Original Article

Normal Tissue Complications following Hypofractionated Chest Wall Radiotherapy in Breast Cancer Patients and Their Correlation with Patient, Tumor, and Treatment Characteristics

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Abstract

Introduction: Normal tissue complications following chest wall radiotherapy (RT) are inevitable, and the long-term data on hypofractionation are still limited. To quantify the late effects of hypofractionated RT on cardiac, pulmonary, brachial plexus, and regional lymphatics and their correlation with patient, tumor, and treatment characteristics is the main objective of this study. **Materials and Methods:** Two hundred and sixteen breast cancer patients following mastectomy were treated with hypofractionated schedules either 40 Gy in 15 fractions or 42.5 Gy in 16 fractions. Common Toxicity Criteria version 3.0 was utilized to quantify the late effects of hypofractionation on cardiac, pulmonary, brachial plexus, and lymphedema at a maximum follow-up of 5 years. **Results:** Median follow-up was 42 months. Median age was 49 years. 14.8% developed ≥Grade (Gr) 2 late cardiac toxicity. 10.2% developed ≥Gr2 late pulmonary toxicity. There were 28.7% patients who developed ≥Gr2 lymphedema. Sixty-seven out of 216 patients had symptomatic brachial plexopathy at 5-year follow-up. Variables found to increase the incidence of these adverse events included smoking, hypertension, diabetes mellitus, body mass index ≥25, extent of axillary dissection, and use of supraclavicular field. **Conclusion:** Hypofractionation leads to increased risk of normal tissue complications partly influenced by some patient- and treatment-related factors, but these were manageable and minimally disabling.

Keywords: *Breast cancer, hypofractionation, postmastectomy*

Introduction

Radiation plays an important role in the management of breast cancer. Postmastectomy radiotherapy (RT) is highly effective in preventing chest wall recurrences.[1] Postoperative RT to chest wall after mastectomy is usually given in 25 fractions of 2 Gy fraction size in 5 weeks followed by a boost if needed. Hypofractionated RT, whereby a fraction size of >2 Gy is utilized, has gained significant popularity as adjuvant treatment postbreast conserving surgery, based on the results of various randomized trials.[2-5] However, the data on the use of postmastectomy hypofractionated RT and its effects on normal tissues are still limited.

Based on the radiobiological predictions, it is clear that the use of >2 Gy produces unfavorable long-term sequelae. Adhering to the radiobiological principles, it has been quantified that the healthy tissues of breast and underlying structures are sensitive to fraction size, volume irradiated, and total dose delivered. Using linear quadratic model, α/β values for late reacting tissues are found to be 5 Gy or less.[6] α/β ratio is the dose D at which the components of cell killing that are proportional to dose, i.e., αD equal those that are proportional to the square of dose, i.e., $\beta D2$. Therefore, even small changes in fraction sizes can produce relatively large changes in effects of RT on the late-reacting tissues. Postmastectomy, chest wall irradiation exposes organs such as lungs and heart to a significant amount of radiation which increases the normal tissue complications. These complications are inevitable, and given the long-term survival of breast cancer patients, these long-term adverse effects should be quantified. Moreover, although new modalities such as intensity-modulated RT and three-dimensional RT have come a long way in sparing normal tissues, use of

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two-dimensional treatment with cobalt 60 is still prevalent in developing countries like ours.

Using postmastectomy hypofractionated RT in conjunction with conventional planning can impair normal tissue function in the long run. To quantify the late effects of hypofractionated RT on pulmonary, cardiac, brachial plexus, and lymphedema sequelae is the main objective of this study, and to find out the correlation of patient, tumor, and treatment characteristics with these late effects is the secondary objective to carry out this study.

Materials and Methods

Patients

A total of 216 female patients with breast cancer following mastectomy were followed from January 2011 to January 2016. Study was approved by the Local Ethics Committee. Eligibility criteria include female patients, postmastectomy, with histologically proven disease, >20 years age group with either stage 1–3. All patients with breast-conserving surgery, positive margins, chest malformations, chronic cardiac or pulmonary disease, pregnant or lactating were excluded from evaluation.

Radiotherapy

Hypofractionated schedules used were either 42.5 Gy in 16 fractions with 2.65 Gy fraction in 22 days or 40 Gy in 15 fractions with 2.66 Gy fraction in 19 days depending on physician's preference. RT was delivered by Theratron 780 teletherapy cobalt 60 machine, with the intention to treat chest wall along with regional lymphatics depending on the histopathology report. Tangential RT portals were utilized for chest wall RT and direct portal for supraclavicular/axillary fields. Bolus was used on alternate days. Two-dimensional planning was done.

Patient assessment

Echocardiography and pulmonary function tests (PFTs) were done for all patients before the start of RT and then after 3 monthly intervals till 1 year, followed by 6 monthly assessments till last follow-up. Percentage decline in ejection fraction was used to evaluate cardiac reactions, while for pulmonary function, measurements were recorded as percentages of predicted values. For lymphedema, grading percentage change in inter-limb discrepancy in volume or circumference at point of greatest visible difference in conjunction with other points such as obscuration of anatomic architecture, pitting edema, and interference with daily life was taken into account. And finally, for brachial plexopathy, grading patient's symptomatology along with active daily life score was used. This grading is in accordance with the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

Descriptive statistics were used to present the data. For repeated measurements, analysis of variance was utilized to assess the difference in function values at different times and to correlate the respective function values at different times with multiple demographic variables. Pearson Chi-square test was used to assess correlation of numerical variables.

Results

Patient characteristics

A total of 216 patients were followed from January 2011 to January 2016 for the effects of hypofractionated RT on normal tissue toxicity especially pertaining to cardiac, pulmonary, brachial plexus, and lymphedema sequelae in postmastectomy breast cancer patients. Median follow-up was 42 months. The majority of the patients were in 40–60 years age group, with median age of 49 years [Table 1]. Sixteen percent of the females were either active or ex-smokers. Twenty-two percent had diabetes, and 24.5% were known hypertensive. The majority had stage two or three disease with ductal histology being more common. Axillary dissection was done in 175 patients with adequate dissection meaning more than equal to ten nodes dissected was performed in 117 patients. All patients were given full course of chemotherapy before the start of RT. Tamoxifen was prescribed as hormonal therapy to 103 patients, while 39 were given aromatase inhibitor (either anastrozole or letrozole). The supraclavicular field was prescribed to 131 patients based on their histopathological features.

Toxicity analysis

We mainly restricted our analysis to late adverse events which are described as those occurring >6 months after the completion of RT [Table 2]. Our main organs of interest were heart, lungs, brachial plexus, and lymphedema, because these are the main organs at risk during chest wall irradiation, and their long-term toxicity adversely affects the quality of life of an individual.

Cardiac

Thirty-two out of 216 patients developed ≥ Grade (Gr) 2 late cardiac toxicity, and out of which, one patient had congestive cardiac failure which was poorly controlled by medication.

Pulmonary

About 10.2% of patients had ≥Gr2 late pulmonary toxicity. Although symptomatic pneumonitis was rare in our study, 5 patients had clinically significant percentage decline in PFTs over their predicted values.

Lymphedema

Arm circumference was taken 5 cm above and below the olecranon and at wrist level and was compared with the opposite arm. Sixty-two patients developed >10% inter-limb discrepancy accompanied with easily observed swelling or obscuration of anatomic structures. Twenty

Table 1: Patient, tumor, and treatment characteristics

Characteristic	*n*
Age (years)	
≤45	75
>45	141
Smoking	
Smokers/ex-smokers	35
Nonsmokers	181
Diabetes mellitus	
Yes	47
No	169
Hypertension	
Yes	53
No	163
BMI	
<25	102
≥25	114
Histology	
Ductal	201
Lobular	15
Others	1
Nodal dissection	
Adequate (≥10)	117
Inadequate (<10)	99
Stage grouping	
1	8
2	109
3	99
Grade	
1	63
2	117
3	36
LVSI	
Present	60
Absent	156
ECE	
Present	25
Absent	191
Receptor status	
ER/PR positive	142
ER and PR negative	74
Her2/neu	
Positive	43
Negative	50
Unknown	123
Chemotherapy used	
CAF	42
TAC	60
AC-TC	114
Supraclavicular field	
Yes	131
No	85

BMI – Body mass index; LVSI – Lymphovascular space invasion; ECE – Extracapsular extension; ER – Estrogen receptor; PR – Progesterone receptor; C – Cyclophosphamide; A – Adriamycin; F – 5-fluorouracil; T – Taxane; Her2 – Human epidermal growth factor receptor 2

Table 2: Toxicity analysis (*n*=216)

Grade	Acute toxicity/late toxicity (i.e. <90 days/ >6 months follow-up)			
	Cardiac	Pulmonary	Lymphedema	Brachial plexopathy
0	176/120	183/160	98/97	211/100
1	31/64	33/34	98/57	5/49
2	9/17	0/17	20/42	0/61
3	0/14	0/4	0/20	0/6
4	0/1	0/1	0/0	0/0

patients had lymphedema which interfered with their active daily life.

Brachial plexopathy

Clinically symptomatic/significant brachial plexopathy was observed in 12.5% of the patients. Only six patients developed brachial plexopathy interfering with active daily life. There were none with disabling brachial plexopathy observed after a median follow-up of 42 months.

Discussion

Hypofractionated RT was introduced to ease the burden of patients and hospitals alike. However, use of hypofractionation leads to unacceptably high percentage of severe complications.[7-9] Fractional size of >2 Gy produces unacceptable late adverse sequelae.[10] Due to their close proximity to chest wall, certain organs/structures suffer radiation-induced toxicities. These late adverse effects can significantly impact the quality of life in long run. Opposed tangential portals with or without supraclavicular field expose structures such as heart, lungs, brachial plexus, and regional lymphatics to significant amounts of radiation doses. Moreover, all these structures are particularly sensitive to fractionation. As for this study, keeping in view the late reactions, the biologically effective doses delivered with two schedules came out to be 80.3 Gy for 40 Gy in 15 fractions and 75.3 Gy for 42.5 Gy in 16 fractions.

To add to this, there are certain patient-, disease-, and treatment-related factors which influence the risk of chest wall irradiation such as age, personal history of patient, extent of nodal dissection, number of nodes dissected, use of supraclavicular/axillary field, and so on. These factors have been shown by a number of studies to increase the incidence of normal tissue complications. However, the majorities were carried out in conjunction with conventional fractionation regimes. There is very scarce data on the relevance of these factors in the era of hypofractionated RT, especially in the postmastectomy settings, where the likelihood of normal tissue complications increases with time. Moreover, to collect data on how these factors influence the effects of hypofractionated RT on normal tissue functions was also one of the aims of this study.

First, for cardiac tissues [Table 3], we reported an incidence of 14.8% of ≥Gr2 late cardiac toxicity, with statistically significant difference when left-sided disease was compared

with the right side ($P < 0.05$). This is in agreement with Darby *et al*.[11] study, who reported an increased risk of cardiac deaths after treatment for left-sided breast cancer. Age at irradiation has been demonstrated to increase the risk. Hooning *et al*.[12] reported that younger age <35 years have a relative risk of 6.5 as compared to the general population for radiation-induced heart disease. We, however, observed no statistically significant difference for cardiac toxicity for patients <45 years versus >45 years. King *et al*.[13] showed that factors such as hypertension, being overweight, and diabetes influence the overall risk of radiation-induced heart injury. We too observed that 21 out of 47 patients with diabetes and 25 out of 53 hypertensives suffered ≥Gr2 cardiac toxicity with results being statistically significant. Furthermore, patients with body mass index (BMI) ≥25 had statistically significant late adverse effects. Smoking also increases the risk, with 60% of active/ex-smokers developing ≥Gr2 cardiac toxicity. Radiation potentiates the cardiotoxic effects of some chemotherapeutic agents such as anthracyclines, and this interaction is dose dependent.[14] The total cumulative dose of anthracycline in our study was well below 360 mg/m^2. Our trial found no statistically significant late adverse effect in patients receiving chemotherapy, with no influence of the type of regime utilized. Concerning hormonal therapy, no statistically significant difference was found.

Second, for lung tissues [Table 4], we observed 10.2% of late ≥Gr2 adverse events at 42 months of median follow-up. Lind *et al*.[15] reported that use of axillary/supraclavicular portals in addition to tangential portals increased the incidence of pulmonary complications. We reported statistically significant incidence of late pulmonary toxicity in those who received supraclavicular RT ($P = 0.03$) as compared to those who did not. Age and smoking have also been considered as risk factors contributing to radiation-induced lung injury.[16-21] In our series, although we observed no statistically significant effect of age on pulmonary adverse effects, smoking definitely potentiates the side effect of hypofractionation on pulmonary functions with 17 out of 35 smokers/ex-smokers suffering ≥Gr2 toxicity, the results being statistically significant ($P < 0.005$). Lingos *et al*.[22] found increased incidence of radiation-induced lung injury in patients receiving chemotherapy. The impact of hormonal therapy on radiation pneumonitis has also been demonstrated in a number of trials.[23,24] In our study, we found that both chemotherapy and hormonal therapy do increase the risk of lung injury when combined with hypofractionated RT. Being diabetic or hypertensive also increased the risk of pulmonary toxicity with statistically significant results for ≥Gr2 late lung toxicity.

Table 3: Cardiac toxicity in association with demographic variables

Variable	<Gr2 toxicity	≥Gr2 toxicity	*P*
Age (years)			
≤45	68	7	0.09
>45	116	25	
Smoking			
Smokers/ex-smokers	14	21	<0.05
Nonsmokers	170	11	
Diabetes mellitus			
Yes	26	21	<0.05
No	158	11	
Hypertension			
Yes	28	25	<0.05
No	156	7	
BMI			
<25	95	7	0.002
≥25	89	25	
Laterality			
Left	81	28	<0.05
Right	103	4	
Chemotherapy			
CAF	31	11	0.068
TAC	53	7	
AC-TC	100	14	
Hormonal therapy			
Tamoxifen	79	24	0.72
Aromatase inhibitor	31	8	

BMI – Body mass index; C – Cyclophosphamide; A – Adriamycin; F – 5-fluorouracil; T – Taxane; Gr2 – Grade 2

Table 4: Pulmonary toxicity in association with demographic variables

Variable	<Gr2 toxicity	≥Gr2 toxicity	*P*
Age (years)			
≤45	71	4	0.08
>45	123	18	
Smoking			
Smokers/ex-smokers	18	17	<0.05
Nonsmokers	176	5	
Diabetes mellitus			
Yes	33	14	<0.05
No	161	8	
Hypertension			
Yes	43	10	0.016
No	151	12	
BMI			
<25	92	10	0.86
≥25	102	12	
Supraclavicular field			
Yes	113	18	0.03
No	81	4	
Chemotherapy			
CAF	38	4	0.009
TAC	48	12	
AC-TC	108	6	
Hormonal therapy			
Tamoxifen	92	11	0.009
Aromatase inhibitor	28	11	

BMI – Body mass index; C – Cyclophosphamide; A – Adriamycin; F – 5-fluorouracil; T – Taxane; Gr2 – Grade 2

Concerning lymphedema, various studies quote 5%–42% rate of lymphedema following breast cancer treatment.[25] Risk increases when axillary dissection is combined with axillary RT. In our study, we reported the risk of clinically significant ≥Gr2 lymphedema at 28.7% [Table 5], and this risk was more in patients who underwent axillary dissection (57 out of 175), and especially increased in those who had ≥10 lymph nodes dissected ($P = 0.0005$). Other risk factors associated with increased incidence of lymphedema included smoking ($P < 0.05$), BMI ≥25 ($P < 0.05$), and hypertension ($P < 0.05$). Segerström *et al*.[26] found that being obese increased the risk of arm edema in patients. Böhler *et al*.[27] in another series described hypertension as the risk factor for lymphedema after axillary surgery and RT. Adjuvant chemotherapy and hormonal therapy were not found to influence the risk of lymphedema in our study.

Finally, regarding brachial plexopathy, there is a concern that hypofractionated schedules may be associated with the higher risk of late complications to the brachial plexus. The risk of developing brachial plexopathy after conventionally fractionated megavoltage RT is estimated to be below 1%.[28,29] Galecki *et al*.[30] in a review article estimated that the risk of brachial plexopathy ranged from 1.7% up to 73% with the use of doses per fraction in the range from 2.2 to 4.58 Gy with the total doses between 43.5 and 60 Gy. They also concluded that surgical manipulations in the axilla and chemotherapy have to be taken into account as additional factors which may increase the risk of brachial plexopathy. In our present study, we observed an overall incidence of 30.6% [Table 6] for any Gr of brachial plexopathy at a maximum follow-up of 5 years, with 12.5% incidence of ≥Gr2 brachial plexopathy. The extent of axillary dissection in conjunction with use of supraclavicular field significantly influenced the appearance of clinically symptomatic brachial plexopathy with $P < 0.05$. Other factors which increased the risk of brachial plexopathy included smoking ($P = 0.00002$), diabetes mellitus ($P < 0.05$), and use of hormonal therapy ($P = 0.007$).

Hypofractionated schedules have gained a great impetus in present times following the publications of Standardisation of Breast Radiotherapy A and B trials. These studies

Table 5: Association of lymphedema with different demographic variables

Variable	<Gr2 toxicity	≥Gr2 toxicity	*P*
Age (years)			
≤45	57	18	0.27
>45	97	44	
Smoking			
Smokers/ex-smokers	11	24	<0.05
Nonsmokers	143	38	
Diabetes mellitus			
Yes	34	13	0.86
No	120	49	
Hypertension			
Yes	13	40	<0.05
No	141	22	
BMI			
<25	86	16	<0.05
≥25	68	46	
Axillary dissection			
Yes	118	57	0.009
No	36	5	
Nodes dissected			
≥10	70	47	0.00005
<10	84	15	
Chemotherapy			
CAF	32	10	0.68
TAC	41	19	
AC-TC	81	33	
Supraclavicular field			
Yes	97	34	0.26
No	57	28	

BMI – Body mass index; C – Cyclophosphamide; A – Adriamycin; F – 5-fluorouracil; T – Taxane

Table 6: Association of brachial plexopathy with different variables

Variable	<Gr2 toxicity	≥Gr2 toxicity	*P*
Age (years)			
≤45	66	9	0.87
>45	123	18	
Smoking			
Smokers/ex-smokers	23	12	0.00002
Nonsmokers	166	15	
Diabetes mellitus			
Yes	29	18	<0.05
No	160	9	
Hypertension			
Yes	43	10	0.10
No	146	17	
BMI			
<25	91	11	0.47
≥25	98	16	
Axillary dissection			
Yes	149	26	0.03
No	40	1	
Nodes dissected			
≥10	95	22	0.002
<10	94	5	
Chemotherapy			
CAF	36	6	0.77
TAC	54	6	
AC-TC	99	15	
Supraclavicular field			
Yes	108	23	0.005
No	81	4	

BMI – Body mass index; C – Cyclophosphamide; A – Adriamycin; F – 5-fluorouracil; T – Taxane; Gr2 – Grade 2

have equated hypofractionation with conventional regime following breast conservation therapy with limited data in postmastectomy settings. Although the normal tissues studied in this trial are sensitive to fractionation with α/β values of ≤ 3 Gy, we observed clinically few to none disabling adverse events even at a maximum follow-up period of 5 years. However, there are certain risk factors pertaining to patient, disease, and treatment such as smoking, hypertension, diabetes mellitus, BMI, extent of axillary dissection, and use of supraclavicular/axillary field and hormonal therapy, which significantly influence the development of cardiac, pulmonary, lymphedema, and brachial plexopathy and late adverse effects. Moreover, although these adverse events were symptomatic and interfered with active daily life of patient, they are manageable.

Conclusion

Results from this study clearly support the use of hypofractionated RT regimes for chest wall irradiation in postmastectomy settings with no fear of disabling/nonmanageable long-term normal tissue complications although more longer follow-up data are still warranted.

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Conflicts of interest

There are no conflicts of interest.

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