ASSESSMENT AND COMPARISON OF QUALITY OF LIFE AND SYMPTOM RELIEF IN PATIENT OF INOPERABLE NON-METASTATIC NON SMALL CELL LUNG CANCER UNDERGOING DIFFERENT PALLIATIVE RADIATION THERAPY.

General Medicine

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ABSTRACT

Lung cancer incidence in Indian men is 54000, with mortality at 49000 and in females at much less 17000 with mortality at 15,000. The aim of our study is Health related QoL changes: By using EORTC Quality of Life Questionnaire (QLQ)-C30 and QLQ-LC13. All histology proven patients of locally advanced NSCLC attending Department of Radiotherapy, R.G.Kar Medical College & Hospital during study period from January, 2017 to July 2018. Patient with poor performance status and inoperable NSCLC causing pulmonary symptoms, hypofractionated, involved field radiotherapy 8.5 Gy in two fractions offer acceptable palliation with minimal toxicity. A clear advantage of the very short hypofractionated regimen is that it enable patients with a short expected survival time to spend more of their remaining time away from their hospital. Palliative radiotherapy plays an important role of palliation of symptomatic intrathoracic disease and in preservation of health related quality of life (HRQOL) in patients who have limited expected survival time and/or intolerance to combined chemotherapy and radical radiotherapy regimen.

KEYWORDS

Quality Of Life , Non-Metastatic Non Small Cell Lung Cancer , Palliative Radiation Therapy.

INTRODUCTION

Cancers remains one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012.^{1,2}

Lung cancer scenario in India compared to the western population is increasing contributed by rampant tobacco intake and ever increasing air pollution. According to Globocan 2012, lung cancer incidence in Indian men is 54000, with mortality at 49000 and in females at much less 17000 with mortality at 15,000.³ According to the Indian Council of Medical Research cancer registry, 57,795 new cases were reported in 2010, which is projected to rise up to 67,000 new cases annually by the year 2020.⁴

The mean age according to Globocan 2012 is 54.6 years. The male female ratio increased progressively upto 51-60 years and then remained same. The smoker to non-smoker ratio is high up to 20:1 in various studies. Upto 40 years of age small cell type predominates and has less association with smoking. After the age of 40 years squamous cell type is commonest in smokers and adenocarcinoma in non-smokers.³

The causes for lung cancer are basically divided into smoking and non-smoking.² While active smoking in forms of beedi, hookah, cigarette use accounts for majority of the disease, the Global Adult Tobacco Survey (GATS) India, showed that 52% of the adults (rural-58%, urban-39%) were exposed to more passive second hand smoking at home. the other potential causes are asbestosis, occupational exposures to carcinogens in iron and steel industry, scar tissue formation by infections like Chlamydia pneumoniae or tuberculosis, and dietary deficiencies.

Staging of NSCLC is done by the American Joint Committee on Cancer (AJCC)(7th edition) TNM staging as proposed by Goldstraw et al in 2007 on the IASLC Lung Cancer Staging Project and adapted in 2010.⁵ Recently 8th edition of TNM classification of lung cancer has been published (2017). In our study we used AJCC 7th Edition staging.

In the past, radiotherapy was considered the standard therapy in IIIA and IIIB but demonstrated very low survival, poor local control and

early development of distant disease. Patients with inoperable stage III treated only with thoracic radiotherapy experienced a median survival of 9-11 months, 2-year survival of 10-20% and 3-year survival of 5-10%.⁶ Concurrent chemoradiotherapy remains the standard care for nonsurgical treatment of stage III NSCLC with good performance status. Although radiation dose escalation/acceleration in locally advanced NSCLC, 60 to 66 Gy with concurrent chemotherapy remains the standard regimen in community setting. Sequential CT-RT have been tried and compared with concurrent CT-RT in RTOG 9410 trial which was a 3-arm randomized trial comparing sequential (SEQ) chemotherapy followed by RT (once daily, total dose 63 Gy) with 2 different concurrent chemoradiotherapy regimens. The latter consisted of either concurrent once daily RT, total dose 63 Gy (CON-QD), or concurrent twice-daily RT, total dose 69.6 Gy (CON-BID). The SEQ and CON-QD arms each included 2 cycles of cisplatin and vinblastine. The CON-BID used 2 cycles of cisplatin and VP-16 based on the experience in RTOG 9204. Acute toxicity was worst in the CON-BID arm. Although time to in-field progression was best in the CON-BID arm, this did not translate into a survival benefit. The best survival times were in the CON-QD arm, which were significantly better than in the SEQ arm (P=.046). Median survival times in the 3 arms were 14.6 months (SEQ), 17 months (CON-QD), and 15.2 months (CON-BID).⁷

(1) Primary aim (symptom control)

The QLQ-LC13 module contains items for measuring dyspnoea, cough, haemoptysis, mucositis, dysphagia, peripheral neuropathy, alopecia, pain, and analgesic consumption or effect. Mean scores for cough, haemoptysis, dyspnoea, and chest pain was taken at base line, 1, 6 and 16 weeks after the end of RT. All these symptoms were linearly transformed to a scale from 0 to 100, with a higher score on the scale indicating a high degree of symptoms.

(2) For Secondary aims

- Health related QoL changes: By using EORTC Quality of Life Questionnaire (QLQ)-C30 and QLQ-LC13.
- Tumor control: CT chest scans to assess the tumor response within the RT fields were obtained at 6 weeks and/or 4 months after RT. (These were categorized into five radiographic responses: complete response, partial response (tumor regression >50%), stable disease (no change in lesion size or <25% increase or decrease), and progressive disease (growth in irradiated volume of >25%).

MATERIAL AND METHOD

- Definition of population:** All histology proven patients of locally advanced NSCLC attending Department of Radiotherapy, R.G.Kar Medical College & Hospital during study period from January, 2017 to July 2018.

Inclusion criteria of the eligible patients were:

- Histologically or cytologically confirmed non-metastatic NSCLC
- Aged over 18 -70 years.
- Eastern Cooperative Oncology Group (ECOG) Performance status (PS) 2-3.
- Expected survival more than 3 months.
- Patients had intra-thoracic symptoms.
- No history of previous Thoracic RT.

Study procedure:

- Patients so recruited in the study was randomized into 2 study arms for thoracic radiotherapy (TRT). TRT was administered with parallel opposed AP/PA fields encompassing the primary tumor with 1.5-2 cm margin using Co⁶⁰ isotope in THERATRON 780 E External beam Cobalt machine, mean energy 1.25MeV. Mediastinal and supraclavicular region was not routinely included in the portals unless enlarged node caused symptoms. Fractionated Radiotherapy schedules were as follows: Arm A: 17 Gy in 2 fractions in one week apart – Experimental arm. Arm B: 20 Gy in 5 fractions in one week –Control arm

- Arm A: 17 Gy in 2 fractions in one week apart – Experimental arm.
- Arm B: 20 Gy in 5 fractions in one week –Control arm.
- The option of addition of chemotherapy oral or i.v in sequential manner with TRT was depend on assessment of patients in the post RT period and the subset analysis was done based on CT protocol.
- Schedule of data collection:** Study design proforma making data collection –statistical analysis.
- Symptom palliation** was assessed by EORTC QLQ-C30 & EORTC QLQ-Lc13

STATISTICAL ANALYSIS PLAN:

Statistical analysis was done using SPSS version 17. The categorical data was summarized as percentages and compared using Chi Square test while for continuous data, Independent t test was for comparison of mean $\pm$ s.d. All tests was two tailed with p value < 0.05 as significant. Overall Survival was measured from the date of inclusion in study to the date of last visit or lost to follow up or death due to same cancer. The OS was determined using the Kaplan Meier survival analysis with Log Rank test for comparing the DFS.

RESULT AND ANALYSIS

Total 100 patients are evaluated for eligibility for the study. They were randomised into two arms. For Arm A patients (experimental arm) 17 Gy in 2 fractions in one week apart was administered. Arm B patients (control arm) 20 Gy in 5 fractions in one week was administered.

Baseline profiles of the patients in the Arms were comparable in terms of age distribution, sex distribution, pre-treatment performance status, tumor(T) status, nodal(N) status and histology.

Comparison of demographic profiles among different treatment arms showed no statistically significant difference [p value>0.05].

The male patients accounted for 84% in arm A and 74% in arm B. The female patients accounted for 16% in arm A and 26% in arm B. So, in both arm sex distribution is comparable. (p value-0.22).

Median age of the patient population is around 50. ECOG performance status was comparable in both the arms (p value-0.407)

Occupation was comparable in both groups (p value-0.523). Smoking and Tobacco intake are comparable in both groups but pack years of smoking are statistically different in both groups.

CONSIDERATIONS MADE DURING CALCULATIONS OF SCORES.

- During the calculations for LC 13, all patients informed that they had taken analgesics like NSAIDS alone with or without tramadol, often without valid prescriptions and none had pain relief as per

their assessment at the time of recruitment in the study.

- Following the guidelines of scoring manual for LC 13, 70% patients had no access to staircases in home, so for dyspnoea calculations used items 33 and 34 separately and omitted item 35 for all individuals.
- The sequence of treatment included chemotherapy usually 6 cycles followed by radiation in 90% of patients. Our study was not entitled to compare the response rate and adverse events between different chemotherapy regimens. Randomizations into 2 study arms were done at the time of recruitment.
- 19 patients in arm A and 18 patients in arm B had features of SVCO for which palliative EBRT was started prior to initiation of chemotherapy.
- 10 patients had complaints of severe hemoptysis for which EBRT had to started early. Of these 10 individuals, 4 had SVCO symptoms requiring immediate EBRT. For other patients EBRT was started after completion of chemotherapy.
- Our assessments were essentially based on baseline values i.e prior to starting of EBRT and thereafter at 6 weeks and 4 months. LC 13 and QOL scores were influenced in patients who received sequential chemotherapy and this remains a drawback for our study.

By using repeated measures analysis of General Linear Model (GLM), Greenhouse – Geisser was not statistically different, F (1.000, 98) = 0.162, p value 0.688.

- HEMOPTYSIS (Item 32 of LC 13)

All patients had complained of hemoptysis, from scanty to frank severe hemoptysis, which one of presenting symptoms for consulting physicians.

Adverse events

- None of patients during the course of EBRT and 4 months follow-up had anemia. Similarly none had neutropenia or thrombocytopenia during the three observations.
- Esophagitis were comparable in both arms. 6 patients in Arm A had grade 3 esophagitis against 7 patients in Arm B. 5 patients in arm A against 8 individuals in arm B had grade 2 esophagitis.
- Skin adverse events were less reported in both arms, with 5 individuals in arm A against 7 in arm B reporting grade 1 adverse events.
- Radiation induced pneumonitis features were not evident in any individual.

PROGRESSION FREE SURVIVAL (months)

Our intent of treatment was essentially palliative. Progression free survival was calculated from recruitment in study till disease progression locally and/or with distant metastasis. Patients who had stable disease or disease progression were started on second line chemotherapy and palliative non thoracic metastatic site irradiation.

DISCUSSION

Lung cancer is one of the most common malignancies worldwide. Analysis of data from 22 cancer registries in 5 continents revealed that cumulative lung cancer risk was higher in males than in female³. Approximately 80% of non-small cell lung cancer (NSCLC) in male are directly attributable to cigarette smoking. Smoking is present 42% of patients in Arm A against 48% in arm B. Pack year of smoking; median value 30 years in Arm A and 37.5 years in Arm B respectively. These features was also encountered in our study population.

Majority of patients was early fifty. Median age in arm A was 57 years and arm B was 51 years.

I have selected this (17 Gy in 2 fractions one week apart) palliative radiotherapy regime for inoperable nonmetastatic NSCLC from hospotal point of view due to logistic purpose and from patient point of view due to low socioeconomic status.

In our study, majority of patients were male, 84 % in arm A and 74% in arm B. Majority of Indian studies show male preponderance due to smoking and tobacco intake in any form. ECOG status 2&3 in majority of the patients.

According to occupation, we have divided the patients in labour and service group. However better discrepency was observed depending on type of work done. Industry related factor may be

predisposing to lung carcinoma. In our study labour class in Arm A 70%, in Arm B 64% and service class in Arm A 30% & in Arm B 36%. Both Arm are comparable (p value-0.523).

In our study patient with lower socioeconomic status was 70% in Arm A & 66% in Arm B and with upper socioeconomic status 30% in arm A and 34% in Arm B. (p value-0.668).

In our study two types of lung carcinoma had been encountered i.e. adenocarcinoma & squamous cell carcinoma. Adenocarcinoma in Arm A was 58% and in Arm B 52%. Squamous cell carcinoma in Arm A was 42% and in Arm B 48%. Among these, Moderately differentiated carcinoma was 40% in Arm A & 22% in Arm B. Poorly differentiated was in Arm A 28% & 36% in Arm B. Well differentiated was 32% in Arm A & was 42% in Arm B. Tumor invasion (p value-0.51) & nodal involvement (p value-0.138) in both Arms is comparable. In our study most common drugs used in adenocarcinoma were Gem/Carbo, Pacli/carbo, Pem/Cis, Pem/Carbo. In squamous cell carcinoma were Gem/carbo & Doce/Carbo. This sequence of treatment included chemotherapy usually 6 cycles followed by radiation in 90% of patients.

All of the patients had presented with shortness of breath and 66% of the patients in both arms were relieved. Palliation of Haemoptysis occurred in 82% in arm A and 80% in Arm B, cough was relieved in 54% in arm A and 72% in Arm B, chest pain relieved in 70.3% in Arm A and 53.1% in Arm B, anorexia was relieved in 64% in Arm A and 60% in Arm B, SVCO was relieved in 57.9% in Arm A and 61.1% in Arm B.

Response after completion of treatment was assessed by RECISTv 1.1 criteria. Complete response was 26% in Arm A and 22% in Arm B.

None of patients during the course of EBRT and 4 months follow-up had anemia. Similarly none had neutropenia or thrombocytopenia during the three observations. Esophagitis were comparable in both arms. 6 patients in Arm A had grade 3 Esophagitis against 7 patients in Arm B. 5 patients in arm A against 8 individuals in arm B had grade 2. 4 patients in each arm had grade 1 adverse events. None developed grade 4 adverse events. Skin adverse events were less reported in both arms, with 5 individuals in arm A against 7 in arm B reporting grade 1 adverse events. Radiation induced pneumonitis features were not evident in any individual.

Our intent of treatment was essentially palliative. Progression free survival was calculated from recruitment in study till disease progression locally and/or with distant metastases. Patients who had stable disease or disease progression were started on second line chemotherapy and palliative non thoracic metastatic site irradiation.

CONCLUSION

Patient with poor performance status and inoperable NSCLC causing pulmonary symptoms, hypofractionated, involved field radiotherapy 8.5 Gy in two fractions offer acceptable palliation with minimal toxicity. A clear advantage of the very short hypofractionated regimen is that it enable patients with a short expected survival time to spend more of their remaining time away from their hospital.

Palliative radiotherapy plays an important role of palliation of symptomatic intrathoracic disease and in preservation of health related quality of life (HRQOL) in patients who have limited expected survival time and/or intolerance to combined chemotherapy and radical radiotherapy regimen.

REFERENCE

1. LUNG CANCER IN INDIA -D Behera, New Delhi, Vol. 22, Medicine Update 2012, 401-407.
2. World Cancer Report 2018.
3. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. In Lung cancer and personalized medicine 2016 (pp. 1-19). Springer, Cham.
4. Mala R, Celsia AR, Devi SM, Geerthika S. Comparison on Bactericidal and Cytotoxic Effect of Silver Nanoparticles Synthesized by Different Methods. In IOP Conference Series: Mate. Sci. Eng 2017 Aug (Vol. 225, No. 1, p. 012155).
5. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. Journal of thoracic oncology 2007;2:706-14.
6. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(19):1452-60.
7. Chang JY, Kestin LL, Barriger RB, Chetty JJ, Ginsburg ME, Kumar S, Loo Jr BW, Movsas B, Rimner A, Rosenzweig KE, Stinchcombe TE. ACR Appropriateness

Criteria® Nonsurgical Treatment for Locally Advanced Non-Small-Cell Lung Cancer: Good Performance Status/Definitive Intent. Oncology. 2014 Aug 15;28(8).
 8. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Global Oncology. 2020 Jul;6:1063-75.