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Outcome of Hypo Fractionated Radiotherapy in Early Breast Cancer

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Abstract

Introduction: *The standard radiotherapy fractionation in breast cancers practised in worldwide is 50Gy in 25 fractions. Some trials have tested the hypothesis that breast cancer is as sensitive to fraction size as the normal tissues of the breast and underlying rib cage and that a more effective strategy would be to deliver fewer, larger fractions to a lower total dose regimens (hypofractionation). The purpose of this study is to assess the tissue toxicity, quality of life and local recurrence of patients undergoing hypofractionated radiotherapy for early breast cancer.*

Objectives

1. *To assess the tissue toxicity of hypo fractionated radiotherapy for early breast cancer.*
2. *To assess the quality of life in patients on hypo fractionated radiotherapy for early breast cancer*
3. *To assess the local recurrence of patients on hypo fractionated radiotherapy for early breast cancer.*

Methods: *42 Patients with invasive early breast cancer who had underwent mastectomy or breast conservation surgery and who had indications for post op RT were subjected to a fractionation schedule of 40 Gy in 15 fractions to the chest wall or breast. Planning was done with conventional techniques. Tissue toxicity and quality of life of the patients were assessed during RT and on further follow up. Findings were graded using RTOG toxicity scale and EORTC questionnaire.*

Results: *Most of the patients were in the age group of 51-60 years, with 59.5% of patients in post menopausal group. All patients had grade 1 skin reaction. Two patients developed grade 2 skin reaction and one patient showed grade 4 reaction. Grade 1 mucositis, as throat pain was present in 76.2 % of patients. There were no grade 2, grade 3, or grade 4 mucositis. Grade1 lung toxicity was seen in 14.3% of patients during RT and 81% had moderate amount of arm edema during follow up. No patients had any cardiac or neurological symptoms and any local recurrence. Quality of life assessment showed worsening during RT which improved later on follow up. But shows decrease on comparison with pre RT status.*

Conclusion: *Adjuvant hypo fractionated radiotherapy after surgery to early breast cancer is generally well tolerated and is a viable alternative to the conventional fractionation with acceptable tissue toxicity, quality of life and local control. it provides a shorter treatment time and better patient compliance. This could prove especially useful in resource limited centres with high patient load.*

Keywords: *Hypofractionation – early-breast cancer – tissue toxicity – quality of life-local recurrence.*

Introduction

Breast cancer is the most common tumour in women worldwide[1]. It is also the principle cause of death from cancer among woman globally. Due to the relatively favourable prognosis of early-

stage disease, in the past 5 years[2] who have had breast cancer, almost 4 million women are alive.

In India for the last 10 years breast cancer has been rising steadily, and for the first time in 2012, breast cancer became the most common cancer in women[3] in our country.The age adjusted incidence rate of carcinoma of the breast was found as high as 41 per 100,000 women for Delhi, followed by Chennai (37.9), Bangalore (34.4) and Thiruvananthapuram District (33.7)[4]. In Kerala also the incidence of breast cancer has been increasing and now contributes to nearly a third of all cancers amongst females in the state[5].

Radiotherapy remains one of the most effective modalities of treatment for breast cancer. Radiotherapy reduces the risk of local relapse by about 70% and reduces breast cancer mortality .Radiotherapy to the chest wall after mastectomy is indicated in selected patients in whom the risks of local recurrence are high and to all patients after local tumour excision.[6].

The most frequently used schedule of radiotherapy in treatment of carcinoma breast worldwide is 50 Gy , delivered in 25 fractions of 2·0 Gy over 5 weeks[7]. It has been thought previously that breast cancer is insensitive to fraction size and was treated with fractions of 2Gy or less. However, some trials have tested the hypothesis that breast cancer is as sensitive to fraction size as the normal tissues of the breast and underlying rib cage.[8] And small fraction sizes of 2·0 Gy or lower offer no therapeutic advantage, and that a more effective strategy would be to deliver fewer, larger fractions to a lower total dose regimens.[9]

The UK Standardisation of Breast Radiotherapy (START) Trial A, randomized patients to receive either 50 Gy in 25 fractions of 2.0 Gy or 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3 Gy over 5 weeks after surgery . The authors concluded that a lower total dose in a smaller number of fractions could offer similar rates of tumor control as standard fractionation.[10].

The UK START Trial B randomized patients with early breast cancer at 23 centers in the UK who were assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks.[11] With a median follow-up of 6 years, the rate of local-regional tumour relapse at 5 years was 2.2% in the 40Gy group and 3.3% in the 50 Gy group, representing an absolute difference of –0.7% .

The early results of these trials suggest that toxicity and cosmesis are acceptable [12] and this regimen may also be more convenient for patients and less resource intensive than the standard schedule. Low rates of local recurrence and limited radiation-induced morbidity have been reported with such approaches.[13] So in this study we intend to assess the effect of hypo fractionated radiotherapy in early breast cancer patients in terms of tissue toxicity and quality of life.

Objectives

1. To assess the tissue toxicity of hypo fractionated radiotherapy for early breast cancer.
2. To assess the quality of life in patients on hypo fractionated radiotherapy for early breast cancer
3. To assess the local recurrence of patients on hypo fractionated radiotherapy for early breast cancer.

Study Setting: Department of Radiotherapy, Government Medical College, Thrissur, Kerala, India.

Study Design: Prospective Observational study

Study Population: Patients attending the radiotherapy OPD, with histologically proven breast cancer after primary surgery.

Inclusion Criteria

1) Histologically proven invasive carcinoma of breast.
2) Patients after Breast Conservation Surgery or mastectomy
3) Age <70yrs
4) Tumors of size </=5 cm.
5) < /=3 positive lymph nodes.
6) Presence of lympho vascular space invasion

7) Positive deep resected margin
8) Close resected margin of <1mm
9) No evidence of any metastasis

Exclusion Criteria

1) Presence of only insitu carcinoma
2) Tumours of >5cm
   >3positive lymph nodes
3) Age >70yrs
4) Patients with cardiac disease
5) Presence of metastasis
6) Previous history of radiotherapy to chest wall

Sample Size Calculation: Sample size is calculated using the formula 3.8pq/d. Where p is the percentage of patients who achieved target in the study conducted in a tertiary care center in eastern India by Nandi M, Mahata A, Mallick I, Achari R, Chatterjee S., published in Asian Pacific journal of cancer prevention: APJCP·March 2014 .q=100-p, d=20% of p (20% is the maximum allowed error). Considering p in terms of patients without severe tissue toxicity, p=80%, n=25

Study Period: $1^{1/2}$ year from the date of ethical committee clearance .

Data Collection: All the breast cancer patients coming to the radiotherapy department after the primary surgery, who satisfied the inclusion criteria were selected for the study after the completion of chemotherapy, taking an informed consent. After that patients details were collected including name, age, occupation, presence of comorbid illness ,marital status, menstrual status, obstetric history, family history, histopathological report, details of surgery performed and chemotherapy taken. Detailed clinical examination done including breast/chest wall, axilla, supraclavicular fossa, contralateral breast, axilla and supraclavicular fossa, and other systems. Blood examination like CBC, RFT, LFT, and SE done to assess the general condition of patient and chest x ray, USG abdomen, taken to rule out metastasis.

Materials and Methods

Radiotherapy was given at least 3 weeks after the completion of chemotherapy. Radiation planning was done using conventional methods. Patient was positioned in supine with ipsilateral arm abducted and placed over the head level. Field borders were determined clinically, and marked. Appropriate field sizes, covering the target volume were chosen and center of the fields were tattood. All the patients after MRM had given 40 Gy of RT as midplane dose in 15 fractions, one fraction per day, over three weeks. For BCS patients 40 Gy of RT was given over 15 fractions followed by boost of 10 Gy in 4 fractions. SCF RT was given in indicated patients as 45Gy in 15 fractions as on field therapy, one fraction per day over three weeks.

During the radiotherapy, all patients were reviewed in RT OPD once weekly. After the radiotherapy patients were reviewed at 2 weeks, 6 weeks and 3 monthly thereafter. During each visit patient were asked regarding any symptoms and asked to fill a symptom check list, and detailed clinical examination done for any signs of toxicity, recurrence of disease or metastasis. Patients were given symptomatic medications

Results

Among the beast cancer patients registered in the department of radiotherapy, during the study period of 1.5 years,42 patients satisfied the inclusion criteria and were taken up for study with their consent.

Patient Characteristics

Age

The mean age of the study population was 50 years, ranging from 34 to 69 years. Age wise distribution is shown in table. Most of the patients are in the age group of 51-60 years (40.5%).10 patients (23.8%) in the age group of 31-40 years, 19% of patients in the age group of 41-50 years and 16.7 % of patients in 61-70 years of age.

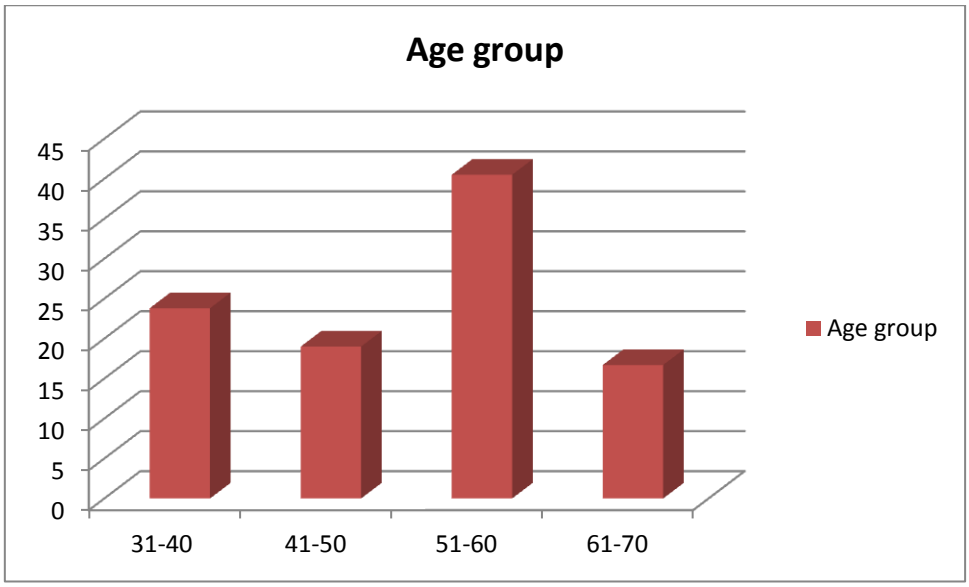

Figure 1 Age wise classification

Menstrual status: of the 42 patients, 17 patients were premenopausal and 25 patients were post menopausal.

Type of surgery

Almost all the patients had modified radical mastectomy, except one patient who had breast conservation surgery.

Table 1. Type of surgery

Type	Frequency	Percent
Modified radical mastectomy	41	97.6
Brest conservation surgery	1	2.4
Total	42	100.0

T status

According to histopathological reports tumor size of each patient was noted.16.7% of the patients had T1 tumor (<2cm) and 83.3% of patients had T2 tumors (2-5cm)

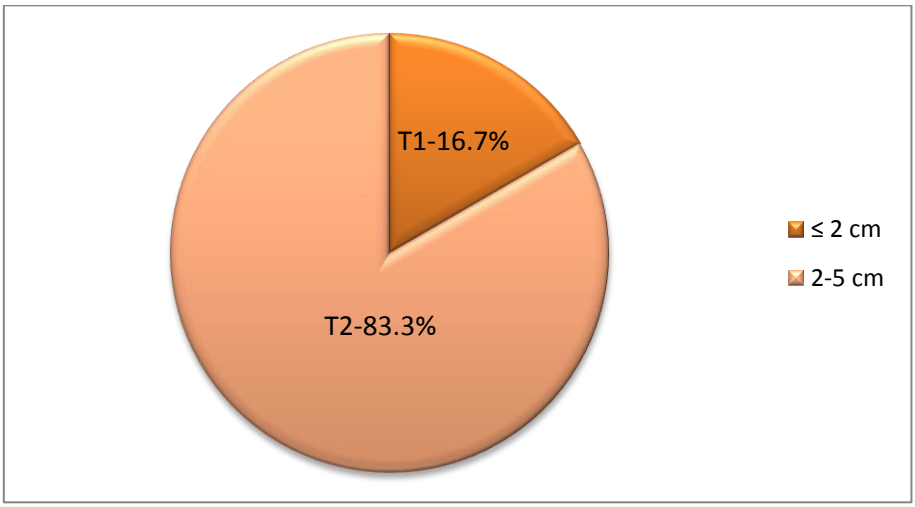

Figure 2 Tumour status

Hormone status and Molecular Typing

32 patients (76.2%) were ER/PR positive and 10 patients were ER/PR negative. In 31patients HER 2 was negative and in 11 patients HER2 was positive. considering molecular type ,19 patients were luminal A,6 patients were luminal B HER2 negative, 7 patients were luminal B HER2 positive, 4 patients were HER 2 enriched and 6 patients were triple negative.

Table 2. ER/PR status

ER/PR	Frequency	Percent
Negative	10	23.8
Positive	32	76.2
Total	42	100.0

Table 3. Human epidermal receptor 2 status

Human epidermal receptor 2	Frequency	Percent
Negative	31	73.8
Positive	11	26.2
Total	42	100.0

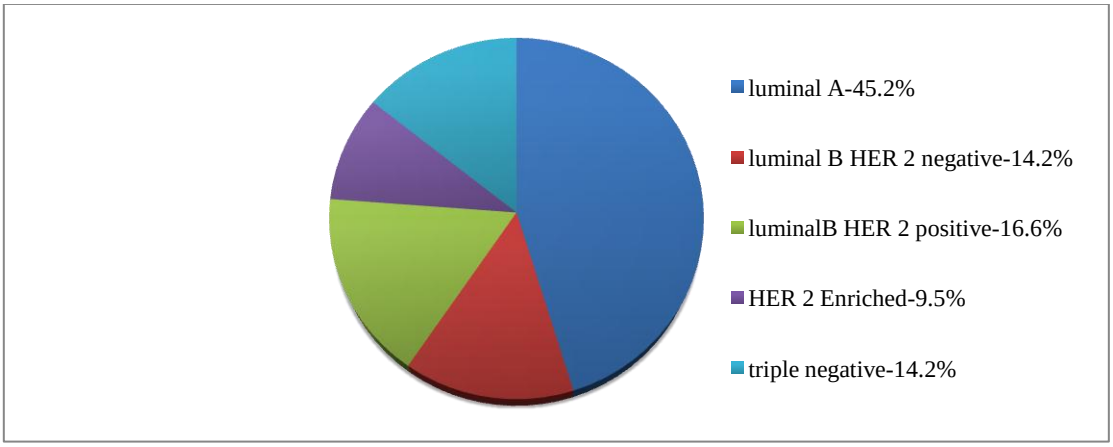

Figure 3 Molecular Subtyping

RT to chest wall/breast

RT to chest wall/ breast was given for all the patients

RT to supraclavicular fossa

76.2% of patients were given RT to supraclavicular fossa and for 23.8% of patient's supraclavicular fossa RT were not given.

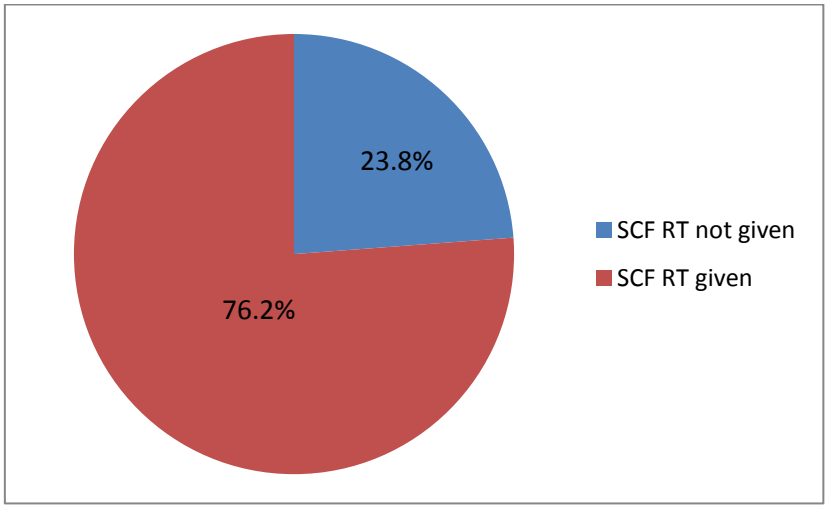

Figure 4 RT to supraclavicular fossa

Comparison of toxicity

Erythema of Skin

Before starting the radiation no patients had any erythema of breast or chest wall. But during RT 14 patients (33.3%) had a little erythema and 28 patients (66.7%) had moderate erythema. Later after RT erythema of all patients resolved gradually.

Table 4 Erythema of skin

Erythema of skin	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100			42	100
A little			14	33.3		
Moderate			28	66.7		
Total	42	100	42	100	42	100

Dry desquamation

Before RT no patients had any desqua mation of skin. But during RT 19% of patients (8) had a little dry desquamation of skin and 81% of patients (34) had moderate dry desquamation. Later after RT 16 patients (38.1 %) had a little dry desquamation ,on follow up.

Table 5 Dry Desquamation

Dry desquamation	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100			42	100
A little			8	19.0		
Moderate			34	81.0		
Total	42	100	42	100	42	100

Wet desquamation

During RT, 2 patients (4. 8%) developed wet desquamation of skin.

Table 6. Wet Desquamation

Wet desquamation	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100	40	95.2	42	100
A little			2	4.8		
Total	42	100	42	100	42	100

Ulceration of skin

During RT, 1 patient (2.4%) developed ulceration of skin.

Table 7 Ulceration of skin

Ulceration of skin	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100	40	97.6	42	100
A little			1	2.4		
Total	42	100	42	100	42	100

Pigmentation of skin

During RT 30 patients (71.4%) developed moderate hyper pigmentation of skin and 12 patients (28.6%) developed little pigmentation. But after RT all patients had little persistent hyper pigmentation on follow up.

Table 8. Pigmentation of skin

Pigmentation of skin	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100				
A little			12	28.6	42	100
Moderate			30	71.4		
Total	42	100	42	100	42	100

Dryness of skin

During RT no patients had dryness of skin, but after RT all patients had a little dryness of skin on follow up.

Table 9. Dryness of skin

Dryness of skin	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100	42	100		
A little					42	100
Total	42	100	42	100	42	100

Throat Pain

During RT 28 patients had a little throat pain and 4 patients (9.5%) had moderate throat pain. No patient had persistent throat pain after RT.

Table 10 Throat Pain

Throat pain	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100	10	23.8	42	100
A little			28	66.7		
Moderate			4	9.5		
Total	42	100	42	100	42	100

Edema of arm

During RT all the patients had a little amount of arm edema. But after RT 34 patients (81%) had moderate and 8 patients (19%) had little edema during follow up.

Table 11 Edema of arm

Edema of arm	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100				
A little			42	100	8	19.0
Moderate					34	81.0
Total	42	100	42	100	42	100

Cough /breathlessness

During RT 6 patient (14.3%) developed mild cough. No patient had any breathlessness.

Table 12 Cough /breathlessness

Cough /breathlessness	Before		During		After	
	Frequency	Per cent	Frequency	Per cent	Frequency	Percent
Not at all	42	100	36	85.7	42	100
A little			6	14.3		
Total	42	100	42	100	42	100

Radiating pain / numbness of arm

No patients had any radiating pain or numbness of arm during RT or after RT on follow up.

Local recurrence

No patients had any evidence of local recurrences such as chest wall nodules, axillary lymph nodes or supraclavicular lymph nodes.

Discussion

The purpose of this study was to assess the early tissue toxicity, quality of life and local recurrence of patients receiving hypo fractionated radiotherapy for early breast cancer. All the patients had completed initial surgery and adjuvant chemotherapy before radiotherapy. The compliance of the patients were excellent. All patients willingly responded to questions when approached.

In this study, most of the patients were in the age group of 51-60 years, with 59.5% of patients in post menopausal group and 40.5% in premenopausal group. Except one case of breast conservation surgery, all underwent modified radical mastectomy (97.6%).

On histopathological assessment, 85.7% of patients had invasive ductal carcinoma and 14.3%

had invasive lobular carcinoma.19% of patients had presence of ductal carcinoma in situ.16.7% of patients had T1 tumour and 83.3% of patients had T2. 23.8 % of patients were without any lymph node involvement (N0). Single lymph node involvement was seen in 42.9% of patients.28.6% and 4.8% of patients had two and three lymph node involvement respectively. Most of the patients had grade 2 tumour (59.5%)

Considering the margin status, 19 % of patients had margin positivity and in 40.5% of patients lymphovascular emboli was present. Majority of the tumours were ER positive (76.2%), and 26.2% of patients were HER2 positive. On molecular subtyping,45.2% was luminal A,14.2% luminal B HER2 negative,16.6% luminal B HER 2 positive,9.5% HER2 enriched and 14.2% was triple negative.

All patients received adjuvant chemotherapy. Majority of them were given TAC regimen (47.6%), followed by FEC in 31 % of patients ,AC followed by Taxanes in 11.9% of patients and FAC in 9.5% of patients. All patients were given chest wall or breast radiation as hypo fractionated regimen and 76.2 % of them received supraclavicular fossa radiation also.

All patients had grade 1 skin reaction in the form of erythema of skin and dry desquamation, which subsided after RT gradually. Two of them (4.8%) developed grade 2 skin reaction as little wet desquamation and only one patient (2.4%) showed grade 4 reaction as ulceration. In 71 % of patients moderate hyperpigmentation of skin was seen during RT, and all patients had slight hyperpigmentation and dryness of skin during follow up.

In the study conducted in a tertiary care centre in India, on hypo fractionated radiotherapy shows that more than 80% of study population had grade 1 skin toxicity and higher graded toxicity is only less than 5 %. This is comparable to our results.

Grade 1 mucositis, as throat pain was present in 76.2 % of patients, who had received supraclavicular fossa radiation. There were no grade 2, grade 3, or grade 4 mucositis.

Acute lung toxicity was seen in 14.3% of patients, which was of grade 1 and presented clinically as mild dry cough. All patients had mild edema of ipsilateral arm. 81% had moderate amount of arm edema during follow up. No patients had any cardiac or neurological symptoms during RT or follow up.

None of the patients in the study group had any local recurrence as chest wall nodules, axillary nodes, supraclavicular nodes and systemic metastasis during the follow up period. Long term follow up study of START A and START B trials showed that hypofractionated radiation is as effective as conventional radiation for early breast cancer considering both tissue toxicity and local control. On comparison with present study acute toxicity is acceptable and there is no local failure during follow up time. But to assess the long term effects of hypofractionated regimen we need further follow up.

Quality of life evaluation reveals that global health status, physical functioning, role functioning, emotional functioning and social functioning which were poor during RT showed improvement following RT. Even though physical functioning and role functioning got improved after RT, as compared to that during RT, improvement is significantly lesser than pre- RT state as most of them had difficulty in their daily work due to edema of arm.

Most of the patients suffered from increased fatigue, nausea, loss of appetite, insomnia and pain during treatment which got significantly improved after treatment. Patients, who had significant financial difficulties during RT in the form of treatment, travel and stay expenses had significantly less financial burden after RT.

Sexual functioning, sexual enjoyment and body appearance which were poor during RT got improved following treatment. But on comparing with pre-RT status there were no improvement. Breast symptoms got worse during RT, which got improved after RT. Arm symptoms which were significantly present during RT became worse following RT.

Conclusion

Adjuvant hypofractionated radiotherapy after surgery to early breast cancer is generally well tolerated and is a viable alternative to the conventional fractionation with acceptable tissue toxicity, quality of life and local control. Having proved to be non inferior to conventional fractionation in terms of both biological effectiveness and side effect profile in many large randomized control trials, hypofractionated breast radiation provides a shorter treatment time and better patient compliance. This could prove especially useful in resource limited centers with high patient load.

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