Usefulness of low-dose spiral CT of the chest in regular follow-up of postoperative non-small cell lung cancer patients: Preliminary report

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Objectives: There is no consensus for the best postoperative follow-up in patients after complete resection of non-small cell lung cancer. Low-dose computed tomography of chest proves valuable in screening primary lung cancer and may be a useful tool in postoperative surveillance.

Methods: In part 1, 30 patients who underwent surgical resection of non-small cell lung cancer and were at the first (n = 14), second (n = 9), or fifth (n = 7) annual postoperative surveillance were selected chronologically and subjected to chest radiography, low-dose computed tomography, and standard-dose computed tomography to verify the diagnostic accuracy of low-dose computed tomography. In part 2, 43 patients were prospectively enrolled and followed up regularly after complete resection of non-small cell lung cancer. The follow-up protocol included physical examination, sputum cytology, serum carcinoembryonic antigen, chest radiography, and low-dose computed tomography every 3 months in the first 2 years postoperatively until tumor recurrence.

Results: In part 1, tumor recurrence was detected by standard-dose computed tomography in 7 cases. Low-dose computed tomography and chest radiography missed 1 and 5 of 7 cases, respectively. In part 2, tumor recurrence was found in 14 cases with 19 metastatic sites. Thirteen of the 14 (92.9%) cases were detected by scheduled visiting and 11 (78.6%) detected by low-dose computed tomography including the 7 without symptoms. Of the 19 recurrent sites found in 14 patients, 11 ones (57.9%) were detected by low-dose computed tomography.

Conclusions: Low-dose computed tomography may be of considerable value in early detection of tumor recurrence in postoperative non-small cell lung cancer patients. Further large prospective studies are needed to verify this issue.

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Lung cancer is the leading cause of cancer-related death in many countries, including Taiwan.¹ Despite recent progress in surgical and medical treatment, the 5-year survival rate of lung cancer patients has improved little. About 80% of lung cancers are non-small cell lung cancer (NSCLC), but only 20% of the patients can undergo curative surgical resection. Furthermore, almost half of the initially regarded as "completely" removed NSCLC will recur within 5 years.^{2,3} Regular postoperative follow-up is mandatory because of high rate of tumor recurrence and increased lifetime risk of developing second primary lung cancer in these patients. Nevertheless, the follow-up strategies appear to be divergent and no consensus has

ever been made.⁴ Several studies attempted to verify this issue but failed to show the survival benefit of regular postoperative follow-up.^{3,5-7} The reasons remain unknown. However, the limitation of retrospective studies reported^{3,5-7} and the inadequate intensity and/or detection methods used in follow-up strategies may explain it in part. Accordingly, prospective studies designed to evaluate the benefit of intensive follow-up protocol, including new detecting methods for postoperative NSCLC patients, are warranted. To our knowledge, there was only one prospective study designed to evaluate the feasibility of an intensive follow-up protocol.⁸

Because of the inherent good contrast and low radiation absorption of lungs, low-dose CT (LDCT) of chest was applied to lung cancer screening with promising results.⁹ Therefore, we designed a follow-up strategy using LDCT as the major surveillance tool for patients with NSCLC who underwent complete resection. In this study, the frequency of chest CT was double that used in a previous prospective study,⁸ but the same as that for chest radiography used in most previous retrospective studies.^{3,5-7} In this 2-part study, we liked to verify the diagnostic accuracy of LDCT at first and next to evaluate the clinical significance of LDCT in detecting tumor recurrence of postoperative NSCLC patients.

Patients and Methods

Patients

In part 1, patients who underwent complete resection of NSCLC in the past 5 years and were subjected to annual postoperative surveillance at our hospital were eligible for this study. The patient selection criteria were as follows: (1) the patients were regularly followed up at our hospital; (2) no evidence of tumor recurrence on last visit; (3) just at the time of the first, second, or fifth annual surveillance for tumor recurrence when this study was conducted. In the beginning of this study, the first 30 patients who met the criteria were enrolled and the surveillance procedures included physical examination, chest radiography (frontal and lateral projections), LDCT, and contrast-enhanced standard-dose CT (SDCT) of chest.

In part 2, the patients subjected to completely surgical resection of NSCLC from January 2000 were invited to participate in this study. The patient exclusion criteria were as follows: (1) premenopausal woman; (2) patients aged 18 years or younger; (3) patients with another malignancy in the past 5 years; (4) patients with reluctance to join the study; or (5) patients having participated in other follow-up protocols. The preoperative staging work-up was done as usual at our institute and included chest CT, bronchoscopy, and whole body bone scan. Abdominal sonography, brain CT, and mediastinoscopy would be done when clinically indicated or the disease appeared to be locally advanced. Patients included in part 2 of the study were informed to visit outpatient clinics every 3 months in the first 2 years and every 6 months for the next 3 years. Physical examination, sputum cytology, serum carcinoembryonic antigen, chest radiography, and LDCT of chest were performed at each scheduled visit.

The Institutional Review Board of our hospital approved this study and informed consents were obtained from all patients.

Spiral CT of Chest

The spiral CT scan was performed with Somatom Plus 4 (Siemens, Forchheim, Germany). After contrast medium injection, SDCT was obtained from apex to bilateral adrenal glands at 120 kVp, 240 mAs, with 8-mm collimation and table speed of 10 mm/s. We used the phantom as model and reduced the tube current of spiral CT from 240 mAs gradually. Finally, we found 43 mAs was the lowest current that preserved the acceptable image quality. LDCT of chest was then designed to obtain images at 140 kVp, 43 mAs, with 10-mm collimation and table speed of 20 mm/s. The entire lungs were scanned without contrast medium. Both CT scans were performed in a single breath-hold at the end of inspiration and the films of lung and mediastinum windows were provided to 2 senior chest radiologists for interpretation. To verify the diagnostic accuracy of LDCT, the images of LDCT in part 1 of the study were read and discussed by 2 chest radiologists and the consensus became final. The images of SDCT in part 1 of the study and LDCT in part 2 of the study were interpreted independently.

The spiral CT findings were classified into three categories. Pulmonary findings were defined as “negative,” “equivocal,” or “definite” for newly developed pulmonary lesions. The mediastinal lymph nodes were defined as “negative,” “positive, insignificant,” or “positive, significant.” The presence of at least one node larger than 1 cm in its short axis or the size enlarged as compared with previous CT was considered significant. The changes of pleura were recorded as “negative or mild pleural thickening,” “pleural effusion,” or “suspected metastasis.” The final conclusion of each CT examination was categorized as “stable,” “suspicious,” or “suggested recurrence.” Chest radiographs were read in a blind fashion and categorized as “stable,” “suspicious,” or “suggested recurrence.”

Recurrence

Patients suspected to have tumor recurrence were admitted and subjected to brain CT, abdominal sonography, fiberoptic bronchoscopy, and whole body bone scans. Other diagnostic procedures were done as indicated. Tissue or fluid specimens were obtained for cytopathological diagnosis whenever possible. It was categorized “pathological recurrence” if cytopathological examination of the specimens proved malignancy with same histopathologic type as the primary tumor. A diagnosis of “clinical recurrence” was made when clinical features and results of examinations were highly suggestive of multiple metastases but tissue diagnosis was risky or unnecessary.

Statistical Analysis

The agreement of the findings between LDCT and SDCT was analyzed by Kappa statistics. A *P* value < .05 was considered significant. Statistical analysis was carried out with SPSS software, version 10 (SPSS Inc, Chicago, Ill).

Results

Part 1

In total, 30 cases were included and all underwent chest radiography, LDCT, and SDCT. The patients at the first, second, and fifth annual postoperative surveillance were 14, 9, and 7, respectively. The characteristics of the patients are

TABLE 1. General characteristics of patients in part 1 of this study

	No. of patients (%)		
	Recurrence	Stable disease	Total
Number	7 (23.3)	23 (76.7)	30
Age (y)			
Median/range	66/43-82	69/46-82	69/43-82
Sex			
Male/female	4/3	20/3	24/6
Postoperative years			
1	4 (28.6)	10 (71.4)	14
2	3 (33.3)	6 (66.6)	9
5		7 (100)	7
Histology			
Adenocarcinoma	5 (23.8)	16 (76.2)	21
Squamous cell carcinoma	2 (22.2)	7 (77.8)	9
Pathological staging			
T1 N0 M0	2 (28.6)	5 (71.4)	7
T2 N0 M0	4 (26.7)	11 (73.3)	15
T2 N1 M0	1 (50)	1 (50)	2
T3 N0 M0		1 (100)	1
T1 N2 M0		1 (100)	1
T2 N2 M0		4 (100)	4

summarized in Table 1. SDCT detected 7 recurrent cases, 4 at the first and 3 at the second annual surveillances. LDCT missed only 1 patient who had diffuse minute metastases in both lungs with all lesions <1 mm in diameter. The agreement of interpretation between LDCT and SDCT were good (Table 2). On the contrary, chest radiographs detected only 2 of the 7 with recurrent disease. One was found to have solitary pulmonary nodule and another had pleural effusion, nevertheless, chest radiographs failed to detect concurrent pulmonary metastatic lesions in the later case. Compared with SDCT, the recurrent case-detection rates of LDCT and chest radiography were 85.7% and 28.6%, respectively.

Solitary pulmonary nodule was found in 2 of 7 patients with recurrent disease. One of the 2 patients was a candidate for second curative operation. After wedge resection of the tumor and subsequent adjuvant chemotherapy with paclitaxel and cisplatin for 6 courses, the patient was included in part 2 of the study.

Part 2

Between January 2000 and October 2000, 100 patients underwent surgical resection of proved NSCLC or of solitary pulmonary lesion suspected to be malignant at our hospital. All were visited preoperatively and invited to participate in this study if their lung lesions were proved to be NSCLC and removed completely. The lesions were benign diseases in 27 cases, NSCLC in 68, metastatic carcinoma in 3, and SCLC and atypical carcinoid tumor in 1 each postoperatively. Twenty-five of 68 patients with NSCLC were excluded based on the following reasons:

TABLE 2. Agreement on analyses between low-dose CT and standard-dose CT

	Kappa value	95% CI	P value
Pulmonary lesions	0.430	0.165-0.695	.001
Mediastinal lymph node status	0.427	0.174-0.680	.003
Pleural lesions	0.737	0.452-1.016	<.001
Overall conclusion	0.902	0.714-1.090	<.001

CI, Confidence interval.

unresectable disease in 12 cases, death before the first follow-up visit in 3, and inability to participate in this study in 10. The remaining 43 patients were enrolled and followed up with at least one time of LDCT. The characteristics of the patients are summarized in Table 3. The median follow-up time was 15.5 months (3.1-23.5 months). Until January 2002, 5 patients quit and the follow-up rate was 88.4%.

From January 2000 to January 2002, 14 of 38 patients were found to have recurrent disease. Thirteen of the 14 (92.9%) patients were detected by the surveillance protocol. The remaining 1 was detected at the unscheduled visit presenting with generalized bone pain and proved to have multiple bony metastases by whole body bone scans. Of the 13 patients with recurrent disease detected by surveillance protocol, 7 were asymptomatic at tumor recurrence. Tumor recurrence was detected in 11 of 14 patients by LDCT giving a recurrent case-detection rate of 78.6%. All patients with evidence or high suspicion of recurrent disease were admitted to establish a cytopathological diagnosis and research for other metastatic sites (Table 4). One patient who had solitary pulmonary metastasis was subjected to curative resection and no tumor recurrence was found in the following 8 months.

According to the study design, 180 series of LDCT should be performed on a fixed schedule. Sixteen series were carried out using SDCT protocol and another 1 was missed due to personal reason. Then, a total of 163 series of LDCT were obtained and analyzed. Among the 19 metastatic sites found in 14 cases with recurrent disease, LDCT could detect 11 and provided a recurrent site-detection rate of 57.9% (11/19). Consequently, every 15 LDCT could detect 1 recurrent site. In contrast, only 3 patients were suspected to have recurrent diseases by chest radiography taken simultaneously.

Discussion

The major rationale of close postoperative follow-up is based on the findings that the occurrence of second primary lung cancer is not uncommon and some of the patients with recurrent disease detected early enough are amenable to further surgical resection with curative intent.¹¹ The risk of postoperative NSCLC patients to develop second primary lung cancer is high and substantial, and estimated about

1%-2% per year.¹² Accordingly, the patients appear to be the ones with the highest risk to develop second primary lung cancer. Furthermore, once recurrent disease occurs, salvage management is theoretically more effective if tumor burden is small.¹³ Consequently, it is plausible that early detection of tumor recurrence may be of significant merit. Nevertheless, previous studies revealed no significant difference in the survival time of NSCLC patients who underwent either intensive follow-up or less frequent surveillance postoperatively.^{3,5-7} The causes remain unknown. There are two possible explanations. First, most related studies were retrospective and both the surveillance tests and follow-up frequency varied widely. Accordingly, the results derived from these studies are limited. Second, although the experience of lung cancer screening by chest radiography indicated that early detection did not necessarily translate into survival benefit,¹⁴ a more sensitive screening tool like LDCT may detect lung cancer in an earlier stage compared with chest radiography and provide resultant survival benefit. The promising results of LDCT in primary lung cancer screening did support this rationale.⁹ In addition, there are other reasons to support the necessity of regular postoperative follow-up, including the attempts to keep a good patient-doctor relationship, deal with medicolegal liability, reduce patient anxiety, and improve surgeons' technique by feedback.

Although the definition of local, regional, and distant recurrence of postoperative lung cancer reported in previous studies remains inconsistent, most studies indicated that about one third of first recurrent sites were locoregional and the rests were distant metastases.^{2,3,5,15,16} The major sites of distant metastases were brain, bone, and contralateral lung and each one accounted for about one third of all distant metastases. Consequently, it is expected that about half of the initial recurrent sites might be located in the thorax. To our knowledge, there was only one published report regarding to prospective follow-up of postoperative NSCLC patients.⁸ Their follow-up strategy included physical examination and chest radiography 1 month after operation and every 3 months thereafter, and chest CT and fiberoptic bronchoscopy every 6 months for the first 3 years. For the next 4 years, chest radiography was performed every 6 months, and chest CT and fiberoptic bronchoscopy once a year. The results⁸ showed that the survival time was significantly longer in patients without symptoms at tumor recurrence than in those with. These did support the fact that intensive follow-up may be of considerable value in early detection of asymptomatic recurrent disease in patients after complete resection of NSCLC and improve the survival of the patients when the recurrent disease is amenable to curative intent. In addition, the authors⁸ observed that asymptomatic recurrent disease was more likely located in the thorax and readily detected by chest CT and fiberoptic

TABLE 3. General characteristics of patients in part 2 of this study

Characteristics	Enrollment (n = 43)	Recurrence (n = 14)*
Age (y)		
Median/range	71/51-80	70/62-80
Sex		
Male/female	39/4	12/2
Histology		
Adenocarcinoma	26	9 (34.6)
Squamous cell carcinoma	10	2 (20)
Adenosquamous cell carcinoma	3	2 (66.7)
Large cell carcinoma	4	1 (25)
Type of operation		
Pneumonectomy	1	1 (100)
Bilobectomy	2	1 (50)
Lobectomy	34	12 (27.9)
Segmentectomy/wedge resection	6	0 (0)
Pathological staging†		
IA	6	0 (0)
IB	20	6 (30)
IIA	0	0 (0)
IIB	4	1 (25)
IIIA	9	6 (66.7)
IIIB	2‡	1 (50)
IV	1§	0 (0)
Recurrent lung cancer	1	0 (0)

*The figures indicate the ratio of recurrent cases over the respective patient numbers in each subgroup. Values in parentheses are percentages.

†TNM classification and staging was based on the revised international system for staging lung cancer in 1997.¹⁰

‡These 2 patients were found to have satellite lesions in the same lobes during operation. All these tumors were resected completely.

§This patient had a main tumor in LLL. A metastatic nodule in LUL was found during operation. Both of the lesions were removed completely.

bronchoscopy. However, the conclusions drawn from this study⁸ should be carefully interpreted because of their biased patient population. About 60% of the patients underwent pneumonectomy. The skewed characteristics of the patients might contribute to inordinately high rate of locoregional recurrence and overestimate the importance of fiberoptic bronchoscopy included in the follow-up strategy. Despite these flaws, the results seemed encouraging but the power was not. It was estimated that 2973 patients should be included in study to provide a 5% survival advantage with their follow-up strategy.⁸ We speculate that chest CT can be a most useful tool in surveillance of recurrent disease in NSCLC patients after surgical resection if the frequency of follow-up protocol is adequate.

LDCT of chest has more advantages than does conventional CT in the surveillance of tumor recurrence. First, the radiation dose is acceptable for repeated examination. The radiation dose of LDCT can be reduced to about 10%-20% of SDCT without significant loss of information.¹⁷ Accordingly, the radiation dose of 4 LDCT is less than that of 1

TABLE 4. Characteristics of individual recurrent patients

No.	Sex	Age	Diagnosis	Initial stage	Symptom	Detection method	Disease-free (mos)	Initial metastatic foci
1	M	63	Adenocarcinoma	T2 N0 M0	No	LDCT	3	Lung
2	M	67	Adenocarcinoma	T2 N2 M0	No	LDCT	6	Lung
3	M	80	Large cell carcinoma	T4 N0 M0	No	LDCT	6	Mediastinal lymph nodes
4	M	76	Adenocarcinoma	T2 N0 M0	Dyspnea	LDCT	6	Pleura, stump, skin
5	M	71	Adenocarcinoma	T2 N2 M0	No	LDCT	6	Pleura
6	M	69	Adenosquamous cell carcinoma	T2 N0 M0	No	LDCT	9	Pleura
7	M	66	Squamous cell carcinoma	T2 N2 M0	Cough	LDCT	9	Pleura
8	M	77	Squamous cell carcinoma	T3 N0 M0	Chest pain	LDCT	9	Bone
9	M	79	Adenocarcinoma	T2 N2 M0	Dyspnea	LDCT	12	Pleura, bone, brain
10	F	67	Adenosquamous cell carcinoma	T2 N2 M0	No	LDCT	12	Lung
11	M	63	Adenocarcinoma	T2 N0 M0	No	LDCT	15	Lung (solitary nodule)
12*	M	67	Adenocarcinoma	T2 N0 M0	No	US	6	Adrenal, liver
13†	M	79	Adenocarcinoma	T2 N2 M0	Back pain	PET	9	Bone
14	F	79	Adenocarcinoma	T2 N0 M0	Bone pain	WBBS	5.3	Bone

US, Ultrasonography; PET, positron emission tomography; WBBS, whole-body bone scan.

*Recurrence was initially suspected by elevated serum carcinoembryonic antigen (CEA) level. Abdominal ultrasonography was performed and liver and adrenal metastases were found. Pathological diagnosis was obtained by liver biopsy.

†Recurrence was suspected due to progressive elevation of serum CEA level and low back pain. Although whole-body bone scan was negative, PET scan revealed a hot spot over lumbar spine, location of which was compatible with clinical symptom.

SDCT in a year. Second, LDCT can be completed in a single breath-hold without contrast medium injection. Without the risk of anaphylaxis and acute renal failure, LDCT can be easily and safely performed at outpatient clinics. In addition, we found that it was not difficult to identify enlarged mediastinal lymph nodes on noncontrasted LDCT if preoperative and serial postoperative CT images were available for comparison.

In this 2-year pilot study, we regularly followed 38 postoperative NSCLC patients with LDCT every 3 months and found 14 cases with tumor recurrence. The recurrent pattern was as follows: locoregional in 5 (35.7%), distant in 7 (50%), and both in 2 (14.3%) (Table 4). We searched for any possible metastatic foci in every patient with newly diagnosed recurrent disease by brain CT, abdominal sonography, fiberoptic bronchoscopy, and whole body bone scans. Other examinations were performed based on clinical features. We found a total of 19 first-metastatic sites in 14 patients with recurrent disease, including pleura in 5, lungs in 4, bones in 4, and mediastinal lymph node, stump, brain, liver, adrenal gland and skin in 1 each (Table 4). As a whole, LDCT alone detected 11 of the 14 cases (78.6%) with recurrent disease and 11 of the 19 first-metastatic sites (57.9%). Both figures were far beyond our expectation at the beginning of this study. The reasons were multifactorial. First, the median follow-up time was 15 months, not long enough, and the results might just depict the "early" recurrent pattern. Second, the recurrent pattern may be somewhat distorted by the surveillance strategies. We had done our best to search for other occult metastatic foci, however, we could still miss the asymptomatic distant metastatic foci due to limitation of the used screening modalities. Third, the

patient number was limited and the recurrent pattern may be biased. Of note, pleural metastasis presenting as either malignant pleural effusion or pleural nodules occurred in 5 of the 14 patients (35.7%) with recurrent disease. The rate of tumor recurrence located in pleura was unexpectedly high and has never been reported before. It is uncertain that tumor recurrence on pleura is an important but undiscovered clinical finding or just a biased result. Further studies are needed to verify this issue.

In our study design, LDCT was substituted for chest radiography due to the superiority of CT in detecting lesions in the stump, mediastinal lymph nodes, and pulmonary parenchyma. Unexpectedly, chest CT proved valuable in detecting the lesions on chest wall and pleura. Ipsilateral pleural effusion was not an uncommon finding in NSCLC patients after complete resection. However, it was absorbed within 3 to 6 months in most cases. The new-onset or increasing amount of ipsilateral pleural effusion was highly suggestive of tumor recurrence on pleura based on this study. It was readily detected by chest CT but not by chest radiography attributed to the influence of postoperative pleural change. In addition, the presence of pleural lesions provided a safe and easy access for tissue diagnosis of tumor recurrence. In fact, cytopathologic diagnosis was made in 8 of 14 patients with recurrent disease in this study and 5 of the 8 patients was relied on the pleura.

Solitary pulmonary metastasis was found in 3 cases, 2 in part 1 and 1 in part 2 of this study. The lesion was <1 cm in diameter in 2 of the 3 cases and both cases were missed by chest radiography. They were clinically asymptomatic at tumor recurrence and subjected to curative management. One underwent wedge resection and another lobectomy.

Adjuvant chemotherapy was given in both patients after operation and no evidence of tumor recurrence was found at the 22- and 8-month follow-up, respectively.

In summary, our results indicated that thorax was the most common site of tumor recurrence in NSCLC patients after complete resection and readily detected by chest CT. In terms of detecting recurrent disease in such patients, LDCT of chest was comparable to SDCT but superior to chest radiography. Postoperative follow-up of NSCLC patients with LDCT every 3 months in the first 2 years may be of considerable value in early detection of recurrent disease. Further studies with larger population and longer studied period are needed to verify this issue and the cost-benefit.

References

1. Health and vital statistics, Republic of China 1999. Department of Health, the Executive Yuan, Republic of China; 2000.
2. Immerman SC, Vanecko RM, Fry WA, Head LR, Shields TW. Site of recurrence in patients with stage I and II carcinoma of the lung resected for cure. *Ann Thorac Surg.* 1981;32:23-7.
3. Vigro KS, McKirgan LW, Caputo MCA, Mahurin DM, Chao LC, Caputo NA, et al. Post-treatment management options for patients with lung cancer. *Ann Surg.* 1995;222:700-10.
4. Naunheim KS, Virgo KS, Coplin MA, Johnson FE. Clinical surveillance testing after lung cancer surgery. *Ann Thorac Surg.* 1995;60:1612-16.
5. Walsh GL, O'Conner M, Willis KM, Milas M, Wong RS, Nesbitt JC, et al. Is follow-up of lung cancer patients after resection medically indicated and cost-effective? *Ann Thorac Surg.* 1995;60:1563-72.
6. Virgo KS, Naunheim KS, McKirgan LW, Kissing ME, Lin JC, Johnson FE. Cost of patient follow-up after potentially curative lung cancer treatment. *J Thorac Cardiovasc Surg.* 1996;112:356-63.
7. Younes RN, Gross JL, Deheinzelin D. Follow-up in lung cancer—how often and for what purpose? *Chest.* 1999;115:1494-9.
8. Westeel V, Choma D, Clement F, Woronoff-Lemsi MC, Pugin JF, Dubiez A, et al. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. *Ann Thorac Surg.* 2000;70:1185-90.
9. Van Klaveren RJ, Habbema JDF, Pedersen JH, De Koning HJ, Oudkerk M, Hoogsteden HC. Lung cancer screening by low-dose spiral computed tomography. *Eur Respir J.* 2001;18:857-66.
10. Mountain CF. Revisions in the international system for staging lung cancer. *Chest.* 1997;111:1710-7.
11. Martini N, Ginsberg RJ. Postresection follow-up. In: Pearson FG, Deslauriers J, Ginsberg RJ, Hiebert CA, McKneally MF, Urschel HC, editors. *Thoracic surgery*. 1st ed. New York: Churchill Livingstone, 1995. p. 759-63.
12. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst.* 1998;90:1335-45.
13. Goldie D, Coldman A. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep.* 1979;63:1727-33.
14. Eddy DM. Screening for lung cancer. *Ann Intern Med.* 1989;111:232-7.
15. Martini N, Bains MS, Burt ME, Zakowski MF, McCormack P, Rusch VW, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg.* 1995;109:120-9.
16. Baldini EH, DeCamp MM, Katz MS, Berman SM, Swanson SJ, Mentzer SJ, et al. Patterns of recurrence and outcome for patients with clinical stage II non-small-cell lung cancer. *Am J Clin Oncol.* 1999;22:8-14.
17. Diederich S, Lenzen H, Windmann R, Puskas Z, Yelbuz TM, Henneken S et al. Pulmonary nodules: experimental and clinical studies at low-dose CT. *Radiology.* 1999;213:289-98.