Original Article

Post Mastectomy Adjuvant Radiotherapy in breast cancer: A comparision of three Hypofractionated Protocols

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Abstract

Objectives: To compare three hypofractionated protocols in postmastectomy cancinoma breast in terms of local control, toxicity and work load.

Methods: A total of three hundred patients suffering from cancer breast stage T2-4, N any were randomized into three arms after mastectomy. All the patients were treated with four fields on Co60 i.e. two tangential portals for chest wall, one anterior supraclavicular and axillary field and a posterior axillary boost and were randomized into three arms i.e. 2700 CGy in 5 fractions (one week) arm A, 3500 CGy in 10 fractions (2 weeks) arm B and 4000 CGy in 15 fractions (3 weeks) arm C. Skin, cardiac, pulmonary and haematological toxicities and lymphoedema were compared in addition to local control and work load.

Results: The locoregional relapses were 11%, 12% and 10% in arms A, B and C respectively. 26%, 24% and 28% patients developed metastatic disease and 17%, 18% and 20% died in the three arms. G3 and G4 skin toxicities were 37%, 28% and 14%. G2 and G3 lymphedoema was 21%, 22% and 27%. Cardiac toxicity was 5%, 6% and 5% while pulmonary toxicity was 4%, 5% and 5% respectively. All the differences except skin toxicity were statistically insignificant. There were no cases of haematological depression or rib fractures.

Conclusion: All the three short protocols were equally effective in locoregional disease control and toxicity was also comparable. They were helpful in reducing the work load and can be safely recommended for routine clinical use (JPMA 59:282; 2009).

Introduction

Breast cancer is the most common malignancy in women.[1] The incidence varies from region to region and country to country. In Pakistan although no population based data is available yet the cancer registry statistics in different oncology institutes and departments verify that breast cancer is the commonest female cancer in the country. At INMOL our data for last five years shows that about 40% female patients came for breast cancer treatment.

Mastectomy is the usual surgical procedure carried out in many parts of the world including Pakistan, after the diagnosis of breast cancer has been established. Unfortunately there is usually no standard practice for surgery in our set up because simple, radical or modified radical mastectomies are all being performed in different centres. The status of axillary nodes dissection is again a neglected and controversial issue. Sometimes the axilla is not even touched and sometimes only sampling is performed, while axillary clearance is done at other occasions. Keeping all these points in view, post mastectomy adjuvant radiation to the chest wall and axilla is an essential part of treatment for carcinoma breast in our setup.

For patients with operable breast cancer undergoing mastectomy, radiation therapy to the chest wall and regional lymph nodes to a total dose of 5000-6000 CGy is usually employed.[2] Recent randomized trials suggest that post mastectomy patients with any number of positive nodes, derive a disease free and overall survival benefit from radiotherapy. There are many published trials in which patients were randomized after radical, modified radical, or total mastectomy to post-operative radiotherapy or no further treatment in the absence of systemic therapy. Radiation clearly showed reduction in the incidence of local recurrence in all and also improved survival in some.[3-5]

Most of our patients require radiation treatment in adjuvant setting after primary surgery and chemotherapy.[6] The conventional dose is 5000 CGy in 5 weeks delivering 200 CGy daily and for 5 days a week . As this is a big work load, a hypofractionated protocol i.e reducing both the number of fractions and total treatment duration is being practiced at Christie Hospital, Manchester, UK. It delivers 4000 CGy in 3 weeks in 15 fractions. This is accepted as a fairly standard dosage world over and at our centre we have about 10 years experience with this protocol. It is very well tolerated and its toxicity is comparable to the five weeks protocol.

The work load at our institute has tremendously increased during the last one decade and we are now planning to further shorten this 3 weeks protocol. The concept of

hypofractionation in cancer treatment is not new. It has been a routine clinical practice in many parts of the world to use this approach in palliative settings e.g. bone pain relief, cereberal metastases, SVC syndrome and haemostasis. Different schedules have been developed to minimize the burden on machines and operators e.g. 3000 CGy in 10 fractions, 3000 CGy in 8 fractions, 2000 CGy in 4 or 5 fractions or 800 CGy single fraction.

Due to these encouraging data there has been increasing interest of the world about using hypofractionation in curative setting also. It has been tried quite extensively in breast conservation setting and a lot of data is now available which shows very good local control, acceptable toxicity and equivalent cosmetic outcome.[7-10]

Patients and Methods

The objectives of this study in which accrual was started in 1998 and completed in 2004 were to compare the local control and toxicity of three hypofractionated protocols and to reduce the cost and workload at the institute in postmastectomy breast cancer patients in adjuvant setting.The patients were blindly randomized after informed consent and approval of the Ethical Review Board, into following three protocols.

- ARM- A 27 Gy in 1week (5.4 Gy x 5 fractions)
- ARM- B 35 Gy in 2weeks (3.5 Gy x10 fractions)
- ARM- C 40 Gy in 3 weeks (2.66 Gy x15 fractions)

All three protocols were biologically equivalent as calculated by TDF table. The TDF factor being 76, 78 and 77 respectively.[11] Biologically effective doses (BED) were verified by utilizing the following formula,

$$\mathbf{BED} = \mathbf{TD}\left(1 + \frac{d}{\alpha/\beta}\right)$$

Where TD = Total dose and d = daily dose

For delayed effects utilizing $\alpha/\beta = 3$

- 27 (1 + 5.4/3)
  27 (1+ 1.80) = 75.6 (ARM-A)
- 35 (1 + 3.5/3)
  35 (1 + 1.16) = 75.6 (ARM-B)
- 40 (1 + 2.66/3)
  40 (1 + 0.88) = 75.2 (ARM-C)

For early effects utilizing $\alpha/\beta = 10$

- 27 (1 + 5.4/10)
  27 (1 + .54) = 41.58 (ARM-A)
- 35 (1 + 3.5/10)
  35 (1 + .35) = 47.25 (ARM-B)
- 40 (1 + 2. 66/10)
  40 (1 + 0.266) = 50.64 (ARM-C)

Following inclusion criteria was followed:

Female patients of 20-60 years. T2, T3 or T4 primary lesion and N1, N2, N3, Nx, N0 nodal status. Post mastectomy status with or without axillary dissection.

Metastatic work up including isotope bone scan, X-ray chest and abdominal ultrasound were required to be normal. Adjuvant chemotherapy was completed before radiation.

Patients were planned on 2D planning system and treated on Co 60. Two tangential portals for the chest wall were planned on simulator with lung slice not exceeding 2.5 cm. Direct anterior filed to the supraclavicular and axillary areas was planned with 0.5 cm gap junction from tangential fields. Superior divergence of tangential portals was eliminated by 5° couch rotation. Inferior border divergence of anterior nodal field was removed by moving the gantry a few degrees following a 90° couch rotation. Head of humerus was shielded. A posterior axillary boost was added to compensate the midline dose twice a week treated at 80 cm SSD. The lung and heart slice included in the tangential portals and brachial plexus in the nodal fields received the full prescribed dose.

The number of patients in three arms were equal i.e. 100 in each and 300 in total. Written consent was taken before starting the treatment. Following expected toxicities of radiation along with local control and work load were compared.

A. Skin reactions were categorized according to RTOG recommendations.

RT0G - 0 No visible change to skin.

RT0G - 1 Faint or dull erythema.

RT0G - 2 Tender or bright erythema
Patchy moist desquamation, moist edema.

RT0G - 3 Confluent moist desquamation.

RT0G - 4 Ulceration, Huge necrosis

B. There was some risk of bone marrow suppression with shorter protocols. Complete blood counts were recommended according to the protocol before starting radiation, at completion, at one week, four weeks and six months.

The haematological depression in any of the components was graded as mild (10-20%),moderate (20-30%) and severe (>30%).

C. Lymphoedema was taken as a clinical finding. The arm circumference was measured at 20 cm above and below the

olecranon process of ulna. Measurements were taken at 1 week, 4 weeks, 8 weeks, 4 months, 6 months, 8 months, 10 months and one year and were categorized as G0 (no change in circumference), G1 (0-1cm), G2 (1-2cm) and G3 (>2cm).

D. The protocol recommendation was to get the echocardiography of all the patients done before radiation and at two months after radiation . A fall of more than 10% in ejection fraction was taken as significant reduction in the LVEF whether symptomatic or not. The patients who had a base line EF of <55% were not included in the trial.

E. X-Ray chest was performed before starting radiation,and at 4 weeks and 6 months after completion of treatment for assessing any pulmonary toxicity.

F. Any injury to the brachial plexus causing its damage and weakness of the arm was documented.

Patients were blindly randomized into three protocols. All the three groups were quite similar as far as the year wise accrual, stages of the disease, age groups of patients and chemotherapy regimens were concerned.

Age distribution in the three arms was as follows.21-30 years 12%,10%,10% in arms A,B,C respectively, 31-40 years 28%,25%,26%, 41-50 years 30%,33%,32% and 51-60 years 30%,32%,32%.

In 1998, 19, 18 and 16 patients were registered in arm A, B and C respectively. In 1999, 11,14, 11, in 2000, 15,15,13,in 2001,13,12,11,in 2002,09,08,10,in 2003, 20, 20, 24 and in 2004, 13, 13, 15 patients were accrued.

The distribution of chemo protocols was also similar i.e CMF 41%,39%,38% in arms A,B ,C respectively, FAC/FEC/AC 51%,54%,52% and AC-T/TAC 8%,7%,10% (Figure 1).

The data was analyzed by SPSS statistical software version 14. Pearson Chi Square was used to determine the statistical significance between the three arms. A p-value of < 0.05 was regarded as statistically significant.

Results

Eleven percent patients in arm A, 12% in arm B and 10% in arm C developed locoregional relapses. The

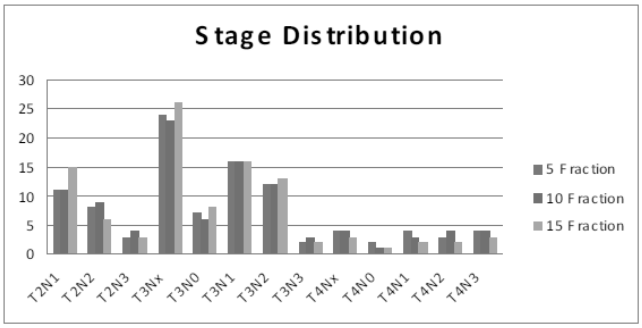

Figure 1.

differences were statistically insignificant (p=0.91) and clearly proved that the shorter protocols were as effective in controlling the local relapses as the three weeks protocol. The mastectomy scar was the most common site of loco regional relapse in all the three groups (80%), followed by ipsilateral supraclavicular area (15%) and axilla (5%). Metastatic disease was seen in 26% patients in arm A, 24% in arm B and 28% in arm C on follow up. Mortality due to the disease was encountered in 17% patients in arm A, 18% in arm B and 20% in arm C. The number of deaths was again statistically insignificant in the three arms (p=0.88).

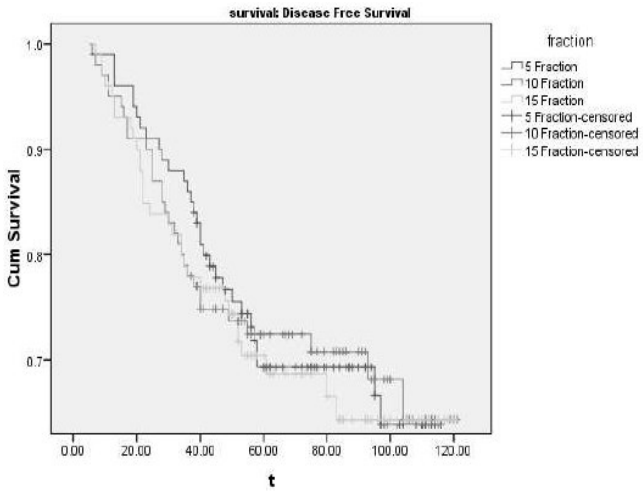

Figure 2.

Table: Results an Overview.

	AWD(LR)	AWD(M)	AWD(L+M)	DEAD (M)	DEAD (L+M)	DEAD OTHER (CAUSFS)	ALIVE (NED)
5 FR	04	07	03	12	04	01	69
10 FR	06	04	02	14	04	0	70
15 FR	03	06	02	15	05	0	69

AWD (LR): Alive with disease (Loco Regional Relapse).
AWD (M): Alive with Disease (Metastatic).
AWD (L+M): Alive with Disease (Loco regional+Metastatic).
Dead (M): Dead with metastatic disease.
Dead (L+M): Dead with loco regional & metastatic disease
Alive (NED): Alive with no evidence of disease.

The disease free and overall survivals derived by Kaplan- Meier curves were again statistically insignificant. Five years 0S was 87%, 83% and 82% in arms A, B and C (p=0.89) while 5 years DFS was 71%, 72% and 71% in the three arms respectively (p=0.968) (Figure 2) Table.

Toxicity:

Skin reactions in different arms were as follows. G1 33%, G2 30%, G3 26%, G4 11% in arm A, G1 35%, G2 37%, G3 19%, G4 9% arm B, and G1 62%, G2 24%, G3 11%, G4 3% arm C.

Incidence of lymphoedma in the three arms was as follows: G0 65%, G1 14%, G2 11%, G3 10% arm A, G0 66%, G1 12%, G2 13%, G3 9% arm B, GO 59 %, G1 14%, G2 13%, G3 14% arm C.

Five percent patients in arm A, 6% in arm B and 5% in arm C developed >10% drop in LVEF. Four percent in arm A, 5% in arm B & 5% in arm C showed radiation pneumonitis while 18% in arm A, 20% in arm B and 15% in arm C developed sore throat and dysphagia.All these values were statistically insignificant.

As far as the work load on radiotherapy equipment, technologists, physicians and indoor is concerned it was reduced significantly by using short protocols. There was a saving of about 50 minutes (arm B) and 100 minutes (arm A) per patient on the machine. The number of re-markings was 1%(arm A), 10% (arm B) and 35% (arm C).

Total days of hospital admission were 92 (arm A), 214 (arm B) and 526 (arm C).

Discussion

The data analysis of three well balanced groups with the study protocol allowing T2, T3, and T4 lesions with N0, N1, N2, N3 or Nx nodal status, showed similar results of all three arms.

These figures prove the hypothesis of categorizing for breast cancer closer to late reacting tissues and thus larger fractions are equally effective in controlling the loco regional disease.[11-13] Similarly when the data of metastatic disease, mortality due to breast cancer and survivals was analyzed no significant difference could be found.

There were more G3 and G4 reactions in 1 week and 2 weeks protocols as compared to the three weeks protocols. It is quite obvious that the reactions with 15 fractions were mainly (>85%) G1 and G2 while G3 reactions in 5 fraction arm were more than double as compared to 15 fractions (11% Vs 26%).

Similarly number of G4 reactions was more than 3 times i.e. 03% vs 11%. The reactions with 10 fractions were in between the two groups as expected.

Inspite of very close watch on the blood counts, as recommended by the protocol, no reduction in any of the blood components was observed.

Radiation pneumunitis, a well known toxicity of chest wall and supraclavicular radiotherapy, can be asymptomatic. In a retrospective study of 1624 patients, Lingos et al reported radiation pneumonitis in 1% of patients after surgery and radiation. The frequency was about 9% when three fields plus concurrent chemo was administered compared to only 1.3% when two fields and sequential chemoradiation was used.[14] Plataniotis GA et al evaluated radiation pneumunitis in hypofractionation setting (42.5 Gy / 16 Fr) by HRCT in early breast cancer patients, and reported minimal and minor effects on the underlying lung parenchyma.[15] In our study CT scan was not a requirement of the study. We experienced symptomatic radiation pneumunitis in only one patient in the 10 fractions protocol, which settled with steroids and antibiotics. Otherwise the pulmonary fibrosis was an incidental X-Ray finding. There was no relation to the fractionation schedule.

Lymphoedema is an established complication of both axillary lymph node dissection (ALND) and axillary radiotherapy. As is evident from our results that almost 2/3rd patients never developed this problem in any of the protocols whereas grade 3 lymphoedema was seen in 10% (5 fractions), 9% (10 fractions) and 14% (15 fractions) patients. The incidence of G2 and G3 lymphoedema collectively was in the range of 21 - 27 % in all the groups and was statistically insignificant thus proving the safety of shorter protocols

The frequency varies in different series. Chua B reported 9.5% arm oedema with axillary dissection, 6.1% with radiation and 31% when the two modalities were combined (P<.001).[16] In a comprehensive review Erickson VS et al reported 26% lymphoedema after breast cancer treatment.[17] Petrek JA in seven selected reports showed lymphoedema in the range of 6-30%. At Memorial Sloan Kettering cancer centre the experience from 1977 to 1979, based on a cohort of 20 years breast cancer survivors, measurable lymphedema documented as 31%.[18,19] Powel SN reported that axillary radiotherapy doubles the figures of lymphoedema against axillary surgery alone.[20] Meek AG reported 2-5% of lymphoedema when radiation alone was given to the axilla.[21]

There has always been a deep concern about cardiotoxicity in left sided breast cancer due to chest wall radiotherapy. Due to the contour of the chest wall some portion of the heart has to be included in the tangential portals. Another important factor in this regard is the administration of anthracyclines which again cause cardiotoxicity.

Different techniques have been used in different trials to assess the cardiotoxicity of chest wall radiotherapy. They include. ECG, echocardiography, cardiac perfusion imaging,

cardiac perfusion with SPECT, incidence of myocardial infarction and cardiac deaths.

In our study echocardiography performed by a single operator was used as a standard procedure for evaluating cardiotoxicity. Radiotherapy following mastectomy has been seen to increase the risk of death due to cardiac reasons at almost 10-15 years after treatment.[22]

The Swedish cancer registry data showed an increased risk of death due to myocardial infarction for patients with left sided lesions (RR 1.09).

In the Oslo and Stockholm trials, the retrospective analysis showed that increase in non breast cancer deaths was due to cardiac mortality. No increase was seen in right sided breast cancer.

Gustavsson et al in a study of 90 patients, (34 Right side, 33 left side and 23 not radiated) reported no cardiac deaths.[23] Our study as already described showed more than 10% drop in LVEF in 5% (Group A),6% (Group B) and 5% (Group C) patients. All of these patients had left sided lesions and all had already received anthracycline based chemotherapy. There was no relationship with age and all the women who developed a drop in LVEF were between 30-58 years. One patient in the 5 fractions protocol died of myocardial infarction and she was the only patient who died of non breast cancer cause.

Damage to the brachial plexus is fortunatey rare with supraclavicular radiotherapy but involvement upto 1% has been described in literature. Matchline over dosage could be the cause of this toxicity.[24] We have routinely been using a gap junction technique. The damage to brachial plexus is said to be greater with larger fraction size. But in our series no such problem was encountered. The diagnosis is usually clinical and CT Scan helps to differentiate it from tumour recurrence. One patient in our series who was treated with 5 fractions protocol complained of severe pain in the shoulder. No brachial plexus injury could be documented. Probably it was arthritic pain which gradually settled in about 04 months. As far as other rare toxicities like rib fractures, severe subcutaneous fibrosis and development of sarcomas is concerned no such case was noted.

Approximately 700-800 new breast cancer patients are registered at INMOL annually. A big percentage of these patients require radiotherapy which require time according to the fractions needed. For 15 fractions protocol 51 fields have to be treated .In contrast for 10 fractions the number of fields are reduced to 34 and with 5 fractions to 17 only. This saves about 50 -100 minutes if average time for setting one field is taken as 3 minutes. Therefore if 20 patients of breast cancer are being treated in one day, approximately 15-30 working hours can be saved.

During radiotherapy the patients visit their treating physicians once or twice a week for minor complaints. This amounts to six visits for three weeks protocol. This can be reduced to 4 visits for a 2 week protocol and 2 visits for a one week protocol. Very often the consultant has to mark the radiation fields again. By reducing the total span of treatment from three weeks to two or one week this problem is also minimized .

Some patients have no places to live in the period of therapy, and have to be admitted in the wards. With the three weeks protocol the patient has to stay for 19 days, while it is reduced to 12 days for 2 weeks protocol and to 5 days only for one week protocol. The study concluded that the short protocols are equally effective, with managable toxicity and reduce the work load of the hospital.

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