Comparison of Different Fractionation Schedules in Post Mastectomy Chest Wall Irradiation (PMRT) of Carcinoma Breast

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ABSTRACT

Introduction: The most common malignant neoplasm in female worldwide is breast cancer and it is also the cancer with maximum number of deaths in women. Comparison of two different radiation fractionation schedules is done in post mastectomy breast cancer cases in relation to loco regional control, acute and late toxicities, survival and overall treatment time (O.T.T). The patient, tumor and treatment related parameters have also been studied.

Material and Methods: Between December 2011 and December 2013, hundred patients of stage II to III carcinoma breast treated with surgery and chemotherapy received adjuvant radiation therapy with two different fractionation regimes:

- (Regimen-1, 50 patients) - 42.5 Gray /16 fractions / 3.1 weeks with 2.6 Gray / fraction (#).
- (Regimen-2, 50 patients) - 50 Gray / 25 fractions / 5 weeks with 2 Gray / fraction (#).

Assessment was done for loco regional and distant control rate, acute and late radiation toxicities, and quality of life related parameters.

Results: Maximum numbers of patients were of 40-50 year age, post-menopausal, with invasive ductal carcinoma of grade III and stage II or, III. Regimen 1 in comparison to Regimen 2 resulted in comparable loco regional and distant control rate. It also led to significantly less O.T.T. without any significant difference regarding acute and late radiation toxicities. It resulted in significant improvement in patient's quality of life parameters related to O.T.T.

Conclusion: In breast cancer patients undergoing post mastectomy radiotherapy, accelerated hypofractionated radiation (42.5Gy /16 #/3.1weeks) in comparison to the conventional radiotherapy (50Gy/25#/5weeks) results in comparable loco regional and distant control rates without any significant difference regarding acute and late radiation toxicities. It also leads to significant reduction in overall treatment time with significant improvement in patient's quality of life parameters related to O.T.T.

Keywords: Carcinoma breast, post mastectomy radiotherapy (PMRT), neoadjuvant chemotherapy, radiation fractionation schedules.

INTRODUCTION

The most common malignant neoplasm in female worldwide is breast cancer and it is also the cancer with maximum number of deaths in women.[1] The approach to breast carcinoma is multimodal including surgery, radiotherapy and systemic therapy.[2] In the past locoregional radiation therapy after surgery had shown significant reduction in locoregional recurrence rates. Now various trials and meta analysis have shown that it also increases survival in patients with high risk breast cancer.[3-5] Conventional course of radiation therapy {50 Gray (Gy) over 5 weeks} often leads to poor compliance of patients. Due to this long course, adjuvant treatment is sequenced so as to start radiation therapy after completion of adjuvant chemotherapy. Radiobiological models predict that ∞/ß ratio for breast cancer is low (2-3). Tissues with low ∞/ß ratio have been shown to be more sensitive to the radiotherapy fraction size. Shorter over all treatment time is likely to have better control of clonogenic cell repopulation with improved loco regional control rates. Use of high dose per fraction schedule with shorter duration of treatment (accelerated hypofractionated radiotherapy) has shown comparable local control as well as quality of life to conventional radiotherapy without significant increase in treatment related toxicities.

In this study, comparison of two different dose fractionation schedules of post mastectomy radiotherapy (PMRT) is done in terms of loco regional and distant control rate, acute and late radiation toxicities, overall treatment time and patient's quality of life parameters. The patient, tumor and treatment related parameters have also been studied.

MATERIAL AND METHODS

The patients included in this study were mainly selected from the out patient department (OPD) cases. All of them were adult females belonging to mixed population from rural and urban areas. Most of the patients were of post menopausal status presenting with locally advanced breast cancer (LABC). All of them had undergone modified radical mastectomy (MRM) and received chemotherapy before the start of radiotherapy. They received adjuvant radiation therapy between December 2011 and December 2013.

Sample size and sample technique – The total number of patient included in this study was hundred (100). Fifty patients were included in regimen 1 group (hypofractionated RT) and fifty were included in regimen 2 group (conventional fractionated RT). These patients were selected randomly by computer. The below mentioned Inclusion and Exclusion

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Criterias were used for the selection of patients in this study. All the patients are alive and are on regular follow up. After meticulous work up, patients with stage II and stage III disease were included in our study. The patient's agreement and a written consent to participate in the study were taken. All the cases had to undergo an approval of the tumor board.

Inclusion Criteria

1. Patients willing to participate in the study and also agreeing to come for regular follow up.
2. Biopsy proven carcinoma.
3. Patient's age between 25-70 years.
4. Good Karnofsky performance scale (>70%).
5. Stage II and III breast cancer.
6. Any women with clinical/pathological tumor size ≥ 5 cm, or more than three positive axillary lymph nodes.
7. Surgery done for the tumor is modified radical mastectomy.
8. Radiography and chemotherapy naive patients.
9. Time gap of three weeks to be maintained after completion of chemotherapy and subsequent start of radiation therapy.
10. Interfield breast bridge separation not more than 25cm.

Exclusion Criteria

1. Karnofsky performance status (KPS) <70.
2. Co-morbid conditions; uncontrolled hypertension, diabetes mellitus or cardiac disease.
3. Connective tissue disorders like SLE etc.
4. Pregnant women.
5. Previous history of irradiation to chest wall.
6. Inoperable cases even after neoadjuvant chemotherapy.
7. Any surgery other than modified radical mastectomy.
8. Patients with distant metastasis.

All patients were treated with a continuous course of radiation therapy with once daily fractionation. They were treated 5 days a week from Monday to Friday. The fractionation regime was either:

- Accelerated Hypofractionated Schedule (Regimen-1) - 42.5 Gy / 16 fractions / 3.1 weeks with 2.6 Gy / fraction.
- Conventional Fractionation Schedule (Regimen-2) - 50 Gy / 25 fractions / 5 weeks with 2 Gy / fraction.

It was 2.6 Gy / fraction (Regimen-1) in 50/100 (50%) patients and 2 Gy / fraction (Regimen-2) in 50/100 (50%) patients.

Age Group	Regimen 1 (n=50)		Regimen 2 (n=50)		p Value
	No.	%	No.	%	
< 30 Yr.	04	08	01	02	0.36
31-40 Yr.	10	20	08	16	0.8
41-50 Yr.	18	36	16	32	0.8
51-60 Yr.	12	24	18	36	0.27
>60 Yr.	06	12	07	14	0.7
Total	50	100	50	100	
Menopausal Status					
Premenopausal	14	28	09	18	0.34
Postmenopausal	18	36	25	50	0.2
Perimenopausal	14	28	12	24	0.8
Not Known	04	08	04	08	1.0
Total	50	100	50	100	
Parameter	**Regimen 1 (n=50)**		**Regimen 2(n=50)**		**p Value**
1.Age at 1st Childbirth	**No. (%)**		**No. (%)**		
<30 yrs.	48 (96%)		48 (96%)		1.0
>30 yrs.	02 (04%)		02 (04%)		1.0
2. Breast Feeding	**No. (%)**		**No. (%)**		
Present	48 (96%)		48 (96%)		1.0
Absent	02 (04%)		02 (04%)		1.0
3. H/O Benign Breast Disease	**No. (%)**		**No. (%)**		
Present	05 (10%)		04 (08%)		0.7
Absent	45 (90%)		46 (92%)		0.7
4. Family H/O Breast Cancer	**No. (%)**		**No. (%)**		
Present	02 (04%)		04 (08%)		0.67
Absent	48 (96%)		46 (92%)		0.67

Table-1: Patient Related Characteristics

Involved Breast Quadrant	Regimen 1 (n=50)	Regimen 2 (n=50)	p Value
	No. (%)	No. (%)	
Upper Outer	32 (64%)	30 (60%)	0.8
Central	08 (16%)	12 (24%)	0.45
Upper Inner	05 (10%)	03 (06%)	0.7
Lower Outer	04 (08%)	02 (04%)	0.67
Lower Inner	01(02%)	03 (06%)	0.6

Tumor Stage	Regimen 1 (n=50)		Regimen 2 (n=50)		p Value
	(No.)	(%)	(No.)	(%)	
IIB	07	14	05	10	0.7
IIIA	24	48	22	44	0.8
IIIB	17	34	20	40	0.67
Unknown	02	04	03	06	0.6
Total	50	100	50	100	
Histological Type	**Regimen 1 (n=50)**		**Regimen 2 (n=50)**		**p Value**
	No.	**%**	**No.**	**%**	
Ductal	41	82	43	86	0.78
Colloidal	02	04	01	02	0.5
Papillary	01	02	02	04	0.5
Lobular	06	12	04	08	0.7
Total	50	100	50	100	
Tumor Grade	**Regimen 1 (n=50)**		**Regimen 2 (n=50)**		**p Value**
	No.	**%**	**No.**	**%**	
Grade I	12	24	14	28	0.8
Grade II	20	40	16	32	0.5
Grade III	18	36	20	40	0.8
Total	50	100	50	100	
Receptor Status	**Regimen 1 (n=50)**		**Regimen 2 (n=50)**		**p Value**
	No.	**%**	**No.**	**%**	
ER (+)	25	50	30	60	0.4
ER (-)	20	40	16	32	0.5
PR (+)	10	20	05	10	0.26
PR (-)	35	70	41	82	0.2
Unknown	05	10	04	08	0.7
Total	50	100	50	100	

Table-2: Tumor Related Characteristics

Acute Radiation Reaction	Regimen 1 (n=50) – No. (%)	Regimen 2 (n=50) – No. (%)	p Value
Skin			
Grade 0	00 (0%)	00 (0%)	NS
Grade I	20 (40%)	27 (54%)	0.2
Grade II	27 (54%)	21 (42%)	0.3
Grade III	03 (06%)	02 (04%)	0.6
Subcutaneous Tissue			
Grade 0	00 (0%)	00 (0%)	NS
Grade I	25 (50%)	27 (54%)	0.8
Grade II	23 (46%)	22 (44%)	0.8
Grade III	02 (04%)	01 (02%)	0.5
Esophagus			
Grade 0	36 (72%)	40 (80%)	0.48
Grade I	10 (20%)	07 (14%)	0.6
Grade II	04 (08%)	03 (06%)	0.7
Grade III	00 (0%)	00 (0%)	NS
Lung			
Grade 0	42 (84%)	45 (90%)	0.5
Grade I	08 (16%)	05 (10%)	0.5
Grade II	00 (0%)	00 (0%)	NS
Grade III	00 (0%)	00 (0%)	NS
Shoulder Restriction			
Grade 0	39 (78%)	42 (84%)	0.6
Grade I	06 (12%)	03 (06%)	0.48
Grade II	04 (08%)	04 (08%)	1.0
Grade III	01 (02%)	01 (02%)	1.0
Arm Edema			
Grade 0	45 (90%)	46 (92%)	0.7
Grade I	01 (02%)	01 (02%)	1.0
Grade II	02 (04%)	02 (04%)	1.0
Grade III	02 (04%)	01 (02%)	0.5
Chronic Radiation Reaction	**Regimen 1 (n=50) – No. (%)**	**Regimen 2 (n=50) – No. (%)**	**p Value**
Skin			
Grade 0	03 (06%)	02 (04%)	0.6
Grade I	20 (40%)	26 (52%)	0.3
Grade II	25 (50%)	21 (42%)	0.5
Grade III	02 (04%)	01 (02%)	0.5
Subcutaneous Tissue			
Grade 0	02 (04%)	02 (04%)	1.0
Grade I	25 (50%)	28 (56%)	0.68
Grade II	20 (40%)	19 (38%)	0.8
Grade III	03 (06%)	01 (02%)	0.6
Esophagus			
Grade 0	33 (66%)	39 (78%)	0.26
Grade I	14 (28%)	09 (18%)	0.34
Grade II	03 (06%)	02 (04%)	0.6
Grade III	00 (0%)	00 (0%)	NS
Lung			
Grade 0	31 (62%)	37 (74%)	0.28
Grade I	10 (20%)	08 (16%)	0.79
Grade II	08 (16%)	05 (10%)	0.5
Grade III	01 (02%)	00 (0%)	0.06
Bone			
Grade 0	36 (72%)	42 (84%)	0.2
Grade I	10 (20%)	06 (12%)	0.4
Grade II	03 (06%)	02 (04%)	0.6
Grade III	00 (0%)	00 (0%)	NS
Grade IV	01 (02%)	00 (0%)	0.06
Shoulder Restriction			
Grade 0	25 (50%)	24 (48%)	0.8
Grade I	12 (24%)	13 (26%)	0.8
Grade II	08 (16%)	09 (18%)	0.8
Grade III	05 (10%)	04 (08%)	0.7
Arm Edema			
Grade 0	34 (68%)	36 (72%)	0.8
Grade I	08 (16%)	09 (18%)	0.8
Grade II	04 (08%)	02 (04%)	0.67
Grade III	04 (08%)	03 (06%)	0.7

Table-3: Radiation Reaction Grading in Regimen 1 (n= 50) and Regimen 2 (n=50)

Monitoring of the patients on radiotherapy

Acute toxicity was charted according to *RTOG Acute Radiation Morbidity Scoring Criteria.*

And late toxicity according to *RTOG/EORTC Late Radiation Morbidity Scoring Schema*. Arm edema was graded according to *LENT SOMA scale*.

For acute and late toxicity assessment, at least 7 parameters were noted and grading was done accordingly. The parameters were related to Skin, Subcutaneous tissue, Esophagus, Lung, Bone, Arm Edema and Restriction of shoulder joint movement (Grade 0 to IV). All the patients completed their planned treatment in stipulated time and none had to discontinue their treatment due to acute toxicity.

Follow up after treatment

Patients were followed up regularly at increasing intervals. On each follow up patients were evaluated for:

- Loco Regional Control.
- Symptom and sign suggestive of distant metastasis.
- Late toxicity of radiation therapy.

Assessment of Quality of Life (QoL): To assess it, we used *EORTC QoL* (European Organization Research and Treatment of Cancer – Quality of Life) questionnaire *(EORTC QLQ – BR23)* available for this purpose. In addition to these questionnaires, we added two more questions related to the impact of overall treatment time on their QoL.

STATISTICAL ANALYSIS

Analysis was done using statistical tool SPSS 11.0. Two-tailed corrected chi-square test and unpaired *t*-test were used for p value calculation. The results were studied on an intention-to-treat basis.

RESULTS

Pretreatment characteristics observed were as follows: The cardinal presenting symptom was lump in the breast. Most of the patients presented with progressively increasing painless or, slightly painful breast lump. The average duration of breast lump in all the patients was 6 months. Other impor-

tant complaints included bloody nipple discharge, abnormal mammogram, skin changes in breast and axillary lymphadenopathy. Six patients were addicted to some kind of tobacco product. Patient related and tumor related parameters are detailed below in Table 1 and Table 2 respectively.

Outcome after Radiotherapy

Follow up period of patients ranged from 6 months to 24 months with a median follow up of 15 months. Overall in our study, the local control rate was 92% with 8 out of 100 (8%) patients had clinically and pathologically proven chest wall recurrence. The regional axillary nodal failure was seen in 7 out of 100 patients (7%). The most common site of distant metastasis in both regimen groups was lung followed by bone.

The difference in incidence of local, regional nodal, and distant metastatic recurrence rate was nonsignificant between the two regimens.

Radiation related acute and late toxicities are detailed below in Table 3.

Overall Treatment Time (OTT)

The OTT for regimen 1 patients ranged from 21 to 24 (mean 22.5) days, while it was from 34 to 39 (mean 36.42) days for regimen-2 patients (p Value = 0.0001). Statistically this difference is considered to be extremely significant.

P value – 0.0001

Quality of Life (QoL) Assessment

QoL related result is detailed below in Table 4. These results are based on below described questions asked to the patients.

DISCUSSION

Surgery and radiotherapy are important for loco regional control in carcinoma breast.[2,6]

Meta-analyses and Randomized Controlled Trials (at least 18 RCTs) of loco regional PMRT have consistently demonstrated that PMRT reduces the risk of loco regional failure by approximately two-thirds.[5,7-14] Later on, 3 large RCTs[5,11,12] and various meta-analyses[8-10,14,15] demonstrated that PMRT improves disease-free and overall survival. In our study, the loco regional control rate and overall locoregional control rate including salvage treatment at 2 years was 84% and 100% for regimen 1 group whereas it was 86% and 100% for regimen 2 group. Likewise the distant metastatic rate was 20% (10/50) in regimen 1 and 16% (8/50) in regimen 2. Regarding the locoregional recurrence rate our result was similar to the above mentioned studies. The distant metastatic rate in our study (18%) is much less than the above studies due to short period of follow-up and small number of patients included.

Data from randomized trials that compared hypofractionated radiation therapy with conventional radiation therapy, demonstrated no difference in late radiation morbidity or local recurrence.[16-21] A shorter fractionation schedule will lessen the burden of treatment for women, and will have important quality-of-life benefits with respect to convenience and less time away from home and work.

Question	Regimen 1 (n=50)		Regimen 2 (n=50)		p Value
	Number	Percentage	Number	Percentage	
01.	25	50	26	52	0.8
02	16	32	14	28	0.8
03.	25	50	26	52	0.8
04.	32	64	30	60	0.8
05.	16	32	14	28	0.8
06.	15	30	12	24	0.6
07.	47	94	48	96	0.6
08.	32	64	45	90	0.004
09.	34	68	46	92	0.006

Question	Regimen 1 (n=50)				Regimen 2 (n=50)			
	Score1 (No.)	Score2 (No.)	Score3 (No.)	Score4 (No.)	Score1 (No.)	Score2 (No.)	Score3 (No.)	Score4 (No.)
01.	25	08	12	05	24	10	12	04
02.	34	05	07	04	36	05	06	03
03.	25	10	10	05	24	10	12	04
04.	18	12	14	06	20	12	13	05
05.	34	05	07	04	36	05	06	03
06.	35	06	07	02	38	04	07	01
07.	03	18	26	03	02	20	26	02
08.	18	12	12	08	05	19	20	06
09.	16	13	16	05	04	20	22	04

[No. – Number of Patients

Questions asked to the patients: **1)**Did you have any pain in your arm or shoulder? **2)** Did you have a swollen arm or hand? **3)** Was it difficult to raise your arm or to move it sideways? **4)** Have you had any pain in the area of your affected breast? **5)** Was the area of your affected breast swollen? **6)** Was the area of your affected breast oversensitive? **7)** Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? **8)** Did you feel physical or mental stress due to prolonged overall treatment time of radiotherapy? **9)** Did you have economical problem due to prolonged treatment time?]

Table-4: Comparison of the number and percentage of patients having QoL related problem in the two regimen group against the different questionnaires

Regarding dose fractionation schedule of PMRT, there is no general agreement in literature.[22-24] The doses, ranging from 32.5 Gy / 3 weeks to 60 Gy / 10 to 14 weeks have been given.[22-26] It is not clear whether one fractionation scheme has any advantages over another.[22-26]

Earliest report of fractionation in PMRT was by *Kim et al,* who compared four different fractionation schedules.[27] They found no difference in locoregional control rates as well as acute reactions in all four fractionation schedules.

Ragaz et al, successfully used 37.5 Gy /16Fr to chest wall at the rate of 234cGy / Fr without significant acute or late sequelae.[5]

Goel et al, compared 45 Gy / 20Fr / 4 weeks versus 40 Gy / 17 Fr / 3.2 weeks in 108 patients of PMRT and found similar locoregional control rates as well as acute and late sequelae.[28]

Whelan et al, randomized patients to receive whole breast irradiation of 42.5 Gy in 16 fractions over 22 days (short arm) or, 50 Gy in 25 fractions over 35 days (long arm).[16] Five-year local recurrence-free, disease-free or overall survival rates were equivalent in both arms. The percentages of patients with an excellent or good global cosmetic outcome at 5 years were also equivalent. It concluded that the more convenient 22-day fractionation schedule appears to be an acceptable alternative to the 35-day schedule. A number of centers in Canada have already switched to this shorter fractionation course. Equal survival, local control, toxicity, and cosmetic outcomes at 5 years in the two arms with short fractionation (i.e., 16 fractions) after breast-conserving surgery have been reported in the recent *British Columbia Cancer Agency* randomized trials of aspirin versus no aspirin.[17]

In our study, patients were treated by two regimens – conventional and accelerated hypofractionated. There was no significant difference between the two regimens regarding locoregional and distant failure rates, although there was significant difference in the overall treatment time. Patients in both the regimen groups tolerated the treatment well with nonsignificant difference in acute and late radiation toxicities. Our results are in consistent with the studies using accelerated hypofractionated radiotherapy in breast cancer.

CONCLUSION

In post mastectomy radiotherapy of breast cancer, use of high dose per fraction schedule with shorter duration of treatment (Regimen 1 – 42.5 Gy/ 16 #/ 3.1 weeks) in comparison to the protracted course of conventional radiotherapy (Regimen 2 – 50 Gy/ 25 #/ 5 weeks) results in comparable loco regional and distant control rate. The overall treatment time (O.T.T.) in Regimen 1 is significantly less in comparison to Regimen 2 without any significant difference regarding acute and late radiation toxicities of all the normal structures included in the radiation field (skin, subcutaneous tissue, esophagus, lung, bone, shoulder joint and arm oedema). Regimen 1 leads to significant improvement in patient's quality of life parameters related to O.T.T. Shorter overall treatment time can be of great advantage in terms of time, cost, comfort and acceptability by the patients and it also reduces the heavy workload of already overburdened radiotherapy setup in a developing country like ours with scarcity of resources.

REFERENCES

1. Pisani P, Parkin DM, Ferlay J. Estimates of the world wide mortality from eighteen major cancers in 1985. Implication for prevention and projections of future burden. Int J Cancer. 1993;55:891-903.
2. Carlos A, Perez CA, Taylor ME. Breast: Stage Tis, T1 and T2 tumors. In: Perez CA, editors. Principles and practice of radiation oncology. Philadelphia: Lippincott – Raven; 1996. p.1269-396.
3. Overgaard M, Hansen PS, Overgaard J, et al. Post mastectomy irradiation in high risk breast cancer patients: present status of Danish Breast Cancer Cooperative Group trials. Acta Oncl. 1988;27:707-14.
4. Ragaz J, Jackson SM, Plenderleith IH, et al. Adjuvant radiotherapy and chemotherapy in node positive premenopausal women with breast cancer. N Engl J Med. 1997;337:956-62.
5. Ragaz J, Olivotto IA, Spinelli JJ, et al. Loco regional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97:116-26.
6. Will BP, LePetit C, Berthelot JM, Tomiak EM, Verma S. Diagnostic and therapeutic approaches for non-metastatic breast cancer in Canada, and their associated costs. Br J Cancer. 1999;79:1428-36.
7. Cuzick J, Stewart H, Peto R, Baum M, Fisher B, Host H, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep. 1987;71:15-29.
8. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol. 1994;12:447-53.
9. Early Breast Cancer Trialists' Collaborative Group. 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.
10. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. Lancet. 2000;355:1757-70.
11. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337:949-55.
12. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group (DBCG) 82c randomized trial. Lancet. 1999;353:1641-8.
13. Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19:1539-69.
14. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiotherapy improve survival in breast cancer? A meta-analysis. J Clin Oncol. 2000;18:1220-9.
15. Van de Steene J, Soete G, Storme G. Adjuvant ra-

diotherapy for breast cancer significantly improves overall survival: The missing link. Radiother Oncol. 2000;55:263-72.
16. Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143-50.
17. Olivotto IA, Kim-Sing C, Bajdik CD, Trevisan CH, Ludgate CM, Weir LM, et al. Effect of acetylsalicylic acid on radiation and cosmetic results after conservative surgery for early breast cancer: a randomized trial. Radiother Oncol. 1996;41:1-6.
18. Bates TD. The 10-year results of a prospective trial of post-operative radiotherapy delivered in 3 fractions per week versus 2 fractions per week in breast carcinoma. Br J Radiol. 1988;61:625-30.
19. Baillet F, Housset M, Maylin C, Boisserie G, Bettahar R, Delanian S, et al. The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. Int J Radiat Oncol Biol Phys. 1990;19:1131-3.
20. Yarnold JR, Owen JR, Bliss JM, Regan J, Broad B, Davidson J, et al. Randomised comparison of a 13 fraction schedule with a conventional 25 fraction schedule of radiotherapy after local excision of early breast cancer. Preliminary analysis. Br J Cancer. 1994;70(Suppl)XXII(04):p.10.
21. Whelan T, Olivotto I, Levine M. Clinical Practice guidelines for the care and treatment of breast cancer; Breast Radiotherapy after breast conserving surgery (2003 Update). CMAJ. 2003;168:437-9.
22. McWhirter R. Simple mastectomy and radiotherapy in the treatment of breast cancer. Brit J Radio. 1955;28:128-39.
23. Magee B, Ribeiro GG, Williams P, Swindell R. Use of an electron beam for post mastectomy radiotherapy. Clin Oncol. 1991;3:310-4.
24. Fletcher GH. Local results of irradiation in the primary management of localized breast cancer. Cancer. 1972;5:545-51.
25. Brown GR, Horiot JC, Fletcher GH, White EC, Ange DW. Simple mastectomy and radiation therapy for locally advanced breast cancers technically suitable for radical mastectomy. Am J Roent. 1974;120:67-73.
26. Archambault M, Griem ML, Lochman DJ. Results of ultrafraction radiation therapy in breast carcinoma. Am J Roent. 1964;91:61-6.
27. Kim JH, Chu FCH, Hilaris B. The influence of dose fractionation on acute and late reactions in patients with post operative radiotherapy for carcinoma breast. Cancer. 1975;35:1583-6.
28. Goel A, Kaushal V, Hooda HS, Das BP. Comparison of two radiation dose schedules in post mastectomy carcinoma of the breast. Indian J Med Sci. 2000;54:278-83.

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