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Radiation-induced late Pulmonary Toxicity In Carcinoma Breast patients: A retrospective study

Virendra Bhandari[1], Paragi Goyal[2], Ashar Iqbal Lodi[3], Amresh Kumar[4]

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Abstract

Normal cells and cancer cells can be differentiated clearly during insulin induced hypoglycaemia because of the difference in number of insulin receptors on cell membrane as well as the biologic response which insulin modifies. This helps in targeting the chemotherapy drugs more specifically and effectively inside the cells. Under insulin this occurs in cancer cells with low doses of chemotherapy drugs with lesser side effects. With this aim we did this randomised study in advanced head and neck cancer cases comparing low doses of cisplatin under hypoglycaemia with usual weekly dose of cisplatin along with full dose of radiotherapy. There was 77.7% complete response and 11.1% partial response in low dose and 90% complete respone in full dose chemotherapy with minimal side effects in low dose arm and no neurologic or cardiac toxicity was observed in hypoglycaemia arm. Thus we conclude that the use of low dose chemotherapy is equally effective with minimum side effects when given under hypoglycaemia.

Keywords: Breast, Radiation, Late Pulmonary Toxicity.

INTRODUCTION

Breast cancer is the most common cancer among women and one of the most important causes of death among them. Breast cancer is a multifactorial disease and various factors contribute to its occurrence. Female Breast cancer is the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths. Among women, breast cancer accounts for 1 in 4 cancer cases and for 1 in 6 cancer deaths, ranking first for incidence in the vast majority of countries and for mortality in 110 countries.

There is considerable geographic, ethnic, and racial variability in breast cancer incidence. Ethnicity and national origin rank highly as predictors of risk for breast cancer, with up to a 10-fold variation throughout the world. Compared with other well-established risk factors such as the age of menarche and menopause, age at first childbirth, and family history, geographic and ethnic variability.

With the exception of the female gender, increasing age is the most consistent and significant

Author Affiliation: [1]Professor, [2,4]Registrar [3]Assistant Professor, Department of Radiation Oncology, Sri Aurobindo Medical College and PG Institute, Indore 453555, Madhya Pradesh, India.

Corresponding Author: Virendra Bhandari, Professor, Department of Radiation Onclogy, Sri Aurobindo Medical College and PG Institute, Indore 453555, Madhya Pradesh, India.

E-mail: virencancer@yahoo.co.in

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risk factor, with most populations demonstrating increasing incidence rates with age. Other risk factors include personal history and family history of breast cancer along with mutation of BRCA1 and BRCA 2, nulliparity or late age at first childbirth, early menarche and late menopause, prior breast biopsy with hyperplasia or atypical hyperplasia, high breast tissue density, radiation exposure at a young age, alcohol consumption, and use of postmenopausal hormone therapy.

Primary breast carcinoma may be managed surgically with either mastectomy or breast-conserving surgery. Although radiotherapy following breast-conserving surgery is widely accepted, the role of post-mastectomy radiotherapy (PMRT) has been a subject of debate for many years. The absolute benefit gained from PMRT is believed to be greatest for those at high risk of Local Regional failure (LRF). There is consensus that PMRT should be considered when the risk of LRF is greater than 20%, such as for patients with four or more positive axillary lymph nodes, primary tumour size>5 cm, T4 disease, and positive/very close margin.[1] PMRT is not indicated in patients with tumors less than 5 cm in size and negative axillary nodes, as there is only a small benefit in terms of locoregional control and insignificant absolute survival advantage.

Neal and Yarnold defined the central lung distance (CLD) as the distance between the midpoint of the posterior field and the edge of the chest wall was a predictor of lung doses. It has been reported that CLD is the best predictor of the amount of dose received by the ipsilateral lung, which is included in the tangential fields. During the treatment, patients were weekly followed up and their acute symptoms were also noted. [(2)]By using CT-based conformal Radiotherapy plans, it makes it possible to directly measure the lung volume irradiated, with using dose-volume histograms (DVH) that have been generated by a treatment planning system, and help to identify certain parameters that are useful for the prediction of Pulmonary Toxicity.[2]

Complications of Radiation therapy on breast

Early: Weeks to months - Skin thickening with breast edema,Fat necrosis, Dystrophic calcifications, Radiation-induced pneumonia, Pleural effusion.

Intermediate: Months to years - Skin retraction with breast fibrosis, Glandular atrophy, Lactation difficulty, Overlying bone fracture, Pulmonary fibrosis, Pericardial disease.

Late: More than 10 years - Cardiomyopathy, Radiation-induced malignancy.

Despite giving the best results, radiation therapy has got a few side effects, including acute and late pulmonary toxicities.

Acute toxicities consist of breathlessness, productive cough.

Late toxicities presenting after 120 days of irradiation including dry cough, breathlessness on exertion, chest pain which are primarily associated with Post radiation Pulmonary fibrosis and pneumonitis.

Pulmonary fibrosis is a late injury due to interstitial damage involving the parenchyma as well as the pleura. Severity is related to a number of factors, including the volume of the irradiated lung, radiation dose, fractionation, or concomitant use of some chemotherapy regimens. It appears that relatively sharp marginated fibrosis is localized in the radiation field.[3]

The patients with apical lung fibrosis are frequently without pulmonary symptoms. This lack of symptoms may be explained by the relatively small portion of the total lung volume affected. When lung-damage scores from the part of the lung exposed to the electron field are considered, a significant correlation exists between radiologic lung changes and patient symptoms, and enhancement of radiation-induced fibrosis be considered in other series of patients receiving radiotherapy with or without or without simultaneous.

MATERIALS AND METHODS

All the female patients with Carcinoma Breast who underwent Radiation Therapy at the Department of Radiation Oncology in SAIMS from 2018 to 2022 were listed. The females were asked to come for follow-up. Their pre-radiation CT scan and chest X-ray, was compared with the post-radiation CT Scan and chest X-ray, which was done after 6 months of completion of treatment on follow-up. Data collection was retrospective. All the patients fulfilling the inclusion criteria such as Female Patients more than 30 years of age, Patients who are Biopsy proven along with IHC, Karnofsky Performance status (KPS)> 70%, Patients who completed their treatment and came for regular follow-up, and gave consent were included. 250 patients were evaluated for late pulmonary toxicities, and treated with Adjuvant local radiotherapy upto a dose of 50Gy for carcinoma breast at our institute using a static, field-in-field, and Dynamic technique from 2018 to 2022. Patients were stratified according to the mean age at presentation of carcinoma, hormonal status,

incidence of recurrence/metastasis, side of breast, technique use (3D CRT or IMRT).

Central lung distance for ipsilateral lung, dose received by ipsilateral lung, V20 of the ipsilateral lung, dose received by the contralateral lung were calculated.

During the treatment, patients were weekly followed up and their acute symptoms were noted. After the completion of treatment the patients were assessed on a regular basis after 6 months and 1 year for the late effects of radiation therapy on the basis of their symptoms, CT Scan PFT (Pulmonary Function Test) or PET Scan reports.

RESULT

The age group at the time of presentation of carcinoma was 30-80 years. (Median age = 49 years). Out of 250 Patients treated with radiation therapy, 61 patients developed Pulmonary Fibrosis. Out of these 61 patients, 32 females had Right sided disease and 29 patients had Left sided disease. The number of Patients who underwent MRM were 50. The number of Patients with Intact Breast / Lumpectomy were 11. (2 underwent lumpectomy). The patient who received radiation via (IMRT) Forward Planning and IMRT(Inverse Planning) were 53 and 8, respectively.

The mean dose of Ipsilateral Lung received in IMRT Forward Planning (16.99) is less than that received by IMRT Inverse Planning (17.82). (Table no. 1)

Mean Central Lung distance is Less in Lung treated with IMRT Forward Planning (2.47cm) than by IMRT Inverse Planning (2.69cm) (Table no.1).

Similarly, the Earliest Lung Fibrosis in a Patient was seen soon after 4 months and Late by 24 months.

Table 1: Comparison of dose received by Ipsilateral and contralateral lung and central lung distance in IMRT forward and inverse planning.

	IMRT Forward Planning (n = 53 patients)			**IMRT Inverse Planning (n = 8 patients)**		
	Min	**Max**	**Mean**	**Min**	**Max**	**Mean**
Mean dose of I/L lung (GY)	12.7	23.19	16.99	13.97	21.53	17.82
V20 of I/L Lung (%)	22.9	38.20	32.15	22	46	34.22
CLD (Central lung distance) (cm)	1.66	3.21	2.47	2.36	3.22	2.69
Mean dose of C/L Lung (Gy)	0.05	1.22	0.404	1.45	6.62	4.22

The Mean Dose received by Contralateral Lung is more in the IMRT Inverse Planning technique (Table 1).

V20 of comparable Ipsilateral Lung were found out to be 35.5% and 35.48% for IMRT Forward Planning and IMRT Inverse Planning technique respectively. The omission of supraclavicular filed brought down the V20 to the ipsilateral lung to 32.52% as observed in 4 out of 53 Patients.

Average total volume of the radiated Lung was more in Right sided Breast treatment compared to left-sided disease due to anatomical differences.

The average volume of I/L Lung radiated:1267 cc Right Lung vs. 910 cc Left lung.

Table 2: Comparison of different parameters in Earliest Lung Fibrosis and Later Lung Fibrosis found.

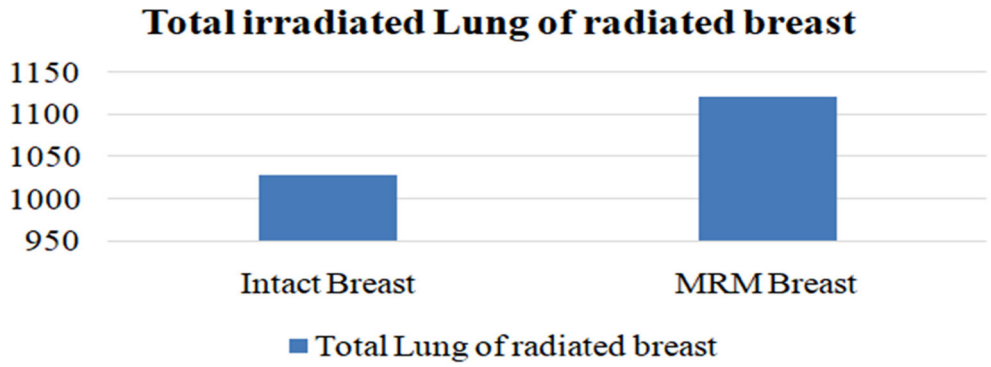
	Earliest Lung Fibrosis	**Late Lung Fibrosis**
Time from the last radiation (months)	4	24
Treated breast	Left	Left
Planning	IMRT Inverse Planning	IMRT Forward Planning

Table Cont...

CLD	2.92cm	2.72cm
Mean dose of I/L	16.04Gy	18.79 Gy
V20 of Lung	27.60%	36.60%
Mean dose of C/L lung	6.62Gy	0.66 Gy
Fibrosed Lung	Left	Left
Total lung Volume	640cc	1227cc

Total Lung Volume Irradiated was more in Modified Radical Mastectomy (MRM) than in Intact Breast (Graph 1)

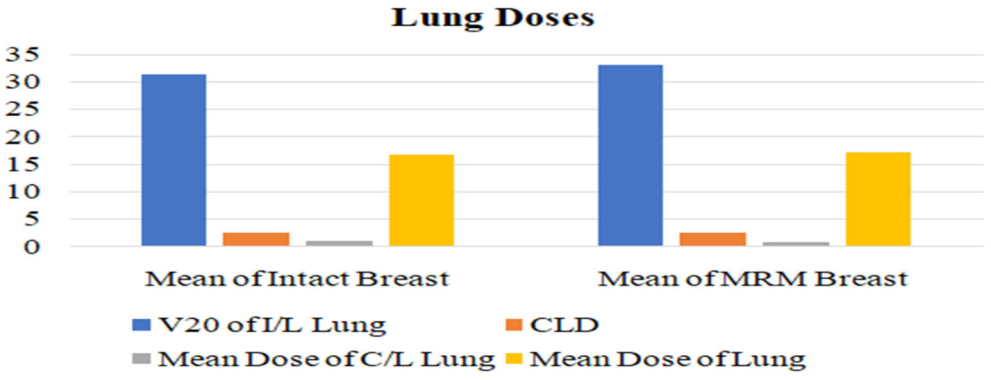
The mean dose delivered to the lungpost-MRM (17.17 Gy) is more than the dose delivered to the intact breast (16.78Gy), so the chances of Lungfibrosis are more in patients who underwent MRM (Table 3) (Graph 2)



Graph 1: Comparison between Total Lung irradiated in Intact breast and Post MRM

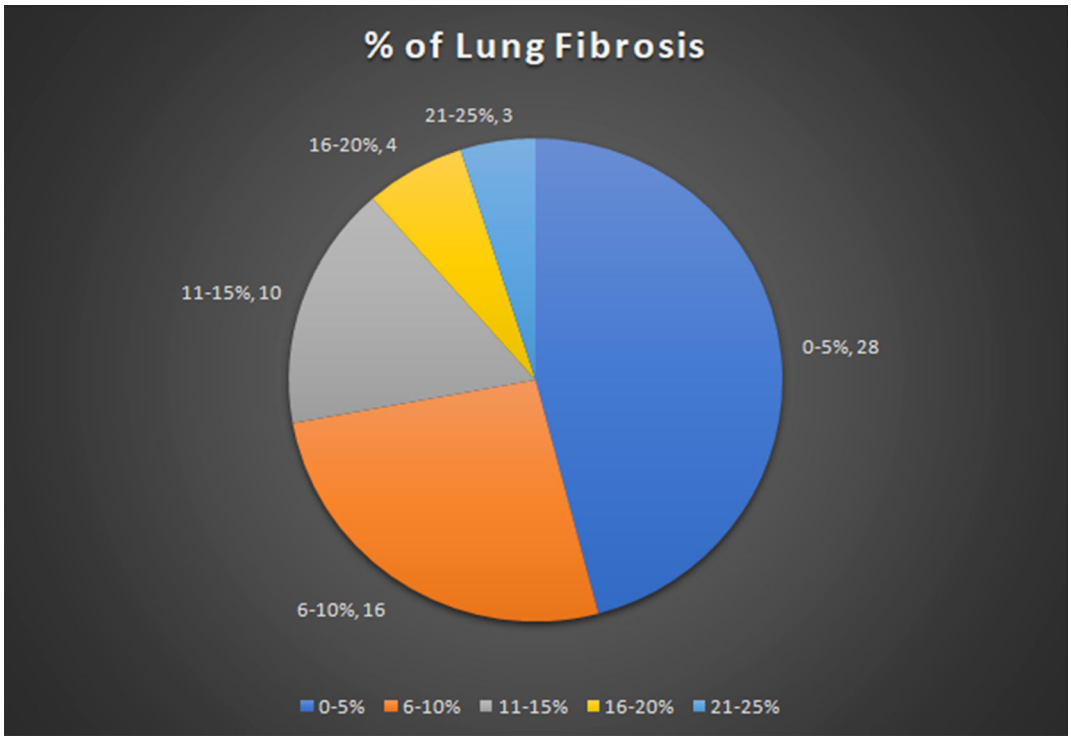
Table 3: Comparison of different parameters (Mean Lung Dose, CLD, dose to C/L Lung) between Intact Breast and Post MRM breast.

	V20 of I/L /Lung	CLD	Mean Dose of C/L Lung	Mean Dose of Lung	Total Lung of Radiated Breast
Intact Breast N=11	31.45%	2.48	1.05	16.78	1029.27
Mrm Breast N=50	33.15%	2.6	0.87	17.17	1121.36



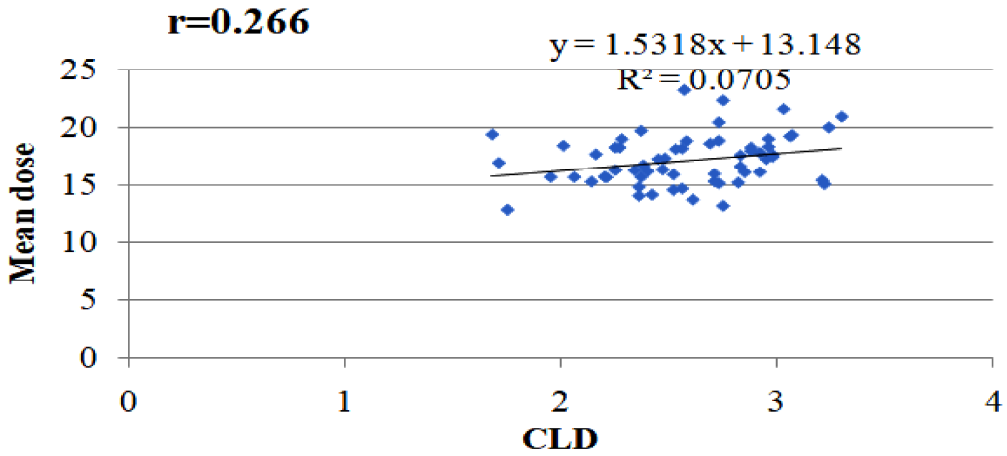
Graph 2: Comparison between Mean dose of V20 of Ipsilateral Lung, Central Lung Distance, Mean dose of Contralateral Lung and Total lung dose in Intact Breast and Post MRM breast.

Percentage of Lung Fibrosis 0-5% in 28, 5-10% in 16, 10-15% in 10, 15-20% in 4, 20-25% in 3 was observed According to RTOG Guidelines for Pulmonary Fibrosis. All 3 patients who developed fibrosis between 20-25% were treated by the IMRT Inverse Planning technique (Graph 3).

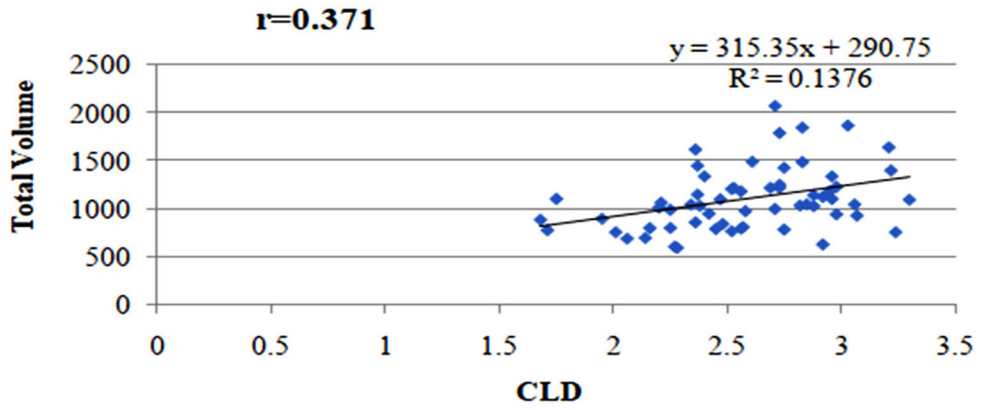


Graph 3: Percentage of Lung Fibrosis in 61 Patients according to Radiology Guidelines of Pulmonary fibrosis on CT Scan.

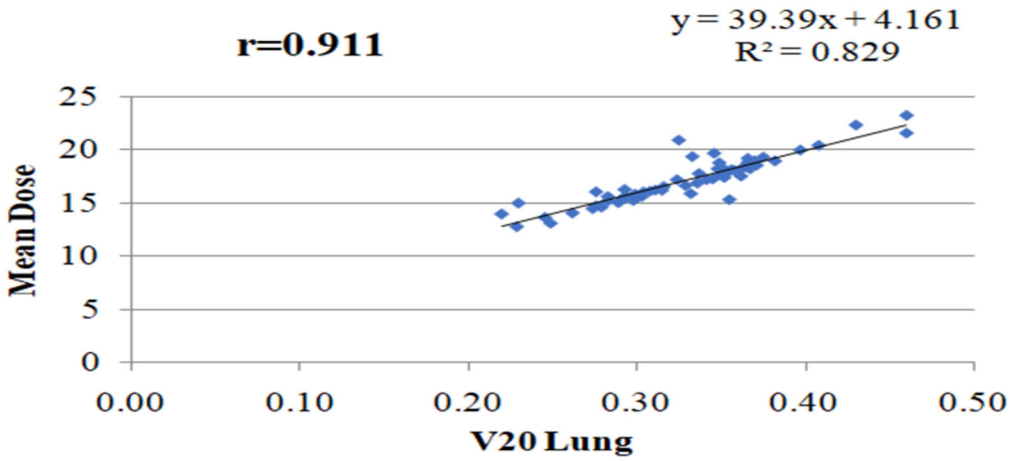
There is a Linear relationship between the Mean dose and CLD (Graph 4). Similarly, there is linear relationship between Total Volume and CLD (Graph 5), and also a linear relationship between Mean dose and V20 Illustrated in the graphs (Graph 6).



Graph 4: Graph showing Linear Relationship between Central Lung Distance in Cm and Mean dose received by Ipsilateral Lung.



Graph 5: Graph showing Linear Relationship between Central Lung Distance in Cm and Total Volume of Ipsilateral Lung.



Graph 6: Graph showing Linear Relationship between Central Lung Distance in Cm and Total Volume of Ipsilateral Lung.

DISCUSSION

According to Alina et al.[1], Both algorithms (forward and Inverse Planning) are equivalent in removing the hot spots on the inframammary fold, where acute skin reactions occur more frequently using a conventional wedge technique. Based on these results, they recommend that both forward and inverse algorithms should be considered for breast IMRT planning, Similarly in our study, we got very less Skin reactions in both the arms as less shielding was good so acute skin reaction in the inframmary region were very less.

According to the RTOG guidelines, 45% had Grade 1 type of fibrosis, which was at some point of time converted into Grade 2 but was reversible .where as in a study done by Huang et al.[3], Only Grade 1 radiation-induced late pulmonary toxicity was noted in 33 patients (29%). Patients who received Radiation via IMRT (Inverse Planning) developed lung Fibrosis earlier than those who had radiation via IMRT (Forward Planning) 17.6% patients had Grade 1 Fibrosis, 4% had grade 2 fibrosis, 2.8% had grade 3 fibrosis, but there was no change in pulmonary function test and vital capacity on PFT, similarly the study of Sacco M et al.[4] says that the Pulmonary fibrosis can been seen but it do not cause any defect in Vital Capacity on PFT. CLD and Mean dose received by the I/L lung is directly proportional and have a positive linear relationship. CLD, Mean dose of I/L lung and Pulmonary Fibrosis are directly proportional and have a positive relationship, more the CLD more Is the lung fibrosis. In our study around 28% patients had lung fibrosis around 0-5%, 16% in between 5-10%.

In a study by Suma S et al.[5] and Bentzen et al.[6], Pulmonary fibrosis developed in 26 of 74 patients who were treated with Radiotherapy and Tamoxifen combination and concluded that Tamoxifen increases the Probability of Having Pulmonary Fibrosis Post Mastectomy Radiotherapy but we did not gave Tamoxifen to any of our Patients during the treatment. There are certain Studies by Rampinelli et al.[7], in which they compared the EBRT and IORT and concluded that EBRT is better but none of the methods were followed by us. IMRT (Forward Planning) is a comparatively a better technique for treating Breast patients, as the I/L and C/L lung receive less dose and leads to less lung fibrosis. In IMRT (Inverse Planning) patient receive moredose to ipsilateral lung as well as to the contralateral lung and CLD is also more, but according to Mihai et al.[8], Inverse planning is better. According to Kim H et al.[9] Radiologic lung damage were not infrequently detected in follow-up CT after whole breast FIMRT (forward Intensity Modulated Radiotherapy). More detected cases of RLD among younger patients so as we concluded in our study too.

In Yang B et al.[10] study, a tangent in the breast board reduces the field size in the Supraclavicular area leading to reduce dose to lung leading to Less toxicity to lung so in our study patients in which Supraclavicular lymph nodes were radiated had more fibrosis though even we used a breast board with a tangent conclude that Supraclavicular lymph node radiation lead to more dose delivery to lung.

According to Yi A, Kim HH et al.[11] Complication of Radiation therapy on breast can be seen as early as within 7 days or late by years comparing the Acute and Late toxicities we found only Skin reactions in Axilla as Acute toxicities and none had breathlessness, pleural effusion, pneumonia and very few had cough. Whereas none manifested late toxicities as cardiomyopathy or Radiation-induced malignancy.

CONCLUSION

The incidence of Lung Fibrosis in Carcinoma Breast Patients who underwent radiation was 24.4% in our institute (n=250). Patients with Grade 1 and 2 fibrosis were reversible whereas grade 3 fibrosis were asymptomatic. Patients who received Radiation via IMRT (Inverse Planning) developed lung Fibrosis earlier than those who had radiation via IMRT (Forward Planning). Forward planning is better than Inverse planning for Ca Breast Patient for pulmonary toxicities.

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