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Comparative Study of Different Dose Fraction Schedule of Palliative Thoracic Radiotherapy (10 Fractions of 3 Gray VS 5 Fractions of 4 Gray) for Carcinoma Lung Stage III and IV

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Abstract –

INTRODUCTION: Lung cancer is the world's most diagnosed cancer and kills around 1-2 million people per year. It is the fourth most frequently diagnosed cancer among females globally and the second most prevalent cause of mortality from cancer. Palliative thoracic radiation is an useful way to treat the symptoms. This palliative radiotherapy is also used to treat svc syndrome in carcinoma lung. The palliative radiotherapy schedule varies considerably in different centres. The purpose of above mentioned topic is to compare two palliative dose fraction (10 FRACTIONS OF 3GRAY VS 5FRACTIONS OF 4GRAY) in view of symptom relief, disease control, toxic effect.

MATERIALS AND METHODS: A total of 50 patients of locally advanced or metastatic carcinoma of lung taken for the study. All patients are histological proven cases of carcinoma lung. All (50) patients in study were divided in two equal arms- arm A & arm B. This arm A patients received 3Gy/fraction, 10 fractions from EBRT co60 over 2 weeks, and the arm B patients received 4Gy/fraction 5fractions from EBRT co60 over 1 week.

All the patients were treated in supine position and assessed for symptom relief on 1st day 4th day followed by last day of treatment 1st month 2nd month and 3rd month of starting of treatment. Also assessed for toxicity like skin reaction, pneumonitis, esophagitis.

The treatment stopped when the patient developed grade 4 skin reactions or pneumonitis or esophagitis. At the end of 1month post radiotherapy X ray chest were taken and compared the size of the mass with X ray taken before radiotherapy, based on that disease response to palliative radiotherapy were assessed and compared.

RESULTS: This Study population had median age at presentation of 65 years with a range of 30-89 years, median age of 65yrs for males and 55 years for females in both arms. Majority of patients were in 6th decade of life (48%) at presentation & 24% of the patients were having age less than 50 years. In the population studied male: female sex ratio was 11.5:1. In present study population, most of the patients were having multiple symptoms at presentation. Dyspnea (92% in arm A & arm B), Cough (92% in arm B & 88% in arm B) Chest pain (80% in arm A, 72% in arm B) & hemoptysis (40% in arm A & 44% in arm B) were most common presentation. On completion of treatment 52% patients in arm & 16% patients in arm B got symptom control for dyspnea, 28% patients in arm A & 24% patients in arm B got symptom control for cough, 52% patients in arm A & 20% patients in arm B got symptom control for chest pain, 16% patients in arm A & 8% patients in arm B got symptom control for hemoptysis. In this study toxicities like oesophagitis, pneumonitis, skin reaction were noticed. Skin reactions were more commonly noticed (28% in arm A & 52% in arm B) among toxicities, after that pneumonitis (24% in arm A & 40% in arm B) and esophagitis (8% in arm A & 20% in arm B). Toxicities are more with arm B than arm A. There is no

grade III and grade IV toxicities noticed in this study. There was no complete response of disease to radiation in both arms. Partial response noticed in 36% of patients in arm A & 20% of patients in arm B at the end of treatment (p value >0.05, non significant), progression of disease observed in both arms and it was noticed that disease progression is more seen in arm B than arm A.

CONCLUSION: The above study was performed for 50 patients and reached a conclusion that, 3Gy/fraction, 10 fractions regime provided better results in symptom relief and disease control with minimal radiation induced toxicity when compared to 4Gy/fraction, 5 fractions. This study shows non inferiority of 4Gy/fraction, 5 fractions as compared to the established 3 Gy/ fraction, 10 fractions regime, with good symptom response and acceptable toxicity.

Key Words – Ca Lung, Palliative Radiation Therapy.

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INTRODUCTION

Cancer constitutes an enormous burden on society in economically developed and developing countries alike. Increasing cancer occurrences due to the growing population and the increasing life expectancy of the population, an increased prevalence of established risk factors, such as smoking, overweight and physical inactivity, changing urbanisation reproductive patterns and economic development contribute also to the cancer burden1. By 2040, world burden of 27.5 million new cancer cases and 16.3 million cancer deaths are projected to increase solely because of population expansion and ageing. In economically transitional nations like India the future burden is probable to be much higher owing to increased prevalence of risk-enhancing variables such as smoking, healthy diets, physical inactivity and births2. The burden has moved over the years to less developed nations, now accounting for 57% of cases and 65% of cancer deaths globally. Lung cancer is the world's most diagnosed cancer and kills around 1-2 million people per year. It is the fourth most frequently diagnosed cancer among females globally and the second most prevalent cause of mortality from cancer. Among both women and men, the incidence of lung cancer is low in people aged <40 years and increases up to age 75–80 years in most populations. There are numerous risk factors implicated in the development of lung cancer. Among them, smoking is an important primary risk factor, accounting for 90% of cases in men and 70% in women. Although lung cancer can also arise in non-smokers, the overwhelming etiology for lung cancer remains in tobacco use. Amongst the many causes of lung cancer are

environmental factors, There are still significant individual variations in respiratory cancer susceptibility, increasing industrial air pollution from gases and dust, road asphalt, greater vehicle transport, World War I gas exposure, the 1918 influenza pandemic, and benzene or gasoline employment. Intra-thoracic primary tumour symptoms such as dyspnea, chest discomfort, cough and hemoptysis are typically present in locally progressed / metastatic lung carcinoms. The efficient method of treatment in alleviating the symptoms is Thoracic palliative therapy. This palliative radiotherapy is also used to treat svc syndrome in carcinoma lung. The purpose of this study is to compare two palliative dose fraction (10 FRACTIONS OF 3GRAY VS 5FRACTIONS OF 4GRAY) in view of symptom relief, disease control, toxic effect.

AIM AND OBJECTIVE:

- The primary aim is to evaluate management of symptoms with the use of two distinct palliative radiation regimes for patients with inoperatives, local progressed or metastatic lung cancers stage III and IV. (30Gy/10fractions vs 20Gy/5fractions).
- Secondary objective was to determine; toxicity profile, tumor control.

MATERIALS AND METHODS:

This research has been performed in the Department of Radiation, Regional Cancer Treatment and Research Institute Acharya Tulsi, Medical College Sardar Patel and the affiliated hospital group, Bikaner. A total of 50 individuals were received for the trial with advanced or metastatic lung cancer. All patients are histological proven cases of carcinoma lung with age >18yrs with ECOG performance status p1, p2, p3. Patients with associated other severe comorbid diseases, Previously treated with thoracic RT, any other concurrent malignancy, pregnant and lactating women were excluded from the study.

Methodology:, All (50) patients in study were divided in two equal arms- arm A & arm B. This arm A patients received 3Gy/fraction, 10 fractions from EBRT co60 over 2 weeks, and the arm B patients received 4Gy/fraction 5fractions from EBRT co60 over 1 week.

All the patients were treated in supine position and assessed for symptom relief on 1st day 4th day followed by last day of treatment 1st month 2nd month and 3rd month of starting of treatment. Also

assessed for toxicity like skin reaction, pneumonitis, esophagitis.

The treatment stopped when the patient developed grade 4 skin reactions or pneumonitis or esophagitis. At the end of 1month post radiotherapy X ray chest were taken and compared the size of the mass with X ray taken before radiotherapy, based on that disease response to palliative radiotherapy were assessed and compared.

OBSERVATION TABLES AND RESULTS:

AGE GROUP IN YEARS	ARM A	ARM B
30-39	1(4%)	0(0%)
40-49	2(8%)	3(12%)
50-59	7(28%)	6(24%)
60-69	12(48%)	12(48%)
70-79	5(20%)	2(8%)
80-89	0(0%)	1(4%)

SEX	ARM A	ARM B
MALE	23(92%)	23(92%)
FEMALE	2(8%)	2(8%)

This Study population had median age at presentation of 65 years with a range of 30-89 years, median age of 65yrs for males and 55 years for females in both arms. Majority of patients were in 6th decade of life (48%) at presentation and 24% of the patients were having age less than 50 years. In the population studied male: female sex ratio was 11.5:1

SYMPTOMS	ARM A	ARM B
DYSPNOEA	23(92%)	23(92%)
COUGH	23(92%)	22(88%)
CHEST PAIN	20(80%)	18(72%)
HEMOPTYSIS	10(40%)	11(44%)

In this study population four symptoms were taken for evaluation. Dyspnea (92% in arm A and arm B) and cough (92% in arm A, 88% in arm B) are most common symptoms. Other symptoms are chest pain (80% in arm A, 72% in arm B), hemoptysis (40% in arm A and 44% in arm B). In both arms symptoms are comparable.

SYMPTOM CONTROL (DYSPNOEA)	DAY1	DAY4	COMPLETION OFRT	1ST MONTH	2ND MONTH	3RD MONTH
ARM A	0(0%)	11(44%)	13(52%)	4(16%)	0(0%)	0(0%)
ARM B	0(0%)	11(44%)	4(16%)	2(8%)	0(0%)	0(0%)

SYMPTOM CONTROL (COUGH)	DAY1	DAY4	COMPLETION OFRT	1ST MONTH	2ND MONTH	3RD MONTH
ARM A	0(0%)	5(20%)	7(28%)	0(0%)	0(0%)	0(0%)
ARM B	0(0%)	14(56%)	6(24%)	0(0%)	0(0%)	0(0%)

SYMPTOM CONTROL (HEMOPTYSIS)	DAY1	DAY4	COMPLETIONOF RT	1ST MONTH	2ND MONTH	3RD MONTH
ARM A	0(0%)	3(12%)	4(16%)	0(0%)	0(0%)	0(0%)
ARM B	0(0%)	0(0%)	2(8%)	0(0%)	0(0%)	0(0%)

SYMPTOM CONTROL (CHEST PAIN)	DAY1	DAY4	COMPLETION OF RT	1ST MONTH	2ND MONTH	3RD MONTH
ARM A	0(0%)	4(16%)	11(52%)	2(8%)	0(0%)	0(0%)
ARM B	0(0%)	5(20%)	5(20%)	2(8%)	0(0%)	0(0%)

TOXICITY	GRADE	ARM A	ARM B
OESOPHAGITIS	I	1(4%)	2(8%)
	II	1(4%)	3(12%)
	III	0(0%)	0(0%)
	IV	0(0%)	0(0%)
PNUEMONITIS	I	3(12%)	4(16%)
	II	3(12%)	6(24%)
	III	0(0%)	0(0%)
	IV	0(0%)	0(%)
SKIN REACTION	I	3(12%)	4(16%)
	II	4(16%)	9(36%)
	III	0(0%)	0(0%)
	IV	0(0%)	0(0%)

Toxicity more seen in ARM B than ARM A, Most common toxicity is skin reaction followed by pneumonitis and esophagitis. There is no grade III grade IV toxicity in both arms.

DISEASE CONTROL	ARM A				ARM B			
	CR	PR	PD	SD	CR	PR	PD	SD
END OF TREATMENT	0(0%)	9(36%)	0(0%)	16(64%)	0(0%)	5(20%)	1(4%)	19(76%)
1 MONTH OF F/U	0(0%)	9(36%)	0(0%)	15(60%)	0(0%)	5(20%)	2(8%)	16(64%)
2 MONTH OF F/U	0(0%)	9(36%)	2(8%)	10(40%)	0(0%)	5(20%)	4(16%)	11(44%)
3 MONTH OF F/U	0(0%)	9(36%)	3(12%)	6(24%)	0(0%)	5(20%)	5(20%)	6(24%)

In both arms there is no complete response(CR). Partial response more with arm A (36%) than arm B (20%). Disease progression is seen in both arms during 2nd and 3rd month follow up. PD more in arm B on follow up.

(X2 = 1.58, P value = 0.208, non significant).

DISCUSSION:

Lung cancer is a global illness that is avoidable and although its prevalence in the rich world is declining, there is an epidemic in the developing nations of unnarrative proportions. The largest series from Indian population reported by *jindal and Behera* had a median age of 54.6yrs for males and 52.8 years for females with a male: female sex ratio of 5.6:1. Literature reports development of lung cancer in later decades of life with less than 11% population below the age of 40 years. *Buccheri et al.* states that lung cancer usually presents with multiple symptoms which can be constitutional or respiratory. In present study population, most of the patients were having multiple symptoms at presentation. This reflects diverse interaction of disease both locally and systematically to manifest clinically. Review of literature on symptomatology highlights diverse symptomatic presentation of lung cancer. Cough, chest pain, weight loss, dyspnea, hemoptysis were most common presentations and rare ones were stridor, change in voice, dysphagia, fatigue, anorexia, pain in other body parts. Study conducted regarding symptoms response, prognostic factors influencing the response of superior vena caval obstruction and related survival outcomes in advanced non small cell lung cancer by *H N Lee,*

M.S Tiwana, S.Saini, S.K Verma, N Jain, M. Gupta(STM Cancer institute Dehradun India), 250 patients were taken for study and divided into groups, for this 61% patients was prescribed 4Gy/fraction schedule for RT plan of 20Gy in 5fractionsand remaining 39% received 3Gy/fraction for a planned schedule of 30Gy in 10fractions. After the prescribed dose got completed, follow up analysis started and compared dose regimes based on symptom relief, toxicity and disease status, and concluded that RT fraction >3Gy/day have shown better results than conventional fractions. *E Senkus-Konefka,1, R Dziadziuszko1, E Bednaruk-Młyn´ ski1, A Pliszka1, J Kubrak2, A Lewandowska3, K Małachowski4, M Wierzchowski5, M Matecka-Nowak6 and J* Jassem1 conducted a study100 20 Gy/5 (fr)/5 days (arm A) or 16 Gy/2 Fr/day 1 and 8 patients have been allocated randomly (arm B). There were 90 men and 10 women aged 47–81 years (mean 66), performance status 1–4 (median 2). In all groups the main clinical features and frequency and extent of symptoms associated with early illness were comparable. Treatment tolerance was good and did not differ between study arms. The level of alleviation of all analysed symptoms was not shown to have significant variations across arms of the research. The total survival duration for bra B varied substantially (mean 8.0 versus 5.3 months; P = 0.016). Both irradiation regimens were similar and beneficial for tumor-related symptoms to be palliated. The improved overall survival and treatment convenience of 2-fraction schedule suggest its usefulness in the routine management of symptomatic inoperable NSCLC. *N.A. Eldeeb a, A.M. Bela a, A.A. Eganady b.A.S. Radwan* The prospective clinical research included 30 patients allocated randomly in two groups; group (A) 15 patients received 10 fractions of Gy 3 over 2 weeks of RT at a total dose of 30 Gy; and group (B) 15 patients received two fractions of Gy 1 and 8 at a total dose of 17 Gy. RT was allocated at two groups. And the outcome has been as well The hypo-fragmented RT protocol for this research was as efficient in palliating intrathoracic symptoms, tolerance to therapy, HRQOL and overall survival as the prolonged regimen. In our study, on completion of treatment 52% patients in arm A &16% patients in arm B got symptom control for dyspnea, 28% patients in arm A & 24% patients in arm B got symptom control for cough, 52% patients in arm A & 20% patients in arm B got symptom control for chest pain, 16% patients in arm A & 8% patients in arm B got symptom control for hemoptysis. In this study toxicities like oesophagitis, pneumonitis, skin reaction were noticed. Skin reactions were more commonly noticed (28% in arm A & 52% in arm B) among toxicities, after that pneumonitis (24% in arm A & 40% in arm B) and esophagitis (8% in arm A & 20% in arm B). There is no grade III and grade IV toxicities noticed in this study. In arm A, skin reaction is more common (grade II 16% & grade I 12%) after that pneumonitis (grade I & II 12% each), oesophagitis (4% in grade I & grade II). In arm B Skin reactions are more common toxicity (16% grade I & 36% grade II), after that pneumonitis (16% grade I & 24% grade II), oesophagitis (8% grade I & 12% grade II).

Toxicities are more with arm B than arm A. Grade II toxicities are more in arm B than grade I toxicities. In this study response of disease to radiation treatment was analysed by imaging technique (x ray chest) during the end of treatment, during follow up 1stmonth , 2nd month, 3rd month of treatment. There was no complete response of disease to radiation in both arms. Partial response noticed in 36% of patients in arm A and 20% of patients in arm B, progression of disease observed in both arms and it was noticed that disease progression is more seen in arm B than arm A. During 1st month of follow up 4% of patients in arm B developed progression of disease and in arm A no progression of disease. In 2nd month of follow up 16% of patients in arm B developed disease progression and in arm A 8% patients develop disease progression. In 3rd month of follow up arm B observed with more progression of disease than arm A (12% in arm A and 20% in arm B), also it was observed that stable disease is more seen with arm A than arm B. In this study based on Yale's grading svc symptoms were compared in both arms, here it was observed that rapid relief noticed with arm B than arm A and it was noticed that reappearance of symptoms noticed more with arm B than arm A. It was observed that 16 patients expired during the study period. 7 patients expired in arm A and 9 patients expired in arm B.

So in this study based on symptom relief, disease response, toxicity it was observed that arm A is better treatment regime than arm B.

X ray imaging during follow up for disease response evaluation and smaller number of patients remains the major limitations of this study. Here we can overcome these problems by using CECT thorax instead of x ray imaging for follow up, So that accurate evaluation of disease status will possible and we have to take large number of patients for study.

CONCLUSION

This single institute comparative study evaluated and compared two dose fraction regimes of palliative thoracic radiotherapy for carcinoma lung stage III & IV.

The study was performed for 50 patients and reached a conclusion that, 3Gy/fraction, 10 fractions regime provided better results in symptom relief and disease control with minimal radiation induced toxicity when compared to 4Gy/fraction, 5 fractions. This study shows non inferiority of 4Gy/fraction, 5 fractions as compared to the established 3 Gy/ fraction, 10 fractions regime, with good symptom response and acceptable toxicity. Longer follow up and more number of patients will go a long way to

establish this study arm as a standard palliative treatment regime.

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