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Assessment of the clinicodemographic parameters and treatment outcomes of locally advanced and metastatic lung cancer cases – A retrospective study from northeast India

Satya Sadhan Sarangi[1], Munlima Hazarika[2], Partha S Roy[3], Nithin D Raj[4], Partha P Medhi[5], Anupam Sarma[6]

[1,4,5]Assistant Professor, [2,3,6]Professor, Department of Medical Oncology, Dr. Bhubaneswar Borooah Cancer Institute, Guwahati - 781 016, Assam, India.

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ABSTRACT

Background: There are many lacunae in our current understanding of the shifting epidemiological trends of lung cancer as well as lack of data among Northeast Indian patients. **Aims and Objectives:** This study tried to assess the clinicodemographic and treatment outcomes of advanced lung cancer cases. **Materials and Methods:** This was a retrospective hospital-based study. Patients with histopathologically confirmed locally advanced and metastatic lung cancer and were registered at Dr. Bhubaneswar Borooah Cancer Institute between January and December 2017 who were included in the study. A record was made of patient demographic-, clinical-, and treatment-related parameters. Kaplan–Meier survival curves were obtained. A two-tailed $P<0.05$ was considered statistically significant. **Results:** Majority of the patients were elderly males (median = 60 years), with a history of smoking in three quarter of them. Non-small-cell lung carcinoma (94%) type was the most common histology. About 93% of patients presented with TNM stage IV disease. The most common palliative chemotherapy (CT) regimen used was taxanes and platinum doublet (n = 24, 35%). With a median follow-up of 6 months (range 0–37), the median progression-free survival and overall survival were 8 months and 10 months, respectively. The median survival was significantly longer in patients younger than 60 years. (13 months; $P=0.021$) and in those with non-small-cell histology (10 months). **Conclusion:** In this audit of resource-limited population with advanced lung cancer, palliative CT remains the mainstay of treatment. There is a further need to improve the survival of these advanced cases in a cost-effective manner.

Key words: Lung cancer; Treatment outcomes; Northeast India; Audit; Clinicodemography; Epidemiology

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INTRODUCTION

Lung cancer is a major health concern in India, with significant morbidity and mortality rates. Although several epidemiological studies have been conducted across several demographic cohorts in India, there are gaps in our understanding of the changing trends of lung cancer among Indian patients. Furthermore, such studies confirm the significant burden and cancer related morbidity and mortality of lung cancer in India.[1] The quality of the data acquired from Indian hospital-based registries and regional cancer registries may be mired by incomplete penetrance of disease registration across the different states of India, resulting in an underestimation of the overall burden. In India, the incidence is around 63,000 new cases per year, with approximately one-third patients presenting at a locally advanced stage.[2] The estimated overall lung cancer mortality in India in 2012 was 63,759 with lung cancer being the most common cause of death in males (estimated mortality in males and females are 48,697 and 15,062, respectively).[3]

Address for Correspondence:
Dr. Satya Sadhan Sarangi, Assistant Professor, Department of Medical Oncology, Dr. Bhubaneswar Borooah Cancer Institute, Guwahati - 781 016, Assam, India. **Mobile:** +91-9795909502. **E-mail:** satyasarangi1991@gmail.com

More than 95% of lung cancers consist of one of the four major histologic types: Squamous cell carcinoma, adenocarcinoma, large-cell, or small-cell carcinoma. Adenocarcinoma, large-cell cancer, and squamous cell cancer are collectively known as non-small-cell lung cancer (NSCLC). NSCLC is the most common histology (85%), while SCLC contributes to only 15% of all cases of lung cancer.[4] For patients with NSCLC, initial treatment is based on the stage of disease. For patients with the early-stage disease, surgical resection offers the best opportunity for cure, while concurrent chemoradiotherapy (CCRT) is preferred for those with more extensive intrathoracic disease.[5,6] In contrast, patients with advanced disease are managed with palliative intent using systemic therapy and/or local palliative modalities. In case of patients with SCLC, systemic chemotherapy (CT) is an important component of treatment, because it is disseminated at presentation in almost all patients.

Treatment options for lung cancer depend on the stage of disease, with surgical resection being the best option for the early-stage NSCLC, and systemic CT being the primary treatment for SCLC. Despite advances in lung cancer treatments, patient selection and prognosis evaluation remain important factors for improving treatment outcomes.

Since there is a lack of information about lung cancer in Northeast India, our study aimed to evaluate the clinicodemographic features and treatment outcomes of patients with locally advanced and metastatic lung cancer who visited Dr. Bhubaneswar Borooah cancer institute (BBCI) in Guwahati, Assam, India. The purpose of this study is to bridge the knowledge gap about lung cancer in this region by collecting and analyzing data from a specific population of patients with advanced lung cancer. By doing so, we aim to gain insights that can help improve treatment and their outcomes for lung cancer patients in Northeast India.

Aims and objectives

The aim of the study was to assess the clinico-demographic and treatment outcomes of advanced lung cancer cases of tertiary cancer care hospital of Guwahati, Assam.

MATERIALS AND METHODS

Study design and patient population

This retrospective study examined the medical records of patients diagnosed with locally advanced and metastatic cancer lung registered at Dr. BBCI, Guwahati between January and December 2017 and those fulfilling the inclusion criteria were enrolled. The study inclusion criteria were: (i) patients of either gender aged 18 years or older; (ii) histopathologically and cytologically confirmed carcinoma of lung (both NSCLC and SCLC included); (iii) locally advanced and metastatic lung cancer (Stage III–IV); (iv) patients having available baseline complete blood count parameters; and (v) patients having available information on the demographic characteristics and clinical outcomes. Patients who had cancer other than lung cancer were excluded from this study. The study was conducted after due approval from Institutional Medical Ethics Committee of Dr. B. Borooah Cancer Institute, Guwahati, India.

Sample size, study procedure and assessments

Between January 2017 and December 2017, 546 patients with locally advanced and metastatic lung cancer were registered the Dr. B. Borooah Cancer Institute hospital-based cancer registry (HBCR). A total of 202 patients were qualified for our retrospective study who fulfilled the inclusion criteria and constituted the sample size (Figure 1). The demographic and clinicopathological information was extracted by reviewing the patients' medical files/charts and Dr. B. Borooah Cancer Institute Hospital medical records. A record was made of patient age, gender, occupation, distance travelled to reach hospital, Eastern cooperative oncology group (ECOG) performance status (PS), date of registration, date of diagnosis, pathological diagnosis, tumor histology, tumor stage, treatment, progression, last visit date, and exitus date of patients who died. Staging of the patients was

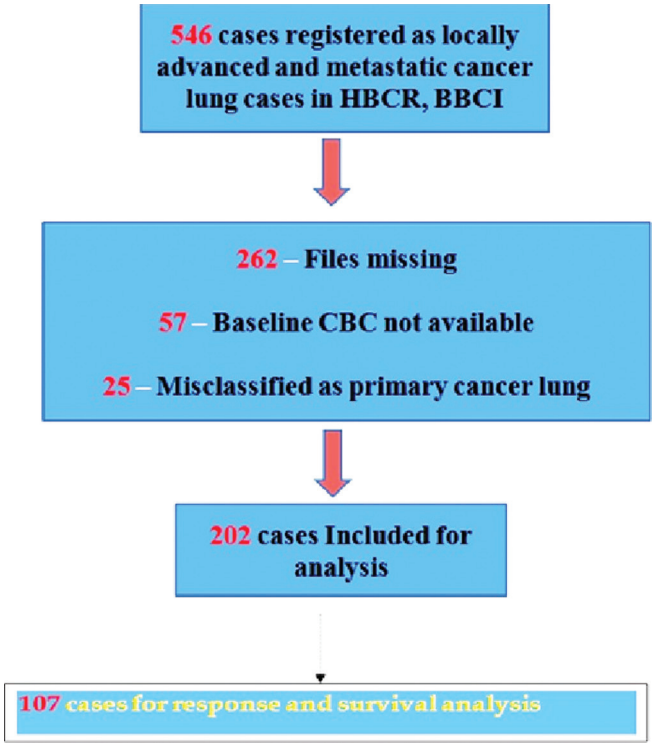

Figure 1: Consort flow diagram depicting selection of patient population

performed clinically and radiologically using chest X-ray, contrast-enhanced computed tomography of chest, abdomen and pelvis, bone scan, 18-fluorodeoxyglucose positron emission tomography (as per feasibility), cranial magnetic resonance imaging (when indicated), and clinically according to the seventh American Joint Committee on Cancer classification.[7] Tumor histology was classified as SCLC and NSCLC.[8] NSCLC was further characterized as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, or poorly differentiated carcinoma. EGFR and ALK mutation status was also assessed in some patients, wherever possible.

Patients with Stage III lung cancer were either treated with concurrent CCRT and neoadjuvant CT (NACT) followed by sequential radiotherapy (RT) or RT alone as per clinician discretion and disease status. CCRT consisted of 60 Gy EBRT in 30 fractions once daily over 6 weeks with concurrent CT in the form of either two cycles of cisplatin (CP) at a dose of 75 mg/m^2 day 1 (D1) and etoposide 100 mg/m^2 on day 1–3 (D1- D3; every 3 weekly) followed by two cycles of (same chemoregimen) adjuvant CT or weekly regimen of paclitaxel 45 mg/m^2 on D1 and carboplatin at a dose of area under curve (AUC) of 2 on D1. Single-agent weekly concurrent CP 35 mg/m^2 was also used in less fit patients. NACT consisted of 3–4 cycles of 3 weekly regimen of pemetrexed 500 mg/m^2 on D1 and CP 75 mg/m^2 on D1 (or carboplatin AUC 5 on D1) for adenocarcinoma histology and 3–4 cycles of paclitaxel 175 mg/m^2 and CP 75 mg/m^2 on D1 (or carboplatin AUC 5 on D1) or 3 weekly regimen of gemcitabine 1 g/m^2 on D1, D8, and CP 75 mg/m^2 on D1 (or carboplatin AUC 5 on D1) for squamous cell histology. The small-cell histology was treated with CP 75 mg/m^2 on D1 and etoposide 100 mg/m^2 on D1–D3 every 3 weekly. All patients with metastatic disease and good PS were treated with palliative CT. CT regimen varied from patient to patient as per disease biology, patient preference, and clinician's judgment. Those patients who had EGFR and ALK mutation positive were treated with oral tyrosine kinase inhibitors (gefitinib, erlotinib for EGFR positive NSCLC, and crizotinib for ALK positive NSCLC) as first-line agents. Palliative RT at a dose of 8 Gray (Gy) single fraction and consolidative RT with dose 30 Gy in ten fractions were also used as per clinical indications, wherever needed. Patients having good PS after failing first-line CT were treated with second-line CT. Second-line CT regimens consisted of either 4–6 cycles of single-agent docetaxel at a dose of 75 mg/m^2 every 3 weekly, single-agent platinum- or gemcitabine-based regimens. For patients with poor PS, best supportive/palliative care was given.

Statistical analysis

Statistical analyses were performed using SPSS® for Windows®, version 18.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as percentage, mean, standard deviation, range, and median values with quartiles. Chi-squared statistics or Fisher's exact test were used for comparing the differences between the groups. Independent variables predicting survival were evaluated using the Cox proportional hazards model. A two-tailed $P<0.05$ was considered statistically significant. Survival curves were obtained with Kaplan–Meier survival curves, and log-rank test were used for comparison between groups. Survival status was determined from the date of registration for each patient at BBCI. The progression-free survival (PFS) was calculated from the date of pathological diagnosis to the date of progression, date of death or to the date of last follow-up for patients who had not died before the censor date. The overall survival (OS) is calculated as time from treatment to death due to any cause; for patients who were still alive at the time of data analysis or who were lost to follow-up, OS was censored at the last recorded date that the patient was known to be alive.

RESULTS

Patient demographic characteristics

The median age of presentation was 60 years (range: 30–96 years). Of 202 patients, 156 (77%) patients were males, whereas, 46 (23%) were female, with a male-to-female ratio of 3.3:1. The median distance that patients had to travel to reach the hospital was 145 km (range10–700 km). The most common district in Assam from where patients were referred to BBCI was Kamrup district (25 patients; 12%). Thirteen (7%) patients were referred to BBCI from outside the state of Assam. Majority of the patients were farmers (45%) by occupation (Table 1).

Disease characteristics

Weight loss, which is defined as loss of more than 5 kg in 3 months' time period, was the most common presentation (in 59% patients). Non-small-cell carcinoma (94%) type was the most common histology. Among the non-small-cell cancer group, adenocarcinoma was the most common histology in 122 (60%) of patients, followed by squamous cell carcinoma in 59 (29%) of patients. More than 93% of patients presented with TNM stage IV followed by stage III in 7% of patients (Table 2).

Treatment characteristics

Of the 202 patients, 13 patients were treated with radical intent and 189 patients were treated with palliative intent. Ninety-five patients (47%) did not receive any form of treatment either due to their poor PS or loss to follow-up before starting treatment. For the remaining 107 patients, 4 (4%) were treated with concurrent CCRT, 57 (53%) with CT alone with or without maintenance regimen, 7 (6.5%) with RT

Table 1: Demographic characteristics of patients

Characteristics (n=202)	Frequency (%)
Age in years	
Mean±SD, Range	60±12; 30–96
Median, Q1-Q3	60; 53–70
Gender	
Male	156 (77)
Female	46 (23)
ECOG performance status	
0	6 (3)
1	106 (52)
2	57 (28)
3	33 (17)
History of smoking	
Yes	153 (75)
No	49 (25)
Distance from native place (in kms)	
Mean±SD, Range	185±141, 10–700
Median, Q1–Q3	145, 83–270
Place of referral	
State of Assam	189 (93)
Outside state of Assam	7 (13)
Occupation	
Farmer	91 (45)
Housewife	43 (21)
Businessman	21 (11)
Government employee	26 (13)
Manual laborer	19 (9)
Others	2 (1)

ECOG: Eastern co-operative oncology group

Table 2: Disease characteristics

Characteristics (n=202)	Frequency (%)
History of weight loss	
Yes	119 (59)
No	75 (37)
Unknown	8 (4)
TNM stage	
III	13 (7)
IV	189 (93)
Histological group	
NSCLC	190 (94)
SCLC	12 (6)
Histological subtype	
Adenocarcinoma	122 (60)
Squamous cell carcinoma	59 (29)
Small-cell carcinoma	11 (6)
Poorly differentiated carcinoma	4 (2)
Others	6 (3)
Mutational analysis	
Done	45 (22)
Not done	157 (78)
Mutational analysis (n=45)	
Present	9 (20)
Absent	36 (80)

NSCLC: Non-small-cell lung cancer, SCLC: Small-cell lung cancer

alone (including both palliative and radical RT), 7 (6.5%) with CT followed by RT, and 32 (30%) patients received targeted therapy. For the patients receiving any type of CT (68/107), the most common regimen was platinum and taxane-based (24; 35%) with a total of six cycles (Table 3).

Table 3: Treatment characteristics

Characteristics (n=202)	Frequency (%)
Intent of therapy	
Radical	13 (7)
Palliative	189 (93)
Any treatment received	
Yes	107 (53)
No	95 (47)
Type of treatment (n=107)	
CCRT	4 (4)
CT alone with or without maintenance	57 (53)
CT followed by RT	7 (6.5)
RT alone	7 (6.5)
Targeted therapy alone	32 (30)
Chemotherapy regimen (n=68)	
Platinum+Taxane	24 (35)
Platinum+Pemetrexed	22 (32)
Platinum+Etoposide	10 (15)
Platinum+Gemcitabine	10 (15)
Single-agent Platinum	2 (3)

CT: Chemotherapy, CCRT: Concurrent chemo-radiotherapy, RT: Radiotherapy

Response and survival parameters

For the response and survival analysis, 107 patients who underwent any type of treatment were included in the study. Seventy-one (66%) patients had a response to initial therapy (partial response [PR] – 32%; stable disease – 34%). With a median follow-up of 6 months (range 0–37), the median PFS and OS was 8 months (Figure 2) and 10 months (Figure 3), respectively. Progressive disease was detected in 73 patients (68%) on further follow-up. Salvage therapy was attempted in 23 patients (31%), mostly in the form of second line CT. At the time of data analysis, 3 (2.8%) patients were alive, 52 (48.6%) were dead, and 52 (48.6%) were lost to follow-up (Table 4).

Median survival time in patients ≤at years (13 months) was significantly longer than that of patients aged >60 years (9 months) (P=0.021). There was also a significant difference between median survival time in patients with NSCLC (10 months) versus patients with SCLC (6 months) (P=0.021) (Table 5).

Clinical factors such as age, gender, stage, histology, PS, and weight of patient does not correlate as an independent predictive factor for longer survival on multivariate cox regression analysis. However, there was a trend toward significance for younger age (≤age years vs. >60 years) (hazard ratio [HR] 0.55, 95% CI: 0.304–1.023, P=0.059) and PS (ECOG PS "0 and 1" vs. "2 and 3") (HR 0.65, 95% CI: 0.440–1.115, P=0.085). In addition, for neutrophil-to-lymphocyte ratio (NLR), HR was found to be 0.76 at an interval range of 0.379–1.537, which considered as non-significant (P=0.449) (Table 6).

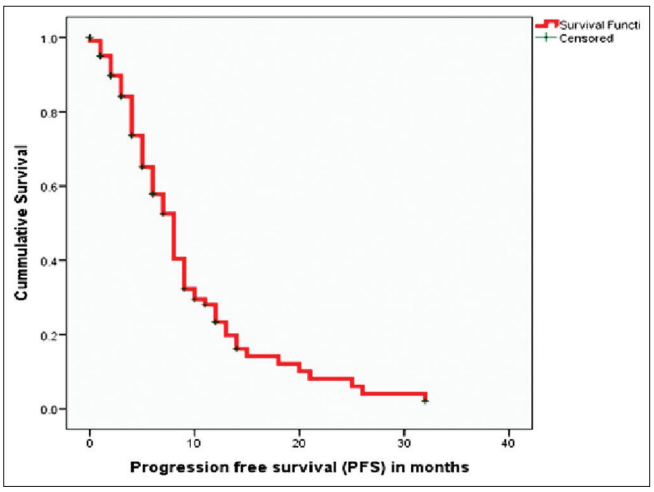

Figure 2: Kaplan Meir curve showing progression free survival of patients with locally advanced and metastatic lung cancer

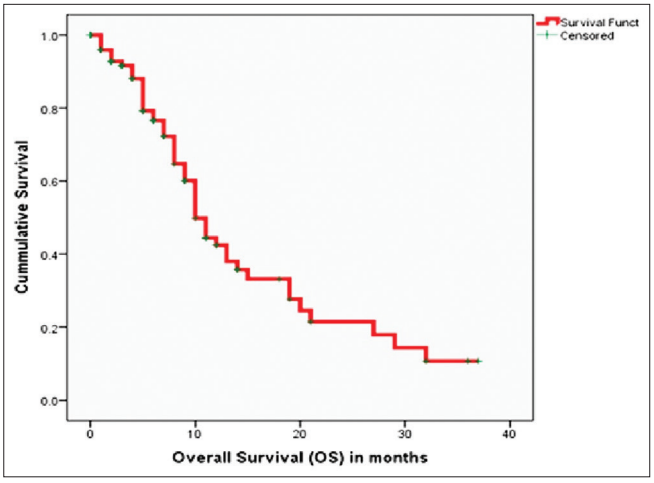

Figure 3: Kaplan Meir curve showing overall survival of patients with locally advanced and metastatic lung cancer

DISCUSSION

In this retrospective study, we tried to evaluate the demography, clinical characteristics, and treatment parameters in patients with advanced lung cancer. With an increment in life expectancy and the heightened risk of cancer with aging, lung cancer is common in elderly age group. Around 50% of lung cancer cases are diagnosed in patients aged >65 years.[9-11] The median age at diagnosis of lung cancer is between 64 and 70 years as reported in various studies.[10,11] The median age at diagnosis (60 years) in the present study was in line with the previous published studies. As per the GLOBOCAN 2008 report,[12] there was a male predominance with a male: female ratio of 4.5:1 and this ratio varies with age and smoking status. In this study also, the male: female ratio was 3.3: 1, was similar to GLOBOCAN data. The history of published data on lung cancer epidemiology in India reflects the impact of industrialization and smoking trends on cancer in the community.[13] The percentages of tobacco-related products smoked in India are beedis (28.4–79%), cigarettes (9.0–53.7), hookah (3.4–77.3), and mixed (7.5–13.6).[13] Although, in this study, the type of products smoked was not documented, but the history of smoking was seen in 75% of patients. This high rate of smoking could be attributed to local cultural practices. Rural patients for many reasons are deprived from better health-care services and, they constitute a population at risk of poorer prognosis.[14] A

Table 4: Response and survival analysis

Characteristics (n=107)	Frequency (%)
Treatment response	
CR	0 (0)
PR	35 (32)
SD	36 (34)
PD	23 (22)
Unknown/not documented	13 (12)
Status at last follow-up	
Alive	3 (2.8)
Dead	52 (48.6)
Loss to follow-up	52 (48.6)
Progression	
Yes	73 (68)
No	2 (2)
Unknown	32 (30)
Salvage therapy (n=73)	
Yes	23 (31)
No	52 (69)

PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease

Table 5: Median overall survivals time of according to basic characteristics

Group	Median (in months)	95% confidence interval	P-value
Gender			
Male	10	9.040–10.960	0.313
Female	14	7.678–20.322	
Age (years)			
≤age	13	8.358–17.642	0.021
>60	9	7.743–10.257	
Smoking			
Yes	10	8.271–11.729	0.205
No	14	8.159–19.841	
Histology group			
NSCLC	10	8.513–11.487	0.021
SCLC	6	0.001–9.544	
TNM stage			
III	11	8.868–13.404	0.826
IV	10	8.596–11.132	
ECOG PS			
0	13	1.913–24.087	0.084
1	11	8.719–13.281	
2	10	6.118–13.882	
3	5	2.299–8.868	
Weight loss (in kg)			
Yes	10	7.167–12.833	0.230
No	11	7.935–14.065	
Unknown	13	1.024–24.976	

ECOG: Eastern cooperative oncology group, PS: Performance status, NSCLC: Non-small-cell lung cancer, SCLC: Small-cell lung cancer

Table 6: Multivariate cox regression analysis showing independent risk factors for survival

Characteristics	Overall survival		
	Hazard ratio	95% confidence interval	P-value
Age (≤60 vs. >60)	0.55	0.304–1.023	0.059
Gender (male vs. female)	1.10	0.434–2.832	0.830
Smoking (yes vs. no/unknown)	0.63	0.229–1.754	0.379
Histology (NSCLC vs. SCLC)	0.59	0.140-2.562	0.490
ECOG PS (0–1 vs. 2-3)	0.65	0.440–1.115	0.085
Stage (III vs. IV)	1.46	0.466–4.619	0.513
NLR (≤3 vs. >3)	0.76	0.379–1.537	0.449

NSCLC: Non-small-cell lung cancer, ECOG: Eastern cooperative oncology group, PS: Performance status, NLR: Neutrophil-to-lymphocyte ratio, SCLC: Small-cell lung cancer

study by Paquette and Finlayson 2007, showed that patients from outlying rural areas had poorer survival.[15] Another study by Westeel et al.,[16] showed that 30–35% of lung cancer patients belong to rural areas, whereas in developing country, this number is even much higher. In our study, there were 45% of patients who were farmers from rural parts of Assam and had to travel approximately 150 km to reach the hospital. Possible causes of poor survival rate in patients living in rural areas include more advanced disease at the time of diagnosis and delay in treatments due to financial constraints and logistic issues (distance from heath-care center). Several studies have indicated that weight loss at presentation may be an independent prognostic variable of outcome in both NSCLC and SCLC.[17-20] Weight loss is associated with reduced tolerance to CT and, increased toxicity. According to Cancer Research, United Kingdom, weight loss is seen in 60% of lung cancer cases, which is similar to the results seen in this present study. Half of the patients in the present study have PS of ECOG 1, also reported by previous published studies.[21-23]

Single center studies reporting from the established tertiary cancer centers suggest adenocarcinoma being the most common NSCLC subtype. Krishnamurthy et al.,[24] in their retrospective analysis of data, extracted from a total of 25 consecutive hospital in patients with lung cancer at Adyar in Chennai between January 2003 and December 2007 reported that the most common histology was adenocarcinoma (42.6%), followed by squamous cell carcinoma (15.6%), large-cell carcinoma (2.3%), and others (7%). Malik et al.,[25] analyzed 434 pathologically confirmed lung cancer cases registered at the All India Institute of Medical Sciences, Delhi, for 3 years between July 2008 and June 2011. Among the biopsy slides which were subjected to independent review, squamous cell carcinoma was the most common histological subtype (33.33%) as per the initial report, but after expert pathological review, adenocarcinoma was found to be the most common histology (37.3%). This emphasizes the critical role of pathology review in lung cancer in the present era of personalized treatment. Our study results are also in line with these reports from various part of India, with adenocarcinoma being the most common subtype. Among 202 patients, 53% (1013/1803) received disease-specific treatment (CT, targeted therapy and RT). The remaining participants were either unwilling for CT, unsuitable due to poor PS, opted for alternative systems of medicine, (ayurvedic or homeopathic), or were those in whom treatment details were not known. Other Indian studies have also reported a high proportion of patients unwilling or unsuitable for cancer-specific treatment for reasons similar to what we observed.[23,26] A study by Mohan et al.,[23] showed that majority of the lung cancer patients received CT (87.5%) followed by RT (15.3%), targeted therapy (8.6%), and surgery (3.0%). The most common CT regimen used in their study was carboplatin-paclitaxel (53.4%), followed by CP-etoposide (18.4%), carboplatin-gemcitabine (7.4%), and carboplatin-pemetrexed (9.0%). Our results are consistent with the above study findings, with CT being used in 53 % of cases and a combination of taxane- and platinum-based CT regimen was the most common regimen used. The EGFR positivity rate in our study was 20%, which is similar to that reported in Indian studies but higher than most Western reports.[23,27]

The median OS in our study was 10 months, which is marginally better than that reported in various other Indian studies (6.0–7.8 months), especially in advanced NSCLC.[23,25,28,29] This modest improvement in OS seen in our study might be due to censoring of lost to follow-up cases and exclusion of patients from survival analysis who did not underwent any type of disease specific treatment. A retrospective study by Rajappa et al.,[28] reported objective response rate (CR+PR) of 35.4% and median PFS of 6 months with various platinum doublets. Similarly, our study also showed 32% overall objective response rate (CR+PR) but with a slightly better PFS of 8 months. A phase III trial by Scagliotti et al.,[30] which compared gemcitabine and CP (CG) to pemetrexed and CP also showed a median OS of 10.3 months for the entire cohort.

There are several strengths of this study as well. Despite the limited availability of data for lung cancer patients in Northeast India, our study has contributed valuable

information to this field. By emphasizing the real-life experiences of these patients, our study sheds light on the unique challenges they face, which may differ from those observed in clinical trials.

Limitations of the study

Our study has several limitations that should be carefully considered. Firstly, this was a single institutional retrospective study. Secondly, it has high loss to follow up rate and many patients were excluded because of missing records. Thirdly, toxicity profile was not analyzed. Finally, there were inequalities in sample size among various subgroups (Stage, Histology, and performance status and weight loss).

CONCLUSION

In this retrospective audit of resource-limited population with locally advanced and metastatic lung cancer cases, majority were farmers belonging to lower socioeconomic status. They were presenting with Stage IV most commonly, with adenocarcinoma being the most common histology and with palliative CT being the mainstay of treatment. Furthermore, there is a high incidence of smoking in our patients. Although our survival was in line with data from other centers of Indian subcontinent, there is much scope for improvement in terms of smoking cessation, awareness, and better therapeutic strategies and that too in affordable way for our patients.

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DECLARATION

This study was conducted as part of DM dissertation, a part of which is sent for publication in Journal of the Egyptian National Cancer Institute study titled "To assess prognostic utility of baseline NLR in locally advanced and metastatic cancer lung cases: A retrospective study from tertiary care centee in north east India" (UNDER REVIEW), which was the primary end point of DM thesis. In this paper, we are trying to publish the secondary end point of DM thesis. Furthermore, as this was a retrospective study, there was waiver of consent by the Institute Ethical Committee.

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Authors Contribution:
SSS- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article, coordination and manuscript revision; **MH**- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **PSR**- Design of study, statistical analysis and interpretation; **NDR**- Review manuscript; **PPM**-Review manuscript; **AS**- Literature survey and preparation of figures.

Work attributed to:
Department of Medical Oncology, Dr. Bhubaneswar Borooah Cancer Institute Guwahati, Assam-781016, India

Orcid ID:
Satya S. Sarangi - https://orcid.org/0000-0003-2868-5526
Munlima Hazarika - https://orcid.org/0000-0002-8314-6018
Partha S. Roy - https://orcid.org/0000-0002-2778-1164
Nithin D. Raj - https://orcid.org/0009-0005-0360-4330
Partha P. Medhi - https://orcid.org/0000-0002-3997-4350
Anupam Sarma - https://orcid.org/0000-0001-8631-2651

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