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ORIGINAL ARTICLE

Survival of patients with resected pIIIa - N2 non small cell lung cancer: suggestion for subclassification

G. Andjelić[1], V. Stanić[2], B. Gulić[2], A. Ristanović[2], V. Cvijanović[2]

[1]Institute for Medical Research, [2]Clinic for Cardiothoracic Surgery, Military Medical Academy, Beograd, Serbia and Montenegro

Summary

Purpose: *The group of completely resected stage IIIa-N2 non small cell lung cancer (NSCLC) patients is considered heterogeneous in various aspects including survival and pattern of recurrence. The prognostic factors still remain controversial. Clinical trials dealing with multimodal strategy for N2 NSCLC are being watched with keen interest, and the feasibility of this strategy is to be confirmed. In the present study we attempted to clarify the role of different clinicopathological factors which separate patients into high and low-risk groups based on the disease-free and overall survival.*

Patients and methods: *The study comprised 60 consecutive patients with pathologically (p) proven N2 NSCLC who had undergone complete surgical disease resection with curative intent between January 1997 and September 2000. All patients had an apparently resectable disease at preoperative staging and thoracotomy. Extensive mediastinal lymph node dissection was performed when possible and consisted of removal of all ipsilateral mediastinal lymph nodes. Patients were submitted to postoperative split course adjuvant radiotherapy. Cumulative survival rates were calculated by the Kaplan-Meier method. The analyzed prognostic factors were age, histological type and grade of differentiation, clinical (c) stage, cN status and tumor size and were tested for statistical significance by univariate analysis using log-rank test and Willcoxon test.*

Results: *The median follow-up period was 36 months (range 24-72 months). Tumor size, cN status and age were significant predictors of survival. Large tumor size (T3) was significantly worse predictor compared to T1 (p=0.046) and cN2 status evaluated by computed tomography (CT) also showed statistically significant unfavorable prognosis in comparison with cN0 and cN1 (p=0.0185). Patients over 65 years had significantly worse prognosis compared to those under 65 years (p=0.008).*

Conclusion: *This study identified stage IIIa - N2 NSCLC prognostic subgroups and suggests different therapeutic approach according to the subgroup profile.*

Key words: non small cell lung cancer, prognostic factors, stage IIIa-N2, survival

Introduction

Lung cancer still remains the leading cause of cancer-related deaths worldwide, not only amongst men, but recently also among women. Since novel therapeutic strategies did not improve survival considerably, early diagnosis and creation of individual therapeutic protocols based on more precise subclassification profiles still remain the only promising tools for attempting to attain better survival.

Patients suffering from N2 NSCLC i.e., with ipsilateral mediastinal lymph node involvement, are generally considered by most physicians to have locally advanced disease resulting in poor outcome, although these patients can be divided into heterogeneous subpopulations, such as those with bulky extranodal metastases and those with either multiple or single N2 involvement [1]. A number of controversies plague this subgroup of patients with respect to staging and treatment, which often makes it difficult to interpret the large

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Author and address for correspondence:

Gordana Andjelić, MD
Institute for Medical Research
Military Medical Academy
Crnotravska 17
11000 Beograd
Serbia and Montenegro
Tel: +381 11 3608626
Fax: +381 11 662722
E-mail: ajulija@beotel.yu

amount of literature data concerning these patients. Two decades ago, Naruke et al., Martini et al. and Pearson et al. reported that surgery could cure a small proportion of these patients [2-4]. Since then, many series [5] have reported 5-year survival rates ranging from 6 to 35% after surgery. These series suggested that preoperative detection of N2 disease, involvement of multiple lymph node levels, subcarinal involvement, and adenocarcinoma subtype were associated with worse prognosis [5]. The small number of patients included in these studies and the differences in inclusion criteria clearly account for the heterogeneity of these results and for the confusion concerning the prognosis of N2 patients. Against this background, the indications for surgery for N2 NSCLC remain somewhat ambiguous. Several prognostic factors have recently been defined by historical studies, which have shown that complete resection, single lymph node metastasis, cN0-1 factor, low pT factor, and small tumor size are predictors of better prognosis in these patients [1,6,7]. However, the kind of patients with N2 NSCLC who can benefit most from a thoracotomy has not been clarified.

A recent meta-analysis found no benefit for resected N2 disease treated with postoperative radiotherapy [8].

We retrospectively studied patients with N2 NSCLC treated at the Clinic for Cardiothoracic Surgery, Military Medical Academy, Beograd, by analyzing prognostic factors to identify subpopulations with good operative indications and those who need adjuvant therapeutic approaches and to clarify the impact that different clinical and pathological factors, which separate patients into high and low- risk groups, could have on survival.

Patients and methods

Patients

The medical records of 60 patients with pathologically verified NSCLC who had undergone a thoracotomy between January 1997 and September 2000 and had pathologically confirmed positive ipsilateral mediastinal lymph nodes were reviewed. Forty-eight (80%) were men and 12 (20%) women, with a median age of 58 years (range 43-69 years).

Methods

Preoperative diagnosis was performed by using chest radiography and CT imaging, as well as fiberoptic bronchoscopy. Mediastinal nodes larger than 1 cm in the short axes were defined as cN2 disease. A mediastinoscopy was carried out in selected patients with suspected cN2 disease in imaging studies.

Clinical stage was defined by bronchoscopy and chest CT, as well as by brain CT or magnetic resonance imaging (MRI), upper abdominal CT and bone scintigraphy, used to detect distant metastases.

Preoperative histological and cytological diagnosis (bronchoscopical tissue sample and/or sputum cytology) was performed in all patients and indicated the histological subtype of NSCLC. Postoperative biopsy confirmed 32 squamous cell carcinomas, 20 adenocarcinomas, 5 large cell carcinomas and 3 adenosquamous carcinomas.

All patients underwent complete tumor resection (without macroscopically residual lesions and with microscopically free margins around the tumor site) and radical lymph node dissection. As for lymph node dissection, in patients with a tumor in right upper-middle lobe, the superior mediastinal, paratracheal, pretracheal, tracheobronchial, and subcarinal nodes were removed. In those with a tumor in the left upper lobe, the tracheobronchial, subaortic, paraaortic and subcarinal nodes were removed. In addition to these nodes, paraesophageal and pulmonary ligament nodes were dissected in patients with tumors in both lower lobes. Dissection of the pretracheal nodes in patients with a left-sided tumor and the anterior and posterior mediastinal nodes was optional. Patients with pleural dissemination or malignant pleural effusion were excluded from the study as they were considered to have incomplete resection, even if there was no macroscopic residual lesions after the pulmonary resection. Pathological confirmation of metastatic mediastinal lymph nodes was done in all patients who had undergone pulmonary resection. Postoperative staging was performed according to the 1997 TNM classification [9]. Adjuvant split course radiation therapy was delivered to all patients.

Statistical analysis

Disease-free survival was defined as the period from the date of initial surgical treatment to the development of disease recurrence or distant metastasis. Overall survival was defined as the period from the date of initial surgical treatment to death or last follow-up. The probability of survival was calculated by using the Kaplan-Meier method [10]. The prognostic influence of the studied variables on survival was analyzed by using log-rank test and Willcoxon test.

Results

The median follow-up period was 36 months (range 24-72 months).

According to the preoperative (clinical) stage of the disease, 16 (26.7%) patients had cIIIa stage, 12 (20%) cIIb, 12 (20%) cIIa and 20 (33.3%) cIb stage. Concerning cN status 20 (33.3%) patients had cN0, 31 (51.7%) cN1 and 9 (15%) had cN2 disease. Post-operative determination of T status confirmed 16 (26.7%) patients having pT1, 33 (55%) pT2 and 11 (18.3%) pT3 disease.

The median overall survival for all patients with pIIIa-N2 NSCLC was 19 months (95% confidence interval -C.I.- 16-22 months) (probability of survival p=0.1164), and the median disease-free survival was 14 months (95% C.I. 11-17 months, p=0.115; Figures 1 and 2). During follow-up 39 (65%) patients developed distant metastasis and 15 (25%) locoregional recurrence. Six (10%) patients were disease-free at the end of the follow-up period. Eight (13%) patients survived and 52 (87%) died during follow-up.

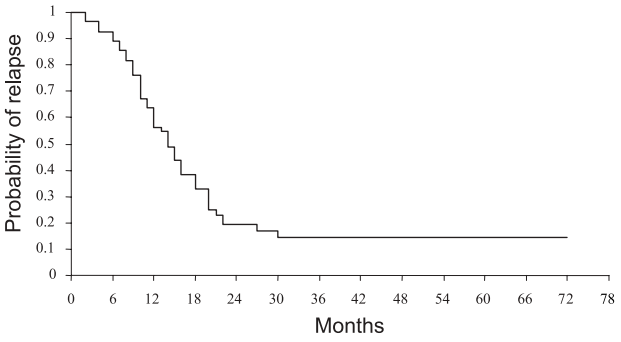

Figure 1. Disease-free survival for 60 patients with pIIIa – N2 NSCLC with complete disease resection.

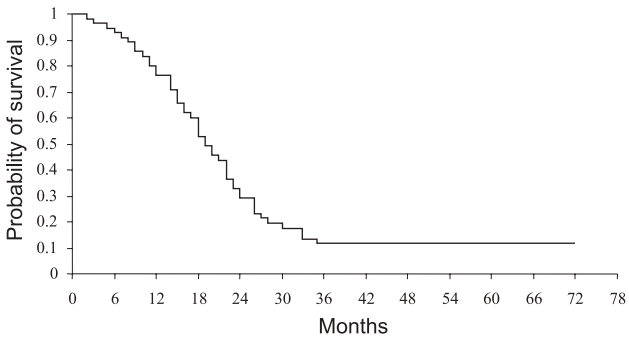

Figure 2. Overall survival for 60 patients with pIIIa – N2 NSCLC with complete disease resection.

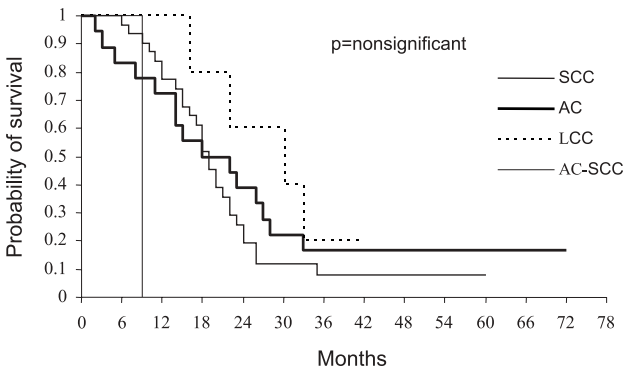

Figure 3. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to histological tumor type.

Histologically, 32 (53.3%) patients had squamous cell carcinoma, 20 (33.3%) adenocarcinoma, 5 (8.3%) large cell carcinoma, and 3 (5%) patients adenosquamous carcinoma. No significant differences in survival according to histological tumor type were registered (Figure 3).

Also, no statistically significant difference in relation to grade of differentiation was shown (Figure 4).

Significant difference in the survival of patients over 65 years, who had significantly worse prognosis, compared to those under 65 years was found (p= 0.008; Figure 5). In contrast, there was no significant difference in survival between patients with different clinical stages (Figure 6). Regarding other characteristics, statistically significant difference in overall survival was found with different cN status (p=0.0185; Figure 7). Patients with cN0 had a median overall survival of 18 months (95% C.I. 13-23 months), whilst cN2 patients had a median overall survival of 15 months (95% C.I. 12-16 months; p=0.0185). Similarly, pT3 patients had significantly worse survival compared with pT1 patients (p=0.046; Figure 8).

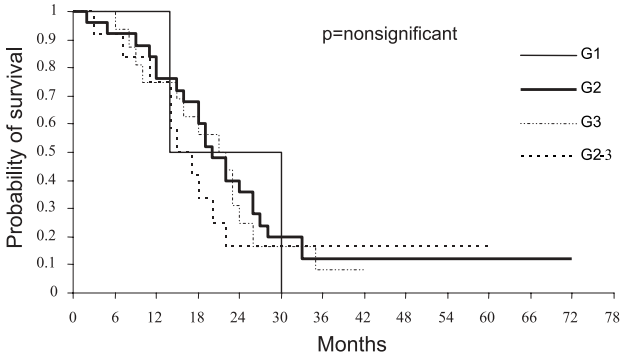

Figure 4. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to tumor grade of differentiation.

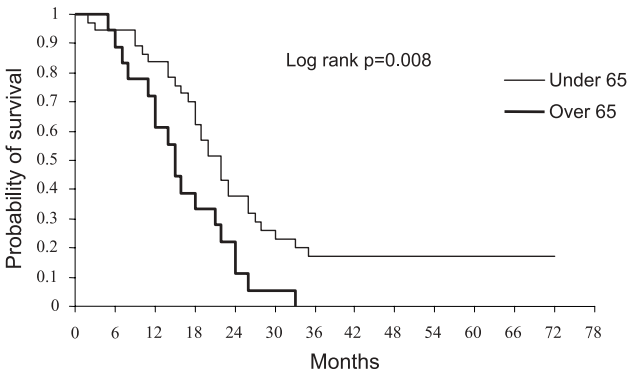

Figure 5. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to age.

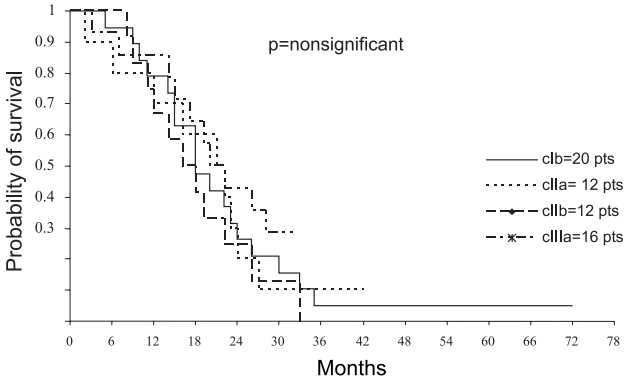

Figure 6. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to clinical stage.

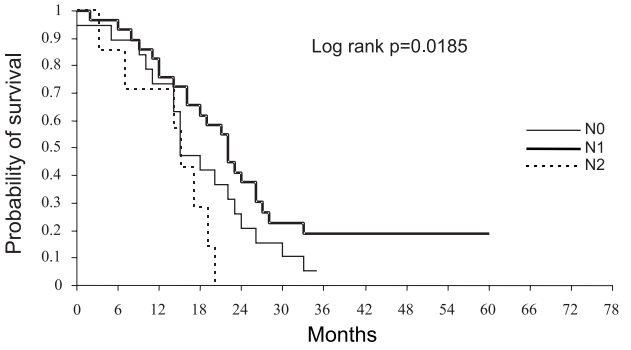

Figure 7. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to cN status.

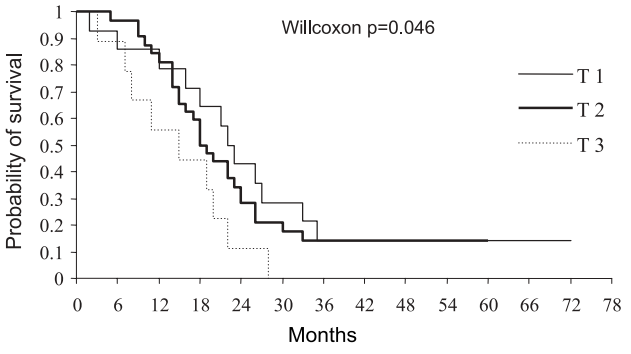

Figure 8. Probability of survival for patients with pIIIa – N2 NSCLC with complete resection according to pT status.

Discussion

In the present study overall survival for patients with pIIIa-N2 NSCLC was 13% at the end of the follow-up period (6 years). In other studies estimating 5-year survival, the relevant figures were a little higher, probably due to the shorter follow-up period [4, 11-13]. Distant metastasis occurred in 65% of our patients and this figure is lower than in other series [14].

We assessed survival by histological type and grade of differentiation and found no statistical difference between histological types of NSCLC. However, Inoue et al. found that patients with squamous cell carcinoma had better prognosis than patients with large cell carcinoma (p=0.020). Furthermore, patients with squamous cell carcinoma also tended to live longer than adenocarcinoma patients although the difference was not significant [15].

cN factor was a significant survival prognosticator. Other clinical trials dealing with prognostic factors for pIIIa – N2 disease also confirmed that preoperative cN factor, determined by chest CT, was able to predict survival because patients with surgically discovered N2 disease had a better survival than those with a preoperative diagnosis of cN2 disease [7, 15-17]. Many clinical trials analyzed the number of N2 stations in relation to survival of patients with resected IIIa-N2 NSCLC and concluded that the number of involved N2 stations is a crucial prognostic factor for these patients [1,7,17-19].

In the present study age was a significant prognostic factor, since patients older than 65 years had a significantly worse prognosis (p=0.008). Other authors came to the same conclusion with univariate and multivariate analyses [6].

This study showed no significant difference in prognosis between clinical disease stages (cTNM), albeit in some studies clinical stage was a significant predictor of survival [20]. Larger tumor size was also of significant prognostic value in some studies [6,7], which was also found in our study for T3 factor compared to smaller tumor size (T1-2).

Experience with clinically occult stage IIIa (N2) NSCLC suggests that multiple levels of mediastinal lymph node metastases predict treatment failure in patients following resection and that adjuvant mediastinal radiation improves disease-free but not overall survival [19].

According to Tanaka et al. in cT1-2N2M0 or pT1-2N2M0 patients, a good prognosis can be realized by complete tumor resection with mediastinal lymph nodes dissection. In contrast, surgical treatment should not be justified in cT3N2M0 or pT3N2M0 patients

[20]. Our investigation confirmed poor prognosis of pT3N2M0 patients and also found surgery an insufficient treatment, requiring additional treatment modalities, such as chemotherapy.

In lung cancer, the anatomical definition of N1 stations, its boundary to N2 stations, and its prognostic implication are yet to be defined. Metastasis in lymph nodes close to the pleural reflection has been classified differently as N1 or N2 according to the lymph node maps promulgated so far. In terms of prognosis, a pleural reflection does not seem an appropriate anatomical boundary between N1 and N2 stations in lung cancer [21]. This is also a point to be clarified for more precise staging of NSCLC, helping thus in the treatment decision-making for different stages and substages of the disease.

Recent efforts to add new factors that could be used for staging and substaging of NSCLC patients have been reported. A group of investigators from Yokohama conducted a study using cDNA microarray analysis to determine whether expression levels of genes in tumors were correlated with survival. Some survival-related genes were detected in tumor tissue of lung cancer patients. The authors concluded that a prospective study is required to confirm whether expression levels of these genes can be used for prognosis [22]. Also, authors from Philadelphia identified 19 novel genes that have neither been described in NSCLC (i.e., cdc2, cullin 4A, ZAC, p57, DP-1, GADD45, PISSLRE, cdc20) nor in any other tumors (i.e., cyclin F, cullin 5, p34). These results identified several potential cell cycle genes altered in lung cancer [23]. Gene alterations in NSCLC are a promising new tool for lung cancer diagnosis, prognosis and prediction of radio- and chemosensitivity of the tumor. They may be added to clinical and pathological factors for subclassification of all stages of NSCLC.

In conclusion, our study revealed subgroups of pIIIa-N2 NSCLC with particularly unfavorable prognosis that require additional postoperative treatment (radio- or chemotherapy).

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