

## Pn1 Involvement Independently Affects Long-Term Survival of Pn2 Stage Non-Small Cell Lung Cancer after Thoracic Surgery

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### Abstract

**Background:** Lung cancer remains the most common cause of cancer death worldwide. Anatomical lung resection remains the standard in early-stage lung cancer, but the ideal therapy for advance-stage Non-Small Cell Lung Cancer (NSCLC) with pN2 lymph node involvement remains controversial. In most cases pN1 and pN2 lymph nodes are affected consecutively (N1N2). Nevertheless, pN2 metastases also occur without pN1 involvement-termed skip-N2 metastases (N0N2). We reviewed current literature regarding the overall survival of N0N2. Furthermore, we discussed the possibilities of implementing N0N2 into the guidelines and if those patients would benefit from a different treatment modality.

**Summary:** According to the literature, N0N2 is a prognostic factor for long-term survival in pN2 stage patients compared to N1N2. The overall survival of N0N2 patients is similar to pN1 stage NSCLC patients. Despite significant long-term survival differences, the current guidelines do not distinguish between N0N2 and N1N2. In our opinion, patients with N0N2 and N1N2 should receive different therapies. It would be beneficial to evaluate the pN1 involvement preoperatively, in order to provide different therapeutic approaches for N0N2 and N1N2 patients. However, such a strategy is dependent on the efficiency of intrapulmonary lymph node assessment.

**Key messages:** N0N2 patients show significantly higher survival rates compared to patients with N1N2. Overall, pN2-stage NSCLC patients would benefit from a more sophisticated preoperative intrapulmonary lymph node assessment allowing for a more precise multimodal therapy.

**Keywords:** Non-small cell lung cancer; Lymph-nodes; Adjuvant chemo radiation therapy; Radical lymphadenectomy; Stage N2 disease

### Introduction

Despite significant improvements in therapy and diagnostics over the past decade, lung cancer remains the most common cause of cancer death worldwide [1]. Even though, pulmonary resection remains the gold standard in the therapy of early-stage lung-cancer [2], the therapy of locally advanced Non-Small-Cell-Lung-Cancer (NSCLC) remains controversial [3]. Besides tumour size, lymph node involvement in particular contributes substantially to the prognosis of NSCLC patients. Therefore radical lymphadenectomy during surgical resection is mandatory during thoracic surgery. Dependent on the involvement of hilar, intralobular or mediastinal lymph nodes, lymph node involvement is classified into pN0, pN1 (hilar and intralobular lymph nodes), pN2 (mediastinal) and pN3 (contralateral). pN0 patients have no detectable lymph node involvement. According to guidelines, pN1 patients should receive adjuvant chemotherapy, whereas pN2 stage patients receive a combined adjuvant chemo radiation therapy [2,4]. Patients in pN3 stage are not considered suitable for surgical intervention. Mostly, pN1 and pN2. Mostly, pN1 and pN2 lymph nodes are affected consecutively as continuous-N2 metastases (N1N2), but pN2 metastases may also occur in the absence of pN1 metastases as skip-N2 metastases (N0N2). In those cases, N0N2 patients skip the hilar lymph nodes with direct drainage from tumour cells to the mediastinum, by vessels neglected by intrapulmonary lymph nodes. This anomaly is described since 1980 [5] and is detectable in approximately 20%-30% of examined cases [6,7]. It appears that patients with N0N2 have favourable long-term prognosis compared to patients with N1N2 [6-8].

This work is intended to review the current literature surrounding the survival rates of skip-N2 metastases, discuss the possibilities of

implementing N0N2 and N1N2 into the guidelines and to debate about different treatment modalities.

### Are Skip-N2 Metastases a Prognostic Factor for Long-Term Survival in pN2 Stage Patients?

Several studies indicated a significantly improving survival in N0N2 patients compared to N1N2 patients [8-10]. Very recently Li et al. reported from a Chinese collective where they included 2653 patients into a retrospective study [8]. 881(32%) were diagnosed with N0N2. The authors demonstrated a significant better overall survival of N0N2 patients (p=0.0019) compared to patients with N1N2. The study published by Li et al. is currently the largest analysis dealing with skip-N2 metastases [8]. Our study group presented comparable results identifying skip-N2 metastases as an independent factor for a better long term survival [9]. Apart from significantly worse long-term survival for N1N2 patients, Cao et al. and Yazgan et al. demonstrated, that the

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overall of survival of N0N2 patients was similar to patients with a pN1 stage NSCLC [11,12]. Yagzan et al. showed that the pN1 stage patients in their cohort had a median survival of 73.1 months, patients with N0N2 of 60.3 months and patients with N1N2 of 21.8 months [2,11]. All these significant results naturally raise the question of whether the distinction between N0N2 and N1N2 is underrepresented in the current guidelines.

### Implementing Skip-N2 Metastases into the Guidelines

Skip-N2 metastases are not addressed in the guidelines on pN2 stage NSCLC so far [2,13]. But the International Association for the Study of Lung Cancer (IASLC) already proposed to include subcategories of pN2 disease, like N0N2, for a potential revision of the current UICC 8 staging model [3,14]. Hopefully, we are able to contribute with the previous work as well as this work a part to keep the discussion going [9].

### Should we Treat Patients with N1N2 Differently?

PN2 stage NSCLC patients clearly benefit from a neo adjuvant therapy approach [15,16]. However, there are to date no clear recommendations for neo adjuvant therapy by any professional societies [2,13]. Due to their poor overall survival especially N1N2 patients could benefit substantially from this therapeutic approach. Hence, patients with N0N2 could be directly subjected to surgery followed by an adjuvant therapy. A preoperative differentiation between N0N2 and N1N2, in patients with a reasonable suspicion of N2 involvement in the Positron Emission Tomography-CT scans (PET-CT), would be possible if i.e., N1 lymph nodes X and XI and N2 lymph nodes VII and VIII were biopsied *via* End Bronchial Ultra-Sound (EBUS), respectively. However, such a strategy is dependent on the efficiency and the availability of preoperative intrapulmonary lymph node assessment. Currently, there are no particular pneumological or pathological protocols for this particular approach of preoperative extensive lymph node staging.

### Is the Adjuvant Therapy for pN2 Stage NSCLC Patients Still Appropriate?

At least according to European guidelines pN2 stage NSCLC patients irrespective of their pN1 involvement, receive Cisplatin and Vinorelbine or Cisplatin and Etoposide as first-line adjuvant chemotherapy for four to six cycles and a radiation therapy with 60 Gray radiation doses [2,4]. Therefore, the currently available adjuvant therapy potential is exhausted. Furthermore, especially Platin-based therapies have severe side effects, like polyneuropathies and chronic kidney injury [17]. Unfortunately, N1N2 patients still have poor survival rates [8,9]. It is plausible that N0N2 patients are over treated and/or N1N2 patients are undertreated with the current therapeutic approach, in particular keeping in mind the significantly better survival rates of N0N2 patients, which are similar to pN1 stage patients [11,12], it is more likely that the treatment of N1N2 patients should be revised. Targeted and immune therapies are well established in stage IV lung cancer [18].

Unfortunately, these treatments are not yet approved as the first line adjuvant therapy, but instead are only considered in the event of relapse. N1N2 patients in particular might benefit from the implementation of these therapies as first-line adjuvant therapy. Obviously, a modification of the treatment of N0N2 patients would also be conceivable. Due to the current guidelines pN1-stage patients receive a platin-based chemotherapy [13]. If pN2 lymph nodes are affected consecutively this is followed by a mediastinal radiation therapy [2]. Now, of course, if no N1 lymph nodes are affected, as in the N0N2 patients, one could

postulate that exclusive mediastinal irradiation would be sufficient for these patients.

### Conclusion

Patients with skip-N2 metastases showed significantly better survival rates compared to patients with continuous-N2 metastases. The studies included in this review agree that pN2-NSCLC patients would benefit from a more sophisticated preoperative intrapulmonary lymph node assessment in order to implement a more precise multimodal therapy.

### Conflict of Interest

No Conflict of Interest

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