). However, some guidelines on hypofractionated accelerated WBRT raise some controversies regarding the cardiac safety of these treatment methods (8). In other hands, some

investigators believe that heart will be spared better with accelerated regimes, i.e., the dose to the heart, adjusted for fraction size using the linear-quadratic model, will generally be lower after hypofractionated compared with normofractionated schedules, even for very low values of α/β (17). Notwithstanding these findings, as stated by Morrow et al.,"radiation oncologist should operate on the principle that there is no totally safe radiation dose to the heart, and that the heart dose should be kept as low as possible"(18). It is worth mentioning that the present study is among unique studies that assessed the subclinical cardiac function changes before and after radiotherapy. Unfortunately, the V20 of the heart was relatively high, despite any attempts to spare it. It could be the contributing factor of observation of considerable abnormalities in the cardiac function of patients after WBRT.

We observed that lungs V20, short term, and long term spirometric changes were similar in both groups. Previous studies reported similar results (9,16). In a study on the frequency of radiation-induced pneumonitis after conventional and hypofractionated WBRT, the authors concluded that hypofractionated WBRT does not increase the risk of pulmonary toxicity (19). This pneumonitis usually manifests as restrictive changes in the spirometry and as patchy consolidation, ground-glass opacities, and pleural reactions on the computed tomography imaging and present with shortness of breath, dry cough, and a mild fever (20). Its occurrence is related to the ipsilateral lung dose-volume parameters, doxorubicin- or taxane-based chemotherapy, previous history of smoking, and concurrent treatment with tamoxifen (21,22). Considering the fact that all patients in the present study were node-negative, therefore no additional attempt was made to treat the regional lymph nodes resulting in a decrease in the volume of lungs that are irradiated.

This trial has some limitations which have to be pointed out. This study was performed on patients with early breast cancer (pT1-2No). Thus, its results cannot be extrapolated to patients with lymph node metastasis nor patients with tumors greater than 5 cm. Furthermore, patients with comorbidities like diabetes mellitus or collagen vascular disease and any patient with abnormalities in their baseline pulmonary/cardiac function tests were excluded. Therefore the safety of a higher dose per fraction in these settingscannot be concluded. Finally, because of resource limitation, we could not perform thoracic high-resolution computed tomography, which has higher sensitivity for assessment of pulmonary toxicity of irradiation. However, this will

be the subject of ongoing studies. In this randomized clinical trial, patients with early-stage breast cancer after breast-conserving surgery allocated to receive conventional whole-breast radiotherapy with a dose of 50.0 Gy in 25 fractions or to receive the hypofractionated whole-breast radiotherapy at a dose of 42.5 Gy in 16 fractions. Boost was delivered in a considerable number of patients of both groups with the same fraction size. After decades of performing clinical trials, it has been clear that hypofractionated whole-breast radiotherapy at dose 42.5 Gy during 16 fractions is a clinically efficient and safe method of adjuvant radiotherapy for patients with early breast cancer who underwent breast-conserving surgery. Our results provide support for the use of accelerated, hypofractionated, WBRT in women with invasive breast cancer less than five cm and node-negative after breast-conserving surgery, which provides a shorter course of radiotherapy with a comparable cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile.

In conclusion, the results of our study support the use of accelerated hypofractionated WBRT in women with invasive breast cancer equal or less than five cm and node-negative after breast-conserving surgery which provides a more convenient shorter course of radiotherapy with a comparable cosmetic outcome and cutaneous, cardiac, and pulmonary toxicity profile. However, the toxicity of a therapeutic approach is one of the requisites for supporting a treatment approach. The other necessity is its effect on survival, loco-regional control, etc. that wasn't in the objectives of the present study. In other words, this study can't absolutely support the hypofractionated approach because it doesn't contain the results of survival, loco-regional control, etc.

Acknowledgments

References

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106.
2. Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev 2017;11:Cd011987.
3. Lievens Y. Hypofractionated breast radiotherapy: financial and economic consequences. Breast 2010;19:192-7.
4. Salek R, Shahidsales S, Mozafari V. Changing pattern in the clinical presentation of breast cancer in the absence of a screening program over a period of thirty-three years in Iran. Breast 2016;28:95-9.
5. Pinnarò P, Soriani A, Landoni V, Giordano C, Papale M, Marsella A, et al. Accelerated hypofractionated radiotherapy as adjuvant regimen after conserving surgery for early breast cancer: interim report of toxicity after a minimum follow up of 3 years. J Exp Clin Cancer Res 2010;29:9.
6. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-20.
7. Ciammella P, Podgornii A, Galeandro M, Micera R, Ramundo D, Palmieri T, et al. Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors. Radiat Oncol 2014;9:97.
8. Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenbergh PH, Ibbott GS, et al. Fractionation for Whole Breast Irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. International Int J Radiat Oncol Biol Phys 2011;81:59-68. doi:http://doi.org/10.1016/j.ijrobp.2010.04.042.
9. Van Parijs H, Miedema G, Vinh-Hung V, Verbanck S, Adriaenssens N, Kerkhove D, et al. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. Radiat Oncol 2012;7:80.
10. Cante D, Rosa La Porta M, Casanova-Borca V, Sciacero P, Girelli G, Pasquino M, et al. Accelerated hypofractionated adjuvant whole breast radiotherapy with concomitant photon boost after conserving surgery for early stage breast cancer: a prospective evaluation on 463 patients. Breast J 2011;17:586-93.
11. Hijal T, Al Hamad AA, Niazi T, Sultanem K, Bahoric B, Vuong T, et al. Hypofractionated radiotherapy and adjuvant chemotherapy do not increase radiation-induced dermatitis in breast cancer patients. Curr Oncol 2010;17:22-7.

12. Zygogianni A, Kouloulias V, Kyrgias G, Armpilia C, Antypas C, Theodorou K, et al. comparison of two radiotherapeutic hypofractionated schedules in the application of tumor bed boost. Clin Breast Cancer 2013;13:292-8.

13. Amouzegar Hashemi F, Kalaghchi B, Sebzari AR, Haddad P, Shahabi Z. Comparing the effects of conventional and hypofractionated radiotherapies on early skin toxicity and cosmetic outcomes after breast cancer conserving surgery. Tehran Univ Med J 2012;70:540-7.

14. Erven K, Jurcut R, Weltens C, Giusca S, Ector J, Wildiers H, et al. Acute radiation effects on cardiac function detected by strain rate imaging in breast cancer patients. Int J Radiat Oncol Biol Phys 2011;79:1444-51.

15. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, et al. Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys 2013;85:1172-8.

16. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086-94.

17. Appelt AL, Vogelius IR, Bentzen SM. Modern hypofractionation schedules for tangential whole breast irradiation decrease the fraction size-corrected dose to the heart. Clin Oncol 2013;25:147-52.

18. Morrow M, Burstein HJ, Harris JR. Malignant Tumors of Breast. In: DeVita VT, Lawrence TS, Rosenberg SA, DePinho RA, Weinberg RA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology 10th ed. Philadelphia: Wolters Kluwer, 2015:1117-56.

19. Fragkandrea I, Kouloulias V, Mavridis P, Zettos A, Betsou S, Georgolopoulou P, et al. radiation induced pneumonitis following whole breast radiotherapy treatment in early breast cancer patients treated with breast conserving surgery: a single institution study. Hippokratia 2013;17:233-8.

20. Choi YW, Munden RF, Erasmus JJ, Park KJ, Chung WK, Jeon SC, et al. Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. Radiographics 2004;24:985-97.

21. Beal K, Hudis C, Norton L, Wagman R, McCormick B. Radiation pneumonitis in breast cancer patients treated with taxanes: does sequential radiation therapy lower the risk? Breast J 2005;11:317-20.

22. Bentzen SM, Skoczylas JZ, Overgaard M, Overgaard J. Radiotherapy-related lung fibrosis enhanced by tamoxifen. J Natl Cancer Inst 1996;88:918-22.