T2 tumors larger than five centimeters in diameter can be upgraded to T3 in non–small cell lung cancer

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Objective: Among the TNM criteria, tumor size is a well-assessed factor in the prognosis of small tumors. A 3-cm cutoff point separates T1 from T2 tumors, whereas a size larger than 3 cm is not ascribed any prognostic value. Instead, N2 is considered to be the worst prognostic factor for intrathoracic extended disease.

Method: The prognosis of 545 patients with non–small cell lung cancer larger than 3 cm in diameter (T2, T3, and T4) was studied. These tumors were completely resected by pneumonectomy (n = 126) or lobectomy (n = 411) or were partially resected (n = 8). Survivals were compared according to the following factors: tumor size (3.1-5 cm, 5.1-7 cm, >7 cm), nodal status, age, sex, histologic type, degree of pleural involvement, operative procedure, stage, and T factor. For the multivariate analysis, the Cox proportional hazard model was used with the same variables.

Results: The univariate analysis showed that age, sex, degree of pleural involvement, operative procedure, tumor size, nodal status, and stage were all significant prognostic factors. Further comparison of survival between different tumor sizes (≤5 cm vs >5 cm) in the same nodal category demonstrated a significantly poor prognosis for larger tumors in N0 (P = .00374) and N2+N3 (P = .0157), but not in N1 (P = .3452). T2 tumors (n = 349) were divided, according to size, into T2a (n = 238) and T2b (n = 111), and survival was compared with those in T3 and T4. The 5-year survivals were 51.3%, 35.1%, 47.8%, and 25.3%, respectively. The difference between T2a and T2b was statistically significant (log-rank P = .0170, Breslow P = .0055).

Conclusions: A tumor size of more than 5 cm in diameter was indicative of a poor prognosis in non–small cell lung cancer, because patients with T2b tumors had a significantly different survival from that of patients with T2a tumors, and the survival curve was located between those for patients with T3 and T4 tumors. Consequently, T2b might be upgraded to at least T3.

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Although many reports on the prognostic factors of non–small cell lung cancer (NSCLC) have been published,[1-6] and even though a large tumor size has been thought to be an important factor in a poor prognosis, as shown in a recent review,[7] in the TNM classification provided by the International Union Against Cancer, tumor size has prognostic value only for small tumors. According to the latest revision of the International System for Staging Lung Cancer in 1997,[8] a cutoff point of 3 cm divides patients with T1 N0 M0, stage IA disease, who have the best expectation for survival, from patients with T2 N0 M0, stage IB disease, who have a significantly lower probability of survival.

TABLE 1. Patient characteristics and 5-year survivals

Variables	No. of patients (%)	Five-year survival (%)
Sex		
Male	440 (80.7)	42.1
Female	105 (19.3)	48.6
Age (y)		
<50	57 (10.5)	47.4
50-59	123 (22.6)	56.1
60-69	218 (40.0)	42.2
>70	147 (27.0)	32.7
Histologic type		
Adenocarcinoma	264 (48.4)	40.9
Squamous carcinoma	215 (39.4)	48.8
Large cell carcinoma	47 (8.6)	40.4
Adenosquamous carcinoma	19 (3.5)	21.1
Operative procedure		
Pneumonectomy	126 (23.1)	31.8
Lobectomy	411 (75.4)	47.0
Partial resection	8 (1.5)	37.5
P factor		
P0	209 (38.3)	48.3
P1	125 (22.9)	46.4
P2	39 (7.2)	30.8
P3	172 (31.6)	37.8
Stage		
I	173 (31.7)	60.1
II	134 (24.6)	49.3
III	238 (43.7)	27.7
T factor		
T2	349 (64)	46.1
T2a (<5 cm)	238 (43.7)	51.3
T2b (>5 cm)	111 (20.4)	35.1
T3	113 (20.7)	47.8
T4	83 (15.2)	25.3
Nodal status		
N0	236 (43.3)	58.5
N1	143 (26.2)	42.0
N2+N3	166 (30.5)	22.9
Tumor size		
Group A (<5 cm)	342 (62.8)	48.0
Group B+C (>5 cm)	203 (37.2)	35.5

In this context, many reports have been published on the poor survival for larger NSCLCs and better survival for smaller tumors. Several important contributions appeared in the 1960s and 1970s, when many studies considered size as an autonomous factor in the prognosis: Steele[9] in 1964, Wellons and associates[10] in 1968, Jackman and colleagues[11] in 1969, Yashar and Yashar[12] in 1975, and Soorae and Abbey Smith[13] in 1977 emphasized the very short survival in patients with bulky tumors. The reports in the late 1970s by Soorae and Abbey Smith[13] and in 1984 by Ogata and Naruke[14] described the strong correlation between tumor diameter and lymph node involvement, with the frequency of N2 and N3 increasing in conjunction with an increase in tumor size. These reports raised the possibility that survival, even in patients affected by bulky tumor, basically depended on nodal involvement, because N0 and N1 tumors had a clearly better prognosis than N2-N3 tumors.

However, surgical experience shows an adverse prognosis even for larger N0-N1 tumors that are completely resected. This suggests that tumor size directly affects survival independent of lymph node involvement.

The aim of this study was to determine whether tumor size can be considered an independent factor that affects survival in NSCLC. We analyzed 545 patients with tumors of more than 3 cm in maximum diameter and their survival with regard to size, nodal status, age, sex, pleural involvement, operative procedure, histologic type, stage, and T factor.

Patients and Methods

Patients

From January 1985 to December 1994, a total of 1543 pulmonary resections were performed at the National Cancer Center Hospital, Tokyo, Japan. Of these, 545 patients (35.3%) who had NSCLC more than 3 cm in maximum diameter were selected and included in this retrospective study. Table 1 shows the patients' characteristics with 5-year survivals.

The analysis included patients with T2, T3, and T4 tumors who underwent a complete resection by at least a lobectomy. Also included were 8 patients (1.5%) who underwent a partial resection (5 of these were >70 years old). As for the mode of lymph node dissection, a systematic hilar/mediastinal dissection was performed in 455 patients (83.4%) and hilar dissection was performed in 65 (11.9%), whereas 25 patients (4.6%) had no lymphadenectomy. Initially, all of the patients were divided into 3 groups according to the tumor diameter, regardless of tumor invasion of the surrounding organs: group A (342 patients, 62.8%), with tumor from 3.1 to 5 cm; group B (146 patients, 26.8%), with tumor from 5.1 to 7 cm; and group C (57 patients, 10.5%), with tumors larger than 7 cm. As a consequence of the results of the initial univariate analysis, they were divided into only 2 groups: group A, with tumors ranging from 3.1 to 5 cm (342 patients, 62.8%), and group B+C (203 patients, 37.2%), with tumors larger than 5 cm. Because of the small number of N3 tumors (18 patients, 3.3%), N2 and N3 were grouped together (166 patients, with a cumulative rate of 30.5%). The degree of pleural involvement was described in terms of a "P factor," according to the following Japanese definition: P0, no invasion of the visceral pleura; P1, suspected invasion of, but not through, the visceral pleura; P2, invasion through the visceral pleura; and P3, invasion of the chest wall, diaphragm, mediastinal structures, or adjacent lobes. T, N, M, and the stage of the disease were considered according to the 1987 TNM classification of the International Union Against Cancer.[15] Tumor histologic type was categorized according to the World Health Organization classification[16] as adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, or large cell carcinoma.

Excluded from the analysis were patients with tumors smaller than 3 cm (T1), patients with distant metastasis (stage IV), and patients in whom pathologic examination disclosed infiltration of

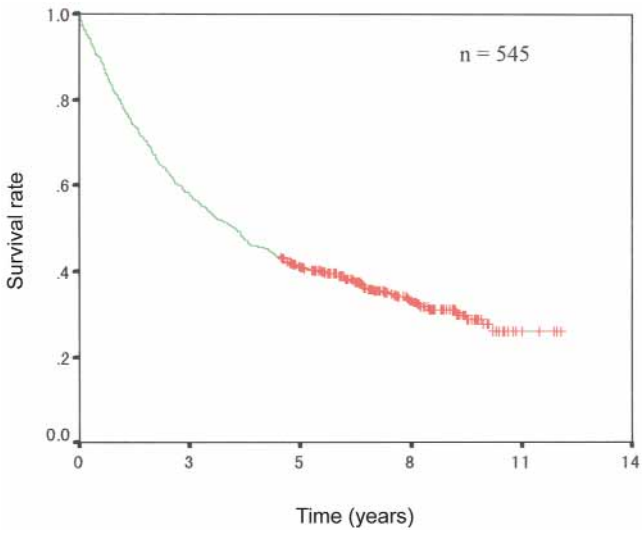

Figure 1. Survival curve for 545 patients with tumors larger than 3 cm. The 5-year survival is 43%.

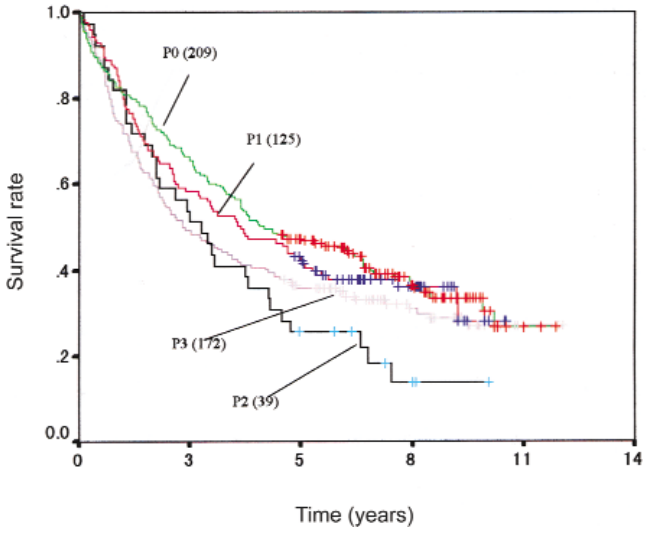

Figure 2. Survival according to the degree of pleural involvement. The survival curves show a significantly worse prognosis for tumor invading through the visceral pleura *(P2)* and the parietal pleura *(P3).*

the bronchial resection margin, low-grade malignant tumors (carcinoids, adenoid cystic carcinomas, mucoepidermoid carcinomas), sarcomas, carcinosarcomas, and bronchioloalveolar carcinomas. Double primary tumors and Nx conditions were also excluded.

Statistical Analysis[17,18]

The following 9 prognostic factors, which have been reported to influence survival, were analyzed by univariate and multivariate analyses: age, sex, histologic type, operative procedure, degree of pleural involvement, tumor size, lymph node involvement, T factor, and stage. The Kaplan–Meier method was used to estimate survival and its 95% confidence interval. The univariate statistical comparison was made by the log-rank and Breslow tests; the day of the operation was considered the beginning day for the analysis, and all deaths, including 30-day postoperative deaths, were included. For the multivariate analysis, the Cox proportional hazard model[19] was used to identify variables that were significantly associated with survival. SPSS version 10 statistical software (SPSS, Inc, Chicago, Ill) was used for the analysis.

Results

Univariate Analysis

The overall survival curve for all 545 patients is shown in Figure 1, and the 5-year survival was 43%. On the basis of the univariate analysis, a significantly worse prognosis was found for patients more than 60 years old (log-rank P = .0000; Breslow P = .0001), men (Breslow P = .0105), tumor invasion through the visceral pleura and extending to the parietal pleura (P2 and P3) compared with P0 (log-rank P = .0442; Breslow P = .0126; Figure 2), pneumonectomy (log-rank P = .0015; Breslow P = .0002), and an advanced stage of disease (log-rank and Breslow P = .0000). There was no evidence of statistically significant differences among the histologic types.

Prognosis by Tumor Size

Initially, a statistically significant difference was found between groups A and B, with 5-year survivals of 48% and 37%, respectively (log-rank P = .0377; Breslow P = .0085), and between groups A and C, with 5-year survivals of 48% and 31.6% (log-rank P = .0039; Breslow P = .0002), but not between groups B and C (log-rank P = .1929; Breslow P = .0928) (Figure 3).

Prognosis by Nodal Status

The survival curves for patients with N0, N1, and N2+N3 disease showed a statistically significant difference among the 3 levels of nodal involvement, with 5-year survivals of 58.5%, 42%, and 22.9%, respectively (log-rank and Breslow P = .0000).

Prognosis by Tumor Size in the Same Nodal Category

Different tumor sizes (group A vs group B+C) were compared within the same nodal category: N0, N1, and N2+N3. A statistically significant difference was found by the Breslow test in N0 (P = .0374; Figure 4) and in N2+N3 (P = .0157; Figure 5), whereas no statistically significant difference was found in N1.

Prognosis by T Factor

The 349 patients with T2 tumors were divided into 2 groups: T2a, with tumors ranging from 3.1 to 5 cm, and T2b, with tumors larger than 5 cm. The 5-year survivals for T2a, T2b, T3, and T4 were 51.3%, 35.1%, 47.8%, and 25.3%, respectively (Figure 6). Statistically significant differences were

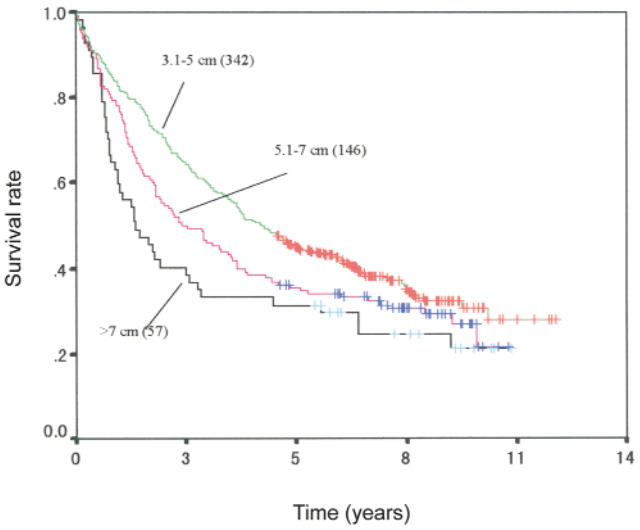

Figure 3. Survival curves according to tumor size. The 5-year survivals for group A (3.1-5 cm), group B (5.1-7 cm), and group C (>7 cm) are 48%, 37%, and 31.6%, respectively. A statistically significant difference was found between groups A and B (log-rank *P* = .0377, Breslow *P* = .0085) and A and C (log-rank *P* = .0039, Breslow *P* = .0002), but not between B and C (log-rank *P* = .1929, Breslow *P* = .0928).

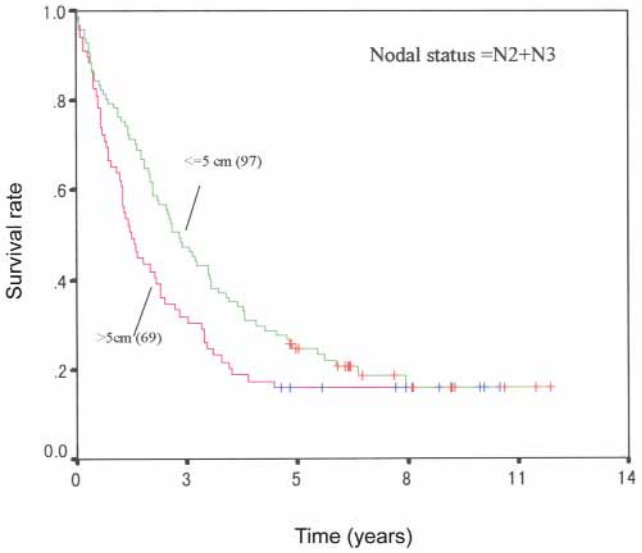

Figure 5. Stratified analysis for patients with N2+N3 disease (n = 166). The 5-year survivals for tumors of 3.1 to 5 cm and more than 5 cm are 27.8% and 15.9%, respectively. A statistically significant difference was found by the Breslow test (*P* = .0157).

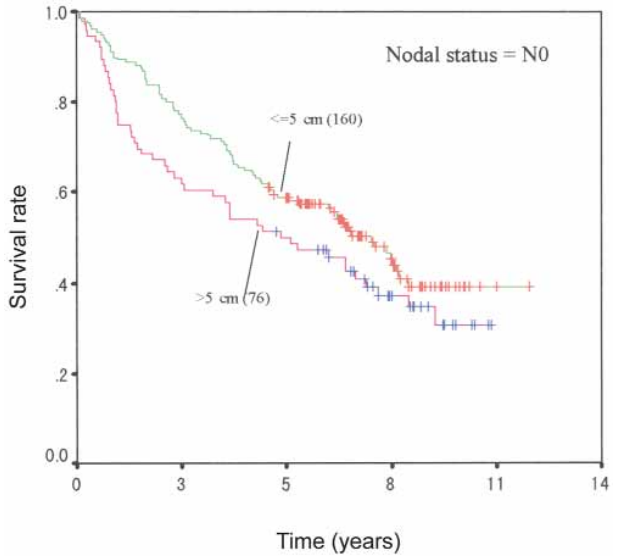

Figure 4. Stratified analysis for patients with N0 disease (n = 236). The 5-year survivals for tumors of 3.1 to 5 cm and more than 5 cm are 61.9% and 51.3%, respectively. A statistically significant difference was found by the Breslow test (*P* = .0374).

found between T2a and T2b (log-rank $P = .0170$; Breslow $P = .0055$), between T2a and T4 (log-rank $P = .0000$; Breslow $P = .0000$), and between T3 and T4 (log-rank $P = .0037$; Breslow $P = .0042$). No difference was found between T2a and T3 (log-rank $P = .5316$; Breslow $P = .3257$), T3 and T2b (log-rank $P = .1645$; Breslow $P = .1975$), or T2b and T4 (log-rank $P = .0964$; Breslow $P = .0786$).

Multivariate Analysis

Of the variables that were entered in the multivariate analysis (Table 2), sex, age, size, nodal status, histologic type, and operative procedure were found to be significantly related to survival.

Discussion

In the TNM Classification for Lung Cancer, tumor size is considered to affect the prognosis only for small tumors (stage I, <3 cm), whereas larger sizes are not thought to have a direct influence on survival, as reported in a recent review by Mountain.[20] In the advanced stage of the disease, invasion of visceral pleura, associated atelectasis, obstructive pneumonia, and extension of tumor within the lung as well as to adjacent structures and organs all represent local progression and are responsible for a poor prognosis, rather than tumor diameter. Therefore, tumor size has not been considered to reflect locally advanced T status. On the other hand, a strong correlation has been shown between tumor size and lymph node involvement,[13,14,21] with a higher percentage of N2 in larger tumors and a proportionally worse prognosis for patients with N2 tumors.[22-25]

Our results show that tumor size directly affects survival, with a significantly worse prognosis for tumors larger than 5 cm than for those ranging from 3 to 5 cm. We also found a significantly poorer survival for patients with T2b tumors,

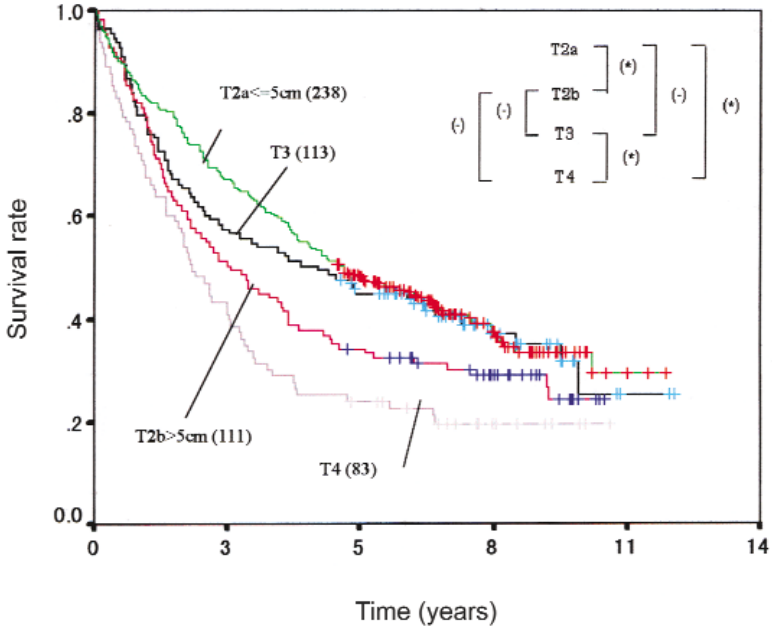

Figure 6. Survival curves according to T factor. The 5-year survivals for T2a (3.1-5 cm), T2b (>5 cm), T3, and T4 are 51.3%, 35.1%, 47.8%, and 25.3%, respectively. A statistically significant difference was found between T2a and T2b (log-rank *P* = .0170, Breslow *P* = .0055), between T2a and T4 (log-rank and Breslow *P* = .0000), and between T3 and T4 (log-rank *P* = .0037, Breslow *P* = .0042). No difference was found between T2a and T3, T3 and T2b, or T2b and T4. *Statistically significant; —, not statistically significant.

TABLE 2. Multivariate analysis (Cox proportional hazard model)

Variables	No. of patients (%)	Five-year survival	*P* value	Risk
Sex				
Male	440 (80.7)	42.1		
Female	105 (19.3)	48.6	.013	0.699
Age (y)			.000	
<50	57 (10.5)	47.4		
50-59	123 (22.6)	56.1	.486	0.859
60-69	218 (40.0)	42.2	.066	1.435
>70	147 (27.0)	32.7	.000	2.376
Size				
3.1-5 cm	342 (62.8)	48.0		
>5 cm	203 (37.2)	35.5	.002	1.430
Nodal status			.000	
N0	236 (43.3)	58.5		
N1	143 (26.2)	42.0	.001	1.608
N2+N3	166 (30.5)	22.9	.000	2.399
Histologic type			.000	
Adenocarcinoma	264 (48.4)	40.9		
Squamous carcinoma	215 (39.4)	48.8	.000	0.569
Adenosquamous carcinoma	19 (3.5)	21.1	.971	0.990
Large cell carcinoma	47 (8.6)	40.4	.293	0.805
Operative procedure			.001	
Pneumonectomy	126 (23.1)	31.8		
Lobectomy	411 (75.4)	47.0	.000	0.612
Partial resection	8 (1.5)	37.5	.768	1.127

closer to that for patients with T4 tumors, with 5-year survivals of 35.1% and 25.3%, respectively. These results suggest that tumor size may be considered an independent factor in determining the prognosis, that tumor size is distinct from other features characterizing T2, T3, and T4 status, and that T2 tumors larger than 5 cm should be upgraded to at least T3. Similar results were reported by Watanabe and associates,[26] who found, in patients with T2 N0 M0 disease, 5-year survivals of 61.0% and 46.3% for tumors less than 5.0 cm and more than 5.1 cm, respectively.

Although lymph node involvement has been shown to significantly affect survival, this analysis found a significant "additive" effect with tumor size, and no significant interaction was found when both variables were considered together, as confirmed by a generalized Wilcoxon test in a stratified univariate analysis. Despite the relationship between size and nodal status, with a cumulative worsening of the 5-year survival, tumor size has an independent effect on the prognosis. In fact, the 5-year survival for N0 patients with tumors larger than 5 cm (51.3%) is significantly less than that for tumors smaller than 5 cm (61.9%). This finding supports the possibility of autonomous spreading,[13] which seems to follow routes different from the more anatomic lymphatic routes. These results are confirmed by the proportional hazard model, in which the estimated relative risk associated with size increases for tumors larger than 5 cm (risk = 1.430).

In conclusion, tumor size was studied independent of other variables in T3 and T4 of the TNM classification and was shown to affect survival independent of nodal metastases. Tumor size appears to play a fundamental role in the prognosis of lung cancer, and a new cutoff point of 5 cm divides tumors larger than 3 cm into 2 groups with significantly different survivals. In addition, the 5-year survival of patients with T2 tumors larger than 5 cm (T2b) is between those for patients with T3 and T4 tumors and actually closer to that for patients with T4 tumors. Thus, T2 tumor larger than 5 cm might be upgraded to at least T3 in the TNM classification.

References

1. Asamura H, Naruke T. Lung carcinoma: prognostic factors in cancer. In: Hermanek P, editor. UICC, International Union Against Cancer. Berlin; New York: Springer-Verlag; 1995.
2. Sakurai M, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Miura K, et al. Prognostic factors in non–small cell lung cancer: multiregression analysis in the National Cancer Center Hospital (Japan). *J Cancer Res Clin Oncol.* 1987;113:563-6.
3. Lipford EH III, Eggleston JC, Lillemoe KD, Sears DL, Moore GW, Baker RR. Prognostic factors in surgically resected limited-stage non–small cell carcinoma of the lung. *Am J Surg Pathol.* 1984;8:357-65.
4. Sorensen JB. Prognosis and prognostic factors in adenocarcinoma of the lung. *Dan Med Bull.* 1992;39:453-63.
5. Katlic M, Carter D. Prognostic implications of histology, size and location of primary tumors. In: Muggia F, Rozencweig M, editors. Lung cancer: progress in therapeutic research. New York: Raven Press; 1979.
6. Treasure T, Belcher JR. Prognosis of peripheral lung tumors related to size of the primary. *Thorax.* 1981;36:5-8.
7. Motta G, Carbone E, Spinelli E, Nahum MA, Testa T, Flocchini GP. Considerations about tumor size as a factor of prognosis in NSCLC. *Ann Ital Chir.* 1999;70:893-7.
8. Mountain CF. Revision in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7.
9. Steele JD. The solitary pulmonary nodule. Springfield (IL): Charles C Thomas; 1964.
10. Wellons HA, Johnson G Jr, Benson WR, Pate D, Wilcox BR, Peter RM. Prognostic factors in malignant tumors of the lung. *Ann Thorac Surg.* 1968;5:228-35.
11. Jackman RJ, Good CA, Clagett OT, Woolner LB. Survival rates in peripheral bronchogenic carcinomas up to four centimeters in diameter presenting as solitary pulmonary nodules. *J Thorac Cardiovasc Surg.* 1969;57:1-8.
12. Yashar J, Yashar JJ. Factors affecting long-term survival of patients with bronchogenic carcinoma. *Am J Surg.* 1975;129:386-93.
13. Soorae AS, Abbey Smith R. Tumor size as a prognostic factor after resection of lung carcinoma. *Thorax.* 1977;32:19-25.
14. Ogata T, Naruke T. Twenty years experience with lymphnode dissection in patients with lung cancer: the mode of lymphnode metastasis and the effect of dissection of node on the prognosis. In: Motta G, editor. Cancer of the lung and pleura. Milan: Masson Italia Ed; 1986. p. 35-46.
15. International Union against Cancer (UICC). Lung tumors (ICDO-0162). In: Hermanek P, Sobin LH, editors. TNM classification of malignant tumors. 4th ed. Berlin: Springer-Verlag; 1987.
16. The World Health Organization. Histological typing of lung tumors. 2nd ed. Geneva: World Health Organization; 1981.
17. Collett D. Modelling survival data in medical research. London: Chapman and Hall; 1994.
18. Klein JP, Moeschberger ML. Survival analysis. New York: Springer-Verlag; 1997.
19. Cox DR. Regression models and life-tables. *J R Stat Soc (B).* 1972;34:187-220.
20. Mountain CF. Prognostic power of tumor size as an independent variable in non–small cell lung cancer. Proceedings of the International Symposium on Tumour Staging and Classification in Lung Cancer. Madrid, Spain, December 3-4, 1999.
21. Nonomura A, Mizukami Y, Shimizu J, Oda M, Murakami S, Watanabe Y, et al. Clinicopathological study of primary malignant tumors of the lung: an analysis of 993 tumors resected at the Kanazawa University Hospital between 1979-1993. *J Surg Oncol.* 1995;58:5-11.
22. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am.* 1987;67:1037-49.
23. Pearson FG, DeLarue NC, Ilves R, Todd TRJ, Cooper JD. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J Thorac Cardiovasc Surg.* 1982;83:1-11.
24. Naruke T, Tsuchiya R, Kondo H, Asamura H, Nakajama H. Implications of staging in lung cancer. *Chest.* 1997;112:2425-85.
25. Shields TW. The significance of ipsilateral mediastinal lymph node metastasis (N2 disease) in non–small cell carcinoma of the lung. *J Thorac Cardiovasc Surg.* 1990;99:48-53.
26. Watanabe Y, Shimizu J, Oda M, Hayashi Y, Iwa T, Nonomura A, et al. Proposal regarding some deficiencies in the New International Staging System for non–small cell lung cancer. *Jpn J Clin Oncol.* 1991;21:160-8.