ORIGINAL ARTICLES

Results of Surgery for Non-Small Cell Cancer With N2 Involvement Unsuspected Before Thoracotomy

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OBJECTIVE: To analyze survival in a group of patients with N2 involvement discovered during or after lung resection for non-small cell lung cancer and to evaluate the variables that affect survival.

PATIENTS AND METHODS: The study included all patients with non-small cell lung cancer who underwent resection between January 1994 and October 2004 and in whom the definitive tumor classification was stage pIIIA due to N2 extension (n=74) detected during surgery. Patients with stage pIIIB who had undergone induction chemotherapy and patients for whom surgery was considered incomplete were excluded.

RESULTS: Mean survival times were significantly different (*P*=.002) between resection types: pneumonectomy, 18.1 months (95% confidence interval [CI], 6.9-29.2 months), and lobectomy, 42.4 months (95% CI, 28.7-56.1 months). The number of lymph-node stations affected did not have a significant effect on survival. However, when only 1 station was involved, mean survival was different for lobectomy and pneumonectomy (48.0 months [95% CI, 31-65 months] vs 14.8 months [95% CI, 4.8-24.7 months], respectively; *P*=.002) but no differences were found when N2 spread involved more than a single station. Adjuvant therapy was used in 50% of cases (n=35): chemotherapy in 6 cases; radiotherapy in 17 cases; and both in 12 cases. The mean survival rate for lobectomy patients with no adjuvant therapy was 31.6 months (95% CI, 15.6-47.5 months) and 46.2 months (95% CI, 32.2-60.1 months) (*P*=.01) with adjuvant therapy, whereas there were no differences in the group of pneumonectomy patients.

CONCLUSIONS: Patients who undergo lobectomy clearly survive longer than those who undergo pneumonectomy when N2 lymph node involvement is found in only 1 station during surgery. Furthermore, adjuvant therapy may increase mean survival times for lobectomy patients.

Key words: *Non-small cell cancer. Lung resection. Mediastinal metastases. Prognosis.*

Resultados de la cirugía del carcinoma de pulmón no microcítico con afectación N2 no sospechada antes de la toracotomía

OBJETIVO: Analizar la supervivencia de un grupo de pacientes con afectación N2 descubierta durante o tras la realización de la cirugía de resección pulmonar reglada por carcinoma de pulmón no microcítico, y valorar las variables que influyen en dicha supervivencia.

PACIENTES Y MÉTODOS: Se incluyó en el estudio a todos los pacientes sometidos a resección pulmonar reglada con diagnóstico de carcinoma de pulmón no microcítico entre enero de 1994 y octubre de 2004, con extensión anatómica definitiva del tumor en el estadio qpIIIA por N2 (n = 74). Se excluyó a aquellos en estadio qpIIIB, con quimioterapia de inducción y aquellos en los que la cirugía se consideró incompleta.

RESULTADOS: La media de supervivencia según el tipo de resección mostró diferencias significativas (p = 0,002) entre la neumonectomía (18,1 meses; intervalo de confianza [IC] del 95%, 6,9-29,2) y la lobectomía (42,4 meses; IC del 95%, 28,7-56,1). El número de estaciones ganglionares no mostró una influencia significativa en la supervivencia. Sin embargo, cuando hubo afectación de una sola estación, las medias de supervivencia fueron diferentes entre la lobectomía (48,0 meses; IC del 95%, 31-65) y la neumonectomía (14,8 meses; IC del 95%, 4,8-24,7; p = 0,002), y no fueron distintas cuando había más de una estación N2. En el 50% de los casos (n = 35) se realizó tratamiento adyuvante (quimioterapia sólo en 6 casos; radioterapia en 17, y ambas en 12). En el grupo de pacientes de lobectomía, la media de supervivencia sin adyuvancia fue de 31,6 meses (IC del 95%, 15,6-47,5) y con adyuvancia de 46,2 meses (IC del 95%, 32,2-60,1) (p = 0,01), mientras que no hubo diferencias en el grupo de neumonectomía.

CONCLUSIONES: Cuando existe afectación N2 de una sola estación descubierta durante la cirugía, la lobectomía ofrece una supervivencia claramente superior a la neumonectomía; además, en este grupo de pacientes el tratamiento adyuvante puede aportar mayor supervivencia.

Palabras clave: *Carcinoma no microcítico. Resección pulmonar. Metástasis mediastínicas. Pronóstico.*

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Introduction

Since the publication of reports of poor results of surgery in patients with non-small cell lung cancer in stage IIIA

due to N2 extension, the treatment of this type of tumor has been under constant debate.[1] Some authors have reported patient series with a mean 5-year survival rate of between 5% and 30%,[2] revealing the heterogeneity of this type of patient and the different biological behavior of tumors receiving the same classification. A review by André et al[3] in 2000 showed that the 5-year survival rate ranged from between 5% in patients with bulky N2 involvement and 35% in patients with microscopic involvement of a single lymph node station. Results of 2 clinical trials designed with the objective of analyzing the role of surgery in the treatment of N2 disease diagnosed in the preoperative period have recently shown that surgery currently provides no advantage over chemotherapy and radiotherapy in terms of overall patient survival.[4,5] Descriptions of patient series, however, have reported satisfactory results for certain types of N2 cancers; specifically, a better outcome can be predicted when N2 disease is discovered during lung-resection surgery than when it is diagnosed in the preoperative period.[6-8] The objective of this study was to analyze survival in a group of patients in whom lymph node involvement was discovered during or after lung resection for non-small cell lung cancer, and to evaluate whether the type of surgery, number of affected lymph nodes, and adjuvant therapy have an effect on survival.

Patients and Methods

Study Design and Population

This was a cross-sectional epidemiological study of all patients who underwent lung resection due to preoperative cytologic or histologic diagnosis of non-small cell lung cancer between January 1994 and October 2004 and in whom the definitive tumor classification was stage pIIIA-B due to N2 extension identified during surgery. In order to improve the uniformity of the study population, patients with stage pIIIB with lymph node involvement detected during surgery who had undergone induction chemotherapy and patients for whom surgery was considered incomplete were excluded.

Source and Quality Control of the Data

The information was obtained from a computerized database in which data had been entered in real time. When the database for this study had been obtained, it was processed by the main author in order to detect errors. In individual cases where errors were detected, the data were compared with the information in the patient's general medical records and corrected accordingly. Complete data were obtained for all the studied variables.

Preoperative and Intraoperative Staging

Bronchoscopy and computed tomography (CT) scans of the chest and abdomen were performed before surgery in all cases. Mediastinoscopy was indicated in cases of mediastinal lymph node enlargement in which the adenopathy was considered accessible and the short axis of the affected lymph node was greater than 1 cm. The possibility of bone or intracranial metastasis was initially evaluated by means of patient interviews and physical examination. Bone scintigraphy, cranial CT, and, in some cases, magnetic resonance imaging were performed when indicated by the patient's history or the results of physical examination. Nonsurgical clinical staging was performed in the nonsurgical departments that referred the patients and in accordance with a previously agreed upon study protocol. None of the patients in the series underwent positron emission tomography. Intraoperative staging was performed by means of lymphadenectomy that included at least the areas recommended by Asamura et al.[9] Systematic lymph-node dissection, as defined in the consensus statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), was not performed.[10]

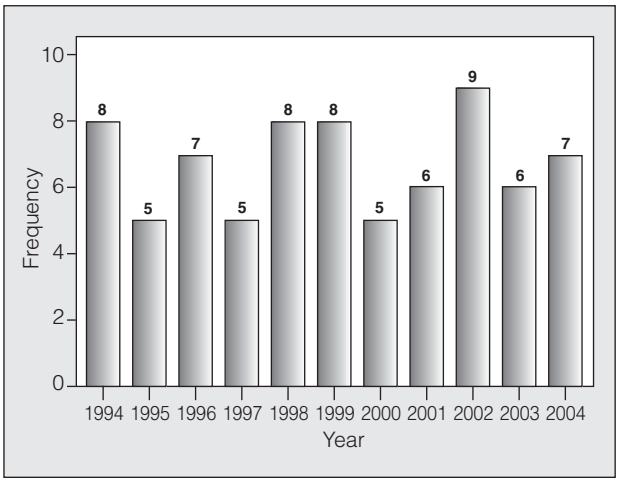

Figure 1. Annual distribution of cases of N2 disease discovered during surgery.

Analyzed Variables

– *Independent variables*: type of surgery (lobectomy or pneumonectomy), number of lymph-node stations involved, and adjuvant therapy (chemotherapy or radiotherapy) received.

– *Dependent variables*: patient survival until death from any cause. Death of the patient in the 30 days following surgery or at any time prior to the patient's discharge was considered as operative mortality. Follow-up data were obtained from the patients' computerized clinical records and, where necessary, by means of telephone calls to the patients, their family members, or referring doctors.

Statistical Analysis

Survival was first analyzed including and then, subsequently, excluding operative mortality. Kaplan-Meier survival analysis was used and the differences were compared using the log-rank test. Statistical analyses were performed using the SPSS program, version 13.0 (SPSS Inc, Chicago, Illinois, USA).

Results

During the study period, N2 involvement was discovered intraoperatively in 74 patients (66 men and 8 women), with a mean age of 63 years (range, 34-78 years). Lobectomy or bilobectomy was performed on 50 patients (68%) and 24 patients (32%) underwent pneumonectomy.

N2 disease was discovered during thoracotomy in 9.1% of the 914 resections due to non-small cell lung cancer; 74 cases, plus 10 patients with stage IIIB who were excluded. This rate was the result of cases distributed

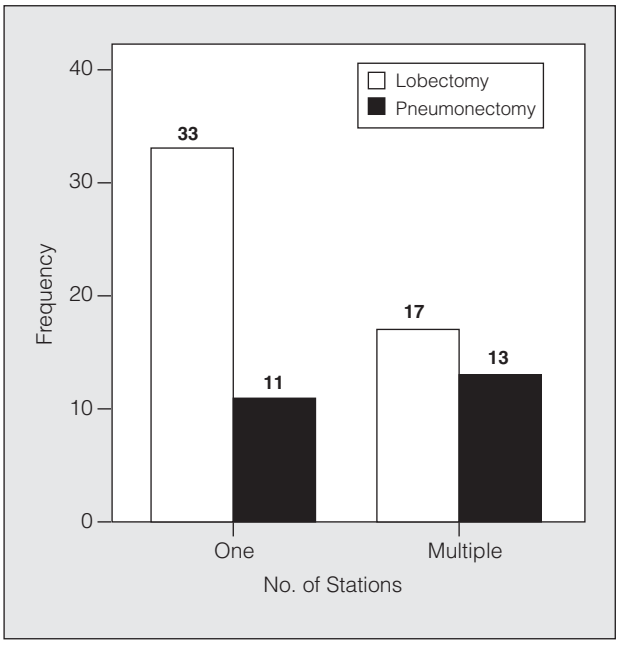

Figure 2. Distribution of type of resection by number of lymph-node stations.

uniformly over the years of the study, with a mean of 7 cases per year (range, 5-9 cases) (Figure 1).

Overall operative mortality for the series was 5.4% (n=4). Operative mortality was 8.3% (n=2) for pneumonectomy and 4% (n=2) for lobectomy.

The mean survival for the series was 35.1 months (95% confidence interval [CI], 24.2-46.0 months). No patients were lost to follow-up. Mean survival by type of resection showed significant differences (*P*=.002) between pneumonectomy (18.1 months; 95% CI, 6.9-29.2 months) and lobectomy (42.4 months; 95% CI, 28.7-56.1 months). Thereafter, with operative mortality excluded, overall mean survival was 37.1 months (95% CI, 25.7-48.5 months) and there continued to be differences in survival (*P*=.002) between pneumonectomy (19.7 months; 95% CI, 7.7-31.6 months) and lobectomy (44.1 months; 95% CI, 30.1-58.2 months).

The number of affected lymph-node stations did not significantly affect survival. However, when the results were stratified by number of affected lymph-node stations (Figure 2) and the type of resection was compared for these groups, we found that there were differences in survival (*P*=.002) between lobectomy (48.0 months; 95% CI, 31-65 months) and pneumonectomy (14.8 months; 95% CI, 4.8-24.7 months) in patients in whom a single lymph-node station was involved, as shown in Figure 3. There were no differences in survival when more than one N2 station was affected.

Adjuvant therapy was used in 50% of cases (n=35): chemotherapy in 6 cases; radiotherapy in 17 cases; and both in 12 cases. Mean survival for patients receiving adjuvant therapy was 38.4 months (95% CI, 26.9-50.0 months) compared to 28.1 months (95% CI, 15.5-40.7 months) for patients without adjuvant therapy (*P*=.01) (Figure 4). The mean survival in the group of patients

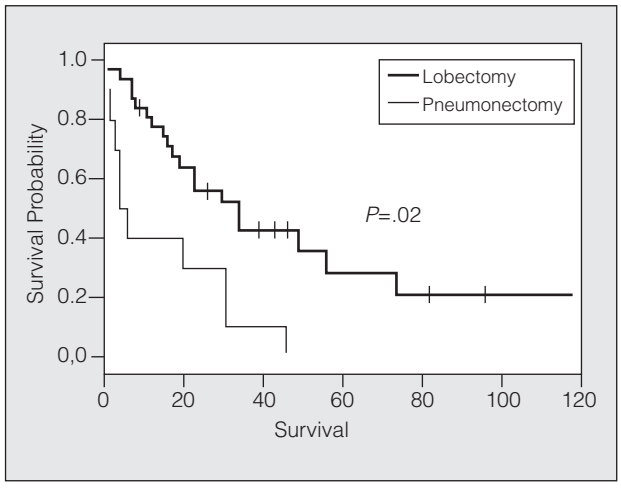

Figure 3. Kaplan-Meier survival analysis. Comparison between lobectomy and pneumonectomy in N2 cases with a single affected station.

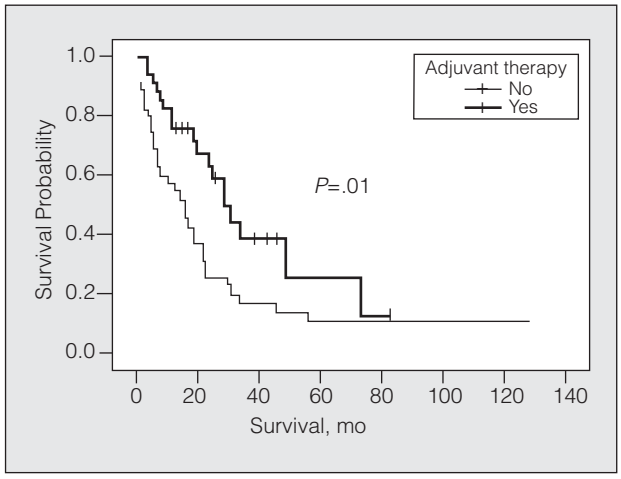

Figure 4. Kaplan-Meier survival analysis. Comparison of adjuvant therapy.

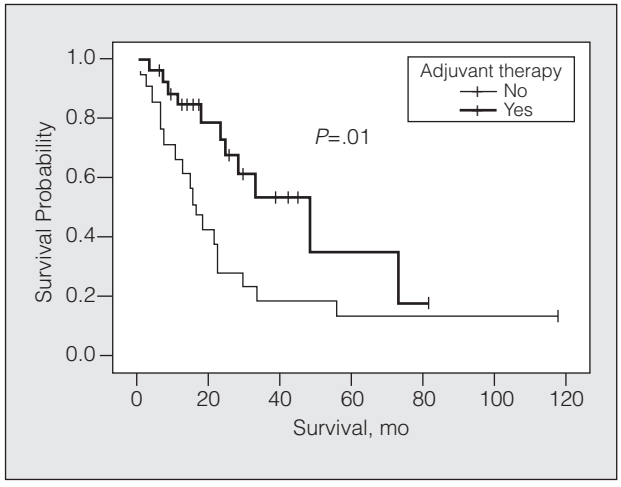

Figure 5. Kaplan-Meier survival analysis. Comparison of adjuvant therapy in patients who underwent lobectomy.

who underwent lobectomy was 31.6 months (95% CI, 15.6-47.5 months) without adjuvant therapy and 46.2 months (95% CI, 32.2-60.1 months) (*P*=.01) with adjuvant therapy. No differences were observed in the group of patients who underwent pneumonectomy.

Discussion

In 1987, Martini and Flehinger[6] showed the heterogeneity of patients with N2 disease and identified 2 groups: patients diagnosed in the preoperative period (called clinical N2) and patients diagnosed during resection surgery (termed minimal N2 disease). The difference in outcome between the 2 groups has been subsequently corroborated by several retrospective studies.[3,8]

In our series, the incidence of this minimal N2 disease, unsuspected before resection, remained stable throughout the study period. The explanation for this distribution may be that the staging criteria were not substantially altered during this period and that systematic performance of positron emission tomography was not included in our preoperative staging protocol.

To facilitate interpretation of the results, we decided to exclude N2 cases discovered during surgery where the patient had previously received adjuvant therapy. Although overall operative mortality was not high (5.4%), mortality in cases of pneumonectomy was twice that in cases of lobectomy (8.3% and 4%, respectively). This difference in mortality in our series has not been observed in series by other authors such as Martin et al.[2]

Operative mortality did not have a statistically significant effect on overall survival or on differences between groups formed according to extent of resection; nevertheless, we decided to exclude it from subsequent between-group analyses.

Most published studies on surgery in patients with N2 disease do not report survival differences by type of resection, once the higher mortality for pneumonectomy has been excluded.[12,13] In our series, however, there was a significant difference in mean survival times between lobectomy and pneumonectomy (44 months and 19 months, respectively).

Keller et al[7] found longer survival times in their series in patients with a single affected lymph-node station. In our series, however, the number of lymph-node stations involved showed no effect on survival—a finding that has also been reported by other authors.[8,14]

One of the important findings from our analysis is the fact that the type of lung resection has a decisive effect on outcome when a single lymph-node station is involved, with a mean survival of 48 months for lobectomy compared to 14 months for pneumonectomy. Our search of the medical literature revealed no studies that link the extent of resection and the number of affected lymph-node stations. Differences according to the extent of resection disappear, however, when multiple lymph nodes are involved.

A recent study published by our group showed that the extent of resection affected the survival of patients with the same tumor staging.[15] As we mentioned in that study, we cannot be sure that the biological behavior of the tumors was similar in both bronchoplasty groups, even though the staging was the same. It is possible that the tumors in the cases requiring pneumonectomy were more biologically aggressive—some authors have indicated that tumors larger than 5 cm may have a less favorable outcome and more frequently express angiogenic factors.[16] Another possibility, reported by some authors, is that the loss of lung function due to the extent of the resection affects medium-term survival since forced expiratory volume in the first second is considered to be an independent factor for predicting mortality due to any cause in the general population.[17]

The other finding of interest in our series is the influence of adjuvant therapy on survival. This effect has been reported by other authors in connection with adjuvant radiotherapy.[4,7] Patients in our series who were treated with postoperative chemotherapy, radiotherapy, or both had significantly longer survival times than those who were untreated. This difference is almost exclusively due to the effect of adjuvant therapy on the lobectomy group as there were no significant differences in the group of patients who underwent pneumonectomy. As there was no evidence to support adjuvant therapy in this type of patient at the time of the study, the decision of whether or not to administer it was left to the discretion of the oncologist responsible for each patient.

Our study is limited by the fact that it was a retrospective study of a limited number of cases from the same hospital and therefore susceptible to possible selection bias, particularly in relation to the decision to prescribe adjuvant therapy.

In conclusion, we have shown that survival times were clearly longer for patients who underwent lobectomy than for those who underwent pneumonectomy when lymph node involvement was found in only 1 station during surgery. Furthermore, adjuvant therapy may increase mean survival times for lobectomy patients.

REFERENCES

1. Mountain CF. A new international staging system for lung cancer. Chest. 1986;89 Suppl 4:225-33.
2. Martin LW, Correa AM, Hofstetter W, Hong WK, Komaki R, Putnam JB, et al. The evolution of treatment outcomes for resected stage IIIA non-small cell lung cancer over 16 years at a single institution. J Thorac Cardiovasc Surg. 2005;130:1601-10.
3. André F, Grunenwald D, Pignon JP, Dujon A, Pujol Jl, Brichon PY, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol. 2000;18:2981-9.
4. Albain KS, Swann RS, Rusch VR, Turrisi AT, Shepherd FA, Smith CJ, et al. North American Lung Cancer Intergroup. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): outcomes update of North American Intergroup 0139 (RTOG 9309) [abstract 7014]. Actas de ASCO Meeting 2005; mayo 13-17; Orlando. Orlando: ASCO; 2005.
5. van Meerbeeck JP, Kramer G, van Schil PE, Legrand C, Smit EF, Schramel FM, et al. EORTC-Lung Cancer Group. A randomized trial of radical surgery (S) versus thoracic radiotherapy (TRT) in patients (pts) with stage IIIA-N2 non-small cell lung cancer (NSCLC) after response to induction chemotherapy (ICT) (EORTC 08941) [abstract 7015]. Minutes of ASCO Meeting 2005; May 13-17; Orlando. Orlando: ASCO; 2005.

6. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. Surg Clin North Am. 1987;67:1037-49.
7. Keller SM, Vangel MG, Wagner H, Schiller JH, Herskovic A, Komaki R, et al. Prolonged survival in patients with resected nonsmall cell lung cancer and single-level N2 disease. J Thorac Cardiovasc Surg. 2004;128:130-7.
8. Ohta Y, Shimizu Y, Minato H, Matsumoto I, Oda M, Watanabe G. Results of initial operations in non-small cell lung cancer patients with single-level n2 disease. Ann Thorac Surg. 2006;81:427-33.
9. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systematic lymph node dissection for non–small cell lung carcinomas according to a retrospective study of metastasis and prognosis. J Thorac Cardiovasc Surg. 1999;117:1102-11.
10. Estadificación ganglionar intraoperatoria en la cirugía del carcinoma broncogénico. Documento de consenso. Arch Bronconeumol. 2001;37:495-503.
11. Alexiou C, Beggs D, Rogers ML, Beggs L, Asopa S, Salama FD. Pneumonectomy for non-small cell lung cancer: predictors of operative mortality and survival. Eur J Cardiothorac Surg. 2001;20:476-80.
12. Casali C, Stefani A, Natali P, Rossi G, Morandi U. Prognostic factors in surgically resected N2 non-small cell lung cancer: the importance of patterns of mediastinal lymph nodes metastases. Eur J Cardiothorac Surg. 2005;28:33-8.
13. Takeda S, Maeda H, Okada T, Yamaguchi T, Nakagawa M, Yokota S, et al. Results of pulmonary resection following neoadjuvant therapy for locally advanced (IIIA-IIIB) lung cancer. Eur J Cardiothorac Surg. 2006;30:184-9.
14. de Leyn P, Schoonooghe P, Deneffe G, van Raemdonck D, Coosemans W, Vansteenkiste J, et al. Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease). Eur J Cardiothorac Surg. 1996;10:649-55.
15. Jiménez MF, Varela G, Novoa N, Aranda JL. La lobectomía broncoplástica frente a la neumonectomía en el tratamiento del carcinoma de pulmón no microcítico. Arch Bronconeumol. 2006;42:160-4.
16. Ohta Y, Waseda R, Minato H, Endo N, Shimizu Y, Matsumoto I, et al. Surgical results in T2N0M0 nonsmall cell lung cancer patients with large tumors 5 cm or greater in diameter: what regulates outcome? Ann Thorac Surg. 2006;82:1180-4.
17. Schünemann HJ, Dorn J, Grant BJB, Winkelstein W, Trevisan M. Pulmonary function is a long-term predictor of mortality in general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000;118:656-64.