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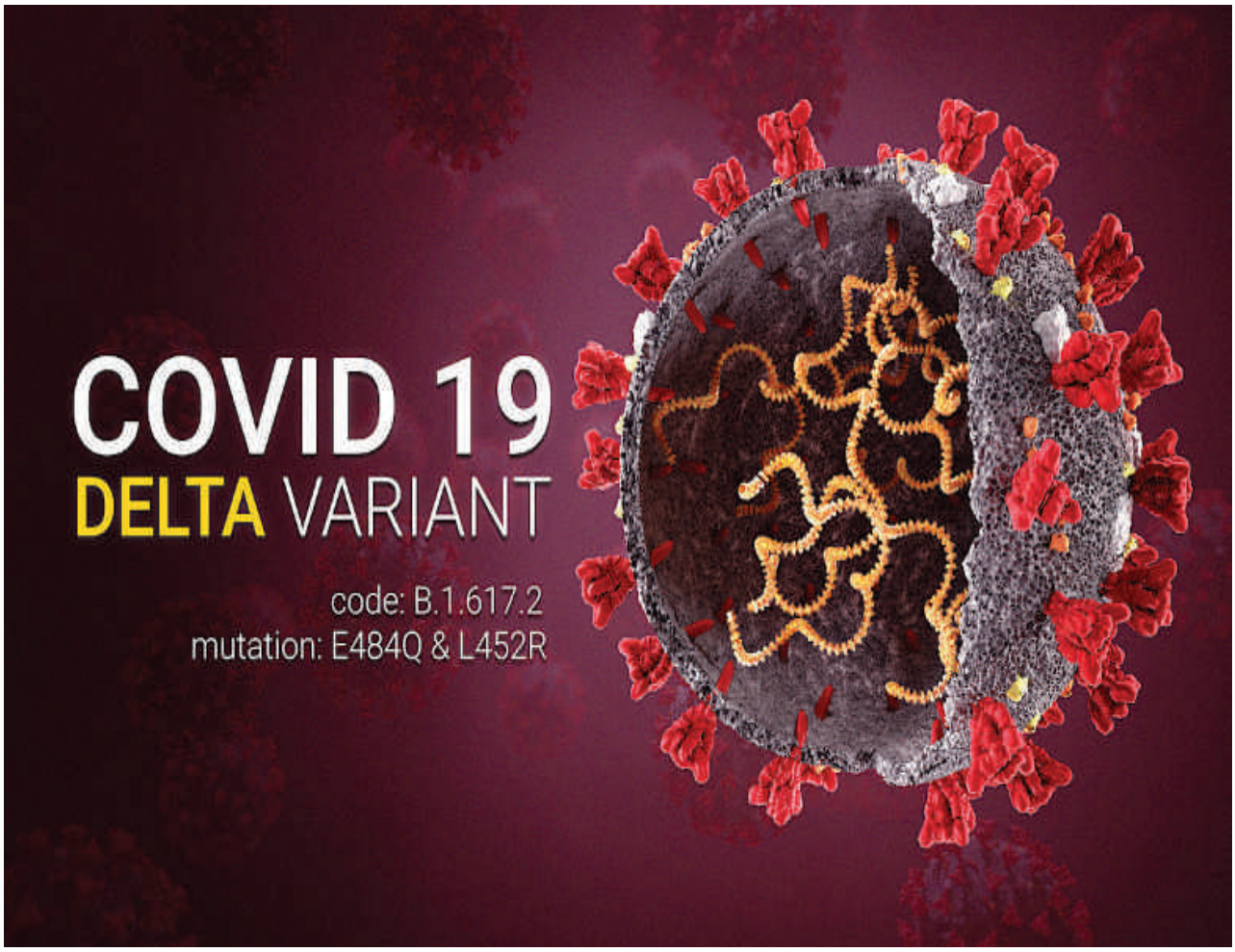

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

A Comparative Study Of Concurrent Chemo–Radiotherapy With or Without Neoadjuvant Chemotherapy in Treatment of Locally Advanced Non Small Cell Lung Cancer.

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Abstract

Introduction: The standard treatment for unresectable stage III non–small–cell lung cancer (NSCLC) is concurrent chemoradiotherapy. This study was undertaken to evaluate whether induction chemotherapy along with concurrent chemoradiotherapy would result in better tumor control, improved symptom control and any variation in toxicity as compared to concurrent chemoradiotherapy alone.

Patients and Methods: Between February 2015 to September 2016, 25 patients each were randomized to control group, in which they received concurrent chemoradiotherapy with weekly cisplatin 40 mg/m^2 intravenous, during chest radiotherapy of 66Gy in 33 fractions for 6.5 weeks, and study group, in which patients received three cycles of induction chemotherapy with Cisplatin 75 mg/m^2 and Paclitaxel 175 mg/m^2 administered every 21 days followed by identical chemoradiotherapy.

Results: The two groups of patients (with induction vs. without induction chemotherapy) were similar in age, performance status, histology, grade, and stage. At 6th month follow–up, complete response was seen in 6 patients in control arm and 7 patients in study arm (χ^2 = 1.603, p = 0.205) and partial response was seen in 13 and 12 patients in control and study arms respectively (χ^2 = 1.932, p = 0.165). Symptom control of cough, hemoptysis, chest pain and dyspnoea were also similar in both groups.

Discussion: In our study, no difference in treatment outcome with respect to the two groups was observed, which was similar to studies which have been conducted previously. Radiation is a good modality for symptom control of cough, hemoptysis, chest pain and dyspnoea. In toxicities, pneumonitis and hematological toxicity was slightly higher in study group even at 6th month follow up.

Conclusion: Slight increase in toxicity with no added benefit in locoregional tumor control and symptom regression, was seen in patients receiving induction chemotherapy followed by chemoradiotherapy. Concurrent chemoradiotherapy alone can thus be used as only modality of treatment in unresectable stage III NSCLC.

Keywords: Non small cell lung cancer, concomitant chemoradiotherapy, locoregional control, toxicity.

Introduction

Worldwide, lung cancer is the most common cancer diagnosed in males and the leading cause of cancer death.[1] In India, the highest cancer Disability Adjusted Life Years (DALYs) among males in 2016 were due to lung cancer, followed by lip and oral cavity cancer.[2] According to the GLOBOCAN 2012 report, the estimated incidence of lung cancer in India was 70,275 in all ages and both sexes and the overall estimated lung cancer mortality in India in 2012 was 63,759, making it the third most common cause of cancer–related mortality in India after breast and cervical cancer. Among Indian males, lung cancer was the most common cause of cancer mortality.[3] In accordance with the tumor nodal metastases (TNM) international staging system, approximately thirty percent of patients affected with non–small cell lung cancer (NSCLC) are diagnosed with locally advanced disease.[4] There has been steady advancement in available therapies for unresectable stage III NSCLC.[5–6] Most of the locally advanced NSCLC patients are deemed non–surgical due

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to disease extension.[7] The studies have demonstrated benefit of concomitant chemoradiotherapy over single modality radiotherapy. [8] Concomitant chemoradiotherapy has become the current standard of care for unresectable NSCLC, as it acts as radiation sensitizer and takes care of early micro–metastatic disease. [6]

Even with the addition of concurrent chemotherapy to radiotherapy and advances in radiation therapy planning and delivery, the prognosis for patients with locally advanced NSCLC has not shown much improvement. [9] Despite of an increase in median survival from 10 to 14 months shown in studies with the addition of induction chemotherapy to radiotherapy without any compromise in local control, induction chemotherapy is still not the recommended treatment.[10] The potential benefits of adding induction chemotherapy include, down staging of disease before local therapy, better drug delivery to tumor, early micro–metastatic disease treatment and assessment of systemic therapy in vivo.[11]

This study was thus undertaken to combine the benefit of systemic control seen with induction chemotherapy and the benefit of locoregional control seen with concurrent chemoradiotherapy. The purpose of this study was to evaluate the treatment outcome and toxicities in locally advanced non–small cell lung cancer treated with conventional chemo–radiotherapy with or without Neo – Adjuvant Chemotherapy (NACT).

Patients and Methods

A total of 50 patients with inoperable, locally advanced, stage IIIA & IIIB NSCLC tumors were prospectively randomized in this study. Patients were enrolled from February 2015 to September 2016. All the patients were histologically proven cases and were staged on the basis of AJCC 2010 TNM staging system. Inclusion criteria were ECOG (*Eastern Cooperative Oncology Group*) performance status 0, 1 & 2, presence of chest symptoms (cough, dyspnoea, haemoptysis, chest pain, dysphagia) and age of patient between 18 – 70 years. Patients with any severe hematological, cardiac, renal or liver function abnormality, previous history of treatment for lung cancer, metastatic disease, history of previous radiotherapy were excluded from the study. CECT Thorax was required in all the patients after registration in this trial. All the patients were required to sign protocol–specific informed consent in accordance with institutional guidelines.

Aims and objective

Comparison of treatment outcome and toxicities in locally advanced non–small cell lung cancer treated with conventional chemo–radiotherapy with or without Neo – Adjuvant Chemotherapy (NACT)

Methods of study and grouping of patients

Twenty five patients each were randomized in study group and control group after satisfying the inclusion and exclusion criteria. In the control group, patients only received concurrent chemoradiotherapy and in the study group, patients received NACT followed by concurrent chemoradiotherapy.

Treatment protocol (Fig.1)

In both arms, patients received a total of 66Gy in 33 fractions (2Gy for each fraction), on Cobalt 60 teletherapy machine administered daily (5 days/week) for 6.5 weeks (standard fractionated/conventional radiotherapy) with weekly cisplatin 40 mg/m^2 intravenous. All patients were planned for radiotherapy and treated in two phases, in phase I the volume included the mediastinum and primary tumor with two cm margin, treated to a dose of 44Gy. The phase II volume included the tumor and known nodal involvement with two cm margin, treated to a dose of 22Gy.

Patients in study group received Neo adjuvant chemotherapy before starting the radiotherapy. In Neo adjuvant chemotherapy, 3 cycles were given, each consisted of platinum based Inj. Cisplatin 75 mg/m^2, given intravenous in divided doses into day 1 and day 2 and taxane based Inj. Paclitaxel 175 mg/m^2 given intravenously on day 1, according to protocol, repeated every 3 weeks.

Observation and Evaluation during treatment

All the study group patients were evaluated for disease status after three weeks of 3rd cycle of chemotherapy. Patients were observed weekly during radiotherapy period in both the control & study arm where patients were assessed for treatment response, control of symptoms and any treatment related morbidity. At the end of radiation therapy, toxicity (acute) and regression of symptoms were assessed.

Follow up

First follow up visit was after 1 month of completion of radiotherapy and patients were assessed for treatment response and regression of symptoms. Complete general–physical examination, haemogram, RFT, CECT Thorax were also done for treatment response and toxicity evaluation.

On subsequent follow up in 3rd & 6th month, detailed systemic examination, CBC, LFT, RFT, RBS, CECT –thorax was done. The result of both the study & control arms were analyzed & compared in terms of various aspects like side effects, tumor response and relief from symptoms.

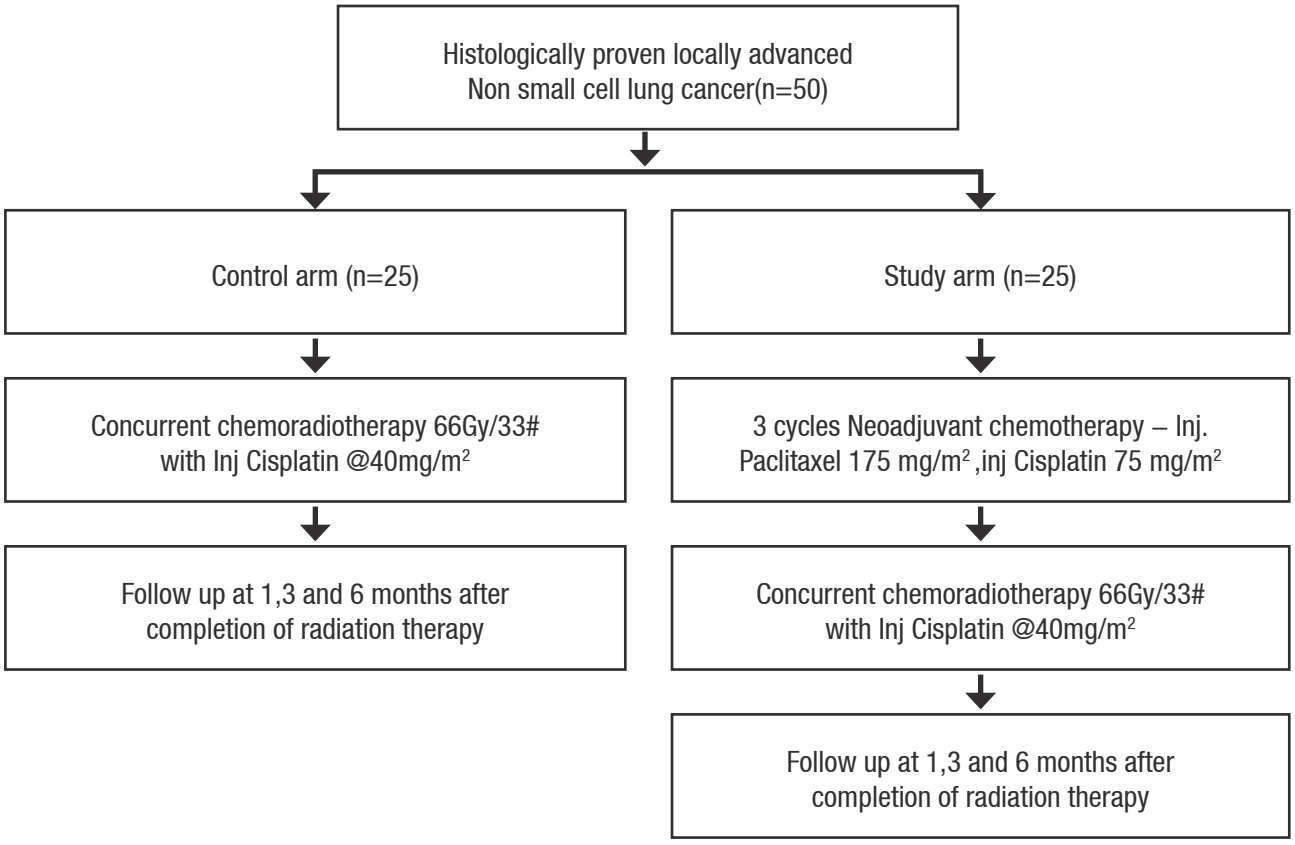


Fig.1: Study design

Endpoints and statistics

Primary endpoint for treatment outcome was locoregional control of disease and to assess treatment related toxicities in both the arms. Disease control was assessed using RECIST version 1.1 Criteria and toxicities i.e. oesophagitis, pneumonitis, skin reactions were assessed according to CTCAE 3.0 version. Regression of symptoms were assessed using symptomatic response grading.

Data Analysis

Data was analyzed using tools like percentage, mean, chi–square test and p–value. Chi–square and p–value was calculated by statistical online software (http://quantpsy.org). P value of ≤ 0.05 was considered as significant.

Results

All the patient characteristics were well balanced between the two groups (table 1). Patients in this study had an age range of 30–70 years with a median age of 59 years. Majority [45(90%)] of patients were males and rest [5(10%)] were females, which was partly due to the associated habits of smoking and tobacco chewing which are generally more seen in males. Habits of cigarette/bidi smoking, tobacco chewing, gutka use etc., were associated with 43 [86% of patients] and rest 7 [14% of patients] did not have any associated habits. Twenty nine [58%] patients were having stage IIIA at presentation while the rest 21 [42%] patients were having IIIB stage. In our study, squamous cell carcinoma was the most common histology 36[72%] followed by adenocarcinoma 14[28%].

In the present study all patients received a full course of treatment. From the population of 50 patients, 11 patients died and 1 patient was lost to follow–up.

Treatment response

At 6th month follow–up, 6 (24%) patients in control arm and 7(28%) patients in study arm had complete response (10 for stage IIIA & 3 for stage IIIB) ($\chi^2 = 1.603$, $p = 0.205$). Thirteen (52%), (9 for stage IIIA & 4 for stage IIIB) and 12 (48%), (8 for IIIA & 4 for stage IIIB) patients had partial response in control arm and study arm respectively ($\chi^2 = 1.932$, $p = 0.165$). No patient had stable disease in both study and control arms.

Characteristics	Control arm 25(100%)	Study arm 25(100%)	Overall 50(100%)
Age			
18–50years	4(16%)	8(32%)	12(24%)
51–60years	11(44%)	7(28%)	18(36%)
61–70years	10(40%)	10(40%)	20(40%)
Gender			
Male	23(92%)	22(88%)	45(90%)
Female	02(8%)	03(12%)	05(10%)
Performance status			
ECOG–1	15(60%)	21(84%)	36(72%)
ECOG–2	10(40%)	04(16%)	14(28%)
Tumor stage			
T2	03(12%)	02(8%)	05(10%)
T3	12(48%)	09(36%)	21(42%)
T4	10(40%)	14(56%)	24(48%)
Nodal stage			
N0	04(16%)	03(12%)	07(14%)
N1	09(36%)	05(20%)	14(28%)
N2	07(28%)	08(32%)	15(30%)
N3	05(20%)	09(36%)	14(28%)
Stage			
IIIA	18(72%)	11(44%)	29(58%)
IIIB	07(28%)	14(56%)	21(42%)
Histopathology			
SCC	16(64%)	20(80%)	36(72%)
Adenocarcinoma	09(36%)	05(20%)	14(28%)
Treatment Compliance			
NACT–1st cycle		25(100%)	
NACT –2nd cycle		25(100%)	
NACT –3rd cycle		25(100%)	
Radiotherapy	24(96%)	25(100%)	49(98%)
Expired– at 6 month	06(24%)	05(20%)	11(22%)
Lost follow up– 6 month		01(4%)	01(2%)

ECOG– Eastern Cooperative Oncology Group, SCC– Squamous cell carcinoma, NACT– Neoadjuvant chemotherapy.

Table 1: Patient Characteristics

	No. of Patients (%)	
	Control Arm	Study Arm
Partial Response	13 (52%)	12 (48%)
Complete Response	6 (24%)	7 (28%)

Table 2: Disease response at 6 months

Symptom control (FIG. 3)

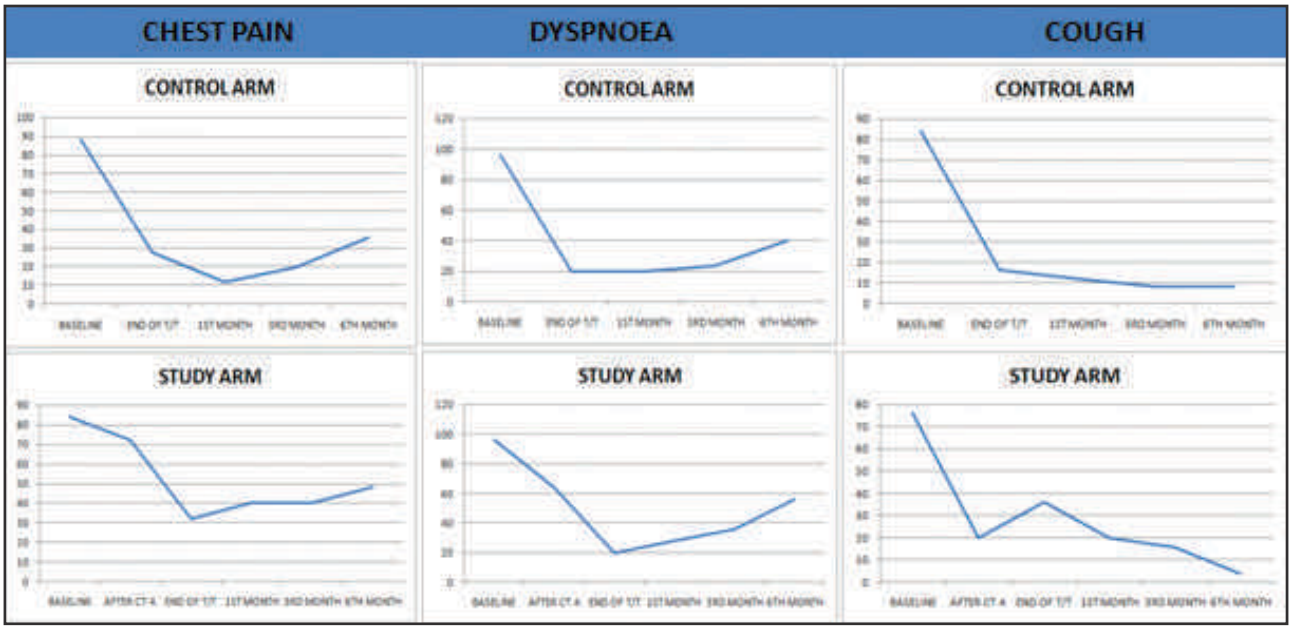
Lesser number of patients had chest pain at 6th month in control arm than study arm and the symptom–free duration was longer in control arm as compared to study arm (x^2 =3.929 and p value = 0.416). Rapid decline in dyspnea was seen at the end of treatment followed by a plateau phase at 1st month in control arm. Thereafter there was a gradual rise in dyspnea. The rise was more rapid in the study arm as compared to a control arm (x^2= 0.863 and p valve is 0.930). There was rapid decline in cough and hemoptysis at the end of treatment followed by gradual decrease in symptoms from 1st month to 6th month in both arms. No patient had hemoptysis at the end of 6th month in both arms. There was a slight increase in cough in study arm patients from after CT 3 to start of radiotherapy (x^2= 3.031 and p value is 0.553).

Acute toxicities at the completion of chemoradiaton

There was no significant difference in skin toxicity in either of the arm (Table 3). There was grade II esophagitis seen in 11 & 14 patients in study and control arm respectively, while grade III was seen in 4 & 1 patients in study and control arm respectively. Renal toxicity, grade 1 was seen in 9 patients in study arm as compared to 2 patients in control arm. Grade 2 (5 patients) and grade 3 (3 patients) with renal toxicity were seen only in study arm. Hematological toxicity, grade 1 was seen in 14 patients in study arm as compared to 6 patients in control arm. Grade 2 (7 patients) and grade 3 (2 patients) with hematological toxicity were seen only in study arm. More number of patients have toxicities in study arm but all are non–significant. There was no grade IV GIT, renal, hematological and skin toxicity seen in either of the arm.

Late toxicities

At 6th month follow up, grade 4 toxicity was not documented in either arm and only significant grade 3 toxicity seen was pneumonitis with 6 patients in study arm (6 vs 0). Grade 2 pneumonitis was also more significantly higher in study arm as compared to control arm (7 vs 4).



Toxicities

	Arm	GIT TOX.	Renal Toxicity	SKIN	Hematological Toxicity
Grade 0	*Study*	*2(8%)*	8(32%)	14(56%)	2(8%)
	Control	*4(16%)*	22(88%)	16(64%)	18(72%)
Grade I	*Study*	*8(32%)*	9(36%)	9(36%)	14(56%)
	Control	*5(20%)*	2(8%)	7(28%)	6(24%)
Grade II	*Study*	*11(44%)*	5(20%)	2(8%)	7(28%)
	Control	*14(56%)*	0	1(4%)	0
Grade III	*Study*	*4(16%)*	3(12%)	0	2(8%)
	Control	*1(4%)*	0	0	0
Grade IV	*Study*	*0*	0	0	0
	Control	*0*	0	0	0

Table 3: Toxicity at end of chemoradiotherapy – acute toxicity

No significant skin toxicity was seen in either arm (Table 4). Only grade 1 (8 patients) and Grade 2 (1 patient) renal toxicity was seen in study arm alone. Grade 2 hematological toxicity was documented only in the study arm with 5 patients. At 6 month fewer patients had mild symptoms of esophagitis and grade 2 esophagitis was seen only in 1 patient in control arm.

Discussion

This is a randomized prospective study to address the role of induction chemotherapy in the context of concomitant chemoradiotherapy for locally advanced NSCLC. This study population median age at presentation was 59 years with the male:female sex ratio of 9:1 as compared to other studies where the ratio of 3:1 has been seen.[12] The prevalence of smoking has increased in community and it is reflected by 7:1 ratio of smoker Vs non–smoker in present study population which is very close to the ratio of 5.5:1 seen in few recent studies [13], and varies a lot as compared to few other studies where ratio is as high as 20:1.[14]

After 1960, worldwide a transition from most common histological subtype of lung cancer i.e. squamous cell carcinoma towards adenocarcinoma has been noticed which has been attributed to the use of cigarette filters and great efforts to reduce smoking.[15] In the present study though, squamous cell carcinoma was the most common histological subtype with a frequency of 72%,

	Arm	GIT TOX.	Renal Toxicity	SKIN	Hematological Toxicity	PNEUMO.
Grade 0	*Study*	*17(68%)*	11(44%)	19(76%)	9(36%)	1(4%)
	Control	*11(44%)*	18(72%)	16(64%)	17(68%)	3(12%)
Grade I	*Study*	*3(12%)*	8(32%)	1(4%)	6(24%)	6(24%)
	Control	*6(24%)*	0	2(8%)	1(4%)	11(44%)
Grade II	*Study*	*0*	1(4%)	0	5(20%)	7(28%)
	Control	*1(4%)*	0	0	0	4(16%)
Grade III	*Study*	*0*	0	0	0	6(24%)
	Control	*0*	0	0	0	0
Grade IV	*Study*	*0*	0	0	0	0
	Control	*0*	0	0	0	0

Table 4: Late toxicity – after Chemo radiotherapy – 6th month

and followed by adenocarcinoma constituting 28% which can be correlated with higher incidence of smoking specially 'bidi' which is more common in present study population. In various Indian studies still squamous cell carcinoma is the most common histology.[16]

Various trials have tried to encompass induction chemotherapy prior to chemoradiotherapy. The CALGB 39801 group compared induction chemotherapy followed by CCRT vs. CCRT alone. Survival differences were not statistically significant (*p value–0* .3), with a median survival in CCRT arm of 12 months versus 14 months in the other arm.[17] These equivocal results are quite similar to those seen in our study, as we also found no difference in treatment outcome with respect to the two groups (complete response p = 0.205 and partial regression p = 0.165). Stage wise, there was better regression in stage IIIA than stage IIIB as out of the 13 patients who had complete response, 10 patients were stage IIIA and 3 patients were stage IIIB.

One more study retrospectively analyzed patients who received definitive treatment with radiation and concurrent chemotherapy with and without induction chemotherapy. Patients who received induction chemotherapy had better overall survival ($p < 0.001$) and distant metastasis–free survival ($p = 0.021$).[18] Though the results were different from our study but survival advantage from adding induction chemotherapy to CCRT was seen only in patients with adenocarcinoma or large–cell carcinoma and in the present study, squamous cell carcinoma was the predominant histology. Another trial, the randomized Phase II Locally Advanced Multi–Modality Protocol (LAMP) was also inconclusive in answering the question that whether adding induction chemotherapy to concurrent chemoradiation will improve clinical outcomes. [19]

We must keep in mind that increased toxicity is seen with thoracic concurrent chemo radiation as compared to sequential therapy. Trials have shown that concurrent chemo radiotherapy is associated with significant toxicity but these toxicities were manageable as was seen in our study also.[20]

Out of the five toxicities which were assessed in this study, pneumonitis and hematological toxicities were slightly higher in induction chemotherapy followed by concurrent chemoradiotherapy arm even at 6th month follow up. It has been seen in few studies that both chemotherapy use and age were associated with large increases in pneumonitis risk.[21] Toxicities due to chemotherapy can be reduced by alterations in doses, intervals or even specific compounds and regimens.[22] Various attempts to reduce the volume of irradiated normal lung, heart and esophagus have been made with the use of highly conformal RT techniques such as IMRT[23], IGRT and use of proton beam therapy.[24] In a secondary analyses of RTOG 0617, IMRT was associated with less grade ≥3 pneumonitis (p = 0.039).[23]

Radiation has the ability to improve local symptoms, which occur as a result of tumor related compression, making thoracic radiotherapy an integral component of treatment algorithms.[25, 26] As per the symptom control in this study is concerned, cough and hemoptysis were significantly reduced in both arms and became nil at the end of 6th month. Chest pain and dyspnoea also showed significant response after the end of treatment.

Various approaches might be investigated in future to improve overall survival. These include feasibility of using novel cytotoxic agents, [27] and integration of targeted agents to radiotherapy which is well supported

by preclinical data.[28–29] In the light of the finding that induction chemotherapy may add little benefit, the role of consolidated chemotherapy should be further investigated. [30]

In conclusion, similar treatment response is seen in terms of locoregional control, tumor regression and symptom control in patients who receive concurrent chemoradiotherapy with and without induction chemotherapy. Toxicity profile is also similar between the two arms except for pneumonitis and hematological toxicity, which is slightly higher, but manageable in patients receiving induction chemotherapy followed by concurrent chemotherapy. Considering the fact that there is lesser treatment time with equal disease response in patients receiving concurrent chemoradiotherapy, it can therefore be considered as standard of care in unresectable stage III NSCLC, but studies with larger patient size and longer follow up are required to establish it as the standard of care.

Conclusion

Slight increase in toxicity with no added benefit in locoregional tumor control and symptom regression, was seen in patients receiving induction chemotherapy followed by chemoradiotherapy. Concurrent chemoradiotherapy alone can thus be used as only modality of treatment in unresectable stage III NSCLC.

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