VOLUME - 12, ISSUE - 11, NOVEMBER - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Radiotherapy

A RANDOMIZED STUDY TO EVALUATE TOLERABILITY AND SAFETY OF CONCURRENT HORMONAL THERAPY WITH HYPOFRACTIONATED RADIOTHERAPY VERSUS HYPOFRACTIONATED RADIOTHERAPY FOLLOWED BY HORMONAL THERAPY IN PATIENTS OF BREAST CANCER

Dr. Ashutosh Mishra	MD Radiation Oncology, Senior Resident, GRMC Gwalior
Dr. Jagdish Patidar	MD Radiation Oncology, Senior Resident, MGM Medical College Indore
Dr. Amit Kumar Soni	MD Radiation Oncology, Medical officer, District Hospital Ujjain
Dr. Vikas Bhalekar*	MD Radiation Oncology, Senior Resident, MGM Medical College Indore *Corresponding Author

ABSTRACT

Background: Hormonal therapy has an important role in management of breast cancers with positive hormone receptors. Also there are numerous toxicities associated with hormonal therapy which may further potentiate toxicities associated with radiotherapy which is also has an integral role in management of breast cancers. **Objective:** This research paper is about to study and compare the of effects of hormonal therapy in patients of breast cancer, when prescribed concurrently with radiation therapy and following completion of radiation therapy. **Methodology:** Patients of breast cancer with Estrogens and progesterone receptors positive reports on immunohistochemistry were divided into two interventional arms. One arm (50 in number) were given concurrent hormonal therapy and radiotherapy while other arm (50 in number) were given hormonal therapy sequentially after completion of radiotherapy. **Results and Conclusion:** Our study revealed that it is reasonable to let the radiotherapy to be completed before commencing hormonal therapy instead of giving concurrently, but the results are found to be statistically insignificant. Hence either of the two approaches can be chosen in treatment plan.

KEYWORDS : Breast cancer, Hypofractionated Radiotherapy, Immunohistochemistry.

INTRODUCTION

Breast cancer is a malignant disease and is a most common cancer in women [1]. All women, especially as they age, are at risk of for developing breast malignancy. Hormonal therapy is an important part of management of breast cancer which interferes with neoplastic mechanism associated due to hormonal action on cancer cells. If estrogen receptors (ER) or progesterone receptors(PR) or both are positive on immuno histochemistry(IHC) tests, then it is said to be hormone positive breast cancer and, hormonal therapy can be administered in such patients of breast cancer. Hormonal therapy is known to lower the risk of breast cancer and risk of recurrence of disease in breast cancer. On one hand hormonal therapy has shown to be protective in breast cancer, while it has many deleterious systemic side effects [2] which could be potentiated during radiation treatment and could interrupt the radiotherapy sessions. Hence motive of the study is to evaluate tolerability and safety of Hormonal therapy when it is given concurrently along with Hypofractionated Radiotherapy and when given sequentially after Hypofractionated Radiotherapy in patients of breast cancer.

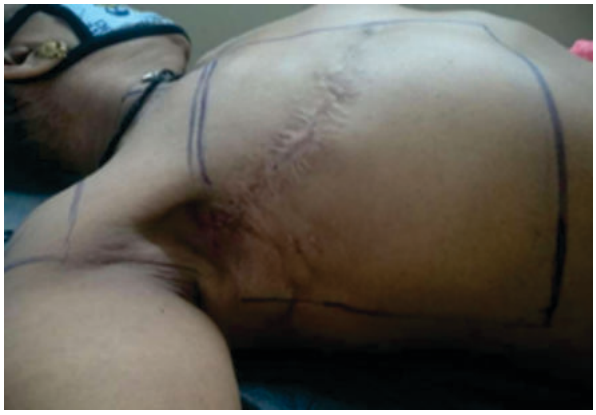
MATERIAL AND METHODS

In this study, 100 patients were taken who were fulfilling all inclusion criteria (>18 years of age, Hormone receptors positive and no documented metastasis). Exclusion criteria were those who has not given consent, pregnant women, Male breast cancer, hormone receptors negative, bilateral breast cancer and breast cancer with distant metastasis. Study group were divided, by means of simple random sampling method, into Group A, (n=50) - the concurrent arm where hormonal therapy were given during radiotherapy & Group B, (n=50) - the sequential arm where hormonal therapy were given after radiotherapy got completed.

After proper selection of patients depending on inclusion and exclusion criteria patients were randomly assigned to either of two groups-One arm receiving hypofractionated radiotherapy with concurrent hormonal therapy (Group A), and Other arm receiving hypofractionated radiotherapy followed by hormonal therapy (Group B). To the concurrent arm hormonal therapy was given as Tamoxifen 20mg once a day in pre menopausal women and Anastrazole 1mg or Letrozole 2.5mg once a day. Radiation therapy was administered by External beam radiotherapy with a megavoltage beam using Theratron 780-C cobalt machine with 80 cm Source to surface Distance (SSD).

Hypofractionation technique of radiation therapy was given as 15 fractions of 270cgy/fraction, 5 fractions/ week over 3 weeks were administered to a total dose of 40.50 Gy.

After completion of radiotherapy, all the patients were followed up every 3 monthly and monitored for 2.5 years for toxicities. Toxicities were graded as per Radiation Therapy Oncology Group guideline (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) [3].



2D planning portals drawn on chest wall including right axilla and right supraclavicular node

RESULTS

Table 1 -Distribution of acute skin toxicities in both arms. Acute toxicities were scored according to the Common

Toxicity Criteria for Events

Dermatitis	Concurrent arm	Sequential Arm	Test	p-Value
Grade 0 (no toxicities)	18	22	Chi- square test	0.791
Grade 1	23	20		
Grade 2	5	3		
Grade 3	3	4		
Grade 4	1	1		
Total	50	50		

Grade 1 skin toxicity noted in most of the patients where they presented with faint patchy erythematous lesions and shedding of skin. Degree of freedom= 4

Table2- Musculoskeletal symptoms due to hormonal agents

Musculoskeletal Symptoms	Concurrent arm	Sequential Arm	Test	p-value
Muscle pain (myalgia)	8	6	Chi- square test	0.548
Joint Stiffness	4	2		
Bone fracture	2	8		
Arthralgia	6	10		
Total	20	26		

Musculoskeletal symptoms noted in most of the patients who were on Anastrazole or letrozole. Arthralgia (joint pain) is the most common symptom patients faced. Degree of freedom= 1

Table 3- Compliance with hormonal therapy

Compliance with hormonal agents	Concurrent Arm	Sequential Arm	Test	P-value
Compliant	39	41	Chi-square test	0.617
Non- compliant	11	9		
Total	50	50		

Comparatively more non-compliance and desertion with hormonal therapy were found in concurrent arm, the most common reason being adverse effects and toxicities due to hormonal agents. On the other hand, the most common reason for loss of compliance in sequential arm was found to be loss of follow up. Degree of freedom= 1

Table 4- Radiation induced lung toxicities

Grading	Concurrent Arm	Sequential Arm	Test	p-value
No toxicities	**38**	**44**	**Chi- square test**	**0.155**
Grade 1	8	4		
Grade 2	4	2		
Grade 3	0	0		
Grade 4	0	0		
Total	50	50		

No significant lung toxicities noted in majority of patients. Very few patients presented with complaints of transient cough, which was relieved by anti-tussive. Degree of freedom= 2

Table 5- Lymphedema In Sample Patients

Lymphedema	Concurrent Arm	Sequential Arm	Test	p-value
Present	**6**	**14**	**Chi- square test**	**0.046**
Absent	44	36		
Total	50	50		

Some patients (maximum from sequential arm) patients presented with swelling on ipsilateral arm, thickening of axilla and difficulty in rotation of shoulder joint. Degree of freedom=1

DISCUSSION

Breast cancer is the most common cancer in women and is one of the major causes of death among them [1]. Incidence of breast cancer varies greatly with ethnicity and race and more in developed city. Breast cancer is a multifactorial disease. Most of the breast cancer arises from ducts (85%) or lobules (15%) in the glandular tissue of the breast. Breast cancer has a multi-modality management where surgery, radiation therapy, chemotherapy and hormonal therapy have an important role. This study emphasized more on radiation therapy and hormonal therapy in management of breast cancer. The study was conducted to decide whether sequencing hormonal therapy had any impact on outcome and toxicities. From a theoretical point of view, there is a proposed contraindication of endocrine therapy given concurrently with radiotherapy due to the anti-proliferative effects of hormonal treatments and a decreased efficacy of radiation on arrested cells. In cell culture studies by, it has been studied that tamoxifen causes arrest of breast cancer cells in culture in the relatively radio resistant G0/G1 phases of the cell cycle. Tamoxifen has been shown to exert a number of nonhormonal as well as hormonal effects of which one such nonhormonal effect of tamoxifen is the induction of Transforming Growth Factor Beta (TGF-ß) secretion which can result in lung fibrosis [4]. Johansen, et al. found grade 2 or greater fibrosis in group that were receiving tamoxifen concurrently with radiotherapy [5]. Out of 147 patients, Azria, et al. noted a significant difference of grade 2-3 subcutaneous fibrosis in patients who were taking tamoxifen concurrently with radiation therapy. Fowble, et al. noted breast edema in patients treated with tamoxifen concurrently with radiation therapy[6] . David Azria studied that letrozole sensitizes breast cancer cells to ionizing radiation. He demonstrated that letrozole inhibits cell proliferation by blocking the cell cycle in G1 phase or by invoking a transition delay, and this provided the basis for the use of concurrent letrozole and radiation therapy in breast cancer patients [7].

Though all these studies were not statistically significant, and were not able to bring significant changes in overall survival (OS), disease free survival (DFS) and recurrences. Therefore sequencing of hormonal therapy with respect to radiation therapy is still a question. Hypofractionation schedule is chosen for this study because hypofractionated radiation [HFRT] therapy could be safe and could be used in post-menopausal and/or in elderly patients with good local control and acceptable toxicities [8] [9].While HFRT alone might theoretically increase skin toxicity, no data has been previously reported on hormone therapy and concurrent HFRT. In present study, hypofractionated radiation therapy was given to the eligible patients at dose of 270cGy in 15 fractions for five days in a week for three weeks.

In current study, most of the enrolled patients were belongs to age group of 45-45 years. In current studies, most of the patients have Stage II breast cancer of invasive ductal carcinoma variety. After radiation therapy ended, patient were advised for regular monthly follow up and were told to visit our institute anytime when she feels uneasy or due to unbearable toxicities. Most of the patients came for follow up in whom general and local examination was conducted to check for any signs or symptoms significantly associated with hormonal therapy and radiation therapy. All necessary investigations were done when required. Some patients of concurrent arm reported subtle abnormal vaginal bleeding, night sweats and slight exertion on walking when tamoxifen was given. These patients were followed up periodically where no serious toxicities were noted, and if had some, got resolved spontaneously without any intervention. Most of the patients in both arms, who were taking Anastrazole or Letrozole, complained of fatigue, joint pain and muscle pain. Their serum calcium were checked and monitored and prophylactic

calcium and vitamin D_3 in tablet form were supplemented.

Few patients,11 in numbers in concurrent arm and 9 in sequential arm were found to be non adherent to hormonal therapy, resulted in loss of follow up and irregular follow up. The reason being unbearable side effects and toxicities due to hormonal agents, forgetfulness due to anxiety, misunderstanding or confusion between hormonal medicines and other symptomatic medicines given alongside to overcome radiation induced side effects and toxicities. Pulmonary fibrosis was noted in 12 patients of concurrent group and 6 patients of sequential group when they came for follow up and were taking tamoxifen concurrently with radiation therapy. Fibrosis was minimal, not significant clinically and radiographically and came into notice after 3 months of follow up. Though 6 patients of sequential group were also noted having pulmonary fibrosis, as visualized on chest X-ray. Patients were encouraged for further strict follow up and spirometry exercises to improve lung volume and capacities. Hormonal toxicities were noted in both arms (concurrent and sequential) .The comparison were found to be statistically insignificant (p- values of all variables is >0.05), hence hormonal therapy can be given by either approach (concurrently as well as sequentially).Patient in both arm tolerated hormonal therapy well.

CONCLUSION

There is no clear evidence to suggest that either concurrent or sequential endocrine and radiation therapy results in a change in clinically important outcomes or adverse events. However, there is literature that suggests that concurrent radiation and hormonal therapy may leads to lung, soft-tissue, and cardiac fibrosis through increased levels of TGFb. It is conceivable that sequential endocrine therapy and radiotherapy may avoid these toxicities. Taken together, it is reasonable for patients to complete endocrine therapy and radiation therapy in a sequential fashion to limit the risk of fibrosis without sacrificing oncologic outcomes. However, due to the limited nature of the trials, this conclusion must be considered with caution.

REFERENCES

1. Clegg LX, Reichman ME, Miller BA, et al (2009). Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control.
2. Jaiyesimi IA, Buzdar AU, Decker DA & Hortobagyi GN 1995 Use of tamoxifen for breast cancer: twenty-eight years later. Journal of Clinical Oncology 13 513–529.
3. JD Cox *et al*. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)
4. S M Benzten, J Z Skoczylas, M Overgaard, J Overgaard 1996 Radiotherapy related lung fibrosis enhanced by tamoxifen S M Bentzan et al. J Natl Cancer Inst. 1996
5. Johansen J, Overgaard J, Overgaard M: Effect of adjuvant systemic treatment on cosmetic outcome and late normal-tissue reactions after breast conservation. Acta Oncol. 2007, 46:525– 33. 10.1080/02841860701291698
6. Fowble B, Fein DA, Hanlon AL, Eisenberg BL, Hoffman JP, Sigurdson ER, Daly MB, Goldstein LJ: The impact of tamoxifen on breast recurrence, cosmesis, complications, and survival in estrogen receptor-positive early-stage breast cancer. Int J Radiat Oncol Biol Phys. 1996, 35:669–77. 10.1016/0360-3016(96)00185-X
7. Azria D, Belkacemi Y, Romieu G, Gourgou S, Gutowski M, Zaman K, Moscardo CL, Lemanski C, Coelho M, Rosenstein B, Fenoglietto P, Crompton NE, Ozsahin M: Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. Lancet Oncol. 2010, 11:258–65. 10.1016/S1470-2045(10)70013-9
8. Kirova YM, Campana F, Savignoni A, Laki F, Muresan M, Dendale R, Bollet MA, Salmon RJ, Fourquet A. Breastconserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2009;75:76-81. [PubMed] [DOI] [Cited in This Article: 2] [Cited by in Crossref: 73] [Cited by in F6Publishing: 45] [Article Influence: 6.1]
9. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-520. [PubMed] [DOI] [Cited in This Article: 4] [Cited by in Crossref: 1008] [Cited by in F6Publishing: 295] [Article Influence: 91.6]