RESEARCH ARTICLE

Number of Mediastinal Lymph Nodes as a Prognostic Factor in PN2 Non Small Cell Lung Cancer: A Single Centre Experience and Review of the Literature

Silvia Takanen*, Caterina Bangrazi, Vanessa Graziano, Alessandro Parisi, Blerina Resuli, Luca Simione, Rossella Caiazzo, Nicola Raffetto, Vincenzo Tombolini

Abstract

Currently the most important prognostic factor in lung cancer is the stage. In the current lung TNM classification system, N category is defined exclusively by anatomic nodal location though, in other type of tumours, number of lymph nodes is confirmed to be a fundamental prognostic factor. Therefore we evaluated the number of mediastinal lymph nodes as a prognostic factor in locally advanced NSCLC after multimodality treatment, observing a significant effect of the number of lymph nodes in terms of OS (p<0.01) and DFS (p<0.001): patients with a low number of positive mediastinal nodes have a better prognosis.

Keywords: Locally advanced NSCLC - number of lymph nodes - prognosis

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Introduction

Lung cancer is one of the most common cause of cancer-related death for men and women in the world. The prevalent histology is non-small cell lung carcinoma (NSCLC), including squamous cell carcinoma, adenocarcinoma and large cell carcinoma (Moretti et al., 2009), with a 5- year survival rate of 67% (stage IA) to <5% (stage IV) (End, 2006).

Currently the most important predictor of survival in lung cancer is the stage (TNM) (Kligerman and Abbot, 2010; Goldstraw, 2009). Despite the new staging system (Kligerman and Abbot, 2010), stage III NSCLC remains a very heterogeneous disease , with a 5-year survival rate ranging from 35% to 5%. There are two major treatment targets for of patients with stage III : locoregional control and control of micrometastases, preventing distant metastatic disease (Penland et al., 2004; Bradley et al., 2005). The standard of care is represented by multimodality treatment, comprehending surgery for resectable disease, perioperative chemotherapy and radiation therapy (RT) for patients with pathological (p) N2 disease (Okamoto, 2008).

In current TNM classification system, N category is defined exclusively by anatomic nodal location, though number of lymph nodes confirmed to be a fundamental prognostic factor as in other type of tumours.

In our study, we assessed, in patients with stage III N2 category NSCLC disease, the prognostic value of the number of lymph nodes after multimodality treatment.

Materials and Methods

We evaluated 65 patients affected by NSCLC, from January 2005 to December 2010, at the "Sapienza" - University of Rome, Policlinico Umberto I, Department of Radiation Oncology.

Clinical records and official pathological reports of patients who underwent surgical resection for primary lung cancer were reviewed retrospectively.

Forty-nine patients were male (75.4%) and 16 female (24.6%). The mean age was 67.13 years (range 29-86). All patients underwent surgery and were completely resected: 60 lobectomy and 5 pneumonectomy.

Forty-one patients (63%%) were classified as IIIA stage and 24 patients (37%) as IIIB. Pathologic staging was carried out according to the current 7th edition of TNM classification. Histological examination showed pathological lymph nodes classified as pN2.

Histology evidenced squamous cell carcinoma in 19 patients (30%), adenocarcinoma in 46 patients (70%). Mediastinal nodal number evaluation were performed after surgery: all patients were divided in three groups based on the number of mediastinal lymph nodes (pN2) involved: <5, 5-7 and >7 or more.

Platinum-based chemotherapy (for almost 3 cycles) was administered in all patients as adjuvant treatment.

Postoperative radiotherapy (PORT) was delivered with a 6 MV linear accelerator, median total dose of 50.4 Gy (daily fraction: 180/200cGy), using a three-dimensional external conformal radiotherapy (3D-ECRT) technique.

[1]*Department of Radiation Oncology, Azienda Policlinico Umberto I, "Sapienza" University of Rome. Viale del Policlinico Italy*
**For correspondence: silvia.takanen@gmail.com*

Target volumes included the bronchial stump, ipsilateral hilum and all mediastinal regions with pathologically involved lymph nodes.

The analysis of survival was conducted according to the Kaplan-Meier method and using the Log-Rank Test analysed overall survival (OS) and disease-free survival (DFS) for each group according to T and N stage.

Results

Median follow-up time was 30 months (range 2-76 months).

For overall patients, median OS was 36.55 months (Figure 1) and median DFS 27.99 months (Figure 2).

OS and DFS were 93.85% and 83.08% respectively at 12 months, 78.46% and 58.46% respectively at 24 months, 53.60% and 38.20% respectively at 36 months, 22,90% and 9.76% respectively at 60 months.

Local lung relapse was observed in 24 patients (37%), in 19 out of field. Mediastinal lymph nodal recurrence was evidenced in 8 patients (12.3%), 3 in field and 5 out of field.

We observed the following acute effects during radiotherapy: 30 patients with lung toxicity (grade 1-2), 24 patients with dysphagia (grade 1-2) and 12 patients with anemia (grade 1). Late heart toxicity was observed in 3 cases (4.6%): 2 patients died for acute myocardial infarction and 1 for chronic heart failure.

We observed a significant effect of the number of lymph nodes (N) in terms of OS (p<0.01) (Figure 3) and DFS (p<0.001) (Figure 4). Specifically, median OS

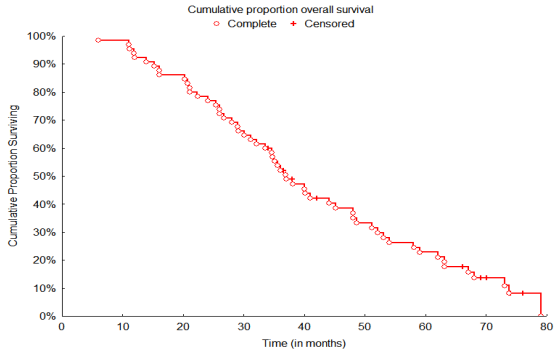

Figure 1. Median OS in Patients Stage III N2 Disease

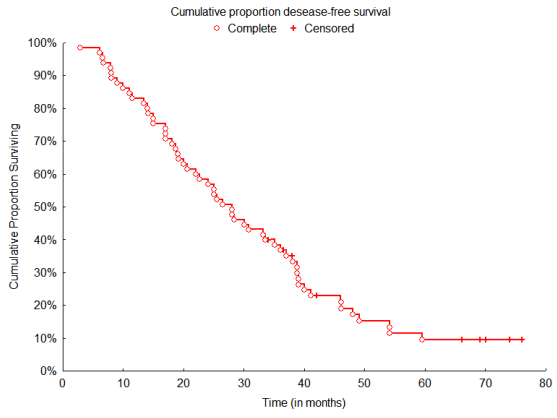

Figure 2. Median DFS in Patients Stage III N2 Disease

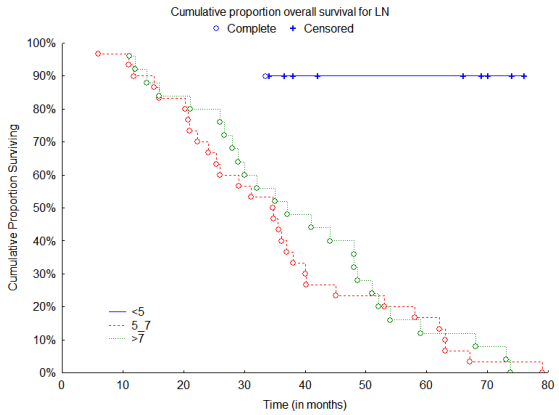

Figure 3. Cumulative Proportion of OS for Nodal Number (p<0.01)

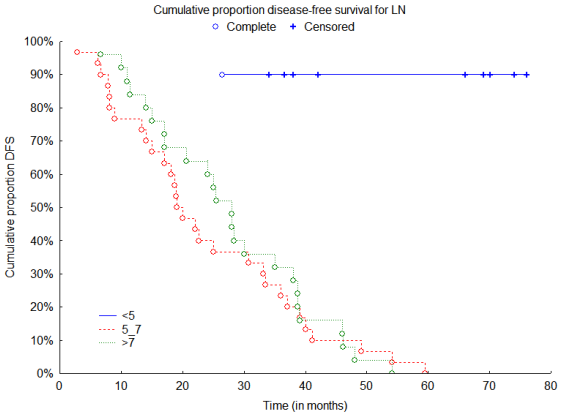

Figure 4. Cumulative Proportion of DFS for Nodal Number (p<0.001)

and DFS for the group with <5 N were 54.07 and 54.06 months respectively, for the group with 5-7 N were 19.57 and 34.72 months respectively, and for the group with more than 7 N were 27.99 and 37.04 months respectively.

Moreover, two-sample log-rank tests revealed longer survival time for patients with <5 lymph nodes than for patients with 5-7 nodes (p<0.001) and with more than 7 (p<0.001) nodes.

Discussion

Currently lymph node status is regarded as a valid risk stratification tool and the most powerful prognostic factor for patients with lung cancer (Osarogiagbon, 2012). However 44% of patients with pathological node negative (pN0) disease still die within 5 years. The number of stations of N2 nodes involved has been considered one of the most important prognostic factors for lung cancer. Though the improvement of the rate of preoperative detection of occult N2 involvement (e.g. with PET scan), many patients are still diagnosed as pN2 after surgery and then selected for multimodality treatment (Saji, 2011).

In this study we analyzed the number of mediastinal lymph nodes as predictors of survival in patients with stage III N2 NSCLC after multimodality treatment.

Recent studies showed that mediastinal nodal involvement independently influences the prognosis of

NSCLC patients, particularly in the case of chest wall invasion (Doddoli et al., 2005; Wakelee et al., 2005; Lee et al. 2012; Mantovani et al., 2012).

Although progress has been made in treatment for locally advanced NSCLC, patients with N2 have a poor outcome even when surgical resection is complete. Currently TNM classification considers the anatomic location for every N category and patients with N2 are included in a very heterogeneous population with multiple subgroups, ranging from microscopic N2 to bulky multistation nodal involvement. Five-year survival rate is very low, from 35% for favourable N2 disease (single lymph node or single-station involvement or microscopic metastases) to <5% in multistation, bulky N2 disease (Moretti et al., 2009). Many studies have evaluated the validity of various prognostic factors among pN2 NSCLC patients in order to identify a more accurate classification system (Nwogu et al., 2012; Macia et al., 2013). The prognosis of N2 NSCLC remaines poor and most oncologists believe that surgery alone is not sufficient for N2 disease. Many patients with N2 disease receive perioperative chemotherapy to improve their survival. It was suggested that some cases can be treat with surgery alone while others should be considered for more intensive treatments.

A recent meta meta-analysis of cisplatin-based adjuvant chemotherapy for NSCLC showed that the 5-year survival benefit in favour of chemotherapy was 5.3% (Bria et al., 2009).

Though some studies have shown that a single station of mediastinal node metastasis was an acceptable prognostic predictor (Doddoli et al., 2005), an increased number of positive nodes was associated with a worse prognosis (Fukui et al., 2006).

The current TNM classification system for lung cancer considers only the anatomical lymph nodal extent to define the N category (Detterbeck et al., 2009 ;Goldstraw, 2009). However the TNM classification for other type of cancers has been updated to include the number of nodal stations involved, that has been shown to be a

more effective prognostic indicator than the anatomical location also in NSCLC (Detterbeck et al., 2009; Saji et al., 2011; Nwogu et al., 2012). It was suggested that a combined anatomically based pN stage classification and numerically based nN stage classification could be a more accurate prognostic determinant in patients with heterogeneous pN2 NSCLC (Saji et al., 2013). Thus we evaluated the number of mediastinal lymph nodes involved as predictor of survival.

Despite the limitations of this retrospective study, mainly represented by the small sample of patients and the unbalanced number of patients for each group, we confirmed that the number of lymph nodes involved has a prognostic value, related to OS and DFS: a lower number of lymph nodes is associated with a better prognosis, considering both OS and DFS, particularly in that group with a number of nodal stations involved up to 5.

Furthermore recent studies support the role of PORT in NSCLC in terms of locoregional control and overall survival benefit (Maximus et al., 2012). Our study confirmed these data with limited toxicity during and after radiation treatment.

For patients with locally advanced disease, ongoing research is focused on appropriately identifying patients who will most benefit from the addition of surgery to a multimodality regime and safely integrating resection with chemotherapy and radiotherapy.

A multimodal strategy with surgery followed by chemotherapy and RT is a safe and reasonable treatment in locally advanced NSCLC, but no clear evidence of prognostic improvement may be assumed at the present time and in this subset of patients adequate selection of the optimal therapeutic strategy remains to be defined.

In conclusion, though the possibility of the use of multimodal strategy, such in our sample, the number of mediastinal lymph nodes involved showed to determine a poor prognosis in locally advanced NSCLC.

Studies are needed to validate the number of mediastinal lymph nodes involved as prognostic factor, in the context of an upcoming revision of TNM classification system in NSCLC.

Further investigation of combined modality treatment is warranted to improve survival in the subset of stage III N2 NSCLC

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ST and CB participated in writing up and revising the manuscript. VG, BR, AP and RC analyzed the patient data and revised the manuscript. LS performed the statistical analysis. NR and VT revised the final manuscript.

All the authors read and approved the final manuscript.

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