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Original article:

Neoadjuvant chemotherapy followed by conformal radiotherapy VS chemoradiation in locally advanced squamous cell carcinoma of lung- original study from a tertiary care center

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Abstract

Background- Lung cancer is the most common malignant disease in the world. Our study aimed at observing the management of inoperable locally advanced squamous cell carcinoma of lung subsequent to neoadjuvant chemotherapy followed by conformal radiotherapy versus chemoradiation.

Method- The present study is a prospective, comparative, randomized, double arm study to compare and evaluate the local response, toxicities, overall survival and disease-free survival between the two arms subsequent to neoadjuvant chemotherapy in inoperable locally advanced squamous cell lung cancer. Patients completing neoadjuvant chemotherapy with complete and partial responders were asked to pick up randomly sealed envelopes containing chits of arm A and arm B. The study was conducted at Kamala Nehru Memorial Hospital - Regional Cancer Center from 2011-2013.

Results- Our study showed significant down staging with neoadjuvant chemotherapy in which 50 out of 64 patients showed significant decrease in the size of the mass thereby decreasing the field of radiation and greater improvement of symptoms. The toxicities in the chemoradiation arm was slightly increased. The disease-free survival and overall survival at 6 months and 1 year were greater in the chemoradiation arm vs radiotherapy only but a larger sample size is necessary for statistical significance.

Conclusion- Management of locally advanced lung cancer is quite challenging more so ever as patients are debilitated with compromised respiratory function. This study definitely showed down-staging in inoperable locally advanced lung cancer. However, a long term study could get conclusive results.

Keywords- Cancer, Chemotherapy, Toxicity, Radiotherapy

Introduction

Worldwide, lung cancer is the most common malignant disease in males and, given the overall increase in tobacco consumption in densely populated regions, this may also be in case in women in the coming years. Over 1 million people die from lung cancer each year and without effective prevention, the lung cancer burden is projected to increase to 2.2 million new cases per annum by 2030.[1] The main types of lung cancer are small-cell lung cancer (SCLC), also called oat cell cancer, and non-small-cell lung cancer (NSCLC). Treatment and prognosis depend on the histological type of cancer, the stage(degree of spread), and the patient's general wellbeing, measured by performance status. Common treatments include, surgery, chemotherapy, radiation therapy and palliative care. If

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investigations confirm lung cancer, CT scan and often positron emission tomography (PET) are used to determine whether the disease is localized and amenable to surgery or whether it has spread to the point where it cannot be cured surgically. Radiation therapy forms an important part of the treatment aspect in NSCLC specially in inoperable patients. Radiation therapy is given with Curative or palliative intent and as adjuvant treatment after surgery where ever indicated. The Radiation therapy techniques have improved anonymously over the last few decades. The 2-D Radiation therapy has been replaced by 4-D Radiation therapy. Conformal radiotherapy permits better adaptation of the dosimetric distribution to the tumour volume, reduction of healthy organs exposure, and on the long term, higher dose of tumour irradiation. Chemotherapy has an increasing role with radiation and can be used in neoadjuvant, adjuvant and concurrent settings.

Materials and Methods

The present study has been conducted in the Department of Radiation Oncology, Kamala Nehru Memorial Hospital, Regional Cancer Centre (RCC), Allahabad, Uttar Pradesh. The study was conducted from May 2011 to May 2013 and patients were assessed with the follow up of minimum 6months. The present study is a ***prospective, comparative, randomized, double arm study*** to compare and evaluate the local response, toxicities, overall survival and disease-free survival between the two arms subsequent to neoadjuvant chemotherapy in inoperable locally advanced squamous cell lung cancer. Patients completing neoadjuvant chemotherapy with complete and partial responders were asked to pick up randomly sealed envelopes containing chits of arm A and arm B. Accordingly patients were enrolled in the respective study arm.

1. **Inclusion Criteria in present study :**

- Squamous cell lung carcinoma.
- Stage IIIA and IIIB,
- Complete and partial responders to neoadjuvant chemotherapy
- Patients with $T_{1\text{-}3}\,N_2$ disease if medically inoperable
- Patient age $\geq$ 18 years.
- Karnofsky performance status (KPS) $\geq$ 70%.
- Weight loss $\leq$ 10% in the 3 months before diagnosis.
- No prior systemic chemotherapy.
- No prior radiation therapy to the thorax or total surgical resection.
- Granulocyte count $\geq$ 2,000/mL.
- Platelet count $\geq$ 100,000/mL.
- Hemoglobin more than 8 mg/dL.
- Bilirubin less than 1.5mg normal.
- Creatinine clearance more than 50 mL/min.

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2. **Exclusion Criteria:**

- Age > 80 years.
- Histology other than squamous cell carcinoma
- No responders to neoadjuvant chemotherapy
- Patients having progressive disease during neoadjuvant chemotherapy
- Stage I & II Lung Cancers
- T1N0, T2N0, T3N0 tumours
- Patients with active concurrent malignancy, serious medical or psychiatric illness, or history of serious cardiac disease.
- Prior radiation therapy to the thorax or total surgical resection.
- Prior systemic chemotherapy.
- Metastatic lung cancer

Basic Protocol

Inoperable locally advanced squamous cell carcinoma of the lung subsequent to neoadjuvant chemotherapy (Inj. Paclitaxel 175mg/m^2 IV day-1 q 3 weekly × 3 Cycles + Inj. Carboplatin AUC 6 Day-2,3 weekly × 3 Cycles). Categorical data was analyzed using Pearson's Chi square test.

Radiotherapy Technique

Pre-treatment planning: Patients for radiotherapy are planned up for a pre-treatment CT scanning in the treatment position for planning the target volumes and selection of the portals. Based on the location of the primary tumor and the area of lymphatic drainage in the hilar region mediastinum, the volume to the treated and the radiation portal arrangement is determined. A margin of 1 to 2cm on the gross tumor and a minimum margin of 1cm around electively treated regional lymph node were determined.

Design of portals were determined with type of tumor its location and stage. If the tumor is located at the upper lobe, supraclavicular region is included with inferior margin 5cm below the carina. If the primary tumor is located in the middle or lower lobe and mediastinal nodes are involved then supraclavicular node are included in the treatment portals. If mediastinal nodes are not involved in the CT scan then supraclavicular regions are excluded from the treatment portals. In locally advanced lung cancers entire mediastinum has been included in the treatment portals.

Treatment portals and dose prescription: Once the target volume is determined, antero-posterior and postero-anterior portals with parallel opposing field are used, and a dose of 40Gy in 4 weeks in 20 fractions were delivered, calculating the dose at the midline. Adequate precautions were taken to overcoming the mediastinal edema with steroids and antibiotics whenever secondary infection was suspected. Adequate food and fluid intake ensured with nutritional supplements, nasogastric feeding or intravenous fluid supplements whenever required.

Conformal boost therapy: A repeat CT scan planning will be done after completion of 40Gy (20fr in 4weeks) for conformal boost therapy. The residual tumor i.e. both primary and nodal region were delineated on the treatment planning system along with the mediastinal structures including cardiac region, normal lung parenchyma and spinal

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cord. A conformal treatment was planned with varying portals either oblique portals, wedge field or conformal portals with the use of micro leaf collimators depending on the site of the tumor.

Dose up to 60Gy in 6 weeks in 30 fractions delivered after sparing the critical structures. Adequate beam energy was chosen depending on the site of tumor.

ARM-B: Radiotherapy technique and dose will be delivered in same manner as in ARM-A concurrently with chemotherapy (inj. Carboplatin AUC 2 weekly × 6, was given on Saturdays).

Results

In the present study of two years, 465 patients of lung cancer patients male and female of various age groups were registered in Regional Cancer Center, Kamala Nehru memorial hospital. Out of which 195 patients were proved as squamous cell carcinoma, Adenocarcinoma, Small cell carcinoma and other histology Among 195 squamous cell carcinoma patients, 120 patients were inoperable but only 64 patients were eligible for study as per inclusion/exclusion criteria, which were included in our present study.

Age-

In our study, no patient was found under age of 40; 17% between 41to 50 years; 56% between 51 and 60 years; 24% between 61 and 70 years; 6% were in more than 70 years of age. The median age in our study was found 58 years. Treatment given to the patient did not depend upon the age distribution as per statistical data.

2.Stage

In present study stage IIIA patients were 18 (28 %) and stage III B were 46 (72%) at the time of presentation.

3. **Neoadjuvant chemotherapy and response-**

In the present study out of 64 patients, 56 patients (87.5%) had completed 3 cycles of NACT, 4 patients (6.5%) not tolerated NACT, 2 patients (3%) lost during NACT and 2 patients (3%) died. Chemotherapy induced nausea and vomiting was the frequent complaint during neoadjuvant chemotherapy and was in acceptable limits. In the present study out of 56 patients who completed NACT, 4 (7.1%) patients showed complete response, 46 (82.1%) patients showed partial response and 6 (10.7%) patients had progressive/ no response disease. The table below explains the above data.

Response	**No. of patients**	**Percentage**
Complete response	4	7.1
Partial response	46	82.1
No response / Progressive disease	6	10.7

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4. **Results post randomization**

A. **Toxicity –** The toxicity was assessed regularly at weekly intervals using the RTOG toxicity Scales. The toxicity table provided below was seen at the end of treatment at approximately 6weeks.

Organ Tissue	**Grade**	**Arm A (60Gy/30 Fr)**	**Arm B (60Gy/30 Fr)**	**Total (n = 50)**
Skin Reactions	I	8 (32%)	5 (20%)	13 (26%)
	II	8 (32%)	9 (36%)	17 (34%)
	III	5 (20%)	7 (28%)	12 (24%)
	IV	1 (4%)	4 (16%)	5 (10%)
Mucositis	I	8 (32%)	6 (24%)	14 (28%)
	II	7 (28%)	9 (36%)	16 (32%)
	III	5 (20%)	6 (24%)	11 (22%)
	IV	0	3 (12%)	3 (6%)
Pharyngitis and Esophagitis	I	6 (12%)	9 (36%)	15 (26%)
	II	3 (12%)	5 (20%)	8 (16%)
	III	4 (16%)	6 (24%)	10 (20%)
	IV	1 (4%)	2 (8%)	3 (6%)
Haematological complications	I	5 (20%)	9 (36%)	13 (26%)
	II	5 (20%)	7 (28%)	12 (24%)
	III	2 (8%)	3 (12%)	5 (8%)
	IV	0	1 (4%)	1 (2%)

At the end of 6th week of radiation acute toxicities like skin reactions, mucositis, pharyngitis / esophagitis and hematological complications are slightly more in ARM B (chemoradiation) than ARM A (radiotherapy alone). The overall results of the weekly assessment were also similar and statistically significant.

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B. **Late Radiation Toxicity-** Late radiation toxicities like pulmonary pneumonitis, pulmonary fibrosis, carditis, pericarditis, esophagitis bone pain, myelitis were assessed clinically and diagnostically at 6 months and results were statistically comparable between both the groups.

Organ Tissue	**RTOG Grading**	**ARM- A** No. of Pts (%)	**ARM-B** No. of Pts (%)
Skin	Grade I	-	1
	Grade II	-	-
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Mucous Membrane	Grade I	-	-
	Grade II	-	-
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Spinal cord	Grade I	-	-
	Grade II	-	-
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Lung	Grade I	2	3
	Grade II	1	2
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Heart	Grade I	1	1
	Grade II	-	1
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Oesophagus	Grade I	2	2
	Grade II	-	1

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	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-
Bone	Grade I	-	-
	Grade II	1	1
	Grade III	-	-
	Grade IV	-	-
	Grade V	-	-

C. **Disease free survival, overall survival at 6 months and 1 year-** At 12th month of follow up local control, disease free survival, overall survival, found in ARM A vs ARM B was 24% vs 32%, 12% vs 20%, 56% vs 68% respectively. However the Chi square p value was 0.817 and was statistically insignificant. The need for a larger sample size is needed to increase the clinical significance of the results.

Treatment response at 1 year	**Arm A**		**Arm B**	
	No of Pts	%	No of Pts	%
Local control	4	16%	6	24%
Disease free survival(DFS)	2	8%	3	12%
Overall survival(OS)	11	44%	13	52%
Progressive disease	5	20%	4	16%
Lost follow up	8	32%	7	28%
Died	6	24%	5	20%

Discussion-

Lung cancer is a disease which tends to be diagnosed in advanced stages where mortality is usually high. With increasingly high incidence and high mortality, the advent of newer treatment approach prompted evaluation of combined treatment options globally for lung cancer.

In our study, no patient was found under age 40; 17% between 41 and 50; 56% between 51 and 60; 24% between 61 and 70; 6% were in more than 70 years of age. The median age in our study was found 58 years. ***Howlader. N et al*** (2012), from 2006-2010, the median age at diagnosis for cancer of the lung and bronchus was 70 years of age. [2]

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In our study, among 64 patients of inoperable locally advanced squamous cell lung cancer with eligible criteria, 72% patients were diagnosed stage IIIB and 28% patients were diagnosed with stage IIIA and have been given neoadjuvant chemotherapy. ***Naruke T et al***

(1988)to evaluate the new TNM staging system for lung cancer, we analyzed records of 1737 patients who underwent pulmonary resection at the National Cancer Center Hospital, Tokyo. With regard to clinical stages, three patients had occult carcinoma; 821 patients had stage I disease; 248 patients, stage II; 465 patients, stage IIIA; 82 patients, stage IIIB; and 118 patients, stage IV. [3]

After completion of neoadjuvant chemotherapy we found radiologically complete response in 4(7.1%) patients, partial response in 46(82.1%) patients and no response/progressive disease in 6 (10.7%) patients. Huber et al. (2006)155: 214 patients with IIIA/B received induction carboplatin/paclitaxel × 2 cycles and if no progression randomized to 60 Gy with or without weekly paclitaxel. Trend for improved MS with chemo-RT (14→19 months) and significantly improved MPFS (6→12 months). No difference in toxicity. ***Dillman et al*** showed: 155 patients with T3 or N2 randomized to RT alone (2/60 Gy) vs. sequential chemotherapy → RT (60 Gy). Induction chemo improved MS (10 → 14 months) and 2/5-year OS (13/7 → 26/19%). Our study showed an increase in early toxicity with chemoradiation arm which was in accordance with the above study. Late radiation toxicities like pulmonary pneumonitis, pulmonary fibrosis, carditis, pericarditis, esophagitis bone pain, myelitis were assessed clinically and diagnostically at 6 & 12 months of follow up and results had found statistically not significant.[4]

At 12th month of follow up local control, disease free survival, overall survival, found in ARM A vs ARM B was 16% vs 24%, 8% vs 12%, 44% vs 52% respectively. Progressive disease and lost follow up in ARM A vs ARM B was found to be 20% vs 16%, 32% vs 28% respectively, and patients died 24% vs 20%. Statistically our data was found not significant. ***Le Chevalier et al*** in a randomized study of chemotherapy plus radiotherapy versus radiotherapy alone in advanced non-small-cell lung cancer: results of a European trial including 612 patients. The overall survival at 12 months was found 41% in radiation alone ARM and 51% in chemoradiation ARM. Hence suggesting the need of a larger sample size for better results.[5]

Conclusion

Management of locally advanced lung cancer is quite challenging more so ever as patients are debilitated with compromised respiratory function. Multimodality treatment approach with judicious choice of combination chemotherapy and radiotherapy is used to give best results without compromising on the toxicities. This study definitely showed down-staging in inoperable locally advanced lung cancer. However a long term and larger randomized trial is required for better and conclusive results.

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