Original Article

Outcomes of patients with unresected stage III and stage IV non-small cell lung cancer: A single institution experience

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ABSTRACT

Introduction: To report on the demographic profile and survival outcomes of North Indian population affected with stage III and stage IV non-small cell lung cancer (NSCLC). **Materials and Methods:** From November 2008 to January 2012, 138 consecutively diagnosed NSCLC patients were included in this study. The patient, tumor and treatment related factors were analyzed. Median overall survival (OS), Kaplan-Meier survival plots, *t*-test, Cox proportional hazards models were generated by multivariate analysis [MVA]) and analyzed on SPSS software (version 19.0; SPSS, Inc., Chicago, IL). **Results:** Median OS of stage III patients was 9.26 ± 1.85 months and 2-year survival rate of 13% while stage IV patients had median OS of 5 ± 1.5 months with a 2-year survival rate of 8%. Cox regression modeling for MVA demonstrated higher biologically equivalent dose (BED) ($P = 0.01$) in stage III while in stage IV non-squamous histology ($P = 0.01$), administration of chemotherapy ($P = 0.02$), partial responders to chemotherapy ($P = 0.001$), higher BED ($P = 0.02$), and those with skeletal metastasis alone ($P = 0.17$) showed a better OS. **Conclusion:** Our data showed that a higher BED is associated with favorable outcomes, indicating a role of dose escalated radiation therapy to the primary lesion in both stage III and essentially in stage IV NSCLC. Additionally, optimal use of chemotherapy relates to better survival. The developing, resource restrained nations need to follow an economically feasible multimodality approach.

KEY WORDS: Biologically equivalent dose, chemotherapy, non-small cell lung cancer, overall survival, radiation therapy

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INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women.[1] Non-small cell lung cancer (NSCLC) represents majority four-fifth of lung cancer cases, and most of these cases will be locally advanced (stage III) or metastatic (stage IV) at the time of presentation.[2-4] The most common treatment approaches are concurrent chemoradiation (CRT) and trimodality therapy, which involves CRT followed by the surgical resection.[5,6] However, this remains a very difficult and controversial area mainly because of the large heterogeneity of different pathological conditions seen in advanced NSCLC. Overall, the commonly employed modality of concurrent CRT therapy produces a median survival of 17-20 months, with a 3-year survival rate of 23% to 27%.[6] On the other hand, patients with stage IV NSCLC typically have a poor prognosis, with a median survival of 6 months.[7] The select patient group is suitable for palliative systemic therapy, which marginally improves survival and disease control. Radiation treatment for symptomatic relief is a common approach utilized in this advanced metastatic setting.[8]

Numerous validated prognostic factors have been established, which relate to survival outcomes in NSCLC cancer. However, in regions with limited resources there are other factors besides conventional ones, which prognosticate the treatment. The primary objective of this study was to report on the demographic profile and overall outcomes in our population afflicted with this malignancy.

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MATERIALS AND METHODS

We retrospectively reviewed the records of patients diagnosed with stage III and IV NSCLC November 2008 through December 2011. Staging/restaging was carried out as per the 7th edition of American Joint Committee on Cancer Staging System.[9] Institutional Review Board approved this study for the analysis. The included patients were evaluated initially by a multidisciplinary team of radiation, medical, and surgical oncologist. Patients who had recurrent lung cancer and/or received prior chemotherapy or radiation therapy (RT) were excluded from the analysis. Pre-treatment staging investigations included chest X-ray, chest computed tomography (CT) scans, bone scans or (18 F) 2-fluoro-2-deoxy-D glucose positron emission tomography scans, and central nervous system imaging with either contrast-enhanced CT or magnetic resonance imaging wherever indicated. Pathological diagnosis was established either by fine needle aspiration cytology (FNAC) or a bronchoscopic biopsy. The performance and financial status, along with the personal choice of the patient guided the choice of diagnostic investigation technique. Our institution is run by a charitable organization, and was primarily built to cater to the needs of people living in the remote regions of Himalayan region. Around 60-70% of patients visiting our institute need financial assistance during the course of their treatment. Below the poverty line category patients were given due financial concessions in their respective treatment at this multidisciplinary tertiary care hospital.

The routine protocol of treatment after obtaining informed consent for stage III NSCLC at our institute is induction chemotherapy (4-6 cycles, 3 weekly) followed by the chest RT. We did not follow concurrent CRT therapy schedules at our institute. This strategy was uninitiated due to added morbidity and poor nutritional status of our patients. Stage IV patients are managed with systemic chemotherapy, guided by performance status and extent of distant disease. Otherwise, only palliative RT is offered to the involved site.

The standard induction chemotherapy regimens employed at out center were either carboplatin (area under the curve, 6) plus paclitaxel (175 mg/m^2); or the more cost effective cisplatin (100 mg/m^2, day 1) along with etoposide (100 mg/m^2, day 1-3).[10] Two patients received gemcitabine/cisplatin combination as part of their induction treatment.

Chest RT in the latter half of 2008 was delivered through two-dimensional planning while three-dimensional conformal RT with CT-based planning was used with effective from 2010 onwards. However, the planning discretion and radiation dose fractionation was varied among the treating radiation oncologists' over the period of study. For patients with 2 gray-unit of radiotherapy dose (Gy) per fraction schedule, total dose prescription ranged from 50 Gy to 66 Gy. While those with 3 Gy or 4 Gy per fraction, total intended prescription was either 39 Gy or 20 Gy, respectively. Only once-daily fractionation schedule was used for all the patients in this study. Treatment planning was carried out with the ONCENTRA planning system (Nucleotron Medical Systems). In order to enable the comparison of the physical dose values with different fractionation schemes, we calculated the biologically equivalent dose (BED) using the linear quadratic formula: BED = (nd) (1 + d/[α/β]), n is the number of fractions, d is the fraction size, α/β ratio is 10 Gy.[11]

Overall survival (OS) was the primary endpoint of this study, which was measured from the start date of any treatment to patients' death from any cause or the last follow-up. Patients at our center are generally followed-up at 3-4 months interval for the 1st 2 years, and then every 6 months thereafter. Although, we request for patients physical presence on every follow-up, we routinely utilize telephonic services to do the same if otherwise. The OS was compared to the grouped variables using the log-rank test. Cox's proportional hazards model was used for multivariate analysis (MVA) to estimate the simultaneous impact of covariate factors on OS. All *P* values were two-sided with $P \leq 0.05$ considered significant. This study was statistically analyzed on SPSS software (version 19.0; SPSS, Inc., Chicago, IL). The retrospective nature of this study did not allow for detailed assessment of treatment related toxicity; however, no related mortality was observed.

RESULTS

Clinical and pathological characteristics

The clinical and pathological characteristics are summarized in Table 1. From 2008 to 2011, 138 patients were eligible for analysis. Patient age ranged from 35 years to 85 years (median 60 years). Sixty-five percent of the patients had Karnofsky Performance Status (KPS) ≥70% while 14% had superior vena cava obstruction syndrome at presentation. Staging thoracic CT scan was carried out in 90% of the patients. Six patients (4%) had PET-CT (Positron Emission Tomography-Computed Tomography) for staging at initial diagnosis. Bronchoscopy guided tissue sampling was done in 26% of the patients while image guided FNAC contributed to the remaining 74% of the pathological diagnosis. Squamous cell histology was established in 25%, adenocarcinoma in 16% of the patient population while 59% were classified as NSCLC NOS (not otherwise specified).

51% had stage III NSCLC; III A-20% and III B-31% and 49% had stage IV NSCLC disease at presentation. Metastatic sites apparent at the time of the presentation included bone (n = 38), brain (n = 16), liver (n = 4), lung nodules (n = 4), malignant pleural effusion (n = 11) and malignant pericardial effusion (n = 2). Out of the 38 patients with the skeletal metastasis, 24 had multiple metastases while 14 had single bone lesions.

Table 1: Clinico-pathological characteristics

Characteristics	No. of patients (%)		
	Entire cohort, *N*=138 (100%)	AJCC stage III *N*=71 (51%)	AJCC stage IV *N*=67 (49%)
Media age (range), years	60 (35-85)	60 (40-87)	60 (18-80)
Sex			
Men	124 (90)	67 (94)	34 (51)
Women	14 (10)	4 (6)	33 (49)
Karnofsky performance status			
<70	48 (35)	20 (28)	28 (42)
≥70	90 (65)	51 (72)	39 (58)
Histology			
NSCLC NOS	81 (59)	40 (56)	41 (61)
Squamous	34 (25)	20 (28)	14 (21)
Adenocarcinoma	23 (16)	11 (16)	12 (18)
AJCC stage			
IIIA	28 (20)		
IIIB	43 (31)		
IV	67 (49)		
SVCO			
Yes	18 (14)	13 (18)	5 (9)
No	120 (86)	58 (82)	62 (91)
CT chest			
Yes	124 (90)	66 (93)	58 (87)
No	14 (10)	5 (7)	9 (13)
Bronchoscopy			
Yes	36 (26)	24 (34)	12 (18)
No	102 (74)	47 (66)	55 (82)

SVCO: Superior vena cava obstruction, CT: Computed tomography, AJCC: American joint committee on cancer, NSCLC: Non-small cell lung cancer, NOS: Not otherwise specified

Table 2: Treatment and outcome characteristics

Variables	No. of patients (%)		
	Entire cohort, *N*=138 (100%)	AJCC stage III *N*=71 (53%)	AJCC stage IV *N*=67 (47%)
Induction chemotherapy	75 (55)	45 (63)	30 (42)
Chemotherapy compliance			
Completed course	55 (73)	35 (78)	20 (67)
Incomplete/defaulted	20 (27)	10 (22)	10 (33)
Chemotherapy response			
Partial	47 (63)	31 (69)	16 (53)
Progressive	24 (32)	12 (27)	12 (40)
Stable/no response	4 (5)	2 (4)	2 (7)
Radiotherapy site			
Primary-thoracic RT	109 (79)	71 (100)	38 (57)
Metastasis	29 (21)		29 (43)
Radiotherapy dose to primary site; BED, Gy			
≤50	63 (58)	34 (48)	29 (76)
>50	46 (42)	37 (52)	9 (24)
Radiotherapy dose fractionation (primary thoracic RT)			
Hypofractionation	60 (55)	30 (42)	30 (79)
Conventional	49 (45)	41 (58)	8 (21)
Radiotherapy compliance			
Completed course	109 (79)	53 (75)	56 (84)
Defaulted	29 (21)	18 (25)	11 (16)
Status at last follow up			
Alive with disease	15 (11)	8 (17)	7 (11)
Died of disease	98 (71)	49 (69)	49 (73)
Lost to follow-up	21 (18)	10 (14)	11 (16)

BED: Biologically equivalent dose, Gy: Gray-unit of radiotherapy dose, RT: Radiation therapy, AJCC: American joint committee on cancer

Treatment and outcome characteristics

Treatment and outcome characteristics are summarized in Table 2. Sevety-five patients (55%) received induction chemotherapy; 55 of these patients were given cisplatin plus etoposide regimen, 17 received paclitaxel plus carboplatin combination while 3 patients were induced with gemcitabine plus carboplatin regimen. A higher number of patients with stage III (n = 45) were given induction chemotherapy in comparison to stage IV patients (n = 30), P = 0.04. Fifty-five (73%) of 75 patients completed the planned induction chemotherapy, and 47 (63%) patients achieved a partial response to this treatment. One hundred-nine (79%) of the patients received primary thoracic RT while 29 (21%) patients received RT only to the metastatic sites. Conventional 2 Gy fractionation was utilized in 45% of the patients while hypofractionation was used in 55% of the patients. Hypofractionation to the primary thoracic site was statistically more favored in stage IV patients (n = 30, 79%) than stage III group (n = 30, 42%), P = 0.001. Median RT-BED dose was 50 Gy (range, 16-79.2 Gy). A lower BED prescription to the primary thoracic site was observed in stage IV NSCLC (≤50 Gy, n = 29, 76%) in comparison to stage III disease (>50 Gy, n = 37, 52%), P = 0.05. Of all the patients who received RT, 79% completed the planned RT prescription.

The median OS for the entire cohort was 8 ± 1.14 months (range, 1-28 months; 95% CI: 5.75, 10.25). Stage-wise median OS distribution for stages III A, III B, and IV was 10.5 ± 1.5 months, 9.7 ± 1.34 months, and 5 ± 1.5 months, respectively. The 1-year, 2-year and 3-year OS for all patients with stage III NSCLC was 34%, 13%, and 9% versus 25%, 8% and not assessable, respectively for stage IV disease. The OS analysis is tabulated in Table 3. In the univariate analysis (UVA), for stage III patients, partial responders to chemotherapy, use of conventional RT fractionation and higher BED yielded superior OS [Figures 1 and 2]. Stage III substages A and B, did not show any inherent differences in the OS or any studied covariates, hence largely they were clubbed together in the overall analysis of this dataset. Stage III patients did not show any survival difference between squamous and non-squamous histologies. For patients with stage IV NSCLC, UVA demonstrated that patients with good KPS, non-squamous histology, administration of chemotherapy, partial responders to chemotherapy, higher BED, and those with skeletal metastasis alone showed a better OS. In the subsequent Cox regression modeling for MVA in stage III group, only higher BED remained significant while in stage IV all the significant UVA covariates maintained their statistical significance as being strong predictors for OS [Table 3].

DISCUSSION

Certain reliable prognostic markers such as age, sex, performance status, disease stage and tumor histology have been linked to survival in NSCLC patients.[12] The overall

Table 3: Overall survival analysis

Prognostic variables		UVA			
		Stage III		Stage IV	
	Group	Median overall survival, OS months±SE (95% CI)	Log rank *P*	OS months±SE (95% CI)	Log rank *P*
Age			NS		NS
Sex			NS		NS
Karnofsky performance scale	≥70		NS	8±1.5 (5.03, 10.9)	0.01
	<70			2±0.35 (1.3, 2.7)	
Histology	Non-squamous		NS	7±1.5 (4, 9.9)	0.03
	Squamous			3±0.57 (1.8, 4.12)	
Chemotherapy	Received		NS	11±2.1 (6.7, 15.2)	0.001
	Not received			3±0.46 (2.1, 3.9)	
Response to chemotherapy	Partial	11±1.14 (8.7, 13.2)	0.013	14±1.5 (10.9, 17)	0.001
	Progressive	5±0.51 (3.9, 6)		3±0.5 (1.9, 4)	
Radiotherapy fractionation	Conventional	10±1.0 (7.9, 12.09)	0.015		NS
	Hypofractionation	5±3.02 (0, 10.9)			
Biologically equivalent dose	>50 Gy	11±1.5 (7.9, 14)	0.001	17±2.6 (11.7, 22.2)	0.03
	≤50 Gy	5±0.90 (3.2, 6.7)		8±1.42 (5.2, 10.7)	
Site of metastasis	Skeletal only			7±2.3 (2.45, 11.54)	0.10
	Visceral			3±0.87 (1.29, 4.7)	
Variable		**MVA**			
	Associated group	**Stage III**		**Stage IV**	
		OS Hazard ratio (95% CI)	***P***	**OS Hazard ratio (95% CI)**	***P***
Histology	Non-squamous		NS	0.05 (0.01, 0.39)	0.01
Chemotherapy	Not received		NS	11.29 (1.38, 92.19)	0.02
Response to chemotherapy	Progressive		NS	53.8 (5.4, 574.8)	0.001
BED	>50 Gy	0.29 (0.12, 0.69)	0.01	0.13 (0.02, 0.79)	0.02
Site of metastasis	Visceral		NS	2.32 (0.68, 7.92)	0.17

NS: Not significant, CI: Confidence interval, BED: Biologically equivalent dose, Gy: Gray-unit of radiotherapy dose, OS: Overall survival, UVA: Univariate analysis, MVA: Multivariate analysis

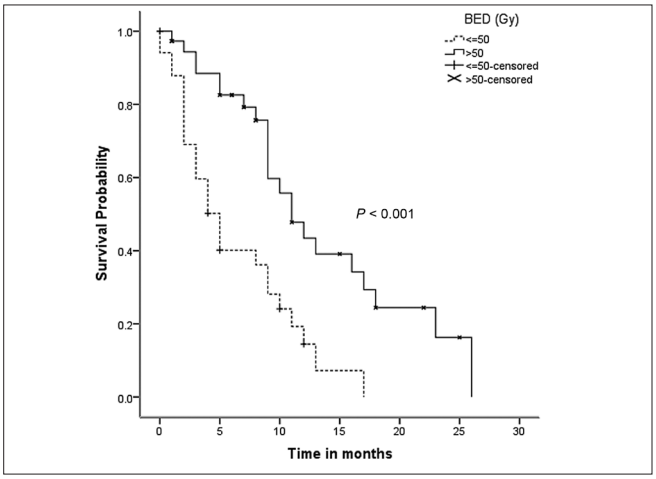

Figure 1: Overall survival in stage III non-small cell lung cancer for the biologically equivalent dose stratification

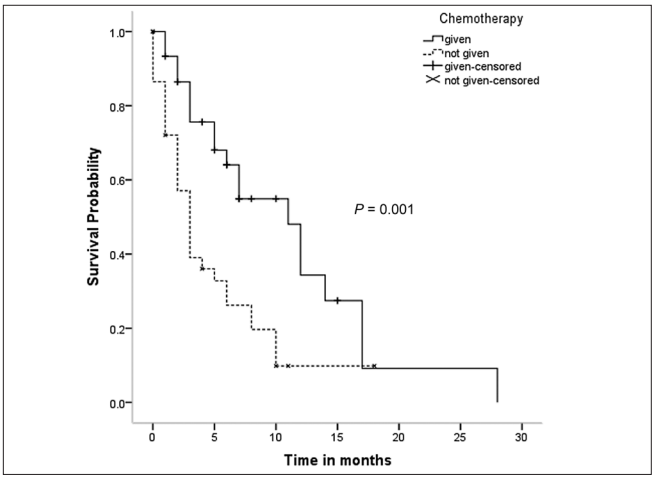

Figure 2: Overall survival in stage IV non-small cell lung cancer for the chemotherapy stratification

5-year survival rate for locally advanced lung cancer is 16%.[1] Additionally surveillance, epidemiology, and end results data reports that 25% are diagnosed with locally advanced, probably unresectable stage III B NSLC and a strong figure of 51% was seen with proven metastasis (stage IV disease) at presentation.[13] In our study, 49% of the entire cohort the metastatic disease while the remaining 51% were unresectable stage III NSCLC. Unresectability was defined through a multidisciplinary consult with the attending surgical oncologist, and was definitely guided by the patients' preference and high surgical mortality involved with this advanced disease. Poor prognosis and mortality is probably the decisive factor in determining the patient's choice. However, the role of surgery, if any, in stage III NSCLC with clinical nodal involvement is rather considered limited.[14] Similarly, adopting less invasive diagnostic modality of FNAC relates to patient's wishes rather than technical expertise.

The standard therapy for such subset of patients is preferentially combined modality of chemotherapy and RT. Combined modality of RT with concurrent or sequential chemotherapy is superior to RT in unresectable stage III B NSCLC.[15] However, concurrent schedules have been shown to have better patient related survival outcomes than sequential therapy.[16,17] However, the inherent toxicity of concurrent schedules seems to be the only logical reason why the oncologists preferred sequential therapy in our study. Fifty-five percent of the study population received induction chemotherapy followed by RT, and none received concurrent regimen. For stage IV NSCLC, palliative RT, or chemotherapy for those with the good performance status is currently the recommended guideline.[18] Cisplatin-based chemotherapy for metastatic non-small-cell lung cancer results in a small, but statistically significant improvement in survival, as compared with supportive care alone.[19] Our study showed a survival benefit in stage IV NSCLC patients who received chemotherapy, non-squamous histology and those with the response to chemotherapy, but overall poor performance status was the main deterrent to the use of chemotherapy as a standard guideline in our clinical setting. Histologic subtype does not reliably provide prognostic importance in patients with advanced NSCLC, despite the different clinical manifestations of non-squamous compared to squamous histology.[20,21]

Radiation dose and use of chemotherapy are independent predictors of OS in stage III/IV NSCLC. The effect of higher radiation doses on survival was independent of whether chemotherapy was given.[22] Higher BED was consistently significant predictor for OS in both stage III and IV NSCLC patients in our study. Unexpectedly, primary RT in stage IV relates to survival, but considering small sample size of our study we should be cautious in interpreting this result. Oncologists may consider that this variable is influenced by performance and socioeconomic status as well. This is one of the few other strong limitations of our study. A small sample size, retrospective nature, and lack of newer systemic chemotherapeutic options inhibit our study to conclude with confidence. In dose escalation studies for NSCLC, the best outcomes were obtained for the hypofractionated schedules.[23,24] Hypofractionated chest radiation is well tolerated and can be administered safely concurrently with chemotherapy. Hypofractionation was more favored regimen in our study; however, it did not show any significant impact on the OS. However, this simplified, convenient regimen could benefit patients in need for both local and systemic palliation.[24,25] This was evidently the main reason why we prescribed RT to the primary site in stage IV disease to relieve local symptoms, despite the lack of evidence in such patients.

Overall, our study shows definite inferior results than western data in similar patient group and successful interventions to increase local and systemic control need to be addressed. The relative dismal performance of our study could be related to an advanced stage, poor performance of patients, and a restricted incorporation of aggressive and newer systemic therapies. Innovations with RT include dose escalation, altered fractionation, and integration with concurrent chemotherapy. Our study suggests that adding a primary RT to metastatic NSCLC patients is of potential benefit. Nonetheless despite this, the important issues, to address include early detection through screening, improving the relatively rigid performance status, developing a guide as to which patients are appropriate for chemotherapy, the survival and palliative impact of chemo-radiotherapy, the optimal economically feasible treatment approach, and its toxicity and decisively discuss the outcomes expectations with the patient and their relatives.

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