

Resected pN1 non-small cell lung cancer: recurrence patterns and nodal risk factors may suggest selection criteria for post-operative radiotherapy

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Abstract

Purpose To describe the pattern of recurrence in resected pN1 non-small cell lung cancer (NSCLC) and to identify factors predicting an increased risk of locoregional recurrence (LR) or distant metastasis (DM) to define a selected population who may benefit from postoperative radiotherapy (PORT).

Methods 285 patients with resected pN1 NSCLC were identified. Patients with positive surgical margins, undergoing neoadjuvant treatment or PORT, were excluded. LR was defined as first event of recurrence at the surgical bed, ipsilateral hilum or mediastinum, and other sites were considered as DM. Kaplan–Meier actuarial estimates of overall survival (OS), progression-free survival (PFS), freedom from LR (FFLR) and freedom from DM (FFDM) in different subgroups were compared with the log-rank test. Multivariate analysis was calculated.

Results 202 patients met the inclusion criteria, 24 % received adjuvant chemotherapy. The median follow-up was 39 months. The total number of recurrences was 118 (64.4 %): 44 (24 %) and 74 (40.4 %) for LR and DM,

respectively. Five-year OS and PFS rates were 39.2 and 33.3 %, respectively. Extra capsular extension (ECE) (RR 2.10, $p = 0.01$) and lymph nodal ratio (LNR) >0.15 (RR 1.68, $p = 0.015$) were associated with a worse PFS. ECE and LNR >0.15 were significantly related to a worst FFLR (RR 3.04 and 4.42, respectively), and adenocarcinoma to an unfavorable FFDM (RR 1.97, $p = 0.013$).

Conclusions Nodal factors as high LNR and ECE can predict an increased risk of worse FFLR and PFS. Prospective data on selected patients, treated with modern radiotherapy techniques, need to be collected to re-evaluate the role of radiotherapy.

Keywords Locoregional recurrence · Distant metastasis · Pathologic N1 · Non-small cell lung cancer · Extra capsular extension · Lymph node ratio

Introduction

Surgical resection represents the standard treatment for patients with non-small cell lung cancer (NSCLC) and hilar lymph nodal metastases (N1). N1 status covers a heterogeneous group of patients, included in stage IIA, IIB and IIIA, according to the 7th edition of the American Joint Committee on Cancer (AJCC) [1]. The 5-year overall survival (OS) rate for N1 patients ranges between 15 and 58 % [1], while rates of local recurrence (LR) and distant metastasis (DM) after surgical treatment range between 20 and 46 % and between 42 and 55 %, respectively [2, 3]. Despite this high risk of failure, the role of adjuvant treatments is not well defined. Several studies investigated platinum-based chemotherapy as a post-operative treatment option for improving survival [4]. However, chemotherapy is burdened with higher toxicity rates and poor compliance.

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Moreover, the number of patients who can benefit from this adjuvant treatment is limited because chemotherapy has been frequently withheld in elderly patients, with poor performance status or comorbidities [5].

The role of postoperative radiotherapy (PORT) is as well controversial. In 1998, a meta-analysis reported a benefit in terms of recurrence-free survival, despite a detrimental effect in overall survival, especially in patients with early stage (N0–N1) completely resected, suggesting that PORT should not be used routinely for such patients [6]. The toxicity rate was high, with a reported 21 % relative increase of death-risk in patients treated with PORT. This meta-analysis, however, included patients treated with 2D or 3D radiotherapy techniques, and the authors themselves suggest the need to investigate the role of more modern radiotherapy techniques, such as conformal radiotherapy or hyperfractionated radiotherapy, in all stages (I, II, and III) of completely resected disease. Thus, there has been a growing interest among radiation oncologists that aim to properly select N1 cases that could potentially benefit from PORT [2, 6, 7].

The present study retrospectively analyzes a single-institution series of N1 NSCLC patients surgically treated, to define the patterns of recurrence and the risk factors for local and distant relapse, focusing on nodal descriptor to emphasize the rationale of local adjuvant treatment.

Materials and methods

Between 2001 and 2011, all consecutive patients who underwent surgery for NSCLC at our hospital and who have been post-surgically classified as N1 were retrospectively reviewed. Neo-adjuvant chemotherapy, pre- or post-operative radiotherapy, and positive surgical margins were considered exclusion criteria for the analysis. Patients deceased perioperatively (in-hospital death within 30 days from surgery) were also removed.

Clinical and therapeutic data were collected from medical records and all the histological examinations were reviewed. Follow-up information was obtained by medical records, reports of general practitioners and radiographic exams (X-ray, computed tomography, positron emission tomography, bone scans, bronchoscopy, endobronchial ultrasound, guided transthoracic needle biopsy and mediastinoscopy).

Local recurrence (LR) was defined as disease relapse at bronchial stump, ipsilateral hilum and mediastinum; all other sites of failure, including supraclavicular fossa and contralateral hilum were considered as distant metastasis (DM), as considered by others authors [2, 8]. Progression-free survival (PFS) was calculated from the date of surgery to the date of first event of failure (local or distant

recurrence) or until the date of the last visit of follow-up or death. LR and DM were scored separately and censored as first event, to evaluate the freedom from local recurrence (FFLR) and freedom from distant metastasis (FFDM). When LR and DM were simultaneous, they were censored for FFDM to obtain a groups of patients with pure LR relapse. Overall survival (OS) was measured from the date of surgery to the date of death (any cause) or until the date of the last follow-up.

Among the variables investigated, the number of examined lymph nodes (LN) was categorized dichotomously: <10 and ≥ 10 , as recommended for an “acceptable” LN dissection [9]. The number of positive LN was categorized as only one positive LN versus more than a single positive LN. The ratio between the number of positive and examined LN (LNR) was considered. The optimal cutoff point of 0.15 was determined by generating a receiver operating characteristic (ROC) curve and calculating the maximal Youden’s index.

The Kaplan–Meier method was used to estimate PFS, OS, FFLR and FFDM. Differences between groups were calculated using the log-rank test. All the variables grouped by type (clinical, therapeutic and nodal) were considered for multivariate analysis that was performed using the Cox proportional hazard regression model.

A p value <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS software (SPSS Statistics v.17.0©).

Results

Between 2001 and 2011, data of 285 patients were reviewed. Eighty-three patients did not meet inclusion criteria and were excluded. A total of 202 patients were, therefore, analyzed. For all of them, a complete pathology report (histology, grading, tumor stage, visceral pleural invasion, extra capsular extension (growth over the nodal capsule) -ECE-, positive and examined LN, LN location and LNR) and the main therapeutic features (surgical procedure, type of LN dissection, chemotherapy) were available. Nineteen patients were excluded from the analysis of PFS, FFLR and FFDM, because they were considered lost to follow-up. Median follow-up of the entire population was 39 months (range 1–166), while median follow-up of living patients was 76 months (range 13–150).

The median age at diagnosis was 67 years (range 43–83). 63 % of patients were 65-years old or more (63 and 78.2 %) were males. The most common histologic subtype was squamous cell carcinoma (52 %) followed by adenocarcinoma (41.1 %). 56.5, 15.3, and 28.2 %, were classified in stage IIA, IIB and IIIA, respectively. Only five patients (2.5 %) underwent wedge resection. 15.8 %

Table 1 Clinical–pathological (a) treatment (b) and nodal (c) factors

Characteristic	N (%)
(a)	
Age at diagnosis	
<65	74 (36.6)
≥65	128 (63.4)
Sex	
M	158 (78.2)
F	44 (21.8)
Histology	
Squamous	105 (52.0)
Adenocarcinoma	83 (41.1)
Others	14 (6.9)
Grading	
G1	2 (1.0)
G2	82 (40.6)
G3	103 (51.0)
Gx	15 (7.4)
pT (TNM VII ed.)	
T1a	15 (7.4)
T1b	35 (17.3)
T2a	68 (33.7)
T2b	31 (15.3)
T3	33 (16.3)
T4	20 (9.9)
Pathologic stage	
II A	114 (56.4)
II B	31 (15.3)
III A	57 (28.2)
VP invasion	
No	97 (48.0)
Yes	66 (32.7)
(b)	
Surgery procedure	
Wedge resection	5 (2.5)
Lobectomy	165 (81.7)
Pneumonectomy	32 (15.8)
LAD	
Hilar LAD	39 (19.3)
Hilar–mediastinal LAD	163 (80.7)
Adjuvant chemotherapy	
No	152 (75.2)
Yes	50 (24.8)
(c)	
LN station	
Hilar/interlobar	134 (66.3)
Peripheral	40 (19.8)
Both	28 (13.9)
ECE	
No	184 (91.1)

Table 1 continued

Characteristic	N (%)
Yes	18 (8.9)
LN positive	
1	87 (43.0)
≥2	115 (56.9)
LN examined	
<10	121 (59.9)
≥10	81 (40.1)
LNR	
≤0.15	61 (30.2)
>0.15	141 (69.8)

VP visceral pleura, LAD lymphadenectomy, ECE extra capsular extension, LN lymph node, LNR lymph node ratio

pneumonectomy, while the most frequent surgical procedure was lobectomy (81.7 %). LN dissection included exclusively hilar LN in 19 % of cases and was extended to mediastinum in the remaining 81 %. LNs were located in station 10 and 11 (hilar and interlobar), 12–14 (peripheral) or both, in 66.3, 19.8 and 13.9 % of the cases, respectively. ECE occurred in 18 cases, corresponding to 8.9 % of cases; the median number of positive LN was 2 (range 1–11) and the median number of examined LN was 8 (range 1–49). The LNR was higher than 0.15 in 69.8 % of cases. Table 1 shows pathological, therapeutic and nodal characteristics.

24.8 % of patients received adjuvant chemotherapy after surgery. Age (≥65 vs <65) was the only variable that correlated with chemotherapy administration. In fact, chemotherapy was frequently withheld in elderly patients (72.4 vs 36 %, $p < 0.001$). No other significant correlations were found with all the other considered variables.

Fifty-nine patients (29.2 %) were alive at the time of the analysis, and 34 (16.8 %) of them without evidence of disease. Among the 143 patients (70.8 %) who died, 103 (51. %) died of lung cancer. Nineteen (9.8 %) patients were lost to follow-up, because any information of their status was available within 6 months after the last visit of follow-up.

The total number of recurrences in the entire series was 118 (64.4 %): 44 (24 %) were LR and 74 (40.4 %) DM; thus, LR and DM accounted for 37.3 and 62.7 % of the recurrences, respectively.

No significant differences in LR and DM rate were noted in the patients' subgroups and in patients who received chemotherapy versus patients who did not.

Median PFS was 24.1 months; 1, 3, and 5-year actuarial PFS were 72.9, 43.1, and 33.3 %, respectively. Median OS was 41.1 months; 1, 3, and 5-year actuarial OS were 84.2, 53.8, and 39.2 %, respectively (Fig. 1). 1, 3 and 5-year FFLR and FFDM were 92, 69.9, 64.5 and 79.2, 61.8, and 51.7 %, respectively (Fig. 2).

Patients with recurrences experienced a statistically worse OS than patients without recurrences ($p < 0.001$), while patients with DM had OS rates significantly worse than those with LR (Fig. 3).

Among relapsing patients, cumulative probability of LR at 1, 3 and 5-years after surgery was 27.3, 86.4 and 95.5 %, respectively, and that of DM was 47.3, 78.4 and 90.5 %, at the same time intervals.

The possible impact on clinical outcomes of all the pathological and therapeutic variables was explored with univariate analysis. The involvement of both hilar and peripheral LN ($p = 0.037$), the presence of ECE ($p = 0.005$) and a high LNR ($p = 0.011$) were all related to a worse PFS. No correlations were found for OS. A non-significant benefit in terms of OS was observed in chemotherapy-treated patients. Wedge resection ($p = 0.014$), positive ECE ($p = 0.002$) and a high LNR ($p < 0.001$) were associated with a worse FFLR, while squamous carcinoma was the only factor statistically related to a better FFDM.

Cox regression analysis elaborated for homogeneous groups of risk factors (clinical pathological, treatment and nodal) confirmed that ECE (RR 2.10, CI 1.19–3.68; $p = 0.01$) and LNR >0.15 (RR 1.68, CI 1.10–2.55; $p = 0.015$) were independent prognostic factors for PFS. In terms of OS, no therapeutic and nodal factor seemed significantly related with outcome, while pathological stage IIB (compared to IIA) has an unfavorable prognostic impact (RR 1.69, CI 1.07–2.67; $p = 0.023$). The presence of ECE and LNR >0.15 resulted independently related with a worse FFLR (RR 3.04, CI 1.34–6.90; and 4.42, CI

1.73–11.29; respectively). Adenocarcinoma histology negatively affected FFDM when compared with squamous cell histology (RR 1.97, CI 1.15–3.36; $p = 0.013$) (Table 2a–c).

Discussion

Chemotherapy remains the standard adjuvant treatment for pN1 NSCLC patients with a modest benefit in survival [4]. Notably, the LACE meta-analysis, favoring the use of platinum-based chemotherapy, reported also a not negligible acute neutropenia rate and an excess of cardiovascular/pulmonary deaths independently from the drug combination and the use of PORT [10]. Furthermore, a subgroup analysis at ANITA trial, seems to emerge an improvement in survival at 5 years in comparison between the control arm (only observation) versus PORT (31.4 vs 42.6 % at 5 years) and a better locoregional control in PORT group patients independently by chemotherapy (11.8 vs 20.3 %), suggesting that at least in pN1 patients who are not candidates for adjuvant chemotherapy, PORT is an alternative and increases the survival over observation [11].

Today, there is no recommendation to PORT in this patient subset, largely because of the results of the PORT meta-analysis [6]. However, it is currently a diffuse opinion that some of the suggestions derived from that meta-analysis need to be reviewed, since they are mostly based on randomized trials dating back up to four decades before the first edition, published in 1998. Data were updated in 2000, 2003 and 2005 without altering the conclusions of

Fig. 1 Kaplan–Meier curves showing overall survival (OS) and progression-free survival (PFS) for entire cohort

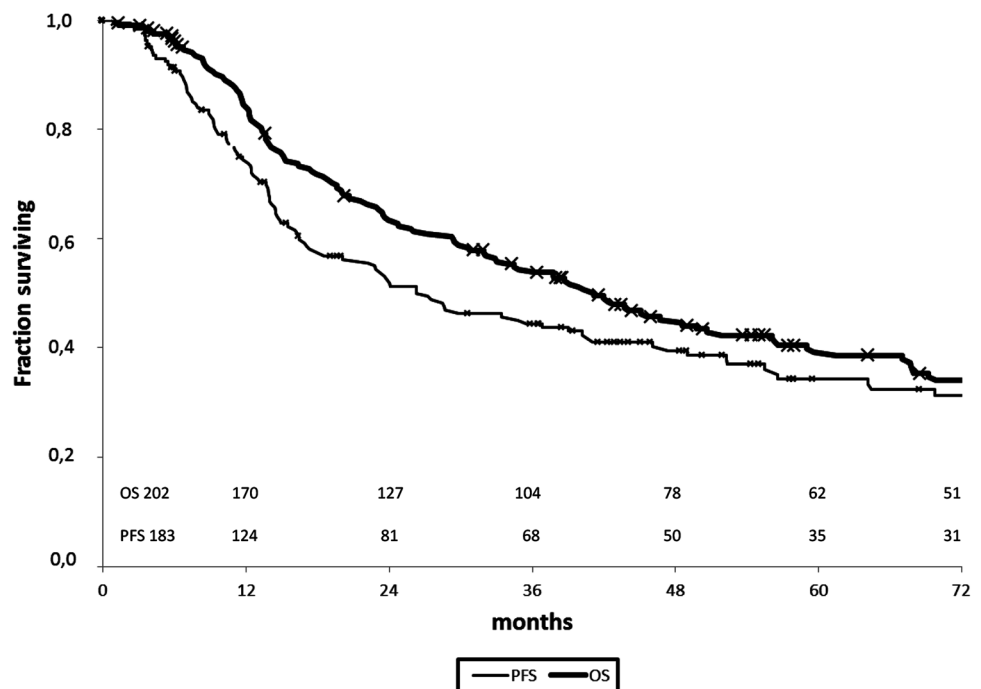
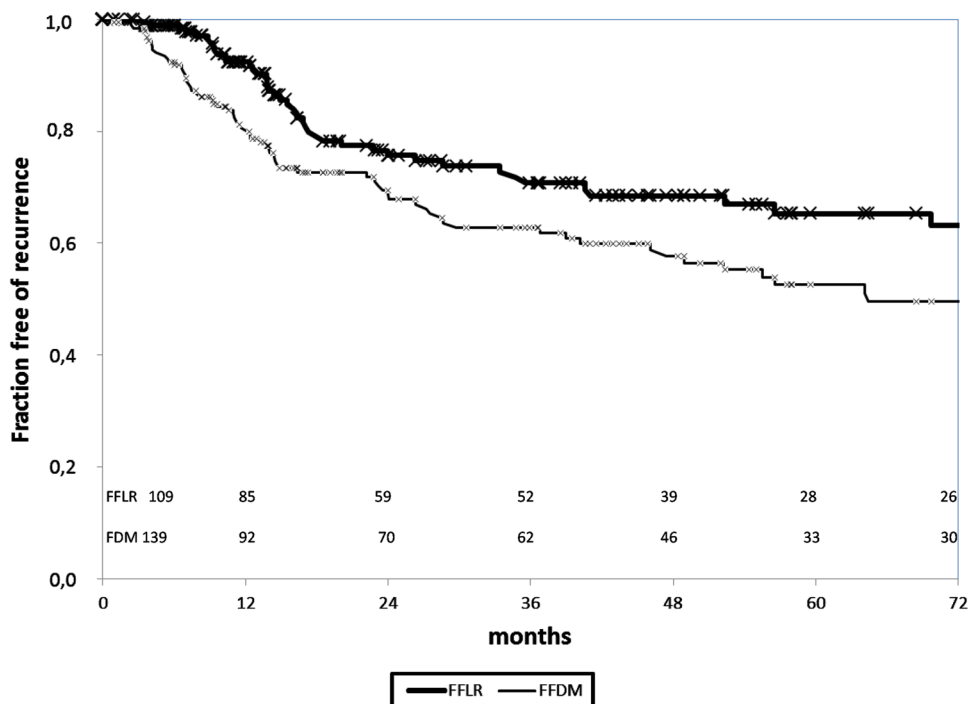


Fig. 2 Kaplan–Meier curves showing freedom from local recurrence (FFLR) and freedom from distant metastasis (FFDM) for entire cohort



the original version [12–14]. Indeed, the trials collected in PORT meta-analysis are characterized by a huge heterogeneity in terms of radiation sources (cobalt machines or linear accelerators), techniques, treated volumes, fractionations and doses. A more recent meta-analysis confirms a detrimental effect on survival, particularly for early stage tumors [4]. The evidence that PORT with modern linear accelerators improves loco-regional control and survival with a lower and acceptable toxicity is proven for pN2 lung cancer patients [15]. No randomized trials have been performed to evaluate if modern three-dimensional conformal radiotherapy (3DCRT) could reduce toxicity in adjuvant treatment for pN1 resected lung cancer. Kepka et al. in a prospective non-randomized study analyzed cardiopulmonary morbidity and quality of life in pN2 NSCLC patients treated with 3DCRT compared to pN1 NSCLC who underwent surgery alone. Their findings supported the hypothesis that morbidity of postoperative 3DCRT is acceptable [16].

Several factors may affect prognosis and predict patterns of recurrence in the heterogeneous population of patients with pN1 NSCLC. As previously reported in literature [2, 3], the rate of recurrence was high in our series, with 64.4 % of patients who experienced a local (24.0 %) or distant relapse (40.4 %). Among 118 relapses, DM were thus the majority and, in addition, appeared earlier on in the course of the disease. Histology resulted the only factor with statistically significant impact on FFDM. LR occurred in approximately one-fourth of the evaluable patients and constitute more than a third of the causes (37.3 %) of the first disease progression after treatment. Patients with LR

lived significantly longer than those with DM but they had a significantly worse OS than patients without recurrences. In our series, chemotherapy did not statistically improve local control and survival.

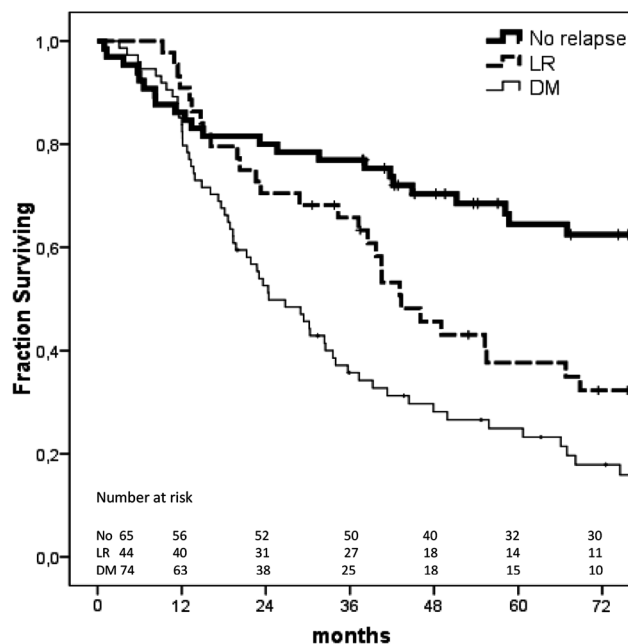


Fig. 3 Comparison of overall survival (OS) in patients without relapse or with locoregional recurrence (LR) or distant metastasis (DM)

Table 2 Multivariate analysis for clinical–pathological (a) treatment (b) and nodal (c) factors

Variables	FFLR		FFDM		PFS		OS	
	RR	<i>P</i>	RR	<i>P</i>	RR	<i>P</i>	RR	<i>P</i>
(a)								
Age		ns		ns		ns		ns
Sex		ns		ns		ns		ns
Histology		ns		0.034		ns		ns
Squamous			1					
Adenocarcinoma			1.97 (1.15–3.36)	0.013				
Altro			2.19 (0.90–5.36)	0.083				
Grading		ns		ns		ns		ns
pT VII ed.		ns		ns		ns		ns
Pathological stage VII ed.		0.074		ns		ns		0.075
IIA	1						1	
IIB	7.60 (1.33–43.53)	0.023					1.69 (1.07–2.67)	0.023
IIIA		ns						ns
VP invasion		ns		ns		ns		ns
(b)								
Surgical procedure		0.031		ns		0.066		ns
Wedge resection	1				1			
Lobectomy	0.21 (0.06–0.68)	0.010			0.38 (0.15–0.93)	0.034		
Pneumonectomy	0.19 (0.05–0.75)	0.018			0.31 (0.11–0.83)	0.020		
LAD		ns		ns		ns		ns
Adjuvant CHT		ns		ns		ns		ns
(c)								
LN station		ns		0.091		ns		ns
Hilar and interlobar (10 e 11)			1					
Peripheral(12-13-14)				ns				
Both			2.01 (1.07–3.77)	0.029				
ECE		0.008		ns		0.010		ns
No	1				1			
Yes	3.04 (1.34–6.90)				2.10 (1.19–3.68)			
Positive LNs		ns		ns		ns		ns
Examined LNs		ns		ns		ns		ns
LNR		0.002		ns		0.015		ns
≤0.15	1				1			
>0.15	4.42 (1.73–11.29)				1.68 (1.10–2.55)			

VP visceral pleura, LAD lymphadenectomy, CHT chemotherapy, ECE extra capsular involvement, LNR lymph node ratio

Recently, Varlotto et al. argued that nodal stage may not be the most appropriate selection factor to consider PORT [8]. To date, data suggest that, when feasible, adjuvant PORT could favorably alter the natural history of resected lung cancer, by reducing LR rate; consequently, factors predicting an higher LR rate could be used to select pN1 patients for whom the benefit of radiotherapy is greater [2, 3]. For these reasons, it seems also reasonable to explore nodal factors affecting clinical outcomes. Our analysis showed that ECE and LNR might be considered good

predictors of FFLR and PFS. ECE has been rarely investigated in pN1 patients with NSCLC, but it is a widely known unfavorable prognostic factor in pN2 cases [17]. Similar results have been found also in other neoplasms; ECE has been identified as an independent prognostic factor for breast cancer, head and neck carcinoma, bladder and rectal cancer [18–24].

On the contrary, the prognostic value of LNR has been the object of many retrospective studies, as an index of both the extent of lymphadenectomy and the

number of positive nodes [7, 9]. Some authors suggest that LNR can provide additional prognostic information in terms of OS [7, 25–27]. Wisnivesky et al. reported a worse OS with an increasing LNR in a series of 1682 pN1 NSCLC patients [26]. Urban et al. in a large series of 6551 pN1 NSCLC patients obtained from the surveillance, epidemiology and end results (SEER) database, showed a significant worsening of OS along with increasing LNR values [7]. Li et al. showed an OS benefit in patients with an LNR ≤ 0.15 after surgical resection for pN1 NSCLC ($p = 0.040$). In the same study, 5-year PFS was equal to 48–33 % in patients with LNR ≤ 0.15 and > 0.15 , respectively ($p = 0.010$) [25]. The present analysis confirmed similar findings (3-year PFS of 58.2 and 36.5 %, respectively, in the group with LNR ≤ 0.15 and LNR > 0.15 , $p = 0.011$). In the present series, LNR has a predictive value for local control [(LNR > 0.15 RR = 4.42 (IC 1.73–11.29) $p < 0001$)] and is, therefore, likely useful to discriminate patients who could be eligible to an adjuvant loco-regional treatment such as radiotherapy.

Therefore, nodal factors appear to be effective predictors of locoregional recurrence and, according to the results of other retrospective series [3, 7, 17], LNR appears to be a more reliable prognostic factor than the number of positive or examined LN alone. Similar results have been found also for breast, esophageal, pancreatic, biliary duct cancers, remarking LNR-independent role to predict prognosis [28–31]. Moreover, LNR seems to have a role as a predictor not only of LR but also of OS and thus it should be considered a cornerstone to select a population who can benefit from adjuvant radiotherapy.

Conclusions

Unfavorable prognostic factors such as nodal risk factors should be considered to select patients that might be the advantage of PORT. A possible benefit from technical advancements in treatment planning and dose delivery needs to be confirmed within a series of NSCLC patients with pN1 disease. Perspective studies based on accurately selected patients and modern radiotherapy could be the key to re-evaluate PORT in pN1.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study (retrospective study), formal consent is not required.

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