Int J Clin Exp Med 2017;10(5):8078-8085
www.ijcem.com /ISSN:1940-5901/IJCEM0045285

Original Article

Prognostic factors for patients with postoperative metastasis from non-small-cell lung cancer

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Received November 28, 2016; Accepted March 16, 2017; Epub May 15, 2017; Published May 30, 2017

Abstract: Background: We sought to analyze prognostic factors for non-small-cell lung cancer (NSCLC) patients with postoperative metastasis to different organs. Methods: Three hundred and ninety-eight NSCLC patients who underwent complete resection and had recurrent cancer were included. Chi-square tests and Kaplan-Meier survival (log-rank test) analysis were used to investigate differences in survival rate by demographic factors, clinical characteristics, tumor characteristics, and surgical approaches. Cox proportional hazards models were used to evaluate the associations between these variables and overall survival time and between different sites of metastasis and survival time. Results: Cox proportional hazards regression models showed that liver metastasis predicted poor survival. Moreover, the following associations were found between metastatic site and initial surgical approach: brain-right upper lobectomy predicted poor survival times (P = 0.033); bone-right pneumonectomy predicted improved survival times (P = 0.042); lung-left pneumonectomy predicted increased survival time (P = 0.021); and polymetastasis-lobectomy and pulmonary resection with conduit reconstruction predicted better survival time (P = 0.014 and 0.017, respectively). Conclusions: Initial metastatic organ and initial surgical approaches in patients with postoperative metastasis were associated with survival time.

Keywords: Non-small cell lung cancer, recurrence, postoperative metastasis, surgery, survival

Introduction

Lung cancer is the leading cause of cancer-induced mortality, especially among patients with postoperative metastasis. Previous studies [1-3] clearly show that overall survival (OS) of lung cancer patients depends on histological type, pathological stage, interval between initial surgery and recurrence, the number of sites of recurrence, and the location of recurrence. However, the relationship between survival time of patients and different modes or locations of resection of lung cancer is not clearly known.

Depending on subtype and pathological stage, resection approach for lung cancer may include lobectomy, pneumonectomy, wedge or segmental resection, thoracotomy, or mediastinal lymph node dissection [4, 5]. Although surgical resection aims to eliminate the tumor, probability of recurrence is high due to incomplete margins, regional lymph node metastasis, tumor thrombi in blood vessels, etc. Location of postoperative recurrence may vary by cancer type. For instance, pulmonary squamous cell carcinoma tends to invade locally to cause intrathoracic recurrence. Yet, pulmonary adenocarcinoma and undifferentiated carcinoma often have distant metastasis, such as to lymph nodes, bone, liver, brain or the contralateral lung [6].

In this study, we evaluated predictors of survival for non-small-cell lung cancer (NSCLC) patients with postoperative metastasis. Furthermore, we sought independent prognostic factors for patients with postoperative metastasis to different organs.

Patients and methods

Study cohort selection

From January 2005 to June 2010, 5680 patients were diagnosed with lung cancer and underwent resection in Shanghai Pulmonary

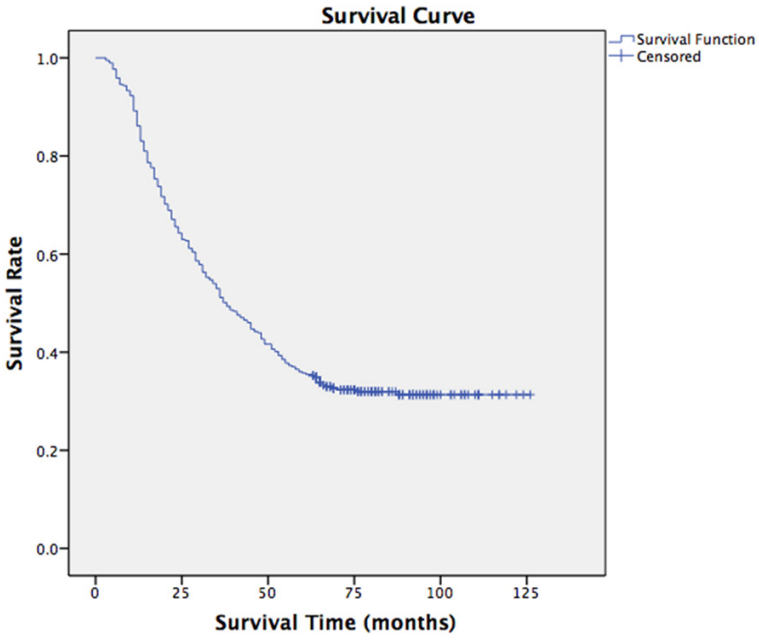

Figure 1. Kaplan-Meier curve showing the overall survival time (in months) after recurrence in 389 patients. The median survival time was 38 months.

Hospital. Among these, 466 patients had recurrences which were diagnosed by physical examination and diagnostic imaging. Histologic confirmation of the initial diagnosis was made when clinical operation was feasible. Inclusion criteria for the study were: 1) no oncologic history; 2) underwent complete surgical resection; 3) had standard postoperative and postrecurrence treatment [7]; and 4) underwent initial surgery before June 2010. Patients were excluded if they: 1) underwent incomplete resection; 2) were diagnosed with small cell lung cancer or lung sarcoma; 3) had distant metastasis before initial surgery (pathologic M stage was 2); or 4) died within 30 days of resection. The final study cohort meeting these criteria consisted of 389 patients (268 male, 121 female), with a mean age of 59.2 years [median age: 59 years (range, 31-86 years)]. All patients provided written informed consent for the operation and inclusion of personal data in a scientific database, and the study was approved by our institutional ethics committee.

Baseline information on selected patients

Clinical data was obtained from a review of medical records in our hospital. Demographic variables included: age at initial diagnosis, gender, smoking history prior to diagnosis, and histological type and pathological stage of the initial tumor.

Recurrence was diagnosed by presentation of symptoms and/or radiological examination. Previous studies have clearly demonstrated that OS of patients with recurrent cancer is correlated with histological type, pathological stage, the time between the initial surgery and recurrence, the number of sites of recurrence, or the location of recurrence, etc. [1-3]. Pathologic stage was determined by several experienced physicians in our hospital on the basis of the 7th edition of the International Association for Study of Lung Cancer [8, 9]. If the patient's pathologic stage was initially classified before these criteria were published, classification was rechecked after the criteria were established. Histology of lung tissue was determined according to World Health Organization classification by three experienced board-certified pathologists. Treatment modalities for recurrence included chemotherapy, surgical resection, radiation, or chemoradiation at recurrent sites [2, 7, 10-12]. The regimen of chemotherapy was selected according to the patient's condition [7, 13-15]. Surgical resection was applied when recurrent disease was limited and could be resected completely [2]. The most common site of postoperative metastasis in the cohort was the brain (125 patients). The number of patients with metastasis in bone and contralateral lung were 84 and 56, respectively. During the course of the study, surgical resection for metastases to the brain, lung, liver, stomach, and bowel was performed. Resection, stereotactic radiation therapy, and whole brain irradiation for brain metastasis were selected according to the patient's general condition, the number of metastatic lesions in the brain, and the size of each metastatic lesion [2, 7, 10]. Radiation or chemoradiation with curative intent was applied when recurrent lesions were limited; otherwise, palliative radiotherapy or chemoradiotherapy was applied [2, 11].

Table 1. Univariate analyses of baseline information for overall survival

Variable	Survival															
	Overall				1-year				3-year				5-year			
	Alive (n)	All (n)	%	*p* value	Alive (n)	All (n)	%	*p* value	Alive (n)	All (n)	%	*p* value	Alive (n)	All (n)	%	*p* value
Age				*0.014*				0.318				0.076				*0.029*
< 60	74	195	37.9		177	195	90.8		112	195	57.4		80	195	41.0	
≥ 60	51	194	26.3		170	194	87.6		94	194	48.5		59	194	30.4	
Gender				0.793				*0.004*				0.389				0.528
Male	85	268	31.7		231	268	86.2		138	268	51.5		93	268	34.7	
Female	40	121	33.1		116	121	95.9		68	121	56.2		46	121	38.0	
Histological Type				0.437				*0.022*				*0.004*				0.243
ADC	64	196	32.7		181	196	92.3		121	196	61.7		75	196	38.3	
SQC	25	98	25.5		86	98	87.8		38	98	38.8		26	98	26.5	
ASC	26	67	38.8		60	67	89.6		34	67	50.7		28	67	41.8	
Others	10	28	35.7		20	30	66.7		13	28	46.4		10	28	35.7	
Pathological Classification				*0.037*				0.336				0.121				*0.097*
I	56	134	41.8		121	134	90.3		81	134	60.4		60	134	44.8	
II	20	68	29.4		61	68	89.7		38	68	55.9		23	68	33.8	
III	49	187	26.2		165	187	88.2		87	187	46.5		56	187	29.9	
Numbers of Recurrent Sites				0.879				0.162				0.690				0.792
One	104	322	32.3		284	322	88.2		172	322	53.4		116	322	36.0	
Two or More	21	67	31.3		63	67	94.0		34	67	50.7		23	67	34.3	
Surgical Mode				0.579				0.193				0.339				0.476
Segmentectomy	2	8	25		6	8	75		2	8	25		2	8	25	
Lobectomy	86	261	33.0		236	261	90.4		147	261	56.3		99	261	37.9	
Bilobectomy	11	24	45.8		22	24	91.7		13	24	54.2		11	24	45.8	
Pneumonectomy	11	38	28.9		32	38	84.2		16	38	42.1		11	38	28.9	
Lobectomy with Segmentectomy	3	7	42.9		7	7	100		3	7	42.9		3	7	42.9	
Resection with Conduit Reconstruction	9	36	25		29	36	80.6		19	36	52.8		10	36	27.8	
Sleeve Resection	3	15	20		15	15	100		6	15	40		3	16	18.8	
Surgical Location				0.458				0.751				0.238				0.489
Right Side	71	234	30.3		206	234	88.0		120	234	51.3		79	234	33.7	
Left Side	51	144	35.4		131	144	91.0		82	144	56.9		62	144	43.0	
Both Sides	3	11	27.3		10	11	90.9		4	11	36.4		3	11	27.3	

Abbreviations: ADC, adenocarcinoma. SQC, squamous cell carcinoma. ASC, adenosquamous carcinoma.

Table 2. Cox proportional hazards regression model for overall survival

Variable	Multivariate Analyses for Hazard Ratio	Overall Survival 95% CI	*p* value
Age	1.280	1.004-1.634	*0.047*
Gender	0.912	0.697-1.194	0.504
Histological Type	1.012	0.921-1.111	0.810
Pathological Classification	1.137	1.047-1.235	*0.002*
Number of Recurrent Sites	0.986	0.714-1.361	0.932
Surgical Mode	1.018	0.940-1.104	0.657
Surgical Location	0.990	0.941-1.041	0.691

Follow-up

Postoperative follow-up data through June 2015 was included in this study. Follow-up data was obtained by reviewing medical records and engaging the follow-up department of our hospital. All patients received medical check-ups and chest radiographs at least twice per year and whole body computed tomography annually. Follow-up information was updated until death or last contact; median follow-up time was 38 months (range, 3-126 months).

Statistical analysis

Our predictors of OS included age, gender, histological type of tumor, pathological classification, initial operation mode, initial recurrent sites, and number of initial recurrent regions (one region versus two or more regions). The effect of these continuous and categorical variables on survival rates (overall, 1-year, 3-year, and 5-year) were examined with chi-square tests. Univariate and multivariate analyses were performed to examine factors affecting survival using the Kaplan-Meier method and Cox proportional hazards regression analysis, respectively. Kaplan-Meier analysis and log-rank tests were used to depict survival curves and compare OS between different subgroups.

Next, patients were divided into eight groups according to the organ of first recurrence after initial surgery, including brain, bone, lung, pleura, liver, lymph nodes, others, and two or more organs. Multivariate analysis using the Cox regression model was performed to test for the effect of initial surgical variables in each group.

Statistical analysis was performed using SPSS software, version 20.0 (SPSS Inc., Chicago, USA). A two-tailed p value < 0.05 was considered statistically significant. Relative risks are presented with their 95% confidential intervals (CIs).

Results

Overall survival and baseline information of the selected cohort

The survival curve for all study subjects is shown in **Figure 1**. The median OS time was 38 months (range, 3-126 months). Since previous studies have demonstrated that treatment approach after relapse is significantly associated with postrecurrence survival (PRS) [2, 7, 10, 11, 13-15], we excluded postoperative treatment from our analysis and focused on predictors of OS.

Univariate analyses of baseline factors predicting overall survival

Poor overall survival rate in NSCLC patients was significantly associated with being over 60 years old (P = 0.014) or having an advanced pathological stage (P = 0.037; see **Table 1**). Male gender (P = 0.004) and squamous cell lung cancer (P = 0.022) were significantly associated with poor 1-year survival rate. Squamous cell lung cancer (P = 0.004) and age over 60 (P = 0.029) were significantly associated with poor 3-year and 5-year survival rate, respectively.

Multivariate analysis for variables related to overall survival

Multivariate analysis using Cox proportional hazards regression model was performed to demonstrate the correlation between OS and predictor variables, including baseline information, clinical characteristics, initial treatment modes, and situation at initial recurrence (**Table 2**). Age (P = 0.047) and tumor pathological type (P = 0.002) were significantly associated with OS. Kaplan-Meier survival analysis and log-rank tests showed the same trend (**Figure 2**).

When looking at metastatic site, only liver metastasis predicted poor survival (**Table 3**). We found that some initial sites of metastasis

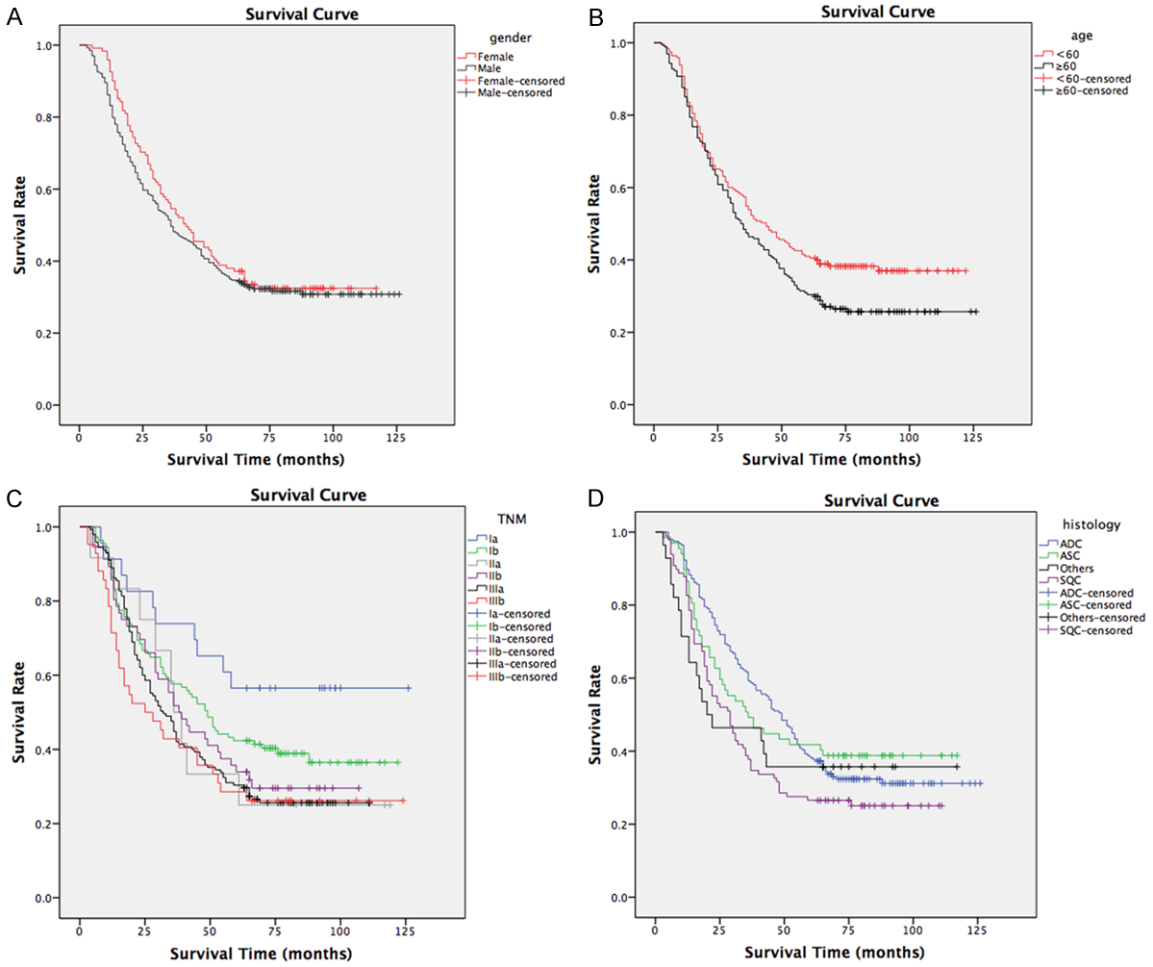

Figure 2. Kaplan-Meier curves of survival (in months) among different subgroups (censored). A: No significant difference between males and females in survival time (Log-rank test: $P = 0.396$). B: Age over 60 years was significantly associated with poor survival ($P = 0.034$). C: Advanced stage was significantly associated with poor survival (Log-rank test: $P = 0.039$). D: The long-term survival time of ADC was significantly better than for SQC ($P < 0.000$). The long- term survival rate of ASC was marginally better than for SQC ($P = 0.061$). ADC: adenocarcinoma. SQC: squamous cell carcinoma. ASC: adenosquamous carcinoma. Censor events indicated by vertical lines.

were associated with the initial surgical location (**Table 4**). Brain metastasis from NSCLC was significantly associated with right upper lobectomy (RUL; $P = 0.033$). In addition, overall survival was significantly increased if patients initially received RUL to treat NSCLC and had postoperative brain metastasis. Right pneumonectomy (RP) was significantly associated with patients who had postoperative bone metastasis ($P = 0.042$), and OS significantly decreased if patients initially received RP to treat NSCLC and had postoperative bone metastasis. Left pneumonectomy (LP) was significantly associated with patients who had postoperative lung metastasis ($P = 0.021$) and predicted better OS. Lobectomy (Lob; $P = 0.014$) and pulmonary resection with conduit reconstruction (ReS+ReC; $P = 0.017$) as initial surgical approaches were significantly associated with patients who initially had polymetastasis and predicted worse OS.

Discussion

In the present retrospective study, we evaluated the correlation between survival rate and different variables for 389 patients who had postoperative metastasis from NSCLC. These variables included baseline information, clinical characteristics, initial surgical approaches, and initial metastatic sites. We demonstrated that age, gender, pathological classification

Table 3. Overall survival by site of metastasis according to Cox proportional hazards regression model

Variable		Overall Survival				
	Patients (n) Alive/All in group	Median Survival Time (months)	Survival Rate (%)	Hazard Ratio	95% CI	*p* value
Recurrent Organ(s)						
Only One Organ		38	32.3			
Brain	36/125	37	28.8	1.096	0.767-1.564	0.615
Bone	25/84	33	29.8	1.153	0.784-1.695	0.470
Lung	25/56	53.5	44.6	0.686	0.435-1.082	0.105
Pleura	7/14	65	50	0.624	0.282-1.382	0.245
Liver	2/16	14	12.5	2.680	1.470-4.885	*0.001*
Lymph Nodes	5/8	78.5	62.5	0.342	0.106-1.100	0.072
Others	4/19	29	21.1	1.177	0.657-2.109	0.583
Polymetastasis	21/67	36	31.3	—	—	—

Table 4. Overall survival after initial surgery based pm site of initial metastasis and surgical approach by Cox Model

Recurrent Site	Surgical Approach	B	*p* value	ExpB
Brain	RUL	3.893	*0.033*	49.065
	RMLL	2.737	0.060	15.438
	RP	2.943	0.075	18.966
	Lob+Seg	-2.176	0.062	0.114
Bone	RLL	-2.830	0.051	0.059
	LLL	-1.821	0.089	0.162
	RP	-3.061	*0.042*	0.047
	Seg	2.201	0.066	9.034
Lung	LP	2.506	*0.021*	12.262
Polymetastasis	Lob	-1.570	*0.014*	0.208
	ReS+ReR	-2.365	*0.017*	0.094

Abbreviations: RUL, right upper lobectomy. RMLL, right middle and lower lobectomy. RP, right pneumonectomy. Lob, lobectomy. Seg, segmentectomy. RLL, right lower lobectomy. LLL, left lower lobectomy. LP, left pneumonectomy. ReS+ReR, pulmonary resection with conduit reconstruction. B, Variables with positive coefficients. ExpB, hazard ratios.

and histological type were significantly associated with patients' survival time and survival rate, which concurs with other reports [1-4, 11]. In addition, Hung *et al*. [16] pointed out that pathological T stage, smoking, and number of mediastinal lymph node metastases were significantly associated with OS. Moreover, Koike *et al*. [17] showed no significant association between OS and surgical modes. However, we found that OS was significantly increased if patients initially received RUL to treat NSCLC and had postoperative brain metastasis. In addition, RP was significantly associated with patients who had postoperative bone metastasis and a poorer OS.

The median OS of patients with postoperative metastasis from NSCLC was 38 months (range, 3-126 months); however, the median OS for those with liver oligometastasis was only 12.5 months ($P = 0.001$). These results were similar to previous studies [15, 18]. Metastasis to lymph nodes (regional and systematic) had the highest survival overall (78.5 months). No other associations were found between organ metastasis and survival in our study. However, Endo *et al*. [19] reported that patients with pleural metastasis had significantly lower survival. Therefore, research should now focus on the mechanism of postoperative liver metastasis from NSCLC, find the predictors of liver metastasis, and reduce the rate of liver metastasis.

The most common postoperative oligometastases from NSCLC occurred in the brain (32.1%), bone (21.6%), and lung (14.4%). In addition to oligometastasis, 67 (17.2%) patients had polymetastasis, defined as recurrence in two or more organs simultaneously. Shimmad *et al*. [12] showed that patients with postoperative bone or liver metastasis or polymetastasis without lung metastasis had significantly lower survival.

Though surgical modes or locations were not significantly associated with OS overall, we did find an effect when looking at them by initial site of metastasis (brain, bone, lung, or two or more organs). The right upper lung or right lung tumor may tend to metastasize to brain or bone. It will be interesting to elucidate the

underlying connections in the future. More attention should be paid to liver and brain metastases, which account for the worst survival and most common postoperative oligometastases.

Limitations

As a retrospective, single-institute study, patient-selection bias and time-trend bias were inevitable. Another obvious limitation of this study is sample size. In the final cohort, we can only analyze patients who had brain, bone, lung and polymetastasis. Data from patients with metastasis to lymph nodes, liver or other organs could not be analyzed by an appropriate analytical model. Thus, we could not determine predictors of survival for patients with metastases to these organs. Further studies should include more patients who had postoperative metastasis from NSCLC.

Conclusion

Initial metastatic organ and initial surgical approaches in patients with postoperative metastasis were associated with survival time. This knowledge can help doctors to optimize treatment regimens after disease recurrence.

Disclosure of conflict of interest

None.

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