Journal of Cancer Research and Treatment, 2017, Vol. 5, No. 2, 55-61
Available online at http://pubs.sciepub.com/jcrt/5/2/3
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DOI:10.12691/jcrt-5-2-3

Prognostic Factors in Advanced Non-Small Cell Lung Cancer and Their Relation to Clinical Outcomes

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Abstract **Background:** Lung cancer is the main cause of cancer deaths worldwide. It is important to identify the prognostic factors of this disease which leads to low survival times despite the advancing treatment modalities. **Aim:** To investigate the role of clincopathological parameters and treatment modality as a prognostic factors affecting survival of patients with advanced non-small cell lung cancer (NSCLC). **Methods:** We retrospectively reviewed the clinical records of patients with inoperable stage III/IV NSCLC, who were treated at the department of Clinical Oncology, Assiut University Hospital between 2009 and 2014. The association between the demographic and clinical characteristics and survival of these patients was analyzed. **Results:** A total of 69 patients (32 stage III& 39 stage IV) were identified and included in this study. Sex (males vs. females, p=0.04), Eastern cooperative Oncology group performance status (0 vs. 1 vs. 2, p=0.001), smoking habit (never vs. current vs. former, p=0.001), stage (IIIA vs. IIIB vs. IV, p=0.008) and the initial treatment (no vs. chemotherapy vs. concurrent chemoradiotherapy, p=0.001) were found to be factors affecting survival in univariate analyses. Sex and histological subtype did not affect survival. Performance status, stage and initial treatment were determined as the independent prognostic factors affecting survival in multivariate analyses. **Conclusion:** Performance status, stage and initial treatment with concurrent chemoradiotherapy in eligible patients were prognostic factors affecting overall survival of patients with advanced NSCLC.

Keywords: *non-small cell lung cancer, prognostic factors, survival*

Cite This Article: Mohamed-Alaa-Eldeen Hassan Mohamed, Samir Shehata Mohamed, Hoda Hassan Essa, and Hebat-Allaa mahmoud Bakri, "Prognostic Factors in Advanced Non-Small Cell Lung Cancer and Their Relation to Clinical Outcomes." *Journal of Cancer Research and Treatment*, vol. 5, no. 2 (2017): 55-61. doi: 10.12691/jcrt-5-2-3.

1. Introduction

Lung cancer is the most common type of cancer worldwide and it is the leading cause of cancer-related mortality in the United States [1].

Lung cancer was divides into small cell carcinomas and non-small cell carcinomas. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers [2].

The 5-year relative survival rate of patients with lung cancer varies markedly depending on the stage at diagnosis, from 49% to 16% to 2% for patients with local, regional, and distant-stage disease, respectively [3].

Thirty percent of patients with NSCLC diagnosed with stage III disease. The survival of clinical stage III NSCLC patients is poor and most patients are not eligible for surgical resection [4]. The usual treatment is radical radiotherapy (RT) or concurrent chemotherapy [5].

It is important to understand the progression of this disease which leads to low survival times despite the advancing treatment modalities. For this reason, many prognostic factors have been investigated in several studies. The most common prognostic factors studied for lung cancer patients are sex, age, stage, performance status, weight loss, smoking history, quality of life, and genetic mutations [6,7].

Treatment modality is an additional important prognostic factor in patients with stage III disease. Radiotherapy dose and treatment modality (chemoradiotherapy, radiotherapy or chemotherapy alone) may be indicators influencing treatment outcomes and survival [8,9]. Investigation of the additional prognostic factors of stage III patients may play an important role in evaluation of optimal treatment options and increasing survival of these patients.

The aim of this study was to analyze the importance of clincopathological parameters and treatment modality as a prognostic factors affecting survival of patients with advanced non-small cell lung cancer.

2. Patients and Methods

This retrospective cohort observational study focuses on prognostic factors of overall survival of patients with unresectable stage III/IV non-small cell lung cancer (NSCLC). We reviewed the clinical data of patients treated at Clinical Oncology department, Assiut University hospital between 2009 and 2014. Overall survival was measured from the date of diagnosis

to date of death from any cause or date of last Follow-up data.

The protocol of the study was approved by the ethics committee of Assiut University, Egypt before data collection.

2.1. Data Collected Included

-Patients age
-Sex
-Performance status was determined according to scoring system of the Eastern Cooperative Oncology Group (ECOG).
-Smoking history (nonsmokers, current smokers and former smokers)
-Histological subtypes (adenocarcinoma, squamous cell carcinoma and large cell carcinoma)
-Stage: Patients were staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC) in 2002, 6th edition and in 2010, 7th edition [10,11].
-Type of initial treatment (First line therapy)

2.2. The Inclusion Criteria Included

-Age; >18 years
-Performance status ≤2
-Diagnosis confirmed by pathological examination
-Stage III/IV NSCLC
-Patients had not been previously treated surgically.

2.3. The exclusion Criteria Included

-Performance status >2
-Absence of pathological diagnosis
-Stage I/II
-Surgical resection of the tumor
-Patients with lost follow-up data.

2.4. Chemotherapy Schedule

Patients with stage III NSCLC were treated by either induction chemotherapy followed by concurrent chemoradiotherapy or sequential chemotherapy/radiotherapy. Four cycles of chemotherapy was given which consisted of: cisplatin 75 mg/m^2 on day 1 over 60 minutes IV infusion and gemcitabine 1000 mg/m^2 on days 1, 8 every 21 days. Hydration and prophylactic antiemetic were administered before chemotherapy according to departmental practice.

Patients with stage IV received 6 cycles of cisplatin and gemcitabine in the same schedule as for stage III unless progressive disease was documented during assessment after 3 cycles. Doctaxel or vinorelbine was administered in combination with cisplatin as a second line of treatment.

2.5. Concurrent Chemoradiotherapy

Two-dimensional treatment planning system was used, while patients in supine position, by conventional x-ray simulation and radiation were delivered with 6-18 Million Volts photon beam energy by linear accelerator or Cobalt-60 devices. The total radiation dose was 60 Gy and the fractional size of 2 Gy was prescribed 5 times a week. The planning target volume (PTV) was defined as the gross tumor volume (post-induction systemic therapy volume) plus 2 cm all-around, ipsilateral hilum and mediastinum (elective nodal irradiation was used).

Patients were treated by parallel-opposed anterior and posterior field to 40 Gy in 20 fractions. After 40 Gy spinal cord was spared and a boost field to the primary tumor and the involved nodes with margin 1.5 cm from oblique parallel opposed fields was used.

Concurrent paclitaxel 45 mg/m^2 as 30 minutes IV infusion and carboplatin 200 mg/m^2 IV infusion over 30 minutes every week to a total 6 weeks with radiation.

Follow-up of the patients started monthly after the end of primary therapy for the first year and every 3 months thereafter.

3. Statistical Analysis

Overall survival was calculated according to the Kaplan–Meier method. For descriptive statistics, the mean, standard deviation and standard error were used. Means were compared using the student's t-test. A multivariate analysis (logistic multiple regression model) was used to evaluate the independent prognostic factors that affected survival. P value <0.05 was considered statistically significant. For statistical analysis, SPSS ver. 21 (SPSS Inc., Chicago, IL) was used.

4. Results

Sixty-nine advanced non-small cell lung cancer (NSCLC) patients were identified and included in the study retrospectively. The median age was found as 57.67 years (range 27-80). Most of the patients were males (62.3%) and smokers (58%) At diagnosis, ECOG PS= 0-1 patients were 66.6%. Histopathologically, adenocarcinoma was diagnosed in 42 (60.9%) patients and squamous cell carcinoma was observed in 17 (24.6%) patients. Thirty-eight (55.1%) patients were diagnosed with stage IV and 31 (44.9%) patients were diagnosed with stage III as shown in Table 1.

Sex (males vs. females, p=0.04), ECOG performance status (0 vs. 1 vs. 2, p=0.001), smoking habit (never vs. current vs. former, p=0.001), stage (IIIA vs. IIIB vs. IV, p=0.008) and the initial treatment (no vs. chemotherapy vs. concurrent chemoradiotherapy, p=0.001) were found to be factors affecting survival in univariate analyses. Sex and histological subtype did not affect survival as shown in Table 2.

Performance status, stage of the disease and the type of initial treatment modality were determined as the independent prognostic factors affecting survival of patients with advanced NSCLC in multivariate analysis as presented in Table 3.

Figure 1 shows the survival curve of the study cohort of NSCLC patients according to PS.

Table 1. Clinical characteristics and treatment modality of advanced non-small cell lung cancer patients

Characteristics	Descriptive "N=69"
-Age "years"	
Mean ± SD	57.67 ± 11.53
(Range)	(27.0-80.0)
<55years.	28 (40.6%)
55years.	41 (59.4%)
- Sex:	
Male	43 (62.3%)
Female	26 (37.7%)
-Performance status (ECOG):	
0	17 (24.6%)
1	29 (42.0%)
2	23 (33.3%)
- Smoking:	
Never	29 (42.0%)
Current	20 (29.0%)
Former	20 (29.0%)
Histologic subtype:	
Adenocarcinoma	42 (60.9%)
Squamous cell carcinoma	17 (24.6%)
Other	10 (14.5%)
Stage:	
IIIA	9 (13.0%)
IIIB	22 (31.9%)
IV	38 (55.1%)
Treatment modality:	
No treatment	9 (13.0%)
Chemotherapy	40 (57.71%)
Concurrent chemoradiotherapy (CRT)	20 (28.97%)

SD: standard deviation, ECOG: Eastern Cooperative Oncology Group.

Table 2. Prognostic factors for overall survival of the study cohort of patients with advanced non-small cell lung cancer

factors	OS, mean ± SE	p-value
-Age "years"		
<55 (N=28)	11.75 ± 2.05	0.320
>55 (N=41)	9.56 ± 1.14	
-Sex:		
Female (N=26)	12.77 ± 2.25	<0.04
Male (N=43)	9.05 ± 1.01	
-PS (ECOG):		
0 (N=17)	18.41 ± 2.50	<0.001
1 (N=29)	10.76 ± 1.39	
2 (N=23)	4.17 ± 0.51	
-Smoking:		
Never (N=29)	12.52 ± 2.05	<0.001
Current (N=20)	7.00 ± 1.04	
Former (N=20)	10.90 ± 1.78	
-Histological subtype:		
Adenocarcinoma (N=42)	9.74 ± 7.64	0.148
Squamous (N=17)	9.00 ± 7.00	
Other (N=10)	11.25 ± 9.91	
-Stage:		
IIIA (N=9)	18.22 ± 2.03	<0.008
IIIB (N=22)	11.05 ± 1.79	
IV (N=38)	8.26 ± 1.43	
-Treatment modality:		
No (N=9)	4.89 ± 1.55	<0.001
Chemotherapy (N=40)	8.08 ± 1.09	
CRT (N=17)	17.76 ± 2.53	

OS: overall survival, SE: standard error, PS: performance status, ECOG: Eastern Cooperative Oncology Group, CRT: chemoradiotherapy.

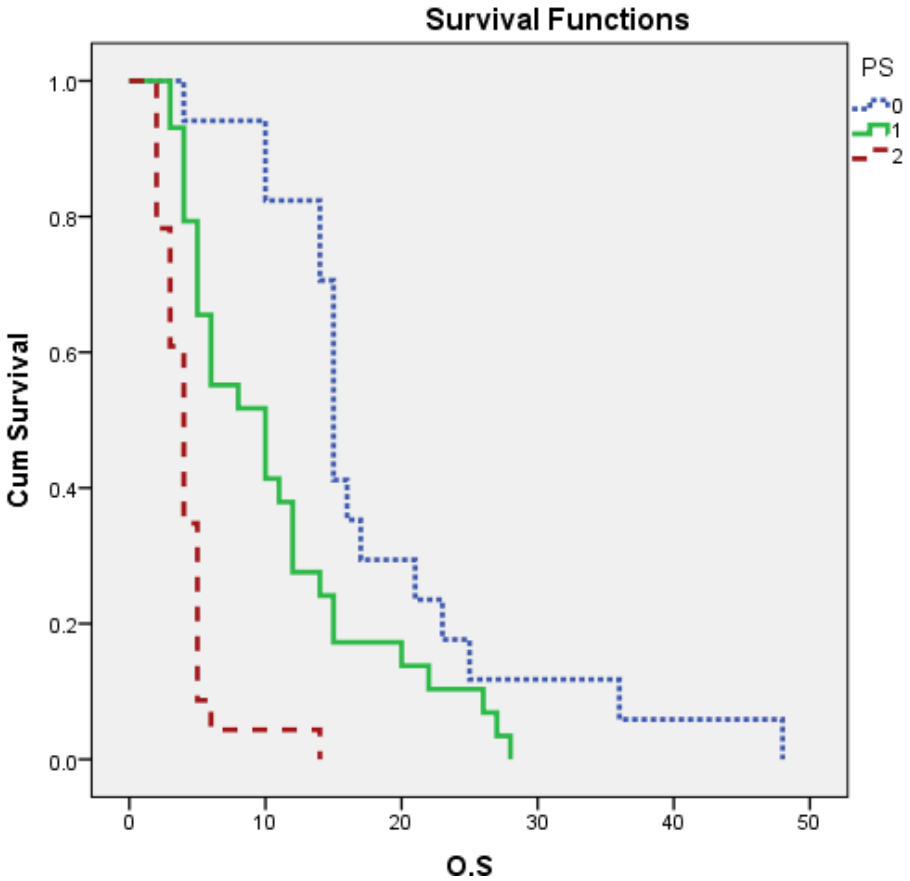

Figure 1. Overall survival (OS) curve according to performance status(PS) of the study cohort of patients with advanced non-small cell lung cancer (mean OS of PS 0= 18.41, PS 1= 10.76, PS 2=4.17 months, p<0.001)

Table 3. Results of the independent prognostic factors of survival of the study cohort of patients with advanced non-small cell lung cancer

Factors	β	SE	Sig (P)
-PS			
(0 vs. 1 vs. 2)	,488	1.392	.001
-Stage			
(III vs. IV)	,155	1.221	.001
-Smoking			
(No vs. smokers)	,020	1.020	.836
-Sex			
(Female vs. male)	.102	.083	.345
-Treatment			
(No vs. CT vs. CRT)	,249	1.278	.019

β: regression coefficient, SE: standard error, Sig (P): probability value.

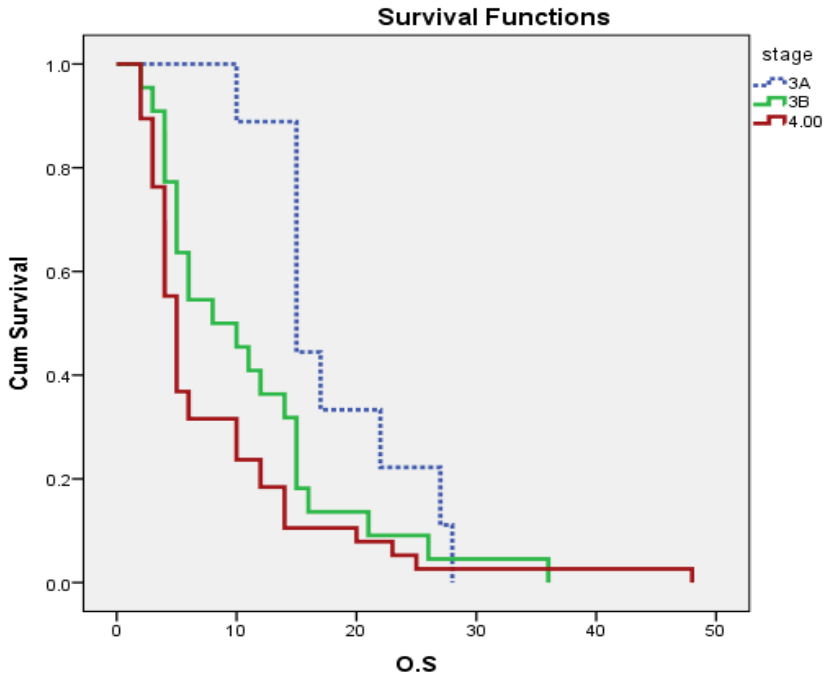

Figure 2. Overall survival (OS) curve according to the stage of the study cohort of patients with advanced non-small cell lung cancer mean OS of stage IIIA= 18.22, IIIB= 11.05, IV= 8.26 months, p<0.008)

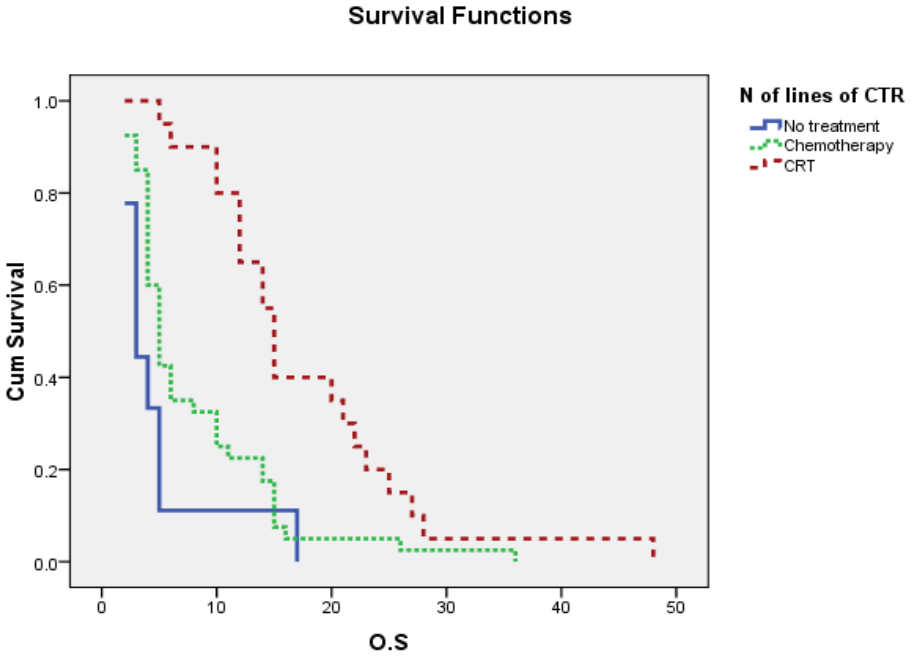

Figure 3. Overall survival (OS) curve according to the treatment modality of the study cohort of patients with advanced non-small cell lung cancer (mean OS of No treatment= 4.89, chemotherapy= 8.08, chemoradiotherapy (CRT) = 17.76 months, p<0.001)

Figure 2 represent the survival curve of the study cohort according to stage.

Figure 3 demonstrates the survival curve according to initial treatment modality.

5. Discussion

Several attempts have been made to prolong survival of patients with advanced non-small cell lung cancer (NSCLC). Many clinical trials provided information on prognostic factors of survival and factors that may predict drug effect in order to optimize treatment of these patients [12].

In this study we analyzed the effects of clinical factors and treatment modality on the survival time of patients with NSCLC.

The predominance of advanced stage disease (stage IV, 55.1%), males (62.3%), and smokers (71.0%) observed in the present study is consistent with the characteristics of other study cohort of NSCLC [13,14,15].

The first prognostic factor we identified was the sex of the patients. Our results showed that female patients had longer survival than males (mean survival, 12.77 vs. 9.05 months).

Our finding is not comparable to the results of the study done by Urvay SE et al 2016 [16] who reported that gender was one of the factors did not affecting survival in patients with stage III NSCLC.

On the reverse, the study of Kumar N et al 2016 [17] showed that female sex was one of the independent prognostic factors for patients with lung cancer spinal metastases.

In our cohort of patients, performance status was one of the prognostic factors affecting survival.

Our findings were in line with previous researches which revealed that performance status was one of the significant prognostic factors in locally advanced and metastatic NSCLC [15,18].

Opposite to these results, Urvay SE et al 2016 [16] reported that performance status had no effect on survival in patients with stage III NSCLC. Young age, stage IIIA, dose of radiotherapy and concomitant chemoradiation were prognostic factors for survival in the cohort of their study.

As regard the age of the patients at presentation, the mean age was 57 years and there was no significant difference in survival between patients ≤55 years and >55 years in our study (mean, 11.75 vs. 9.56 months).

These results are not in agreement with the results of the study done by Urvay SE et al 2016 [16]. The median age was 60 years and in univariate analysis, age (<65 VS ≥ 65 years) was found as one of the prognostic factors affecting survival.

Another study done by Souza MC et al 2016 [15] revealed that the mean age of patients included was 62 years, and the age decreased with advancing of the disease stage (stage I/II 65 years, stage III 62 years and stage IV 60 years). They recorded that age was a significant prognostic factor of survival in all stages.

The risk of lung cancer associated with cigarette smoking was established in many trials. The association between cigar smoking and death from tobacco-related cancer was supported by the results of the study done by Shapiro JA et al 2000 [19].

In the current study, patients with stage III and IV who were nonsmokers had a longer survival than those who were smokers/former smokers.

Our results are consistent and in agreement with previous results reported from other studies [13,15,20].

In a study done by Zhang Y et al 2016 [21] revealed the association of AHRR, 6p21.33, and F2RL3 methylation in blood DNA and the development of lung cancer. These predictive markers might be useful for identification of risk groups for further specific screening, such as computed tomography examination.

After analysis of the effect of social, behavioral and clinical factors on the survival of patients with NSCLC, there is no factor can be modified after diagnosis to improve their survival. Primary prevention by reducing the prevalence of smoking through increasing young people awareness regarding the dangers of smoking is the best method to reduce the number of people who will suffer the consequences of lung cancer [15].

Adenocarcinoma is the most frequently encountered histological type of NSCL [22]. In the present study we found the same results which show that adenocarcinoma constituted 60.9% of patients and squamous cell carcinoma diagnosed in 24.6% of them.

In our study, the mean survival time was found as 9.97 months in patients with adenocarcinoma and 9.0 month in patients with squamous cell carcinoma, and there were no statistically significant difference.

Several studies have shown that histilogical subtypes (squamous vs. non-squamous) did not affect survival of patients with advanced NSCLC [12,16,23]. Histology did not affect outcome of patients with advanced NSCLC in the absence of targeted therapies [24].

There was no influence of histologic subtype in predicting survival of lung cancer patients with spinal metastases [17].

A study was done by Kanzaki H et al 2016 [25] investigated the impact on survival of early tumor reduction during definitive radiotherapy for inoperable stage III NSCLC patients, according to their histological subtypes. Although tumor reduction rate (TRR) had no correlation with overall survival (OS), the higher TRR showed significant associations with better OS and progression-free survival in the squamous cell carcinoma group.

Our study demonstrated that advanced stage was more negatively influence survival. Survival times of stage IIIB patients were shown to be worse by compared to stage IIIA patients and stage IV had the worst survival.

Several studies have demonstrated poor survival of stage IIIA than stage IIIB. The study done by Urvay SE et al 2016 [16] revealed a significant difference in survival of stage IIIA vs. IIIB (p= 0.033). Another study done by Liu H et al 2016 [26] reported the same results.

Blanchon F et al 2006 [27] revealed that the stage was an independent predictor of mortality (stage IIIA vs. IIIB vs. IV).

One of the most important factors affecting survival was primary treatment modality. Studies comparing sequential and concurrent (chemoradiotherapy) CRT regimens in advanced inoperable NSCLC have shown

significant survival advantage with concurrent regimens and thus, concurrent CRT constituted to the standard treatment [28,29].

In the current study, there was a higher survival of patients receive treatment than patients received no treatment. These results are in agreement of the results of the study done by Liu H et al 2016 [26].

Sequential chemotherapy and radiotherapy (RT) or RT alone may be favorable in patients who will not be able to tolerate concurrent treatment [30]. It has been shown that chemotherapies before (induction) and after (consolidation) CRT do not affect overall survival [31].

In our study, similarly, survival times were shown to be superior in concurrent CRT group compared to sequential chemotherapy/RT group (mean survival: 17.76 vs.8.08 months, respectively).

Different platinum-based combinations did not affect survival of advanced NSCLC. Comparison of the efficacy between doublets of third-generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for chemotherapy-naïve advanced NSCLC was done by Jiang J et al 2013 [32] in a literature-based meta-analysis. Results demonstrated that the efficacy of the third-generation doublets, such as vinorelbine plus gemcitabine, vinorelbine plus paclitaxel, gemcitabine plus paclitaxel, and gemcitabine plus docetaxel, was comparable with platinum-based doublets.

A study was done by Lin JH et al [33] to assess the association of clinical prognostic factors with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) efficacy in advanced NSCLC patients. The results of this study revealed that Eastern Cooperative Oncology Group (ECOG) score and timing of targeted therapy were factors affecting progression-free survival.

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 Gy. Radiotherapy dose < 60 Gy negatively affecting survival [16].

To compare the survival rates of patients with stage III non-small cell lung cancer who were treated with either 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT), the study of Kong M et al 2016 [34] reported that the overall survival rates of the IMRT group were higher than those of the 3D-CRT group; however, these differences were not statistically significant.

Additional attempts to improve outcomes of NSCLC have focused on delivering new radiotherapy techniques. A study designed to compare the efficacy of hypofractionated chemoradiotherapy using helical tomotherapy (HT) with conventional fractionation as opposed to using 3D-CRT for stage III NSCLC demonstrated that V20, V30, V40, mean lung dose and max dose of spinal cord were significantly lower in the HT group than in the 3D-CRT group. There was no significant difference in the incidences of acute radiation pneumonitis ≥ grade 2 between the two groups, whereas the incidences of acute radiation esophagitis ≥ grade 2 were significantly lower in the HT group than in the 3D-CRT group. Multivariate analysis indicated that performance status and radiotherapy technique were independent prognostic factors of overall survival [35].

To analyze outcomes and predictors associated with proton radiation therapy for NSCLC compared with photon thoracic RT, a retrospective database study revealed that non-proton radiation therapy was associated with worse survival compared with proton radiation therapy for stage II and III [36].

We concluded that the prognostic factors affecting OS are PS, stage and primary treatment. These results underline the importance of initial treatment and every effort should be made to improve it by the use of new chemotherapy drugs and improving radiation techniques to gain a better survival.

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