

The role of boost dose of radiation after whole breast irradiation in decreasing local recurrence in breast conserving therapy of early stage breast carcinoma

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Abstract: Background: Breast conserving therapy (BCT) was the recommended modality for treating early stage (I-II B) breast carcinoma. So, decreasing late morbidity of both chemotherapy and radiation therapy becomes one of our targets for the sake of expected long survival with good quality of life. **Aim of the study:** The aim of this study is the evaluation of the effect of adding boost dose of radiation therapy to the tumor bed in breast conserving therapy (BCT), significantly affect local recurrence & disease free survival (DFS). **Patients and methods:** Thirty seven patients were included in this study (age range from 35 to 70 years, mean age 53 ± 3.84), all have an early stage breast carcinoma (stage I-II B) and treated surgically with breast conserving surgery (lumpectomy + axillary clearance level one and two lymphadenectomy), followed by adjuvant chemoradiotherapy without boost dose to tumor bed, using 3-D conformal radiation therapy this group (A) was, compared to a historical retrospective group (B), of 40 patients with the same criteria but with boost dose to tumor bed. **Results:** The 3-year disease free survival (DFS) was 78% in group A compared to 83% in group B ($P > 0.05$). On the other hand, boost dose of radiation decreases local recurrence as a cause of failure by about 5% (22% versus 17% in group A & B respectively) $P > 0.05$. In group A most patients who achieved local failure were below the age of 45 years (82.6%) compared to 76.2% in group B, ($P > 0.05$). In group B, breast fibrosis as a late effect of radiation was 11% compared to 8.73% in group A ($P \geq 0.05$) without statistically significant difference. **Conclusion:** In early stage breast cancer (I-II B), giving a boost dose of radiation to tumor bed (12 Gy) insignificantly decreases local failure with improvement of 3-years disease free survival on the sake of increasing grade III breast fibrosis as a late radiation toxicity.

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Keywords: BCT, boost radiation dose, local recurrence, DFS.

1. Introduction

Adjuvant radiotherapy (RT) is currently recommended in all patients after lumpectomy, regardless of the size of the primary disease, age of

patient, and hormonal receptors. A number of studies have focused on whether we can identify subsets of patients in whom radiation therapy (RT) may be safely alienated⁽¹⁾.

Table (1): Lumpectomy and whole breast irradiation versus mastectomy

Institution	years	Patients No.	OS %	Follow up years
Milan	1973-1980	349 (M) 352 (Q + XRT)	same	20
NSABP – Bob	1976-1984	590 (M) 629 (L+ XRT).	same	20
Danish breast cancer cooperative group	1983-1987	429 (M) 430 (L + RT)	82 79	6
Institute Gustave Roussy	1972 - 1979	91 (M) 88 (L+ RT).	65 73	15
NCI	1980 - 1986	116 (M) 121 (L+ RT)	75 77	10
EORTC - 10801	1980 - 1986	426 (M) 456 (L + RT)	63 58	8

Q: Quadrentectomy; M, mastectomy, L, lumpectomy; XRT, whole breast external beam RT.

Most radiation oncologists administer a boost with electrons and on occasion, with photons to administer a higher dose to the lumpectomy site with the objective of improving local control^(2,3,4). Boost irradiation to the tumor bed is recommended after whole breast RT (5-7).

In management of stage I through stage IIB breast carcinoma, the standard of care in breast conserving therapy (BCT) includes adjuvant radiation after lumpectomy. The efficacy of post-operative RT after lumpectomy has been repeatedly demonstrated through various prospective randomized trials^(13, 2, 6).

A number of phase III randomized trials have shown that lumpectomy and axillary dissection followed by RT is equivalent to modified radical mastectomy as shown in table (1). BCT is the preferred treatment option for the majority of patients with early-stage invasive breast cancer and allowed for organ preservation.^(7, 8, 9)

The aim of this study was the evaluation of the role of boost dose (12 Gy) in decreasing local recurrence and increasing 3-years disease free survival (DFS) and its morbidity regarding breast fibrosis and cosmetic failure.

2. Patients and methods

Thirty-seven patients were conducted in the study as group "A" and treated in departments of Clinical Oncology & Nuclear Medicine and General Surgery, in the period from September 2010 to May 2015 with a mean period of follow-up to 40 months, the mean age was 53 ± 3.84 (range from 35-70 years), all patients have an early stage (I- IIB) breast carcinoma and treated surgically with breast conserving therapy (lumpectomy + axillary clearance), followed by adjuvant chemotherapy and radiation therapy. Radiation therapy to whole breast, to a dose of 50 Gy/25 fractions, using 3-D conformal radiation technique, without boost to tumor bed (group A) was compared to a historical group of 40 patients who have been treated with a boost dose of 12 Gy to tumor bed (group B).

Treatment technique and field arrangement:

Breast irradiation had been delivered using computerized 3-D planning system(Linac, Elekta 151204, Presice Plan Release 2.12) machine with high-energy photon beam (6 & 15 MV).

Simulation and field design patients were treated in supine position with customized immobilization device, bilateral arms abducted and externally rotated.

Target volume is the entire breast using tangential fields, and SCF via third field when indicated. The CTV (clinical target volume) is the glandular breast tissue and PTV (planning target volume) is the CTV with a 1cm margin, usually allowing 5mm skin sparing. Patients were treated to a

total dose of 50 Gy to entire breast (2 Gy per fraction, 5 days per week), plus 12 Gy boost to tumor bed (group B). using linac 4-6 MV, to avoid high skin dose with Co 60.

Boost: 6-15 Mev electron energy, depending on the depth of the tumor bed.

Follow-up: Patients were followed every 3 months by clinical examination, mammography ultrasound and CXR.

Bone scan yearly and tumor markers every 6 months.

Statistical analysis:

All data were collected, tabulated and statically analyzed using SPSS 15.0 for windows (SPSS Inc., IL, USA) and Medcalc 13 for windows (Medcalc software bvba).

Continues quantitative variables e.g. age were expressed as the mean \pm SD & median (range), and categorical qualitative variables were expressed absolute frequencies "number" and relative frequencies (percentage). Continues data were checked for normality by using Shapiro-Wilktest.

Mann – Whitney (MW) test as used to compare two groups of non-normally distributed data.

Categorized data were compared using X^2 test. All tests were two sided.

$P < 0.05$ was considered statistically significant (S), $P = 0.01$ was considered highly statistically significant (HS) and $P > 0.05$ were considered non statistically significant (NS).

3. Results

Patient characteristics:

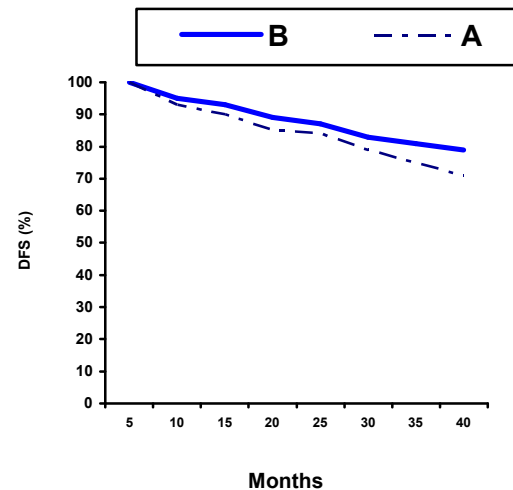


Fig. (1) DFS in both groups

A total of 37 women with early stage invasive breast carcinoma were included as group A and

compared with group B patients (40) who were retrospectively treated in our department using the conventional treatment protocols. Table (2) shows patients characteristics in both groups.

The 3-year disease free survival (DFS) was 78% in group A compared to 83% in group B ($P > 0.05$) and was statistically insignificant. On the other hand, local recurrence was 22% and 17% in both groups A & B respectively (Fig 1, 2).

In group A most patients who achieved local failure were below the age of 45 years (82.6%), compared to (76.2%) in group B patients ($P > 0.05$). In group B patients breast fibrosis as a late effect of radiation was 10% compared to 5.40% in group A ($P > 0.05$) without statistical significant difference.

Postoperatively, there was no significant difference in cosmetic assessment between the two arms, but by 3 years, the patients in the boost arm had a lower rate of excellent/good cosmetic outcome and nearly double the rate of fair outcomes (26.3% vs 12.8) with statistically insignificant difference ($P > 0.05$) table (3).

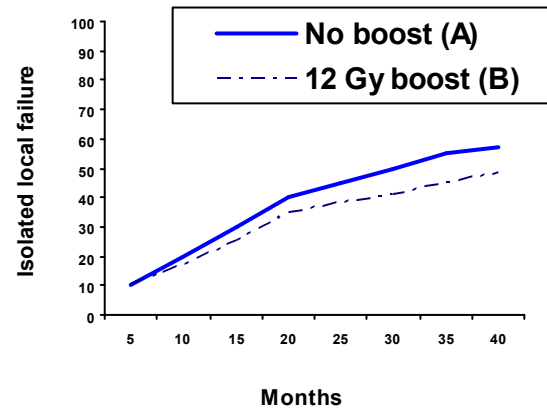


Fig. (2) Local failure in both groups.

Fig (2) showed that the boost dose of radiation decreased local failure by 5% but without statistical significance ($P > 0.05$).

Table (2): Patients characteristics

Characteristic	Group A 37		Group B 40		P value
	No	%	No	%	
Tumor characteristics					
Nodal status					
No	8	21.62	10	25	0.640 (NS)
N1	29	78.38	30	75	
Size					
< 2 cm	13	35.13	15	37.50	0.096
2-5 cm	24	64.87	25	62.50	
Location					
Outer quadrant	28	75.67	23	57.50	0.87
Inner quadrant	9	24.33	17	42.50	
Laterality					
Right	15	40.54	19	47.50	0.077
Left	22	59.46	21	52.50	
Cancer treatment					0.854
Adjuvant chemotherapy					
FAC	25	67.56	27	67.50	
CMF	12	32.44	13	32.50	
Adjuvant hormonal therapy					
Tamoxifene	32	86.49	36	90.00	0.984
Letrozole	5	13.51	4	10.00	
Grade					
1	4	10.81	7	17.50	0.0623
2	18	48.64	21	52.50	
3	15	40.55	12	30.00	
TNM Stage grouping					
Stage I	11	29.73	10	25.00	0.782
Stage II A	22	59.46	22	55.00	
Stage II B	4	10.81	8	20.00	

Table (3): Cosmetic outcome in both study groups

Score (%)	No boost (A)		Boost (B)	
	Post- op.	3 years	Post- op.	3 years
Excellent	38.2	40.9	35.9	31.6
Good	46.2	44.9	46.8	39.8
Fair	14.1	12.8	15.5	26.3
Poor	1.5	1.4	1.8	2.3
	$P = 0.22$		$P = 0.097$	

4. Discussion

Conventional radiation to the breast typically consists of 45 to 50 Gy to the whole breast over approximately 5 weeks, frequently followed by a lumpectomy site boost of 10-16 Gy.⁽¹⁰⁻¹¹⁾

Breast radiation usually starts 4 to 6 weeks after the last surgery if no adjuvant chemotherapy is used. While this fractionation dose have a long track record of safety and efficacy, it is time consuming and living in underserved or rural areas may limit access to breast conservation^(12, 13).

Radiation has consistently been shown to decrease the risk of recurrence within the breast.⁽¹⁴⁻¹⁷⁾

While the initial NSABP experience delivered radiation to the whole breast without additional dose to the lumpectomy site, examination of patterns of failure has shown that local recurrences are most likely to occur at or near the original tumor⁽¹⁸⁾. An additional dose of radiation was therefore given to the lumpectomy site in an attempt to lower further the risk of local recurrence^(13, 19).

Two trials have examined the potential benefit of extra dose of radiation^(20, 21).

Researchers from Lyon^(20, 21) randomized 1024 patients with early stage disease to 50 Gy to whole breast with or without an additional 10 Gy to the lumpectomy site. Their results were reported with a median follow-up of 3.3 years, their five-year local recurrence was 3.6% with the additional dose compared with 4.5% without boost ($P = 0.044$).

In the present study the three-years local recurrence was 17% with boost compared to 22% in those without boost ($P > 0.05$) with statistically insignificant difference. The increased incidence of local recurrence in our study in both groups of patients was due to the small number of patients included in the study compared with Lyon study.

In the present study, breast fibrosis as a late effect of radiation was 11% in group B patients (with boost) compared to 8.13% in group A (without boost) ($P > 0.05$) with insignificant statistical difference.

In their study, Lyon researchers^(20, 21) found more patients receiving the additional radiation developed telangectasia, but there was no difference in a patient-

assessed cosmetic score, which comes in agree with our results^(23, 24, 25).

More robust findings were reported by the European Organization for Research and Treatment of Cancer (EORTC),^(26, 27) 5318 patients were randomized to 50 Gy to the whole breast with or without an additional 16 Gy to the lumpectomy site.

Local recurrence at 10 years (median follow-up 10.8 years) was 6.2% and 10.2% respectively ($P < 0.0001$). Severe fibrosis was modestly, but significantly increased with boost dose of radiation, from 1.6% to 4.4% ($P = 0.0014$) with additional radiation to lumpectomy site.

There was no difference in overall survival between groups. Lastly, they concluded that omission of the boost may be a reasonable option in elderly patients in whom the absolute benefit is minimal; in all others, however, it remains standard treatment. Regarding the effect of the boost on cosmetic results in our study, the patients in group B had a lower rate of excellent/good cosmetic outcome and nearly double the rate of fair outcomes but with statistically insignificant difference ($P > 0.05$), and these results comes in agree with the Milan III trial^(28, 29, 30).

On summary: omission of the boost may be a reasonable option in early stage breast carcinoma (1-2B) treated with breast conserving therapy (BCT) to decrease the incidence of late radiation toxicity, but more trials with larger number of patients are needed to support that option with more longer time of follow-up.

References

1. Fisher B, Anderson S, Bryant J, *et al.* Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *New Eng J Med.* 2002; 347: 1233-1241.
2. Clarke M, Collins R, Darby S, *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(9503):2087-2106.

3. Arriagada R, Le MG, Rochard F, *et al.* Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institute Gustave-Roussy Breast Cancer Group. *J Clin Oncol.*, 1996; 14(5):1558-1564.
4. Veronsi U, Cascinelli N, Mariani L, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New Engl J Med.* 2002; 347(16): I227-I232.
5. Blichert-Toft M, Rose C, Anderson JA, *et al.* Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr.* 1992; Aa:19-25.
6. Van Dongen JA, Voogd AC, Fentiman IS, *et al.* Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 1080I trial. *J Natl Cancer Inst.* 2000;92(14):1143-1150.
7. Freedman G, Fowble B, Hanlon A, *et al.* Patients with early stage invasive cancer with close of positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. *Int J Radiat Oncol Biol Phys.* 1999;44(5): 1005-1015.
8. McIntosh A, Freedman G, Eisenberg D, *et al.* Recurrence rates and analysis of close or positive margins in patients treated without re-excision before radiation for breast cancer. *Am J Clin Oncol.*, 2007; 30 (2): 146-151.
9. Peterson ME, Schulz DJ, Reynolds C, *et al.* Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: the University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys.* 1999; 45(5): 1029-1035.
10. van der Leest M, Evers L, van der Sangen MJ, *et al.* The safety of breast conserving therapy in patients with breast cancer aged < or = 40 years. *Cancer.* 2007;109 (10):1957-1964.
11. Bartelink H, Horiot JC, Poortsmans PM, *et al.* Impact of a higher radiation dose on local control and survival in breast conserving therapy of early stage breast cancer: 10-year results of the randomized boost vs no boost EORTC 22881-10882 trial. *J Clin Oncol.*, 2007; 25 (22): 3259-3265.
12. Kurtz JM, Jacquemier J, Amalric, *et al.* Why are local recurrences after breast-conserving therapy more frequent in younger patients? *J Clin Oncol.*, 1990; 8 (4):591-598.
13. Dahlberg K, Johansson H, Johansson U, *et al.* A randomized trial of long-term adjuvant tamoxifen plus postoperative radiation therapy versus radiation therapy alone for patients with early stage breast carcinoma treated with breast-conserving surgery. Stockholm Breast Cancer Study Group. *Cancer.* 1998; 82 (11): 2204-2211.
14. Haffty BG, Yang Q, Reiss M, *et al.* Locoregional relapse and distant metastasis in conservatively managed triple negative early stage breast cancer. *J Clin Oncol*, 2006; 24(36):5652-5657.
15. Chen AM, Obcdian E, Haffty BG. Breast-conserving therapy in the setting of collagen vascular disease. *Cancer.* 2001;7(6): 480-491.
16. Ross JG, Hussey DH, Mayr N, *et al.* Acute and late reactions to radiation therapy in patients with collagen vascular diseases. *Cancer.* 2006;71(11): 3744-3752.
17. Pierce LJ, Levin AM, Rebbeck TR, *et al.* Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *J Clin Oncol.* 2006;24 (16): 2437-2443.
18. Bellon JR, Come SE, Celman RS, *et al.* Sequencing of chemo-therapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol.* 2005; 23(9): 1934-1940.
19. Assersohn I, Powels TJ, Ashley S, *et al.* Local relapse in primary breast cancer patients with unexcised positive surgical margins after lumpectomy, radiotherapy and endocrine therapy. *Ann Oncol.*, 1999; 10 (12): 1451-1455.
20. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risk of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst.* 2004; 96 (2): 115-121.
21. Punglia RS, Morrow M, Wirier EP, *et al.* Local therapy and survival in breast cancer. *New Engl J Med* 2007; 356 (23): 2399-405.
22. Dolan JT, Granchi TS, Miller CC, 3rd *et al.* Low use of breast conservation surgery in medically indigent populations. *Am J Surg* 1999; 178(6):470-474.
23. Answini GA, Woodard WL, Horton HJ, *et al.* Breast conservation: trends in a major southern metropolitan area compared with surrounding rural counties. *Am Surg.* 2001; 67 (10):994-998.
24. Lim M, Bellon JR, Gelman R, *et al.* A prospective study of conservative surgery without radiation therapy in select patients with stage I breast cancer. *Int. J Radiat Oncol Biol Phys.* 2006; 65(4): 1149-1 154.
25. Holli K, Saaristo R, Isola J, *et al.* Lumpectomy with or without postoperative radiotherapy for

- breast cancer with favourable prognostic features: results of a randomized study. *Br J Cancer*. 2001;84 (2):164-169.
26. Whelan T, Pignol JP, Julian J, *et al*. Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node negative breast cancer. *Breast Cancer Res Treat*. 2007; 106 (1): S6.
 27. Freedman GM, Anderson PR, Goldstein LJ, *et al*. Four-week course of radiation for breast cancer using hypofractionated intensity modulated radiation therapy with an incorporated boost. *Int J Radiat Oncol Biol Phys*. 2007;68(2):347-353.
 28. Start Trialists' Group, Bentzen SM, Agrawal RK, *et al*. The UK Standardization of Breast Radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. *Lancet Oncol*. 2008; 9(4):331-334.
 29. Start Trialists' Group, Bentzen SM, Agrawal RK, *et al*. The UK Standardisation of Breast Radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. *Lancet*. 2008;371(9618):1098-1107.
 30. Romestaing P, Lehingue Y, Carrie C, *et al*. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; 15(3):963-968.

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