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Hypofractionated radiotherapy in young versus older women with breast cancer: a retrospective study from India

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ABSTRACT

Background: Young women with breast cancer (BC) are not represented in the trials on hypofractionation. In this study we compared outcomes in young patients with BC to their older counterparts treated with hypofractionated radiotherapy (RT) in a regional cancer centre in India.

Materials and methods: Between January 1990 to December 2010, women with BC, treated with hypofractionated RT dose of 35–40 Gy/15#/3 weeks were divided into two groups, ≤ 35 years and > 35 years. Outcomes compared were locoregional recurrence rate (LRR), locoregional recurrence-free survival (LRRFS), disease-free survival (DFS), overall survival (OS) and toxicities. LRRFS, DFS and OS were estimated using the Kaplan-Meier method.

Results: Of total 2244 patients, 359 were ≤ 35 years of age and 1885 were > 35 years. Patient and disease characteristics were comparable between the two groups, except that comorbidities were significantly higher in the > 35 years age group, more patients aged ≤ 35 years had nodal N3 disease, received chemotherapy and RT to internal mammary nodes and more patients in the > 35 years group received hormonal therapy. Median follow up was 10 years (range 1–30 years). LRR and distant metastases were comparable between the two groups. However, synchronous LRR and distant metastases were significantly higher in the ≤ 35 years group 18 (5.1%) as compared to the > 35 years group 39 (2.1%) with p = 0.018. Estimated 10-year LRRFS, DFS and OS were 92% *vs*. 94% (p = 0.95), 68% *vs.* 73%(p = 0.058) and 78% *vs.* 76% (p = 0.10) in ≤ 35 years and > 35 years, respectively. OS for stage 1 was comparable between the two groups. However, for stage 2 and 3 it was 77% *vs.* 82% (p = 0.048) and 53% *vs.* 62% (p = 0.045) in the ≤ 35 years and > 35 years group, respectively. Acute and late toxicity were similar in the two groups.

Conclusion: Young BC patients had higher LRR and distant metastases. LRRFS, DFS and toxicities were comparable between the two groups. However, OS was poorer in young BC patients with stage 2 and 3 disease.

Key words: breast cancer; young patients; hypofractionation; outcomes; treatment

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Introduction

Breast cancer (BC) in young women is a relatively uncommon problem but represents a special population within BC patients [1]. It carries poor prognosis [2]. This is due to diagnosis in advanced stage and disease biology. BC in this population have many unfavourable features such as advanced tumour stage at presentation, more positive nodes, higher grade, higher oestrogen and progesterone negative tumours, high proliferative rate, lymphovascular invasion and Her 2neu 3^{+} tumours. They

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have worse outcomes as compared to older counterparts [3–5]. This might be also because these patients are not part of screening programmes. Hypofractionation in BC have been proved to be better than conventional fractionation in patients > 50 years of age in terms of normal tissue toxicities and cosmetic outcomes. Young women with BC were not part of clinical trials on hypofractionation, so there is a lack of data on effectiveness and safety of hypofractionation in younger women with BC [6]. It is also not clear whether young age should be independently considered in treatment decisions. Most of the data in young patients with BC is from the western world. Data from Asia is lacking. In this study we compared clinical outcomes in BC women, ≤ 35 and > 35 years, who were treated with hypofractionated RT in a regional cancer centre in India. We use hypofractionation in BC at our institute since 1976.

Materials and methods

In this retrospective study, 2244 women with primary BC who were registered in Radiation Oncology outpatient department of a Regional Cancer Centre, between January 1990 and December 2010 were analysed. Patients were divided based on their age at the time of diagnosis into ≤ 35 years and > 35 years groups. Patients included were diagnosed with stage I–III confirmed BC, > 18 years of age, post total mastectomy with axillary clearance or breast-conserving surgery (BCS) with axillary clearance. Information on patient and tumor characteristics, treatment given and follow-up or death was collected from the patient's file. Staging was done according to AJCC 8th edition. The two groups were compared for clinical (comorbidity, family history, tumor stage, type of surgery), pathological characteristics (resection margin, grade, lymphovascular invasion, nodes involved and immunohistochemistry) and treatment-related factors, such as surgery, radiotherapy (RT) and systemic therapy.

Treatment

Surgery was total mastectomy with axillary clearance or BCS with axillary clearance. Chemotherapy was administered to patients with high-risk features such as large tumors, positive nodes, lymphovascular invasion and low ER/PR expression or ER/PR negative tumors. Chemotherapy regimen was cyclophosphamide, methotrexate and fluorouracil (CMF) for 6 cycles; fluorouracil, adriamycin and cyclophosphamide (FAC) 4–6 cycles and anthracyclins and taxane based. Hormonal treatment was tamoxifen and aromatase inhibitors for 5–10 years. No ovarian suppression was used.

Radiotherapy

Patients were planned for RT on a 2-dimensional (2D) simulator with two opposed standard tangential fields to the breast/chest wall and a single incident supraclavicular fossa (SCF) field. For the breast/chest wall field borders were; medial — in the midline, lateral — in the mid axillary line, superior — below the medial end of clavicle and inferior — 1 cm below the inframammary fold of the opposite breast. Central lung distance (CLD) was kept between 1–2.5 cm (Fig. 1). CLD is the perpendicular distance from the centre of the posterior border of the tangential field to posterior edge of the chest wall. It is a predictor of the ipsilateral lung volume included in the tangential fields. CLD of 1.5 cm, 2.5 cm and 3.5 cm will irradiate approximately 6%, 16% and 26% of the ipsilateral lung volumes. There was no gap between tangential and SCF field borders. RT dose was 35 Gy/15#/3 wks in postmatectomy and 40 Gy/16#/3 wks in BCS patients. Dose was prescribed at mid-separation. Regional nodal irradiation (RNI) dose was 40 Gy/15#/3 wks. SCF

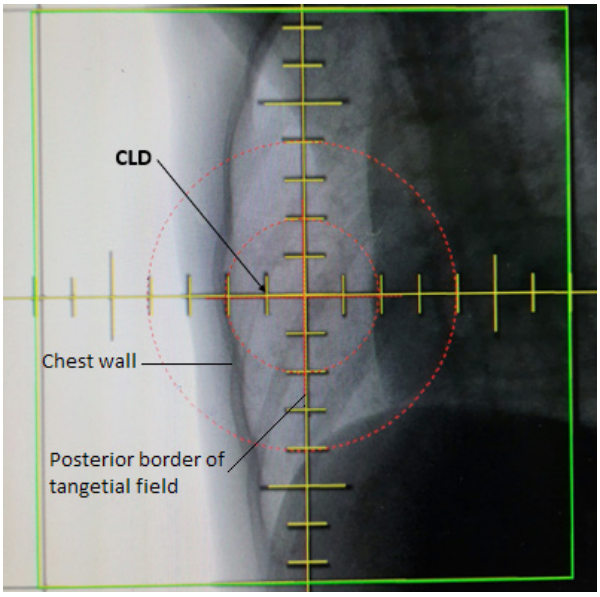

Figure 1. Central lung distance (CLD). CLD in this case is 2 cm

dose was prescribed at d_{max}. Boost was delivered in patients with BCS and those with close or positive margins post mastectomy. Boost dose was 10–16 Gy in 5–8 fractions over 1–1.5 weeks with photons or electrons. Patients with central/inner quadrant T3 tumors and N2 axillary nodal stage were given internal mammary node (IMN) RT. First five intercostal spaces were included in the IMN field. IMNs were treated with a single field. Dose was prescribed at 3 cm depth with photons energy of 4–6MV. BCS patients were treated on linac with 30° wedge. Mastectomy patients were treated on cobalt with breast cone. Few mastectomy patients with chest wall separation > 20 cm were also treated on linac to avoid under dose to the chest wall. Chest wall separation is the distance between medial (midline) and lateral borders (mid-axillary line) of the chest wall/breast fields. Bolus on the chest wall was used during 50% of radiation delivery in postmastectomy patients. No cardiac shielding was used.

Assessments

Patients were examined clinically and radiologically after completion of treatment. First follow up was at 1 month of completion of RT; acute toxicities reported are of this point of time. Follow-up was done every three months during the first year, every four months during the 2nd year, six monthly till 5 years, yearly till 10 years and 2 yearly thereafter. On every visit patients were examined clinically and relevant investigations were done if the patient had symptoms of recurrence or metastases. The physicians assessed acute and late radiation toxicities using RTOG toxicity scoring scale. Late radiation toxicities were assessed with the RTOG LENT and SOMA scale. Late toxicities were defined as any toxicity occurring after 6 months of RT. Late cardiac toxicities were defined as any event of coronary artery disease, myocardial infarction, cardiac failure, valvular heart disease and cardiomyopathy. Second malignancy was defined as any malignancy that occurred after 6 months of BC treatment.

Outcomes

Demographic and patient characteristics as well as adjuvant therapies received were presented as frequency. Outcomes analysed were locoregional recurrence (LRR), locoregional recurrence-free survival (LRRFS), disease-free survival (DFS) and overall survival (OS). OS was calculated using time from diagnosis to death from BC or censoring for end of follow-up whichever came first. DFS was estimated using time from diagnosis to recurrence (local or distant). LRRFS was calculated using time from diagnosis to locoregional recurrence as first event. Kaplan-Meier LRRFS, DFS and OS curve were constructed. All statistical tests were two-sided and p values < 0.05 were deemed significant. Statistical analysis was done using SPSS software version 16.0.

Results

Total 2244 patients were analysed, 359 were ≤ 35 years of age and 1885 were > 35 years. The distribution of patients during 20 years of enrollment is shown in Table 1. Clinical, pathological and treatment characteristics are shown in Table 2. Majority of patients, 82% in both groups underwent mastectomy. Patient and disease characteristics were comparable between the two groups, except comorbidities were significantly($p \leq 0.001$) higher in

Table 1. Distribution of patients during 20 years of enrollment

Year	≤ 35 year	> 35 year
1990	8	33
1991	8	45
1992	9	50
1993	10	38
1994	13	41
1995	15	46
1996	8	34
1997	10	27
1998	10	53
1999	11	49
2000	22	112
2001	29	171
2002	16	39
2003	28	223
2004	19	128
2005	32	180
2006	12	240
2007	39	276
2008	17	31
2009	23	34
2010	20	35
Total	359	1885

Table 2. Patient characteristics

Variable	≤ 35 years (n = 359)	> 35 years (n = 1,885)	p-value Fisher's Exact Test
Laterality			
Right	219 (61.0)	1,162 (61.4)	0.813
Left	140 (39.0)	723 (38.4)	
Co-morbidity			
Yes	8 (2.2)	262 (13.9)	< 0.001
None	351 (97.8)	1,623 (86.1)	
Family history			
Yes	20 (5.6)	87 (4.6)	0.419
No	339 (94.4)	1,798 (95.4)	
Tumour stage			
T1T2	215 (59.9)	1,096 (58.1)	0.559
T3T4	144(40.1)	789 (41.9)	
Surgery			
Mastectomy	295 (82.2)	1,553 (82.4)	0.940
Breast conservation	64 (17.8)	332 (17.6)	
Histology			
Infiltrating ductal	330 (91.2)	1,702 (90.3)	0.508
Infiltrating lobular	9 (2.5)	71 (3.8)	
Other	20 (5.6)	112 (5.9)	
Grade			
I & II	282 (78.6)	1,517 (80.5)	0.427
III	77 (21.4)	368 (19.5)	
Resection margins			
Involved	31 (8.6)	152 (8.1)	0.752
Not involved	328 (91.4)	1,733 (91.9)	
Lymphovascular invasion			
Yes	80 (22.3)	381 (20.2)	0.392
No	279 (77.7)	1,504 (79.8)	
Nodal status			
0	144 (40.1)	833 (44.2)	< 0.001
1	110 (30.6)	585 (31.0)	
2	63 (17.5)	384 (20.4)	
3	42 (11.7)	83 (4.4)	
Dissected nodes			
Median (range)	11 (3–32)	10 (3–36)	
Extracapsular extension			
Yes	37 (10.3)	151 (8.0)	0.147
No	322 (89.7)	1,734 (92.0)	
Estrogen receptor status			
Positive	136 (61.8)	839 (60.8)	0.823
Negative	84 (38.2)	542 (39.2)	
Total	220	1,381	
Unknown	139 (38.7)	584 (31.0)	
Progesterone receptor status			
Positive	107 (49.1)	703 (53.7)	0.213
Negative	111 (50.9)	605 (46.3)	
Total	218	1,308	
Unknown	141 (39.3)	577 (30.6)	
Chemotherapy			
Yes	305 (85.0)	1,105 (58.6)	< 0.001
No	54 (15.0)	780 (41.4)	
Radiotherapy details			
Breast/CW + SCF	305 (85.0)	1,641 (87.1)	0.042
Breast/CW + SCF + IMN	35 (9.7)	117 (6.2)	
Breast/CW only	19 (5.3)	127 (6.4)	
Radiation boost			
Yes	45 (12.5)	228 (12.1)	0.792
No	314 (87.5)	1,657 (87.9)	
Hormonal therapy			
Yes	216 (60.2)	1,493 (79.2)	< 0.001
No	143 (39.8)	392 (20.8)	

CW — chest wall; SCF — supraclavicular fossa; IMN — internal mammary node

the > 35 years age group 262 (13.9%) as compared to 8 (2.2%) in ≤ 35 years. More patients in ≤ 35 years had nodal N3 disease 42 (11.7%) as compared to 83 (4.4%); received chemotherapy 305 (85.5%) *vs.* 1105 (58.6%) and radiotherapy to IMNs 35 (9.7%) *vs.* 117(6.2%). More patients in the > 35 years group received hormonal therapy 1493 (79.2%) as compared to 216(60.2%) in the ≤ 35 years group.

Whole breast/chest wall and supraclavicular RT was delivered in > 85% patients in both groups. Median chest wall separation was 18 cm (range 12–24 cm). Mean CLD was 2 cm (range 1–3 cm). Regional nodal irradiation was delivered in 340 (94.7%) and 1758 (93.3%) women in the ≤ 35 and > 35 year group, respectively. IMNs were irradiated in 35 (9.7%) and 117(6.2%) patients in the ≤ 35 and > 35 years group, respectively. RT boost was delivered in 45 (12.5%) and 228 (12.1%) patients in the ≤ 35 years and > 35 years group, respectively.

Table 3. Recurrence pattern in the two groups

Variable	≤ 35 years (n = 359)	> 35 years (n = 1,885)	p-value Fisher's Exact Test
Recurrence			
Loco-regional	19 (5.3)	95 (5.0)	0.018
Distant metastasis	74 (20.6)	370 (19.6)	
Both	18 (5.0)	39 (2.1)	

Chemotherapy regimen consisted of CMF, anthracyclines and anthracyclines and taxanes in 130 (43%), 120 (39.5%), 75 (24.5%) and 485 (44%), 466 (42%), 154 (14%) in the ≤ 35 year and > 35 years group, respectively. Significantly more patients in the ≤ 35 year age group received anthracyclins and taxanes based chemotherapy 75 (24.5%) as compared to 154 (14%) in > 35 years group (p ≤ 0.001).

Hormonal therapy in the form of tamoxifen was given to 216 (60.2%) patients in the ≤ 35 year group. In the > 35 year group hormonal therapy was tamoxifen in 1440 (96%) and aromatase inhibitors in 53 (4%) patients.

Median follow-up was 120 months (range 12–363 months). Disease recurrence pattern is shown in Table 3. There was no statistically significant difference between the two groups in terms of loco-regional recurrence and distant metastases. LRR was seen in 19 (5.3%) and 95 (5%) patients in the ≤ 35 years and > 35 years groups, respectively. Distant metastases occurred in 74 (20.6%) and 370 (19.6%) patients in the ≤ 35 years and > 35 years groups, respectively. However, both (synchronous) loco-regional recurrence and distant metastases were significantly higher in the ≤ 35 years group 18 (5.1%) as compared to the > 35 years group 39 (2.1%) with p = 0.018 (Tab. 3).

The estimated 10-year LRRFS was 92% *vs.* 94%(p = 0.95) in the ≤ 35 years and > 35 years group, respectively (Fig. 2). The estimated 10-year DFS was 68% *vs.* 73% (p = 0.058) in ≤ 35 years and > 35 years group, respectively (Fig. 3). The estimated 10-year OS was 78% *vs.* 76% (p = 0.10) in ≤ 35 years and > 35 years group, respectively (Fig. 4). Stage wise OS at 10 years is reported in Table 4. 10-year OS was comparable between the two groups for stage 1, 89% *vs.* 90% (p = 0.49) in the ≤ 35 years and > 35 years group. However, for stage 2 and 3, it was 77% *vs.* 82% (p = 0.048) and

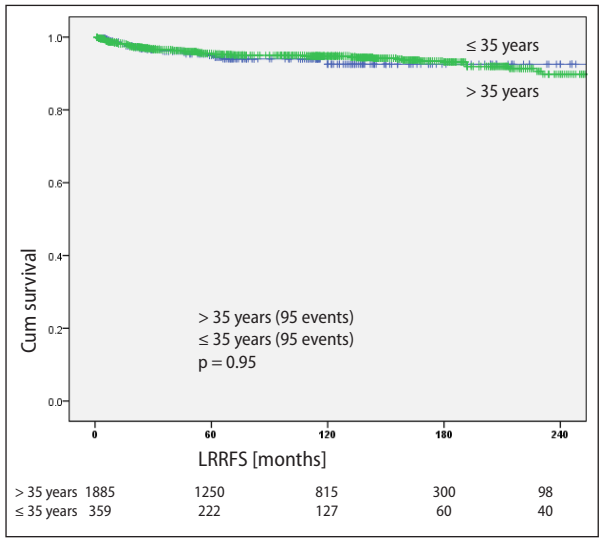

Figure 2. Loco-regional recurrence-free survival (LRRFS)

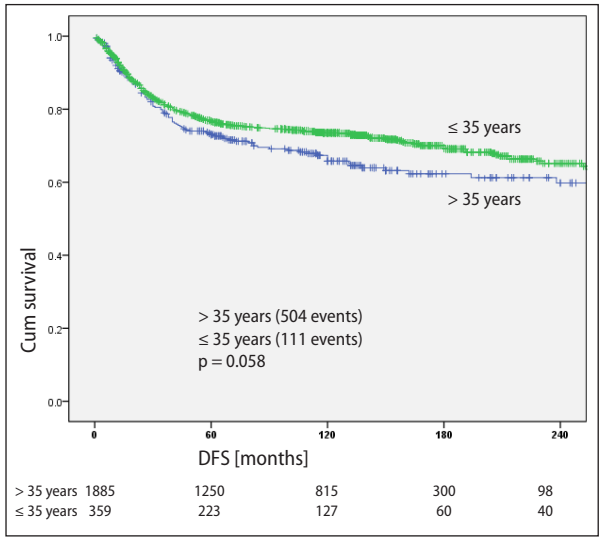

Figure 3. Disease-free survival (DFS)

53% *vs.* 62% (p = 0.045) in the ≤ 35 years and > 35 years group, respectively.

Acute radiation toxicities were comparable between the two groups (Tab. 5). Acute radiation toxicities grade 2 and 3 were observed in 31 (8.6%) and 146 (7.7%); 37 (10.3%) and 131 (6.9%) women in the ≤ 35 years and > 35 years group, respectively. There was no incidence of radiation pneumonitis.

Late-term effects were similar in the two groups (Tab. 5). Arm pain was observed in 26 (7.2%) and 107 (5.7%) patients in the ≤ 35 years and > 35 years groups (p = 0.27), respectively. Lymphedema was seen in 18 (5%) and 84 (4.5%) patients in the ≤ 35 years and > 35 years groups (p = 0.67), respective-

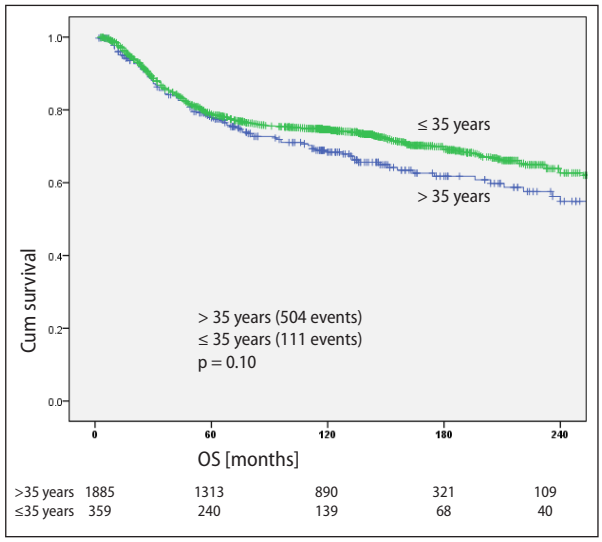

Figure 4. Overall survival (OS)

Table 4. Stage wise survival in the two groups

Stage/Group	10 year overall survival		
	≤ 35 years	> 35 years	p-value
Stage 1	89%	90%	0.49
Stage 2	77%	82%	0.048
Stage 3	53%	62%	0.045

ly. Shoulder stiffness was observed in 24 (6.7%) and 149 (7.9%) patients in the ≤ 35 years and > 35 years groups, respectively (p = 0.51). Late cardiac toxicity in left sided BC was observed in 4 (0.3%) and 7 (0.4%) patients in the ≤ 35 year and > 35 year groups, respectively. In patients with right sided BC it was observed in 1 (0.3%) and 2 (0.1%) patients in the ≤ 35 years and >35 years groups, respectively (p = 0.48). None of the patients developed late lung toxicity, brachial plexopathy or rib fracture.

Second malignancy rate was also similar between the two groups. Second malignancy occurred in 23 (6.4%) and 126 (6.7%) patients in the ≤ 35 years and > 35 years groups, respectively (p = 0.41). Most common second malignancy was contralateral BC in 18 (5%) and 82(4.3%) patients in the ≤ 35 years and > 35 years groups, respectively. Non-breast second malignancies were 5 (1.4%) and 44 (2.3%) in the ≤ 35 years and > 35 years groups, respectively. In patients from the ≤ 35 years group non-breast second malignancies were gynecological in 3 (endometrium 2 and ovary 1), carcinoma of colon and basal cell carcinoma 1 each. In the > 35 years group non-breast second malignancies were gynecological in 26 (endometrium 10, ovary 9 and cervix 7), gastrointestinal 9 (oesophagus 5, colon 2, gall bladder and gastrointesttinal stromal tumor 1 each). Others were thyroid cancer, non-Hodgkins lymphoma, renal cancer 2 each and lung cancer, carcinoma of vallecula and liomyosarcoma in the pelvic area, 1 each.

Table 5. Acute and late toxicity with hypofractionation in the two groups

Variable	≤ 35 years (n = 359)	> 35 years (n = 1,885)	p-value Fisher's Exact Test
Acute toxicity			
Grade 2	31 (8.6)	146 (7.7)	0.065
Grade 3	37 (10.3)	131 (6.9)	
Late toxicity			
Arm pain ≥ Grade 2	26 (7.2)	107 (5.7)	0.271
Arm oedema ≥ Grade 2	18 (5.0)	84 (4.5)	0.678
Shoulder stiffness Mild/moderate	24 (6.7)	149 (7.9)	0.517
Cardiac:			
Left breast	1 (0.3)	7 (0.4)	0.480
Right breast	1 (0.3)	2 (0.1)	
Second malignancy:			
Contralateral breast	18 (5.0)	82 (4.3)	0.415
Non-breast	5 (1.4)	44 (2.3)	

Discussion

This study included 2244 patients with stage I-III BC who were divided into two groups based on their age, ≤ 35 years and > 35 years, at the time of diagnosis and were compared for their clinical outcome after treatment with hypofractionated RT. At 10 years; LRR and distant metastases was higher in patients ≤3 5 years of age. LRRFS, DFS and toxicities were similar between the two groups. However, OS was poorer in young BC patients with stage 2 and 3 disease. From the toxicity profile in the present study, it seems that hypofractionation is safe in younger patients (≤ 35 years) with BC as it is in patients >35 years of age.

Patients included in the study were treated over 20 years from 1990 to 2010. During these years hypofractionation has emerged as a standard RT treatment in patients > 50 years of age because of its proven efficacy, safety, better patient compliance, convenience, logistics ease and economic

gain. However, data on safety and efficacy of hypofractionation in younger patients with BC is lacking which is the main reason for its snail pace adoption in these patients [6]. Younger patients may draw more benefits from hypofractionation because of its economic reasons such as treatment completion in few weeks and shorter leave required from work. They also have young children to look after, hence will have to spend less time away from their family and home. It also reduces waiting time for other patients by making radiation machines free for them.

Optimum dose of hypofractionation in BC still remains unknown. In the present study RT dose fractionation was as per current standards of hypofractionation in BC. Patients were treated with a simple 2D technique, which has now been replaced by 3D or intensity modulated RT (IMRT) techniques in developed countries. But after observing low acute and late toxicities in the current study, which are comparable to the trials with the 3D technique, the 2D technique seems to be as good as 3D. However 3D techniques are better in terms of possible re-irradiation as we can know the exact doses to the organs at risk. The current study also provides an insight into the fact that hypofractionation may be safe in younger patients as well. OS at 10 years of 76–78% reported in the present study is also in line with those reported by other studies (59–75%) in the literature [7–9]. Because of the simplicity of the 2D technique, it is possible to practice it in any resource constraint country where 3D treatment is not possible. We treated most (80%) of our patients on a cobalt machine, so it may be suggested that hypofractionation in BC with a cobalt machine is also possible if the chest wall separation is ≤ 20 cm. It is also of economic importance to low-middle income countries where patients are treated on cobalt machines because of its lower cost, ease of use and lesser maintenance needed as compared to linac.

Acute skin toxicity was similar in both groups. These are in line with the rates reported in other studies [10–12]. Grade 3 acute skin toxicity of 7–10% in our study (Tab. 5) is higher as compared to Wang et al. where it was observed in 3% of patients [12]. It might be because post-mastectomy patients were treated on a cobalt machine with bolus during 50% of fractions (treatment).

Late-term effects in the present study are comparable to those reported by the randomised trials [10–12]. Most of the patients in these trials were > 50 years of age, had early stage BC and surgery was in the form of BCS except in the study by Wang et al. which included post-mastectomy patients [12]. In the present study majority of patients (> 80%) were post-mastectomy and > 55% had advanced stage disease. Target volume for PMRT with hypofractionation is different from WBI, but dose fractionation and techniques of RT are similar.

Ischemic heart disease incidence in START trials was 0.7% which is comparable to 0.1–0.4% in the current study. In the current study, in majority of patients (80%), cardiac events occurred after 15 years of treatment and most of these patients (55%) had comorbidity at the time of diagnosis. Median time for late cardiac toxicities was 23 years (range 9–28 years).

RNI was delivered in > 80% of patients in our study. Late effects in the arm and shoulder (4–8%) in the present study are also comparable to those reported in the START trials (5.8%) [10]. These observations suggest that hypofractionated RT may be acceptable in younger patients with BC who need regional nodal irradiation.

During this study time period, the chemotherapy regimens have changed but the number of patients who received different chemotherapy regimens over these years was similar in the two groups. In a study from Canada it was observed that there was improvement in relapse-free survival in all subtypes of BC over two time periods but patients age < 40 years had poor outcomes during both periods [13]. In our study also younger patients with BC with stage 2 and 3 disease had poor OS as compared to the > 35 years group (Tab. 4). In the present study neoadjuvant chemotherapy was received by 81 (23%) and 319 (17%) patients in the ≤ 35 years and > 35 years groups, respectively. Pathological complete response (pCR) was observed in 20 (25%) and 61 (19%) patients in the ≤ 35 year and > 35 year groups, respectively. These pCR rates are consistent with reported studies with anthracyclin and taxane based chemotherapy [14]. Neoadjuvant chemotherapy has been shown to increase pCR and survival in luminal tumors in patients < 40 years of age as compared to patients > 50 years [15]. In another study it was observed that age was not of prognostic importance in TNBC and hormone receptor negative/Her2neu3+ tumors but in hormone receptor positive/Her2neu- tumors [16].

In the present study, hormonal treatment was exclusively tamoxifen in the ≤ 35 years group. There was no ovarian manipulation in the present study; which might be under-treatment as per the current standards. None of these patients received trastuzumab due to economic constraints. The last two situations are common in low-middle income countries. Hormonal therapy was received by significantly lower number of patients in the ≤ 35 years age group. This was due to lower expression of ER/PR in these patients; hence more number of patients in this group received chemotherapy.

Outcome in patients with BC also depend on molecular subtypes. In a study, Ademuyiwa et al. reported better outcomes in young women with BC who had estrogen receptor (ER) positive disease [17]. In younger women poor outcomes have also been reported in subtypes like luminal B, triple negative and even in Her2 enriched in the past as compared to older patients (> 50 years) [13, 18, 19]. BC in younger patients have been reported to have high proliferative index and over expression of p53, which suggests that these tumors might have originated from less differentiated luminal cells [20]. Other possible factors could be growth factor signalling involved in tumor proliferation, invasion and metastases and down regulation of apoptosis-related genes [7, 21, 22].

It has been seen in some studies that the effect of age is influenced by tumor biology. In a study from Korea, it was observed that the risk of death increased by 5% for every year age reduction in patients < 35 years as compared to 35–50 years patients [23]. In the present study also recurrence and metastases were higher in patients with < 35 years of age which translated in poor OS in these patients (Tab. 4). In another study by Albain et al. the hazard ratio (HR) for disease recurrence (relative to patients > 50 years) was 1.83 for very young and 1.16 for young after adjusting for other prognostic factors, suggesting that the young patients had worse DFS than the older patients [24]. Our results also suggest that treatment decisions for BC patients ≤ 35 years of age should not be based on age without taking into account other patient and disease characteristics.

Limitations of the study are its retrospective nature and single institutional. Few patients were also treated with conventional chemotherapy, hormonal treatment was mainly in the form of tamoxifen alone in the ≤ 35 year group and no ovarian suppression was done due to financial reasons. In SOFT and TEXT trials, exemestane plus ovarian suppression was shown to improve DFS and freedom from distant recurrence in premenopausal patients with early stage BC. These trials also reported that tamoxifen plus ovarian suppression led to significant 8-year OS benefit as compared to tamoxifen alone in these patients [25]. The present study included stage I–III BC patients. No information was available about Her2 neu and Ki67 expression, as these were not routinely done during these years. None of the patients received trastuzumab therapy, which has been shown to improve outcome in patients with Her2 neu over-expression. Radiation was delivered with the 2D technique, which is not the current standard in the developed world but it may be of relevance to the low-middle income countries because of resource constraints [26]. In our previous study [26] we reported a similar (1990–2007) cohort of patients. Apart from the larger cohort, the patients in the present study have been followed up for a longer period with special attention to recording their late term side effects. Arm/shoulder pain and shoulder stiffness rate were less in the present study: 7.2% and 6.7% as compared to 14.3% and 12.3% in the previous study [26]. Lymphedema rate was also slightly less in the present study: 5% as compared to 7.4% in the previous study [26]. The present study also focussed to compare outcomes and late effects in young versus old patients with BC. Patient reported outcomes were not assessed in the present study.

Strengths of the study are large number of patients with long-term follow-up and information on acute and late-term effects with hypofractionated RT in young as well as older patients with BC. RT dose fractionation used was as per the current standards in BC. This may add to evidence on safety and efficacy of hypofractionation in young women with BC. It also reflects the treatment changes over the years. Although deviation from the current standards, this kind of basic treatment is possible in any country in the world. It also helps in reducing treatment cost by 1/3rd [27]. Our findings suggest that age may be of prognostic significance in women with BC because of higher recurrences and poor OS in patients < 35 years of age.

Conclusion

In this study, BC patients treated with hypofractionated RT, there were higher recurrences in young patients. LRRFS and DFS were comparable between the two groups. Acute and late toxicities were also similar between the two groups. However, OS was poorer in young BC patients with stage 2 and 3 disease. These results suggest that that hypofractionation may be safe (in terms of toxicities) in younger patients as well and has its economic implications for the limited resource countries.

Conflict of interest

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