J BUON 2013; 18(1): 169-175
ISSN: 1107-0625 www.bu-on.org/jbuon
E-mail: jbuon@ath.forthnet.gr

ORIGINAL ARTICLE

Characteristics of local recurrence of lung cancer and possibilities for surgical management

D. Stojiljkovic[1], D. Mandaric[2], N. Miletic[1], J. Stojsic[2], I. Markovic[1], D. Gavrilovic[3], G. Pupic[1],T. Stojiljkovic[4], B. Lukac[5], R. Dzodic[1]

[1]Institute of Oncology and Radiology of Serbia, Department of Surgery, Belgrade; [2]Institute of Lung diseases, Clinical Center of Serbia, Faculty of Medicine, Belgrade; [3]Institute of Oncology and Radiology of Serbia, Data Center, Belgrade; [4]Medical Center Smederevo, Department of Radiology, Smederevo; [5]Private consultant for diagnostic imaging, Belgrade, Serbia

Summary

Purpose: To investigate the correlation between stage and histopathological characteristics of patients with lung cancer and local recurrence, as well as the incidence and the characteristics of local recurrence along with the possibility of surgical retreatment.

Methods: Studied were 51 patients with locally relapsing lung cancer, initially treated surgically from 2003 to 2007. The operations performed ranged from conservative wedge resections, standard lobectomies and pneumonectomies to extensive resections of the entire lung and chest wall. All patients underwent regular follow-up including thoracic CT scan every 3 months.

Results: All patients were diagnosed with local recurrence after a median of 10 months (range 1-30) after primary surgery with curative intent. There was no statistically significant link between type of surgery and time to local recurrence. Patients with pathological stage I,II, and IIIa had a significantly longer time to local recurrence than those with stage IIIb and IV. Local recurrence sites were the bronchial stump, mediastinal lymph nodes, the remaining lung parenchyma, chest wall and a combination of these. Surgical retreatment was possible in 20 of 51 patients (39.2%). Chest wall was the commonest localization (20 of 51; 39.2%), also the most frequent in the group of surgically retreated patients (13 of 20; 65%). Squamous cell cancer (SCC) was the predominant histological type (38 of 51; 74.5%), followed by adenocarcinoma (9 of 51; 17.7%).

Conclusion: SCC is the commonest locally relapsing lung cancer. The type of the initial surgical procedure didn't have any impact on the incidence of local recurrence, but the extent and completeness of surgery did. The time to local recurrence heavily depended on the primary tumor pathological stage. Chest wall was the commonest relapse site, and the most suitable for surgical retreatment, which was related to the quality of surgery.

Key words: lung cancer, recurrence, surgery

Correspondence to: Dejan Stojiljkovic, MD, MSc.
Clinic of Oncological Surgery Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia.
Tel:+381 11 2067250, Fax:+381 11 2685300
E-mail:stojdeja@verat.net
Received: 14/05/2012; Accepted: 04/06/2012

Introduction

Lung cancer is the leading cause of cancer-related deaths. Local recurrence is one of the forms of disease relapse. It can be localized in the bronchial stump, mediastinal lymph nodes, the remaining lung parenchyma and in the chest wall. From the clinical point of view, the causes of local recurrence can be divided into two mutually interconnecting groups. The first is related to the achieved level of radicality, i.e. the completeness of resection, and the second one is influenced by the characteristics of the primary tumor itself [1,2].

The opinion that SCC is the most frequent locally recurring cancer prevails at the moment, but there is still much doubt about what affects the speed of recurrence. Our study investigated the correlation between pathological stage and characteristics of lung cancer as well as the incidence and characteristics of local recurrence itself along with the possibility of surgical retreatment.

Methods

Patients

This retrospective study included 51 patients with local recurrence of lung cancer, who were initially treated surgically at the Institute for Lung Diseases of the Clinical Center of Serbia and the Institute for Oncology and Radiology of Serbia in the period 2003-2007.

Table 1. Characteristics of patients with local recurrence

Characteristics	*N (%)*
Age (years)	
Mean (SD)	57.14 (9.33)
Median (range)	57 (37-75)
Gender	
Male	41 (80.4)
Female	10 (19.6)
Environment	
Urban	37 (72.6)
Rural	14 (27.4)
Smoking	
Smokers	49 (96.1)
Non smokers	0 (0)
No data	2 (3.9)
Total	51 (100)

Table 2. Characteristics of the disease and surgical treatment

Characteristics of primary tumor	*Patients, N (%)*
Histopathology	
Squamous cell carcinoma	38 (74.5)
Adenocarcinoma	9 (17.6)
Large cell carcinoma	2 (3.9)
Sarcomatoid carcinoma	1 (2.0)
Squamous cell and small cell carcinoma	1 (2.0)
Pathological stage of primary tumor	
I	7 (13.7)
II	16 (31.4)
IIIa	16 (31.4)
IIIb	7 (13.7)
IV	1 (2.0)
Without pathological stage	4 (7.8)
Operation (types)	
Atypical resection	3 (5.9)
Lobectomy	17 (33.3)
Pneumonectomy	11 (21.6)
Atypical resection with chest wall resection	3 (5.9)
Lobectomy with chest wall resection	14 (27.5)
Pneumonectomy with chest wall resection	3 (5.9)
Total	51 (100)

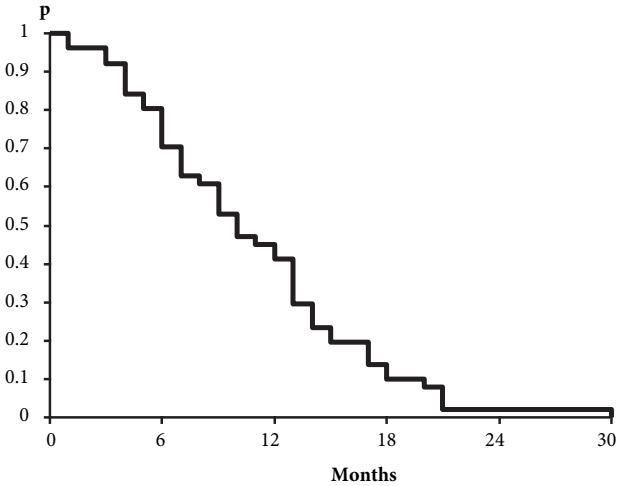

Figure 1. Time from surgery to local disease recurrence.

Patient age ranged from 37 to 75 years, with a median of 57 years. Men were represented with 80.4%, urban population with 72.6% and as many as 96.1% were smokers (Table 1).

Table 3. Time from surgery to local disease recurrence according to the types of primary surgery and pathological stage

Categories	*Patients, N (%)*	*Time (months) Median (95% CI)*	
From surgery to local recurrence	51 (100)	10 (8-13)	-
Operation (types)			
Atypical resection	3 (5.9)	18 (≥5)	x^2_5=3.996
Lobectomy	17 (33.3)	10 (6-15)	p=0.55
Pneumonectomy	11 (21.6)	10 (≥7)	
Atypical resection with chest wall resection	3 (5.9)	9 (≥9)	
Lobectomy with chest wall resection	14 (27.5)	9 (7-14)	
Pneumonectomy with chest wall resection	3 (5.9)	13 (≥13)	
Pathological stage			
$I+II+III_a$	39 (76.5)	12 (9-14)	x^2_1=5.227
III_b+IV	8 (15.7)	7 (≥6)	p=0.002

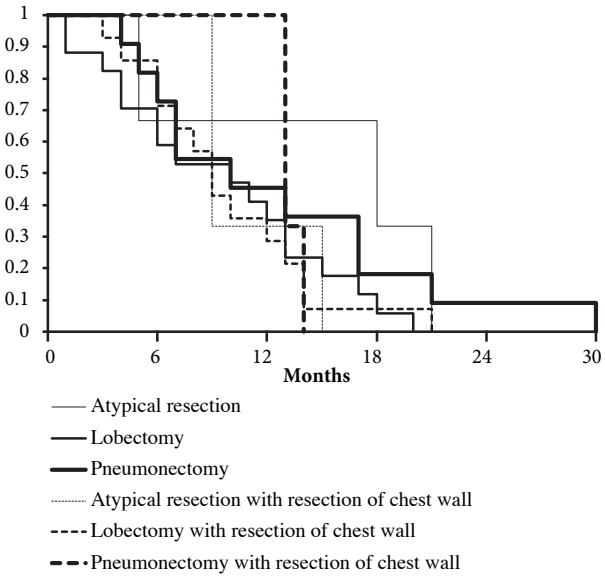

Figure 2. Time to local recurrence according to the primary surgery types. See also Table 3.

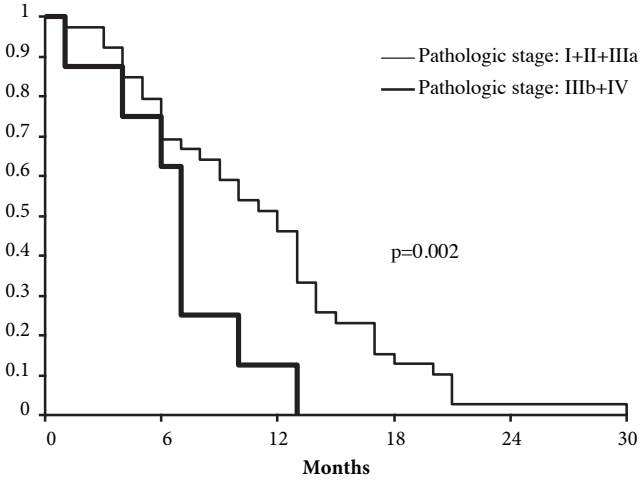

Figure 3. Time to local recurrence according to pathological stage categories. See also Table 3.

The clinical stages of the patients who underwent surgical treatment were I, II and IIIα. One patient with clinical stage IV was operated as well, having a solitary brain metastasis primarily removed. The incidence of local recurrence was analyzed independently from the incidence of systemic metastases. All patients had a chest CT every 3 months during the first 2 postoperative years, and every 6 months thereafter.

Methods

The primary tumor was classified according to the 2002 TNM classification (TNM Classification of Malignant Tumors, 6th edn., 2002) which has been used until 2009. Histopathological verification was done according to the 2004 WHO classification of the malignant epithelial tumors of the lung. CT, bronchoscopic biopsy, percutaneous fine-needle biopsy or a

Table 4. Localization of local recurrence and treatment

Localization of local recurrence	*Total N (%)*	*Surgery N (%)*	*No surgery N (%)*	*Fisher's exact test*
Chest wall	20 (39.2)	13 (65)	7 (22.6)	
Lung parenchyma	8 (15.7)	2 (10)	6 (19.3)	
Bronchial stump	5 (9.8)	1 (5)	4 (12.9)	
Mediastinal lymph nodes	11 (21.6)	2 (10)	9 (29.0)	p=0.09
Bronchial stump and mediastinal nodes	3 (5.9)	1 (5)	2 (6.5)	
Lung parenchyma and mediastinal nodes	2 (3.9)	0 (0)	2 (6.5)	
Chest wall and mediastinal nodes	2 (3.9)	1 (5)	1 (3.2)	
Total	51 (100)	20 (100)	31 (100)	

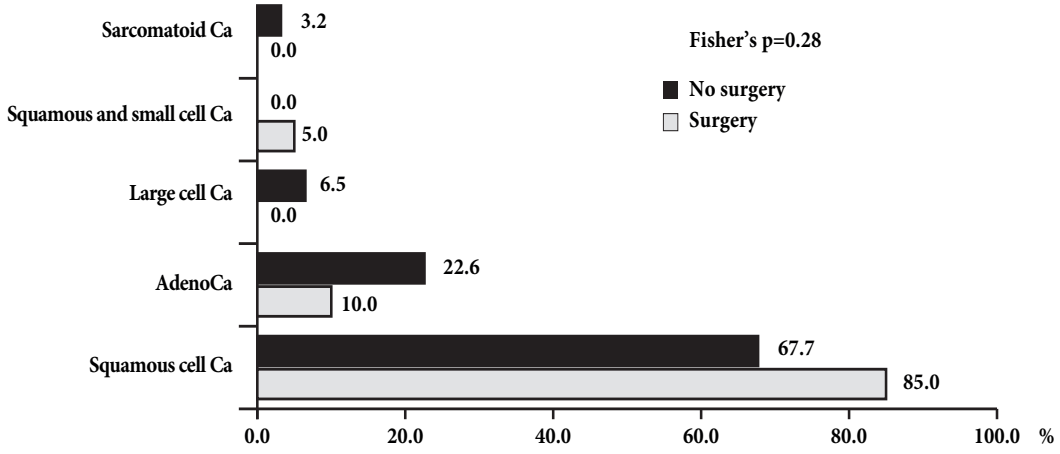

Figure 4. Pathological types of the primary tumor.

new operation were the methods used to confirm the local recurrence. The type of surgical retreatment, depending on the localization of the local recurrence, implied atypical resection of the lung, lobectomy, pneumonectomy, chest wall resection, lymph node dissection, extirpation of the chest wall tumor, or a combination of the mentioned procedures.

Statistics

Statistical analysis included testing of sample distribution for normality (Kolmogorov-Smirnov and Shapiro-Wilk tests), methods of descriptive statistics (frequencies, percentages, mean, median, standard deviation [SD], range) and testing the differences between the parameters (Pearson x^2 test, Fisher's exact test). Cumulative probabilities curves for time to local recurrence were constructed using the Kaplan-Meier product-limit method, described with median and 95% confidence interval (95%CI) and log-rank test was used for group differences estimations. The level of statistical significance was $p< 0.05$. Data analysis was performed using the statistical program R version 2.14.1 (2011-12-22; Copyright (C) 2011; The R Foundation for Statistical Computing; ISBN 3-900051-07-0). Figures were constructed using Microsoft Office Excel 2007.

Results

In our group of 51 patients with local recurrence, males predominated. Most patients came from urban areas, and almost all of them were smokers (Table 1). There were 5 types of epithelial malignant lung

Table 5. Methods of treatment in relation to pathological stage

Pathological stage of primary tumor	*Total N (%)*	*Surgery N (%)*	*No surgery N (%)*	*Fisher's exact test*
Pathological stage				
I_a	2 (3.9)	1 (5)	1 (3.2)	
I_b	5 (9.8)	3 (15)	2 (6.5)	
II_a	1 (2)	0 (0)	1 (3.2)	
II_b	15 (29.4)	8 (40)	7 (22.6)	p=0.41
III_a	16 (31.4)	6 (30)	10 (32.3)	
III_b	7 (13.7)	1 (5)	6 (19.3)	
IV	1 (2)	1 (5)	0 (0)	
Without stage	4 (7.8)	0 (0)	4 (12.9)	
Pathological stage-categories				
Pathological stage I, II, III_a	39 (76.5)	18 (90)	21 (67.7)	p=0.44
Pathological stage III_b, IV	8 (15.7)	2 (10)	6 (19.4)	
Without stage	4 (7.8)	0 (0)	4 (12.9)	
Total	51 (100)	20 (100)	31 (100)	

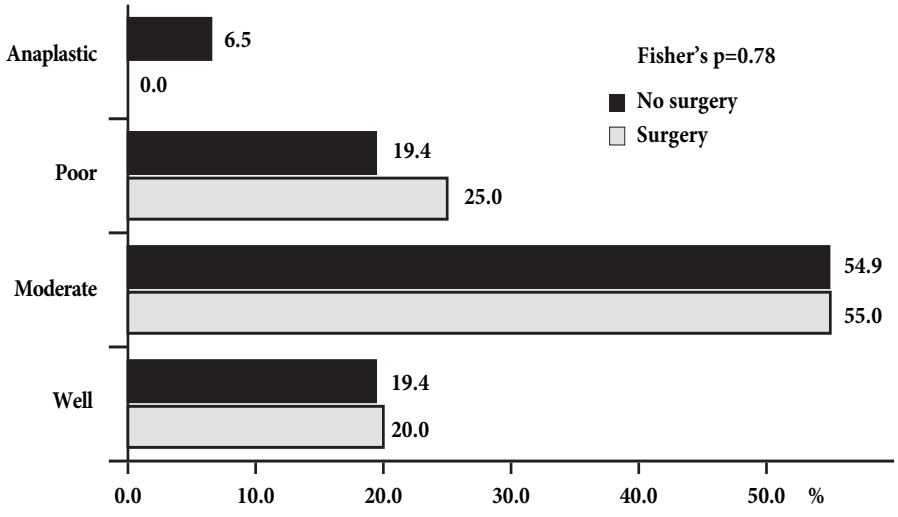

Figure 5. Tumor grades.

tumors, and pathological stages II and IIIa were the most frequently surgically treated. Lobectomy was the most frequent type of primary surgery (Table 2).

Local recurrence was confirmed in all patients 1-30 months after the initial surgical treatment. The median (95% CI) time to local recurrence was 10 (8-13) months (Figure 1).

There was no statistically significant difference in time to local recurrence among the different types of surgical treatment (Table 3 and Figure 2; log-rank p=0.55).

Patients with pathological stage I, II and IIIa had a significantly longer time to local recurrence than patients with stages IIIb and IV (Table 3 and Figure 3; log-rank p=0.002).

The localizations of the LR included the bronchial stump, mediastinal lymph nodes, the remaining lung parenchyma and the chest wall. About 14% of

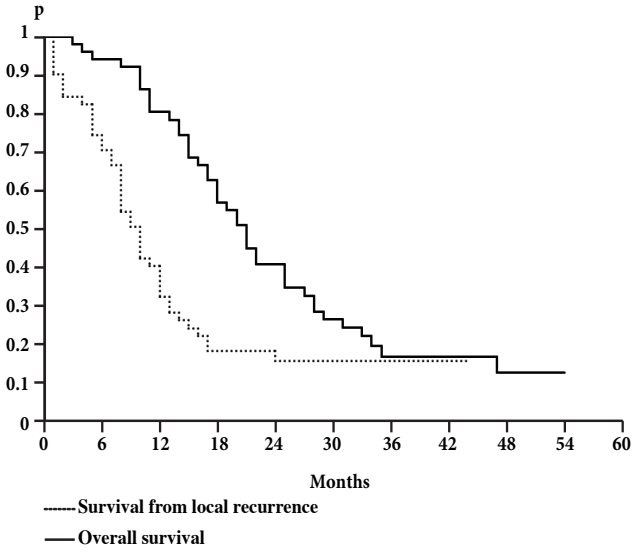

Figure 6. Survival from local recurrence and overall survival.

the patients had a local recurrence in two localizations (Table 4).

Surgical retreatment was possible in 20 of 51 (39.2%) patients with local recurrence. It was most frequently localized in the chest wall (20/51; 39.2%), and this localization was the most frequent in the group of patients who were operated for the second time (13/20; 65%) (Table 4). Removal of the local recurrence in the chest wall was significantly more frequent than surgical management of recurrences in other localizations (Pearson x^2 test; x^2_1=9.21; p=0.002). All other recurrence sites offered far less possibilities for surgical retreatment. There was no statistically significant difference in the localization of local recurrence between the surgically and non-surgically treated groups (Fisher's exact test, p=0.09; Table 4).

SCC was the most frequent locally relapsing tumor (38/51;74.5%) and was followed by adenocarcinoma (9/51;17.6%). There was no statistically significant difference in the pathological type of the tumor between the surgically and non-surgically treated patients (Fisher's exact test; p=0.28) (Figure 4).

Also no statistically significant difference was noticed between the surgically and non-surgically treated patients regarding the histological grade of the tumor (Fisher's exact test; p=0.78) (Figure 5).

Due to the small number of patients in the different substages pathological stages of the primary tumor were grouped into potentially resectable (I+II+IIIa) and potentially unresectable (IIIb+IV) according to the protocols (Table 5), and further analysis was performed accordingly.

Chest wall resection was the most frequent type of surgical retreatment in the group of patients in whom it was feasible. Chest wall was also the most frequent site of local recurrence (Table 6).

Survival from local recurrence (median with 95%CI: 10 (8-12) months) and overall survival (median with 95%CI: 21 (18-27) months) are shown in Figure 6.

Discussion

Epidemiological data regarding the influence of gender, urban environment and cigarette smoking habits on the incidence of lung cancer, and later its local recurrence, correlated with the reports of Harpole et al., Goodgame et al., Kawashima et al. and others [3-8].

The most frequent histological type was SCC, because of its characteristic local spreading; this was followed by adenocarcinoma for its feature of producing skip metastases to the regional and mediastinal lymph nodes, which correlated with the works of Al-Kattan et al., Jackevicius et al., and Kelsey et al. [9-11].

Schuchert et al. and Carr et al. came to the conclusion that atypical resection gave almost the same results in survival and the incidence of local recurrence when compared to lobectomy in stage I disease. Iwasaki et al. [12] concluded that in older patients, selective, non-therapeutic vs systemic lymph node dissection had almost the same results in survival and the incidence of local recurrence in stage I disease. In our study, time to local recurrence was not significantly different for the different types of surgery, which probably indicates that the appearance of the local recurrence is primarily influenced by the quality of the performed surgical procedure, i.e. completeness of resection [13-17]. However, patients with pathological stages I-IIIa have a statistically significantly longer time to local recurrence than patients with pathological stages IIIb and IV.

These results lead us to conclude that adequate staging and well-chosen indications for surgery have an impact on the speed with which the disease will re-

lapse [3,4,7,18-20]. Chest wall is the most frequent site of local recurrence, but also the most operable one, and the reason for that may be unreliable *extempore* analysis of the margins of resection, as well as the lower quality of surgical performance. This finding differs from the previously published ones which indicate lung parenchyma and mediastinal lymph nodes as the most frequent sites of local recurrence [8]. Histological type and grade do not significantly influence the possibility of surgical treatment of the local recurrence.

Acknowledgements

We are grateful to Dr. Ljiljana Vuckovic-Dekic for encouragement, assistance and useful suggestions. We also thank Mr Dusko Stojanovski for excellent technical assistance.

References

1. Subotic D (Ed): Lung Cancer Surgery. Lapresing,Valjevo 2010, pp 94-103.
2. Yong SC,Young MS, Kwhanmien K, Jhingook K. Pattern of recurrence after curative resection of local (stage I and II) non-small cell lung cancer: difference according to the histologic type. J Korean Med Sci 2004;19:674-676.
3. Harpole DH Jr, Herndon JE 2nd, Wolfe WG et al. A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation,histopathology,and oncoprotein expression. Cancer Res 1995; 55:51-56.
4. Harpole DH Jr, Herndon JE 2nd,Young WG Jr et al. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. Cancer 1995;76:787-796.
5. Goodgame B,Viswanathan A, Zoole J et al. Risk of recurrence of resected stage I non-small cell lung cancer in elderly patients as compared with younger patients. J Thorac Oncol 2009;4:1370-1374.
6. Hjelde H, Sundstrom S, Odegard A et al. Recurrence and survival after surgical treatment of lung cancer. Tidsskr Nor Laegeforen 2010;130:25-28.
7. Murthy SC, Reznik SI,Ogwudu UC et al. Winning the batlle, losing the war: the noncurative "curative" resection for stage I adenocarcinoma of the lung. Ann Thorac Surg 2010;90:1067-1074.
8. Kawashima O, Ibe T, Kakegawa S et al. Surgical treatment and outcome for postoperative recurrent or second primary lung cancer. Kyobu Geka 2010;63:935-939.
9. Al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. Eur J Cardio-Thoracic Surg 1997;12:380-384.
10. Jackevicius A, Cicenas S, Piscikas DA. The treatment of lung cancer relapse after the lung resection. Medicina (Kaunas) 2004;40:139-141.
11. Kelsey CR, Marks LB, Hollis D et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer 2009;115:5218-5227.
12. Iwasaki A, Hamatake D, Hamanaka W et al. Is systemic node dissection for accuracy staging in clinical stage I non-small cell lung cancer worthwhile in the elderly? Thoracic Cardiovasc Surg 2008;56:37-41.
13. Miura H,Konaka C, Kato H et al. Recurrence at the bronchial stump after resection of lung cancer. Ann Surg 1994;219:306-309.
14. Lequaglie C ,Conti B, Brega Massone PP, Giudice G. Unsuspected residual disease at the resection margin after surgery for lung cancer: fate of patients after long-term follow-up. Eur J Cardiothorac Surg 2003;23:229-232.
15. Campione A, Ligabue T, Luzzi L et al. Comparison between segmentectomy and larger resection of stage IA non-small cell lung carcinoma. J Cardiovasc Surg 2004;45:67-70.
16. Schuchert MJ, Pettiford BL, Keeley S et al. Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. Ann Thoracic Surg 2007;84:926-932.
17. Carr SR, Schuchert MJ, Pennathur A et al. Impact of tumor size on outcomes after anatomic lung resection for stage 1A non-small cell lung cancer based on the current staging system. J Thorac Cardiovasc Surg 2011 Dec (Epub ahead of print).
18. Cangemi V,Volpino P, D'Andrea N et al. Local and/or distant recurrences in T1-2/N0-1 non-small cell lung cancer. Eur J Cardio Thor Surg 1995;9:473-478.
19. Bando T, Miyahara R, Sakai H et al. A follow-up report on a new method of segmental resection for small-sized early lung cancer. Lung Cancer 2009;63:58-62.
20. Kawachi R, Tsukada H, Nakazato Y et al. Early recurrence after surgical resection in patients with pathological stage I non-small cell lung cancer. Thorac Cardiovasc Surg 2009;57:472-475.