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AN OBSERVATIONAL STUDY TO EVALUATE THE RESPONSE AND TOXICITY WITH CONVENTIONAL FRACTIONATION AND HYPO FRACTIONATED RADIOTHERAPY FOR LOCALLY ADVANCED NON SMALL CELL LUNG CARCINOMA FOLLOWING INDUCTION CHEMOTHERAPY

Oncology

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ABSTRACT

Aims & Objectives: To evaluate the response and toxicity with Conventional fractionation and hypofractionated radiotherapy for locally advanced NSCLC following induction chemotherapy. To assess and compare following for locally advanced NSCLC with Conventional and hypo fractionated radiotherapy following induction chemotherapy.

Materials And Methods: This prospective observational study was conducted at Saroj Gupta Cancer Centre and Research Institute, Kolkata; accrual was from June 2016 to September 2017. Data was collected from all patients who had been cytological / histopathologically and radiological proven stage III Non Small Cell Lung Carcinoma; fulfilling eligibility criteria, were recruited after obtaining informed consent.

Results And Analysis: We found that the association between response at the END OF RT in two groups was not statistically significant (p=0.8559). Association between Dermatitis highest grade at end of RT in two groups was not statistically significant (p=0.5201). Association between Response 6 months after RT in two groups was not statistically significant (p=0.7667). Association between Response 9 months after RT in two groups was not statistically significant (p=0.9255). Association between Dermatitis.

Conclusion & Summary: Our study showed hypofractionated radiotherapy is non-inferior to Conventional radiotherapy with equivalent overall response and toxicity and well tolerable.

In patients with poor performance status who cannot tolerate concurrent chemo radiation, induction chemotherapy with hypofractionated radiotherapy regimen can be considered as a treatment of choice with manageable toxicities.

KEYWORDS

Conventional fractionation, Hypo fractionated radiotherapy, Non small cell lung carcinoma and Induction chemotherapy

INTRODUCTION

Lung cancer is one of the most common cancers and also the most common cause of cancer related deaths worldwide [1]. In 2008 there were 1.61 million new cases, and 1.38 million deaths due to lung cancer, and it has increased to 1.8 million new cases in 2012 (12.9% of the total) which estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total)[2]. The highest rates are in Europe and North America. With increased smoking in developing countries, the rates are expected to increase in the next few years, notably in India [3] and China. In India, lung cancer constitutes second most common cancer in male and contributes to significant mortality in both male and female. The incidence of lung cancer in India is 70,000 per year out of which mortality is 64000 per year. Majority of the patients are detected with non-small cell lung cancer (NSCLC) with a mean age of diagnosis at 66 years, i.e., it is a disease affecting the elderly people [1]. In developed countries, lung cancer patients usually present in early stage; while in developing countries like India, they present in locally advanced stage (stage III)[2].

Lung cancer is broadly classified into small cell lung carcinoma and non-small cell lung carcinoma. Non-small cell lung cancer constitutes 75-80% of all lung cancers. More than 70% of them are in Stage III and IV when diagnosed making curative surgery difficult. Small cell lung carcinoma which constitutes 20% is in the extensive stage when diagnosed in 70% of patients. This distinction is important because the treatment varies; small cell lung carcinoma (SCLC) usually responds better to chemotherapy, non-small cell lung carcinoma (NSCLC) is treated with surgery in the early stages, but in locally advanced (stage III) cases combined modality treatments are practiced in recent days, like concurrent chemo radiation therapy, systemic chemotherapy and radiotherapy to residual disease, radiation therapy alone, sequential chemo radiation therapy. In concurrent chemo radiation therapy, it can be induction/ concurrent, and/ or concurrent/ consolidation.

At Saroj Gupta Cancer Centre & Research Institute (SGCC&RI), locally advanced non metastatic non-small cell lung cancer patients are mostly elderly with co-morbidities (e.g. diabetes mellitus, hypertension etc.) having commonly poor(>1) Eastern Co-operative Oncology Group (ECOG) Performance Status (PS). Those patients are deemed inappropriate for concurrent chemoradiation due to the anticipated toxicities and poor tolerance. They are treated with sequential chemoradiation using either Conventional or hypofractionated radiation therapy based upon the decision of tumor board. Radiation therapy is given mainly as a daycare based procedure and hypofractionated radiation therapy is preferred for patients coming from distant places in view of early completion of treatment.

Although enough trials are there to justify the use of hypo-fractionated radiotherapy in locally advanced NSCLC, till now there is no Indian data regarding the same.[4]

We have a huge number of patients coming with locally advanced NSCLC at our institution and it seems prudent to conduct a study observing the response and toxicity of the two radiotherapy schedules.
To evaluate the response and toxicity with Conventional fractionation and hypofractionated radiotherapy for locally advanced NSCLC following induction chemotherapy.

To assess and compare following for locally advanced NSCLC with Conventional and hypo fractionated radiotherapy following induction chemotherapy-

Response assessment at the end of treatment and at 3 months, 6 months and 9 months using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria17.
1. Toxicity assessment (radiation dermatitis, esophagitis, pneumonitis) at the end of treatment and at 3 months, 6 months and 9 months after completion of radiation using Radiation.
2. Additionally, Disease Free Survival and Progression Free Survival at 3 months, 6 months, 9 months after completion of treatment.

MATERIALS AND METHODS

Source Of Data:-

This prospective observational study was conducted at Saroj Gupta Cancer Centre and Research Institute, Kolkata; accrual was from June 2016 to September 2017. Data was collected from all patients who had been cytological / histopathologically and radiological proven stage III Non Small Cell Lung Carcinoma; fulfilling eligibility criteria, were recruited after obtaining informed consent.

Inclusion Criteria:

i) Biopsy/cytology proven Stage III NSCLC
ii) No prior history of malignancy
iii) ECOG PS >1 who are unfit for concurrent chemoradiation

iv) No prior radiotherapy, chemotherapy or surgery for disease
v) Age <80 years of either sex
vi) Weight loss >5% over 3months
vii) No distant metastasis
viii) LVEF >60%
ix) BUN <25mg/dl
x) Serum creatinine <1.5mg/dl
xi) Serum bilirubin <1.5mg/dl
xii) Baseline Hemoglobin > 10 gm/dl
xiii) Absolute Neutrophil Count > 1500/µl
xiv) Platelets > 1, 00,000/µl.
xv) Has signed written informed consent.

Exclusion Criteria
i) Patients with age > 80 years
ii) Patients with clinical or radiological evidence of distant metastasis.
iii) Patients who are restless being unsuitable for radiation therapy
iv) Patients with pregnancy or breast feeding
v) Patients with history of allergic reaction to iodinated contrast media
vi) Patients who have participated in any other study on lung cancer.
vii) Patient's refusal to undergo chemotherapy and/or radiotherapy.

Treatment Plan
Radiotherapy Protocol STUDY TOOLS:
Case Performa, standard hematological, biochemical and radiological investigations
i. Siemens Somatomscope 16 slice helical CT scanner
ii. Siemens Primus Linear Accelerator (LINAC) single energy 6MV with 29 pairs of multileaf collimators
iii. Oncentra v4.3– treatment planning system (developed by Nucletron and maintained by Elekta)
iv. Inj. Paclitaxel (175mg/m2) with necessary premedication and fluids
v. Inj. Carboplatin (AUC5) with necessary premedication and fluids

RESULTS AND ANALYSIS

Our study showed that the difference of mean age in two groups was not statistically significant. Thus age was matched in two groups. There was no statistically significant difference in age distribution between the groups. Numerical variables between groups compared by t-test; (p=0.7452). Association between age in two groups was not statistically significant (p=0.4430). Association between sex in two groups was not statistically significant (p=0.7232). Association between ECOG PS in two groups was not statistically significant (p=0.9298). Distribution of stage in two groups was not statistically significant (p=1.000). Association between histopathology in two groups was not statistically significant (p=0.3111). Association between comorbidity in two groups was not statistically significant (p=0.4308). Association between habit in two groups was not statistically significant (p=0.1417). Association between tumor size in two groups was not statistically significant (p=0.3705). Association between lymph node involvement in two groups was not statistically significant (p=0.9402). All the patients had received induction chemotherapy in both groups.

We found that the association between response at END OF RT in two groups was not statistically significant (p=0.8559). Association between Response 3 months after RT in two groups was not statistically significant (p=0.7659). Association between Response 6 months after RT in two groups was not statistically significant (p=0.7667). Association between Response 9 months after RT in two groups was not statistically significant (p=0.9255). Association between Dermatitis highest grade at end of RT in two groups was not statistically significant (p=0.5201). Association between Esophagitis highest grade at end of RT in two groups was not statistically significant (p=0.4283). Association between Pneumonitis highest grade at end of RT in two groups was not statistically significant (p=1.000). Association between Dermatitis 3 months after RT in two groups was not statistically significant (p=0.5968). Association between Dermatitis 6 months after RT in two groups was not statistically significant (p=0.31118). No patient had dermatitis 9 months after RT. Association between Esophagitis 3 months after RT in two groups was not statistically significant (p=0.3421). Association between Esophagitis 6 months after RT in two groups was not statistically significant (p=0.3111).

DISCUSSION

The present study was undertaken in Department of Radiotherapy, SGCC & RI, Kolkata. The patients with newly diagnosed, histological proven stage IIIA and IIIB lung cancers were presented in hospital tumour board and after board decision, treatment was decided.

Epidemiological Comparison:
In this study, approximately 95% of patients were more than 50 years of age at presentation with median age of 72 years in "Conventional arm" and 69 years in "hypo arm". This is consistent with the expected age distribution ranging from 5th to 7th decades of life as quoted in literature by Yamamoto et al [5] and Belani et al [6]; and with an average age of 68 years as quoted in literature. The incidence of lung cancer increases with age, especially after 60 years of age.Lung cancer is more common in males. In Analysis of data from 22 cancer registries in 5 continents revealed that cumulative lung cancer risks were higher in males than females. In our study, "Conventional arm" has 75% male and "hypo arm" has 70% male patients.

Cigarette smoking associated with an increased risk of lung cancers. Approximately 80% of cases of non–small cell lung cancer (NSCLC) in men and 50% of these neoplasms in women worldwide are directly attributable to cigarette smoking.

In a study by Amini et al [7] 92% of patients of his study group were smokers. Our study had only 50% smokers averaged over both groups. In a study by P. Iyengar et al [8], 53% had Squamous Cell Carcinoma and 47% Adeno Carcinoma. In our study, approximately 70% squamous Cell and 30% Adeno Carcinoma averaged over both groups.

In most of the studies including those conducted by Amini et al [7], there were no significant differences in the distribution of stages IIIA and IIIB between the two groups. In our study, 45% are Stage IIIA and 55% are Stage IIIB.

Induction chemotherapy was used in studies by P. Iyengar et al [8], Din Os et al [9] and Amini et al [7] with hypofractionated Radiotherapy. In our study, Paclitaxel 175mg/m2 and Carboplatin AUC5 are used for induction chemotherapy.

Response Evaluation:
It has been shown time and again that sequential chemo-radiotherapy is a good treatment option for patients with Stage III NSCLC who are unsuitable for concurrent chemoradiation due to older age, poor performance status and medical co-morbidities. Lung Cancer is a disease of older age group and most of the patients cannot tolerate the toxicities of concurrent chemo-radiation as shown by the landmark trial of RTOG 9410 where less than 30% of Stage III NSCLC patients were fit for concurrent chemo-radiation [4], which is also supported by D. De Ruysscher [10] et al and in Indian context.

Such patients are often non-compliant to prolonged 6 weeks standard radiation protocol. Hypofractionated Radiotherapy is an effective protocol owing to early termination of radiation keeping them more adherent to treatment. Radiobiologically also Hypofractionation prevents accelerated tumor repopulation by virtue of early completion of treatment.

In our study, we reported the overall treatment response rates between the Conventional RT group and the hypo fractionated RT group at the end of treatment, at 3 months, 6 months and 9 months after completion of treatment.

A study by Nguyen LN et al [8] showed that hypofractionated group had 14% CR, 38% PR while Conventional group had 25% CR, 42% PR.

In a study by Zhu ZF et al [11] the median and 3-year overall survival, PFS were 19 months in 32.1% and 10 months in 29.8%, respectively. The 1, 2 and 3-year LR-PFS were 69.6%, 60.9% and60.9% respectively. No patient experienced isolated elective nodal failure as the first site of failure. This study suggested that accelerated Hypofractionated radiotherapy using 3D-CRT omitting ENI can be used in combination with sequential chemotherapy in locally advanced NSCLC.

CONCLUSION & SUMMARY

Our study showed hypofractionated radiotherapy is non-inferior to Conventional radiotherapy with equivalent overall response and toxicity and well tolerable.

In patients with poor performance status who cannot tolerate concurrent chemo radiation, induction chemotherapy with

hypofractionated radiotherapy regimen can be considered as a treatment of choice with manageable toxicities.

There was no statistical difference between Conventional and hypofractionated radiotherapy for locally advanced NSCLC as far as tumor control and toxicities were concerned.

All toxicities occurred in our study were well manageable with best supportive care.

A prospective randomized study with large number of patients and longer period of follow-up is needed to extract safe conclusion about the superiority of Conventional vs hypofractionated radiotherapy.

The study titled "Observational Study To Evaluate The Response And Toxicity With Conventional Fractionation And Hypofractionated Radiotherapy For Locally Advanced Non-Small Cell Lung Carcinoma Following Induction Chemotherapy", was performed in the department of Radiotherapy, Saroj Gupta Cancer Centre & Research Institute, Kolkata from June 2016 to September 2017.

40 patients of non-small cell lung cancers of stage IIIA & IIIB satisfying the eligibility criteria were enrolled for the study. In this study, we had given induction chemotherapy [3 weekly Paclitaxel (175 mg/m2) / Carboplatin (AUC5) for 3 cycles] followed by radiotherapy either in Conventional fractionation or Hypofractionated radiotherapy. The radiation dose delivered in Conventional fractionation was 60Gy in 30 fractions (2 Gy/fraction, 5 days/week) in 6 weeks. The radiation dose delivered in Hypofractionated radiotherapy was 55Gy in 20 fractions (2.75Gy /fraction, 5 days/week) in 4 weeks.

Table: Distribution Of Stage In Two Groups

GROUP RT			
STAGE	**Conventional**	**Hypofractionated**	**TOTAL**
IIIA	9	9	18
Row %	50.0	50.0	100.0
Col %	45.0	45.0	45.0
IIIB	11	11	22
Row %	50.0	50.0	100.0
Col %	55.0	55.0	55.0
TOTAL	20	20	40
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Table: Distribution Of Histopathology In Two Groups

GROUP RT			
HISTOPATHOLOGY	**Conventional**	**Hypofractionated**	**TOTAL**
Adenocarcinoma	8	5	13
Row %	61.5	38.5	100.0
Col %	40.0	25.0	32.5
Squamous cell carcinoma	12	15	27
Row %	44.4	55.6	100.0
Col %	60.0	75.0	67.5
TOTAL	20	20	40
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

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