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RESEARCH ARTICLE

Comparison between the risk of ipsilateral breast tumor recurrence after breast-conserving surgery in early breast cancer cases treated by whole breast irradiation with and without boost in patients ≥ 50 years old

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ABSTRACT

Background: Breast-conserving therapy (BCT) is the standard treatment for early breast cancer (BC). Radiotherapy after breast-conserving surgery (BCS) decreases the local recurrence and reduces mortality. Being young is documented as an important poor prognostic factor for disease control. Boost irradiation induces some pitfalls, including moderate to severe fibrosis, impaired cosmoses, and the higher cost of an additional boost therapy. **Patient and Methods**: It is a multicentric retrospective comparative study done at the Clinical Oncology and Nuclear Medicine Department, Mansura University Hospital and Zagazig University and Medical Oncology unit at Oncology Center of Mansoura University, Egypt from January 2016 to December 2017. We analyzed 120 cases of early BC patients with negative margins and low-grade tumors after BCS. They were treated with whole-breast irradiation (WBI) without (group A) and with (group B) boost. **Results**: The median follow-up was 44 months. The local recurrences occur only in 2 cases (3%) and 3 cases (5%) of groups A and B respectively (P = 0.6). Distant metastasis were found in 2 cases (3%) and 4 cases (7%) of group A and B respectively (P = 0.3). The mean overall survival (OS) was 52.8 and 53.2 months for groups A & B respectively (P = 0.6). The mean disease-free survival (DFS) was 54.6 and 52.1 months for groups A and B respectively (P = 0.3). **Conclusion**: We did not find any difference between boost and no boost radiotherapy after BCS in patients ≥50 years old with early BC regarding local failure, DFS and OS.

Keywords: BCS, Radiotherapy boost, local recurrence, WBI, BC

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INTRODUCTION

Breast-conserving therapy (BCT) is considered the standard treatment for early stages as stage I & II breast cancer patients and the results as regard survival were equal after mastectomy (Bartelink et al., 2007).

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has found that radiotherapy after breast-conserving surgery (BCS) minimizes the possibility of recurrence and mortality from breast cancer (BC). Radiotherapy after BCS decreases the chance of disease recurrence to half and reduces BC mortality by about a sixth. The analysis reported that the possibility of ipsilateral breast tumor recurrence (IBTR) could be minimized after whole breast irradiation (WBI) by the booster dose (Bartelink et al., 2015; Early Breast Cancer Trialists' Collaborative Group, 2011; Ono et al., 2019).

Being young is documented by many researchers as an important poor prognostic factor for local control. However, others are still debating this concept (Bollet et al., 2007). Komoike et al. (2006) reported that Being young was one of the major predictors for local failure, and the IBTR was associated markedly with sequencing systemic recurrences (Komoike et al., 2006). The EBCTCG has mentioned that decreased local failure rate after BCS in the conserved breast could modify fifteen-year BC

survival to better survival rates and there are more advantages with the additional boost in younger patients (Ono et al., 2019).

The EORTC 22881-10882 trial searched for the adding of a 16 Gy to the tumor bed after WBI by 50Gy. After ten years of follow-up, the boost markedly decreased the incidence of local failure by 41% in all ages. However, the absolute benefit was smaller in patients older in age than 40 years, who's absolute 10-year risk of recurrence is also the lowest. There were was an increased rate of moderate to severe fibrosis from 13% to 28% with the boost, confirming the worse cosmetic outcome found at 3 years follow-up (Bartelink et al., 2007; Collette et al., 2008). American Society for Radiation Oncology (ASTRO) guidelines concluded that boost irradiation should not be defined by the surgical margin width, to decrease the chance of IBTR in patients with negative safety margins of 'no ink on tumor' (Moran et al., 2014). On the contrary, boost irradiation had some pitfalls, including moderate to severe fibrosis, impaired cosmoses, and the higher cost of an additional boost therapy (Bartelink et al., 2015; Bollet et al., 2007; Collette et al., 2008; Franco et al., 2018).

St. Gallen (2017) on the main treatment of early BC, summarized that boost radiotherapy could be canceled in female patients older than 60 years, patients with low-grade tumors, or patients with good biological characters. Also, the National Comprehensive Cancer Network (NCCN) advised that to give boost radiation to the tumor bed in patients with high-grade tumors and less than or equal to 50 years old (Ono et al., 2019). Also, Franco et al. reported that local control and less late side effects could be achieved when the boost to tumor bed is recommended for younger females (less than forty years) with large tumors and/ or GIII tumors, close surgical margins, high proliferative index, ER and PR negativity and extensive CIS components (Franco et al., 2018).

So, regarding this debate, we wished to investigate in our institutes the effect of boost versus no boost on the incidence of IBTR in females ≥ 50 years old with early BC treated with BCT regarding local failure rate, disease-free survival (DFS) and overall survival (OS).

PATIENTS & METHODS

This research is a multicentric retrospective comparative study performed in the Clinical Oncology and Nuclear medicine department at Mansura University Hospital, Medical Oncology unit at Oncology Center of Mansoura University and Clinical Oncology department at Zagazig University. We collected 120 cases (92 patients from Mansoura and 28 patients from Zagazig) of early BC patients (T1, 2- N0,1- M0) with negative margins (safety margin more than 5 mm) and low-grade tumors (GI, GII) after BCS. They were treated with WBI without (group A) and with (group B) boost irradiation. This study was approved by the institutional research board of the faculty of medicine, Mansoura University by code Number (R.21.03.1274).

The surgical margin was defined as negative or close when it was ≥ 5mm and < 5 mm, respectively. From January 2016 to December 2017 inclusive, 119 patients were diagnosed by pathological examination with invasive carcinoma. They were treated with BCS at our institutions plus definitive radiotherapy with or without boost plus or minus neoadjuvant, adjuvant chemotherapy and hormonal treatment. They were divided into two groups one without boost and the other group with boost.

Treatment

BCS were done to all the patients where partial resection was done to the breast plus axillary lymph node dissection or sentinel lymph node biopsy. The tumors plus a 1-2 cm margin of macroscopically normal tissue were resected.

Planning was done by CT planning with contrast with slices each 3-5 mm using 3D Precise Treatment Planning System version 2.12. Three-dimensional CRT WBI was delivered by a high-energy linear accelerator (Elekta, Precise Treatment System), Version 5, with two tangential opposing photon beams 6 or 15 MEV photon energy. The regional lymph nodes were irradiated also according to indications for that. A median dose of 40 Gy was delivered to both groups who received a boost and those without a boost. The boost dose was 1600 cGy in 8 treatment fractions using electrons or wedged oblique photon beams following the end of the

whole breast dose (40 Gy/ 3 weeks/ 5 fractions per week).

All the patients received their chemotherapy and hormonal treatment when indicated according to the risk factors. Patients were followed up four times per year in the first 2 years then every 4-6 months in the last 3 years by clinical examination, sono-mammography, chest X. ray or CT and abdomino-pelvic US or CT when indicated.

The end points: The end-points of the study are comparing the local failure, DFS and OS in both groups who received no boost and boost radiotherapy after WBI. The OS was calculated as the time from 1st diagnosis of the disease till the patient death or the last follow-up contact (censored). The DFS was calculated as the time from the end of primary treatment till the date of 1st evidence of local or systemic failure.

Statistical methods

Data entry and analysis were done by a statistical package of social sciences "SPSS" version 23. Qualitative variables are summarized in number & percent. The Chi-square test is used to compare qualitative variables in groups. Mann-Whitney test are used to compare quantitative variables with the non-normally distribution. Log-rank test is used to compare between two survival curves. Kaplan Meir curves are used to describe cumulative survival among studied groups.

A level of significance less than 0.05 is considered statistically significant. The overall survival was calculated as the time from 1st diagnosis of the disease till the patient s' death or the last follow-up contact (censored). The disease-free survival was calculated as the time from the end of primary treatment till the date of 1st evidence of local or systemic failure.

RESULTS

Between January 2016, and December 2017, we analyzed 120 patients of early breast cancer patients (T1, 2- N0, 1- M0) with negative margins (safety margin ≥ 5 mm) and low-grade tumors (GI, GII) after BCS. They were treated with WBI with and without boost irradiation. They were divided into two groups, one with no boost; group A (62 patients) and the other group with a boost; group B (57 patients), one patient out of the 120 cases was excluded as she lost to follow up after ending her treatment. The baseline characteristics of the patients were described in Table 1. The mean age of no boost group was (60.6 years) and (56.6 years) for the boost group with a significant difference between both of them with P value = 0.003. Regarding menopausal status; there were strongly significant differences between both groups with P value = 0.002.

Most cases of both groups were with pathological T stage 1 and 2 (except one patient in group A was T3) with a significant difference between both of them with (p value = 0.01). As regard pathological N stage, 73% of cases of group A were N0 versus 47% of group B with a highly significant difference between both groups with (p value = 0.005) as shown in Table 1**.**

The majority of cases of both groups had no lymphovascular invasion or perineural invasion. The majority of cases of both groups were ER and PR positive (77%, 75 %) and (69%, 72%) for groups A and B respectively. The median Ki67 of group A was 10 and 15 for group B. Group A patients were negative Her-2 with74% and 75% for group B with no statistical significance**.**

The neoadjuvant and adjuvant chemotherapy and hormonal treatment were mentioned in Table 2 with no significant differences between both groups. The median follow-up period of the cases was 44 months. The local recurrences occur only in 2 cases (3%) of group A and 3 cases (5%) of group B with no statistically significant difference with P value= 0.6. Distant Metastasis was found in 2 cases (3%) of group A, while 4 cases (7%) of group B with no statistically significant difference with P value=0.3 (Table 2). The mean overall survival (OS) was 52.8 months for group A and 53.2 months for group B with no statistical difference between them (P= 0.6) (Table 3) (Figure 1). The mean disease-free survival (DFS) was 54.6 months and 52.1 months for groups A and B respectively with no statistical difference between them (P= 0.3) (Table 4) (Figure 2)

Table 1. Baseline characteristics of studied breast cancer cases

	No Boost Therapy Group (A) n=62	Boost Therapy Group (B) n=57	P value
Age (Mean)	60.6 (7.7)	56.6 (6.4)	**0.003***
Menopausal status			
Premenopausal	3 (4.8%)	11 (19.3%)	
Peri-menopausal	11 (17.7%)	16 (28.1%)	**0.002***
Postmenopausal	48 (77.4%)	30 (52.2%)	
Side of the breast			
Right	34 (54.8%)	30 (52.6%)	
Left	27 (43.5%)	27 (47.4%)	0.9
Bilateral	1 (1.6%)	0 (0%)	
Pathological T stage			
0	1(1.6%)	0 (0)	
1	29 (46.8%)	14(24.6%)	**0.01***
2	31 (50%)	43(75.4%)	
3	1(1.6%)	0 (0)	
Pathological stage N			
0	(72.6) 45	(47.4) 27	**0.005***
1	(27.4) 17	(52.6) 30	
Pathological types			
IDC	60(96.8)	52(91.3%)	
ILC	0(0)	2(3.5%)	0.3
Mucinous	2(3.2%)	2(3.5%)	
Cribriform	0(0)	1(1.8%)	
Tumor grade			
1	8(12.9)	5(8.8)	0.4
2	54(87.1)	52(91.2)	
LVI			1.00
No	58(93.5%)	53(93.0%)	
yes	4(6.5%)	4(7.0%)	
PNI			1.00
No	57(91.9%)	52(91.2%)	
yes	5(8.1%)	5(8.8%)	
^Ki67 Median (min-max)	10 (0-90)	15 (0-70)	**0.057**
ER			0.7
Negative	14(22.6%)	14(24.6%)	
Positive	48(77.4%)	43(75.4%)	
PR			
Negative	19(30.6%)	16(28.1%)	0.8
Positive	43(69.4%)	41(71.9%)	
HER			
Negative	46(74.2%)	43(75.4%)	0.8
Positive	16(25.8%)	14(24.6%)	

*Significant difference when $P < 0.05$.

DISCUSSION

Over the last decades, the frequency of BCS has increased due to the awareness of screening for breast cancer by screening programs using mammography and to the usage of new agents and multimodality therapeutic strategy treatments (Arcadipane et al., 2016). BCS followed by WBI and optionally a boost to the tumor bed (according to the treatment team decision), is the standard therapeutic choice for early-stage BC patients.

Postoperative radiotherapy in general decreases the chance of disease recurrence to half and reduces BC mortality by about a sixth (Early Breast Cancer Trialists' Collaborative Group, 2011).

Table 2. Adjuvant or neoadjuvant treatment received and the fate of patients

	No Boost Therapy n=62	Boost Therapy n=57	P-value
Lines of Chemotherapy			
6 cycles FEC/FAC	9 (20%)	12 (24%)	
4 cycles AC & 12 week Taxol	14(31.1%)	15(30%)	
4 FEC and Taxotere	10(22.2%)	12(24%)	0.3
Herceptin	5(11.1%)	8(16%)	
Taxol & Herceptin	7(15.6%)	3(6%)	
Hormonal treatment			
no hormonal	15(24.1%)	12(21.1%)	
Tamofen	12(19.4%)	25(43.8%)	0.2
AI	31(50%)	17(29.8%)	
Tamofen then Ais	4(6.5%)	3(5.3%)	
Local recurrence			
No	60(96.8%)	54(94.7%)	0.6
yes	2(3.2%)	3(5.3%)	
Distant metastasis			
No	60(96.8%)	53(93.0%)	0.3
yes	2(3.2%)	4(7%)	
Fate of the patients			
Dead	17(27.4%)	17(29.8%)	0.7
Alive	45(72.6%)	40(70.2%)	

Table 3. Mean OS according to boost therapy among studied cases

Boost therapy	Mean (St error)	95% Confidence interval	Log-rank test
No boost (group A)	52.8(1.7)	49.3-56.3	0.6
Received Boost therapy (group B)	53.2 (2.2)	48.7-57.6	
Overall	54.007(1.5)	51.08-56.9	

Table 4. Mean DFS according to boost therapy among studied cases

Boost therapy	Mean (St error)	95% Confidence interval	Log-rank test
No boost (group A)	54.6(0.9)	52.8-56.5	0.3
Received Boost therapy (group B)	52.1 (1.3)	49.4-54.8	
Overall	53.8(0.8)	52.1-55.5	

However, doubts about the total radiation dose needed for patients treated with conservative surgery and whether or not a boost is necessary for this situation which may harm than good. Acute side effects of the radiotherapy boost include fatigue, breast edema, skin erythema and hyperpigmentation, while the late risks include fibrosis, scarring of connective tissue, radiation pneumonitis, rib fractures, cardiotoxicity, and radiation-induced second malignancies.

Guidelines on using boost to the tumor bed or not, remain unclear. Various techniques have been developed to optimize treatment plans and doses given to the tumor bed, that include conventional radiation, 3D-conformal radiation, intensity-modulated radiation therapy, intraoperative radiation, or proton irradiation. There is also a wide range of fractionation schedules ranging from standard fractionation, hypofractionation or even single shot radiotherapy. Possible consequences of adding a boost dose to the tumor bed are poor cosmoses, as well as higher treatment costs and increased treatment times.

Data points out that between 44% and 90% of local recurrences are located at or near the primary tumor site (Bartelink et al., 2007; Vaidya et al., 2010) and these percentages are the same as the pathological findings from Holland and colleagues (Holland et al., 1985). That means tumor bed boost is given to eliminate microscopical residual cancer cells (Bartelink et al., 2015; van Werkhoven et al., 2011).

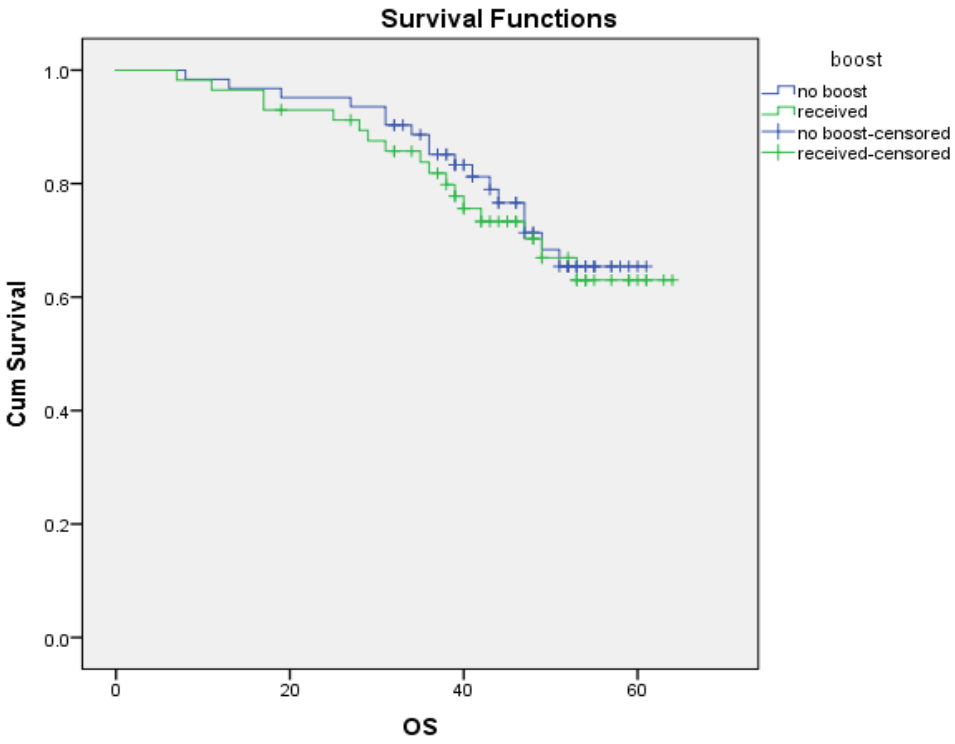

Figure 1. Kaplan Meier curve for overall survival according to boost therapy

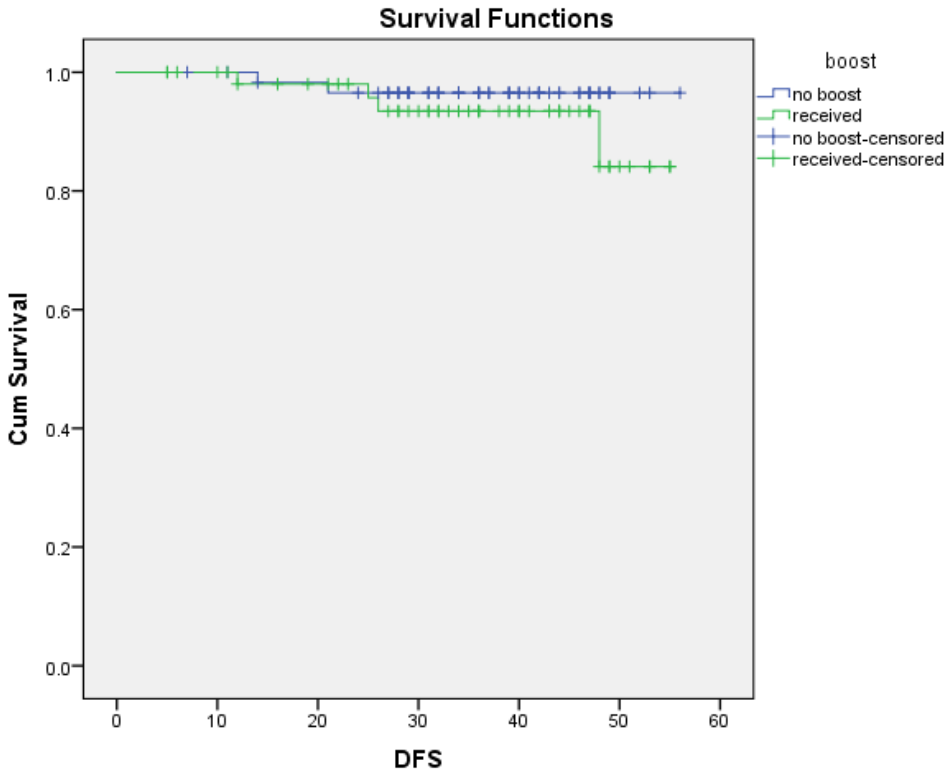

Figure 2. Kaplan Meier curve for disease-free survival according to boost therapy

During our study design, there was no clear cut-off margin regarding the age group that benefits the most from the boost dose in the literature. We chose the age of patients to be 50 years or more as an inclusion criterion as it has been used by a lot of researchers. ASTRO for example advised tumor bed boost for patients aged ≤50 years with any grade (Vaidya et al., 2010). Moreover, European guidelines recommend a boost to the tumor bed in patients with one of the following risk factors at least: age up to 50 years, high-grade tumors (III), excessive DCIS, vascular invasion, and possibly when there is non-radical tumor excision (Senkus et al., 2015). Also, C. Vrieling and his colleagues concluded that the analysis of the long-term follow-up of patients with prognostic factors associated with local control in the EORTC boost no boost trial showed that being young and the DCIS increase the opportunity of IBTR (Conny Vrieling et al., 2017).

Earlier than that, omission of radiation boost for patients older than or equal to 60 years, cases with low-grade tumors, or cases with a good biological pattern was recommended by 2017 St.Gallen international expert conference (Khaled et al., 2018). On the other hand, younger age groups were investigated too. A retrospective study of 209 premenopausal females, < 40 years old, received their treatment at the Institute Curie between 1985 and 1995 for early BC. Thirty-seven years old was the median age at diagnosis and only being young was markedly associated with a decreased loco-regional control. The relative risk of loco-regional failures was improved by 7% for every year of decrease in age (Bollet et al., 2007).

In our retrospective study, there were no statistical differences in the distribution of the clinico-pathological characteristics between the two tested groups (‘boost’ and ‘no boost’) except for age (less in the boost arm) , menopausal status (which is subsequently dependent on age) , TN staging (higher in the boost arm). These retrospective data reflect the common trend for the treatment panels in those different centers from which we took our data and this coincides with many studies all over the world defining patients at high risk of loco-regional recurrence in the presence of negative margins (age, staging and tumor grading) and accordingly in need for booster dose after WBI following BCS. Many studies reported that young patients had more loco-regional recurrences (Bollet et al., 2007; Elkhuizen et al., 1998; Vrieling et al., 2003).

A twenty-year follow-up randomized phase III trial done by Bartelink et al showed that an additional radiotherapy dose to the tumor bed led to better local control after BCS and accordingly, less salvage mastectomy surgeries. Surprisingly, the relative advantage of a boost dose was the same in all age groups; the absolute gain of a boost dose was more obvious in cases younger than 51 years. However, better local control was related to more fibrosis, and cosmetic results were somewhat worse (Bartelink et al., 2015).

After a median follow-up period of 44 months, only 3.2% and 5.3% of our patients had experienced local recurrences in the boost and no boost groups respectively. This difference between the two groups did not reach any statistical significance. These numbers are less than that reported in the literature, that ranged from 12% to 70% (Gage et al., 1995; Huang et al., 2002; Smith et al., 2000; Touboul et al., 1999; Veronesi et al., 2002), mostly dependent on the length of follow-up and the presence or absence of local recurrence risk factors which were definitely less common in our study depending on choosing patients at or more than 50 years old with a safety margin wider than 5mm.

The annual risk of local failure has an early peak during the first few years following the adjuvant treatment and is mainly dependent on local failures occurring at the tumor bed. This must reflect the occurrence of true recurrences of the primary tumor not completely removed by surgery and not eradicated by adjuvant treatment i.e., in the case of our patient’s radiotherapy with or without chemotherapy (Recht et al., 1988).

In our research, there was no statistical difference between the two compared groups (boost or no boost) regarding both the OS (P = 0.6) and the DFS (P = 0.3), and this result was expected based on statistical data we obtained

earlier regarding the loco-regional failure rates between the two groups.

The effect of loco-regional failures on both DFS and OS has been studied thoroughly in the literature; however, there is a lot of contradiction in this matter. A meta-analysis study done by Clarke et al showed that the extent of loco-regional therapies (surgery and/or radiotherapy) does not only affect the loco-regional control but also it changes the distant disease-free and overall survivals especially after considerable follow-up periods (Early Breast Cancer Trialists' Collaborative Group, 2005). However, it is fair to say that these large collaborative meta-analyses were done on 42,000 women in 78 randomized treatment comparisons (radiotherapy versus no radiotherapy, 23,500; more versus less surgery, 9300; more surgery versus radiotherapy, 9300) so boost versus no boost issue was not evaluated.

In contrast, Kindts et al analyzed data taken from large five randomized controlled trials that included 8325 women, comparing the effect of adding and omission of the booster dose to the tumor bed of early BC tumor. Local control was better for patients receiving a tumor bed boost in comparison to those who did not receive any (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55 to 0.75; 5 studies, 8315 women, low-quality evidence). On the other hand, overall survival was not statistically significant between the two groups (HR 1.04, 95% CI 0.94 to 1.14; 2 studies, 6342 women, moderate-quality evidence). Disease-free survival did not differ with or without a tumor bed boost (HR 0.94, 95% CI 0.87 to 1.02; 3 studies, 6549 women, low-quality evidence) (Kindts et al. , 2017).

To our current information, there are few studies evaluating the rate of local failure and subsequently DFS and OS in patients with early BC and a negative surgical margin >5 mm and without radiation boost and at the same time receiving modern neoadjuvant and adjuvant systemic treatments (Anthracycline-based protocols, Taxanes-based protocols, and optionally Trastuzumab) because using the boost radiotherapy was recommended based on the results of the well-known EORTC study which was done between 1989 and 1996 (Bartelink et al., 2007). In this trial, a negative margin was defined as no tumor cells on the ink. Therefore, these recommendations may not be fully applicable to cases with our definition in our centers of negative margin (being more than 5mm) receiving one or more chemotherapy with or without Trastuzumab according to the decision of the treatment panel.

Apart from conservation, preservation of the breast and achieving BC control, an important part of BCT is to maintain good cosmoses. The extra radiation dose to the tumor bed will continue to be used in women at high risk of local failure (age, tumor grade, safety margin), but in women at lower risk; it is less widely accepted. It remains a cost-benefit issue as it increases the time and cost of treatment and the potential side effects are not negligible.

CONCLUSION

In conclusion, we did not find any difference between having boost or no boost radiotherapy after BCS in patients older than 50 years old with early BC regarding local failure, DFS and OS. So, we can omit the boost settings to overcome the high cost of radiation and the long waiting list in our machines which are overwhelmed with patients and increased its maintenance finances as we are one of the developing countries with minimal resources. Also; to overcome the treatment toxicities regarding post-radiotherapy fibrosis and cosmoses issues in the remaining breast.

Compliance with ethical standards

Ethical approval was obtained from Institutional Research Board (IRB) at the Faculty of Medicine, Mansoura University, Egypt (R.21.03.1274). All procedures were done in accordance with the current revision of Helsinki Declaration of medical research involving human subjects.

CONFLICT OF INTEREST

The authors declare that no conflict of interest to disclose.

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