



# Risk of cerebral metastases for postoperative locally advanced non-small-cell lung cancer

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## ABSTRACT

**Background:** Cerebral metastases are the main determining factor in the failure of locally advanced non-small-cell lung cancer (NSCLC) management. Our study assessed the risk factors of brain metastases in patients with postoperative, locally advanced NSCLC. Implications for PCI treatment are discussed.

**Methods:** Two hundred twenty-three patients treated with surgical resection for stage III–N2 NSCLC were retrospectively analyzed to elucidate risk factors for development of brain metastases, and to establish a mathematical model.

**Results:** Median survival time for this patient population was 29.5 months. Frequency of brain metastases in the entire patient population was 38.1% (85/223). Frequency of brain metastases in patients with single mediastinal lymph-node region with metastases at 1, 2, and 3 years was 5.6%, 14.0%, and 19.0%, respectively. The frequency of brain metastases in patients with multiple mediastinal lymph-node regions with metastases was 31.8%, 60.3%, 68.0%, respectively ( $P < 0.001$ ). The frequency of brain metastases among patients with mediastinal metastasis number less than 4, 4–6, and more than 6 was significantly different ( $P < 0.001$ ). There were also significant differences in brain metastases frequency between patients with complete versus incomplete resection ( $P = 0.001$ ), and patients with non-squamous versus squamous ( $P = 0.029$ ), and patients administered adjuvant chemotherapy versus none ( $P = 0.032$ ).

**Conclusion:** A mathematical model to predict brain metastases risk was developed. It can aid in selection of patients with locally advanced NSCLC for PCI in clinical trials.

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## 1. Introduction

Locally advanced non-small-cell lung cancer (LA-NSCLC) is referred to as stage IIIA/IIIB NSCLC, which involves the mediastinal lymph nodes N2, part of N3 and T4. LA-NSCLC comprises 31–44% of all NSCLC. About 50% patients with LANSCLC will develop brain metastases during the course of treatments [1,2]. High risk of brain metastases has become the critical factor influencing the prognosis of LA-NSCLC patients [1–3]. Prophylactic cranial irradiation (PCI) has been demonstrated to decrease the frequency of brain metastases and increase overall survival in small cell lung cancer patients with complete response (CR) [4]. Because PCI has shown effectiveness in small-cell lung cancer (SCLC), several groups have applied PCI for the treatment of NSCLC. To date, results indicate that PCI has decreased development of brain metastases by approximately 50% in LA-NSCLC [5–10]. These studies raise the issue whether

all patients with LANSCLC should receive PCI. The purpose of this analysis was to evaluate the risk of cerebral metastases for postoperative, locally advanced NSCLC, and to assess potential benefit of PCI.

## 2. Materials and methods

This study was formally approved by the Committee on Human Research at the Medical School of Sun yet-sen University (SUMS) before collection of all patient information. The 223 locally advanced NSCLC patients who underwent definitive surgical resection between December 1998 and December 2003 were retrospectively reviewed. No patient had a history of prior malignancy. Patients were retrospectively staged IIIA (N2)/IIIB (T4) (additional nodules in the primary lobe or tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina) in accordance with 1997 NSCLC guidelines using postoperative pathology. All patients had negative pretreatment head computed tomography (CT) scan or MRI as part of their initial staging preoperatively.

The surgical procedure consisted of lobectomy, pneumonectomy or wedge excision, plus resection of mediastinal lymph node.

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Resection of primary tumor and mediastinal lymph node dissection with negative bronchial residuals was defined as complete resection. Incomplete resection was defined as leaving residual primary tumor, mediastinal lymph node(s), or tumor-positive bronchial regions. Mediastinal lymph nodes using the lung cancer mediastinal lymph node map were divided into 3 areas: (1) Superior mediastinal area, which consisted of highest mediastinal node, upper paratracheal node, pre-vascular and retrotracheal node and lower paratracheal. (2) Aortic area, which consisted of subaortic node and para-aortic node. (3) Inferior mediastinal area, which consisted of subcarinal node, paraesophageal node and pulmonary ligament node. Tumor involvement of mediastinal lymph nodes was scored as single area (L1), two areas (L2) and three areas (L3) when metastases occurred in lymph nodes from only 1 region, 2 regions, or all 3 regions, respectively. About half of the patients received postoperative platinum based chemotherapy. All the patients with incomplete resection were administered postoperative radiotherapy.

Long-term outcome was determined from hospital records and correspondence with referring physicians. Both the initial and subsequent sites of recurrence were also documented. Follow-up schedule was defined from the time of pulmonary resection. Follow-up imaging included chest X-ray and abdomen B-ultrasound every 3 months, chest CT every 6 months, and cranial CT/MRI each year. A coherence assessment was performed immediately when symptoms arose. Last follow-up for all patients' was March 30th, 2006.

Overall survival (OS) was estimated by the Kaplan–Meier method. Comparisons of prognostic factors were tested by the log-rank test. The incidence rate of brain metastases was estimated by the life table method. Patients who died without evidence of brain metastases were placed in the no brain metastases group at their time of death. The Wilcoxon (Gehan) test was used in the univariate analysis of potential risk factors for development of brain metastases. The variables considered were age, sex, histology, tumor size, nodal status, resection type, and postoperative chemotherapy. Univariate logistic regression analysis was used initially to assess the association between each risk variable and incidence of brain metastases. Multivariate stepwise logistic regression analysis determined variable selection (with entry cutoff level of 0.1 and stay cutoff of 0.2). Stepwise variable selection was performed on all sampled data to develop a brain metastases prediction model. The analysis was performed using the SPSS11.0 statistics software.

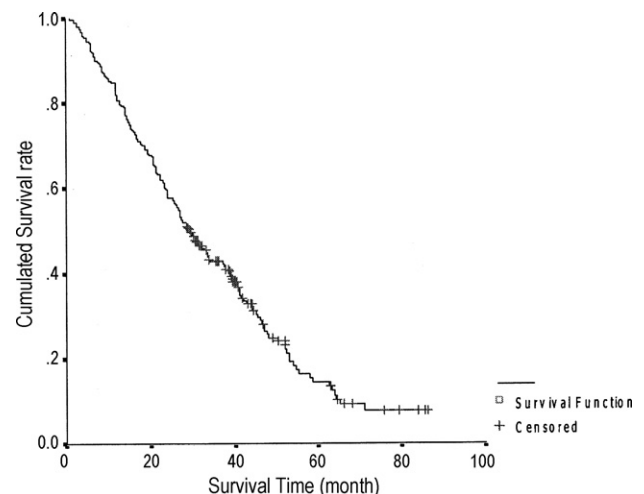
### 3. Results

Table 1 outlines the clinical and disease characteristics of the 223 patients which were 165 males and 58 females. The median age was 56 years (range, 24–77). Distribution of surgical procedure was: 161 lobectomy, 50 pneumonectomy, and 12 wedge excision. Postoperative histology included 69 (31%) squamous cell carcinoma, and 154 (69%) non-squamous cell carcinoma. TNM stage was: 187 (84%) IIIA, 36 (16%) IIIB, with 36 (16%) T4. Surgical resection was: 179 (80%) complete resection, 44 (20%) incomplete resection. After operation, 117 patients received platinum based chemotherapy. A total of 85 patients (38.1%) developed brain metastases, and 59 of these patients (26.5%) developed brain metastases as the first site of relapse.

Median survival for the entire patient population was 29.5 months (Fig. 1). The overall survivals at 1, 2, and 3 years were 82.1%, 59.2%, and 42.8%, respectively. Table 2 reveals the factors which influence overall survival. Overall survival (OS) of patients with metastases in multiple mediastinal lymphnode regions (L2 and L3) was significantly worse than patients with single area metastases

**Table 1**  
Characteristics of patients (N = 223)

| Characteristics                           | Total patients (%) |
|-------------------------------------------|--------------------|
| Age (year)                                |                    |
| Media                                     | 56                 |
| Range                                     | 24–77              |
| Gender                                    |                    |
| Male                                      | 165 (74)           |
| Female                                    | 58 (26)            |
| Histology                                 |                    |
| Squamous cell                             | 69 (31)            |
| Non-squamous cell                         | 154 (69)           |
| Pathology stage                           |                    |
| IIIA                                      | 187 (84)           |
| IIIB                                      | 36 (16)            |
| T staging                                 |                    |
| T1                                        | 10 (4)             |
| T2                                        | 109 (49)           |
| T3                                        | 68 (31)            |
| T4                                        | 36 (16)            |
| N staging                                 |                    |
| Region of lymph nodes involvement         |                    |
| L1                                        | 133 (60)           |
| L2                                        | 75 (33)            |
| L3                                        | 15 (7)             |
| Number of lymph nodes involvement         |                    |
| 1–3                                       | 135 (60)           |
| 4–6                                       | 64 (29)            |
| >6                                        | 24 (11)            |
| Surgical procedure                        |                    |
| Lobectomy                                 | 161 (72)           |
| Pneumoectomy                              | 50 (23)            |
| Wedge excision                            | 12 (5)             |
| Surgical resection                        |                    |
| Complete                                  | 179 (80)           |
| Incomplete                                | 44 (20)            |
| Adjuvant chemotherapy                     |                    |
| No                                        | 106 (48)           |
| Yes                                       | 117 (52)           |
| Postoperative metastases                  |                    |
| Brain metastases                          | 85 (38)            |
| Brain metastases as first site of relapse | 59 (27)            |



**Fig. 1.** Overall survival 223 patients.

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