## ORIGINAL RESEARCH

# NONSMALL CELL LUNG CANCER: EVALUATION OF 737 CONSECUTIVE PATIENTS IN A SINGLE INSTITUTION

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**OBJECTIVE:** To analyze surgical and pathological parameters and outcome and prognostic factors of patients with nonsmall cell lung cancer (NSCLC) who were admitted to a single institution, as well as to correlate these findings to the current staging system.

**METHOD:** Seven hundred and thirty seven patients were diagnosed with NSCLC and admitted to Hospital do Cancer A. C. Camargo from 1990 to 2000. All patients were included in a continuous prospective database, and their data was analyzed. Following staging, a multidisciplinary team decision on adequate management was established. Variables included in this analysis were age, gender, histology, Karnofsky index, weight loss, clinical stage, surgical stage, chemotherapy, radiotherapy, and survival rates.

**RESULTS:** 75.5% of patients were males. The distribution of histologic type was squamous cell carcinoma 51.8%, adenocarcinoma 43.1%, and undifferentiated large cell carcinoma 5.1%. Most patients (73%) presented significant weight loss and a Karnofsky index of 80%. Clinical staging was IA 3.8%, IB 9.2%, IIA 1.4%, IIB 8.1%, IIIA 20.9%, IIIB 22.4%, IV 30.9%. Complete tumor resection was performed in 24.6% of all patients. Surgical stage distribution was IA 25.3%, IB 1.4%, IIB 17.1%, IIIA 16.1%, IIIB 20.3%, IV 11.5%. Chemotherapy and radiotherapy were considered therapeutic options in 43% and 72%, respectively. The overall 5-year survival rate of nonsmall cell lung cancer patients in our study was 28%. Median survival was 18.9 months.

**CONCLUSIONS:** Patients with NSCLC who were admitted to our institution presented with histopathologic and clinical characteristics that were similar to previously published series in cancer hospitals. The best prognosis was associated with complete tumor resection with lymph node dissection, which is only achievable in earlier clinical stages.

KEY WORDS: **Lung cancer. Nonsmall cell carcinoma. Prognostic factors. Staging. Treatment outcome.**

In the past few years, lung cancer has become the most prevalent and aggressive cancer in the world. In the United States, malignant pulmonary tumors account for more deaths than any other type of cancer, including female breast cancer. The same is true for Europe, where lung cancer is responsible for nearly 28% of all deaths due to cancer.[1] In Brazil, it is estimated that in 2002, 18000 deaths have occurred due to lung cancer.[2]

Smoking is considered the main factor in the genesis of lung cancer.[3] It is estimated that approximately one third of the Brazilian adult population smokes, resulting in an extremely large number of people at high risk of developing tumors of the upper respiratory and digestive tracts, especially in the lungs.[2]

Pulmonary carcinoma has been classically divided into 2 histological groups as a result of the clearly distinct biological behavior: small cell (SCLC) and nonsmall cell lung cancer (NSCLC). The latter occurs in 70% to 80% of all patients.[1] It is estimated

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that 75% of these patients present locally advanced or metastatic disease at the time of diagnosis.[1,4]

The outcome for patients with NSCLC is directly related to the stage of disease, as well as to the treatment strategy. Most studies present data originating from randomized or strictly controlled prospective trials. Retrospective series generally include chart reviews of patients admitted over a long period of time, usually decades, with the obvious implications of major differences over time of staging methods, treatment strategies, perioperative surgical care, as well as different chemotherapy and radiotherapy regimens and methods.

The present study presents data from a prospective database on consecutive patients admitted with NSCLC between 1990 and 2000 in a single institution in Brazil. Clinical, surgical, and pathological parameters as well as outcomes of the patients are analyzed, and prognostic factors aredetailed. Correlation with the current staging system is performed.

## MATERIALS AND METHOD

Between 1990 and 2000, 1132 patients were evaluated at the Department of Thoracic Surgery of Hospital do Câncer AC Camargo with diagnosed lung cancer. Of these, 840 were admitted for complete management, which included diagnostic review and confirmation of histologic type, clinical staging, and treatment. The other 292 patients were excluded from the analysis for the following reasons: unavailable biopsy for reconfirmation of the diagnosis, treated elsewhere, or lost from follow-up before any intervention in our hospital. Most patients (n = 737) presented with NSCLC that was confirmed by the Pathology Department from cytology or histology specimens from different sources: bronchoscopy, trans-thoracic needle biopsy, or incisional or excisional biopsy of the primary tumor or its metastases. All patients were included in a continuous prospective database, and their data was analyzed. The staging routine in our department included CT scan of the thorax and upper abdomen, CT scan of the central nervous system, and bone scan. Following clinical extrathoracic staging, a multidisciplinary team decision on adequate management was established. Clinical status was routinely determined by the evaluation of pneumonologists and anesthesiologists as to the operative risks for all patient candidates regarding operative procedures. Staging was determined according to the current system. Whenever clinical status permitted, routine management of NSCLC was as follows: patients at stages I and II underwent surgical resection of their primary tumor. Lobectomy or pneumonectomy were considered standard procedures, with mediastinal lymph node dissection. Resection was considered complete whenever all margins of the resected specimen were confirmed microscopically to be negative and the highest mediastinal lymph node resected was free of cancer spread. For patients at resected stage IIIa, adjuvant radiotherapy of the lung and mediastinum was indicated. Patients with unresectable IIIa and IIIb tumors underwent either radiotherapy alone or chemoradiation. Patients at stage IV, with no brain metastases, underwent systemic chemotherapy. On the other hand, patients with NSCLC and central nervous system metastases underwent whole brain radiation, followed by palliative treatment for extra-cerebral lesions. All patients were followed up on a routine basis after completion of the treatment, with scheduled radiological and clinical evaluations. Our follow-up policy consisted of routine chest X-ray and medical evaluation every 3 months for the first 2 years, then every 6 months until the fifth year, then every year. No scans or blood tests were performed unless the clinical situation or new symptoms warranted specific tests.

### Statistical Analysis

Data on patients evaluated in this study were collected and analyzed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, Illinois, USA).

Variables included in this analysis were age, gender, histology, Karnofsky index, weight loss, clinical stage, surgical stage, chemotherapy, radiotherapy, and survival rates determined by the Kaplan-Meier survival curves. Differences between groups were assessed by the log-rank test and were considered significant at $P < 0.05$.

## RESULTS

### Gender

Most patients (75.5%) with NSCLC were males (Table 1) with age at admission ranging from 18 to 87.6 years (median = 59.5 years).

### Histology

The nonsmall cell lung cancer patients were classified as having squamous cell carcinoma (51.8%), adenocarcinoma (43.1%), or undifferentiated large cell carcinoma (5.1%). The use of immunohistochemical methods for diagnosis has lead to an increase in the sensitivity and specificity of the diagnosis of both squamous cell carcinoma and adenocarcinoma, decreasing the number of undifferentiated large cell carcinoma diagnoses.

In 61.2% of nonsmall cell lung cancer patients, surgery was not performed, reflecting the advanced stag-

**Table 1 -** Patient characteristics at admission.

| | |
|---|---|
| **Gender** | |
| Male | |
| 75.5% | |
| Female | 24.5% |
| **Age (years)** | |
| < 50 | 9.7% |
| 51-60 | 59.5% |
| 61-70 | 26.6% |
| > 70 | 4.2% |
| **Histology** | |
| Squamous cell carcinoma | 51.8% |
| Adenocarcinoma | 43.1% |
| Large cell carcinoma | 5.1% |
| **Karnofsky Index** | |
| < 70 | 3.8% |
| 70 | 10.1% |
| 80 | 65.4% |
| 90 | 15.5% |
| 100 | 5.1% |
| **Weight Loss** | |
| ≤ 10% | 72.8% |
| > 10% | 27.2% |
| **Clinical Stage** | |
| IA | 3.8% |
| IB | 9.2% |
| IIA | 1.4% |
| IIB | 8.1% |
| IIIA | 20.9% |
| IIIB | 22.4% |
| IV | 30.9% |

ing of the studied population. Of all patients included in this study, only 24.6% had complete tumor resection. On the other hand, 86.3% of the patients that underwent surgery with a curative intent had their tumors completely resected.

**Surgical Stage**

Following surgery, staging is more effective due to histologic confirmation of the spread of the disease. Those patients that had surgery were biased towards a less aggressive stage (52.1% were stages I or II). Many of the patients with clinical stages IIIB or IV did not undergo surgery. The stage distribution of surgical patients was: 25.3% - IA (n = 72), 1.4% - IB (n = 4), 8.3% - IIA (n = 24) 17.1% - IIB (n = 49), 16.1% - IIIA (n = 6), 20.3% - IIIB (n = 58), 11.5% - IV (n = 33). Patients at stage IIIB and IV underwent surgery in order to make pathologic confirmation of the presence of distant metastases, mediastinal invasion, or pleural metastases.

**Chemotherapy**

Chemotherapy was indicated at some point during treatment in 43% of the patients.

**Neoadjuvant Treatment**

Neoadjuvant treatment was not considered routine at any stage for NSCLC patients in our institution. Therefore, few patients (17%) received any neoadjuvant therapy; these were participating in clinical trials.

**Choice of Chemotherapy**

The chemotherapy drugs used and the drug combinations employed in the Hospital do Cancer between 1990 and 2000 reflected tendencies in cancer centers around the world. Cisplatin or carboplatin were established as the standard treatment for the majority of the patients. Lately, the introduction of novel drugs, such as taxanes, gemcitabine, and vinorelbine has significantly expanded the prospects of systemic treatment of nonsmall cell lung cancer. Chemotherapy regimens most commonly included: MVP (mitomycin, vinblastin, and cisplatinum); carboplatin and paclitaxel; and vinorelbine, gemcitabine, and docetaxel associated with a platinum-derived drug (cisplatinum or carboplatinum) whenever clinically adequate.

**Number of Drugs Used in Chemotherapy**

Most patients (48.3%) received a combination of 2 drugs. A few (12.1%) received only 1 drug, and 39.6% received a regimen containing 3 drugs.

**Chemotherapy Cycles**

Patients routinely received 2 chemotherapy cycles, followed by an evaluation of both tumor response to therapy and the patient's tolerance to the treatment. Of the total number of patients, 26.2% received 1 cycle of chemotherapy and 22% received 2 cycles. Upon confirmation of tumor response and acceptable toxicity, patients received up to 6 cycles (20.1% - 3 cycles, 11.3% - 4 cycles, 6.8% - 5 cycles, and 9.4% - 6 cycles). Rarely were more than 6 cycles administered (4.2%).

**Radiotherapy**

In total, 71.6% of the patients received radiotherapy at any point during treatment. Of these, only 3.1% received neoadjuvant radiotherapy. A larger group (19.1%) had adjuvant radiotherapy following resection of the primary tumor. All other patients received radiation therapy as their primary treatment for the primary tumor or its metastases.

**Radiotherapy Dose**

Most patients (56.5%) received doses smaller than 5000 cGy (43.7% received less than 4000 cGy and 12.8% between 4000 and 5000 cGy). Another 28.4% received between 5000 and 6000 cGy, and 15.3% received more than 6000 cGy. Three-dimensional conformal radiotherapy was not available in the Hospital do Câncer A.C. Camargo during the period between 1990 and 2000.

**Survival**

The overall 5-year survival rate of nonsmall cell lung cancer patients in our study was 28%. Median survival time was 18.9 months.

Prognostic factors for long-term

survival were evaluated in the patient population (Table 2).

Survival is significantly associated with clinical stage upon diagnosis (Figure 1) and surgical stage confirmed by pathology analysis during surgery (Figure 2). Weight loss significantly affected long-term survival, mainly in patients with extra-CNS metastases (Figure 3).

Tumor histology (squamous cell, adenocarcinoma, or undifferentiated large cell) also had an impact on survival. Undifferentiated large cell carcinoma had a significantly lower survival rate than squamous cell carcinoma and adenocarcinoma ($P < 0.05$).

Complete resection had a significant impact on 5-year survival of patients with nonsmall cell lung cancer.

**Table 2 -** Prognostic factors at overall 5-year survival rates.

| Variable | Median survival (months) | *P* |
|---|---|---|
| Clinical Stage | | < 0.001 |
| IA | n.a | |
| IB | 95 | |
| IIA | 78 | |
| IIB | 73 | |
| IIIA | 23 | |
| IIIB | 16 | |
| IV | 10 | |
| Histology | | 0.001 |
| Squamous cell carcinoma | 21 | |
| Adenocarcinoma | 19 | |
| Large cell carcinoma | 11 | |
| Type of resection | | < 0.001 |
| Complete | 109 | |
| Incomplete | 16 | |
| Surgical Stage | | < 0.001 |
| IA | n.a | |
| IB | n.a | |
| IIA | 86 | |
| IIB | 66 | |
| IIIA | 33 | |
| IIIB | 32 | |
| IV | 19 | |

## DISCUSSION

Lung cancer has been a widely studied subject, especially due to its high prevalence and poor prognosis, particularly in advanced stages. Smoking is classically associated with the development of these tumors.[3] Lung cancer has a male predominance (both regarding incidence and mortality) that seems to be due to historically higher levels of men who smoke, as confirmed by our results. However, recent data reveal increased incidence and mortality of women with lung cancer and a corresponding rise of the number of smokers as well.[2,5] Most patients with NSCLC are diagnosed at a productive age, with limited long-term prognosis for 5-year survival. Studies in the literature, as well as our own results, confirmed that the highest incidence of the disease is between 50 and 70 years of age, with a relatively lower incidence in younger patients.[2,6,7]

The distribution of nonsmall cell lung cancers by histologic type has changed, as compared to the distribution in this same institution in the

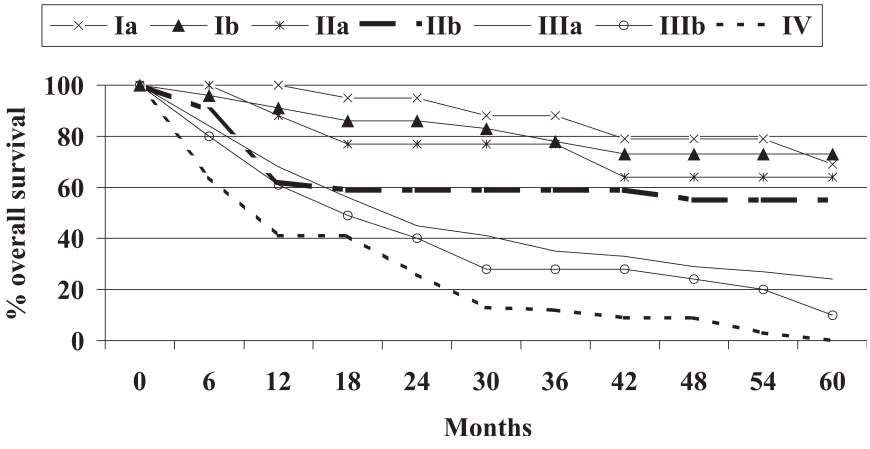


**Figure 1.** Overall survival and clinical stage upon diagnosis.

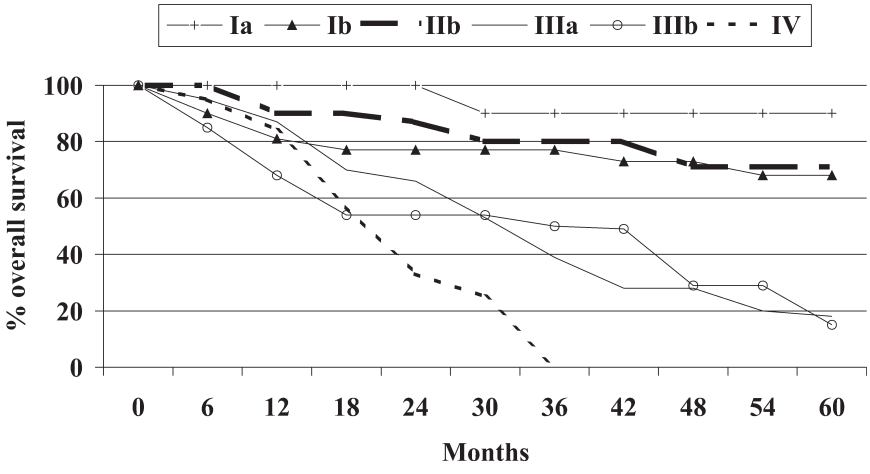


**Figure 2 -** Overall survival and surgical stage.

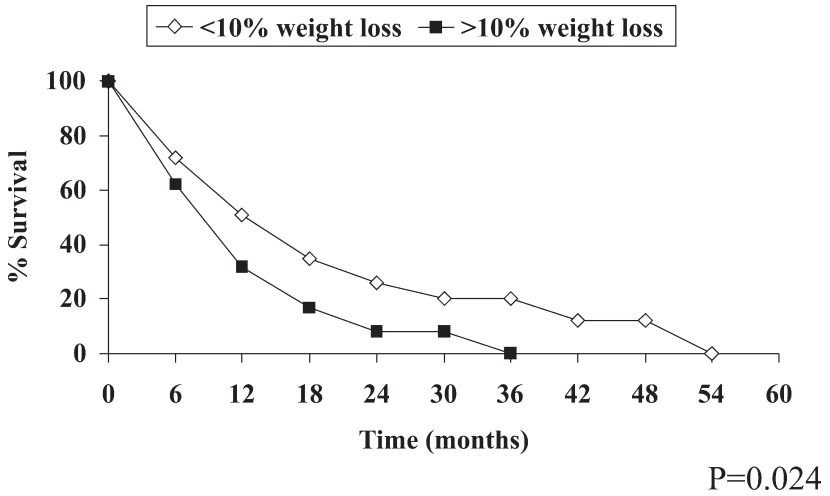


**Figure 3** - Overall survival and weight loss in patients with stage IV disease (extra-CNS metastases only).

1970s and 1980s (unpublished data). The present data showed a shift towards adenocarcinoma, particularly in the male population. This trend is similar to previously published series in other centers around the world.[5,8-11] Our results have also shown a significantly less favorable prognosis in patients presenting with undifferentiated large cell carcinoma, similar to other studies previously published.[12] On the other hand, there were no significant survival differences between adenocarcinoma and squamous cell carcinoma, results confirmed by other studies.[13]

The Karnofsky index (Performance Status-KPS) effectively assessed the general clinical condition of the patient on admission,[12,14] indicating their capability to undergo the proposed treatment with acceptable tolerance.[15,16] The results of the present study showed that approximately 90% of our patients present with a KPS of 80% or 90%. This distribution might not exactly represent the reality of all lung cancer population in Brazil, since it reflects those patients referred to a specialized cancer hospital.

Most data from the medical literature has shown that only 5% to 20% of all lung cancer patients are asymptomatic at the time of diagnosis.[11,17-19] Reports in the literature have estimated 46% to 61% of patients with lung cancer experience significant weight loss by the time of diagnosis.[20-22] In the present study, the results confirmed that nearly three quarters of NSCLC patients presented with significant weight loss (> 10%). Several multivariate analyses correlate the amount of weight lost with a worst prognosis, for these patients are less tolerant to aggressive treatment as well as have poorer survival rates[12,15,16,23].

Our data is comparable to world epidemiological patterns, in which most patients are diagnosed with more advanced tumors (IIIB and IV).[24-27] Patients that are diagnosed at an early stage (and are therefore best indicated for aggressive treatment and present with the best prognosis) are less common.

As for the 1997 TNM staging, our results show that it is an effective method to establish therapeutic and prognostic differences in our patient population. Other authors have previously published similar results from other cancer centers.[28,29]

Nonsmall cell lung cancer patients undergo several surgical procedures, including diagnostic biopsies, resection of primary tumors, and resection of metastasis. Computed tomography-guided cutting-needle biopsy has high sensitivity and specificity and low rates of complications in the diagnosis of indeterminate pulmonary lesions.[30] Our data regarding operable patients is similar to that of the literature, in which an estimated 20% to 38% of patients are candidates for complete resection of the tumor.[31-33]

As shown in most series, in our study, surgical staging proved to be more accurate than clinical staging.[34,35]

It has already been shown that complete tumor resection remains the best therapeutic option for patients presenting with early stage NSCLC.[31,35-39] Our results also indicated that with the more detailed preoperative imaging procedures most patients undergoing surgery were treated with complete surgical resection; unnecessary thoracotomies are mostly avoided.[58]

In the 1990s, the role of systemic treatment of nonsmall cell lung cancer became clearer, with higher efficiency and tolerance of newer drug combinations.[40] Indications for chemotherapy also evolved, with several modalities of treatment: neoadjuvant (preoperative), adjuvant (postoperative), exclusive (in more advanced stages), and associated with radiotherapy. In the Hospital do Câncer A.C. Camargo, 43% of patients received some modality of chemotherapy during the course of their disease.

Adjuvant chemotherapy, following complete resection of the lung cancer, is being intensively studied in multiple centers around the globe, with no convincing data yet. Our hospital participated in a prospective, randomized study of systemic adjuvant treatment following complete resection of lung tumors, stages I to IIIA (IALT), even though adjuvant chemotherapy was not a routine protocol in our institution. Following the recent publication of the results of that trial,[59] adjuvant chemotherapy has been offered on a routine basis to patients with com-

pletely resected nonsmall cell lung cancer in our department.

Lung cancer chemotherapy has changed significantly in the past decade. In the early 1990s, chemotherapy consisted mainly of the MVP combination (mitomycin C, vinblastin, and cisplatin).[41] In more recent years, this has been replaced with 2-drug combinations. Several studies have compared combinations of paclitaxel + carboplatin with high efficiency and tolerance,[40] gemcitabine + cisplatin also with high efficiency and without impairing quality of life, especially in borderline KPS,[44,46] or vinorelbine + cisplatin.[40,43] These studies have led oncologists to expand the indication of chemotherapy to include older patients (> 70 years). Single drug chemotherapy or combinations that mainly include gemcitabine or vinorelbine have been suggested in prospective studies, with both high efficiency and tolerability in elderly patients.[44] On the other hand, Frasci et al.[1] advocated that cisplatin + paclitaxel, carboplatin + paclitaxel, and cisplatin + gemcitabine show no substantial superiority over standard treatments. This could suggest that the addition of a single agent to a platinum compound could be insufficient.[1] Our results show no significant difference between different chemotherapy regimens used.

The question of how many chemotherapy cycles are adequate to achieve maximal tumor response with minimal side effects and complications has been assessed in several studies, which clearly showed no survival advantage for patients that received more than 6 cycles of any given drug combination.[45,46] Accordingly, our data showed that only 4.2% of our patients received more than 6 cycles of chemotherapy. Chemotherapy in stage IV NSCLC not metastatic to the brain has been associated with significantly increased survival rates when compared to best supportive care.[47] Moreover, histopathologic data may help predict the chemotherapy response in small cell lung cancer.[48]

Radiotherapy plays a fundamental role in the treatment of nonsmall cell lung cancer patients. Several indications for radiotherapy have been established, especially in patients with inoperable intrathoracic disease. Radiotherapy may be neoadjuvant, adjuvant, exclusive (in patients with inoperable localized cancers in the thorax), palliative (treatment of central nervous system or bone metastasis or tumors that obstruct airways), or in combination with chemotherapy (for locally advanced disease). The radiotherapy dose depends basically on the type of treatment (neoadjuvant, adjuvant, etc.), tumor volume and location, as well as general health and tolerance of the individual patient.

Currently, the role of postoperative radiotherapy is being evaluated worldwide. A meta-analysis including 2128 patients from 9 different trials concluded that postoperative radiotherapy should not be routinely used for completely resected N0 or N1 patients. For N2 patients, further investigation is recommended.[49] Sawyer showed that postoperative radiotherapy may have been beneficial for patients who underwent surgical resection with N2 and therefore had a higher local recurrence rate.[50,51] Accordingly, standard treatment in our service indicates adjuvant thoracic radiation only for patients with completely resected N2 disease.

However, even though the treatment of lung cancer has evolved, an epidemiological study done in the National Cancer Institute, NIH, Bethesda, has shown that global survival of patients with lung cancer has improved very little (at the general population level) since the 1970s. In 1970, only 10% of the patients diagnosed with lung cancer survived 5 years. In 1998, this rate was only at 14%. These results reflect the diagnosis of most patients at advanced stages of disease and the lack of adequate treatment options for these patients. Our improved overall 5-year survival rate (28%), when compared with figures in the United States, probably reflects the fact that our group represents a selected population from the city of São Paulo—those referred to the Hospital do Câncer A.C. Camargo.

It is widely accepted that survival time is intimately related to the stage of disease at diagnosis and the disease stage as confirmed by pathology samples taken during surgery. The histologic grade of the tumor is another factor that is associated with survival time of these patients. For squamous cell carcinoma, staging, incomplete tumor resection, and nucleus-cytoplasm ratio as well as expression of nucleolar organizer regions identified by an argyrophilic technique[53] have been associated with survival rates[52]. Currently, complete resection of the primary tumor (with free margins)[36,52,54] and dissection of mediastinal lymph nodes[36,55] offer the best chances for long-term survival in these patients.

A more cost-effective follow-up in lung cancer should be performed, which will not compromise overall survival in cases of completely resected NSCLC, since recurrence is more often diagnosed on the basis of symptoms rather than by routine tests.[56]

From the data presented above, one may conclude that nonsmall cell lung cancer is a disease that requires special attention, especially due to its high mortality rates. Even with all available modern treatments, the best prognosis is for patients that undergo complete tumor resection with lymph node dissection, and this is only achievable for earlier clinical stages, demonstrating once more the importance of early detection of disease.

**RESUMO**

YOUNES RN e col. Carcinoma de pulmão não pequena células: validação do sistema de estadiamento em uma única instituição (1990-200). **Rev. Hosp. Clin. Fac. Med. S. Paulo 59**(3):119-127, 2004.

**OBJETIVO:** Analisar o resultado e fatores prognósticos de patients com CPNPC admitidos em uma única instituição e correlacionar os dados com o sistema atual de estadiamento.

**MÉTODO:** Setecentos e trinta e sete pacientes com diagnóstico de CPNPC foram admitidos ao Hospital do Cancer A. C. Camargo entre 1990 e 2000. Todos os pacientes foram incluídos em um banco de dados contínuo prospectivo e seus dados foram analisados. Após o estadiamento, uma equipe multidisciplinar estabeleceu decisões sobre o manejo adequado para o caso. Variáveis analisadas incluíram idade, sexo, tipo histológico, índice de Karnofsky, perda de peso, estadio clínico, estadio cirúrgico, quimioterapia, radioterapia e taxa de sobrevida.

**RESULTADOS:** 75,5% dos pacientes eram do sexo masculino. A distribuição dos tipos histológicos foi carcinoma espino celular 51,8%, adenocarcinoma 43,% e carcinoma indiferenciado de grandes células 5,1%. A maior parte apresentou perda de peso significativa e um Karnofsky Index de 80%. O estadiamento clínico foi IA 3,8%, IB 9,2%, IIA 1,4%, IIB 8,1%, IIIA 20,9%, IIIB 22,4%, IV 30,9%. A ressecção total do tumor foi possível em 24,6% dos casos. A distribuição do estadiamento cirúrgico foi IA 25,3%, IB 1,4%, IIA 1,4%, IIB 17,1%, IIIA 16,1%, IIIB 20,3%, IV 11,5%. Quimioterapia e radioterapia também foram consideradas opções terapêuticas. A sobrevida global de 5 anos em nosso estudo foi de 28%, sendo a sobrevida mediana de18,9 meses.

**CONCLUSÕES:** CPNPC é uma doença que requer atenção especial, devido aos altos índices de morbi-mortalidade. Melhor prognóstico está associado à ressecção completa do tumor, com dissecção de linfonodos. Todavia, isso só é possível em estadios clínicos mais precoces.

UNITERMOS: **Cancer Pulmão. Carcinoma células não-pequenas. Fatores prognósticos. Estadiamento. Resultado tratamento.**

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