Effect of Surgery on The Prognosis of Stage ⅢB non-Small Cell Lung Cancer

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Abstract

For patients with stage IIIB non-small cell lung cancer (NSCLC), the current recommended immunotherapy maintenance treatment after concurrent chemoradiotherapy is not demonstrated whether such patients can be benefit from surgical treatment. We collected clinical data from patients with stage IIIB NSCLC from the surveillance, epidemiological, and final results (SEER) databases. Kaplan-Meier analysis and Cox proportional hazards model were used to analyze the effect of surgical treatment on the survival of stage IIIB NSCLC. We use surgery as a variable to divide into surgical and non-surgical groups. Between the two groups, only age is different (p = 0.017), and there is no significant difference at race (P = 0.531), gender (P = 0.051), tumor primary site (P = 0.385), tumor differentiation grade (P = 0.103), T stage (P = 0.094), and N stage (P = 0.071). Univariate and multivariate analysis showed that gender, tumor differentiation, stage and primary site had an effect on overall survival. Kaplan-Meier analysis showed that the median survival time of stage IIIB NSCLC in the surgical group (13 months, 95% CI (7.400 to 18.600 months)) was higher than that in the non-surgical group (3 months, 95% CI (2.482 to 3.518 months)) was significantly prolonged by 10 months (P < 0.001). The Cox proportional hazard modelled analysis showed that the overall survival of stage IIIB NSCLC was 2.395 times the 95% CI (1.77 to 3.241 months) for the non-surgical group (P < 0.001). We conclude that some patients with stage IIIB NSCLC who can tolerate surgery may benefit from surgery.

Introduction

Cancer has become the leading cause of death in China, and lung cancer is the most common cancer and the leading cause of cancer death(1). More than 85% of these lung cancers are non-small cell lung cancer(2). The main histological types of non-small cell lung cancer include about 50% of lung adenocarcinoma and approximately 40% of lung squamous cell carcinoma(3). The early diagnosis of lung cancer depends on the findings of CT physical examination(4–6), but most patients ignore the importance of annual physical examination. When coughing, hemoptysis and other symptoms appear, the lung cancer has reached the advanced stage. Surgical treatment is mainly used for stage □~□A NSCLC, combined with radiotherapy and chemotherapy as the standard treatment(7, 8). For stage IIIB NSCLC, surgical resection is currently not recommended, and the 5-year survival rate is only about 15%(9); the PACIFFIC study recommends Durvalumab immunotherapy maintenance treatment after concurrent chemoradiotherapy. Although the survival time is extended, only about 10% of patients Benefit from immunotherapy(10, 11). Surgical treatment is an important method for the treatment of malignant tumors. With the deepening of research and the updating of ideas, many advanced cancer patients, such as IV stage colorectal cancer and IV stage breast cancer, can be treated by surgery on the basis of transformation therapy(12), and achieved good results. The treatment effect of stage IIIB NSCLC is currently not satisfactory. Whether such patients can benefit from surgical treatment has not been fully demonstrated.

Materials And Methods

Data Source: The SEER database is one of the most representative large tumor registration databases in North America, and it collects a large amount of data related to evidence-based medicine. The database records information on the morbidity, mortality, and prevalence of millions of patients with malignant tumors in some states and counties in the United States.

Patient selection: We obtained patient information for NSCLC from 2004 to 2015 from the Surveillance, Epidemiology and Final Results (SEER) database. First, remove the data that are unknown about race, tumor differentiation and radiotherapy and chemotherapy information. Then ensure the integrity of the data source and the reliability of the follow-up. Finally, the data of stage ⅡB NSCLC were selected according to the 7th edition of the American Joint Commission on Cancer (AJCC)(13). We were divided into surgical group (n = 67) and non-surgical group (n = 589) according to the presence or absence of surgical treatment. (Fig. 1)

Statistical analysis. Chi-square test and Fisher exact test were used to analyze the differences between the groups. Survival analysis was performed using the Kaplan-Meier method. The Cox regression proportional hazard model was used to assess the effect of prognostic factors on cumulative survival time. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS statistics software version 25

Result

This study selected 656 eligible medical records from the surveillance, epidemiological and final results (SEER) database for a controlled study. They were divided into the surgical group (n = 67) and the non-surgical group (n = 589) according to the presence or absence of surgical treatment. We compared the basic characteristics of the two groups, including age, gender, race, degree of tumor differentiation, primary tumor site, T stage, and N stage. Except for the differences between the age groups (P = 0.017), the characteristics of the other groups were balanced. (Table 1)

Table 1
Characteristics of Patients with Stage III NSCLC (n = 656)

Surgery type			
No surgery surgery Pvalue			
Age(year)			0.017
< 65	139	25	
≥ 65	450	42	
Race			0.531
White	475	57	
Black	73	5	
Other	41	5	
Sex			0.051
Male	320	45	
Female	269	22	
Primary Site			0.385
Main bronchus	36	2	
Upper lobe, lung	329	37	
Middle lobe, lung	33	3	
Lower lobe, lung	139	15	
Overlapping lesion of lung	8	3	
Lung, NOS	44	7	
Grade			0.103
Well differentiated; Grade I	38	10	
Moderately differentiated; Grade II	203	23	
Poorly differentiated; Grade III	341	34	
Undifferentiated; anaplastic; Grade IV	7	0	
Derived AJCC T, 7th			0.094
T1	54	11	
T2	117	10	
T3	74	4	

Surgery type			
No surgery	surgery	Pvalue	
T4	344	42	
Derived AJCC N, 7th			0.071
N2	288	41	
N3	301	26	

Then we used Kaplan-Meier to analyze the effect of each independent factor on cumulative survival and draw a survival curve (Fig. 2). The K-m curve shows that there is a statistically significant difference between women and men in the gender group (P = 0.007). The tumors in Main bronchus were statistically different from Upper lobe, lung, Middle lobe, lung, Lower lobe, lung, Overlapping lesion of lung, Lung, NOS (P = 0.032). There was statistically significant difference between well differentiated tumors, poorly differentiated tumors, moderately differentiated tumors, and undifferentiated tumors (P = 0.001). There was a statistically significant difference between T1, T2, T3 and T4 (P = 0.001). There was statistical difference between the operation group and the non-operation group (P < 0.001). Generally speaking, age (P = 0.432) and N stage (P = 0.181) play important roles in the prognosis of patients with NSCLC(14–16). Our results are inconsistent with the traditional one, which may be caused by the difference in age between the groups and the too small sample size. Age, gender, race, degree of tumor differentiation, primary site, stage T and stage N, and median survival time with or without surgery (Fig. 3).It can be seen that the median survival time of females is 5 months 95%CI (4.026 to 5.974 months), which is higher than that of males 3 months 95%CI (2.423 to 3.577 months). The median survival time of other races was 9 months 95%CI (4.851 to 13.149 months), higher than that of whites 3 months 95%CI (2.438 to 3.562 months) and the median survival time of blacks 3 months 95%CI (1.558 to 4.442 months). The median survival time of well-differentiated tumors was 9 months, 95% CI (3.431 to 14.569 months) was higher than the average median survival time of tumor differentiation, 3 months, 95% CI (2.325 to 3.675 months). The median survival time at T1 stage was 8 months and 95% CI (5.743 to 10.257 months) was higher than the average median survival time at T stage of 3 months and 95% CI (2.325 to 3.675 months). The median survival time of the operation group was 13 months 95%CI (7.400 to 18.600 months), compared with the median survival time of 3 months 95%CI of the non-operation group (2.482 to 3.518 months). The cumulative survival time of the patients was higher than that of the non-operation group

In order to further eliminate the mixed bias of multiple factors, we used Cox proportional hazard model analysis (Table 2). Because age and N staging have an impact on the cumulative survival rate of patients with non-small cell lung cancer, we also included age and N staging in Cox proportional hazard model analysis. The results showed that gender, grade of tumor differentiation and surgical treatment had influence on the prognosis of the patients. The results showed that gender (P < 0.001), grade of tumor differentiation (P < 0.041) and surgical treatment (P < 0.05) had influence on the prognosis of the patients.

Table 2
Multivariate Analysis of IIIB NSCLC Based on Cox Proportional Risk Model(N = 656)

Overall survival		
HR (95% CI) P value		
Age(year)	0.925(0.768 ~ 1.115)	0.415
< 65		
≥ 65		
Sex	1.292(1.097 ~ 1.522)	0.002
Male		
Female		
Primary Site		0.073
Main bronchus		
Upper lobe, lung	1.42(0.909 ~ 2.217)	
Middle lobe, lung	1.185(0.869 ~ 1.618)	
Lower lobe, lung	0.873(0.553 ~ 1.38)	
Overlapping lesion of lung	1.038(0.741 ~ 1.455)	
Lung, NOS	2.078(1.069 ~ 4.039)	
Grade		0.041
Well differentiated; Grade I		
Moderately differentiated; Grade II	0.809(0.351 ~ 1.862)	
Poorly differentiated; Grade III	1.122(0.515 ~ 2.445)	
Undifferentiated; anaplastic; Grade IV	1.279(0.591 ~ 2.769)	
Derived AJCC T, 7th		0.227
T1		
T2	0.691(0.469 ~ 1.018)	
T3	0.897(0.643 ~ 1.252)	
T4	0.942(0.659 ~ 1.346)	
Derived AJCC N, 7th	1.031(0.763 ~ 1.393)	0.843
N2		

Overall survival HR (95% CI) P value		
N3		
Surgery type	2.395(1.77 ~ 3.241)	< 0.001
No Surgery		
Surgery		

The cumulative survival time for patients after the previously reported surgery has been significantly extended. We further analyzed the effects of preoperative radiotherapy, postoperative radiotherapy, preoperative plus postoperative radiotherapy on the cumulative survival time of patients with stage IIIB NSCLC. Because the number of patients undergoing stage IIIB surgery was originally small, the sample size was too small Not conducive to further analysis (Table 3). However, in general, most patients choose radiotherapy before or after surgery.

Table 3
A descriptive study of the radiotherapy sequence in patients with □B NSCLC

	Number
Radiation prior to surgery	132
Radiation after surgery	235
Radiation before and after surgery	12
Surgery both before and after radiation	2
Total	381

Discussion

As the specific treatment criteria for stage IIIB NSCLC are not yet clear, we obtained data from the surveillance, epidemiological and final results (SEER) database and used Kaplan-Meier analysis and the Cox proportional hazard model to study the surgery for stage IIIB Impact of Prognosis in Patients with NSCLC. Our results show that there are differences in gender(17), primary site of tumor, grade of tumor differentiation, T stage, and whether the prognosis of the patient is affected by surgery. In particular, tumors occur in the middle bronchus, are well differentiated, have an early T stage, and surgery can significantly improve the patient's cumulative survival time.

The low degree of tumor differentiation and low T stage have significantly improved the survival rate of lung cancer, which is consistent with the results of Goldstraw P, Gester F and others(18–20). What makes us interesting is that age and N stage are supposed to be closely related to the prognosis, but they are not consistent with our results. It may be due to the difference between the age groups at the time of the

initial matching grouping that led to the difference in the final results. The N stage may be due to the small number of our medical records and our IIIB medical records are mainly concentrated in the N2, N3 stages, resulting in no difference in results. We are pleased that the cumulative survival time of patients in the surgical group is significantly longer than that in the non-surgical group, which provides clinical guidance for patients with stage IIIB NSCLC to undergo surgery. As we further study the impact of timing of radiotherapy in the surgical group on patient prognosis. Due to too few clinical data to proceed, only descriptive analysis was performed. Most patients focused on preoperative and postoperative radiotherapy.

For our study, there are also deficiencies. First, there is a difference in the age between the groups when grouping. Second, the radiotherapy and chemotherapy information in the seer database are not specific. In addition to the baseline characteristics we described above, the seed database does not record other health conditions of patients. In the end, there is confounding bias in any research, and we can only minimize it.

In conclusion, Standard clinical treatments for patients with stage IIIB NSCLC have not yet been established. Our results show that surgical treatment of patients with stage IIIB NSCLC can significantly improve the cumulative survival time of patients.

Declarations

Acknowledgements

This study used a database of surveillance, epidemiological and end result (SEER) procedures. We thank the National Cancer Institute for their contributions in creating the database.

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Availability of data and materials

All original data are available on request.

Authors' contributions

All authors contributed to the design, implementation, analysis of results and revision of the paper, and agreed to the final manuscript.

Ethics approval and consent to participate

The study was based on publicly available data from the SEER database and a data usage agreement was signed without the patient's informed consent. In addition, this research was conducted in

accordance with the Helsinki Declaration.

Patient consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

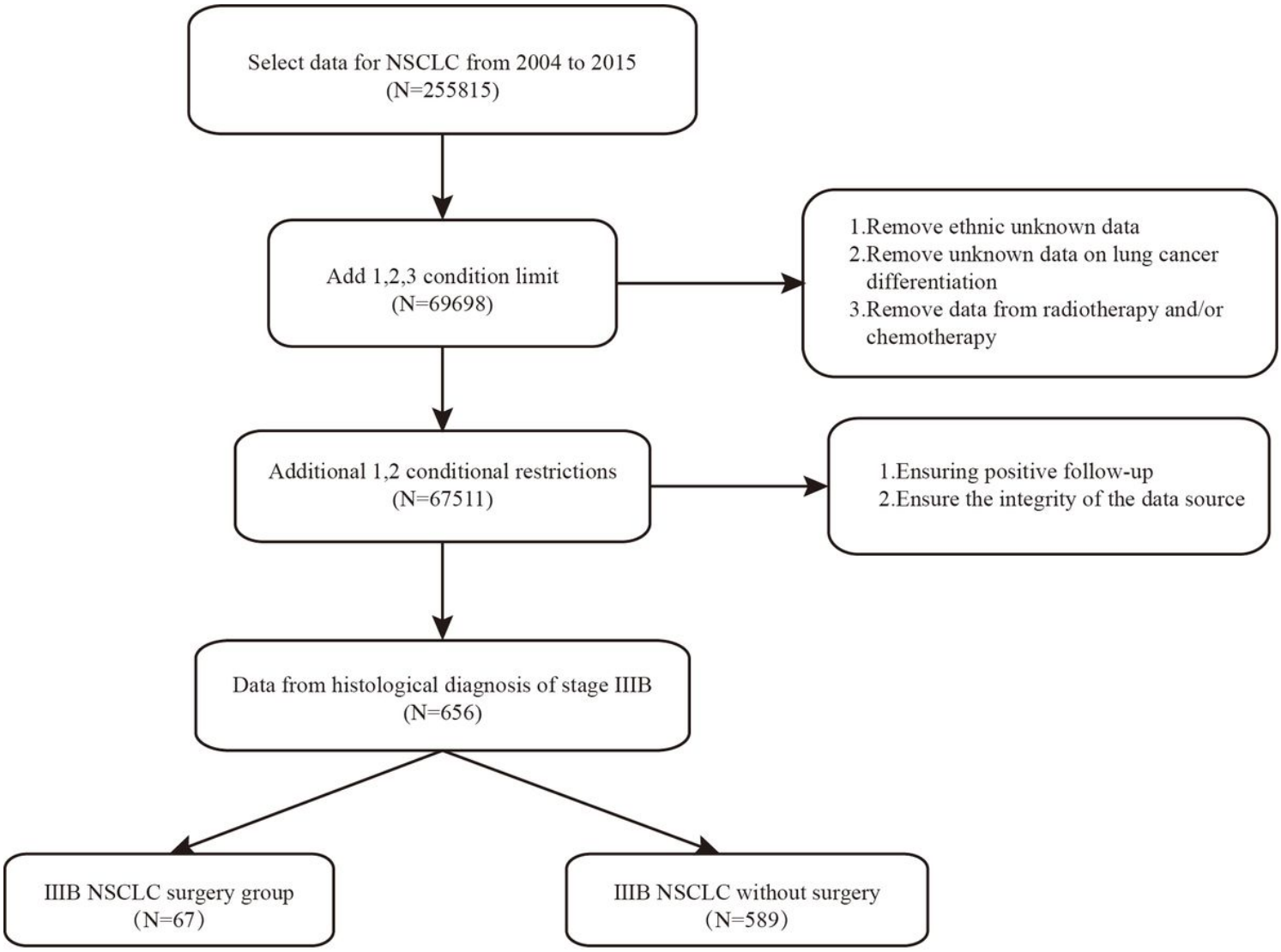

Figure 1

Patient inclusion and exclusion diagram.

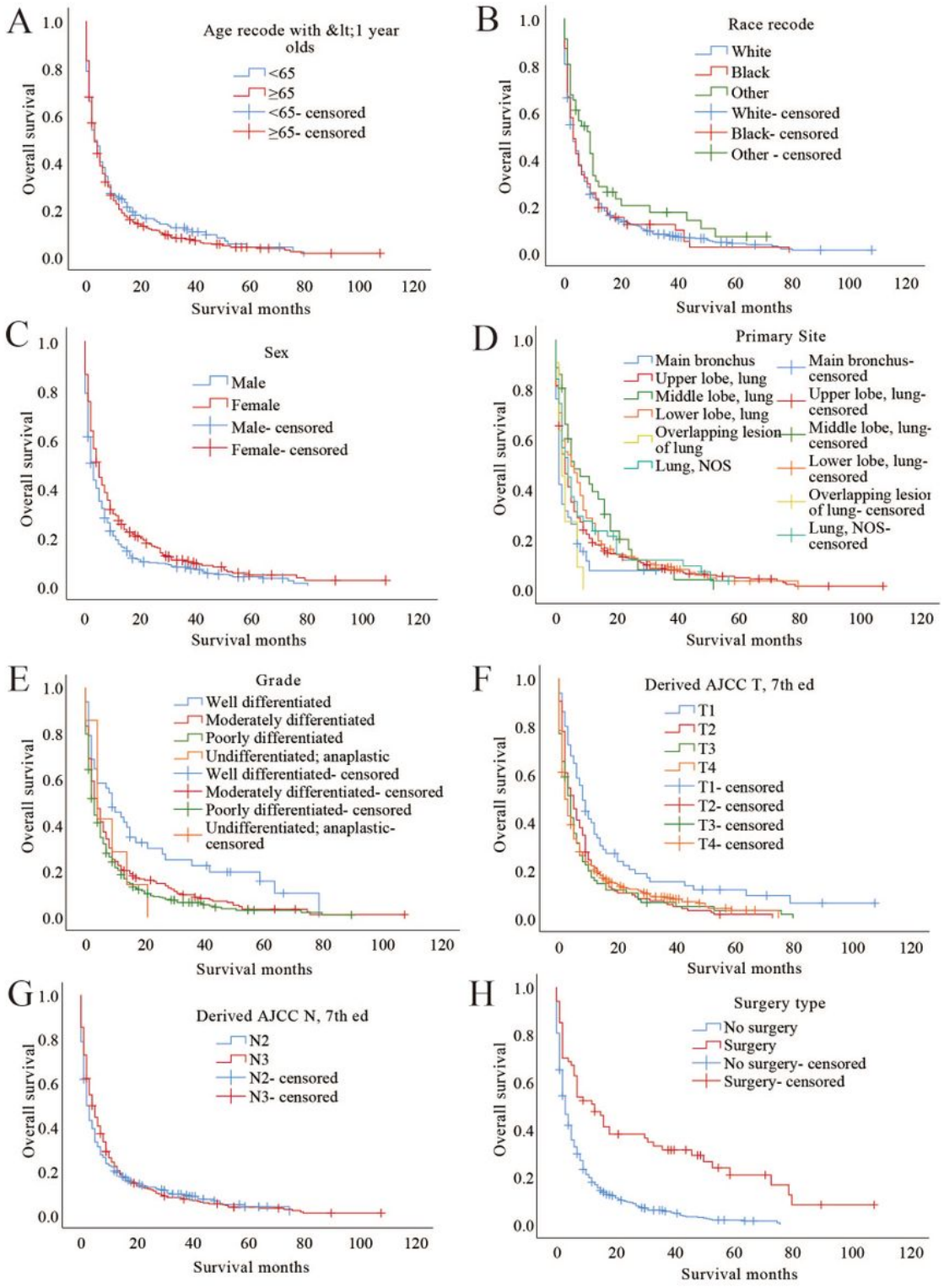

Figure 2

Survival analysis based on univariate effects on overall survival of stage IIIB NSCLC.A. The effect of age on overall survival. B. The impact of race on overall survival. C. Impact of gender on overall survival. D. Impact of tumor primary site on overall survival. E. The effect of tumor differentiation degree on overall survival. F. Impact of T staging on overall survival. G. Impact of N staging on overall survival. H. Impact of surgery and non-surgical treatment on overall survival.

	Median survival (95% CI)	P value
Age	3.000 (2.325~3.675)	0.432
<65	3.000 (1.805~4.195)	
≥65	3.000 (2.314~3.686)	
Race	3.000 (2.325~3.675)	
White	3.000 (2.438~3.562)	0.07
Black	3.000 (1.558~4.442)	
Other	9.000 (4.851~13.149)	
Sex	3.000 (2.325~3.675)	0.001
Male	3.000 (2.423~3.577)	
Female	5.000 (4.026~5.974)	
Primary Site	3.000 (2.325~3.675)	0.032
Main bronchus	1.000 (0.541~1.459)	
Upper lobe, lung	3.000 (2.372 ~3.628)	
Middle lobe, lung	6.000 (0.000~12.453)	
Lower lobe, lung	5.000 (2.440~7.560)	
Overlapping lesion of lung	2.000 (0.382~3.618)	
Lung, NOS	4.000 (1.911~6.089)	
Grade	3.000 (2.325~3.675)	0.001
Well differentiated; Grade I	9.000 (3.431~14.569)	
Moderately differentiated; Grade II	4.000 (2.897~5.103)	
Poorly differentiated; Grade III	3.000 (2.492~3.508)	
Undifferentiated; anaplastic; Grade IV	4.000 (0.578~7.422)	
Derived AJCC T, 7th	3.000 (2.325~3.675)	0.001
T1	8.000 (5.743~10.257)	
T2	5.000 (3.240~6.760)	
T3	4.000 (2.707~5.293)	
T4	2.000 (1.452~2.548)	
Derived AJCC N, 7th	3.000 (2.325~3.675)	0.181
N2	2.000 (1.420~2.580)	
N3	4.000 (3.073~4.927)	
Surgery type	3.000 (2.325~3.675)	<0.001
No Surgery	3.000 (2.482~3.518)	
Surgery	13.000 (7.400~18.600)	

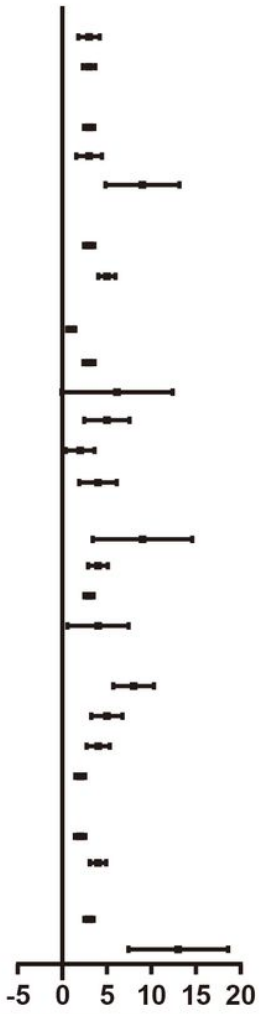

Figure 3

Forest plot and 95% CI based on single factor effect on median survival time of stage IIIB NSCLC.