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Does treatment delay affect survival in non-small cell lung cancer? A retrospective analysis from a single UK centre

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Abstract

We analysed survival in relation both to time to treatment and other clinical parameters in the care pathway of non-small cell lung cancer (NSCLC) patients. Medical notes of 189 patients diagnosed with NSCLC presenting in 1998 were reviewed. Median time to treatment in all patients was 48 days. In multivariate analysis, time to treatment did not affect survival in patients with any stage of disease. Referral from general practitioner to chest department ($P = 0.032$, HR = 0.08), and absence of use of surgery ($P = 0.006$, HR = 30.30) were independently significant predictors of survival in stages 1 and 2 subgroup. In stage 3 patients, absence of laboratory abnormality ($P = 0.002$, HR = 0.39), and use of combined treatment ($P = 0.015$, HR = 0.17) were independent prognosticators. Lastly, in patients with stage 4 disease, presence of bone and/or liver metastasis ($P = 0.005$, HR = 2.65), and absence of use of chemotherapy ($P < 0.001$, HR = 6.25) were significantly associated with shorter survival. As survival is dependent on classical prognosticators, but not on time from referral to treatment (hospital delay), expanding resources in oncology (equipment, drugs and personnel), and, perhaps, reducing patient delay, rather than reducing hospital delay alone, could be better strategies to improve NSCLC survival.

Keywords: Lung cancer; Treatment delay; Prognostic factors; Radiotherapy; Chemotherapy; Surgery

1. Introduction

Early cancer diagnosis and treatment is naturally desirable [1]. It is of proven value in oral cancer [2] and cervical cancer [3,4]. However, in breast cancer two recently published papers have given conflicting results [5,6]. In non-small cell lung cancer (NSCLC) there appears to be no published evidence to date.

Cancer survival in Britain is lower than in her European neighbours both in general [7] and in lung cancer [8]. The mean survival in UK is under 6 months [9]. It is unclear whether Britain's poor performance relates to treatment delay, lack of treatment facilities [10] or an environmental factor.

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Waiting time targets in the care pathway of NSCLC is a popular issue. In order to prevent treatment delay, the National Health Service policy is now for patients with suspected lung cancer to be seen by a specialist within 2 weeks of referral from the general practitioner (GP). The British Thoracic Society (BTS) and the Joint Collegiate Council for Oncology have also made recommendations on the times for referrals and waiting times in the treatment pathway [11,12]. However, it is not known at present how time to treatment (i.e. patient, referral or hospital delay) affects NSCLC patients' survival.

Numerous studies have analysed the importance of various prognostic factors in NSCLC. Performance status, gender, stage, number of metastatic sites and response to chemotherapy have been shown significant in predicting survival, in addition to a large number of parameters such as albumin, calcium, haemoglobin (Hb), lymphocyte count, lactate dehydrogenase (LDH), BUN, white cell count, neutrophil count, histological grading, arterial invasion, lymph vessel invasion, aneuploidy, tumour proliferative activity, microvessel count, Ki-67 antigen labelling and p53 gene mutation [13–22].

For these reasons, we wished to analyse survival in relation both to time to treatment (hospital delay) and other known prognosticators, in a cohort of NSCLC patients presenting in 1 year in a UK Hospital with thoracic surgery and clinical oncology departments.

2. Subjects and methods

2.1. Subjects

The medical records of all patients presenting to the Norfolk & Norwich Hospital and diagnosed as having NSCLC in 1998 were reviewed. NSCLC was diagnosed in 203 patients but medical records were not available to us in 14, so 189 medical records were reviewed. The inclusion criteria were either pathologically diagnosed NSCLC ($n = 170$) or patients with a clinical diagnosis of lung cancer whose histology could not be obtained such as those unfit for bronchoscopy, those requiring emergency treatment etc. ($n = 19$) presenting between 01.01.98 and 31.12.98. Thus, patients with a pathological diagnosis of small cell lung cancer (SCLC) were excluded from the study due to different biological and clinical features of SCLC, as well as the fact that the primary focus of the study was the prognostic factors in NSCLC. Case notes were reviewed by the same physician, but for patients treated surgically, data from the operating theatre database were also included. Case notes were analysed to ascertain: age, gender, stage of tumour, histology, performance status, sites of metastases, weight loss (defined as present if the patient complained of it), route of referral to the hospital and the treatment pathway. Medical records were also analysed for pre-treatment laboratory parameters: serum albumin, calcium, Hb, lymphocyte count and LDH. Permission was obtained from the Clinical Audit Department and Departments of Respiratory Medicine and Thoracic Surgery to analyse these patients' medical records.

2.2. Definitions

Waiting times, i.e. intervals along the patient's pathway were defined as follows:

Time to treatment (measure of hospital delay): time from receipt of referral letter from GP/referring physician to first treatment.

Referral time (measure of referral delay): time from receipt of GP/referring physician referral letter to first appointment in Norfolk & Norwich Hospital. It actually is a component of time to treatment.

Waiting times were recorded in days. Use was made of the departmental stamp, which recorded the receipt of referral letter in each case.

For some laboratory parameters, there was a substantial degree of missing data e.g., 16 for albumin, 41 for calcium, 13 for Hb, 14 for lymphocyte count, 76 for LDH. Since albumin, calcium and Hb were significantly inter-related in our cohort and significantly affected survival on univariate survival analysis while lymphocyte count did not, we created a new categorical variable: laboratory abnormality. Laboratory abnormality was defined as being present if serum

calcium was >2.6 mmol/l and/or albumin <35 g/l and/or Hb <12 g/dl. LDH was not used in the construction of the variable laboratory abnormality due to the abundance of missing data.

2.3. Definitive treatment and diagnostic work-up

Definitive surgical treatment was lobectomy or pneumonectomy, and in an overlapping proportion of patients, surgical diagnostic intervention was carried out. Radical radiotherapy consisted of either 55 Gy in 20 fractions in 4 weeks or 66 Gy in 33 fractions in 6.5 weeks, while palliative radiotherapy was commonly 20 Gy in five fractions in 1 week or 14–16 Gy in two fractions in 1 week. The chemotherapy regime consisted of mitomycin 6 mg/m^2, ifosfamide 3 g/m^2 and cisplatin 50 mg/m^2 all on day 1 with mesna 3 g/m^2 given to reduce urotoxicity (MIC). Combined treatment was accepted as the use of any two or three of the treatments; surgery, chemotherapy, or radiotherapy.

For clinically operable patients, mediastinoscopy was done in the vast majority. At more advanced stages, depending on the clinical picture, additional scans other than chest CT scans were ordered. Complete blood count and the blood chemistry were routine.

3. Statistical analysis

3.1. Correlation

We used Spearman rank correlation to analyse the bivariate associations of the pre-treatment laboratory parameters studied (serum albumin, calcium, lymphocyte count, Hb and LDH). These parameters were not normally distributed.

3.2. Survival analysis

Survival was calculated from the beginning of first treatment to date last seen or death. If no specific cancer treatment (surgery, chemotherapy or radiotherapy) was utilised, survival was calculated from the beginning of supportive treatment again to date last seen or death. Each of the following variables was first separately entered in to Cox Proportional Hazard Model [23]: age, gender, histology (squamous carcinoma, adenocarcinoma, other), ECOG performance status, laboratory abnormality, lymphocyte count (log transformation), site of metastasis (bone and/or liver involvement, other distant metastases); route of referral (from GP to chest department, from GP to other department, other); time to treatment (log transformation); treatment by surgery; treatment by radiotherapy; treatment by chemotherapy; combined treatment (defined as any two or three of the preceding treatments). Additionally, patients were stratified for stage (stages 1–4) in both univariate and multivariate analyses. Only, time to treatment (hospital delay), but not other treatment delay variables like patient or referral delay, was used as a covariate in the Cox Regression Models.

Variables showing a significance of $P<0.10$ in the univariate analysis were then entered into a multivariate Cox Proportional Hazard Model with forward stepwise selection according to the likelihood ratio. Kaplan–Meier survival curves [24] were drawn in relation to some of the independently significant factors. All tests of significance were given as two-tailed P values. A P value <0.05 was considered significant. Statistical package for social sciences (SPSS 9.0) was used for data analysis.

4. Results

NSCLC was diagnosed in 203 patients at the Norfolk & Norwich Hospital in 1998. Medical records of 14 were not available to us. Six of these patients had advanced disease (stages 3 and 4) while eight had early stage disease (stages 1 and 2) and were surgically treated. Excluding these cases, we reviewed 189 patients in our study. One hundred and seventy cases had a histological diagnosis, while 19 had a clinical diagnosis only.

Patient and tumour demographics are presented in Table 1. There were no patients in ECOG scale 4. Pre-treatment laboratory values are also shown in Table 1. Significant correlations were observed for some of the parameters studied. Hb and albumin were strongly correlated (Spearman's

$\rho = 0.594$, $P < 0.001$). Similarly Hb and lymphocyte count, albumin and calcium, albumin and lympho-cyte count were correlated ($\rho = 0.211$, 0.216, 0.168; $P = 0.007$, 0.024, 0.036, respectively). Routes of referral and treatment modalities are shown in Table 2.

Table 1
Patient and tumour demographics

Variables	Cases no. (%)	Median	Range	Mean
No. of patients	189 (100.0)	–	–	–
Age	–	70	37–89	–
Gender				
Male	135 (71.4)	–	–	–
Female	54 (28.6)	–	–	–
Performance status (ECOG)				
0	7 (3.8)	–	–	–
1	65 (34.9)	–	–	–
2	95 (51.1)	–	–	–
3	19 (10.2)	–	–	–
Stage				
1	23 (12.2)	–	–	–
2	23 (12.2)	–	–	–
3	84 (44.4)	–	–	–
4	59 (31.2)	–	–	–
Histology				
Squamous cell	84 (44.4)	–	–	–
Adenocarcinoma	47 (24.9)	–	–	–
Others, unknown	58 (30.7)	–	–	–
Weight loss[a]				
Yes	50 (26.5)	–	–	–
No	139 (73.5)	–	–	–
Site of metastasis				
Bone and/or liver	25 (13.2)	–	–	–
Other distant	35 (18.5)	–	–	–
No distant metastasis	129 (68.3)	–	–	–
LDH[b] *(U/l)*	–	–	383–2109	776
Calcium[c] *(mmol/l)*	–	–	1.83–3.39	2.36
Hemoglobin[d] *(g/dl)*	–	–	6.7–16.1	12.4
Lymphocyte count[e] *($\times 10^9$/dl)*	–	–	0.50–5.06	1.60
Albumin[f] *(g/l)*	–	–	21–48	36
Laboratory abnormality[g,h]				
Yes	80 (47.9)	–	–	–
No	87 (52.1)	–	–	–

[a] Any recent weight loss reported by the patient.
[b] Number of valid cases: 46.
[c] Number of valid cases: 111.
[d] Number of valid cases: 165.
[e] Number of valid cases: 163.
[f] Number of valid cases: 158.
[g] Number of valid cases: 167.
[h] Laboratory abnormality: calcium > 2.6 mmol/l or Hb < 12 g/dl or albumin < 35 g/l.

Table 2
Routes of referral and treatment

Variables	Cases no. (%)
No. of patients	189 (100)
Route of referral[a]	
From GP to chest department	84 (45.4)
From GP to other department	26 (14.1)
Other, unknown	75 (40.5)
Treatment	
Chemotherapy	12 (6.4)
Chemotherapy + radiotherapy	15 (7.9)
Chemotherapy + radiotherapy + surgery	0 (0)
Radiotherapy	106 (56.1)
Surgery	40 (21.2)
Surgery + chemotherapy	0 (0)
Surgery + radiotherapy	2 (1)
Supportive care only	14 (7.4)
Radiotherapy	
Radical	12 (6.3)
Palliative	111 (58.7)
Surgery	
Lobectomy	32 (16.9)
Pneumectomy	10 (5.3)
Diagnostic intervention	35 (18.5)
Combined treatment	
Yes[b]	17 (9.0)
No	172 (91.0)

[a] $n = 185$, missing data for four cases.
[b] 2/17 cases are radiotherapy + surgery and 15/17 are radiotherapy + chemotherapy.

The median survival for the whole group of patients was 147, 81, 158 days and not reached, respectively, for stages 4, 3, 1 and 2 subgroups. At the time of analysis, there were 119 deaths and 37% censored cases for the whole group. The median time to treatment in the whole group was 48 days, and the median referral time, 11 days.

Fig. 1 shows Kaplan–Meier survival curves in relation to some independently significant prognostic factors. Corresponding median survival times are as follows: in patients with early stage disease (stages 1 and 2), when route of referral was from GP to chest department, median survival was not reached, but when a different route was used, 121 days (Fig. 1a). In patients that underwent surgery, median survival was not reached, but in those who did not undergo surgery, it was 131 days. In stage 3 subgroup, the patients who received combined treatment had a median survival of 354 days, whereas those who did not receive had a median survival of 149 days (Fig. 1b). Those having laboratory abnormality had a median survival of 128 days as opposed to 224 days of those not having laboratory abnormality (Fig. 1c). In patients with stage 4 disease, median survival times were 51 and 110 days, respectively in patients with liver and/or bone metastasis and those with other metastasis. Those having chemotherapy had a median survival of 245 days as compared those not having it with a median survival of 60 days.

Results of univariate survival analysis are shown in Table 3. For the stages 1 and 2 subgroup, the following gave a P value < 0.10, with P value in brackets: age (0.014), performance status (0.010), weight loss (0.062), laboratory abnormality (0.014), route of referral (0.055), radiotherapy usage (0.093), and surgical treatment status (0.082). In the stage 3 patients, again age (0.089), weight loss (0.002), laboratory abnormality (< 0.001), route of referral (0.066), radiotherapy usage (0.018), and combined therapy usage (0.008) were significant. In patients with stage 4 disease, sex (0.062), laboratory abnormality (0.038), site of metastasis (0.102), chemotherapy usage (0.008), and combined therapy usage (0.010) had a P value < 0.10, and thus, were selected for the multivariate analysis.

In multivariate survival analysis for patients with early stage disease (stages 1 and 2), only two factors were chosen by the forward stepwise selection procedure (Table 3). These were route of referral (referral from GP to chest department or other routes, $P = 0.032$, HR = 0.08), and absence of surgery ($P = 0.006$, HR = 30.30). In stage 3 patients, multivariate model again selected two factors, absence of laboratory abnormality ($P = 0.002$, HR = 0.39), and combined treatment usage ($P = 0.015$, HR = 0.17). A total of seven stage 3 patients (8.3% of 84 stage 3 cases) had received combined treatment (sequential chemoradiotherapy). Similarly, combined treatment, as we defined in the subjects and methods, had also been used in other stages in the form of radiotherapy and chemotherapy for eight of the 59 stage 4

Table 3
Survival analysis

Variable	Univariate analysis						Multivariate analysis											
	Stages 1 and 2		Stage 3		Stage 4		Stages 1 and 2				Stage 3				Stage 4			
	P value	HR	*P* value	HR	*P* value	HR	*P* value	Wald	HR	95% CI	*P* value	Wald	HR	95% CI	*P* value	Wald	HR	95% CI
Age	*0.015*	1.10	*0.089*	1.03	0.403	0.99	0.256	1.30	–		0.872	0.03						
Sex	0.548	–	0.504	–	*0.062*	–	–	–	–						0.474	0.51		
Male	–	1	–	1	–	1	–	–	–									
Female	–	0.69	–	1.22	–	0.53	–	–	–									
Pathology	0.443	–	0.381	–	0.851	–	–	–	–									
Other	–	1	–	1	–	1	–	–	–									
Squamous cell	–	2.14	–	0.79	–	0.86	–	–	–									
Adenocarcinoma	–	0.95	–	0.58	–	0.82	–	–	–									
Performance status (ECOG)	*0.010*	3.69	0.461	1.17	0.451	1.17	0.655	0.20	–									
Weight loss	*0.062*	–	*0.002*	–	0.505	–	–	–	–		0.16	1.98						
No	–	1	–	1	–	1	–	–	–									
Yes	–	3.91	–	2.44	–	1.22	–	–	–									
Labdummy (laboratory abnormality)	*0.014*	–	*<0.001*	–	*0.038*	–	0.069	3.32	–		*0.002*	10.13			0.079	3.09		
Yes	–	1	–	1	–	1	–	–	–				1					
No	–	0.17	–	0.35	–	0.50	–	–	–				0.39	0.22–0.69				
Log lymphocyte count	0.218	0.05	0.566	0.66	0.293	0.38	–	–	–									
Site of metastasis	n/a	–	n/a	–	*0.102*	–	–	–	–						*0.005*	8.05		
Distant metastasis except bone and/or liver	–	–	–	–	–	1	–	–	–								1	
Bone and/or liver	–	–	–	–	–	1.61	–	–	–								2.65	1.35–5.18
Route of referral	*0.055*	–	*0.066*	–	0.692	–	*0.032*	–	–		0.124	2.36						
Other routes	–	1	–	1	–	1	–	–	1									
From GP to chest department	–	0.29	–	0.62	–	1.31	–	4.63	0.08	0.01–0.80								
From GP to other department[a]	–	–	–	1.35	–	1.09	–	–	–									
Log time to treatment	0.284	0.43	0.550	1.30	0.220	0.668	–	–	–									
Use of chemotherapy	N/a	–	0.133	–	*0.004*	–	–	–	–						*<0.001*	13.57		
Chemotherapy	–	–	–	1	–	1	–	–	–								1	
No chemotherapy	–	–	–	1.79	–	3.35	–	–	–								6.25	2.33–16.67
Use of radiotherapy	*0.093*	–	*0.018*	–	0.132	–	0.198	1.66	–		0.092	2.84						
Radiotherapy	–	1	–	1	–	1	–	–	–									
No radiotherapy	–	0.35	–	2.00	–	1.87	–	–	–									
Use of surgery	*0.082*	–	0.845	–	n/a	–	*0.006*	7.66	–									
Surgery	–	1	–	1	–	–	–	–	1									
No surgery	–	3.23	–	0.93	–	–	–	–	30.30	2.71–344.83								
Combined treatment	N/a[b]	–	*0.008*	–	*0.010*	–	–	–	–		*0.015*	5.97			0.951	0.04		
No	–	–	–	1	–	1	–	–	–				1					
Yes	–	–	–	0.14	–	0.31	–	–	–				0.17	0.04–0.70				

[a] 'From GP to other department' category was pooled with 'other routes' category only for stages 1 and 2 patients due to insufficient number of patients in 'from GP to other department' category.
[b] Analysis not possible due to insufficient number of cases (2) for stages 1 and 2.

patients (13.6%) in any sequence during the course of their disease; surgery and post-operative radiotherapy in two of the 46 patients (4.4%) with stage 1 or 2 disease with no apparent effect on prognosis. Finally, in patients with stage 4 disease, absence of chemotherapy usage ($P < 0.001$, HR = 6.25), and site of metastasis ($P = 0.005$, HR = 2.65) were independently significant.

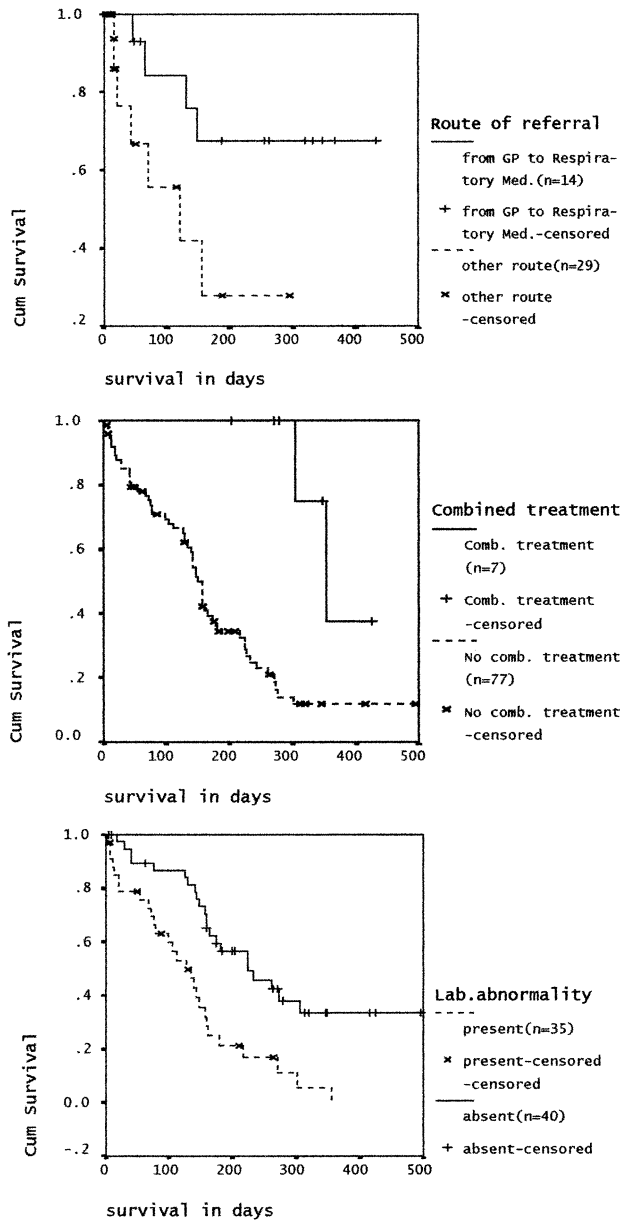

Fig. 1. Kaplan–Meier survival curves for some of the prognostic factors. (a) Route of referral for patients with stages 1 and 2 disease ($n_{\text{analysed}} = 43$, $n_{\text{unavailable}} = 3$, n_{total} (stages 1 and 2) = 46). (b) Use of combined treatment in stage 3 disease ($n_{\text{analysed}} = 84$, $n_{\text{unavailable}} = 0$, n_{total} (stage 3) = 84). (c) Laboratory abnormality in stage 3 disease (see text for definition) ($n_{\text{analysed}} = 75$, $n_{\text{unavailable}} = 9$, n_{total} (stage 3) = 84).

5. Discussion

NSCLC is a disease of the older population and our median age of 70 years affirms this. The sex ratio of 71.4 M, 28.6% F and histological pattern of 44.4% squamous carcinoma, 24.9% adenocarcinoma point out the predominance of the male gender and of these two histological subtypes which is generally characteristic for this disease. The great majority (86%) were ECOG status 1 or 2 or were in stages 3 or 4 (75.6%, Table 1).

22.2% (42/189) patients were treated surgically (Table 2). This compares favourably with UK average of 11%, reflecting the presence of a thoracic surgery unit based in our centre. Sixty-five per cent of patients (123/189) received radiotherapy though only 6.3% radical radiotherapy (10.3% of radiotherapy patients). 14.3% of patients (27/189) received chemotherapy. This compares with 2.5% radical radiotherapy and 10.2% chemotherapy in another UK series [25] which included small cell cancer.

For the first time, our study demonstrates in patients with NSCLC that time to treatment (hospital delay) does not affect survival. Therefore, there was no survival difference between those who waited longer after referral for treatment and those who waited less. In univariate analysis, the shorter delay was in fact insignificantly associated with shorter survival across all stage subgroups ($HR < 1$ for log time to treatment in stages 1–4 subgroups, Table 3). This may reflect more rapid progress through the system of more symptomatic cases. A recent review of breast cancer showed no evidence that delays of longer than 90 days adversely influenced survival and patients who were treated in under 30 days had significantly worse outcomes [5]. By contrast another review in breast cancer found that patients with delays of 3 months or more had 12% lower 5-year survival [6,26]. Waiting time was not significantly associated with local relapse in laryngeal cancer treated by radiotherapy [27]or in T1 nasopharyngeal cancer [28] yet was associated with reduced local control in tonsillar tumours [29].

It is important that time to treatment, as we described in this study, is a measure of hospital delay, but not of referral or patient delay. The latter two are hard to calculate, because, for example, patient delay reports by the patients are generally subjective. Taking account of patient delay in addition to hospital delay when calculating time to treatment, it might be possible to find an association between time from the onset of first symptoms to treatment and survival of patients with NSCLC. Parallel to that, Christensen et al. found that delay, in general, to surgery for NSCLC was associated with more advanced stage [30]. So, it is possible that neglecting patient delay from the analysis might have biased our results. On the contrary, it is not likely that omitting referral delay from the statistical analysis could have affected the survival analysis results due to the fact that it is totally represented in time to treatment as defined in this study.

Hypo-albuminaemia [31], hypercalcaemia and anaemia [32] are all known survival determinants. The correlation between pre-treatment laboratory values was high. It was for this reason, and in order to overcome the problem of missing data, that we defined the variable 'laboratory abnormality'. Presence of laboratory abnormality, i.e. abnormality in at least one of the parameters; calcium, albumin or Hb, was strongly associated with poor survival, as expected, in our patients with stage 3 NSCLC.

Univariate survival analysis in our study shows 11 significant variables that are related to survival in patients with different stages of NSCLC. Some of these, e.g., performance status, weight loss, site of metastasis, use of surgery and chemotherapy are well known prognosticators [32–36]. In this sense, our study confirms the validity of these prognostic factors in our cohort. Additionally, our results show that for patients with stage 3 disease, use of combined modality therapy is independently associated with better survival in accordance with previous work [37].

A second novel finding of this study other than the lack of prognostic value of time to treatment as a measure of hospital delay is the association of route of referral with survival in stages 1 and 2 NSCLC. 45.4% of patients were referred from GP to respiratory medicine (Table 2). In stages 1 and 2 subgroup, such patients survived better in univariate and multivariate analysis than those re-

ferred by other routes (Table 3). When all patients are considered, almost as many were not referred by GP (40.5%) and along with those referred from GP to other departments, are likely to have presented acutely. Additionally, a hospital specialist mostly referred these patients from another hospital, therefore, these cases might have been subjected to referral delay. Patient delay also cannot be excluded, as we have no data on this. These possibilities may explain why referral from GP to other department or other referral routes (routes other than from GP to chest department) is associated with shorter survival significantly in stages 1 and 2 subgroup and insignificantly in stage 3 patients. This is in accordance with the BTS recommendation that all patients should be referred to a respiratory physician. However, our data suggest that even if all GP referrals were GP-respiratory medicine referrals, this would still only represent 59.5%.

Four potential weaknesses in our study are: it is retrospective, of relatively small size and does not take account of patient delay, or, quality of life. A randomised trial of treatment delay would be clinically and ethically unacceptable. Therefore, waiting time can only be studied retrospectively [28]. Studies from larger centres have used random sampling but the number of medical records examined was little larger than in our series [25]. Patient delay is difficult to quantify and is subjective [27]. Quality of life cannot be measured retrospectively but studies in place are assessing the effect of oncology treatments on quality of life in lung cancer.

In summary, our study shows that survival in NSCLC is not affected by hospital delay, but, in addition to classical prognosticators, is strongly dependent on route of referral in early stages and use of combined-modality treatment in locally advanced disease. This, therefore, suggests that more progress in controlling the disease may be made by increasing resources in oncology to make radiotherapy [38] and cytotoxic chemotherapy [10] more widely available than primarily focusing on reducing hospital delay. Additionally, further research is needed to explore the prognostic significance of patient and referral delay for NSCLC patients.

6. Conclusion

Hospital delay does not appear to effect survival of patients with NSCLC. Since, treatment factors and route of referral, in addition to other clinical parameters, are independent prognostic factors, it is important to increase resources to optimise treatment conditions. Furthermore, our results suggest that referral delay may be associated with poor survival, therefore, further studies need to be conducted to better test the clinical significance of referral and/or patient delay for patients with NSCLC.

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