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Radiotherapy

AN OBSERVATIONAL STUDY TO EVALUATE THE TOXICITIES OF CONCURRENT HYPERFRACTIONATED CHEMORADIOTHERAPY IN NON SMALL CELL LUNG CANCER.

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ABSTRACT

Background: Lung cancer is the most common cancer Worldwide. It accounts for 11.6% (2.6 million) of the total cases of cancer and 18.4% (2.4 million) of the cancer-related deaths based on 2018 GLOBOCON DATA. Among males, it is the most commonly diagnosed cancer and also the leading cause of cancer death. Among females it is the fourth most commonly diagnosed cancer and the second leading cause of death. The overall 5-year survival rate for lung cancer is approximately 16%, for all stages of lung cancer. In India according to GLOBOCON DATA 2018 lung cancer is the 4th most common cancer and also leading to 3rd common cause of cancer related death in India incidence of lung cancer in India is 70,275 (for all ages and both genders) with an age standardized Incidence rate being 6.9 per 100,000 of our population. The lag in the trend of lung cancer in women compared with men reflects historical differences in cigarette smoking between the sexes; cigarette smoking in women peaked about 20 years later than in men. Most lung cancer cases are attributable to cigarette smoking. Voluntary or involuntary cigarette exposure accounts for 80% to 90% of all cases of lung cancer. Indoor radon exposure is considered as the second leading cause of lung cancer in the United States. Radiotherapy has an important role in the management of approximately 85% of patients with non- small cell lung cancers with both curative and palliative intent.

Objective: To analyze toxicities of hyperfractionated radiotherapy in locally advanced non-small cell lung cancer.

Method: This prospective clinical study involved 27 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. Informed written consent, detail history and complete Physical examination were performed in every patient. Patient were immobilized by help of immobilization device and simulated on CT simulator then treatment was executed with Rapid Arc (RA) technique as per fractionation schedule for the study i.e 1.8 Gy per fraction, 2 daily doses 6 hrs. Apart for 72 Gy in 6wks. Patients were assessed every week for acute toxicities. Frequency tables were used to describe impact of treatment on different stages using chi -square test.

Result: In this study the majority of patients had stage IIIB and IIIA disease, 12 out of 27 (44.4%) had IIIB disease, 4 out of 27(14.8%) patients had stage IIIA disease and 3 out of 27 (11.11) patients had IIIC disease. In our study maximum number of patients 42.86% belonged to 50-60 years age group followed by 21.43% in 60-70 year group and 17% in 40-50 years age group. Acute toxicity seen was mostly dysphagia (Grade 2) in 55.56% patients which occurred sooner and was severe in nature this was subsided later and decreased to 21.16% till 6th month. Dysponea Grade 1 and 3 was seen in 55.14 % patients. Among Late toxicities late radiation pneumonitis dysponea Grade 3 was seen among 55.16 % patients which persisted till 3 months and gradually subsided but grade 2 toxicity was seen among 60.61% patients which persisted till 6 month and grade 2 dysphagia which was seen in 80.67% decreased to 21.08%.

Conclusion: Hyper fractionated radiotherapy definitely has beneficial role in treatment of non-small cell lung cancer although the patients were presented in late stages. Surgical procedure such as lobectomy / pneumonectomy are not often performed in many institutes due to lack of equipment, expertises and dedicated manpower. Screening for lung cancers can be very beneficial to diagnose the lung cancers in very early stages.

KEYWORDS : Non-Small cell cancer, Hyperfractionation, Rapid Arc, Immobilization

INTRODUCTION

Lung cancer is the most common cancer worldwide. It accounts for 11.6% (2.6 million) of the total cases of cancer and 18.4% (2.4 million) of the cancer-related deaths based on 2018 GLOBOCON DATA. [1] Among males, it is the most commonly diagnosed cancer and also the leading cause of cancer death. Among females it is the fourth most commonly diagnosed cancer and the second leading cause of death. The incidence of lung cancer is declining in males while it is static in female. The American Cancer Society estimates 156,940 people in the United States died of lung cancer in 2011, including 85,600 men and 71,340 women. [2] The overall 5- year survival rate for lung cancer is approximately 16% for all stages of lung cancer. [3]

In India according to GLOBOCON DATA 2018 lung cancer is the 4th most common cancer and also leading to 3rd common cause of cancer related death in India i.e. (8.82). [1] Most lung cancer cases are attributable to cigarette smoking. Voluntary or involuntary cigarette exposure accounts for 80% to 90% of all cases of lung cancer. [4] The management of lung cancer is decided on the basis of stage of the disease. In Stage I and II if disease is operable treatment of choice is surgery (lobectomy/ segmentectomy) and If considered inoperable then radiotherapy in form of SRT. In Stage III and IV the definitive treatment of choice is radiotherapy with different fractionation schedule. Radiotherapy has an important role in the management of approximately 85% of patients with non- small cell lung cancers with both curative and palliative intent. It is the most common treatment modality in majority of patients as majority Of patients present with bulky disease, hilar or mediastinal lymphadenopathy, associated comorbidities and poor lung function make patients unsuitable for surgery. Among various fractionation one is hyperfractionation in which more than one fraction is delivered each day but the overall treatment time remains similar to that for conventional fractionation i.e. 1.2 to 1.3 Gy/fraction, two fractions per day, with an increase in total dose of the order of 20% to account for increased repair at the lower dose per fraction.[5]The rationale for hyper fractionation is to take full advantage of the difference in repair capacity of late-reacting normal tissues compared with tumors. If conventional radiotherapy are not producing particularly good clinical results evident, hyper fractionation regimes can be delivered. To treat with higher than 1.3 Gy/fraction at more than one fraction per day may exceed acute tolerance, and to use <1.2 Gy/fraction will require three fractions per day in order to not overly increase overall treatment time, with at least 6 hours between fractions required for complete repair. [6]

Objective: To evaluate the toxicities of concurrent hyperfractionated chemoradiotherapy in Non small cell lung cancer.

Method: This prospective clinical study involved 27 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college And Regional cancer centre (RCC) of Dr. BRAM Hospital Raipur.

Patient Inclusion Criteria

1. Histopathological proven cases of carcinoma lung (Non-small cell lung cancer).
2. ECOG performance score of 0 or 1.
3. Patient with normal liver function test, renal function test and haematological parameters.
4. Patient with normal electrocardiogram.

Patient Exclusion Criteria

1) Pregnant and lactating women with carcinoma lung.
2) Patient with any other malignancy.

Major Variables

1) Age
2) Sex
3) Histopathology
4). Target volumes (Gtv, Ptv, Ctv)
5. Dose (objective organs and OAR)

Outcome Variables

1) Acute Toxicities.
2) Late toxicities.

Methodology

- This study was performed in the Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Memorial Medical College & Dr BRAM Hospital Raipur, C.G.
- 27 Histopathological proven cases of non small cell carcinoma of lung were taken for this study.
- Informed written consent was taken from every patient.
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint.
- Physical examination was done on all patients including general, local and systemic examination.
- All the routine investigations including CBC, RFT, LFT, X-ray chest, ECG, CT scan of thorax was done on all the cases.
- Patients were simulated with appropriate immobilization technique then planned with Rapid Arc. Evaluation of the plan for dose to primary site and dose to organ at risk was done and best better plan was executed.
- Treatment planning was performed using ECLIPSE TPS and treatment was delivered using Rapid Arc (RA) technique.
- Fractionation schedule used for this study was 1.8Gy per #/ 2 daily doses/ 6 hrs apart/ 72 Gy in 6wks.
- Patients were assessed every week for acute toxicity.
- After completion of treatment patients were on follow up for 6 weeks to asses for late toxicities with clinical assessment plus radiological imaging.
- Patients were on follow up protocol i.e. every month for next 6 month and thereafter every 3 months.

Calculation Of Result:

In this study, clinical characteristics between the two treatments were compared using chi-square test. A p- value of <0.05 was taken as significant. Data were analysed using the chi- square test.

***Follow Up*:**

After completion of treatment patients were on follow up for 6 weeks to asses for late toxicities with clinical assessment plus radiological imaging. Patients were on follow up protocol i.e. every month for next 6 month and thereafter every 3 months. They were assessed for loco-regional recurrence and /or distant metastasis by clinical examination and/or by necessary investigations.

RESULTS

This prospective observational study involves 27 histological proven, haematological stable cases carcinoma lung (Non-small cell lung cancer) was conducted during October 2017-December 2018 in the Department Of Radiotherapy, Pt. JNM Medical College and Regional Cancer Centre (RCC) Of Dr. BRAM Hospital Raipur. All patients were evaluated with a detailed history, clinical examination, haematological and radiological investigations. The patients were assessed in 1st, 3rd and 6th month the results were as follows

Age

12 out of 27 patients (44.44%) were belonged to 50-60 years age group followed by 21.43% in 60-70 year group and 17% in 40-50 years age group shows that non-small lung cancer is common among old people.

Table 1 Age Wise Distribution Of Patients

Age Range(Yrs)	Male		Female		Total	
	N	%	N	%	N	%
21-30	3	10.71	1	12.5	3	10.71
31-40	2	7.41	1	12.5	2	7.14
41-50	4	17.86	3	37.5	5	17.86
51-60	12	42.6	2	25	12	42.86
61-70	6	21.43	1	12.5	6	21.43
Total	27	100	8	100	27	100

Gender

In our study we found that male patients were 19 out of 27 (71%) and females were 8 out of 27 (29%) which showed that non-small cancer of lung is more common among men compare to women.

Table 2 Gender Wise Distribution

Gender	Number	Percentage
Male	19	70.37
Female	8	29.57
Total	27	100

Site

According to site in our study we observed that the non-small lung cancer affected the right lung in 14 out of 27 patients (51.57%) while on left side it is 48.43%.

Table 3 Site Wise Distribution

Site	Number	Percentage
Right	14	51.57
Left	13	48.43
Total	27	100

Histology

22 out 27 (88.89%) patients had adenocarcinoma variant of histology, and rest of the patients 11.71% had squamus cell carcinoma.

Table 4 Histology Wise Distribution Of Patients

Type of Carcinoma	Number	Percent
1. Squamous Cell Carcinoma	4	11.71
2. Adenocarcinoma	22	88.89
Total	26	100.0

Stage

16 out of 27(59.3%) patients had disease in stage IIIA, 5 out of 27(18.5%) patients were in stage IIIB, and 22.2% patients had stage IIIC diseases.

Table 5 Staging Wise Distribution Of Patients

Stage	Number	Percentage
IIIA	16	59.3
IIIB	5	18.5
IIIC	6	22.2
Total	27	100.0

Acute Toxicities

All patients were assessed for acute toxicity of chemoradiation and radiation alone during & immediately after treatment according to R.T.O.G toxicity criteria. Treatment was well tolerated without delay or interruption, upper gastrointestinal toxicities, and dysponea toxicity was more in hyperfractionated chemoradiotherapy.

Acute Toxicities In 1st Week

19.23% patients showed acute toxicity of grade 1 in pharynx and 57.69% of patients had dysponea as acute toxicities at the end of 1st week.

Table 6 *Acute Toxicities In 1st Week*

1ST WEEK	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	26(100)	0	0	0	0
PHARYNX	21(80.77)	5(19.23)	0	0	0
DYSPHAGIA	20(7.69)	6(23.07)	0	0	0
DYSPONEA	11(42.30)	15(57.69)	0	0	0

Acute toxicities in 2nd week

57.9% pts developed dysphasia of grade 2 whereas 38.46% showed dysphagia of grade 1,pharyngitis of grade 2 were seen in 53.85% patients and dysponea of grade 2 were observed in 14 pts at the end of 2nd week of treatment.

Table 7 ***Acute Toxicities In 2nd Week***

2nd WEEK	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	26(100)	0	0	0	0
PHARYNX	0	11(42.30)	14(53.85	1(3.86)	0
DYSPHAGIA	0	10(38.46)	15(57.9)	1(3.86)	0
DYSPONEA	0	12(46.15)	14(53.85)	0	0

Acute toxicities in 5th week

Grade 3 pharyngitis was observed in 5 pts, 19 pts had dysphagia of grade 2, 57.69% pts developed dysponea of grade 3 at the end of 5th week of treatment as chemo radiotherapy.

Table 8 ***Acute Toxicities In 5th Week***

5th WEEK	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	19(73.07)	7(26.9)	0	0	0
PHARYNX	0	3(7.77)	18(73.07)	5(19.23)	0
DYSPHAGIA	0	2(7.77)	19(73.07)	5(19.23)	0
DYSPONEA	0	1(3.86)	10(38.6)	15(57.69)	0

Acute Toxicities In 1st Month

All most all pts. developed grade 5 dysphasia, grade 5dysponea, and grade 5 hematological toxicities at the end of 1st month of treatment whereas 18 pts had come up with nil hematological toxicities.

Table 9 ***Acute Toxicities In 1st Month***

1st month	No Toxicities	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Dysphagia	0(0%)	3(11.54 %)	21(80.7 7%)	2(7.69 %)	0(0%)	26(100 %)
Dysponea	0(0%)	1(3.7%)	11(40.7 4%)	15(55.5 6%)	0(0%)	26(100 %)
Hematology	18(69.23 %)	6(23.08 %)	2(7.69 %)	0(0%)	0(0%)	26(100 %)

Acute Toxicities In 3rd Month

All most all pts. developed grade 5 dysphasia, grade 5dysponea, and grade 5 hematological toxicities at the end of 1st month of treatment whereas 17 pts did not show any hematological toxicities.

Table 10 ***Acute Toxicities In 3rd Month***

3rd month	No Toxicities	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Dysphagia	5(19.23%)	6(23.08 %)	14(53.8 5%)	1(3.85 %)	0(0%)	26(100 %)
Dysponea	0(0%)	4(15.44 %)	16(57.1 4%)	6(21.43 %)	0(0%)	26(100 %)
Hematology	17(65.38 %)	6(23.08 %)	3(11.54 %)	0(0%)	0(0%)	26(100 %)

Late Toxicities In 6th Month

At the end of 6th month of completion of treatment all most all pts had grade 5 dysphasia, dysponea, and hematological toxicities whereas 10 pts were shown recovered from dysphagia, 19 pts were recovered from hematological toxicities.

Table 11 ***Acute Toxicities In 3rd Month***

6th month	No Toxicities	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Dysphagia	10(38.46 %)	10(38.4 6%)	6(23.08 %)	0(0%)	0(0%)	26(100 %)
Dysponea	1(3.57%)	8(28.57 %)	15(60.7 1%)	2(7.14 %)	0(0%)	26(100 %)
Hematology	19(73.08 %)	6(23.08 %)	1(3.85 %)	0(0%)	0(0%)	26(100 %)

DISCUSSION

Worldwide, lung cancer is the most common cancer in both incidence and mortality leading to 1.35 million new cases and 1.18 million deaths annually i.e. the leading cause of cancer death in men (22.0%), i.e. about one in 5 of all cancer deaths). [1] Total number of cases in USA in 2018 was 234030, Male 121680 while female cases 112,350, it is the second most Commonly diagnosed cancer, with approximately 222,520 new diagnoses in year 2010, accounting for 105,770 female and 116,750 male patients; lung cancer is responsible for 28%3 of all cancer-related death each year (~160,000), more than all of breast, colorectal, and prostate cancers. [3] In India the cases of lung cancer are also increasing according to globocon. [2] Smoking is the leading cause of lung cancer. Association between cigarettes and lung cancer has been proven by large cohort studies. Tobacco use has been reported to be the main cause of 90% of male and 79% of female lung cancers. [7] 90% of deaths from lung cancer are estimated to be due to smoking. The risk of lung cancer development is 20-40 times higher in lifelong smokers compared to non-smokers. [8] Second-hand tobacco smoke is sometimes referred to as 'environmental' tobacco smoke. Carcinogens that occur in secondhand tobacco smoke include benzene, 1,3-butadiene, benzo[a]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others. The concentrations of respirable particles may be elevated substantially in enclosed spaces containing second-hand tobacco smoke. In a Surveillance Epidemiology and End Results (SEER) analysis involving all lung cancer histology, 15% of all cases of lung cancer were localized to the primary site at initial diagnosis; 22% had regional lymph node spread and 56% distant metastasis; and the remaining 7% were stage unknown. [9] In non–small cell lung cancer (NSCLC) about half the patients present with localized or locally advanced disease and half with advanced disease. In small cell lung cancer (SCLC), 20% to 30% present with locally advanced disease, and 70% to 80% present with advanced disease. Small- cell carcinoma's metastases were most commonly found in the liver (in more than 35% of individuals), followed by adrenal glands (nearly 20%), bone (17.6%), and CNS and myocardium (13.7% and 13.7%). [9] Radiation therapy is a clinical modality dealing with the use of ionizing radiations in the treatment of patients with malignant neoplasias (and occasionally benign diseases). [10] It plays a major role in cancer management in the effective palliation or prevention of symptoms of the disease. It has an important role in the management of approx 85% of patients with non small cell lung cancers. [11] It is the most common treatment modality in majority of patients in India as: – Majority of the patients present with hilar or mediastinal disease. – Disease bulk prevents the use of surgical techniques. – Surgical oncology facilities are not available widely. – Associated co morbidities and poor lung function make patients not suitable for surgery in early cases stage I - IIA the treatment of choice is surgery / stereotactic radio surgery or stereotactic ablative radiotherapy. In case from stage III –IV the treatment of choice is radiotherapy (CCRT) 60 Gy/30# or 66 Gy /33#.

Advantages of IMRT: - It produces more conformal dose distributions than standard 3DCRT. Dose distributions within the PTV can be more homogeneous and a sharper fall off within PTV is achieved so the volume of normal tissues exposed to high doses may be reduced significantly. IMRT plan produces more homogeneous dose distribution (dose conformality), multileaf collimator (MLC) present which helps in better dose deposition. [12] Large fields and boosts can be integrated into a single treatment plan, thus helps in delivering lower dose per fraction to normal tissues while delivering higher dose per fraction to the target volume. Higher dose per fraction also reduces the number of fractions and hence lowers the cost and burden to the patient for a treatment course. [13] A hyper fractionated course of radiotherapy is one in which more than one fraction is delivered each day but the overall treatment time remains similar to that for conventional fractionation. Typically, this means 1.2 to 1.3 Gy/fraction, two fractions a day, with an increase in total dose of the order of 20% to account for increased repair at the lower dose per fraction. The major rationale for hyperfractionation is to take full advantage of the difference in repair capacity of late reacting normal tissues compared with tumours. If conventional radiotherapy is not producing particularly good clinical results evident, hyperfractionation regimes can be delivered. Doses have to be delivered at about 1.2 to 1.3 Gy/fraction, two fractions a day. To treat with higher than 1.3 Gy/fraction at more than one fraction per day may exceed acute tolerance, and to use 65 years) with stage III NSCLC demonstrated that patients treated with chemo radiotherapy had a 4.4 months median survival benefit relative to radiotherapy alone.

CONCLUSION

This prospective observational study involves 27 histological proven, haematological stable cases carcinoma lung (Non-small cell lung cancer) was conducted during October 2017-December 2018 in the Department Of Radiotherapy, Pt. JNM Medical College and Regional

Cancer Center (RCC) Of Dr. BRAM Hospital Raipur. Fractionation schedule used for this study was 1.8Gy per #/ 2 daily doses/ 6 hrs apart/ 72 Gy in 6wks. Patients were assessed every week for acute toxicity. After completion of treatment patients were on follow up for 6 weeks to asses late toxicities with clinical assessment plus radiological imaging. We found non-small lung cancer is common among old people i.e. 44.44% were belonged to 50-60 years age group followed by 21.43% in 60- 70 year group,71% were males and rest 29% were females in our study which suggested that non-small cancer of lung is more common among men compare to women. According to site in our study we observed that the non-small lung cancer affected the right lung in 14 out of 27 patients (51.57%) while on left side it is 48.43%. 19.23% patients showed acute toxicity of grade 1 in pharynx and 57.69% of patients had dysponea as acute toxicities at the end of 1st week. 57.9% pts developed dysphasia of grade 2 whereas 38.46% showed dysphagia of grade 1,pharyngitis of grade 2 were seen in 53.85% patients and dysponea of grade 2 were observed in 14 pts at the end of 2nd week of treatment. At the end of 6th month of completion of treatment all most all pts had grade 5 dysphasia, dysponea, and hematological toxicities whereas 10 pts were shown recovered from dysphagia, 19 pts were recovered from hematological toxicities.

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