

Original Research Article

SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS IN BRONCHOGENIC CARCINOMA: A PROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE IN SOUTH INDIA

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ABSTRACT

Background: Bronchogenic carcinoma is a leading cause of cancer death. In Indian hospital practice most patients present with advanced disease, and South Indian survival data remain limited. **Objectives:** To estimate overall survival and identify clinical and demographic factors associated with survival in patients with histologically confirmed bronchogenic carcinoma.

Materials and Methods: This prospective study included 160 patients with tissue-confirmed bronchogenic carcinoma at a tertiary care centre in South India. Other malignancies, and malignant pleural effusion without definite evidence of bronchogenic carcinoma, were excluded. Survival was measured from tissue diagnosis to death or last contact. Vital status was compared by the chi-square test. Survival was estimated by the Kaplan–Meier method and compared with the log-rank test. Variables significant on initial analysis were entered into a Cox proportional-hazards model.

Results: Twenty-three patients (14.4%) were alive and 137 (85.6%) had died. Median survival was 9.0 months at age 60 years or younger and 7.0 months beyond 60 years; 10.0 months in non-smokers and 8.0 months in smokers; and 11.0, 8.0 and 5.0 months in early-stage non-small-cell lung cancer, advanced non-small-cell lung cancer and small-cell carcinoma. On multivariable analysis, stage remained associated with mortality (hazard ratio 2.350; 95% confidence interval 1.448–3.814; $p=0.001$). Comorbidity burden was also reported as significant (hazard ratio 5.503; $p=0.019$); its printed confidence interval was internally inconsistent and is not reported.

Conclusions: Overall survival was poor and was most clearly related to disease stage. Earlier diagnosis, and explicit attention to comorbid illness, are the practical implications. Histology should not be treated as an independent prognostic factor on these data.

Keywords: Lung neoplasms; carcinoma, bronchogenic; survival analysis; prognosis; comorbidity.

INTRODUCTION

Bronchogenic carcinoma remains among the leading causes of cancer incidence and death worldwide.^[1,2] Outcome is poor for most patients because the disease is commonly diagnosed after it has spread beyond a resectable field.^[3] Anatomical stage, as set out in the eighth edition of the tumour–node–

metastasis classification, is the main determinant of survival and of treatment intent.^[4]

Indian series differ in case mix from many Western cohorts. Never-smokers form a substantial minority, adenocarcinoma has become more frequent, and the great majority of non-small-cell lung cancers are still diagnosed at stage III or IV.^[5-7] In a North Indian cohort of 1,862 patients the median overall survival

was 8.8 months, and 12.6 months among those who started disease-directed treatment.^[7] Age, smoking, performance status, weight loss and comorbidity have each been linked to survival, although their independent contribution depends on stage and on the treatment that can actually be given.^[8-10] Prospective estimates from South Indian pulmonary practice are scarce. Differences in smoking pattern, access to oncology services and stage at presentation limit the direct use of figures from other regions. This study estimated overall survival and examined the demographic and clinical factors associated with survival among patients with histologically confirmed bronchogenic carcinoma at a tertiary care centre in South India.

MATERIALS AND METHODS

Design and Setting

A prospective observational study was conducted in the Department of Pulmonary Medicine of a tertiary care centre in South India. The study was intended to comply with the Declaration of Helsinki. The recruitment period, the named institution and the institutional ethics committee approval number are to be stated in the final submission, together with the form of consent obtained.

Participants

Patients with a histological or cytological diagnosis of bronchogenic carcinoma were eligible. Patients with another active malignancy were excluded, as were patients who had malignant pleural effusion without definite evidence of bronchogenic carcinoma. One hundred and sixty patients met these criteria and were analysed. No sample-size calculation was recorded in the source protocol.

Follow-up and Outcome

Patients, or a relative, were contacted every month. Overall survival was defined as the time from the date of tissue diagnosis to death from any cause. Patients lost to follow-up were censored at the last date on which they were known to be alive, including the date of the last telephone contact. Median follow-up and the number censored for loss to follow-up, separate from those alive at study closure, were not available.

Variables

Age was grouped as 60 years or younger and older than 60 years. Smoking was recorded as present or absent; current and former smoking were not separated. Stage was recorded as stage 1, 2, 3a, 3b or 4, or under the source labels SCLS and SCES. These two labels are reported as small-cell limited stage and small-cell extensive stage, because the two groups together equal the 15 small-cell carcinomas. For

survival comparison, disease was also grouped as early-stage non-small-cell lung cancer (n=14), advanced non-small-cell lung cancer (n=131) and small-cell carcinoma (n=15). That early-stage group is not identical to stages 1, 2 and 3a combined (n=12), so the operational definition used in the survival table could not be reconstructed and is reported as printed. Symptom count was grouped as one or fewer versus two or more, comorbidity as one or fewer versus two or more conditions, and World Health Organization performance status as 1 or lower versus 2 or higher. Weight loss, metastasis and histological subtype were recorded. Treatment modality was listed among the planned variables but was not tabulated.

Statistical Analysis

Vital status was compared across groups with the chi-square test. Survival was estimated by the Kaplan–Meier method and compared with the log-rank test. Variables associated with survival on the initial analysis were entered into a Cox proportional-hazards model. Hazard ratios, 95% confidence intervals and p values were taken from the source output. A two-sided p value below 0.05 was regarded as statistically significant. One printed confidence interval was incompatible with its hazard ratio and is not reproduced. One printed mean survival was biologically impossible and is not reproduced. The original dataset was not available for re-analysis. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology statement as far as the records permit.^[11]

RESULTS

Baseline Characteristics

The cohort comprised 160 patients. Seventy-three (45.6%) were aged 60 years or younger and 87 (54.4%) were older. One hundred and sixteen (72.5%) were smokers and 44 (27.5%) were not. Weight loss was present in 98 (61.3%). Two or more comorbid conditions were present in 134 (83.8%). Metastasis was recorded in 80 (50.0%). Only 15 patients (9.4%) had a World Health Organization performance status of 1 or lower; 145 (90.6%) had a status of 2 or higher. At last contact, 23 patients (14.4%) were alive and 137 (85.6%) had died.

Stage was distributed as stage 1 in 1 patient, stage 2 in 6, stage 3a in 5, stage 3b in 33 and stage 4 in 100. Five patients were coded SCLS and 10 SCES. These seven categories account for the whole cohort. On the vital-status histology table, 53 patients had squamous-cell carcinoma, 71 adenocarcinoma, 15 small-cell carcinoma, 3 large-cell carcinoma and 18 non-specific histology.

Table 1: Vital status according to clinical characteristics

Characteristic	Alive, n (%)	Dead, n (%)	Total	p value
Age ≤60 years	16 (21.9)	57 (78.1)	73	0.013
Age >60 years	7 (8.0)	80 (92.0)	87	
Smoker	12 (10.3)	104 (89.7)	116	0.018
Non-smoker	11 (25.0)	33 (75.0)	44	
Stage 1	1 (100)	0 (0)	1	0.001

Stage 2	2 (33.3)	4 (66.7)	6	
Stage 3a	1 (20.0)	4 (80.0)	5	
Stage 3b	12 (36.4)	21 (63.6)	33	
Stage 4	7 (7.0)	93 (93.0)	100	
Small-cell limited stage	0 (0)	5 (100)	5	
Small-cell extensive stage	0 (0)	10 (100)	10	
Squamous-cell carcinoma	7 (13.2)	46 (86.8)	53	0.719
Adenocarcinoma	12 (16.9)	59 (83.1)	71	
Small-cell carcinoma	0 (0)	15 (100)	15	
Large-cell carcinoma	0 (0)	3 (100)	3	
Non-specific histology	4 (22.2)	14 (77.8)	18	
Weight loss present	4 (4.1)	94 (95.9)	98	0.001
Weight loss absent	19 (30.6)	43 (69.4)	62	
Symptoms, up to 1	14 (42.4)	19 (57.6)	33	0.001
Symptoms, 2 or more	9 (7.1)	118 (92.9)	127	
Comorbidity, up to 1	18 (69.2)	8 (30.8)	26	<0.001
Comorbidity, 2 or more	5 (3.7)	129 (96.3)	134	
Metastasis present	6 (7.5)	74 (92.5)	80	0.013
Metastasis absent	17 (21.3)	63 (78.8)	80	
Performance status ≤ 1	10 (66.7)	5 (33.3)	15	<0.001
Performance status ≥ 2	13 (9.0)	132 (91.0)	145	

SCLS and SCES in the source table are reported as small-cell limited and extensive stage. The source cell for small-cell deaths read 3 against a row total of 15 and 0% alive; deaths are given as 15 so that the row is internally consistent. The source *p* values for comorbidity and performance status were printed as 0.001 and are shown as <0.001. The stage chi-square (27.3 on 6 degrees of freedom) uses several cells with expected counts below 5.

Factors Associated with Vital Status

Patients aged 60 years or younger were more often alive than older patients (21.9% versus 8.0%; $p=0.013$). Non-smokers were more often alive than smokers (25.0% versus 10.3%; $p=0.018$). Stage was strongly associated with vital status ($p=0.001$). The single patient with stage 1 disease was alive. All 15 patients with small-cell limited or extensive disease had died, as had 93 of 100 patients with stage 4 disease. Alive proportions were 4.1% with weight loss and 30.6% without ($p=0.001$); 7.1% with two or more symptoms and 42.4% with one or fewer ($p=0.001$); 3.7% with two or more comorbidities and 69.2% with one or fewer ($p<0.001$); 7.5% with metastasis and 21.3% without ($p=0.013$); and 9.0% with performance status of 2 or higher against 66.7% with performance status of 1 or lower ($p<0.001$). Histological subtype was not associated with vital status ($p=0.719$).

Kaplan–Meier Estimates

Median survival was 9.0 months among patients aged 60 years or younger and 7.0 months among those

older than 60 years (log-rank $p=0.001$). It was 9.0 months with one or fewer symptoms and 8.0 months with two or more ($p=0.002$); 10.0 months in non-smokers and 8.0 months in smokers ($p=0.001$); 9.0 months without weight loss and 8.0 months with weight loss ($p=0.001$); and 9.0 months without metastasis and 7.0 months with metastasis ($p=0.008$). The source survival table did not give a median for the two favourable groups with the fewest events. Mean survival was 10.6 months with one or fewer comorbidities, against a median of 8.0 months with two or more ($p=0.001$), and 10.5 months with performance status of 1 or lower, against a median of 8.0 months with performance status of 2 or higher ($p=0.001$). These means are not reported as medians. By the printed stage grouping, median survival was 11.0 months in early-stage non-small-cell lung cancer, 8.0 months in advanced non-small-cell lung cancer and 5.0 months in small-cell carcinoma (mean 5.4 months; overall $p=0.001$).

Table 2: Kaplan–Meier survival by clinical group

Group	n	Deaths	Mean (months)	Median (months)	Log-rank p
Age ≤ 60 years	73	57	9.0	9.0	0.001
Age >60 years	87	80	7.4	7.0	
Symptoms, up to 1	33	19	9.3	9.0	0.002
Symptoms, 2 or more	127	118	7.9	8.0	
Comorbidity, up to 1	26	8	10.6	Not estimated	0.001
Comorbidity, 2 or more	134	129	7.7	8.0	
Performance status ≤ 1	15	5	10.5	Not estimated	0.001
Performance status ≥ 2	145	132	7.9	8.0	
Smoker	116	104	7.7	8.0	0.001
Non-smoker	44	33	9.4	10.0	
Weight loss present	98	94	7.7	8.0	0.001
Weight loss absent	62	43	8.9	9.0	
Metastasis present	80	74	7.5	7.0	0.008
Metastasis absent	80	63	8.8	9.0	
Early-stage NSCLC	14	10	10.3	11.0	0.001
Advanced NSCLC	131	112	8.2	8.0	
Small-cell carcinoma	15	15	5.4	5.0	
Squamous-cell carcinoma	55	48	7.3	7.0	0.001

Adenocarcinoma	69	57	9.2	10.0	
Large-cell carcinoma	3	3	Not reported	7.0	
Small-cell carcinoma	15	15	5.4	5.0	
Non-specific histology	18	14	9.1	9.0	

NSCLC, non-small-cell lung cancer. Medians left blank in the source table are shown as not estimated. The printed large-cell mean of 737 months is omitted. Histology denominators in this table (squamous-cell carcinoma 55, adenocarcinoma 69) differ by two patients from Table 1 (53 and 71). Early-stage NSCLC (n=14) is not the same total as stages 1, 2 and 3a (n=12).

Histological Subtype

Reported median survival was 10.0 months for adenocarcinoma, 9.0 months for non-specific histology, 7.0 months for squamous-cell carcinoma, 7.0 months for large-cell carcinoma and 5.0 months for small-cell carcinoma. The log-rank test on this table gave $p=0.001$. The same variable was not associated with vital status ($p=0.719$) and was not significant in the Cox model ($p=0.342$). Two patients also shift between squamous-cell carcinoma and adenocarcinoma across the two tables. Histology is therefore not interpreted as an independent prognostic factor. The short survival of small-cell carcinoma is the only subtype finding that is consistent across the tables. The three large-cell cases cannot support a comparison.

Multivariable Analysis

In the Cox model, stage remained associated with mortality (hazard ratio 2.350; 95% confidence

interval 1.448–3.814; $p=0.001$). Comorbidity burden was reported as significant (hazard ratio 5.503; $p=0.019$). The confidence interval printed with that ratio, 1.159 to 5.404, does not contain the point estimate and is not reported. Age, symptom burden, performance status, smoking, weight loss, metastasis and histology were not statistically significant after adjustment.

The adjusted hazard ratios for smoking (0.710), weight loss (0.834) and metastasis (0.889) lie below 1, which is the opposite direction from the univariable results. If the coded category was the exposed group, these ratios would imply lower rather than higher mortality. They are more consistent with reference-category coding or with collinearity, particularly between stage and metastasis, than with a protective effect. None of the three was statistically significant.

Table 3: Cox proportional-hazards model for death

Variable	Hazard ratio	95% confidence interval	p value
Age	1.291	0.893–1.867	0.175
Symptom burden	1.434	0.845–2.433	0.182
Comorbidity burden	5.503	Not reported	0.019
Performance status	1.988	0.774–5.107	0.153
Smoking	0.710	0.470–1.071	0.102
Weight loss	0.834	0.569–1.222	0.352
Metastasis	0.889	0.627–1.261	0.509
Stage	2.350	1.448–3.814	0.001
Histology	0.928	0.796–1.082	0.342

The source interval for comorbidity (1.159–5.404) is incompatible with the hazard ratio and is omitted. Reference categories were not stated in the source output.

DISCUSSION

In this prospective cohort, death was the usual outcome and survival was measured in months. The result sits with Indian hospital series in which advanced disease is the rule and median survival is close to nine months.^{5,7} Stage was the only association that remained both statistically significant and numerically coherent after adjustment.

Stage

Median survival was 11.0 months in the early-stage non-small-cell group, 8.0 months in advanced non-small-cell disease and 5.0 months in small-cell carcinoma. Every patient coded as small-cell limited or extensive stage had died. The adjusted hazard ratio for stage was 2.35, in the expected direction and consistent with the relationship between anatomical extent and survival in the International Association for the Study of Lung Cancer staging project.^[4,12] Two cautions apply. The early-stage estimate rests on

14 patients, and that group is two patients away from the sum of stages 1, 2 and 3a. The stage chi-square also depends on cells with very small expected counts. The direction of the stage effect is secure; a precise stage-specific survival curve needs the analysis file and a stated definition of the early-stage group.

Comorbidity and Performance Status

Comorbidity produced the widest univariable gap in this cohort: 69.2% of patients with one or fewer conditions were alive, compared with 3.7% of those with two or more. A separation of that size can destabilise a Cox model, which is a credible explanation of the hazard ratio of 5.5 and of a confidence interval that does not contain it. Comorbidity is nonetheless a recognised prognostic factor in non-small-cell lung cancer and a practical constraint on chemotherapy and radiotherapy.^[8,9] Until the model is re-estimated, comorbidity should be described as a strong unadjusted association, not as a fivefold independent risk. Performance status showed the same pattern on a still smaller favourable

group of 15 patients. Symptom count and weight loss shifted median survival by one month and did not remain significant after adjustment, as expected if they overlap with stage and performance status.

Age, Smoking and Metastasis

Younger patients and non-smokers lived about two months longer. Neither difference was significant in the Cox model. Indian never-smokers with lung cancer are younger, more often women, and more often have adenocarcinoma and a targetable driver mutation, any of which may improve survival.^[5,7] Sex and molecular results were not available here, and current smoking was not separated from former smoking. Metastasis shortened median survival from 9.0 to 7.0 months but was not significant after adjustment. Entering metastasis together with stage splits the same anatomical information and can reverse the adjusted coefficient. The smoking, weight-loss and metastasis ratios below 1 should not be read as protective effects.

Histology

Small-cell carcinoma had the shortest and most consistent survival. Adenocarcinoma had a longer reported median than squamous-cell carcinoma, in keeping with some contemporary series, but the conflicting p values and the two-patient shift between tables prevent a claim of independent effect.^[7,16] Large-cell carcinoma was too uncommon for comparison. A printed mean survival of 737 months for those three patients was discarded as a transcription error.

Comparison with Indian Cohorts

The proportion of smokers, 72.5%, is closer to North Indian pulmonary series than to a Mumbai thoracic-oncology cohort in which about half the patients had never smoked.^[5-7] Both major non-small-cell subtypes were well represented. The stage mix, dominated by stage 3b, stage 4 and small-cell disease, matches the observation that about 95% of non-small-cell lung cancers in a large Indian cohort were advanced at diagnosis.^[7] The survival range of 5 to 11 months by disease group is in the same region as the 8.8-month median from that cohort. The study could not examine the contribution of treatment, which in the North Indian series separated untreated patients from those who started disease-directed therapy.^[7,13]

Limitations

The study was conducted at a single centre, and the centre. Most patients already had advanced disease and a poor performance status, so estimates for early-stage disease and for good performance status are imprecise. Follow-up was partly by telephone. Treatment, although listed in the methods, was not analysed, and molecular markers were not available. Sex was named as a planned variable and does not appear in the results. The original dataset could not be re-analysed. Remaining defects in the source output are an incompatible confidence interval for comorbidity, disagreement between histology counts and histology p values, an early-stage grouping that does not match the TNM totals, and blank medians

for the two groups with the fewest deaths. The stage chi-square should be read as approximate because several expected cell counts are below 5.

CONCLUSION

Among 160 patients with histologically confirmed bronchogenic carcinoma, 85.6% had died by last contact. Median survival was 11.0 months in early-stage non-small-cell disease, 8.0 months in advanced non-small-cell disease and 5.0 months in small-cell carcinoma. Age, smoking, stage, symptom burden, comorbidity, performance status, weight loss and metastasis were associated with outcome before adjustment. After adjustment, stage remained associated with mortality. Comorbidity was reported as significant, but its confidence interval was not usable. Histology was not an independent prognostic factor. The findings support earlier diagnosis and deliberate management of comorbid disease.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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