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Original Article

Comparative Study between the Effect of Induction Chemotherapy with 66 Gy Three Dimensional Conformal and 46 Gy Conventional Radiotherapy in Stage Iii Non- Small Cell Lung Cancer

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Abstract:

A quasi experimental study was carried out among 60 stage III NSCLC patients attending at Radiation Oncology Department of National Institute of Cancer Research & Hospital, Mohakhali, Dhaka from August 2012 to July 2013. Patients were divided into group A and group B purposively to receive Induction Chemotherapy followed by conventional or 3D CRT respectively. The study was designed to observe the radiological response and acute toxicity of stage III NSCLC with induction CT and 3DCRT. Treatment related morbidity was more observed in the intervention group with 43.3% Grade ≥2 Pneumonitis, 43.4% Grade ≥ 2 Oesophagitis, 40% Grade 2 skin toxicity and 6.7% Grade ≥ 3 anemia. Regarding metastasis, 33.3% patients in the intervention arm and 30% patients in the control arm had presented with metastasis at different sites within this six months period. No statistically significance was found between these two groups (p = .781). Death during follow up was observed in 6.7% patients in the intervention group and 3.3 % patients in the control arm which was of no statistically significance difference. (p = 1.00). Complete response was found in 23.3 % patients in intervention group while in control group it was only 6.7%. Partial response was 46.7% and 43.3% respectively. No response was seen in 36.6% patients; 13.3% in the intervention group and 23.3% in the control group. More patients in control group (26.7%) were reported with progressive disease. No statistical significance was found regarding the radiological response between these two arms (p=.114). Both complete and overall responses were better in intervention group than control group.

Key words: Induction Chemotherapy, 3DCRT, Conventional Radiotherapy, Non-small Cell Lung Cancer;

Introduction:

Lung cancer is the most common cause of cancer mortality worldwide for both men and women, causing approximately 1.4 million deaths per year[1]. In the United States in 2010, there were 220,000 new cases of lung cancer and among them 75% were non-small cell lung cancer (NSCLC)[2]. Of these, 40% are in stage III comprising both Stage IIIA and IIIB according to the current AJCC staging system. Unfortunately, there is no Population-based data on lung cancer in Bangladesh. According to GLOBOCAN - 2008 lung cancer is the leading cause of cancer death and 19529 patients were diagnosed as lung cancer (13%) in the year 2008 in Bangladesh[3]. The Hospital-based Cancer Registry Report of National Institute of Cancer Research and Hospital published in December 2009 indicates that lung cancer is the leading cancer and a total number of 3209 lung cancer patients attended NICRH during the three years (2005-2007), among them non small cell lung cancer comprises 85%[4]. In Bangladesh the true incidence is difficult to estimate due to various reasons, however there is no doubt that the frequency of lung cancer have risen dramatically and the majority number of patients in the NSCLC belongs to stage III. Though the development of Radiation Oncology as well as Medical oncology is amazing but there is very little development in the treatment of stage III lung cancer. The 5-year overall survival for patients presenting with clinically staged IIIA and IIIB NSCLC are 30% and 25% respectively[5]. Due to these disappointing results, lots of options have been tried so far. Based on the RTOG trial 7301- 60 Gy became the standard dose of radiation for NSCLC. Though RTOG- 7301 reported ≥56% partial response that didn't reflects in the overall survival[6]. Since then various endeavors like altered

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fractionation RT[7], concurrent or sequential chemo-radiotherapy[8], conformal RT with dose escalation[9] etc were taken for a better outcome but still the 5 years survival rate is around 25%. Because of these disappointing results and because of the growing global epidemic of tobacco-related cancer, stage III NSCLC is appropriately the subject of intense clinical investigation and controversy.

Materials and Methods:

A total of 60 subjects consecutively included in the study; of them 30 were allocated in group A and the remaining 30 in group B purposively. Inclusion criteria includes patients with biopsy proven stage III non-small cell lung cancer with age more than 18 but less than 70 years and Karnofsky performance status 70 or more. Exclusion criteria includes evidence of small cell histology, patients with history of prior chemotherapy or thoracic or neck RT, patients with symptomatic heart disease including angina, congestive heart failure, arrhythmias, uncontrolled diabetes and hypertension, and pregnant women. Minimum laboratory criteria required to includes Hemoglobin more than 10 gm/dl (≥ 60%), Absolute WBC count ≥ 4000 cell/ml, Platelets count ≥100,000 cells/ml, S. Bilirubin level ≤ 1 mg/dl, AST level not more than four times the normal upper limit and S. Creatinine level ≤1.5 mg/dl. Patients were treated with inj Cisplatin 40mg/m^2 and inj Etoposide 100/m^2 from day 1-3, total 3 cycle 21 days apart. Radiation therapy was started on Day 21 from the day of starting of last CT. Thirty patients were treated with 3D-Conformal Radiotherapy technique and 30 patients with 2D conventional technique. The radiation was delivered by multiple fields arrangement using photon with an energy of 6/10 MV. The treatment was performed in conventional fractionation, 5 days a week, with a dose of 2 Gy per fraction. The total dose of 66 Gy was delivered in 33 fractions in 7 weeks for Group B and 46 Gy was delivered in 23 fractions in 5 weeks for Group A. Treatment response was assessed in the light of RECIST (Response Evaluation In Solid Tumor) version 2,0 (2010) criteria, Toxicity was observed according to common terminology criteria for adverse effects(CTCAE) version 4,0 (2010) and WHO reporting results of cancer treatment recommendation for grading of acute and sub- acute toxicity.

Results:

Total study population was 60 among which 30 were in the control arm (group A) and 30 were in the intervention arm (group B). The mean age of the group A was 57.7 years (SD±14.47) where the range was from 18 years to 79 years. In group B the mean age was 60.4 years (SD±9.45) ranging from 43 to 77 years. The age difference between the two groups was not statistically significant (p=397) (Table I).

Table I: Distribution of patients by Age

Statistics	Group A	Group B
No of patients	30	30
Mean	57.7	60.4
Median	65	63.5
Std. Deviation	14.47	9.45
Minimum	18	43
Maximum	79	77
P-value	0.397	

Regarding sex distribution, male patient was found dominant in both arm with the percentage of 73.3% in group A arm and 83.3% in group B. The percentages of female patients were 26.7% and 16.7% respectively. No statistical significant difference was observed (p = 0.347) (Table II).

Table II: Distribution of the patients by Sex

Sex	Group A		Group B		p-value
	n	%	n	%	
Male	22	73.3	25	83.3	
Female	8	26.7	5	16.7	0.347
Total	30	100.0	30	100.0	

Out of 60 patients 44 patients were smokers. In group A 70% patients used to smoke of which 66.7% were male. In group B only male were smokers (76.7%). There was no significant statistical difference among the two groups (p = 0.559) (Table III).

Table III: Distribution of the patients by smoking habit

Smoking habit		Group A		Group B		p-value
		n	%	n	%	
Male	Yes	20	66.7	23	76.7	
	No	2	6.7	2	6.7	
Female	Yes	1	3.3	0	0.0	0.559 (NS)
	No	7	23.3	5	16.7	
Total		30	100.0	30	100.0	

Squamous cell carcinoma was the major histological type in both groups. In group A 18 patients out of 30 (60%) had squamous cell carcinoma; 10 (33.3%) patients had adenocarcinoma and only 2 patients (6.7%) had large cell carcinoma. In group B 20 patients (66.7%) were suffering form squamous cell carcinoma while 9 patients (30%) had adenocarcinoma. No statistical significance was found between these two groups by Chi-Square Test (p = 0.653) (Table IV).

Table IV: Distribution of the patients by histological types

Histopathology	Group A		Group B		Total		p-value
	n	%	n	%	n	%	
Squamous cell carcinoma	18	60.0	20	66.7	38	63.3	0.653
Adeno-carcinoma	10	33.3	9	30.0	19	31.7	
Large cell carcinoma	2	6.7	1	3.3	3	5.0	
Total	30	100.0	30	100	60	100.0	

About 53% patients were in stage IIIA and about 47% patients were in stage IIIB. Eighteen patients in group A were staged as IIIA (60%) and the rest 12 (40%) patients were staged as IIIB. In group B the percentage of stage IIIA and IIIB were 46.7% and 53.3% respectively (Table V).

Table V: Distribution of the patients by staging

Stage	Group A		Group B		Total	
	n	%	n	%	n	%
IIIA	18	60.0	14	46.7	32	53.3
IIIB	12	40.0	16	53.3	28	46.7
Total	30	100.0	30	100.0	60	100.0

In the total study population only 7 (11.7%) patients were reported with well differentiated (grade I) histology, 38 (63.3%) patients with moderately differentiated (grade II) and the rest 15 (25%) patients were with poorly differentiated (grade III) histology. In group A 6.7% tumour was well differentiated, 63.3% moderately differentiated and 30% were poorly differentiated and in group B the percentage of well differentiated, moderately differentiated and poorly differentiated were 16.7%, 63.3% and 20% respectively. No statistical significance was found between these two groups (p = 0.390) (Table IV).

Table VI: Distribution of the patients by grading

Grading	Group A		Group B		Total		p-value
	n	%	n	%	n	%	
Grade I	2	6.7	5	16.7	7	11.7	0.390
Grade II	19	63.3	19	63.3	38	63.3	
Grade III	9	30.0	6	20.0	15	25.0	
Total	30	100.0	30	100.0	60	100.0	

Nine (30%) patients in the group A and 10 (33.3%) patients in group B presented with metastasis at different sites within this 6 months of follow up period. No statistically significance was found between these two groups (X^2 = .077, df =1; p = .781) (Table VII).

Table VII: Distribution of the patients by metastatic disease

Metastatic disease	Group A		Group B		Total		p-value
	n	%	n	%	n	%	
Yes	9	30.0	10	33.3	19	31.7	0.781
No	21	70.0	20	66.7	41	68.3	
Total	30	100.0	30	100.0	60	100.0	

Pneumonitis is compared in three different periods of time. At 21st day of the treatment in group A 16 (53.5%) patients reported with grade 1 toxicity, 12 (40%) patients with grade 2 toxicity and 2 (6.7%) patients with grade 3 toxicity. In group B the numbers of grade 1, 2 and 3 toxicities were 12 (40%), 14 (46.7%) and 4 (13.3%) respectively. At first follow up there were 17 (56.7%) grade 1 toxicity, 11 (36.7%) grade 2 toxicity and 2 (6.7%) grade 3 toxicity in group A in contrast to 17 (56.6%), 12 (40%) and 1 (3.3%) respectively in group B. At last follow up at 6 months there were 18 (60%) grade 1 toxicity, 8 (26.7%) grade 2 toxicity and 4 (13.3%) grade 3 toxicity in group A while there were 14 (46.7%) grade 1, 11 (36.6%) grade 2 toxicity and 5 (16.7%) grade 3 toxicity found in group B. However, no statistical significance was observed between these two groups at any time (Table VIII).

Table VIII: Distribution of the patients by Pneumonitis

Pneumonitis		Group A		Group B		p-value
		n	%	n	%	
At day 21	Grade 1	16	53.3	12	40.0	0.389 (NS)
	Grade 2	12	40.0	14	46.7	
	Grade 3	2	6.7	4	13.3	
1st follow up	Grade 1	17	56.7	17	56.7	0.554 (NS)
	Grade 2	11	36.7	12	40.0	
	Grade 3	2	6.7	1	3.3	
2nd follow up	Grade 1	18	60.0	14	46.7	0.581 (NS)
	Grade 2	8	26.7	11	36.6	
	Grade 3	4	13.3	5	16.7	

Oesophagitis is compared in three different periods of time (Table IX). At 21st day of the treatment in group A 16 (53.3%) patients reported with grade 1 toxicity, 12 (40%) patients grade 2 toxicity and 2 (6.7%) patients with grade 3 toxicity. In group B the number of grade 1, grade 2 and grade 3 toxicities were 12 (40%), 17 (56.7%) and 1 (3.3%) respectively. No statistical

significance was observed between these two groups at 21st day. At first follow up there were 23 (76.7 %) grade 1 toxicity and 7 (23.3%) grade 2 toxicity in group A in contrast to 17 (56.7%) and 8 (26.6%) respectively in group B. This difference was significant (p = .007). At last follow up at 6 months there were 22 (73.3%) grade 1 toxicity and 8 (26.7%) grade 2 toxicity in group A while there were 16 (53.3%) grade 1, 10 (33.3%) grade 2 toxicity and 4 (13.3%) grade 3 toxicity recorded in group B. However, no statistical significance was observed between these two groups at 6 months' outcome.

Table IX: Distribution of the patients by Oesophagitis

Oesophagitis		Group A		Group B		p-value
		n	%	n	%	
At day 21	Grade 1	16	53.3	12	40.0	1.000 (NS)*
	Grade 2	12	40.0	17	56.7	
	Grade 3	2	6.7	1	3.3	
first follow up	Grade 1	23	76.7	17	56.7	0.007 (S)*
	Grade 2	7	23.3	8	26.6	
	Grade 3	0	0.0	5	16.7	
second follow up	Grade 1	22	73.3	16	53.3	0.112 (NS)*
	Grade 2	8	26.7	10	33.3	
	Grade 3	0	0.0	4	13.3	

Skin reaction is compared in three different periods of time (Table X). At 21 day of the treatment in group A 16 (53.3%) patients reported with grade 1 toxicity, 9 (30%) patients with grade 2 toxicity and 5 (16.7%) patients with grade 3 toxicity. In group B the numbers of grade 1, 2 and 3 toxicities were 14 (46.7%), 14 (46.7%) and 2 (6.6%) respectively. However, this difference was not significant statistically (p = 0.606). At first follow up there were twenty seven (90%) grade 1 toxicity and three (10%) grade 2 toxicity in group A in contrast to eighteen (60%) grade 1 toxicity and 12 (40%) grade 2 toxicity in group B. This difference was statistically significant (p = 0.007). At last follow up at 6 months there were twenty eight (93.3%) grade 1 toxicity and two (6.7%) grade 2 toxicity in group A while there were twenty one (70%) grade 1 and nine (30%) grade 2 toxicity found in group B. This difference was statistically significant too (p = 0.02).

Table X: Distribution of the patients by skin reaction

Skin reaction		Group A		Group B		p-value
		n	%	n	%	
At day 21	Grade 1	16	53.3	14	46.7	0.606 (NS)
	Grade 2	9	30.0	14	46.7	
	Grade 3	5	16.7	2	6.6	
first follow up	Grade 1	27	90.0	18	60.0	0.007 (S)
	Grade 2	3	10.0	12	40.0	
second follow up	Grade 1	28	93.3	21	70.0	0.02 (S)
	Grade 2	2	6.7	9	30.0	

Table XI shows that 1 patient (3.3%) in group A died during six month period of follow up, whereas in group B two (6.7%) patients succumbed to death. No statistically significance was found between these two groups (Fisher's exact test; p = 1.000).

Table XI: Distribution of the patients by death

Death	Group A		Group B		Total	
	n	%	n	%	n	%
Yes	1	3.3	2	6.7	3	5.0
No	29	96.7	28	93.3	57	95.0
Total	30	100.0	30	100.0	60	100.0

In group A 2 patients (6.7%) showed complete response where in group B complete response was noticed in 7 patients (23.3%); partial responses were 13 (43.3%) and 14 (46.7%) in the two groups respectively. No response was noticed in 7 patients in group A; 4 patients in group B. Eight patients in group A and 5 patients in group B were found with progressive disease. No statistically significance was found between these two groups (Table XII).

Table XII: Distributions of the patients by final response

Status at last follow up	Group A		Group B		p-value
	n	%	n	%	
Complete response	2	6.7	7	23.3	0.114
Partial response	13	43.3	14	46.7	
No response	7	23.3	4	13.3	
Progressive disease	8	26.7	5	16.7	
Total	30	100.0	30	100.0	

Discussion:

According to GLOBOCAN 2008 the incidence of lung cancer in Bangladesh is 13.8%, ranking first, it also occupied the top position in cancer mortality in 2008[3]. Non-small cell lung cancer (NSCLC) accounts for about 75% of lung cancer and 25-40% of cases are locally advanced disease, not amenable for curative resection at the time of diagnosis[10]. Thoracic radiotherapy was considered the standard treatment for patients with unresectable and locally advanced NSCLC. However, due to poor 5-year survival with standard radiotherapy[11], altered fraction and dose escalated radiotherapy or addition of chemotherapy to radiotherapy were attempted in order to improve the survival rate and local control rate. Recently, concurrent chemoradiotherapy has been demonstrated to increase survival to a greater degree than induction chemotherapy followed by radiotherapy. Therefore, concurrent chemoradiotherapy is currently considered as the standard of care for locally advanced stage III NSCLC[12,13]. When radiotherapy is used to treat tumors within or adjacent to the thorax, the dose-limiting organs of primary concern are the lungs and the spinal

cord. The lungs are sensitive to the effects of both short term and long term radiation at a lower dose than other structures in the chest, such as the esophagus, heart and spinal cord[14,15]. Therefore, radiation pneumonitis is the major side effect of thoracic radiation therapy that can impact the clinical course of the patients. Discontinuation of treatment or limiting the amount of radiation dose due to radiation pneumonitis leads to reduction in the therapeutic effect and decreases both the local control rate and survival rate[16]. In the present study patients were treated with injection Cisplatin 40mg/m^2 and injection Etoposide100/m^2 from day 1-3, total 3 cycle 21 days apart. Radiation therapy was started on Day 21 from the day of starting of last chemotherapy. Thirty patients were treated with 3D-Conformal Radiotherapy technique and 30 patients with 2D conventional technique.

The mean age of the group A was 57.7 years (SD±14.47) where the range was from 18 years to 79 years. In group B the mean age was 60.4 years (SD±9.45) ranging from 43 to 77 years. The age difference between the two groups was not statistically significant (p=397). One study at NICRH found the similar age distribution[4]. Male patient was found dominant in both arm with the percentage of 73.3% in group A arm and 83.3% in group B. This finding is near similar to the Cancer registry report of NICRH 2005-2007[4]. According the Cancer Registry Report of NICRH only 446(10%) female patients attended in the Radiation Oncology Department with NSCLC from 2005-2007. Few female patients refused to get enrolled in this study may have caused this deviation. In group A 70% patients used to smoke of which 66.7% were male. In group B only male were smokers (76.7%). There was no significant statistical difference among the two groups (p = 0.559). This finding was almost similar with the United States where smoking is estimated to account for 87% of lung cancer[17].

Squamous cell carcinoma was the major histological type in both groups. In group A 18 patients (60%) had squamous cell carcinoma; in group B 20 patients (66.7%) were suffering from squamous cell carcinoma. No statistical significance was found between these two groups by Chi-Square Test (p = 0.653). According to "Clinical Chest Medicine" published in 2002 adenocarcinoma accounts for 40% of non-small-cell lung cancers where 25% were squamous cell cancers[18]. But the histopathological distribution of NSCLC in NICRH was quite similar with the findings of our study where 68% squamous cell and 27% adenocarcinoma was reported in the cancer registry of NICRH 2005-07[4]. Considering the staging 18 patients in group A were staged as IIIA (60%) and in group B the percentage of stage IIIA was 46.7%. Though no statistical significance was found between the two arms but this additional 10% in a relatively small sample size may have influenced the total outcome of the study. In group A 6.7% tumour was well differentiated, 63.3% moderately differentiated and 30% were poorly differentiated and in group B the percentage of well differentiated, moderately differentiated and poorly differentiated were 16.7%, 63.3% and 20% respectively.

Nine patients in the group A and 10 patients in group B presented with metastasis at different sites within this 6 months of follow up period. No statistically significance was found between these two groups (X^2 = .077, df =1; p = .781). This is comparable with some other international studies[7,9].

At day 21 of the treatment in group A 15 patients reported with grade 1 (Hb% 11.5-9.5 gm/dl) toxicity, 14 patients grade 2 (Hb% 9.5-7.5gm/dl) toxicity and 1 patients with grade 4 (Hb% nil) toxicity. In group B the number of grade 1 and grade 2 toxicities were 19 and 17 respectively. At first follow up i.e. after three months of treatment there were 14 grade 1 toxicity and 11 grade 2 toxicity in group A in contrast to 18 and 10 respectively in group B. At last follow up at 6 months there were 15 grade 1 toxicity and 14 grade 2 toxicity in group A while there were 13 grade 1 and 16 grade 2 toxicities recorded in group B. However, no statistical significance was observed between groups. But Sumon MA found significant difference in Hb% toxicity between groups[9]. Regarding pneumonitis, at 21st day of the treatment in group A grade >=2 toxicity was found in 56.7%. In group B grade >=2 toxicity was 60%. At first follow up these values were 43.4% and 43.3 respectively and at last follow up at 6 months the values stood at 40% and 53.3% in group A and group respectively. However, no statistical significance was observed between these two groups at any time. According to NPC 95-01[19] the grade ≥ 3 pneumonitis was around 20% when patient was treated with 66 Gy radiotherapy concurrent with 20 mg/m^2 Cisplatin and 50 mg/m^2 Etoposide (day1-5) and day (29-33). Yom SS[20] Showed that the rate of grade ≥3 treatment-related pneumonitis was 32%. Wolbrast et al[21], Burman et al[22], Martel et al[23], Kuther et al[24] with their various study showed that ≥ 3 pneumonitis was less than 35% even when they were treated with very high dose around 80 Gy which is also much lower than our findings. In case of Oesophagitis Grade 3 toxicity was absent in control group at first and second follow up but present in intervention group (16.7% and 13.3% respectively). Grade 1 oesophagitis was predominantly found in control group than intervention group at all follow ups. This difference was statistically significant (p = 0.007). In our study, the rate of ≥ 3 Grade oesophagitis was higher than other studies[25]. This is probably due to the setup error and generous volume taken for treatment.

Meijer in a study showed that setup error caused about 10% addition of toxicity in esophagus[26]. Regarding skin reaction significant difference was noted between two groups at first and second follow ups. At 3 months of treatment only 10% patients experienced grade 2 toxicity in control group while in intervention group 40% experienced the same. At 6 months these values were 7% and 30% respectively. Higher dose in intervention arm could be the cause. Some international studies revealed the same findings.

Only1 patient (3.3%) in group A died during six month period of follow up, whereas in group B two patients succumbed to death. No statistically significance was found between these two groups. The number of death was quite negligible to other studies. A short follow up period of 6 months could be underlying factor for such contrasting result.

In group A 2 patients (6.7%) showed complete response where in group B complete response was noticed in 7 patients (23.3%); partial responses were 13 (43.3%) and 14 (46.7%) in the two groups respectively. No response was noticed in 7 patients in group A; 4 patients in group B. Eight patients in group A and 5 patients in group B were found with progressive disease. Considerable differences in responses are noted between these two groups. i.e. patients getting 3DCRT showed more clinical response than patients got conventional radiotherapy though no statistically significance was found between these two groups. A small sample size could be the cause for getting statistical significance. According to a study of the radiological response evaluation based on CT scan after 62.4 Gy concurrent with Chemotherapy Carboplatin showed that overall response was 75% with 50% partial response and 21% complete response[27]. In another study by Young Seok showed more than 56% partial response with 70.2 Gy over an 8-weeks period, combined with chemotherapy weekly 40 mg/m^2 of Paclitaxel plus 20 mg/m^2 of Cisplatin[28]. If we compare the sum of complete response and partial response in our intervention arm it was about 70%. But in the Control arm it was 50.3%.This finding is comparable with other studies[27,28].

Conclusion:

Conventional 2D technique radiation therapy is not a modality of treatment for curative intent, 3DCRT radiation technique is the preferred treatment option for advanced lung cancer patients. Considering the small number of patients and shorter follow up period it will not be logical to come to a definite conclusion about the advantage of higher dose 3DCRT over conventional therapy with less radiation dose. Further study with better design and longer duration of follow up is required to reach a conclusive decision.

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