ORIGINAL ARTICLES

Acute and late adverse effects of breast cancer radiation: Two hypo-fractionation protocols

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ABSTRACT

Background: Hypofractionated radiotherapy delivered a lower total dose of radiation in larger dose per-fraction over 3 weeks. Many randomized trials supported the comparable efficacy and toxicities of conventional radiotherapy schedule to different hypofractionated regimens.
Patients and methods: One hundred female patients having breast cancer post-surgery randomized into two arms of accelerated hypofractionation; 39 Gy/13 fractions (group A) and 42.4 Gy/16 fractions (group B) both regimens given as 5 fractions per week.
Results: There was a significant increase of incidence of acute radiation dermatitis in patients receiving 39 Gy. Grade I and II dermatitis reported in 82% and 46% for 39 Gy group and 42.4 Gy group respectively. In-addition, increased chronic subcutaneous fibrosis among patients with group A (28%) compared with (18%) to group B that was statistical significance. Breast conservative surgery is the only factor that had significant effect on incidence of acute radiation dermatitis and chronic subcutaneous fibrosis.
Conclusion: Thirty-nine Gy in 13 fractions has higher acute dermatitis and chronic subcutaneous fibrosis for patients underwent breast conservative surgery. We need longer follow up to evaluate the efficacy of both regimens as regard of local control and survival.

Key Words: Breast, Hypofractionation, Radiation

1. INTRODUCTION

Post-operative radiotherapy is delivered in the majority of our breast cancer patients. Conventional schedule of radiotherapy after surgery requires about 5-7 weeks of daily treatment. It was considered the standard of care.[1,2] This conventional schedule has many disadvantages on both patient and radiotherapy departments. The shorter overall schedule is more convenient for patients and decreases the load and waiting list in radiotherapy departments as well.

Accelerated hypofractionation using 4240 cGy in 16 fractions given in 3 weeks is considered as a standard dosage at our institute for early breast cancer irradiation. It is very tolerable and has comparable toxicity to the conventional schedule.[3] In the UK START Trial A, patients assigned after surgery to three schedules of radiation; 50 Gy in 25 fractions of 2.0 Gy or 41.6 Gy in 13 fractions of 3.2 Gy or 39 Gy in 13 fractions of 3.0 Gy and results confirmed comparable efficacy and toxicities.[4]

Our aim is to compare the toxicities of acute and late effects for two different protocols of hypofractionated radiotherapy in breast cancer patients treated in adjuvant setting.

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2. PATIENTS AND METHODS

This study included 100 female patients having breast cancer. Fifty patients assigned to group A and 50 patients to group B. The study was conducted at our radiotherapy department between December 2009 and February 2012. Consent was obtained from all patients, after the study was approved by our ethical committee.

Eligibility criteria were as follows: A confirmed histology of breast invasive ductal carcinoma, age $\geq$ 18 years, ECOG performance 0-2, negative histological margins, and operable clinical stage I-IIIA. Breast considered technically satisfactory for radiotherapy. Adjuvant radiotherapy is indicated in breast conservative surgery (BCS), and post-mastectomy RT, if tumor size > 5 cm and/or positive axillary nodes. Patient excluded if had lobular carcinoma in situ alone (*i.e.*, no invasive component), locally advanced inflammatory or non-inflammatory carcinoma of breast (cT4, N2-3), non-epithelial malignancies (*e.g.*, lymphoma or sarcoma), previous RT, or pregnancy.

Patients were evaluated at baseline prior to treatment through history and clinical examination with assessment of performance status; Measurement of arm circumference 10 cm above and below olecranon process; 2D Echo-cardiograph in case of left breast cancer; Complete laboratory investigations (complete blood picture, liver enzymes, albumin, bilirubin, serum urea and creatinine); Abdominal ultrasound; Chest radiographs and/ or CT chest.

Patients, after finishing their chemotherapy (if indicated), were randomized into two groups of accelerated hypofractionation; 39 Gy/13 fractions (group A) and 42.4 Gy/16 fractions (group B) both regimens given as 5 fractions per week. All patients who had BCS and younger than 50 years in both groups had received boost dose 14 Gy/7 fractions to tumor bed.

2.1 Radiation techniques

All patients were simulated with 3D planning. Clinical target volumes included whole breast in patients with BCS or chest wall post mastectomy. Ipsilateral supraclavicular lymph node was treated in cases of positive axillary lymph nodes. Medial and lateral tangential fields are used to treat breast and/or chest wall. Anterior supraclavicular field is used with 6 MV photon beams. The treatment plan was acceptable if $\leq$ 10% of the heart volume and $\leq$ 25% of the ipsilateral lung volume received 25 Gy.

Table 1. Patients' characteristics

Variable		Group A		Group B		Total		*p* value
		No.	%	No.	%	No.	%	
Age at diagnosis	< 50 years	27	54	29	58	56	56	> .05
	≥ 50 years	23	46	21	42	44	44	
	Rang	30-66		30-65				
	Median	49		45				
Laterality	Right	25	50	25	50	50	50	> .05
	Left	25	50	25	50	50	50	
Pathological Disease stage	Stage I	3	6	3	6	6	6	> .05
	Stage II	21	42	17	34	38	38	
	Stage III	26	52	30	60	56	56	
Type of surgery	BCS	12	24	10	20	22	22	> .05
	MRM	38	76	40	80	78	78	
Pathological Nodal status	N0	17	34	11	22	28	28	> .05
	N1	13	26	13	26	26	26	
	N2	11	22	17	34	28	28	
	N3	9	18	9	18	18	18	
Hormonal receptor status	Positive	27	54	28	56	55	55	> .05
	Negative	17	34	13	26	30	30	
	Unknown	6	12	9	18	15	15	
Adjuvant systemic therapy	Hormonal therapy	33	66	37	74	70	70	> .05
	Chemotherapy	47	94	49	98	96	96	

Note. BCS: breast conservative surgery; MRM: modified radical mastectomy.

Re-evaluation is done during radiotherapy and one week after by clinical assessment every week for skin complications then re-assessment every 6 months for two years. Skin, subcutaneous and pulmonary side effects were scored using the RTOG/European Organization for Research and Treatment of Cancer Radiation Morbidity Scoring Scheme.[5] Echocardiography of left sided patients was repeated two months after radiation. A fall of more than 10% in ejection fraction was considered as significant reduction in the LVEF whether the patient was symptomatic or not.[6] Lymphedema was monitored by measuring the arm circumference at 10 cm above and below the olecranon process of ulna. Measurements were taken at end of radiation 6 months, one year and two years. Suspected injury to the brachial plexus was evaluated by MRI.

2.2 Statistical analysis

Data represented as numbers, percentages or means ± SD; t-test used to compare between means; Chi-square test for comparison between groups; Local control and disease free survival calculated according to Kaplan-Meier method.

3. RESULTS

Patients' characteristics are listed in Table 1. Both groups are comparable with no significant difference. Most of our patients were younger less than 50 years and the majority had MRM. Pathological stage III disease represented 56% of patients. The histopathological examination of the dissected axillary lymph nodes revealed that 72% had positive lymph nodes.

Table 2. Acute radiation dermatitis in both groups

Variable	Group A (50)		Group B (50)		*p* value
	No.	%	No.	%	
G0	9	18	27	54	
GI	34	68	20	40	.0008
GII	7	14	3	6	

Table 3. Prognostic factors affect incidence and grade of acute radiation dermatitis

Variable	Group A			Group B			*p* value
	G0 (%)	GI (%)	GII (%)	G0 (%)	GI (%)	GII (%)	
Age at diagnosis							
< 50 years	6 (22.2)	15 (55.6)	6 (22.2)	16 (55.5)	10 (34.5)	3 (10.3)	> .05
≥ 50 years	3 (13)	19 (82.6)	1 (3.3)	11 (52.4)	10 (47.6)	0 (0)	
Type of surgery							
CBS	0 (0)	6 (50)	6 (50)	4 (40)	3 (30)	3 (30)	> .05
MRM	9 (23.7)	28 (73.7)	1 (2.6)	23 (57.5)	17 (42.5)	0 (0)	
Laterality							
Right	7 (28)	15 (60)	3 (12)	15 (60)	9 (36)	1 (4)	> .05
Left	2 (8)	19 (76)	4 (16)	12 (48)	11 (44)	2 (8)	
Stage							
I	0 (0)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	> .05
II	4 (19)	13 (61.9)	4 (19)	8 (47)	8 (47)	1 (6)	
III	5 (19.2)	19 (73)	2 (7.7)	18 (60)	11(36.7)	1 (33.3)	
Hormonal therapy							
Yes	7 (21.2)	20 (60.6)	6 (18.2)	19 (51.4)	16 (43.2)	2 (5.4)	> .05
No	2 (11.8)	14 (82.3)	1 (5.9)	8 (61.5)	4 (30.8)	1 (7.7)	

3.1 Skin complications

Acute radiation dermatitis in group A versus Group B is shown in Table 2. It was found that there was significant increase of incidences of acute radiation dermatitis in patients receiving 39 Gy as both grade I and II reported in 82% and 46% for group A and B respectively (p = .0008). Studying the different factors that can affect incidence and grade of acute radiation dermatitis among group A and B represented in Table 3, revealed only "type of surgery" that had been performed had significant effect. According to "type of surgery" in group A, the patients who underwent BCS had more events of acute radiation dermatitis 100%, while in comparison, to only 76.3% (29 out of 38 patients) for patients who underwent MRM (p = .0001). Similarly, in group B, patients underwent BCS had more episodes of acute radiation dermatitis 60%, while only 42.5% (17 out of 40 patients) of patients who underwent MRM (p = .017). Chronic radiation dermatitis developed in 6 patients. Grade

I developed in 4 patients of group A versus one patient of Group B and also one patient had grade II in Group B.

Table 4. Acute pneumonitis in patients in group A *vs.* group B

Variable	Group A (50)		Group B (50)		*p* value
	No.	%	No.	%	
G0	43	86	45	90	
GI	6	12	1	2	> .05
GII	1	2	4	8	

3.2 Pulmonary toxicity

Acute pulmonary symptoms were reported in 12% of all patients (see Table 4), however only 5 patients (one patient in group A and four patients in group B) required medical antitussive therapy (GII) and the remaining 7 patients had mild cough and did not require medical treatment (GI). The different prognostic factors that can influence the pulmonary complications like age, laterality, type of surgery, and hormonal therapy had no significant effect. We had only 8 patients had pulmonary symptoms developed after 6 months (chronic radiation pneumonitis). Seven patients (4 in group A and 3 in group B) were grade I and only one patient grade II in group B had medical treatment. Chest X-ray demonstrated apical opacity in 8 patients; 4 patients in both groups.

Table 5. Subcutaneous fibrosis reported in group A and B

Subcutaneous fibrosis	Group A (50)		Group B (50)		*p* value
	No.	%	No.	%	
G0	36	72	42	82	
GI	4	8	7	14	.02
GII	10	20	2	4	

3.3 Subcutaneous fibrosis

Incidence of chronic subcutaneous fibrosis was reported among 28% patients with group A versus 18% in group B that was statistical significance (see Table 5). Type of surgery was the only statistical significant factor affecting chronic subcutaneous fibrosis (see Table 6). Chronic subcutaneous fibrosis was significant higher post conservative surgery in group A ($p < .0001$). However, it was not significant post MRM in both groups.

Table 6. Prognostic factors affect the incidence of subcutaneous fibrosis in patients in group A *vs.* group B

Subcutaneous fibrosis		Group A (50)				Group B (50)				*p* value
		Total	-ve	+ve	%	Total	-ve	+ve	%	
Age	< 50 years	27	19	8	29.6	29	24	5	17.2	> .05
	≥ 50 years	23	17	6	26	21	17	4	19	> .05
Laterality	RT	25	18	7	28	25	20	5	20	> .05
	LT	25	18	7	28	25	21	4	16	> .05
Surgery	MRM	38	36	2	5.3	40	38	2	5	> .05
	BCS	12	0	12	100	10	3	7	70	< .0001
Stage	I	3	2	1	33.3	3	2	1	33.3	> .05
	II	21	13	8	38.1	17	14	3	17.7	> .05
	III	26	21	5	19.2	30	25	5	16.7	> .05
Hormonal therapy	Yes	33	25	8	24.2	37	31	6	16.2	> .05
	No	17	11	6	35.3	13	10	3	23.1	> .05

3.4 Cardiac toxicities

Cardiac function was assessed by the ejection fraction determined by echocardiography for left-sided patients. Four patients in Group A and 3 patients in Group B had more than 10% reduction in the ejection fraction value.

3.5 Lymphedema

Lymphedema was graded according the changes of arm circumference during follow up compared to pre-radiotherapy measurement. Total G1 and GII toxicities were reported in 38% and 22% of patients for group A and B respectively ($p > .05$). Six patients had GI for each group. However, GII was higher in group A patients (13 *vs.* 5).

3.6 Brachial plexopathy

No patient had any symptoms or signs suggesting brachial plexus radiation injury.

4. DISCUSSION

Post-operative radiotherapy improves both loco-regional control and survival for women treated with BCS and post-mastectomy.[7] Conventional fractionation of radiotherapy

became the standard of care. Long-term results[3,4] of post-operative radiotherapy for early breast cancer patients have confirmed the safety and efficacy of hypo fractionated schedule using 2.6 Gy per fraction to total doses of 40-42.6 Gy over 3 weeks. These trials, with 10 years follow-up, have reported that this schedule of radiotherapy is associated with equivalent local control and similar or lower rates of late side effects compared to conventional radiotherapy. However, other data have reported high rate of late effects among patients treated with over 12 fractions.[8]

Hypofractionated schedule radiotherapy as an accepted protocol for breast alone is supported by evidence from large randomized trials, meta-analyses, and systematic reviews.[9,10] However, the use of hypofractionated radiotherapy to both breast and regional lymph nodes is still controversial. This is because there is a concern about the benefits and the concerns regarding late effects of normal tissues.

We reported high incidence of only GI, and GII acute dermatitis and chronic subcutaneous fibrosis post BCS for patients treated with 39 Gy protocol. Data of acute radiation dermatitis is available from the START A and B trials. Although acute radiation dermatitis was mild in most patients regardless of the fractionation regimen used, the risk of skin events was considerably lower in the arms of hypofractionated radiotherapy. Hypofractionated radiotherapy was significantly less toxic as regard of breast shrinkage, breast edema, and teleangiectasia after 10 years follow up.[11] The incidence of all other late side effects such as heart disease, rib fractures, lung toxicities, plexopathy, and second cancers was low in all arms of all trials.[3,4,11]

Results of START B trial,[12] 40 Gy delivered in 15 fractions of 2.67 Gy over 3 weeks, had significantly less toxicity and had a marginal lower incidence of ipsilateral recurrence and a significantly reduced distant metastasis rate which significantly improved overall survival as well. In view of no significant differences in local control and no trend towards the same relationship in the similarly designed Ontario trial,[13] we cannot rule out the beneficial effect as the result of the substantially hypofractionated radiotherapy regimens. Although 39 Gy in 13 fractions was associated with less episodes of acute and late effects compared to conventionally schedule, there was a slightly increased ipsilateral recurrence in two trials (START Pilot and START A).[9]

Many questions are still not answered about the hypofractionated radiotherapy. Should it be considered as the standard protocol for all patients? What about younger patients less than 40 years, with locally advanced disease? And what about those underwent mastectomy with positive axillary LN? Some national treatment guidelines do not support hypofractionated radiotherapy for these patients,[14–16] whereas others do.[17] What about the effect of chemotherapy and anti-HER2 on hypofractionated radiotherapy? Approximately 65%-90% of patients in hypofractionated trials did not receive chemotherapy and none of the patients received trastuzumab.

5. Conclusion

There is a significant increase of incidences of acute radiation dermatitis in patient receiving 39 Gy. Grade I and II reported in 82% versus 46% for 42.4 Gy group. In-addition increased chronic subcutaneous fibrosis among patient with group A (28%) in comparison to group B (18%) that reach statistical significance. Both acute dermatitis and chronic subcutaneous fibrosis are significant higher post BCS. We need to follow up our patients long time to evaluate the 5-years local control and survival.

Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest statement.

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