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A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer☆

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ABSTRACT

Background: The number of resected lymph-nodes (#RNs) has proven prognostic in breast and colorectal cancer. Here we evaluated its prognostic impact in a series of resected NSCLC patients.
Methods: A panel of established prognostic factors plus (1) #RNs or (2) the ratio between the number of metastatic nodes and #RNs (NR) were correlated to overall- (OS), cancer-specific- (CSS), and disease-free-survival (DFS), using the Cox-model. Risk-classes according to hazard ratios (HR) were generated. Internal and external validation was accomplished.
Results: A dataset of 415 resected NSCLC patients was retrieved. At multivariate analysis, #RNs and NR were independent factor for longer OS, CSS and DFS ($p < 0.0001$). Patients with a #RNs > 10 (identified optimal cut-off) had a statistically significant OS ($p = 0.02$) and DFS ($p = 0.0005$) benefit. In node-positive patients, a NR < 9% significantly correlated with better outcome. Stratification into High-, Medium-, and Low-Risk classes, based on High- (HRFs: stage, N-status, age, #RNs) and Intermediate-Risk Factors (IRFs: sex, grading, histology), efficiently predicted outcomes ($p < 0.0001$). The risk class model performance was externally validated in and independent dataset of 297 patients.
Conclusions: These results contribute to complete the panel of prognostic factors for resected NSCLC. A prospective larger validation and comparison with molecular prognostic tools is warranted.

1. Introduction

Lung cancer accounts for 160,000 deaths each year in the United States, and represents the leading cause of cancer death regardless of gender, with an overall 5-year survival rate of 16% [1,2]; non-small-cell lung cancer (NSCLC) accounts for about 80% of all lung cancers [3]. Approximately 30% of patients present with early-stage disease, a proportion that is expected to increase as newer diagnostic tools and more widespread use of screening techniques gain popularity [3]. Complete surgical removal of both primary tumor (either lobectomy/bilobectomy or pneumonectomy) and loco-regional lymph-nodes represents the standard of care for such group of patients; despite optimal treatment, which today encompasses radical surgery and adjuvant chemotherapy; however, half of early-stage patients will die due to lung cancer.

While the impact on outcome provided by the extent of lymphoadenectomy in patients undergoing surgery for early NSCLC is still controversial, the nodal involvement must be considered as the most important independent prognostic factor for survival [4]. Indeed, whether the extent of nodal dissection is prognostic, therapeutic or both is currently under debate, although several reports have documented a non-significant effect of such procedure on both disease-free and overall-survival [5,6].

Several clinical parameters taking into account the involvement of loco-regional nodes have been reported [7]; however, none of them has shown to have a better prognostic potential, as compared to the 'classical' TNM staging system.

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This issue is of particular importance in a rapidly changing landscape, such as that of early NSCLC, where major changes in the current staging system are expected shortly [8] and the routine use of adjuvant chemotherapy is gaining increasingly popularity. With respect to the latter, the predicted benefits are small and need to be weighted against substantial toxicity [9–11], making the identification of 'high-risk' populations that are likely to benefit most from adjuvant approaches of paramount importance.

Recent data obtained in early-stage breast, colo-rectal, and bladder cancer have suggested a prognostic value of the number of resected lymph-nodes, regardless of their metastatic involvement [12–14]. We have, therefore, investigated the prognostic impact of the number of resected lymph-nodes in context with other established clinical prognostic factors in a series of 415 consecutive NSCLC patients who were surgically treated at the Regina Elena National Cancer Institute.

2. Materials and methods

A step-by-step protocol was followed according to the methodological approach for building a nomogram for cancer prognosis proposed by Iasonos et al. [15].

2.1. Patient population

All resected NSCLC patients who underwent surgery at the Regina Elena National Cancer Institute of Rome (Italy) between 2001 and 2006 were considered eligible for the retrospective analysis of clinical prognostic factors (single institution data source).

2.2. Surgical approach

Complete lympho-adenectomy was routinely performed in all the radical resections for NSCLC. Complete mediastinal lymphatic dissection has been performed as described by Cahan and revised by Martini and Naruke [16–18]. By adopting this approach, the mediastinal space is completely exposed up to the highest stations and station 7 is explored up the controlateral bronchus.

2.3. Outcomes of interest

The aim of the current analysis was to generate risk classes with the available known prognostic clinico-pathological factors (age, sex, type of surgery, histology, tumor size, lymph-node involvement, n.7 mediastinal station, more than 4 nodal stations involved, tumor grading and adjuvant chemotherapy) plus either (1) the Number of Surgically Removed Lymph-Nodes, (#RNs) and (2) the ratio between the number of positive nodes and number of removed nodes (NR: node ratio), as predictors under consideration (investigational factors).

2.4. Statistical analysis

Descriptive statistics were used to summarize pertinent study information. Follow-up has been analyzed and reported according to Shuster [19]. The Hazard Ratio (HR) and the 95% confidence intervals (95% CI) were estimated for each variable using the Cox univariate model [20,21]. A multivariate Cox proportional hazard model was developed using stepwise regression (forward selection). Enter limit and remove limit were $p = 0.10$ and $p = 0.15$ respectively. The Cox model for overall survival (OS: time between diagnosis and death for any cause), cancer specific survival (CSS: time between diagnosis and death due to cancer progression), and disease free survival (DFS: time between diagnosis and local or distant recurrence, secondary cancer, or death for any cause) was tested considering age, #RNs and NR as continuous variables.

For continuous variables, the Martingale Residual Plots (MRP) analysis was applied to check the functional form of investigational variables (#RNs and NR); in presence of non-linear distribution of ratios, the classification and regression trees (C&RT) analysis and the analysis by means of maximally selected log-rank statistics were performed to find optimal cut-offs capable of splitting patients into groups with different outcomes probabilities. Cut-offs allowed transforming continuous into categorical variables, with the aim of finally generating risk classes.

The C&RT analysis is a nonparametric statistical procedure that identifies mutually exclusive and exhaustive subgroups of a population whose members share common characteristics that influence the dependent variable of interest. To confirm cut-offs identified by C&RT, the analysis by means of maximally selected log-rank statistics was used.

Outcomes were calculated by the Kaplan–Meier product-limit method from the date of the surgery until relapse or death [22]. The log-rank test was used to assess differences between subgroups. Significance was defined at the $p < 0.05$ level.

The SPSS (version 13.0), R-Software (version 2.6.1) and SAS (version 9.0) statistical programs were used for all analyses.

2.5. Internal validation

In order to address the multivariate model overfit and to validate the results, a cross-validation technique which evaluates the replication stability of the final Cox multivariate model in predicting all outcomes was also investigated, using a re-sampling procedure [15,23,24]. This technique generates a number of simulation datasets (each approximately 80% of the original size), by randomly selecting patients from the original sample, in order to establish the consistency of the model across less-powered patient' samples.

2.6. External validation

An external, single-institution, similar dataset was considered for external validation of the results.

3. Results

3.1. Patient characteristics

A retrospective series of 415 patients (median age 67 years, range 28–86) who underwent surgery with curative intent for NSCLC was retrieved from the original files of the Regina Elena National Cancer Institute. Median number of resected nodes was 15 (range 1–85); 136 (32.8%) had involved nodes (Table 1 and Supplementary table S1). Follow-up data were obtained from hospital charts and corresponding with the referring physicians.

3.2. Survival analysis

The first and last retrieved patients underwent surgery in May, 2001 and July, 2006, respectively; last follow-up visit was in September 2007. Median OS and DFS were 55 (95% CI 44–66) and 39 (95% CI 30–48) months, respectively (median CSS was not reached). Three-year OS, CSS and DFS rates were 62.7%, 67% and 51.4%, respectively. One hundred and twenty-nine deaths due to cancer and 24 due to other causes had occurred at the time of the analysis.

Three hundred-sixty-nine patients were evaluable for multivariate analysis. In our series, adjuvant treatment (24 patients chemotherapy only, 21 sequential chemo-radiation) did not significantly impact on survival. Among factors exploring nodal involvement, only N status was independently prognostic for CSS and DFS, but not OS (Table 2). When the model was built with #RNs as the continuous variable investigating nodal involvement,

Table 1
Patient's characteristics.

Factor	Categories	No.	%
Sex	Male	300	72.3
	Female	115	27.7
Surgery	Lobectomy	364	87.7
	Bilobectomy	21	5.1
	Pneumonectomy	30	7.2
T category	T1	148	35.7
	T2	201	48.4
	T3	39	9.4
	T4	14	3.4
	Unknown	13	3.1
Grading	G1	18	4.4
	G2	152	36.6
	G3	216	52.0
	Unknown	29	7.0
Histology	Adenocarcinoma	168	40.5
	Other	247	59.5
Lymph-nodes	Negative	263	63.4
	Positive	136	32.8
	N1	55	13.3
	N2	81	19.5
	Unknown	16	3.9
Stage	IA	101	24.3
	IB	112	27.2
	IIA	14	3.4
	IIB	54	13.0
	IIIA	104	25.1
	Unknown	29	7.0

#RNs was an independent prognostic factor for OS (HR 0.98, 95% CI 0.96–0.99), CSS (HR 0.98, 95% CI 0.96–0.99), and DFS (HR 0.97, 95% CI 0.96–0.99) (Supplementary Table S2). None of 'investigational' prognostic factors for nodal involvement which have resulted to be significantly independent at the multivariate analysis with categorical variables (i.e. #RNs, stage, N-status) as shown in Table 2 (already adjusted for the effect of each variable) showed significant interaction with any of the other parameters. In particular: OS, #RNs/Stage interaction $p = 0.52$; CSS, #RNs/Stage interaction ($p = 0.46$), #RNs/N-status interaction ($p = 0.74$); DFS, #RNs/Stage interaction ($p = 0.28$), #RNs/N-status interaction ($p = 0.83$).

MRP showed a non-linear form of the #RNs function (Supplementary Figure S1a). C&RT identified 10 as the optimal cut-off when considering the #RNs as a categorical variable; maximally selected log-rank statistics analysis confirmed such cut-off (Supplementary Figure S1b).

Unadjusted Kaplan–Meier curves stratifying patients according categorical #RNs are shown in Fig. 1. Patients with a #RNs > 10 had a statistically significant benefit in both OS and DFS ($p = 0.02$ and 0.0005, respectively); CSS curves visually separated from the early beginning, but this difference did not reach statistical significance (Fig. 1b).

Table 3
Risk classes definition, according to the presence/absence of risk factors.

Risk factors	Risk classes		
HRFs: •Stage •N-status •Age •#RNs	HIGH	MEDIUM	LOW
IRFs: •Sex •Grading •Histology	•>1 HRFs, regardless of any IRFs	•1 HRF regardless of any IRFs, or no HRFs and >1 IRFs	•≤1 IRFs

HRF: high-risk factor; IRF: intermediate-risk factor.

When the model was built with NR, NR was also independently prognostic for OS, CSS and DFS (Supplementary Table S3). However, MRP showed an almost linear form of the NR function in the overall population (Supplementary Figure S2). Conversely, in the node-positive subgroup, the NR could be used as a categorical variable with a cut-off of 9% as identified by C&RT analysis and confirmed by the maximally selected log-rank statistics (Supplementary Figures S3 and S4). Within node positive patients, dichotomized NR was an independent factor for longer OS (HR 2.02, 95% CI 1.17–3.49, $p = 0.01$), CSS (HR 2.17, 95% CI 1.22–3.86, $p = 0.009$), and DFS (HR 2.30, 95% CI 1.38–3.83, $p = 0.001$). Node-positive patients with 9% or less NR had a statistically significant benefit in OS, CSS, and DFS (Fig. 1d–f).

The robustness of the multivariate model was investigated by the cross-validation re-sampling procedure for internal validation, at 100 generated simulation datasets: the replication rate for the 7 independent variables ranged from 6% to 100%. Four variables (stage, N-status, age and the #RNs) had a mean or median HR >1.5 (replication rate 39–100%), while 3 variables (sex, grading and histology) had a mean or median HR <1.5 (replication rate 6–65%) (Supplementary Table S4).

3.3. Risk classes

Risk classes were generated based on multivariate analysis (Table 2). Since NR did not reveal any peak in the overall population, it was not included for the risk classes generation. Risk factors were defined as High Risk Factors (HRFs) if they had a HR >1.5 for any of the outcome considered and as Intermediate Risk Factors (IRFs) if their HR was ≤1.5. Accordingly, stage, N-status, age and the #RNs were HRFs, while sex, grading and histology were IRFs. Cross-validation analysis confirmed the choice of HRFs and IRFs in terms of HRs and replication rates (Supplementary Table S4).

Three classes were generated: High-Risk, which gathered patients with >1 HRFs, regardless of the presence of any IRFs; Medium-Risk, which gathered patients with 1 HRF regardless of any IRFs, or >1 IRFs in the absence of HRFs; Low-Risk, which gathered patients with ≤1 IRFs or none (Table 3). A highly significant

Table 2
Multivariate analysis for risk-classes generation.

	OS		CSS		DFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex	1.46 (0.95–2.27)	0.08	1.58 (0.97–2.57)	0.06	–	ns
Stage	2.72 (2.41–4.98)	<0.0001	3.01 (1.59–5.68)	0.001	2.33 (1.31–4.12)	0.004
N	–	ns	1.79 (1.00–3.19)	0.049	1.78 (1.03–3.07)	0.04
Grading	1.46 (1.01–2.11)	0.04	1.39 (0.93–2.07)	0.11	1.36 (0.97–1.90)	0.07
Histology	1.19 (0.83–1.72)	0.32	–	ns	1.33 (0.96–1.87)	0.09
Age*	1.67 (1.17–2.40)	0.005	1.43 (0.97–2.11)	0.07	–	ns
#RNs*	1.76 (1.23–2.52)	0.002	1.57 (1.05–2.34)	0.02	1.95 (1.38–2.74)	<0.0001

OS: overall survival; CSS: cancer-specific survival; DFS: disease-free survival; HR: Hazard Ratio; CI: confidence interval; *p*: *p*-value; ns: not significant; N: nodal positivity; #RNs: number of resected nodes; *categorical variables, considering the median value (67 years) as age cut-off and 10 as cut-off for #RNs.

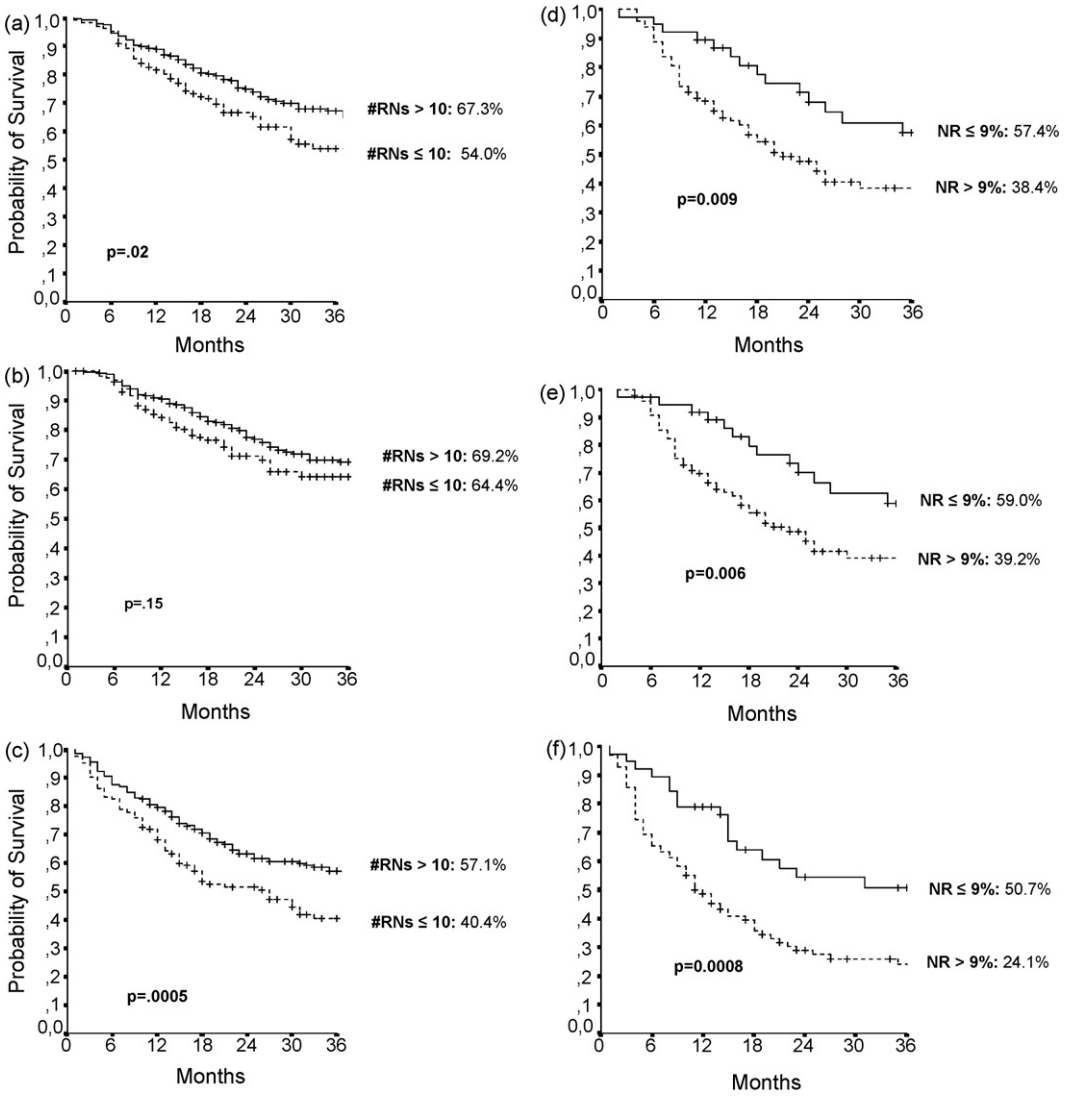

Fig. 1. (a) Overall Survival (OS) – #RNs, 10 nodes as cut-off determined with C&RT and MRPs analyses. (b) Cancer specific survival (CSS) – #RNs, 10 nodes as cut-off determined with C&RT and MRPs analyses. (c) Disease free survival (DFS) – #RNs, 10 nodes as cut-off determined with C&RT and MRPs analyses. (d) Overall Survival (OS) Node-positive population – NR, 9% as cut-off determined with C&RT and MRPs analyses. (e) Cancer Specific Survival (CSS) Node-positive population – NR, 9% as cut-off determined with C&RT and population NR, 9% as cut off determined with C&RT and MRPs analyses. (f) Disease-Free Survival (DFS) Node-positive population – NR, 9% as cut-off determined with C&RT and MRPs analyses.

difference ($p < 0.0001$) between risk classes was found for each considered outcome (Fig. 2a–c). In particular, a significant difference in 3-year OS between high- and medium- (45.2% vs 78.0%, $p < 0.0001$), as well as between medium- and low- risk classes (78.0% vs 100.0%, $p < 0.0001$).

For the external validation of the risk class model, a retrospective series of 297 patients (median age 69, range 32–94) who underwent surgery for NSCLC was gathered from the original files of the Thoracic Surgery of the University of Chieti (Supplementary Table S5). Median number of resected nodes was 11 (range 1–42); 88 (29.6%) had node-positive disease. With a median follow-up time of 36 months, a significant difference in 3-year OS between high- and medium-risk classes was found (50.1% vs 70.4%, $p = 0.003$) (Fig. 3a). The proposed risk class model performed well in the external dataset when comparing medium- and high-risk classes with log-rank test ($p = 0.10$ and $p = 0.41$, respectively) (Fig. 3b). This was confirmed by estimating the HRs for the medium- and high-risk classes of the original data set and the validation set (HR 0.67, 95% CI 0.41–1.09, $p = 0.107$; HR 1.12, 95% CI 0.84–1.51, $p = 0.41$, respectively). Even when a meta-analytic approach was adopted by considering the event-based medium and high-risk Odds Ratios, no significant heterogeneity was found ($p = 0.12$, Q-value = 2.42, Supplementary Figure S5). However, an unexpectedly high number of overall deaths occurred in the low-risk group of the validation dataset, resulting in a significant difference when compared with the low-risk group of the original population ($p = 0.005$).

4. Discussion

Here we report for the first time on the prognostic role of the #RNs and NR in the setting of surgically treated early NSCLC. Within our dataset, both #RNs and NR clearly outperformed other parameters taking into account nodal involvement**.** In addition, risk classes incorporating a dichotomized #RNs parameter were able to discriminate between high, medium, and low risk patients for all considered outcomes (Fig. 2). The performance of the proposed prognostic model in predicting overall survival was validated further using an external dataset.

Nodal involvement is arguably one of the most important prognostic factors influencing survival of patients undergoing surgery

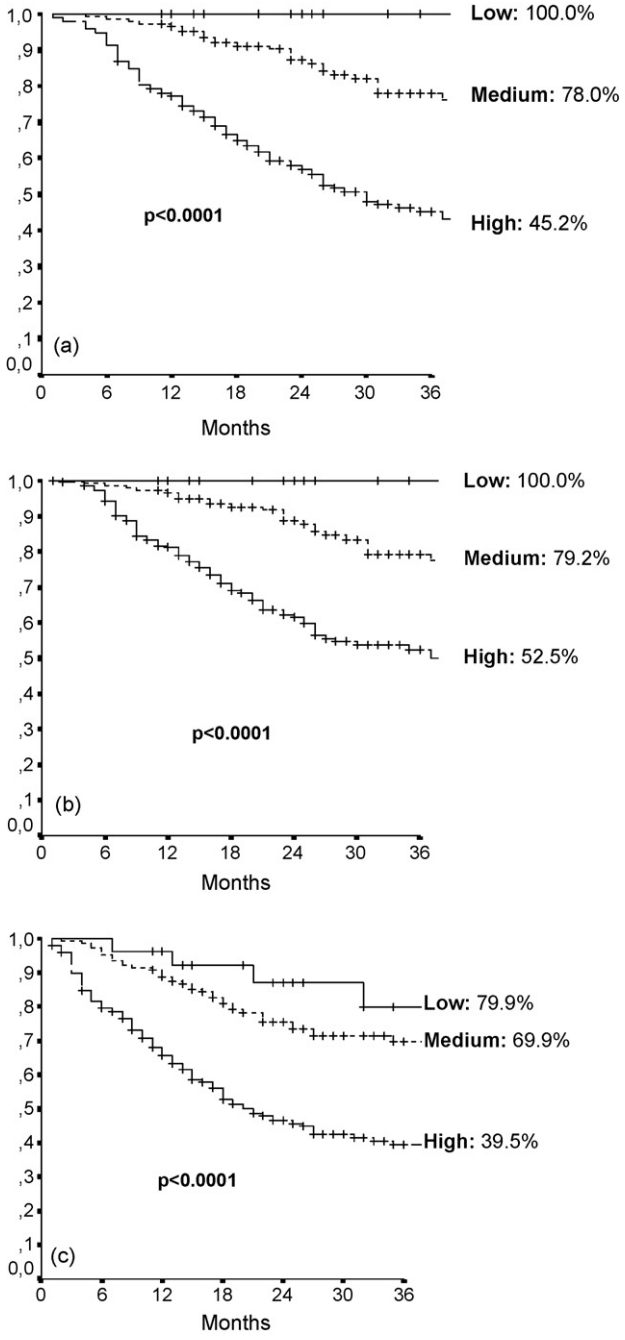

Fig. 2. (a) Overall survival (OS) at 3 years according to risk-classes. (b) Cancer-specific survival (CSS) at 3 years according to risk-classes. (c) Disease-free survival (DFS) at 3 years according to risk-classes.

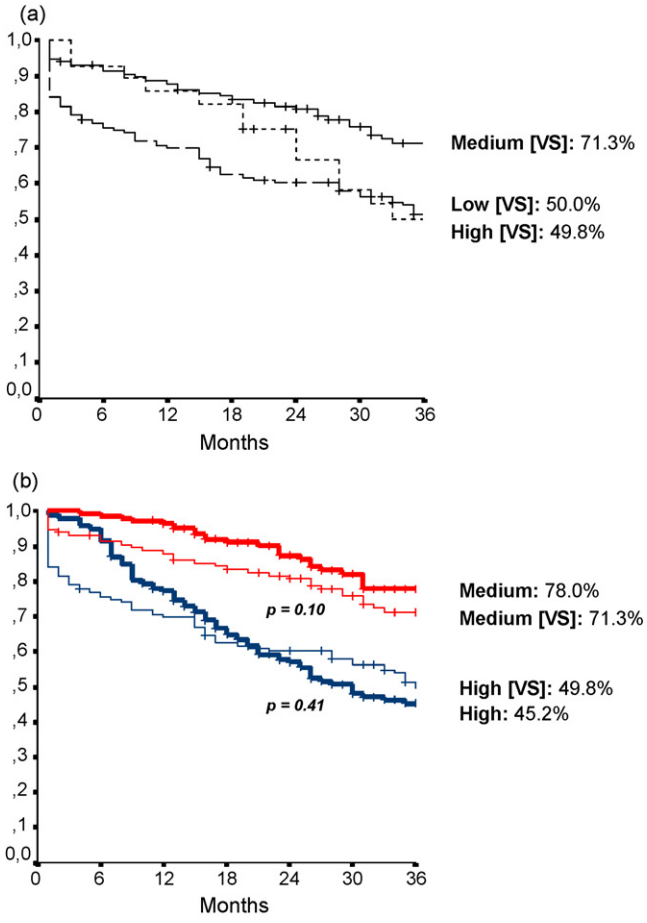

Fig. 3. (a) Validation Set [VS] – Overall survival (OS) at 3 years according to risk-classes. (b) Overall survival (OS) at 3 years according to High- and Medium-risk-classes.

for NSCLC [4]. Indeed, according to the ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition), patients undergoing resection for stage I–II NSCLC, are recommended (level IB) to receive systematic mediastinal lymph node sampling or dissection for accurate pathologic staging [6]. According to the National Comprehensive Cancer Network guidelines (NCCN v.2007), 'N1 and N2 node dissection and mapping (minimum of three N2 stations sampled or complete lymph-node dissection)' should be performed (category 2A recommendations) [25]. In addition to the current TNM staging system, numerous reports have evaluated the validity of nodal descriptors and have suggested that these could be refined to provide more accurate prognostic stratification by subdividing them according to either specific anatomical locations or the number of involved lymph nodes [4,26,27]. However, none of the 'novel' nodal predictors has outperformed the classical N1-2 classification, that will be maintained in the forthcoming revision of the TNM staging system [28]. The two novel variables describing nodal involvement introduced in our study (#RNs and NR) are clearly more potent than the other considered N-descriptors (N-status, n.7 station involvement, >4 nodal stations involved). Within our dataset, only N-status was a statistically significant independent prognostic factor for CSS but not for OS and DFS, while #RNs showed a high discrimination power for all outcomes (Table 2). In this respect, our findings are in agreement with other reports indicating that variables taking into account the number of uninvolved lymph-nodes bear a great prognostic potential in breast, colorectal and bladder cancer [12–14]. Even in the small subset of node-positive patients, the NR parameter is able to identify patients cohorts with an approximately 20% absolute difference in 3-year survival rates (Fig. 1).

Accurate prognostication in the setting of early NSCLC is of paramount importance to really appreciate the value of therapeutic approaches, such as adjuvant chemotherapy, that have only recently been introduced in routine clinical practice. This is especially important considering the small absolute benefit provided by adjuvant chemotherapy on one hand [9–11,29], and the unexpected excess of late deaths recently documented in chemotherapy-treated patients [30] on the other. Risk modeling by prognostic nomograms or risk class stratification, may provide a powerful tool for individualized outcome predictive and/or stratification of patients for clinical trials [15].

The risk-class model proposed herein, which incorporates #RNs, is able to discriminate between patients with low-, medium- and high-risk of relapse and death with striking efficiency (absolute difference in 3-year OS 22% between low- and medium-risk and 33% between medium- and high-risk, respectively, Fig. 2a). To avoid over-interpretation of the prognostic ability of our model, the stability and the choice of the independent predictors was internally validated by 100 simulations of different patients' cohorts [15].

The generalizability of any predictive model, including ours, may be hampered by several factors: (1) the use of #RNs as a predictor could be compromised by the presence of systematic inter-institutional differences in the surgical approach with regard to inspecting, sampling and resecting nodes [6]. Moreover, the extent of lymphadenectomy and the thoroughness of lymph node retrieval decide the total number of resected lymph nodes for each specimen and vary the significance of the number categories between countries and institutions. This is crucial for several tumors, such as gastric cancer, where extended lymphadenectomy leads to an increase in the number of nodes with metastases; (2) differences in pathologic reporting and identification of fragmented nodes may be potential confounding factors. Indeed, in the surgical practice, sometimes one lymph node may be divided into a few pieces or it is found to be difficult to separate each node exactly from the "en bloc" dissected tissue; (3) prognostic predictions may be affected by stage migration consequent to more accurate mediastinal staging (stage migration). For these reasons, we sought external validation of our risk-class model using an independent patient cohort from a different institution.

While this approach clearly validated the reproducibility of the performance of our model for medium- and high-risk classes, whatever comparison tool was applied (see results and Fig. 3b), the low-risk classes significantly differed between the two datasets (Fig. 3b). In particular, low-risk patients in the validation dataset, performed significantly worse than those in the original one ($p = 0.005$). This may be due to several factors, such as an unexpectedly high number of non-cancer deaths in the low risk group of the validation set (35.7%) and a lower median number of resected nodes in the validation as compared to the original dataset (11 vs 15, respectively). Alternatively, purely clinical prognosticators, such as those employed herein, may not be able to discriminate tumors with distinct biology, prompting the in-depth investigation of molecular predictors particularly to identify patients with a low risk of relapse that may not benefit from adjuvant therapy.

The necessity of further validation of our prognostic model notwithstanding, we believe that novel N-predictors (#NRs and NR) and the risk class stratification proposed herein may be useful, hypothesis-generating steps towards a better prognosis prediction. Although this model will need to be validated in the context of the upcoming revision on the TNM staging system [28], the fact that the revision will mainly deal with tumor size and metastases-related parameters rather than the N-factor, it is likely that our model may be of use also in that context. Another important point for further research will be the validation of our prognostic model within series of patients treated with adjuvant chemotherapy after surgery. This step will be pivotal to understand whether the risk class prognostic model we developed may also be used as a predictive model helping to better select patients who may benefit from adjuvant treatment.

Molecular profiling is expected to radically change our way to look at NSCLC prognosis and treatment, and several examples of molecular stratification have recently been released in literature [31–33]. While conceptually extremely fascinating, such approaches are unlikely to be widely available (at least in the short term) for routine clinical practice, and their discrimination power will need to be validated in large series. In this context, we believe that the relatively simple, clinically-based, risk stratification model proposed herein can be of practical value for early NSCLC patients candidate to curative surgical resection.

Conflict of interest

Supported by a grant of the National Ministry of Health and the Italian Association for Cancer Research (AIRC). There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.lungcan.2009.02.024.

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