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Treatment Outcome and Skin Complications in Tumor Bed Boost Radiotherapy Using Photons or Electrons in Breast Cancer Patients after Breast-Conserving Surgery

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ABSTRACT

Background and Objective: In patients with breast cancer, the administration of an additional dose of radiotherapy to the tumor bed after breast treatment is associated with a decrease in local recurrence. Electron source is mainly used due to proper dose distribution and lack of skin irradiation. Nevertheless, access to electrons is not possible in all medical centers. Therefore, continuing treatment using smaller photon fields may be a reasonable option. The aim of this study is to investigate and compare the outcome of treatment and skin complications in tumor bed boost radiotherapy using photons or electrons in breast cancer patients after breast-conserving surgery.

Methods: In this retrospective cohort, 280 patients with non-metastatic breast cancer who underwent breast-conserving surgery and adjuvant radiotherapy were included in the study. After whole breast radiotherapy with conventional regimen (50 Gy in 25 sessions), the patients underwent tumor bed boost with electrons or photons (with a dose of 10 Gy in 5 sessions) (electron: 145 people, photon: 135 people). Survival values, cosmetic results (Harvard Harris criteria) and skin toxicity (5th edition of General Toxicity Criteria and Adverse Effects) were compared between the two groups during the follow-up of patients.

Findings: Recurrence-free survival in the same breast was not significantly different in two groups (recurrence-free survival in photon boost 95% (with a 95% confidence interval between 9% and 97%) and electron boost 93% (with a 95% confidence interval between 79% and 97) (p=0.69). There was no difference between radiotherapy-induced dermatitis and subcutaneous toxicity at the end of the treatment between the two treatment groups. However, one month after the end of the treatment, the cases of severe radiotherapy-induced dermatitis were higher in the photon treatment group (88% vs. 65.5%, p=0.007). However, the subcutaneous toxicity 2 months after the end of treatment was significantly higher in the electron boost group (0% vs. 7.5%, p<0.05). Mild pain in the same breast 6 months after the end of the treatment was higher in the photon treatment group (0% vs. 8.9%, p<0.001).

Conclusion: Based on the results of the present study, using an electron or photon source to boost the dose to the tumor bed following whole breast radiotherapy in breast cancer patients undergoing breast-conserving surgery is associated with similar treatment results in terms of recurrence in the same breast. Of course, the toxicity profile, especially the skin toxicity, is different between the two approaches.

Keywords: *Breast Cancer, Tumor Bed Boost Radiotherapy, Adjuvant Radiotherapy, Photon, Electron*.

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Introduction

Breast cancer is a major health problem all over the world, which has a high prevalence in Iran and the world, and it is classified as the most common malignancy in women (1). Breast cancer treatment is a multidisciplinary issue that includes a combination of surgery, radiotherapy, chemotherapy and hormone therapy (2). Breast conserving surgery followed by whole breast radiotherapy has been replacing mastectomy in local breast cancer patients (without metastasis) for several decades and is considered as the definitive treatment for these patients (3, 4).

In women with breast cancer who have undergone breast-conserving surgery, regardless of the presence or absence of regional lymph node involvement, whole breast radiotherapy reduces the rate of local recurrence and eliminates the need for mastectomy (5-8). In a meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group, the results have shown that breast radiotherapy after breast-conserving surgery is associated with a reduction in breast cancer mortality (9).

Radiotherapy for breast cancer cases that have undergone breast conserving surgery is 60-66 Gy during 6-7.5 weeks, which is usually administered 45-50 Gy to the whole breast in 25 sessions, daily from 1.8 to 2 Gy during five weeks and then 10-16 Gy is administered to the tumor bed (2, 5). Considering that the highest rate of recurrence in the affected breast occurs around the tumor bed, administering an increased dose to the tumor bed (Tumor Bed Boost) is associated with a significant reduction in local recurrence. The intensified dose can be administered using external beam irradiation, brachytherapy and intraoperative radiation therapy (IORT) (8), which is the conventional method of using external radiation therapy for this purpose (9-13). In each of these radiotherapy approaches (external or intracavity), it is possible to use electron or photon beams with the aim of boosting the dose of the tumor bed, which, considering the relatively shallow depth of the tumor bed, suitable field size, better protection of healthy organs and appropriate dose distribution, in most cases, external radiotherapy using electrons is the basis for dose boost of the tumor bed (9) and this (use of photons instead of electrons) is very important in Iran due to the unavailability of electrons in all centers. It is one of the reasons for the importance of addressing this issue, because in some studies such as the study of Kovacs et al. and Toscas et al. (14, 15), the use of photons was preferable to electrons and better results were obtained. However, in some other studies, such as the studies of Rajan et al. and Verhoeven et al., no difference was found for boost with electrons or photons (13, 16).

Of course, in order to benefit from these electron beams, a high-energy accelerator is needed, which due to the significant costs of these devices, there is no wide access to them for all patients. Therefore, continuing the treatment using photons with limited fields is a logical option. This is despite the fact that there is no evidence regarding the use of a photon field instead of a single electron field. Therefore, the electron source is routinely used mainly due to the appropriate dose distribution and lack of skin irradiation. However, due to the lack of access to electrons in all centers of Iran, it is not possible to use electrons. Therefore, continuing the treatment using smaller photon fields may be a reasonable option. The purpose of this study is to investigate and compare the treatment outcome and toxicity in tumor bed boost radiotherapy using photons or electrons in breast cancer patients after breast-conserving surgery.

Methods

In this retrospective cohort study, after approval by the Ethics Committee of Babol University of Medical Sciences with code IR.MUBABOL.REC.1399.234, 280 patients with non-metastatic breast cancer, undergoing breast-conserving surgery and adjuvant radiotherapy, who referred to Shahid Rajaei Hospital affiliated to Babol University of Medical Sciences, during the years 2020 to 2021, and at least one year had

passed since the completion of their radiotherapy, were included in the study. After full breast radiotherapy with a conventional regimen (50 Gy in 25 sessions), the patients were subjected to tumor bed boost radiotherapy with electrons or photons (with a dose of 10 Gy in 5 sessions) (electron receiving group: 145 people, photon receiving group: 135 people). Survival values, cosmetic results (Harvard Harris criteria) and skin toxicity (5th edition of General Toxicity Criteria and Adverse Effects) were compared between the two groups with follow-up of patients. Patients receiving electrons, after receiving 25 sessions of radiotherapy, were referred to other centers with electrons, including various centers in Tehran or Sari, to receive Boost, and were treated in the same way as recommended in oncology sources in RTOG, and observations were recorded in the patients' oncology records. Patients were evaluated according to the type of tumor bed boost after whole breast radiotherapy. Patients underwent tumor bed boost radiotherapy with electrons or photons after whole breast radiotherapy with a dose of 10 Gy (during 5 sessions). Recurrence in the involved quadrant, recurrence in the opposite breast or recurrence in other areas (including distant metastasis), skin and breast tissue toxicity were considered. Aesthetic results and late skin toxicity were respectively evaluated using the modified Harvard Harris Cosmetic Scale (17) and the 5th edition of Common Terminology Criteria for Adverse Events (CTCAE v.5) (18) by a radiation oncology specialist and recorded and followed up in the patients' oncology records.

The inclusion criteria included consent to participate in the study, age under 70 years, performing breast conserving surgery, receiving all stages of adjuvant radiotherapy treatment and receiving adjuvant radiotherapy with a conventional daily dose (two Gy). The exclusion criteria included a history of receiving radiotherapy before developing malignancy, performing intracavitary radiotherapy during surgery (with the aim of increasing the dose of the surgical bed or definitive treatment), having autoimmune diseases with skin involvement (lupus erythematosus or scleroderma) and receiving a dose of more than 10 Gy for the boost phase.

In the present study, radiotherapy was performed with 3D Conformal Radiotherapy (3D Conformal Radiotherapy/3DCRT) and based on CT scan information. Before radiotherapy, CT Scan simulation was performed for patients in the supine position and on a special bed for breast radiotherapy. During the CT scan, the arm on the side of the involved breast is placed above the head so that the shoulder is placed at an angle of 90 to 120 degrees (the patient's hand was placed in abduction and external rotation position). Skin folds in the supraclavicular area were avoided and the bed was angled 10 to 15 degrees so that the chest wall area was parallel to the bed. In patients who were candidates for radiotherapy treatment based on supraclavicular lymph nodes and level III axilla, the patient's face was turned to the opposite side so that the mandible and spinal cord were out of the supraclavicular field. The breast area for whole breast radiotherapy was determined using RTOG clinical guidelines (11). The tumor bed was determined by using a clip placed in the surgical cavity during breast conserving surgery or with the help of information obtained from pre-surgery imaging (breast ultrasound and mammography) for those patients who did not have a clip.

Whole breast radiotherapy was performed in all patients using photon accelerator 6 MV (Compact device manufactured by Elekta, Sweden) with the help of two opposite tangent fields. In order to administer a dose boost to the tumor bed, in patients treated with photon, treatment was prescribed using two front limited tangent fields, and in patients treated with electrons, treatment was administered with a single anterior field (where the electron energy is determined based on the depth and size of the mass). The treatment dose for whole breast radiotherapy was 50 Gy, which was administered with a daily dose of 2 Gy for five weeks. Dose boost of 10 Gy was administered to the tumor bed using photons or electrons.

Recurrence in the involved quadrant, recurrence in the opposite breast, or recurrence in other areas (including distant metastasis), and the discovery of evidence of disease recurrence in the mentioned areas, which has been confirmed by pathological examination (except for multiple distant metastasis), were considered. Cosmetic results and late skin toxicity were evaluated using the modified Harvard Harris Cosmetic Scale and Common Terminology Criteria for Adverse Events (CTCAE v.5), respectively (12). Data were entered into STATA 14. While presenting descriptive statistics using mean, standard deviation, frequency and percentage, analytical analysis was performed using independent t-test (to compare quantitative data) and Fisher's exact test (to compare qualitative data). Survival analysis was performed using log-rank test and presenting Kaplan-Meier curves, and $p<0.05$ was considered significant.

Results

280 eligible patients were included in this study. The mean age of patients was 47.5±11.1 years (minimum 26 and maximum 69 years). The mean age in the photon group was 47.54±1.02 and in the electron group was 47.72±0.91 years, and the mean tumor size in the photon group was 2.58±0.08 and in the electron group was 2.58±0.11. During the study, 9594 patients were under follow-up, 9 patients (21.3%) of all patients under study had distant metastasis during the follow-up. The median follow-up time of the study was 35 months (minimum 5 and maximum 42 months) and disease-free survival in photon boost was 0.97 (with a 95% confidence interval between 93% and 97%) and in electron boost 0.96 (with a 95% confidence interval between 91% and 98%). In the total follow-up time of the patients in this study (minimum 7 and maximum 42 months of follow-up), we did not reach the median disease-free survival (disease-free survival reaches 50%). The median follow-up time for the overall survival of the patients was 35 months (minimum 9 and maximum 42 months of follow-up) and during the study, all 9 patients with distant metastasis died, all of whom were in the electron boost treatment group. The overall survival of electron boost patients during the study was 0.93 with a 95% confidence interval (88% to 96%) and 100% in photon boost ($p=0.003$). During this study, we also did not reach the median overall survival time of the patients. Table 1 shows the comparison of individual clinical and oncological characteristics of patients with non-metastatic breast cancer according to the type of boost (photon, electron).

Individual clinical and oncology characteristics of patients with non-metastatic breast cancer were statistically the same in the two groups of boost treatment (photon, electron). Only in terms of variable T in disease stage, in the electron therapy group, 14.4% of patients were in stage 3 of the disease, while in the photon therapy group, all patients were in stage 1 and 2 ($p=0.009$) (Table 1).

The comparison of treatment results according to the type of boost shows that the type of boost did not cause any difference in the rate of recurrence in the tumor bed and recurrence in the same breast in the two groups of patients, although the patients whose boost type was photon were free of distant metastasis, while 21.6% of patients with electron boost had distant metastasis ($p=0.002$).

The comparison of complications at the end of the treatment showed that the type of boost in radiotherapy-induced dermatitis and subcutaneous toxicity did not cause any difference in the two treatment groups. However, one month after the completion of the treatment, the cases of severe dermatitis caused by radiotherapy were more in the boost photon treatment group ($p=0.007$). However, the subcutaneous toxicity two months after the end of treatment in the electron boost treatment group was significantly higher than photon ($p<0.05$) and the same breast pain was mild 6 months after the end of treatment in the photon treatment group ($p<0.001$) (Table 2).

Table 1. Comparison of individual, clinical and oncological characteristics of patients with non-metastatic breast cancer according to the type of boost

Variable	Boost type		p-value
	Photon (n=135) Number(%)	Electron (n=145) Number(%)	
T stage of the disease			
1	54(40.0)	70(48.28)	
2	81(60.0)	69(47.59)	0.009[a]
3	0(0)	6(4.14)	
Involvement of lymph nodes			
0	84(62.22)	74(51.03)	
1	39(28.89)	49(33.79)	0.22[b]
2	6(4.44)	10(6.90)	
3	6(4.44)	12(8.28)	
Disease stage			
1	33(24.44)	45(31.03)	
2	90(66.67)	7(53.79)	0.07[b]
3	12(8.89)	22(15.17)	
Disease grade			
1	15(11.11)	32(22.07)	
2	87(64.44)	89(61.38)	0.027[b]
3	33(24.44)	24(16.55)	
Occurrence of estrogen receptor			
Yes	105(77.78)	119(82.07)	0.370[b]
No	30(22.22)	26(17.93)	
Occurrence of progesterone receptor			
Yes	105(77.78)	116(80.0)	0.64[b]
No	30(22.22)	29(20.0)	
Occurrence of hormone receptors			
Yes	105(77.78)	122(84.14)	0.175[b]
No	30(22.22)	23(15.86	
Molecular subgroup			
A	72(53.33)	73(50.34)	
B	24(17.78)	36(24.83)	0.418[b]
Her	21(15.56)	16(11.03)	
TNBC	18(13.33)	20(13.79)	
Tumor location in breast			
Upper external	93(68.89)	103(71.03)	
Lower external	15(11.11)	5(3.45)	
Upper interior	15(11.11)	22(15.17)	0.134[a]
Lower interior	3(2.22)	3(2.07)	
Central	9(6.67)	12(8.288)	
Side involved			
Right	63(46.67)	71(48.97)	0.70[b]
Left	72(53.33)	74(51.03)	

[a]Fisher Exact Test, [b]Pearson Chi[2]

Table 2. Comparison of treatment results and complications according to the type of boost in patients with non-metastatic breast cancer

Variable	Boost type		p-value
	Photon (n=135) Number(%)	Electron (n=145) Number(%)	
Overall survival of patients in the middle follow-up time of the study (35 months) (95%CI)	100%	0.93 (0.88-0.96)	0.003[a]
Distant metastasis			
No	135(100)	136(93.79)	0.002[b]
Yes	0(0)	9(6.21)	
Recurrence in tumor bed			
No	132(97.78)	140(96.55)	0.42[b]
Yes	3(2.22)	5(3.45)	
Recurrence in the same breast			
No	129(95.56)	140(96.55)	0.76[b]
Yes	6(4.44)	5(3.45)	
Dermatitis caused by radiotherapy at the end of the treatment			
Mild	3(2.2)	0(0)	0.11[b]
Severe	132(97.8)	145(100)	
Dermatitis caused by radiotherapy one month after completion of treatment			
Mild	27(20.0)	50(34.5)	0.007[c]
Severe	108(88.0)	95(65.5)	
Subcutaneous toxicity at the end of treatment			
No	51(37.78)	66(45.52)	0.189[c]
Yes	84(62.22)	79(54.48)	
Subcutaneous toxicity one month after completion of treatment			
No	132(97.7)	145(100)	0.11[b]
Yes	3(2.22)	0(0)	
Subcutaneous toxicity 12 months after completion of treatment			
No	135(100)	134(92.41)	0.001[b]
Yes	0(0)	11(7.59)	
Pain in the same breast 6 months after the end of the treatment			
Mild	135(100)	132(91.03)	<0.001[b]
Severe	0(0)	13(8.97)	
Pain in the same breast 12 months after the end of the treatment			
Mild	129(95.6)	142(97.9)	0.216[b]
Severe	6(4.4)	3(2.1)	

[a]T-Test, [b]Fisher Exact Test, [c]Pearson Chi[2]

Comparison of the overall survival of patients according to the type of treatment and its complications showed that the survival in patients with photon boost type was significantly higher than in patients with electron boost (p=0.003) (Figure 1). Of course, there was no significant difference between survival without recurrence in the same breast between the two groups (Figure 2). On the other hand, metastasis-free survival was significantly lower in patients in the electron boost group (p=0.003) (Figure 3), which shows that the significant decrease in overall survival was caused by distant recurrence. Examining the relationship between survival and pain intensity in the same breast 6 and 12 months after the end of treatment also showed that there is no difference in the survival of patients with mild or severe pain in the same breast 6 and 12 months after the end of treatment (Table 3).

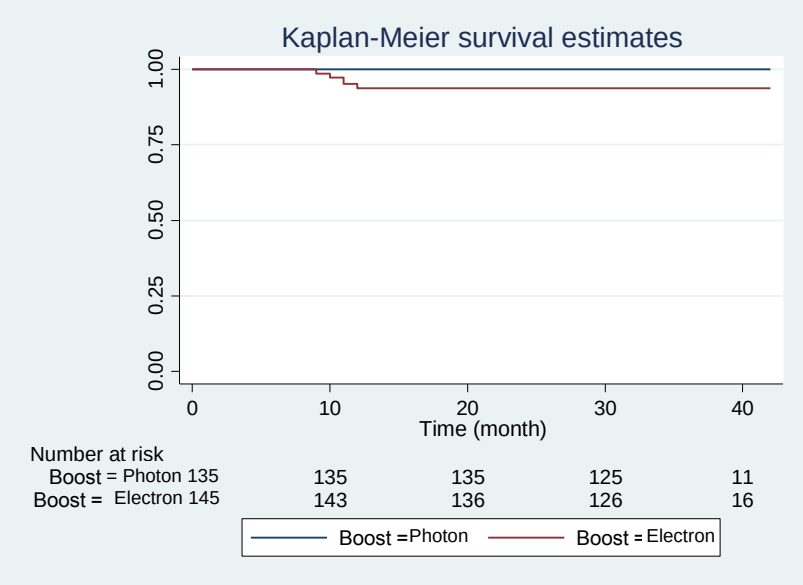

Figure 1. Overall survival of patients according to the type of boost

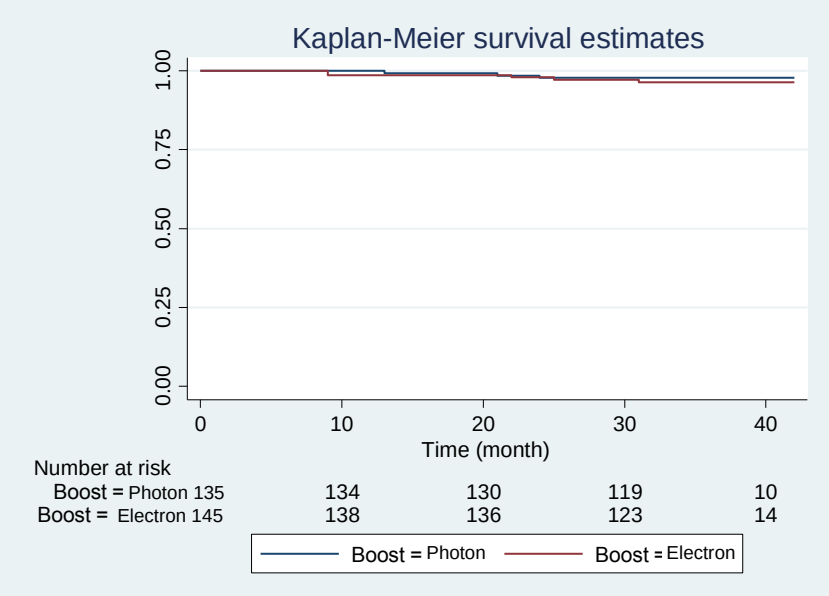

Figure 2. Tumor bed recurrence-free survival according to the type of boost

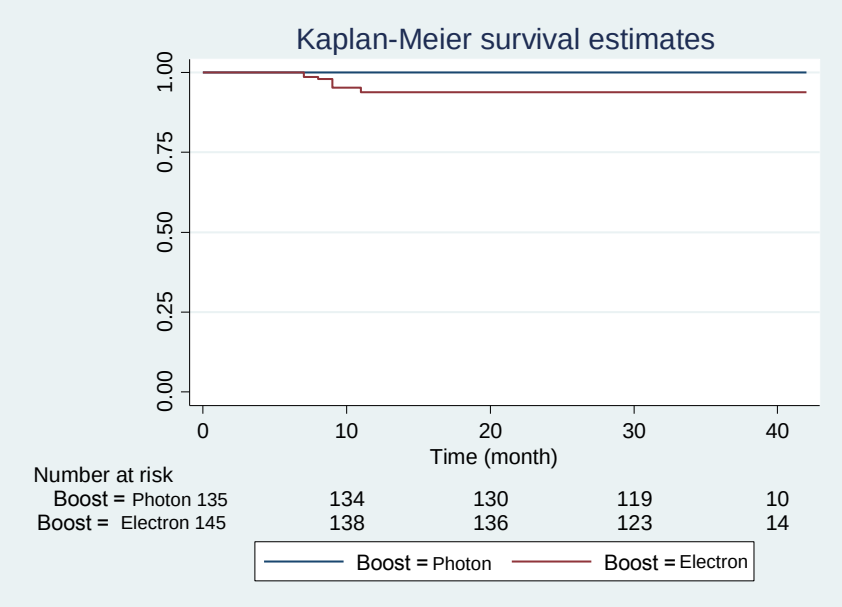

Figure 3. Distant metastasis-free survival according to the type of boost

Table 3. Comparison of the overall survival of patients according to the type of treatment and its complications

Variable	The overall survival of patients in the middle of the follow-up time (35 months) (95% CI)	p-value[a]
Boost type		
Photon (n=135)	100%	0.003
Electron (n=145)	0.93 (0.88-0.96)	
Distant metastasis		
No (n=271)	100%	<0.001
Yes (n=9)	0[**]	
Recurrence in the tumor bed		
No (n=272)	0.97 (0.94-0.98)	<0.001
Yes (n=8)	0.75 (0.31-0.93)	
Recurrence in the same breast		
No (n=269)	0.97 (0.94-0.98)	0.005
Yes (n=11)	0.81 (0.44-0.95)	
Dermatitis caused by radiotherapy at the end of the treatment		
Mild	100%	0.75
Severe	0.96 (0.93-0.98)	
Dermatitis caused by radiotherapy one month after completion of treatment		
Mild	0.90 (0.81-0.95)	<0.001
Severe	0.99 (0.96-0.99)	

Subcutaneous toxicity at the end of treatment		
1	0.92 (0.85-0.95)	<0.001
2	100%	
Subcutaneous toxicity one month after completion of treatment		
No	0.96 (0.93-0.98)	0.750
Yes	100%	
Subcutaneous toxicity 12 months after completion of treatment		
No	100%	<0.001
Yes	0.18 (0.02-0.44)	
Pain in the same breast 6 months after finishing the treatment		
Mild	100%	0.501
Severe	0.96 (0.93-0.98)	
Pain in the same breast 12 months after the end of the treatment		
Mild	100%	0.58
Severe	0.96 (0.93-0.98)	

[a]Log-rank test for equality of survivor functions

[**]All 9 patients with distant metastases died by the 12th month of study follow-up and the overall survival of this group of patients was zero in the middle of the follow-up time, which is the 35th month of the study.

Discussion

In this study, the comparison of treatment results according to the type of boost showed that the type of boost treatment did not cause any difference in the rate of recurrence in the tumor bed and recurrence in the same breast in two groups of patients, although the patients whose boost type was photon were free of distant metastasis, while 21.6% of patients with electron boost had distant metastasis. Moreover, the comparison of complications at the end of the treatment shows that the type of boost in dermatitis caused by radiotherapy and subcutaneous toxicity at the end of the treatment does not cause any difference in the two treatment groups. However, one month after the completion of treatment, the cases of severe dermatitis caused by radiotherapy were higher in the boost photon treatment group. Nevertheless, the subcutaneous toxicity two months after the end of treatment in the electron boost treatment group was significantly higher than that of photon, and the same breast pain was mild six months after the end of treatment in the photon treatment group. Also, the comparison of the overall survival of patients according to the type of treatment and its complications showed that the survival in patients with photon boost type was significantly higher than in patients with electron boost. In addition, patients who were free of recurrence in the tumor bed or recurrence in the same breast during the study had a higher overall survival than other patients, and patients with subcutaneous toxicity 12 months after the end of treatment had the lowest survival rate. As a result, out of 11 patients with this complication, only 2 survived (95% CI=0.02-0.44, OS=0.18%). Examining the relationship between survival and pain intensity in the same breast 6 and 12 months after the end of treatment also showed that there is no difference in the survival of patients with mild or severe pain in the same breast 6 and 12 months after the end of treatment.

Although the individual clinical and oncological characteristics of patients with non-metastatic breast cancer were statistically the same according to the two groups of boost type treatment (photon, electron). However, in terms of variable T in disease stage, in the electron therapy group, 14.4% of patients were in stage 3 of the disease, while in the photon treatment group, all patients were stage 1 and 2.

Comparing the study of Toscas et al. (15) with this study, the use of photon is preferable to electron and has better results. However, in the study of Verhoeven et al. (16), unlike the current study, no difference was made for boost with electrons or photons. Comparing the study of Rajan et al. (13), unlike our study, it was the same in terms of toxicity, but the important point is that, similar to our study, they had the same local recurrence (in our study, the reason for reduced survival in the electron recipient group was distant metastasis, not local relapse).

Furthermore, in the study of Kovacs et al. (14), the results of this study, similar to ours, showed that the coverage index and conformity index were in favor of using the tumor bed with photons. There was no difference between the two groups in terms of external volume index, and the volume of the lung that received the dose also received a lower dose in the photon method.

In this study, it was found that the type of boost treatment did not cause any difference in the rate of recurrence in the tumor bed and recurrence in the same breast and comparing the complications at the end of the treatment in the two groups of patients.

The type of boost treatment did not cause a difference in the rate of recurrence in the tumor bed and recurrence in the same breast in patients of two groups. In addition, comparing the complications at the end of the treatment shows that the type of boost in dermatitis caused by radiotherapy and subcutaneous toxicity at the end of the treatment in the two treatment groups are different and comparing the overall survival of patients according to the type of treatment and its complications showed that the survival in patients with photon boost was significantly higher than in patients with electron boost, which was due to distant metastasis in the group receiving electrons. Also, patients with subcutaneous toxicity had the lowest survival rate 12 months after the end of treatment, so that only 2 of the 11 patients with this complication survived. Finally, considering that the number of radiotherapy devices with high energy is low in Iran and the frequency of breast cancer patients is also high, the optimal use of existing devices to perform boost treatment with existing radiotherapy devices with lower energy in the absence of electrons, problem solve this problem to some extent.

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