Chemotherapy: Open Access
ISSN: 2167-7700

Berardi et al., Chemotherapy 2013, 2:3
DOI: 10.4172/2167-7700.1000120

Research Article Open Access

Prognostic Factors in Early Stage Non-Small Cell Lung Cancer: The Importance of Number of Resected Lymph Nodes and Vascular Invasion

Rossana Berardi[1]*, Alfredo Santinelli[2], Alessandro Brunelli[3], Francesca Morgese[1], Azzurra Onofri[1], Agnese Savini[1], Miriam Caramanti[1], Cecilia Pompili[3], Michele Salati[3], Lina Zuccatosta[4], Paola Mazzanti[1], Armando Sabbatini[3], Stefano Gasparini[4], Italo Bearzi[2] and Stefano Cascinu[1]

[1]*Medical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I – GM Lancisi – G Salesi, Ancona, Italy*
[2]*Section of Pathological Anatomy and Histopathology, Department of Neuroscience - Università Politecnica delle Marche, Ancona, Italy*
[3]*Thoracic Surgery, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I – GM Lancisi – G Salesi, Ancona, Italy*
[4]*Pneumology, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I – GM Lancisi – G Salesi, Ancona, Italy*

Abstract

Background: Despite an appropriate surgical treatment, half of early-stage non-small cell lung cancer patients will die due to lung cancer. The number of resected lymph-nodes and vascular invasion has proved to be a prognostic factor in other solid tumors, as well as breast and colorectal cancer. Here we evaluate their prognostic impact in the largest mono-centric series of resected non-small cell lung cancer patients.

Methods: Clinical and pathological characteristics and prognostic outcomes of four hundred thirty-nine consecutive patients undergoing radical surgical resection for non-small cell lung cancer at our Institution were evaluated.

Results: The multivariate analysis showed that number of resected lymph nodes, vascular invasion and sex had a prognostic impact on overall survival. The optimal cut-off number of lymph nodes with the highest sensitivity and specificity for estimating the outcome was set at ten after Receiver Operating Characteristics curve analysis. Removing ten lymph nodes in our study represents a cut-off with a significant prognostic impact particularly in resected stage II non-small cell lung cancer.

Conclusions: Similarly to other cancer types (for example colorectal cancer), our results suggest that an adequate classification of non-small cell lung cancer should always include an adequate lymph nodes clearance, particularly in stage II non-small cell lung cancer. Again vascular invasion resulted independent prognostic factors for overall survival. Therefore the number of resected lymph nodes, together with vascular invasion, may also drive the selection of non-small cell lung cancer patients for adjuvant treatment. Lung cancer is one of more aggressive tumor. Lung tumor surgery with loco-regional lymphadenectomy represents the only way for the eradication of neoplastic disease. In particular, an adequate lymph nodes clearance, especially in stage II non-small cell lung cancer may modify prognosis.

Keywords: Non-small cell lung cancer; Number of resected lymph-nodes; Vascular invasion; Prognostic factors; Radical surgery; Overall survival

Abbreviations: NSCLC: Non-Small Cell Lung Cancer; TNM: Tumor-Node-Metastasis; pN: pathological Nodes; ECOG: Eastern Cooperative Oncology Group; ROC: Receiver Operating Characteristics; OS: Overall Survival; R0: radical surgery; HR: Hazard Ratio

Introduction

Despite recent progresses in the diagnosis and treatment, lung cancer still remains the leading cause of death due to tumour worldwide [1]. Complete surgical resection of the primary tumour and local nodal metastasis is the only potentially curative treatment, but the prognosis of patients who undergo radical surgery remains poor with a 5-years survival rate of 25-40% [2,3]. Surgical resection alone has been the standard of care for resectable NSCLC, but still some disagreement regarding the benefits of complete lymph node (LN) dissection remains [4].

Tumor-node-metastasis (TNM) staging is essential for therapy assignment and prognosis and has been used widely in the investigation and treatment of this tumor [1,5]. In the latest TNM classification the number of metastatic lymph nodes is included in the definition of pN categories in breast, gastric, and colorectal cancer, showing significant correlation with prognosis [6-10]. In the classification of lung cancer, only the anatomic extent of lymph node metastases defines the pathologic N category [11]. However, few studies have suggested the importance of the number of lymph node metastases in resected NSCLC [12].

An adequate number of retrieved lymph nodes is an essential component in evaluating the prognostic significance of the metastatic lymph nodes. Analysis of data for cancers of the colon, breast, and bladder demonstrated that the number of lymph nodes evaluated during staging is associated with postoperative survival [13-19]. In gastric cancer, we previously showed that an inadequate lymph nodes resection can affect survival and result in a higher incidence of local relapse [20]. In lung cancer, Ludwig and associates [21] recommended that an evaluation of nodal status should include somewhere between

***Corresponding author:** Rossana Berardi, MD, Lecturer in Medical Oncology, Consultant Medical Oncologist, Clinica di Oncologia Medica, Università Politecnica delle Marche, Azienda Ospedaliero–Universitaria, Umberto I – GM Lancisi – G Salesi di Ancona, via Conca 71, 60020 Ancona, Italy, Tel: +390715965715; Fax: +390715965053; E-mail: r.berardi@univpm.it

Received September 01, 2013; **Accepted** December 10, 2013; **Published** December 12, 2013

Citation: Berardi R, Santinelli A, Brunelli A, Morgese F, Onofri A, et al. (2013) Prognostic Factors in Early Stage Non-Small Cell Lung Cancer: The Importance of Number of Resected Lymph Nodes and Vascular Invasion. Chemotherapy 2: 120. doi:10.4172/2167-7700.1000120

11 to 16 lymph nodes. The study from Varlotto et al. [22] evaluated 24,273 patients with stage I NSCLC who underwent a definitive surgical procedure. The optimal number of sampled lymph nodes ensuring the highest staging accuracy should be not less than 11 N1 dissection and 7 N2 dissection lymph nodes.

Two large retrospective reviews conducted by Gajra et al. [23] and Doddoli et al. [24] analyzing 442 and 465 patients, respectively, found that removal of at least 6 lymph nodes (for patients with six or fewer lymph nodes assessed, DFS was 52%, and the patients with more than six lymph nodes assessed had DFS of 75% at 5 years (p= 0.001)) and dissection of at least 3 mediastinal stations or removal of 10 lymph nodes and dissection of at least 2 mediastinal stations, were associated with improved survival [22] (Table 1).

Again, Lee and colleagues supported the conclusion that they can predict patient prognosis after surgery for NSCLC according to the number of lymph node metastases instead of the anatomic extent of lymph node metastases. At the very least, the number of metastatic lymph nodes can add new information to the pN category of the current TNM classification system [6].

Focusing on an homogeneous series of NSCLC patients, this study could therefore give a relevant contribute to understand the role of lymph nodes in this setting. Furthermore, nowadays NSCLC patients are subject of heavy multi-modal treatment with chemotherapy and other biological agents and patients with a localized disease at diagnosis represent a small group, nevertheless studies about prognostic factors can provide information about NSCLC biology and can guide the oncologist to select a particular adjuvant treatment or a certain therapy at the time of relapse.

In addition to the lymph node involvement, several other clinical-pathological factors may have a prognostic role in NSCLC, including intratumoral vascular invasion [4,25,26]. Naito et al. [26] analyzed 826 patients with completely resected NSCLC. Positive vascular invasion was significantly correlated with worse prognosis if compared with absence of infiltration of blood vessels (5-year survival, 90.5% vs 71.0%, p<0.001). This results were observed in each subgroup of T1a (92.9% vs 72.5%, p<0.001), T1b (89.7% vs 77.2%, p= 0.015), and T2a (86.3% vs 65.6%, p<0.001) [26].

Gabor et al. [27] examined 72 patients and reported that vascular invasion at univariate together with multivariate analysis, was a significant prognostic factor in patients with resected, node-negative NSCLC whereas lymph vessel infiltration had no significant impact on outcome. In particular if it was present invasion of the blood vessels the survival rate was 23.5%, in cases without invasion 74.5% (p<or=0.01) [27] (Table 2). In contrast, Fujisawa and colleagues reported both blood (p=0.0046) and lymphatic vessel invasion (p=0.0267) as prognostic factors in 66 NSCLC [13].

Furthermore there are several evidences that the presence of vascular invasion is a strong prognostic factor, in particular in patients with node-negative small lung tumors. Therefore vascular invasion in this setting may have an important role in considering the indications for adjuvant chemotherapy [26].

Vascular invasion seems to correlate with adenocarcinoma histotype, increased tumor dimensions and tumor infiltrating lymphocytes and it is a stronger prognostic indicator than T size in T1a-T2b categories according to the 2009 TNM staging system [28].

The objective of our study was to clarify the role of the number of resected lymph nodes and of vascular invasion as prognostic factors in a large group of patients who underwent surgical resection for NSCLC, with the aim to serve as a tool for a more accurate and rational treatment selection in the adjuvant setting.

Patients and Methods

Patients selection

The study includes 439 patients with a histological diagnosis of clinical stage I–III NSCLC who had undergone radical surgery at the Department of Thoracic Surgery of Polytechnic University of Marche Region from January 1996 to December 2001 and who was then

Author	Year	Patients'number	Staging	N. Lymph Nodes	OS (%)	OS (months)	DFS (%)
Ludwig et al. [21]	2005	16,800	I	5-8 9-12 13-16	12%* 15%* 26%* (5y)	97 (11-12 lymph nodes resected)	
Varlotto et al. [22]	2009	24, 273	I	11-16° 7-10^	68 78 (4y)		79 85%
Gajra et al. [23]	2003	442	I	0-3 4-6 7-9 >9	47 73 76 79		43 67 76 75
Doddoli et al. [24]	2005	465	I	>10	64		
Maeda et al. [25]	2013	439	I-III	<10 >10		38.43 47.34	

*without RT
°N1 dissection
^N2 dissection

Table 1: Published studies focusing on lymph nodes dissection in NSCLC.

Author	Year	Patients'number	Staging	Vascular invasion	OS (%)	OS (months)	DFS (months)
Naito et al. [26]	2010	826	I-IIA	Present Absent	71 93		
Gabor et al. [27]	2004	72	I-IIA	Present Absent	23.5 74.5		16

Table 2: Published studies focusing on vascular invasion in NSCLC.

followed on a regular basis in a specific follow-up program. Neither chemotherapy nor radiotherapy was administered before surgery in this series. Radical surgery was defined as obtaining R0 despite type of surgery. All the patients underwent surgery for curative intent: segmentectomy, lobectomy, pneumonectomy or wedge resections in particular in functionally compromised patients.

Al operations were performed by board-certified thoracic surgeons through a muscle-sparing lateral thoracotomy. Although the current practice in our Hospital is a systematic lymphadenectomy in all patients submitted to lung resection for oncologic reasons, before 2000 and at the time of this study the choice of the extent of lymphadenectomy depended on the surgeon preference and no standard protocol was in place.

Recorded patient characteristics and clinical features included: age, smoking history, sex, Eastern Cooperative Oncology Group (ECOG) performance status, type of surgery, histological type, grading, pathological stage of disease (T, N, M), number of resected lymphnodes and intratumoral vascular invasion.

Methods

The surgical specimens were immediately cut by a pathologist and fixed in buffered 4% neutral formalin, whose volume is about three times that of the specimen size, for 48 hours. The pathological sampling of each specimen included: one paraffin block per centimetre of maximum diameter of the tumour, one block for the bronchial margin, 2-3 blocks in the lung tissue around the tumour and a number of blocks proportional to the number of loco-regional lymph nodes; the lymph nodes greater than 5 millimetres in maximum diameter were bisected and entirely embedded in the same block. For each paraffin block, Haematoxylin and Eosin and all the necessary immunohistochemical staining were performed (Figure 1a, Figure 1b and Figure 2).

Data management and statistical analysis

Primary endpoint of this study was to evaluate the prognostic role of lymphadenectomy and intratumoral vascular invasion. OS was defined as the interval between radical surgery to death or last follow-up visit. Patients who were not reported as died at the time of the analysis were censored at the date they were last known to be alive.

We compared overall survival among subgroups of patients according to the number of resected lymph-nodes and to the presence of intratumoral vascular invasion. The association between categorical variables was estimated by Chi-square test. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on survival.

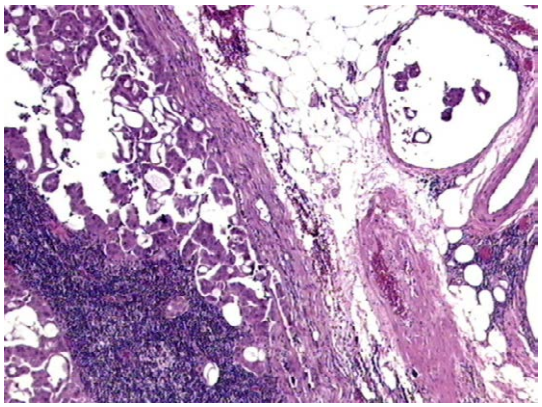

Figure 1a: lymph node metastasis by an adenocarcinoma of the lung with a neoplastic vascular invasion of an afferent lymphatic vessel.

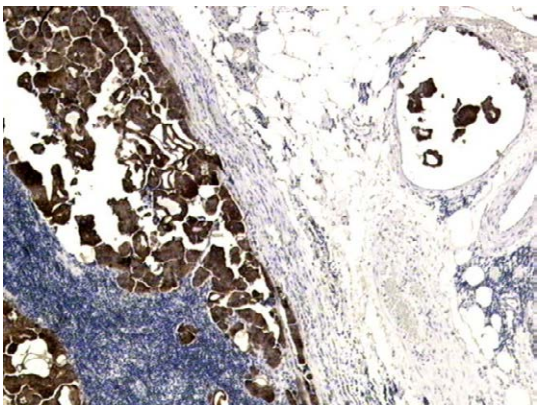

Figure 1b: immunohistochemical staining for pan-cytokeratins (AE1/AE3 antibody).

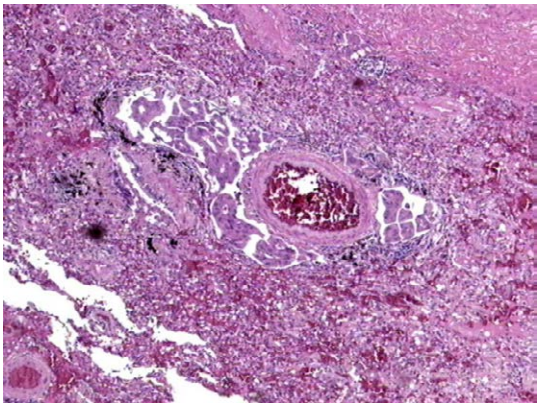

Figure 2: presence of a neoplastic vascular invasion of lymphatic vessels in the lung tissue around a lung adenocarcinoma.

Survival distribution was estimated by the Kaplan—Meier method. Significant differences in probability of surviving between the strata were evaluated by log-rank test. Hazard ratios and 95% confidence intervals were estimated from regression coefficients. A significant level of 0.05 was chosen to assess the statistical significance.

Receiver Operating Characteristics (ROC) curve analysis was performed to determine a cut off value for number of resected lymph nodes.

Statistical analysis was performed with MedCalc package (MedCalc® v9.4.2.0).

Results

Pathologic stage of disease was as follows: IA in 77 patients (17.5%), IB in 149 patients (33.9%), IIA in 15 patients (3.4%), IIB 92 patients (21%) and IIIA and IIIB in 89 (20.3%) and 17 (3.9%) of patients, respectively. Stage IIIB NSCLC patients were resected when stage IIIB was due to another lesion in the same lobe (T4). No patients received adjuvant therapy (Table 3).

At univariate analysis, the following factors had a positive correlation with overall survival: age (≤ 65 vs.>65 years, median

Parameters	N.
Number of patient	439
Sex	
Male	374 (85.2%)
Female	65 (14,8%)
Age at diagnosis	
Median	68
Range	37-84
Smoking	
Yes	380 (86.5%)
No	55 (12.5%)
Not available	4 (1%)
Histology	
Adenocarcinoma	192 (43.7%)
Squamous carcinoma	172 (39.2%)
Undifferentiated carcinoma	25 (5.7%)
Bronchioloalveolar carcinoma (BAC)	21 (4.8%)
Other	29 (6.6%)
Extension of disease	
Stage I	226 (51.5%)
Stage II	107 (24.4%)
Stage III	106 (24.1%)
Lymph nodes	
N0	261 (59.5%)
N1	88 (20%)
N2	90 (20.5%)
Type of surgery	
Segmentectomy	3 (1%)
Lobectomy	262 (60%)
Pneumonectomy	72 (16%)
Other	102 (23%)

Table 3: Patients characteristics.

OS=48.03 months vs 34.62 months, respectively, p=0,046), sex (male vs. female, median OS=36.29 months vs median OS not reached, respectively, p=0,02), number of resected lymph-nodes (≤ 10 vs.>10, median OS=38.43 months vs 47.34 months, respectively, p=0,0321, Figure 3) and vascular invasion (p=0.0038). Number of resected lymph nodes was particularly significant in stage II NSCLC (median OS=16 months vs 29,9 months, p=0,0284).

No significant relationship was found between OS and smoking, even if a positive trend was present in non-smokers patients.

At multivariate analysis, extended lymph node dissection (>10 lymph nodes, HR=0.59, CI 0.37–0.93, p=0.024) and vascular invasion (H.R. 0.82, CI 0.68-0.96, p=0.042) appeared independent prognostic factors for OS, which was also influenced by the sex of the patients (HR=0.42, CI 0.19–0.91, p=0.028) (Table 4).

Furthermore, the number of removed lymph node was analyzed both in N-positive and in N-negative patients and our results were confirmed in this subgroups analysis, separately considering N-positive and N-negative patients. We also calculated the lymph node ratio that was defined as the ratio of the number of metastatic lymph nodes to the number of removed lymph nodes. Again the cut-off number of 10 lymph nodes maintained its significant role, regardless the lymph node ratio.

The optimal cut-off number of lymph nodes was set at ten after Receiver Operating Characteristics curve analysis. Removing ten lymph nodes in our study represents a cut-off with a significant prognostic impact particularly in resected stage II non-small cell lung cancer.

Discussion

In the present analysis, we found a statistically significant difference in OS between patients with a number of resected lymph nodes greater than 10 and lower than 10. In fact, the median OS was 47.34 months vs. 38.43. Again, vascular invasion resulted a prognostic factor. At multivariate analysis, both extended lymph node dissection (>10 lymph nodes) and vascular invasion appeared independent prognostic factors for OS.

Therefore our results seem to suggest that an adequate staging of NSCLC should include an adequate lymph nodes clearance with a minimum of 10. In this regard, a low number of resected lymph nodes (<10) may be an indication for post-operative adjuvant treatment for NSCLC.

The association between postoperative survival and the number of lymph nodes has been recently examined by Ludwig et al. [21] mentioned above, in a large series of 16,800 patients who underwent definitive resection of node-negative (stage IA or stage IB) NSCLC. A modest but statistically significant increase in survival was evident in patients with five to eight lymph nodes examined during surgery in comparison to patients with one to four lymph nodes, with a proportionate hazard ratio (HR) of 0.90 and a 95% confidence interval (CI) of 0.84 to 0.97. Similar results for 9 to 12 lymph nodes and 13 to 16 lymph nodes examined produced further increases in survival, with HRs of 0.86 (95% CI, 0.79 to 0.95) and 0.78 (95% CI, 0.68 to 0.90), respectively. There appeared to be no incremental improvement after evaluating>16 lymph nodes. The highest median survival (97 months) occurred in patients with 10 to 11 lymph nodes evaluated.

Furthermore Fukui et al. [12] retrospectively studied 289 patients with non-small cell lung cancer who underwent surgery, and compared the prognostic significance of the number of positive nodes with the pN number by using multivariate analysis. Patients were classified into four groups according to the number of positive nodes: those without nodal metastasis were n0, those with one to three positive nodes were n1–3, those with four to six were n4–6, and those with more than seven were n7. The 5-year survival rate was 77% in the n0 patients, 58% in n1–3, 42% in n4–6, and 6% in n7, which indicated that an increased number of positive lymph nodes was associated with poor prognosis. Among the pN2 patients, the n1–3 group had a better survival rate than the n4–6 and n7 groups. The study showed that the number category is a strong independent prognostic factor in NSCLC.

Again Lee et al. [6] supported the conclusion that it is possible to predict patient prognosis after surgery for NSCLC according to the number of lymph node metastases instead of the anatomic extent of lymph node metastases. In their study they reviewed 1,081 patients who underwent major pulmonary resection at their institute and were proven to be pathologic stage I through IIIA between 1990 and 2006. Patients were divided into four subgroups (nN category) according to the number of metastatic lymph nodes: those without nodal metastases were nN0, those with 1 to 3 metastatic lymph nodes were nN1–3, those with 4 to 14 were nN4–14, and those with 15 or more were nN>15. The 5-year survival rate was 69.0% for nN0, 42.9% for nN1–3, 30.0% for nN4–14, and 11.5% for nN>15 (p<0.001). Multivariate analysis showed that the nN category was a significant prognostic indicator similar to the pN category. In conclusion this study also underlined how we can predict patient prognosis after surgery for NSCLC according to the number of lymph nodes instead of the anatomic extent of lymph node metastases and how the number of metastatic lymph nodes may add more information to the pN category of the current TNM classification system.

Recently Bria et al. [29] evaluated the prognostic impact of the number of resected lymph nodes or the ratio between the number of metastatic nodes and the number of resected lymph nodes in a series

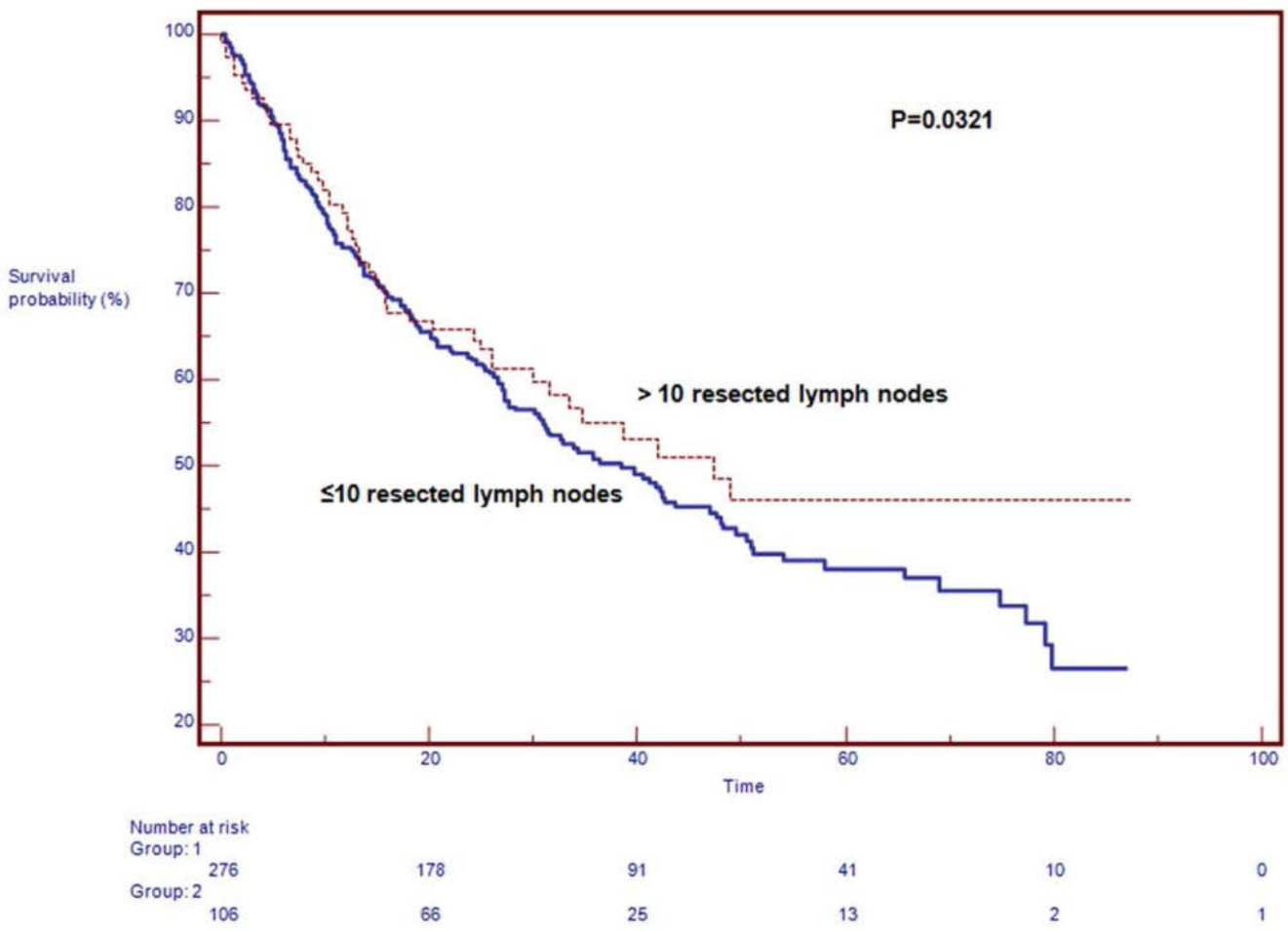

Figure 3: overall survival of patients with ≤ 10 vs. > 10 number of resected lymph-nodes.

Variable	H.R.	95% CI	P
Age (<65 years vs >65 years)	1,3184	0,8648 to 2,0100	0,1988
Smoking history	0,9645	0,4206 to 2,2115	0,9319
ECOG PS	0.8952	0.7645 to 1.1132	0,2437
Vascular invasion	0,8244	0,6800 to 0,9574	0,0421
Number of resected lymph nodes (≤10 vs >10)	0,5888	0,3716 to 0,9329	0,02409
Mucinous histotype	0,7045	0,2262 to 2,1939	0,5456
Sex (Female vs Male)	0,4227	0,1956 to 0,9135	0,02851

Table 4: Hazard ratio (H.R.) and 95% H.R. confidence limits of the variables included in the multivariate analysis.

of resected NSCLC patients. They retrieved a dataset of 415 resected NSCLC patients. At multivariate analysis, they found that the number of resected lymph nodes as well as the number of metastatic lymph nodes was independent factor for longer OS, and DFS (p<0.0001). Patients with a number of resected lymph nodes>10 (identified optimal cut-off) had a statistically significant benefit in OS (p=0.02) and DFS (p=0.0005).

Furthermore vascular invasion, along with other published studies [25-28], in our large series resulted as another strong independent prognostic factor. Although prospective studies are needed, our findings underline the importance of a careful evaluation of lymph nodes and vascular invasion in resected NSCLC as it may provide additional useful information for identifying patients who are at high risk and who may be candidates for further medical treatment after or before surgery.

Although it is known that the treatment strategy of NSCLC is multimodal and includes chemotherapy and biological agents, and that a better knowledge of tumor biology is important to estimate prognosis and to select the most appropriate therapeutic options, nevertheless focusing on an homogeneous series of NSCLC patients, this study could give a relevant contribute in understanding the role of two simple parameters that are available in all pathological reports.

In our study we found that the number category is a strong independent prognostic factor in NSCLC and can add new information to pN status. Moreover vascular invasion represents a significant

prognostic factor which may play an important role in considering the prognosis of resected NSCLC patients and the indications for adjuvant therapy. Consideration of the above mentioned findings should be given to its inclusion in future pathological staging of NSCLC when the system undergoes revision.

Although not demonstrated in our data analysis, which did not directly address the role of adjuvant treatment in NSCLC patients, these findings also seem to question the role of adjuvant chemo-radiotherapy as a standard of practice in all NSCLC cancer patients, whereas its role could be that of a partially compensation for an inadequate pathologic staging during surgery.

The question remains whether novel and effective chemotherapeutic agents could have a role along with optimal surgery, in order to further improve survival in optimally resected NSCLC cancer patients. We also believe that our findings could help planning future trials of postoperative management of lung cancer patients, especially now that new drugs are to be urgently tested in this setting.

Along with other studies, we support the conclusion that we can predict patient prognosis after surgery for NSCLC according to the number of lymph node metastases instead of the anatomic extent of lymph node. The most complex and unsatisfactory aspect of the current TNM staging system in lung cancer is represented by the method of assessing nodal disease. In lung cancer the anatomic extent of lymph node metastasis defines pN categories [12,28]. This current nodal system, based only on the anatomic extent of metastatic lymph nodes, can result in different prognosis even in the same nodal stage, especially with mediastinal (N2) lymph node involvement. In contrast, the number of positive lymph nodes is included in the definition of pN categories in breast, gastric, and colorectal cancers [7-10]. Analysis of data for cancers of the colon, breast and bladder demonstrate that the number of lymph nodes evaluated during staging is associated with postoperative survival [14,16,18]. In gastric cancer, the number of retrieved lymph nodes has an influence on the frequency of metastatic lymph nodes, and the number of retrieved lymph nodes reflects the reliability of the pN classification [30].

In NSCLC not only the number of lymph nodes resected but also the number of nodal stations with metastases has been suggested to be of significance; however, few studies on the numbers of positive lymph nodes have been reported [31-34]. In fact Ueda et al. [32] performed a retrospective study on 147 patients with NSCLC who had undergone major pulmonary surgery with complete mediastinal dissection and found that the incidence of multiple-station metastasis (>or=3 metastatic stations) among N2 patients (35%) was significantly higher than that among N1 patients (2%) ($p<0.001$). In lung cancer the number of metastatic lymph nodes can add new information to the pN category of the current TNM classification system.

Conclusion

Overall the results of this study suggest that an adequate classification of NSCLC should always include an adequate lymph nodes clearance, in particular in stage II NSCLC. Vascular invasion also represents a significant prognostic factor in resected NSCLC patients.

The number of resected lymph nodes and the vascular invasion also could be considered in order to select patients to receive post-operative treatment (radiotherapy +/- chemotherapy) for NSCLC.

Acknowledgements

The study was supported by authors' University Fundings (Università Politecnica delle Marche).

Conflict of Interest

All the authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

References

1. Caldarella A, Crocetti E, Comin CE, Janni A, Pegna AL, et al. (2006) Prognostic variability among nonsmall cell lung cancer patients with pathologic N1 lymph node involvement. Epidemiological figures with strong clinical implications. Cancer 107: 793-798.
2. Van Raemdonck DE, Schneider A, Ginsberg RJ (1992) Surgical treatment for higher stage non-small cell lung cancer. Ann Thorac Surg 54: 999-1013.
3. Parkin DM, Whelan SL, Ferlay J, Thomas DB (2002) Age-standardized and cumulative incidence rates: trachea, branchus and lung. In: Parkin DM, Whelan SL, Ferlay J, Teppo L,Thomas DB (edts) Cancer Incidence in Five Continents. Vol. VIII. Lyon, France: International Agency for Research on Cancer: 579-581.
4. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, et al. (2011) Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 141: 662-670.
5. Watanabe Y (2003) TNM classification for lung cancer. Ann Thorac Cardiovasc Surg 9: 343-350.
6. Lee JG, Lee CY, Park IK, Kim DJ, Park SY, et al. (2008) Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. Ann Thorac Surg 85: 211-215.
7. Greene FL, Page DL, Fleming ID (2002) AJCC Cancer Staging Manual, (6th edn), New York: Springer 113-124.
8. Greene FL, Page DL, Fleming ID (2002) AJCC Cancer Staging Manual, 6th ed. New York: Springer 171-180.
9. Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, et al. (1998) The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. J Am Coll Surg 187: 597-603.
10. Ichikura T, Tomimatsu S, Uefuji K, Kimura M, Uchida T, et al. (1999) Evaluation of the New American Joint Committee on Cancer/International Union Against Cancer classification of lymph node metastasis from gastric carcinoma in comparison with the Japanese classification. Cancer 86: 553-558.
11. Mountain CF (1997) Revisions in the International System for Staging Lung Cancer. Chest 111: 1710-1717.
12. Fukui T, Mori S, Yokoi K, Mitsudomi T (2006) Significance of the number of positive lymph nodes in resected non-small cell lung cancer. J Thorac Oncol 1: 120-125.
13. Fujisawa T, Yamaguchi Y, Saitoh Y, Hiroshima K, Ohwada H (1995) Blood and lymphatic vessel invasion as prognostic factors for patients with primary resected nonsmall cell carcinoma of the lung with intrapulmonary metastases. Cancer 76: 2464-2470.
14. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, et al. (2000) Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 124: 979-994.
15. Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, et al. (2001) Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 19: 157-163.
16. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, et al. (2002) Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol 167: 1295-1298.
17. Herr HW (2003) Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. Urology 61: 105-108.
18. Polednak AP (2003) Survival of lymph node-negative breast cancer patients in relation to number of lymph nodes examined. Ann Surg 237: 163-167.
19. Weir L, Speers C, D'yachkova Y, Olivotto IA (2002) Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. J Clin Oncol 20: 1793-1799.
20. Scartozzi M, Galizia E, Graziano F, Catalano V, Berardi R, et al. (2005) Over-DI dissection may question the value of radiotherapy as a part of an adjuvant

programme in high-risk radically resected gastric cancer patients. Br J Cancer 92: 1051-1054.

21. Ludwig MS, Goodman M, Miller DL, Johnstone PA (2005) Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. Chest 128: 1545-1550.

22. Varlotto JM, Recht A, Nikolov M, Flickinger JC, Decamp MM (2009) Extent of lymphadenectomy and outcome for patients with stage I nonsmall cell lung cancer. Cancer 115: 851-858.

23. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL (2003) Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. J Clin Oncol 21: 1029-1034.

24. Doddoli C, Aragon A, Barlesi F, Chetaille B, Robitail S, et al. (2005) Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg 27: 680-685.

25. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, et al. (2010) Prognostic impact of intratumoral vascular invasion in non-small cell lung cancer patients. Thorax 65: 1092-1098.

26. Naito Y, Goto K, Nagai K, Ishii G, Nishimura M, et al. (2010) Vascular invasion is a strong prognostic factor after complete resection of node-negative non-small cell lung cancer. Chest 138: 1411-1417.

27. Gabor S, Renner H, Popper H, Anegg U, Sankin O, et al. (2004) Invasion of blood vessels as significant prognostic factor in radically resected T1-3N0M0 non-small-cell lung cancer. Eur J Cardiothorac Surg 25: 439-442.

28. Ruffini E, Asioli S, Filosso PL, Buffoni L, Bruna MC, et al. (2011) Significance of the presence of microscopic vascular invasion after complete resection of Stage I-II pT1-T2N0 non-small cell lung cancer and its relation with T-Size categories: did the 2009 7th edition of the TNM staging system miss something? J Thorac Oncol 6: 319-326.

29. Bria E, Milella M, Sperduti I, Alessandrini G, Visca P, et al. (2009) A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer. Lung Cancer 66: 365-371.

30. Sobin LH, Wittekind Ch (1997) TNM classification of malignant tumors, (5th edn), New York: John Wiley & Sons, Inc.

31. Hermanek P (1995) pTNM and residual tumor classifications: problems of assessment and prognostic significance. World J Surg 19: 184-190.

32. Ueda K, Kaneda Y, Sakano H, Tanaka T, Hayashi M, et al. (2003) Independent predictive value of the overall number of metastatic N1 and N2 stations in lung cancer. Jpn J Thorac Cardiovasc Surg 51: 297-301.

33. Nakata M, Saeki H, Kurita A, Takashima S (1999) Prognostic significance of the number of metastatic lymph nodes in surgically resected non-small cell lung cancer. Haigan 39: 421-427.

34. Andre F, Grunenwald D, Pignon JP, Dujon A, Pujol JL, et al. (2000) Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 18: 2981-2989.