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ORIGINAL ARTICLE

Prognostic factors in clinical stage T4N2 locally advanced non-small cell lung cancer

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Summary

Purpose: *Relatively few studies have focused on T4N2 (stage IIIB) locally advanced non-small cell lung cancer (NSCLC). In this study, we tried to identify prognostic factors for patients with clinical stage T4N2 NSCLC.*

Methods: *We retrospectively identified 223 patients, of which 168 met the inclusion criteria. Patients treated with curative intent using concurrent chemoradiotherapy (CRT) with or without adjuvant chemotherapy, or concurrent CRT after induction chemotherapy, were included in this study. Relevant patient, treatment, and disease factors were evaluated for their prognostic significance in both univariate and multivariate analyses using the Cox proportional hazards model.*

Results: *The median progression-free survival (PFS) was 13 months (95% confidence interval [CI], 10.6–15.4). The median overall survival (OS) was 20 months (95% CI, 16.8–23.1), and 71, 40.3 and 28.2% of the patients survived for 1, 2 and 3 years after diagnosis, respectively. Multivariate analysis showed Eastern Cooperative Oncology Group (ECOG) performance status (PS) was independent predictor of PFS (hazard ratio [HR], 0.24; 95% CI, 0.13-0.43; p=0.001), and OS [HR, 0.48; 95% CI, 0.26-0.87; p=0.015). Absence of multifocal T4 tumors was also associated with a significantly longer OS (HR, 046; 95% CI, 0.31-0.7; p=0.001). There was no statistically significant difference in OS and PFS between treatment modalities.*

Conclusion: *PFS and OS were significantly shorter in patients with poor ECOG PS. OS was also significantly shorter in patients with multifocal T4 tumors. There were no differences between the two therapeutic approaches with respect to outcome.*

Key words: *clinical stage T4N2, locally advanced non-small cell lung cancer, patient outcome, prognostic factors, treatment modality, survival*

Introduction

Lung cancer is the most common cancer worldwide [1], and the most common cause of cancer-related deaths amongst both men and women [1]. NSCLC accounts for approximately 85% of all lung cancer cases [2,3], and the majority of patients have advanced disease at the time of diagnosis [3,4]. Indeed, information available in the Surveillance, Epidemiology, and End Result

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(SEER) database reveals that 65% of the patients have stage IIIB or IV disease when diagnosed [5].

The optimal treatment for patients with stage III NSCLC has not been clearly defined and many aspects of therapy continue to be debated. While there are many potential treatment options for advanced NSCLC, none provides a realistic chance of cure, whilst earlier-stage disease (stage I, stage II and some subgroups of stage IIIA) is potentially curable. However, for some patients with stage IIIA disease, a combined modality approach using concurrent CRT is generally preferred [6]. Stage IIIB has a very poor prognosis. Many clinical trials for advanced NSCLC have enrolled patients with stage IIIB or IV disease, and those with stage IIIB have been included in phase III trials, either alone or together with stage IIIA patients, and treated with curative intent using a combined modality that included chemotherapy, radiotherapy and surgery.

The optimal treatment for stage IIIB NSCLC depends on several factors, including age, comorbid risk factors, ECOG PS, weight loss, and the extent of disease. A single modality treatment, consisting of radiotherapy or chemotherapy, has been used to treat patients with poor PS, but concurrent CRT is recommended for most other cases [6]. Although there have been a number studies to identify prognostic factors in advanced NSCLC, the majority of these grouped stage IIIB disease with either stage IIIA or IV disease, and relatively few have focused only on stage IIIB [7-14]. In addition, stage IIIB disease is a heterogeneous group of conditions with different levels of lymph node involvement and T stages, and it has been shown that stage IIIB patients without N3 nodal status have a significantly better outcome [15].

There have been very few previous studies focusing on T4N2 (stage IIIB) locally advanced NSCLC. In this study, we sought to identify prognostic factors that correlated with outcome in patients with such clinical stage.

Methods

Inclusion/exclusion criteria

Between 2002 and 2012, all cases of stage T4N2 NSCLC from tertiary hospitals within our administrative region were evaluated. We retrospectively identified 223 patients, of which 168 were included in this study as they had been staged using the AJCC lung cancer staging guidelines (7th Edn) at the time of diagnosis. Patients with a superior sulcus tumor (Pancoast tumor) were not included in the study. Data was primarily obtained from hospital files, but it was also collected directly by interviewing the patients and/or their relatives.

Clinical stage was defined using computed tomography (CT) of the upper abdomen and thorax, magnetic resonance imaging (MRI) of the brain, whole body bone scintigraphy, fiberoptic bronchoscopy, and, in some cases, mediastinoscopy and intraoperative observations. MRI was used to evaluate suspected invasions of the chest wall, large veins, and vertebrae. From June 2007 onwards, ^{18}F-fluorodeoxyglucose positron emission tomography-CT (PET-CT) was used in some selected patients. The TNM status of all patients was determined in accordance with the standard radiological guidelines. Tissue samples obtained from mediastinoscopy and/or surgery and cytological samples obtained from pleural and/or pericardial fluids were also used in staging. Medical charts were reviewed to obtain patient demographic data including age, sex, ECOG PS, smoking status, weight loss, pathological subtype, and treatment modality.

All of the included patients were treated with curative intent using concurrent CRT with or without adjuvant chemotherapy or with concurrent CRT after induction chemotherapy.

Statistics

Univariate and multivariate survival analyses were used to determine OS and PFS rates. For PFS, progression or death from any cause was taken as an endpoint, and OS was measured from the date of the first histologic diagnosis until the date of death. Univariate Cox regression analysis was applied to the univariate survival rates. Variables analyzed by the univariate method and having a $p<0.1$ were included in the subsequent multivariate Cox regression analysis. In multivariate analysis, variables were selected using the likelihood ratio formula. Survival curves were constructed according to Kaplan-Meier method and compared with the log rank test. Differences with $p<0.05$ were considered to be significant.

Results

Patient and disease characteristics

A total of 55 patients were excluded, either because they underwent palliative treatment instead of treatment with curative intent (48 patients), or because they underwent surgical resection as part of their management (7 patients).

The median follow-up period was 23.1 months (range, 1–138). The median patient age was 59 years (range, 30–80), the majority of the patients were men (90%), and 89% of the patients were smokers, with an average consumption of 50 pack-years (range, 9–160). The majority of the pa-

Table 1. Patient and disease characteristics

Characteristics	*Patients, N (%)*
Age (years)	
<60	87 (52)
≥60	81 (48)
Sex	
Male	151 (90)
Females	17 (10)
Smoking status	
Smoker	150 (89)
Never smoker	18 (11)
Weight loss (%)	
≤5	153 (91)
>5	15 (9)
Co-morbidities	
Present	58 (34.5)
Absent	110 (65.5)
Histological subtype	
Adenocarcinoma	67 (40)
Squamous cell carcinoma	85 (51)
Large cell carcinoma	6 (4)
Not otherwise specified	6 (5)
ECOG-PS	
0	58 (35)
1	96 (57)
2	14 (8)
Multifocal T4 tumors	
Present	40 (24)
Absent	128 (76)
Treatment modality	
Concurrent chemoradiotherapy with or without adjuvant chemotherapy.	97 (57.7)
Definitive radiotherapy or concurrent chemoradiotherapy after induction chemotherapy	71 (42.3)

tients (92%) had good ECOG PS (0 or 1), and 91% had ≤5% weight loss at the time of diagnosis. Fifty eight patients had co-morbidities (34.5%).

The clinical and pathological characteristics of the patients are summarized in Table 1. With respect to tumor histological subtype, 50.9% were squamous cell carcinomas, 40.1% adenocarcinomas, 3.6% large cell carcinomas, and 5.4% were of a not otherwise specified (NOS) type. The majority of the patients (52.4%) had a staging PET-CT scan, 37% had a Wang needle biopsy, and 13% had invasive mediastinal staging with mediastinoscopy. The type of clinical staging method used was decided upon by the thoracic surgeon.

With regard to treatment, the total classical or hyperfractionated dose recommended for definitive radiotherapy was 60-70 Gy. Ninety seven patients (57.7%) received concurrent CRT with or without adjuvant chemotherapy and 71 patients (42.3%) received definitive radiotherapy or concurrent CRT after induction chemotherapy.

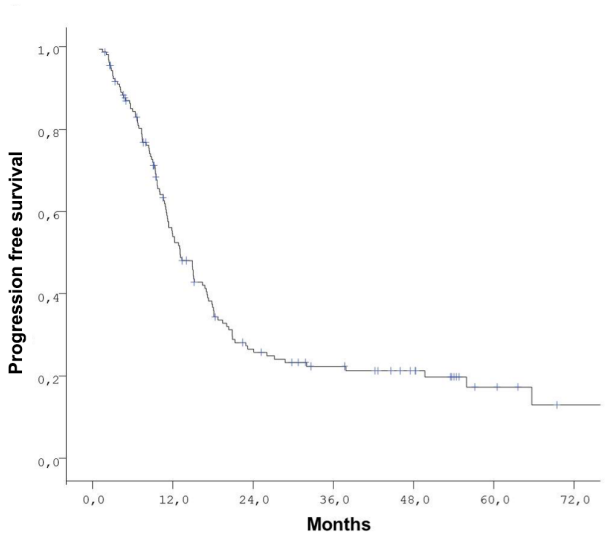

Figure 1. Progression-free survival of patients with stage T4N2 non-small cell lung cancer treated with curative intent at 1, 2, and 3 years

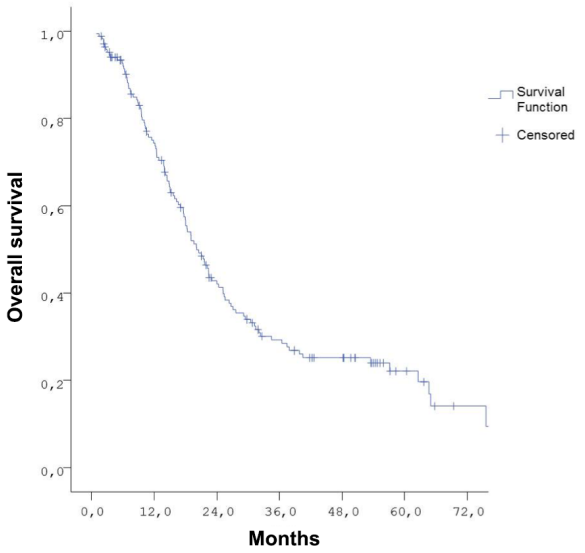

Figure 2. Overall survival of patients with stage T4N2 non-small cell lung cancer treated with curative intent at 1, 2, and 3 years.

Chemotherapy consisted of a cisplatin doublet based regime in each case.

Univariate and multivariate analysis of PFS

The median PFS was 13 months (95% CI, 10.6–15.4) with 1, 2, and 3 year PFS rates of 54, 26.5, and 22.3%, respectively (Figure 1). Factors associated with significantly longer PFS in univariate analysis were age <60 years (HR, 0.7; 95% CI, 0.5-1.06; p=0.09], ECOG PS 0/1 (HR, 0.23; 95%

Table 2. Univariate analysis of overall survival and progression-free survival

Factors	*OS*		*PFS*	
	HR (95% CI)	*p value*	*HR (95% CI)*	*p value*
Age (years) <60 vs ≥60	0.69 (0.4–1.006)	0.054	0.7 (0.5–1.06)	0.09
Sex Male vs female	(0.58–1.94)	0.82	1.38 (0.7–2.5)	0.30
Smoking status Smoker vs never smoker	(0.6–2.21)	0.66	1.4 (0.7–2.7)	0.33
Weight loss (%) ≤5 vs >5	0.92 (0.66–1.66)	0.83	0.9 (0.58–1.41)	0.68
Co-morbidities: Present vs absent	1.19 (0.81–1.74)	0.37	1.09 (0.74–1.68)	0.63
Histological subtype				
Squamous cell carcinoma vs non-squamous cell carcinoma	0.89 (0.61–1.28)	0.54	0.92 (0.63–1.37)	0.66
Adenocarcinoma vs non-adenocarcinoma	0.7 (0.47–1.009)	0.005	0.69 (0.48–1.02)	0.06
ECOG-PS 0-1 vs 2	0.5 (0.28–0.9)	0.002	0.23 (0.13–0.42)	0.001
Multifocal T4 tumors Present vs absent				
Treatment modality Concurrent chemoradiotherapy with or without adjuvant chemotherapy vs definitive radiotherapy or concurrent chemoradiotherapy after induction chemotherapy	0.76 (0.52–1.12)	0.17	0.91 (0.62–1.34)	0.60
Use of PET-CT in staging Yes vs No	0.81 (0.64–1.02)	0.5	0.95 (0.72–1.12)	0.91

HR: hazard ratio, CI: confidence interval, OS: overall survival, PFS: progression-free survival

CI, 0.13-0.42; p =0.001), absence of multifocal T4 tumors (HR, 0.65; 95% CI, 0.42-0.99; p=0.045) and adenocarcinoma histology (HR, 069; 95% CI, 0.48-1.02; p=0.064). Smoking, weight loss, the use of PET-CT in staging, co-morbidities, and treatment modality were not found to affect PFS. In multivariate analyses, only ECOG PS 0/1 (HR, 0.24; 95% CI, 0.13-0.43; p=0.001) was found to be an independent prognostic factor (Table 2, Figure 3).

Univariate and multivariate analysis of OS

The median OS was 20 months (95% CI, 16.8–23.1) with 1, 2, and 3 year OS rates of 71, 40.3 and 28.2%, respectively (Figure 2). In univariate analysis, factors found to be associated with prolonged OS were age <60 years (HR, 0.69; 95% CI, 0.4-1.006; p=0.054), ECOG PS 0/1 (HR, 0.5; 95% CI, 0.28-0.9; p=0.02), absence of multifocal T4 tumors (HR, 0.47; 95% CI, 0.3-0.7; p=0.001) and adenocarcinoma histology (HR, 0.7; 95% CI, 0.47-1.009; p=0.055). Smoking, weight loss, the use of PET-CT in staging, co-morbidities, and treatment modality were not found to affect OS. In multivariate analysis, ECOG PS 0/1 (HR, 0.48; 95% CI, 0.26-0.87; p=0.015) (Figure 4) and absence of multifocal T4 tumors (HR, 0.46; 95% CI, 0.31-0.7; p=0.001) were still significantly associated with longer OS (Table 3, Figure 5).

Treatment modality

The median PFS did not differ significantly (p=0.5), between patients treated using concurrent

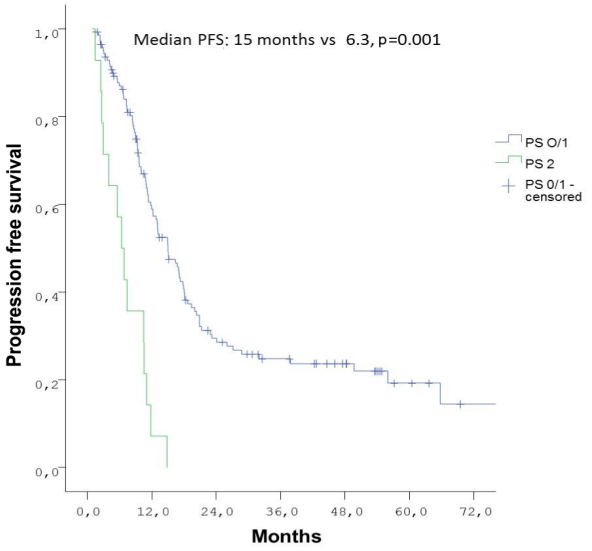

Figure 3. Effect of Eastern Oncology Cooperative Group performance status on progression-free survival in stage T4N2 non-small cell lung cancer patients treated with curative intent

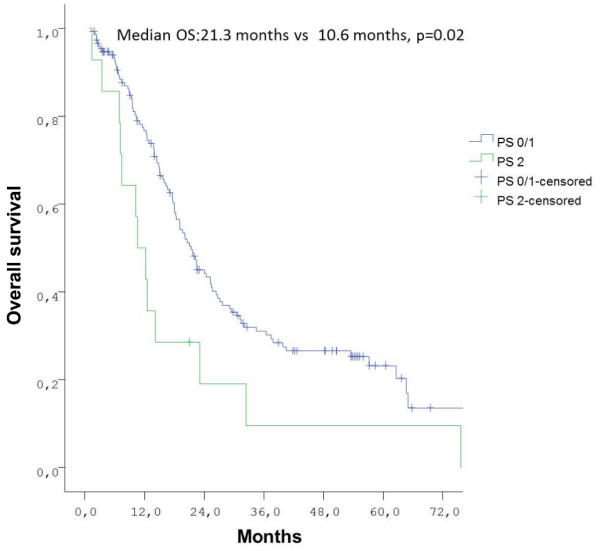

Figure 4. Effect of Eastern Oncology Cooperative Group performance status on overall survival amongst patients with stage T4N2 non-small cell lung cancer treated with curative intent.

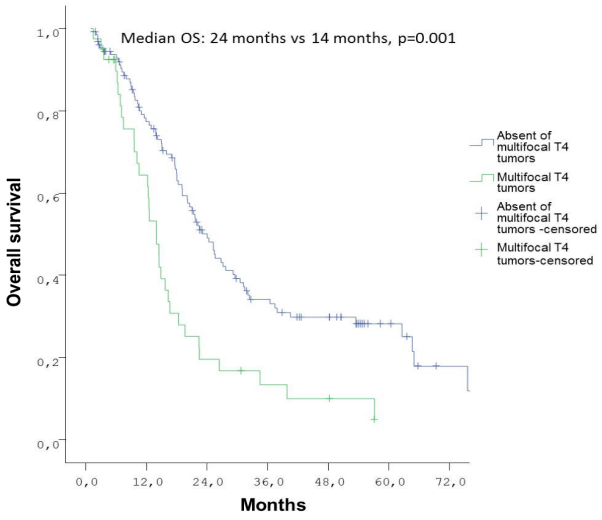

Figure 5. Effect of Eastern Oncology Cooperative Group performance status on overall survival amongst patients with stage T4N2 non-small cell lung cancer treated with curative intent.

CRT or definitive RT after induction chemotherapy (12.2 months; 95% CI, 9.9-14.5) and those treated using concurrent CRT with or without adjuvant chemotherapy (14.9 months; 95% CI, 11.1-18.8). The median OS also did not differ significantly between these groups (22.4 months; 95%CI, 12.5-32.2) for concurrent CRT or definitive RT after induction chemotherapy (19.6 months; 95% CI, 16.5-22.6) for concurrent CRT with or without adjuvant chemotherapy; p=0.14).

Discussion

Based on information available in the SEER database, 17.6% of all NSCLC patients have stage IIIB disease. These patients have a very poor prognosis, with an anticipated 5-year survival probability of only 3 to 7% [16]. Relatively few studies have focused on this disease stage, despite the fact that identifying prognostic factors will help determine which patients should undergo more

Table 3. Multivariate analysis of overall survival and progression-free survival

Factors	*OS*			*PFS*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
ECOG-PS 0-1 vs 2	0.48	0.26-0.87	0.015	0.24	0.13-0.44	0.001
Multifocal T4 tumors Present vs absent	0.46	(0.31-0.7)	0.001	ns	ns	ns

OS: overall survival, PFS: progression-free survival, HR: hazard ratio, ns: nonsignificant

aggressive curative treatment.

In the current study, we have identified prognostic factors that correlated with outcome in patients with clinical stage T4N2 NSCLC. The median OS of these patients was 20 months with 1, 2, and 3-year OS rates of 71, 40.3 and 28.2%, respectively. This broadly matches the findings of most previous trials that evaluated concurrent CRT for stage III NSCLC, in which the OS ranged from 15 to 26 months, with a 3-year OS rate between 17 and 33% [15-21].

Our findings revealed that ECOG PS is an independent predictor of both PFS and OS, and that the absence of multifocal T4 tumors was also associated with a significantly longer OS. This is in agreement with previous studies [22,23],] although –to our knowledge– the study we report here is the first to demonstrate an association between multifocal T4 tumors and survival.

We also found, unexpectedly, that weight loss and sex were not associated with survival, which contrasts the findings of several other studies [8,11,12,14,15,24]. It was previously shown that women had a significantly better prognosis than men with advanced NSCLC [8,12,14], and that weight loss was also associated with outcome in this malignancy [11,15,24]. A study by Jeremic et al. demonstrated that patients with locally advanced stage NSCLC generally had a better outcome if they lost no more than 5% of their body weight. This may be secondary to the relative small proportion of female patients in this study and the small proportion of patients with weight loss.

Janjigian et al. demonstrated that more cigarette smoking, measured in pack-years, was associated with decreased survival after a diagnosis of stage IIIB/IV NSCLC [25]. However, in our trial information on pack-years cigarette smoking was not available in all patients.

In this study patients were treated with curative intent, with either concurrent CRT with or without adjuvant chemotherapy (57.7%) or concurrent CRT after induction chemotherapy (42.3%). Neither the median PFS nor OS differed significantly between these two therapeutic approaches. Our findings are consistent with those of the Cancer and Leukemia Group B trial [26], in which Vokes et al. evaluated whether induction chemotherapy before concurrent CRT could extend survival. They also failed to find a significant difference in survival compared to CRT alone [25] and in addition, they showed that combining induction chemotherapy with concurrent CRT increased toxicity [25].

In conclusion, our study includes one of the largest series of patients with stage T4N2 NSCLC treated with curative intent, and has allowed us to identify prognostic factors that could help determine which patients are most likely to benefit from more aggressive, curative treatment. Furthermore, the addition of induction or adjuvant chemotherapy to CRT did not significantly change treatment outcome.

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