RESEARCH ARTICLE

Prognostic Factors in Stage III Non-Small-Cell Lung Cancer Patients

Semiha Elmaci Urvay¹*, Birsen Yucel², Eda Erdis², Nedim Turan²

Abstract

Aim: The objective of this study is to investigate prognostic factors affecting survival of patients undergoing concurrent or sequential chemoradiotherapy (CRT) for stage III non-small-cell lung cancer (NSCL). Methods and materials: We retrospectively reviewed the clinical records of 148 patients with advanced, inoperable stage III NSCLC, who were treated between 2007 and 2015. Results: The median survival was found to be 19 months and 3-year overall survival was 27%. Age (<65 vs ≥65 years, p=0.026), stage (IIIA vs IIIB, p=0.033), dose of radiotherapy (RT) (<60 vs ≥60 Gy, p=0.024) and treatment method (sequential chemotherapy+RT vs concurrent CRT, p=0.023) were found to be factors affecting survival in univariate analyses. Gender, histological subtype, weight loss during CRT, performance status, induction/consolidation chemotherapy and presence of comorbidities did not affect survival (p>0.050). Conclusion: Young age, stage IIIA, radiotherapy dose and concurrent chemoradiotherapy may positively affect survival in stage III NSCL cases.

Keywords: Non-small lung cancer, prognostic factors, survival.

Asian Pac J Cancer Prev, 17 (10), 4693-4697

Introduction

According to the USA data, lung cancer is the most common cause of cancer death. NSCLC accounts for about 80% of all lung cancers (Siegel et al., 2015; Howlader et al., 2013; Wahbah et al., 2007). The 5 year survival rate is approximately %16 (Siegel et al., 2015; Howlader et al., 2013). About 80% of patients are diagnosed at stage III. The heterogeneity in this patients group makes it difficult to choose the optimal treatment and survival times of patients are quite variable on patient basis. Although surgical resection is treatment of choice for eligible patients in Stage III disease, other available treatment methods include surgery following induction chemo/radiotherapy or CRT.

It is extremely important to understand the progression of this disease which has low survival times despite the advancing treatment modalities. For this purpose, prognostic factors have been investigated and several prognostic factors have been described in a number of studies. The most well-known prognostic factors include diagnosis at early stage, good performance status, absence of significant weight loss and female gender (Finkelstein, 1986). Investigation of the additional prognostic factors that determine survival outcomes and treatment options of Stage III patients may play an important role both in evaluation of optimal treatment options and increasing survival of patients. Several factors such as histopathological type of tumor, age, smoking status, presence of comorbidity, radiotherapy dose and treatment modality (chemoradiotherapy, radiotherapy or chemotherapy alone) may be the other indicators influencing treatment outcomes and survival (Gregory et al., 2003; Movsas et al., 1999; Auperin et al., 2010; Van Baardwijk et al., 2010). The objective of this study is to investigate prognostic factors affecting survival outcome of the patients undergone concurrent or sequential CRT with the diagnosis of stage III non-small-cell lung cancer.

Material and Methods

We retrospectively reviewed the clinical records of 148.0 patients with a diagnosis of advanced, inoperable stage 3A and 3B NSCLC, who were seen and treated at Cumhuriyet University Medical Faculty Education and Research Hospital between 2007 and 2015. Data collected included patients gender, age, performance status, histology, stage, comorbidities, smoking status, weight loss, type of therapy and RT dose. Survival time was measured from the date of diagnosis to date of death from any cause or date of last patient contact.

Tumor staging was done according to the American Joint Committee on Cancer (AJC) TNM 7. All patients were staged by computed tomography scan of the chest, abdomen, and pelvis. Positron emission tomography scan and brain imaging were used for staging in some patients upon the discretion of the treating physician if needed. Patients performance status was determined according

¹Acibadem Hospitals Group, Birsen Yuçel, Kayseri, ²Cumhuriyet University Medical Oncology Department, Sivas, Turkey. *For correspondence: semiha.urvay@acibadem.gov.tr
to scoring system of the Eastern Cooperative Oncology Group (ECOG). Weight loss was defined as a weight loss of 5% during CRT or RT.

The Statistical Package for Social Sciences (SPSS) for Windows 14.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. For descriptive statistics, the mean, standard deviation, frequency, and median were used. The survival rates were calculated according to the Kaplan–Meier method. A multivariate analysis (Cox regression analysis) was used to evaluate the independent risk factors that affected survival. P values ≤0.05 were accepted as statistically significant.

## Results

One hundred forty-eight locally advanced NSCLC patients who were treated with chemoradiotherapy were included in the study retrospectively. The clinical and pathological characteristics of these patients are shown in Table 1. The median age was found as 60 (range 31-81). Most of the patients were male (91%). Histopathologically, squamous cell carcinoma were observed in 100 (%68) patients and adenocarcinoma were diagnosed in 27.0 (%18) patients. 75 (51%) patients had comorbidity. At diagnosis, ECOG PS= 0-1 patients were %81 and none of the patients had ECOG PS= 4.

Twenty-six (17%) patients had received sequential chemotherapy+radiotherapy and 122.0 (83%) patients had received concurrent CRT. Of the patients in the concurrent CRT arm, 87 (71%) had received additional induction/consolidation chemotherapy. A total of 66.6 Gy RT dose was planned in all patients, but 133 (90%) of these patients could receive 60 Gy or higher RT doses.

In mean follow-up of 23±1.7 months, the median survival time was found as 19 months and 3-year OS rate as 27%. In univariate analysis; age (p=0.026), stage (p=0.033), type of treatment (p=0.023) and RT dose (p<0.001) were found as the prognostic factors affecting survival. The results of univariate analysis are shown in Table 1 and the survival curves of important prognostic factors are shown in Figure 1. Similarly; age (HR: 1.58; 95% CI: 1.03-2.43; p=0.034), stage (HR: 1.6; 95% CI:

| Subgroup                        | N (%) | 3 year survival (%) | Median survival (months) | P     |
|---------------------------------|-------|---------------------|--------------------------|-------|
| Age                             |       |                     |                          |       |
| <65                             | 100 (68) | 33                  | 22                       | 0.026 |
| ≥65                             | 48 (32)  | 21                  | 16                       |       |
| Sex                             |       |                     |                          |       |
| Men                             | 135 (91) | 29                  | 19                       | 0.468 |
| Women                           | 13 (19)  | 24                  | 21                       |       |
| Histopathology                  |       |                     |                          |       |
| 1SCC                            | 100 (68) | 32                  | 30                       | 0.172 |
| Adenocarcinoma                  | 27 (18)  | 27                  | 18                       |       |
| 2NOS                            | 21 (14)  | 19                  | 17                       |       |
| Performance score               |       |                     |                          |       |
| 3ECOG0                          | 53 (39)  | 21                  | 17                       | 0.273 |
| ECOG1                           | 57 (42)  | -                   | 24                       |       |
| ECOG2                           | 25 (19)  | -                   | 13                       |       |
| Stage                           |       |                     |                          |       |
| 3A                              | 7 (49)   | 37                  | 24                       | 0.033 |
| 3B                              | 75 (51)  | 21                  | 14                       |       |
| Treatment                       |       |                     |                          |       |
| Sequential 4CT+5RT              | 26 (17)  | 15                  | 15                       | 0.023 |
| Concurrent 6CRT                 | 122 (83) | 30                  | 21                       |       |
| Treatment                       |       |                     |                          |       |
| CRT                             | 35 (29)  | 43                  | 29                       | 0.791 |
| 7Ind/Cons+KRT                   | 87 (71)  | 27                  | 20                       |       |
| RT dose                         |       |                     |                          |       |
| <60 Gy                          | 15 (10)   | 0                   | 7                        | <0.001|
| ≥60 Gy                          | 133 (90) | 30                  | 21                       |       |
| Weight lose                     |       |                     |                          |       |
| No                              | 96 (71)  | 20                  | 10                       | 0.573 |
| Yes                             | 39 (29)  | 25                  | 18                       |       |

SCC, Squamous cell carcinoma; NOS, Not otherwise specified; ECOG, Eastern Cooperative Oncology Group; CT, Chemotherapy; RT, Radiotherapy; CRT, Chemoradiotherapy; Ind/Cons, Induction/Consolidation
Prognostic Factors in Stage III Non-Small-Cell Lung Cancer Patients

The literature no significant difference was found in the patients receiving induction/consolidation chemotherapy compared to those receiving CRT.

Approximately half of patients with NSCLC are 70-year-old or above at the time of diagnosis (Langer et al.,2000). In our study, the average age of the patients were 60. Looking to the studies, young age seems to be a better prognostic factor (Aslan et al.2006). Poorer prognosis in elderly patients might be resulted from lack of directing these patients to the standard curative treatment. Although the standard treatment is CRT in Stage III NSCLC, there are studies in the literature suggesting that, most of elderly patients are not directed to the standard curative treatment, resulting in high mortality and poor survival outcomes (Coate et al.2011; Piccirilo et al.,2004; Fentimen et al.,1990). In a meta-analysis of 6 studies conducted by Auperin et al., no correlation could be established between age and survival in NSCLC patients (Auperin et al., 2010). These results indicate that survival rates of elderly fit patients who are able to receive concurrent CRT are similar to those of younger patients. In our study, survival times of patients under 65 years of age were significantly longer than in patients above 65 years of age (median survival 22 months vs 16 months). Additionally, in multivariate analysis age was shown to be an independent prognostic factor.

Patients performance status and disease stages are important prognostic factors in NSCLC. A poor performance score and advanced disease negatively affect survival (Capewell et al.,1990; Brim et al.2006; Mutlu et al.,2013; Bradley et al.,2015; Langer et al.,2000; Arslan et al.,2014). In our study no correlation could be determined between ECOG PS and survival. But it has been demonstrated that, advanced stage was more negatively influence survival. Survival times of stage IIIIB patients were shown to be worse by 1.6 folds compared to stage IIIA patients and the stage was found as an independent prognostic factor.

Patients performance status and disease stages are important prognostic factors in NSCLC. A poor performance score and advanced disease negatively affect survival (Capewell et al.,1990; Brim et al.2006; Mutlu et al.,2013; Bradley et al.,2015; Langer et al.,2000; Arslan et al.,2014). In our study no correlation could be determined between ECOG PS and survival. But it has been demonstrated that, advanced stage was more negatively influence survival. Survival times of stage IIIIB patients were shown to be worse by 1.6 folds compared to stage IIIA patients and the stage was found as an independent prognostic factor.

Several studies have shown female gender as a good prognostic factor (Wolf et al.,1991; Blanchon et al.,2015). In the present study, no significant difference was found between both sexes in terms of survival (3-year survival...
29% vs 24%). Only a small portion of patients were
woman and that might influenced the statistically results.

Several studies have shown that weight loss at the time
of diagnosis is a poor prognostic factor (Finkelstein et
al.,1986; Feld et al.,1994). Although in the present study
no correlation could be established between weight loss
and survival, patients’ weight loss was defined as losing
more than 5.0% of body weight during RT. No study
was found in the literature investigating the relationship
between weight loss during RT and survival.

Adenocarcinoma is the most frequently encountered
histological type of NSCLC, accounting for about half of
the cases (Wahbah et al.,2007). Unlike the literature, in
this study histological type was found as squamous cell
carcinoma in 100 (68%) The reason for this dissimilarity
is unknown. Some studies demonstrate that squamous
cell cancers are associated with better prognosis and
increased survival, while others not. (Brim et al.,2006;
Vansteenkiste et al.,1997; Abbasi et al.,2011). In a
meta-analysis of 6 studies including 979 patients, Movsas
et al. demonstrated increased median survival times
when patients with squamous cell carcinoma histology
were treated with more aggressive combined treatment
modalities (induction chemotherapy + CRT) (Movsas et
al.,1999). In our study, median survival time was found
as 30 months in patients with adenocarcinoma and 18
month in patients with squamous cell carcinoma, and
there were no statistically significant difference. Some
studies have shown that, patients with squamous cell
carcinoma show rather local/locoregional progression,
while adenocarcinoma subtype progresses more with
distant metastasis (Perez et al.,1987; Gaspar et al.,2005).
Unlike the literature, in this study both locoregional
progression (74%) and distant metastasis (58%) were
more frequently observed in patients with squamous cell
carcinoma.

The most commonly used radiotherapy dose in the
curative radiotherapy in Stage III NSCLC is 60-70 Gy.
The minimum recommended radiotherapy dose is 60.0
Gy. In a RTOG study investigating whether a radiotherapy
dose of 74 Gy is superior, raising the dose to 74 Gy did
not improve the results and was shown to be potentially
harmful (Bradley et al.,2015). In our study, compatible
with the literature; survival of patients who had received
60 Gy or higher RT dose was shown to be better than the
patients who received under 60 Gy doses .

The power of our study was that a relatively
homogenous patient population with stage III NSCLC
who treated with chemoradiotherapy was analyzed. Most
of the previously published prognostic information on
NSCLC is based on patients with heterogenous disease
stage and variable combinations of therapy. Among the
parameters; age, stage and treatment modality (concurrent
chemoradiotherapy) were shown to be independent
prognostic factors for overall survival. The current study
has some limitations. First, the retrospective analysis
of the study and second, the study could not determine
which chemotherapy regimen is recommended for this
group of patient. In this study, although the sequence
and schedule of chemotherapy were heterogeneous, a
platinum-based standart regimen was used most of the
patients. Therefore, the results regarding the efficacy of
concurrent chemoradiotherapy rather than chemotherapy
regimen is reliable.

In conclusion; in the locally advanced NSCLC
patients treated with chemoradiotherapy, the prognostic
factors affecting OS rate are diagnosis age, stage, primary
treatment and RT dose. These results underline once again
the importance of careful staging and the necessity of
concurrent chemoradiotherapy in eligible patients. High
locoregional progression rate seen in patients having
histological subtype of squamous cell carcinoma raises
the question of could higher RT doses be used in these
patients in order to obtain intrathoracic tumor control.

References

Abbsi S, Badheeb A (2011). Prognostic factors in advanced
non-small-cell lung cancer patients:patient characteristics
and type of chemotherapy. Lung Cancer Int, 2011, 1-4.
Arslan D, Bozcuk H, Gunduz S, et al (2014). Survival Results
and Prognostic Factors in T4 NO-3 non-small cell lung
cancer patients according to the AJCC 7th edition staging
system. Asian Pac J Cancer Prev, 15, 2465-72.
Auperin A, Le Peichoux C, Rolland E, et al (2010). Meta-analysis
of concomitant versus sequential radiochemotherapy in
locally advanced non-small-cell lung cancer. J C Oncol,
28, 2181-90.
Birim O, Kappetein AP, Van Klaveren RJ, et al (2006).
Prognostic factors in non-small cell lung cancer surgery.
Eur J Surg Oncol, 32, 12-23.
Blanchon F, Grivaux M, Asselain B, et al (2015). 4-year
mortality in patients with non-small cell lung cancer:
Development and validation of a prognostic index. Lancet
Oncol, 16, 187-99.
Bradley JD, Paulus R, Komaki R, et al (2015). Standart-dose
versus high dose conformal radiotherapy with concurrent
and consolidation carboplatine plus paclitaxel with or
without cetuximab for patients with stage IIIA or III B
non-small cell lung cancer (RTOG 0617): a randomised,
two-by-two factorial phase 3 study. Lancet Oncol, 16,
187-99.
Capewell S, Sudlow MF (1990). Performance and prognosis in
patients with lung cancer. Thorax, 45, 951-6.
Coate LE, Massey C, Hope A, et al (2011). Treatment of the
elderly when cure is the goal: the influence of age on
treatment selection and efficacy for stageIII non-small cell
lung cancer. J Thorac Oncol, 6, 537-44.
Curran WJ Jr, Paulus R, Langer CI, et al (2011). Sequential
vs. Concurrent Chemoradiation for stage III non-small cell
lung cancer: randomised phase III trial RTOG 9410. J Natl
Cancer Inst, 103, 1452-60.
Dillman RO, Herndon J, Seagren SL, et al (1996). Improved
survival in stage III non-small-cell lung cancer: seven year
follow up of cancer and leukemia group B (CALGB)8433
trial. J Natl Cancer Inst, 88, 1210-5.
Feld R, Borges M, Giner V, et al (1994). Prognostic factors in
non-small cell lung cancer. Lung Cancer Nov, 3, 19-23.
Fentiman IS, Tirelli U, Monfardini S, et al (1990). Cancer inthe
elderly: why so badly treated? Lancet, 335, 1020-2.
Finkelstein D, Ettinger DS, Ruckdeschel JC (1986). Long-Term
Survivors in Metastatic Non-Small-Cell Lung Cancer: An
Eastern Cooperative Oncology Group Study. J Clin Oncol,
4, 702-9.
Furuse K, Fukuoka M, Kawahara M, et al (1999). Phase III
study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. *J Clin Oncol*, 17, 2692-9.

Furuse K, Hosoe S, Masuda N, et al (2000). Impact of tumor control on survival in unresectable stage III non-small cell lung cancer (NSCLC) treated with concurrent thoracic radiotherapy and chemotherapy (abstract). *Proc Am Soc Clin Oncol*, 29, 90-6.

Gaspar LE, Chansky K, Albain KS et al (2005). Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol*, 23, 2955-61.

Gregory MM, Videtic Larry W, Stitt A, et al (2003). continued cigarette smoking by patients receiving Cconcurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *J Clin Oncol*, 21, 1544-9.

Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute.

Langer C, Scott C, Byhardt R, et al (2000) Effect of advanced age on outcome in Radiation Therapy Oncology Group studies of locally advanced NSCLC (LA-NSCLC). *Lung Cancer*, 29, 104-10.

Movsas B, Scott C, Sause W, et al (1999) The benefit of treatment intensification is age and histology-dependent in patients with locally advanced nonsmall cell lung cancer (nsclc): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. *Int J Radiat Oncol Biol Phys*, 45, 1143-9.

Mutlu H, Buyukcelik A, Erden A, et al. (2013). Staging with PET-CT in patients with locally advanced non small cell lung cancer is superior to conventional staging methods in terms of survival. *Asian Pac J Cancer Prev*, 14, 3743-6.

O’Rourke N, Roque I Figuls M, Farre Bernado N, et al (2010). Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*, 16, CD002140.

Perez CA, Pajak TF, Rubin P, et al (1987). Long term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. report by the radiation therapy oncology group. *Cancer*, 59, 1874-80.

Piccirillo JF, Tierney RM, Costas I, et al (2004). Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA*, 291, 2441-7.

Sause W, Kolesar P, Taylor S IV , et al (2000).Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: radiation therapy oncology group, eastern cooperative oncology group and southwest oncology group. *Chest*, 117, 358-64.

Siegel RL, Miller KD, Jemal A. Cancer Statics, 2015. *CA Cancer J Clin*, 65, 5-29

Tsujino K, Kurata T, Yamamoto S, et al (2013). Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer?A pooled analyses of the literature. *J Thorac Oncol*, 8, 1181-9.

Van Baardwijk A, Wanders S, Boersma L, et al (2010). Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol*, 28, 1380-6.

Vansteenkiste JF, De Leyn PR, Deneffe GJ, et al (1997). Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. *Ann Thorac Surg*, 36, 1441-50.

Vokes EE, Herndon JE, Kelly MJ, et al (2007). Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer. cancer and leukemia group B. *J Clin Oncol*, 25, 1698-704.

Wolf M, Holle R, Gropp C, et al (1991). Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. *Br J Cancer*, 63, 986-92.

Wahbah M, Boroumand N, Castro C, et al (2007).Changing trends in the distribution of the histologic types of lung cancer: a review of 4,439 cases. *Ann Diagn Pathol*, 11, 89-96.