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THE CLINICOPATHOLOGICAL BEHAVIOR AND PATTERN OF TREATMENT OF INOPERABLE ADVANCED NONSMALL CELL LUNG CANCER PATIENTS

P. Kaur*[1], A. Chauhan [1], M. K. Bharti [1], G. Singh [2], R. Sabharwal [1] and M. Sabharwal [3]

Department of Radiation Oncology[1], Pathology[2] & Department of Health[3], Regional Cancer Centre, PGIMS, Rohtak, Haryana India

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Correspondence to Author:

Dr. Paramjeet Kaur

Assistant Professor, Department of Radiation Oncology, Regional Cancer Centre, PGIMS, Rohtak, Haryana India

ABSTRACT

Abstract: Lung cancer is leading cause of death due to malignancy. Non small cell lung cancer constitutes approximately 85% of all lung cancers. Despite advances in early detection of non small cell lung cancer, about 75%-80% patients with locally advanced or metastatic disease (Stage III & IV) and carries poor prognosis. Majority of these patients are not candidate for a surgical treatment. Treatments such as chemotherapy and radiotherapy or combined modality have been tried in these patients in term of improve survival and quality of life.

Material and Methods: A retrospective analysis of 120 patients with advanced stage NSCLC was undertaken. The clinicopathological behavior observed and pattern of treatment they received such as radical and palliative treatment in form of radiotherapy and chemotherapy evaluated.

Results: Median age of presentation was 58 years, more common in male patients (84%) and smokers. Of total 120 patients only 39 (33%) received radical treatment, palliative treatment was received by 61 (51%) of cases. Whereas 17% patients were not received any treatment.

Conclusions: Combination chemotherapy and radiotherapy improve symptoms and quality of life.

INTRODUCTION: Lung cancer is a leading cause of cancer death and accounts for one third of all cancer related deaths [1]. Non small cell lung cancer is dominant histology accounting for 75% to 80% of lung malignancies [2]. Despite advances in early detection and treatment, non-small cell lung cancer is often diagnosed at an advanced stage. About 40% to 50% of patients presents with metastatic (stage IV) disease. As a consequence large majority of patients are candidate to a palliative treatment. In patients with untreated metastatic NSCLC median survival is four to five months. The survival rate at one year is only 10% and a median survival of only four months with best supportive care [3]. However, studies showed cisplatinum based chemotherapy produced modest clinical benefit and offers the possibility of temporary disease control, an improvement of quality of life in loco regional cases, but in advanced NSCLC treatment is still being debated [4]. Currently, cisplatin or carboplatin in combination of newer agents such as paclitaxel, docetaxel, irinotecan and gemcitabine is considered the standard regimen for these patients.

This study has been undertaken to analyze the clinicopathological behavior, appropriate strategies of management of advanced cases of non-small cell cancer lung and the outcome of therapy administered.

MATERIAL & METHODS: A retrospective analysis of patients with advanced stage NSCLC (Stage III & IV) was undertaken. All patients treated at Unit II, Department of Radiotherapy Pt. BDS PGIMS, Rohtak, Haryana, December 2007 to December 2009 were enrolled. These patients analyzed for various demographic data including age, sex, symptoms, and duration of symptoms. Tumor characteristics including histology subtypes and stage at diagnosis were also reviewed. Staging was done according to AJCC TNM staging system for lung cancers. After staging the patients, they received radiotherapy or chemotherapy accordingly of performance status. The doses and schedules of radiotherapy varied 20 Gy in 5 fractions or 8Gy in single session according to performance status and site of metastases, and symptoms. The chemotherapy was given to patients with comparatively better performance status or adjuvant to palliative radiotherapy. The chemotherapy regimes mostly consisted of carboplatin etoposide, carboplatin paclitaxel or carboplatin, gemcitabine.

RESULT: Total 120 patients of locally advanced inoperable non small cell carcinoma lung patients were evaluated in this study at the Department of Radiotherapy Pt. BDS PGIMS, Rohtak Haryana, between 2007- 2009. There were 101 (84%) male patients and 19 (16%) were female patients. The peak incidence of NSCLC was in 5th decade of life with median age of presentation was 58 years. Most of the patients' experienced acute symptoms with duration of 1-3 months in 43%.

Duration of symptoms of more than one year was observed in only 13% cases. The most common presenting complaints were cough (69%), fatigue (64%) and dysponea (57.5%). The patients belonging to stage III, IV were 57.5% and 42.5 % respectively. Among all evaluated cases 88% were smoker while only 12% of the patients were non smokers. Adenocarcinoma was in 41%, whereas squamous cell carcinoma in 42% and the rest were large cell type and unclassified.

Of total 120 patients only 39 (33%) received radical treatment in form of radiotherapy and chemotherapy. Palliative treatment was received by 61 (51%) of cases (**Table 2**), whereas, 17% patients did not receive any treatment. Patients were given neoadjuvant chemotherapy followed by radiotherapy. Patients received palliative radiotherapy that treated with palliative intention. Twwenty (17%) of these patients improved

symptomatically and in performance status and were given combination chemotherapy 2-3 weeks after completion of this palliative course of radiotherapy, consisting of radiation dose of 20 Gy /5 fractions in one week.

TABLE 1- PATIENTS' CHARACTERISTICS

Sr. No	Characteristic	No of patients (N=120)	%
1.	Age (years)		
	40-50	36	30
	51-60	41	34.16
	61-70	27	22.5
	71-80	16	13.33
	Median	58 years	
2.	Sex		
	Male	101	84
	Female	19	16
3.	Presenting symptoms		
	Fatigue	77	64.16
	Dysponea	69	57.5
	Pain	58	48.33
	Cough	83	69.16
	Hemoptyis	29	24.16
	Hoarseness of voice	35	29
	Anorexia	70	58.33
	weight loss	68	56.66
	Pleural effusion	16	13.33
	Fever	26	22
	SVC syndrome	19	16
4.	Duration of symptoms (Months)		
	1-3	51	43
	3-6	37	31
	6-12	17	14
	More than 1year	15	12.5
5.	Personal Habits		
	Non smoker	15	12.5
	Smoker	105	87.5
6.	Histopathology		
	Squamous cell carcinoma	50	41.6
	Adenocarcinoma	49	40.8
	Large cell carcinoma	16	13.33
	Unclassified	05	4.16
7.	Stage		
	III	51	42.5
	IV	69	57.5
8.	ECOG performance status		
	0	32	27
	1	76	63
	2	12	10
9.	Metastasis		
	Liver	14	11.66
	Adrenals	05	4.16
	Lymph nodes	17	14.12
	Brain	32	27
	Bone	29	24
	Lung	13	11

Of total 120 patients only 39 (33%) received radical treatment in form of radiotherapy and chemotherapy. Palliative treatment was received by 61 (51%) of cases (Table 2), whereas 17% patients not received any treatment. Patients were given neoadjuvant chemotherapy followed by radiotherapy. Those patients (51%) who were treated with palliative intention received palliative radiotherapy. The 20(17%) of these patients improved symptomatically and in performance status and were given combination chemotherapy 2-3 weeks after completion of this palliative course of radiotherapy, consisting of radiation dose of 20 Gy /5 fractions in one week.

TABLE 2: SHOWING TREATMENT PROTOCOL RECEIVED BY PATIENTS

Treatment modality	Radical treatment		Palliative treatment		No treatment	
	No	%	No	%	No	%
Chemotherapy and Radiotherapy	39	33	61	51	20	17

Among 120 patients who evaluated; total 72 patients (60%) received chemotherapy. Of 72 patients 13 % received platinum and etoposide, 27% received platinum and paclitaxel and, 24 % platinum and Gemcitabine. (Table 3)

TABLE 3: SHOWING CHEMOTHERAPY REGIMENS

Sr. No	Chemotherapy Regimes	No of pts (n=72)	%
1.	Carboplatin + Etoposide	12	10
2.	Carboplatin + Paclitaxel	31	26
3.	Carboplatin + Gemcitabine	29	24

TABLE 4: SHOWING THE DOSAGE AND SCHEDULES OF CHEMOTHERAPY SCHEDULES

Sr. No	Regimes	Dose
1.	Carboplatin	450mg IV, 200mg IV
	Etoposide	50 mg tds d 2,3 oral 3 wks cycle
2.	Carboplatin	450mg IV
	Gemcitabine	1.4 gm d 1, 8 IV 3 wk cycle
3.	Carboplatin	450mg IV
	Paclitaxel	260mg IV 3wk cycle

Carboplatin exhibits linear pharmacokinetics over the dosing range studied (300mg/m^2 _ 500mg/m^2) on the basis of this dose of carboplatin was 450mg in all patients.

TABLE 5: SHOWING RADIOTHERAPY SCHEDULES

Sr. No	Radiation therapy	No of pts	%
1.	60Gy/30 fr/ 6 wks	39	33
2.	20 Gy/5 fr	35	29.16
3.	8 Gy single session	26	21.66

Palliative radiotherapy in form of single session 800 cGy delivered at metastatic sites such as painful metastatic bones, vertebrae and symptomatic multiple brain metastases with poor performance to aims at symptomatic relief.

TABLE 6: RESPONSE OF TREATMENT OBSERVED AT 6 MONTHS

Variables	No. of pts	%
Complete response	-	-
Partial response	33	27.5
Stable disease	15	13
Progressive disease	19	16
Overall response rate	21	17.5

A response evaluation criterion in solid tumors (RECIST) was used to assess overall response. None of all evaluated patients showed complete response, 28% patients had partial response, 13% had stable disease, and whereas 16% had progressive disease after treatment. Overall response rate observed was 18%.

TABLE 7: SHOWING RESPONSE OF TREATMENT OBSERVED AT ONE MONTH OF FOLLOW UP

Sr. No	Symptoms	Symptomatic response
1	Hemoptysis	67%
2	Cough	48%
3	Pain	55%
4	Anorexia	34%
5	Dysponea	35%
6	Bone pain	81%
7.	SVC syndrome	79%

DISCUSSION: Non small lung carcinoma is a common neoplasm worldwide. It is now considered as leading cause of cancer death in both developed and developing countries and has become a major health problem.

In present study the peak incidence of nonsmall cell cancer lung was in 5th decade accounting for 34%, followed by 4th and 6th decade. Median age of presentation was 58 years.

Lung cancer is predominantly disease of males in present study out of 120 cases analyzed 84 % were males and 16 % were females.

Most common presenting symptoms in this series were cough 69% followed by fatigue 64% and dysponea (58%). Weight loss, anorexia was associated with advanced lesions. These are comparable with other studies [5]. The duration of symptoms before diagnosis were observed in less than 3 month 43% cases, 3-6 months 31% of cases, and more than 6 month 27% cases. These kinds of symptoms are also commonly observed in pulmonary diseases other than malignancies and may be one of the major causes of delayed presentation and diagnosis and hence poor outcome.

Smoking is considered as most important risk factor of causation of lung cancer. In present series 88% patients having a history of smoking either bidi, hookah and tobacco chewing of at least 20 years duration. In bidi smokers relative risk of developing lung cancer is 2.64 and for cigarette smokers 2.23 with overall relative risk 2.45 [6]. Tobacco smoking remains the leading preventable etiological factor for lung cancer.

Histopathological analysis showed 42% squamous cell tumors, 41% of adenocarcinoma and 13% large cell anaplastic tumors. In contrast to western countries where adenocarcinoma surpassed squamous cell carcinoma in women since 1950s and became the most common lung cancer diagnosis in men in 1990 [7] , in India squamous cell carcinoma is still common histological type [8].

Treatment modality of lung cancer includes surgery, radiotherapy and chemotherapy and more recently targeted therapies. There is no treatment with curative potential however radiotherapy and chemotherapy plays important role in management as local therapy and systemic therapy respectively. [9] The systemic chemotherapy offers the possibility of temporary disease control, an improvement in quality of life, and a modest increase in survival [5].

Type of treatment decided according to performance status of patients, weight loss, and symptoms. In this series only 33% had received treatment comprised of six cycles of chemotherapy followed by radiotherapy in doses of 60 Gy. Most of these patients were of stage III. Where as 50% of cases received palliative treatment in form of radiotherapy and 17% received palliative chemotherapy (Table 2).

Thatcher *et al*., observed in a study that combination chemotherapy produce partial regression in 30% to 40% of patients with stage IV disease, and complete response is rarely achieved [10]. Results from four meta- analysis also showed benefit of chemotherapy [11, 12, 13, 14].

Moreover, now it has been proved in various studies despite improvement in survival chemotherapy also have impact over quality of life; it reduces the symptoms like cough, hemoptyis, pain and dysponea in approximately 70% of patients and improvement in performance status and weight gain [15, 16, 17, 18].

Various chemotherapeutic agents have been tried in these tumors, but most of these active agents having low response rate and single agents have little or no impact on overall survival [9]. In

recent trials third generation agents such as gemcitabine, the taxens, topoisomerase- I interacting agents and vinorlbine have shown significant activity in NSCLC with improved one year survival in stage IV. These agents in combination with cisplatin or carboplatin have consistently demonstrated median survival rates of 8 to 10 months and one year survival rates of 30-40% in advanced stage disease [19, 20]. It has shown from these result that third generation combination chemotherapy with cisplatin and third generation agents to be superior than platinum in combination with an older generation agent with regard to response rate, median survival, and overall survival.

However, in present study combination regimens were given carboplatin etoposide in 10% cases, in those cases that were candidate for chemotherapy but can not afford other regimens. As some patients that presenting at our centre comes from poor socioeconomic strata. Other regimens given were carboplatin paclitaxel in 10% cases and carboplatin Gemcitabine in 24% (Table 3).

The benefit of carboplatin over cisplatin is that it does not significantly add to paclitaxel neurotoxicity, a combination of these two drugs has been well tolerated [4]. With paclitaxel response rate noted above 20% survival rates of 40% at one year [21, 22]. Gemcitabine response rate of over 20% alone and with cisplatin 30% to 58% have been reported [23, 24]. In present study, combination regimes of both Gemcitabine and paclitaxel have been prescribed.

Langer CJ *et al*., in Fox Chase Cancer Center study, which reported an impressive 62% response rate and 54% 1-year survival rate from a regimen involving intrapatient escalation of the paclitaxel dose between 135 and 215mg/m² and carboplatin dosed to achieve an AUC of 7.5mg/mL/min. Based on the reported phase I and II study results, recommended doses for the combination of paclitaxel/carboplatin call for paclitaxel to be given as a 24-hour infusion at 175 mg/m² or, in shorter infusions of 1 or 3 hours, at 200 to 225 mg/m², with carboplatin doses generally targeted to attain an AUC of 6 or 7 [25].

Radiation therapy is effective method in symptoms palliation. The patients with poor performance status and for symptoms palliation such as dysnpnea, chest pain, and metastases bone pain were given palliative radiotherapy also evaluated in presented study. In randomized studies, it is evident that radiation therapy can effectively palliate symptoms and improve performance status [26]. Palliative radiotherapy doses were 20 Gy in 5 fractions given in 29% of cases and 8 Gy in single session were given in 22% of cases (Table 5). The patients presenting with advanced stage disease frequently complain of distressing dysnpnea, hemoptyis, or chest pain were administered a course of radiation therapy with palliative intent consisting of 20Gy in 5 fractions over one week

It is evident from various studies that hypo fractionated radiotherapy (small, frequent dosing) has been shown to provide symptomatic relief with acceptable toxicity [27]. Palliative radiotherapy was also given to palliate bone pain, skull accordingly site of metastasis. Subjective improvement of pain, dysnpnea, cough, anorexia and hemoptyis were noted in about 46 % of cases in present study (Table 7).

A multi-institutional Phase III randomized study compared 10 Gy single-fraction radiotherapy (RT) with 20 Gy in five fractions in the palliation of thoracic symptoms from lung cancer and observed that fractionated RT group had greater improvement in symptoms related to lung cancer ($p = 0.009$), pain ($p = 0.0008$), ability to carry out normal activities ($p = 0.037$), and better global quality of life ($p = 0.039$) [28]. In another study, Donato *et al*. gave five fractions of radiotherapy (20 Gy total) to patients with stage IIIB and stage IV NSCLC with performance status of 0-3. A subjective

relief in dysnpnea, cough, and hemoptyis were observed in 97, 82, and 80%, respectively [29].

Senkus-Konefka *et al*., compared two palliative RT schedules for inoperable symptomatic NSCLC in two arms. One hundred patients were randomly assigned to 20 Gy in five fractions for 5 days or 16 Gy in two fractions for 1 and 8 days. No significant differences observed in term of treatment tolerance, in the degree of relief of symptoms. Both irradiation schedules provided comparable, effective palliation of tumor-related symptoms. The improved overall survival and treatment convenience of a two-fraction schedule suggest its usefulness in the routine management of symptomatic inoperable NSCLC [30].

Eighty one percent of patients with symptomatic bone metastases obtain pain relief with 8 Gy single session radiotherapy. Short course radiotherapy in form of 8 Gy in single session is as effective as higher doses for short term improvement of bone pain [31, 32]. Response to pain relief from bone metastases, in form of complete to partial have been reported is 75-100% [33]. Symptomatic response observed in 79% cases of SVC syndrome with fractionated palliative radiotherapy in this study (Table 7). Kawanami *et al*., in a study observed radiation therapy for SVC syndrome is associated with a good symptomatic response in 82% of patients within 3 days to 4 weeks [34].

In present study none of the patients showed complete response, partial response observed in 28% cases whereas stable disease in13% cases and progressive disease in 16% cases. Overall response rate observed was in 18 %cases.

CONCLUSION: Lung cancer is common cancer and most of the patients diagnosed at advanced stages. Most of the patients with this disease were smoker in present study; and common presenting symptoms were cough, dysponea and pain. Chemotherapy and radiotherapy were given in most of the patients. Patients experienced marked relief in symptoms.

Carboplatin in combination with other cytotoxic agents such as Gemcitabine, Taxens and Etoposide have shown improvement of symptoms. Palliative radiotherapy delivered to patients with locally advanced lung cancer who are not eligible for radical treatment or for patients with metastatic disease with symptoms such as bone pain, cerebral symptoms; palliative radiotherapy to the lung can improve symptoms and improve the quality of life.

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