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Lung Cancer

Lung Cancer Survival in Sri Lanka

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Abstract

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Introduction Lung cancer is the second commonest cancer among males in Sri Lanka. Real-world survival data are scarce, and we conducted a retrospective survival analysis among patients treated for lung cancer.

Methods All patients with primary lung cancer treated at three selected units during 2015–2016 were included in the study. Data on clinicopathological and treatment delivered were extracted from clinic records. Overall survival was considered the primary end-point.

Results The study population comprised 349 patients. The median age was 61 years and majority of patients (74%) were males. Adenocarcinoma (56%) was the commonest histological subtype, followed by squamous cell carcinoma (26%), whereas 6% of patients had small cell lung cancer. Only 10% of patients with non-small cell lung cancer were treated with curative intent, whereas 67% presented with systemic metastases. The median overall survival was 12 months in patients treated with curative intent and there was no significant difference between radical surgery and radiotherapy. The median overall survival was 3 months in those treated palliatively. On multivariate analysis, female gender and first-line treatment with tyrosine kinase inhibitors was associated with superior survival.

Conclusion More than 90% of lung cancer patients in Sri Lanka are treated with palliative intent. Further work is needed to identify patient and care pathway barriers to ensure diagnosis at an earlier stage.

Keywords

- lung cancer
- survival
- Sri Lanka

Introduction

Lung cancer is the leading cause of cancer-related death worldwide and its incidence has been gradually increasing over the past 50 years.[1] It is the most prevalent cancer in Asia, the region which accounts for nearly half of the global burden of lung cancer.[2] In Sri Lanka, lung cancer is the second commonest malignancy among men, and registry data suggests that over 2,000 new cases are detected per year but the actual incidence could be higher due to the potential under-reporting of the cases.[3,4]

Cigarette smoking is responsible for nearly 80% of cases worldwide and although robust anti-tobacco initiatives have

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been implemented, data show that an estimated 29% of all adult Sri Lankan males are current smokers.[5,6] Despite improvement in diagnostics and novel treatment modalities, the prognosis of lung cancer remains poor in developing countries as well as in more affluent settings.[1,2]

Aggressive tumor biology, delayed presentation, and co-existing comorbidities results in poor survival rates for patients with lung cancer with 5-year overall survival rates of just 18% in the United States.[7]

There are no published data on lung cancer survival in Sri Lanka and we conducted this analysis by retrospectively reviewing outcomes of patients treated for lung cancer.

Methods

Patients

All patients with histopathologically or cytologically confirmed primary lung cancer treated in three randomly selected units during 2015–2016 were included in the study. Patients suspected of metastatic spread to the lungs from another primary tumor were excluded.

Data Collection

Clinic records were reviewed after obtaining institutional approval, and data collected on the following variables using a pre-tested data extraction format: age, gender, tumor laterality, histological subtype, stage of the disease, treatment modality, and details and disease outcomes.

Diagnosis

Pathological confirmation was by bronchoscopic biopsy, bronchial washings, radiologically guided core biopsy or fine needle aspiration biopsy of lymph nodes. Immunohistochemistry was performed for confirmation of small cell lung cancer (SCLC) for subtyping of poorly differentiated carcinoma and for exclusion of metastatic spread to the lungs from another primary tumor. Molecular testing for epidermal growth factor receptor (EGFR) mutation analysis was not available in the state health sector, but ad hoc testing was performed in certain patients in private laboratories. Staging was performed using computed tomography scans and in some instances bone scintigraphy. Facilities to perform positron emission tomography scans were not available in Sri Lanka during the study period.

Treatment

Curative Treatment of Non-small Cell Lung Cancer

Fit patients with resectable localized disease underwent lobectomy or pneumonectomy with mediastinal nodal sampling or dissection where appropriate. Adjuvant chemotherapy comprising four cycles of cisplatin and gemcitabine or carboplatin and paclitaxel was delivered after radical surgery in patients with tumors larger than 4 cm or those with nodal involvement. Adjuvant radiotherapy to a dose of 60 Gy in 30 fractions was delivered in selected patients with positive surgical margins or mediastinal nodal involvement.

Patients with unresectable disease or localized tumors but unfit for radical surgery were treated with either radical chemoradiotherapy or radiotherapy alone. Some patients were treated with induction chemotherapy, followed by radical radiotherapy if downstaging of the tumor was deemed necessary prior to treatment with radiotherapy.

Radical chemoradiotherapy was delivered to a dose of 60 Gy in 30 fractions over 6 weeks with concomitant cisplatin and etoposide or carboplatin and paclitaxel. Induction chemotherapy comprised either cisplatin in combination with gemcitabine or carboplatin in combination with paclitaxel. Patients treated with radiotherapy alone (with or without induction chemotherapy) were treated to either 60 Gy in 30 fractions over 6 weeks or to a dose of 55 Gy in 20 fractions over 4 weeks.

Palliative Treatment of Non-small Cell Lung Cancer

Patients with squamous cell carcinoma were treated with palliative chemotherapy comprising a platinum agent with either gemcitabine or paclitaxel if performance status was good. Second-line treatment comprising single-agent docetaxel was delivered in selected patients after progression on first-line chemotherapy.

Metastatic adenocarcinoma was treated with the EGFR inhibitors, such as geftinib or erlotinib in patients with *EGFR* mutations. For patients without *EGFR* mutations, the treatment of choice regimen of cisplatin and pemetrexed was delivered to some patients. However due to limited availability, most patients received paclitaxel and carboplatin. For the same reason, maintenance therapy with pemetrexed was not offered. Others received palliative chemotherapy with either cisplatin and pemetrexed or carboplatin and paclitaxel. Patients treated with first-line chemotherapy were treated with erlotinib second line, while those treated with first-line EGFR inhibitors were treated with either osimertinib or chemotherapy.

Palliative radiotherapy was delivered for control of symptoms from primary disease or metastatic spread in patients with distant metastases. Patients with localized disease who were unfit for curative intent radiotherapy were also treated with palliative radiotherapy to the primary tumor. In the palliative setting, either 20 Gy in 5 fractions over 1 week or 30 Gy in 10 fractions over 2 weeks was the most common regimen.

Treatment of Small Cell Lung Cancer

Patients with limited stage disease were treated with chemoradiotherapy comprising cisplatin and etoposide (1–2 cycles) followed by concurrent chemoradiotherapy with the same regimen. Radiotherapy was delivered to a dose of 40 Gy in 15 fractions over 3 weeks or 60 Gy in 30 fractions over 6 weeks. The Turrisi twice daily regimen of 45 Gy in 30 fractions over 3 weeks was not used due to practical difficulties in delivering twice daily fractions.

Those with extensive disease received treatment with palliative chemotherapy with cisplatin and etoposide for four to six cycles. Patients with at least a partial response to either radical chemoradiotherapy or palliative chemotherapy were consolidated with prophylactic cranial irradiation delivered to a dose of 24 Gy in 10 fractions over 2 weeks.

Some patients with extensive stage disease were treated with palliative radiotherapy to the primary tumor to a dose of 30 Gy in 10 fractions over 2 weeks.

Statistical Analysis

Overall survival, defined as time to death or loss to follow-up, was considered the primary end-point. Statistical analysis was done using the statistical software R version 3.6.2 for Windows. Univariate survival analysis was performed to determine the statistical significance of the following variables: age, gender, histological subtype, stage, and treatment modality. The log-rank test was used for categorical variables and the univariate Cox-proportional hazards test was used for continuous variables. Factors significant on univariable analysis were included in a multivariable analysis using the Cox proportional hazards model.

Results

The study population comprised 349 patients and the distribution of clinicopathological variables is described in ►Table 1. There were 20 (6%) patients diagnosed with small cell lung cancer. Adenocarcinoma was the commonest histological type and 83% of patients presented with IIIB or higher disease. ►Table 2 describes the treatment delivered to patients with non-small cell lung cancer. Nearly 90% of all patients were treated with palliative intent with chemotherapy being the commonest first-line treatment option. Just 3% of patients received first-line EGFR inhibitor treatment, while 19% of patients were treated with supportive care alone. When considering second-line treatment, only 28% of patients received active second-line treatment with 11% receiving palliative radiotherapy and an equal proportion receiving chemotherapy.

►Fig. 1 depicts the overall survival (OS) of the whole cohort and median OS was 4 months (95% confidence interval [CI] 3–5 months). The 2-year OS was 12.1% (95% CI; 9–16.3%). In patients with non-small cell lung cancer treated with curative intent, the median OS was 12 months (95% CI; 2–26 months). The 2-year OS in this group was 26.7% (95% CI; 14.7–48.3). No factors were significant on univariate analysis as shown in ►Table 3. ►Figure 2 shows OS by stage in patients with non-small cell lung cancer. Although stage was not prognostic in the small group of patients treated with curative intent, it was a significant predictor of survival in the full cohort of patients with non-small cell lung cancer (log rank test 0.049). The proportion of non-small cell lung cancer patients with stage I-IIIA disease who were not treated curatively are listed for each stage in ►Supplementary Table S1, available in the online version. The reasons for not offering curative treatment for these patients are listed in ►Supplementary Table S2, available in the online version. In the palliative setting of patients with non-small cell lung cancer, the median OS was

Table 1 Clinicopathological variables of study population

Age		
Mean	61 years (range, 29–88)	
Gender		
Male	257	(74%)
Female	92	(26%)
Histology		
Adenocarcinoma	181	(56%)
Squamous cell carcinoma	85	(26%)
Other non-small cell lung cancer	38	(12%)
Small cell lung cancer	20	(6%)
Unknown	25	(7%)
Tumor laterality (of primary tumor)		
Left lung	123	(41%)
Right lung	176	(59%)
Unknown/bilateral	50	(14%)
Stage		
I	7 (2%)	
IIA	7 (2%)	
IIB	10 (3%)	
IIIA	35 (10%)	
IIIB	41 (12%)	
IIIC	14 (4%)	
IV	230 (67%)	
Unknown	5 (1%)	

Table 2 Treatment of patients with non-small cell lung cancer

Curative intent	30 (10%)
Radical surgery	17 (56%)
Radical radiotherapy	13 (44%)
Radiotherapy alone	2 (7%)
Chemoradiotherapy	6 (20%)
Induction chemotherapy followed by radiotherapy	5 (17%)
Palliative intent	274 (90%)
First-line treatment	
Chemotherapy	171 (57%)
Epithelial growth factor receptor (EGFR) inhibitors	10 (3%)
Radiotherapy	33 (31%)
Supportive care	57 (19%)
Second-line treatment	*77 (28%)*
Chemotherapy	29 (11%)
EGFR Inhibitors	18 (6%)
Radiotherapy	30 (11%)
Patients with incomplete information on stage and treatment	3 (1%)

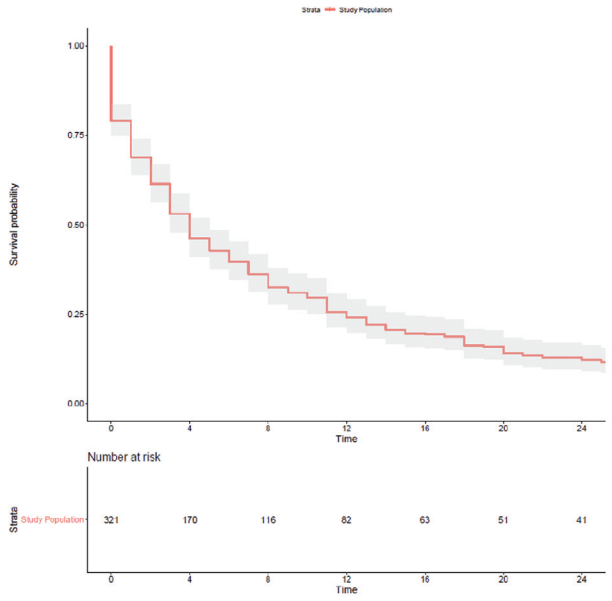

Fig. 1 Overall survival of the whole population.

Table 3 Univariate analysis of patients with non-small cell lung cancer treated with curative intent

Variable	*p*-Value
Age	0.11
Histology	0.45
Laterality	0.31
Stage	0.1
Treatment modality	0.2

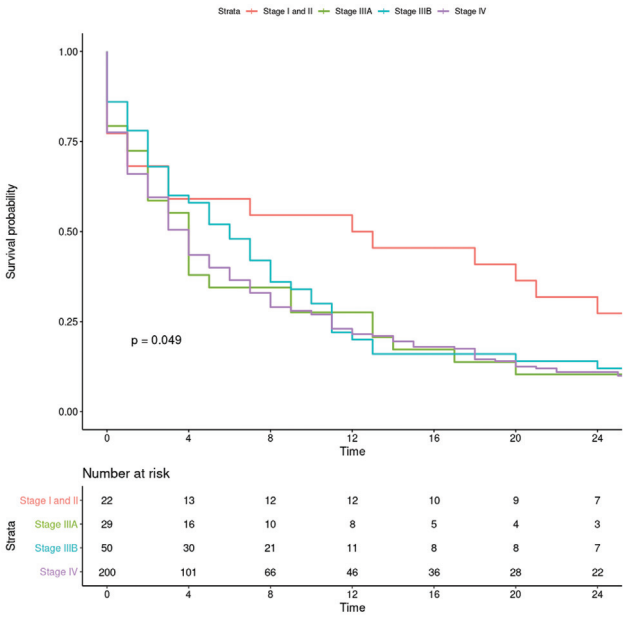

Fig. 2 Overall survival of non-small cell lung cancer patients by stage.

Table 4 Univariate and Multivariate analyses of overall survival in patients with non-small cell lung cancer treated with palliative intent

Variable	Univariate	Multivariate
Age	$p = 0.05$ HR 1.01 [95%CI 1–1.02]	0.78
Gender	$p = 0.002$ Female HR 0.66 [95% CI 0.5–0.86]	$p = 0.007$ Female HR 0.67 [95% CI 0.5–0.9]
Histology	Adenocarcinoma (comparator) Squamous cell carcinoma HR 1.47 [95% CI 1.11–1.95] $p = 0.006$ Undifferentiated NSCLC $p = 0.49$	Adenocarcinoma (comparator) Squamous cell carcinoma $p = 0.3$ Undifferentiated NSCLC $p = 0.54$
Laterality	$p = 0.6$	-
Stage	$p = 0.6$	-
Treatment modality	Best supportive care (comparator) Radiotherapy HR 0.29 [95% CI 0.19–0.45] $p < 0.001$ Chemotherapy HR 0.24 [95% CI 0.17–0.33] $p < 0.001$ EGFR inhibitors HR 0.12 [95% CI 0.06–0.25] $p < 0.001$	Best supportive care (comparator) Radiotherapy HR 0.32 [95% CI 0.21–0.51] $p < 0.001$ Chemotherapy HR 0.24 [95% CI 0.17–0.34] $p < 0.001$ EGFR inhibitors HR 0.11 [95% CI 0.05–0.24] $p < 0.001$

Abbreviation: EGFR, epithelial growth factor receptor.

the same as the whole population. The 2-year OS was 10.7% (95% CI; 7.6–15.1%), and as depicted in ►Table 4, age, gender, and histology were significant on univariate analysis. However, on multivariate analysis, only gender and treatment modality were significant. Female patients and those receiving active anti-cancer treatment had a superior outcome in comparison to best supportive care. As shown in ►Table 4, it can be observed that patients treated with EGFR inhibitors had the best prognosis followed by those receiving chemotherapy. ►Fig. 3 depicts the survival of patients with small cell lung cancer in the study cohort. Only 3/20 patients were treated with curative intent.

Discussion

This is the first ever survival study of lung cancer in Sri Lanka and there are several findings of importance that merit further consideration. First is the advanced stage at presentation as illustrated by the fact that 67% of patients presented with de novo metastatic disease and only 10% of patients could be treated with curative intent. Our data are

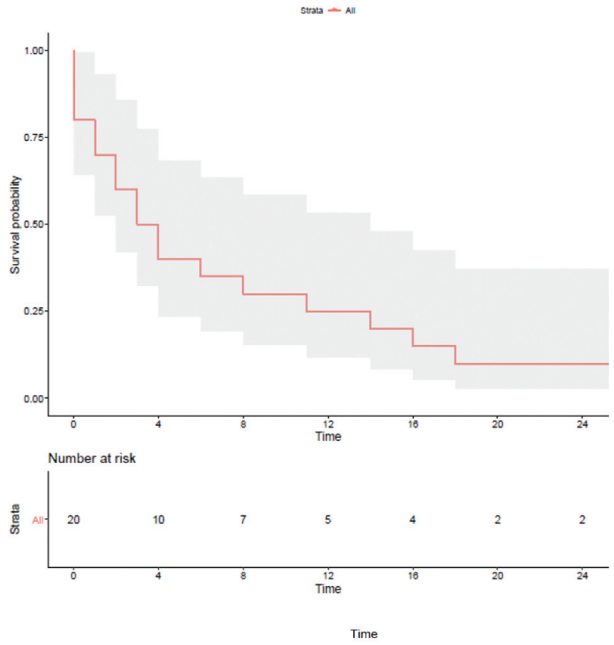

Fig. 3 Overall survival of small cell lung cancer patients.

comparable to that reported by Mohan et al in a cohort of patients in North India, which showed that 66% of patients had de novo metastatic disease.[8] However, in an analysis of the Surveillance, Epidemiology, and End Results Program (SEER) database of the United States, only 40% of patients were found to have stage IV disease at presentation.[9] A further prospective study is needed to identify factors such as patient or care pathway delays that contribute to the high proportion of patients with advanced stage at diagnosis. Nevertheless, our data highlight the urgent need to improve patient education and strengthen diagnostic pathways with a view to enhancing earlier detection of lung cancer.

Adenocarcinoma was the predominant histological subtype in our study, with more than twice as many cases as that of squamous cell carcinoma. Data have been conflicting on this point in the Indian subcontinent, and the proportion of patients with adenocarcinoma in our study is higher than previous studies.[10,11] Another noteworthy feature was the relatively low proportion (6%) of patients with small cell lung cancer in our study, which is significantly lower than the globally reported prevalence of 13% of all cases of lung cancer.[12] A larger study would be needed to determine if this is due to the low prevalence of small cell lung cancer or if it is due to under diagnosis, especially because immunohistochemistry is performed only if there is morphological uncertainty.

The median OS of 4 months for the whole cohort is significantly lower than both regional and global survival rates of lung cancer. In North India, a median OS of 8.8 months has been reported, while it is 16.9 months in the United States.[8,13] The survival of lung cancer is inextricably linked to the stage at presentation. Because only 10% of patients with non-small cell lung cancer could be treated with curative intent, it could be suggested that the dismal OS in our study was due to the advanced stage at diagnosis. Advanced stage at presentation was also identified as a significant contributor for inferior survival of patients with breast and cervical cancer in Sri Lanka.[14,15] However, it is of note that even in patients with stage I-IIIA disease, a significant proportion of patients (22/51) did not receive curative treatment as shown in ►**Supplementary Table S1**, available in the online version. Age, poor performance status, and patients seeking alternative forms of treatment were the main reasons attributable for the failure to deliver curative treatment as evident from ►**Supplementary Table S2**, available in the online version. This suggests that along with more robust early detection strategies, emphasis needs to be placed on improving therapeutic pathways to ensure more patients are offered curative treatment. Moreover, 20% of patients treated with palliative intent were treated with supportive care only and a further 30% were treated with palliative radiotherapy alone. In a study of over 280,655 metastatic lung cancer patients in the SEER database, Bar et al reported a median OS of 4 months and a 2-year OS rate of 12.9%, which is similar to the findings of our study.[16] In patients treated with curative intent the 2-year OS was 26.7%, but even in this setting most patients had stage II or higher disease. Furthermore, because PET scanning was not performed, some of these patients may have had metastatic disease that was not detected on conventional imaging.

Although adenocarcinoma was the most prevalent histological type, only 3% of patients were treated with first-line EGFR inhibitors as access to molecular testing was limited. Because EGFR inhibitors have relatively low toxicity, expanding access to molecular testing and consequent use of these drugs may serve to improve outcomes in patients with metastatic adenocarcinoma of the lungs. Another salient finding was that only 28% of patients went on to receive second-line treatment in the palliative setting, once again re-emphasizing the importance of delivering the most efficacious treatment option first line.

There are several limitations in our study, apart from the fact that it was a retrospective review. Because the study population consisted of patients treated at the clinical oncology department, some patients with very early lung cancers who were treated surgically may not have been included, especially if they did not require adjuvant chemotherapy. In addition, loss to follow-up was considered as an event, thereby leading to under-estimation of survival in some patients. Also, the cause of death could not be accurately determined precluding an analysis of cancer-specific survival.

Conclusion

Our study suggests that the poor survival in lung cancer in Sri Lanka is due to the advanced stage at diagnosis. Better patient education and streamlining of diagnostic pathways are needed to improve outcomes in these patients. Improving access to molecular biology with a view to initiating targeted therapies should also be considered a priority to improve outcomes.

Authors' Contributions

Conception and design: L.A., V.P., and N.J.; Data collection and analysis: All authors; Manuscript writing: L.A.

and N.J.; Manuscript editing: All authors; Manuscript approval: All authors.

Data Availability Statement

Data are available on request from the authors.

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Conflict of Interest

None declared.

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