Survival Analysis of Surgically Resected ypN2 Lung Cancer after Neoadjuvant Therapy

Özgür İşgörücü[1] Necati Citak[2]

[1] Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2] Department of Thoracic Surgery, Dr. Suat Seren Chest Diseases Training and Research Hospital, Izmir, Turkey

Address for correspondence Özgür İşgörücü, MD, Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital, Zuhuratbaba/Bakırköy, Istanbul 34147, Turkey (e-mail: ozgurisgorucu@hotmail.com).

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Abstract

Introduction Surgery is widely accepted today when downstaging of mediastinal lymph nodes after neoadjuvant therapy is achieved. However, the role of surgery in patients with persistent N2 disease is still controversial. This study aims to detail the diagnostic problems, prognostic features, and long-term survival of the persistent N2 non-small cell lung cancer patient group.

Patients and Methods One-hundred fifty patients who received neoadjuvant therapy and subsequently underwent resection, in-between 2003 and 2015, were retrospectively analyzed. In this study, "persistent N2" group refers to patients who received neoadjuvant therapy for clinically or histologically proven N2, who underwent a surgery after having been classified as "downstaged" at restaging, but in whom ypN2 lesions were subsequently confirmed on the operative specimens. Patients with multistation N2 were included in the study. There were 119 patients who met the criteria, whereas persistent ypN2 was detected in 28.5% ($n = 34$) of all patients.

Results Overall 5-year survival rate was 47.2%, while it was 23.4% for patients with persistent N2. Factors that adversely affected survival were to have nonsquamous cell histological type ($p = 0.006$), high ypT stage ($p = 0.001$), persistent N2 ($p = 0.02$), and recurrence during follow-up ($p < 0.001$). A trend toward a shorter survival was observed when the ypN2 zone was subcarinal versus other zones, but did not reach statistical significance ($p = 0.08$). In addition, a trend toward a shorter survival of patients with multiple N2 involvement ($p = 0.412$) was observed.

Conclusion In the persistent N2 group, when multiple involvement or subcarinal involvement was excluded, relatively good survival was detected.

Keywords
- surgery
- chemotherapy
- lung cancer
- diagnosis

Introduction

Around 10% of patients with newly diagnosed non-small cell lung cancer (NSCLC) are classified as stage IIIA-N2.[1] However, N2 positive patients consist of patients with different treatment strategies. The first group of patients has N2 disease, which shows significant invasion into mediastinal structures or large veins, and cannot be resected with bulky N2 characteristics protruding out of the capsule. Besides, surgery is not considered even after neoadjuvant therapy.[2] The second group has "unpredictable N2" disease, with clinical N0–1 disease, in which surprise positive mediastinal lymph node metastasis is detected during thoracotomy after negative mediastinoscopy. The 5-year survival (5YS) of this group has been reported as 20 to 25%.[3,4] According to the American College of Chest physicians (ACCP) guidelines, if N2

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Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

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is detected during surgery, surgery should be continued with mediastinal lymphadenectomy, and adjuvant chemotherapy should be recommended when complete resection of lymph nodes and R0 resection for the primary tumor is technically feasible (recommendation grade: 2C).[5]

Another group has potentially resectable N2-NSCLC, and the diagnosis of pathologically proven ipsilateral mediastinal lymph node metastasis is made during initial clinical staging. Mediastinal lymph nodes may be radiologically normal or enlarged. After neoadjuvant therapy, surgery is possible with acceptable mortality and morbidity,[6–8] and it provides a better 5YS rate compared with resection alone. Focusing on the details of the results of this particular group, 5YS after postneoadjuvant surgical resection has been reported as 40% in patients with pN0 disease,[9] and even 65% in patients with pathological complete response ypT0N0.[10] It achieved a 5YS rate of 20% in patients with persistent pN2.[9] Because of the low survival, patient selection after neoadjuvant and the role of surgery in patients with persistent N2 disease are controversial. The present study primarily aims to determine prognostic factors by evaluating single-centered results in patients with potentially resectable stage IIIA-N2 NSCLC.

The secondary aim is to detail the diagnostic problems, prognostic features, and long-term survival of the persistent N2 patient group.

Materials and Methods

One-hundred fifty patients with a mean age of 54.9 ± 8.3 years who received neoadjuvant therapy and who were subsequently performed resection, in-between 2003 and 2015, were retrospectively analyzed. In this study, "persistent N2" group refers to patients who received neoadjuvant therapy for clinically or histologically proven N2, who underwent a surgery after having been classified as "downstaged" at restaging, but in whom ypN2 lesions were subsequently confirmed on the operative specimens. Exclusion criteria were to receive N3-cause neoadjuvant treatment ($n = 8$), presence of macroscopic incomplete resection (R2) ($n = 1$), presence of microscopic incomplete resection (R1) ($n = 5$), tapering of the therapy due to chemotherapy toxicity ($n = 11$), and increase in TNM stage during neoadjuvant therapy ($n = 6$). Patients with multistation N2 were included in the study and 119 patients met the criteria.

In detail, the patients in the study were individuals with locally advanced (T1–T4 N2) NSCLC who were recommended surgery if downstaging was detected in restaging after neoadjuvant therapy by ACCP.[11]

First Staging, Neoadjuvant Therapy, Restaging

Patients with clinical N-cause advanced stage NSCLC or histopathologically proven positive mediastinal lymph nodes (►**Fig. 1**) were carefully selected for neoadjuvant therapy by a multidisciplinary council. Patients interpreted as N-cause locally advanced stage were staged clinically (suspected on computed tomography [CT], lymph node >1 cm and/or positron emission tomography [PET]/CT, maximum standardized uptake value >3.5) or invasively (transbronchial lymph node biopsy, endobronchial ultrasound [EBUS], mediastinoscopy, mediastinotomy). Between two to six cycles of platinum-based chemotherapy and/or 45 to 50.4 Gy radiotherapy were administered. Seventy-five patients received chemoradiotherapy (CRT), whereas 44 of them received chemotherapy.

Sixty-seven patients underwent mediastinal restaging (transbronchial lymph node biopsy, EBUS, standard cervical or extended mediastinoscopy, remediastinoscopy, mediastinotomy), whereas clinical remediastinal staging (PET-CT or CT) were performed in 52 patients (►**Fig. 1**).

Surgery

Patients who were found to be downstaging as a result of remediastinal and clinical staging were prepared for surgery approximately 2 weeks later (6–8 weeks after the last treatment). Mediastinal lymph node dissection was performed in accordance with oncological principles.[12]

Pathological examination was performed using standard techniques, and immunohistochemical staining was performed when applicable. With the decision of the multidisciplinary oncological council, patients who were deemed suitable for adjuvant therapy were treated. The clinical staging of the cases whose pathological staging was performed using the eighth staging system was also updated according to the same staging system.[12]

Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (version 11.5; SPSS Inc., Chicago, Illinois, United States). The survival rate was estimated by the Kaplan–Meier's method, and a comparison of the survival rates between the groups was performed by using the log-rank analysis. Multivariate survival analysis was performed using the Cox's proportional hazards model. The Student's *t*-test and chi-square test were used for other comparisons. The Fisher's exact test was used when there was a small number of groups. A $p < 0.05$ was considered statistically significant.

Results

Patients

Induction therapy was given to 98 of the cases (82.3%) due to pathologically proven N2 (pN2) and 21 of them (17.7%) due to clinically diagnosed N2 (cN2). In the first staging, the most frequently involved lymph node zone was paratracheal with 52.1% ($n = 66$), the second was the subcarinal zone with 28.5% ($n = 34$), the third was the aortopulmonary window with 9.2% ($n = 11$), and the fourth was both paratracheal and subcarinal zones involvement with 10% ($n = 12$). Diagnostic details of the cases in the first evaluation are shown in ►**Fig. 1a**. Basic clinical characteristics of the patients are shown in ►**Table 1**. CRT was performed in 62.7% of the cases, whereas the remaining 37.3% were treated with chemotherapy only.

Evaluation after Neoadjuvant Therapy

Four to six weeks after the completion of neoadjuvant therapy, all patients were re-evaluated with a CT scan using

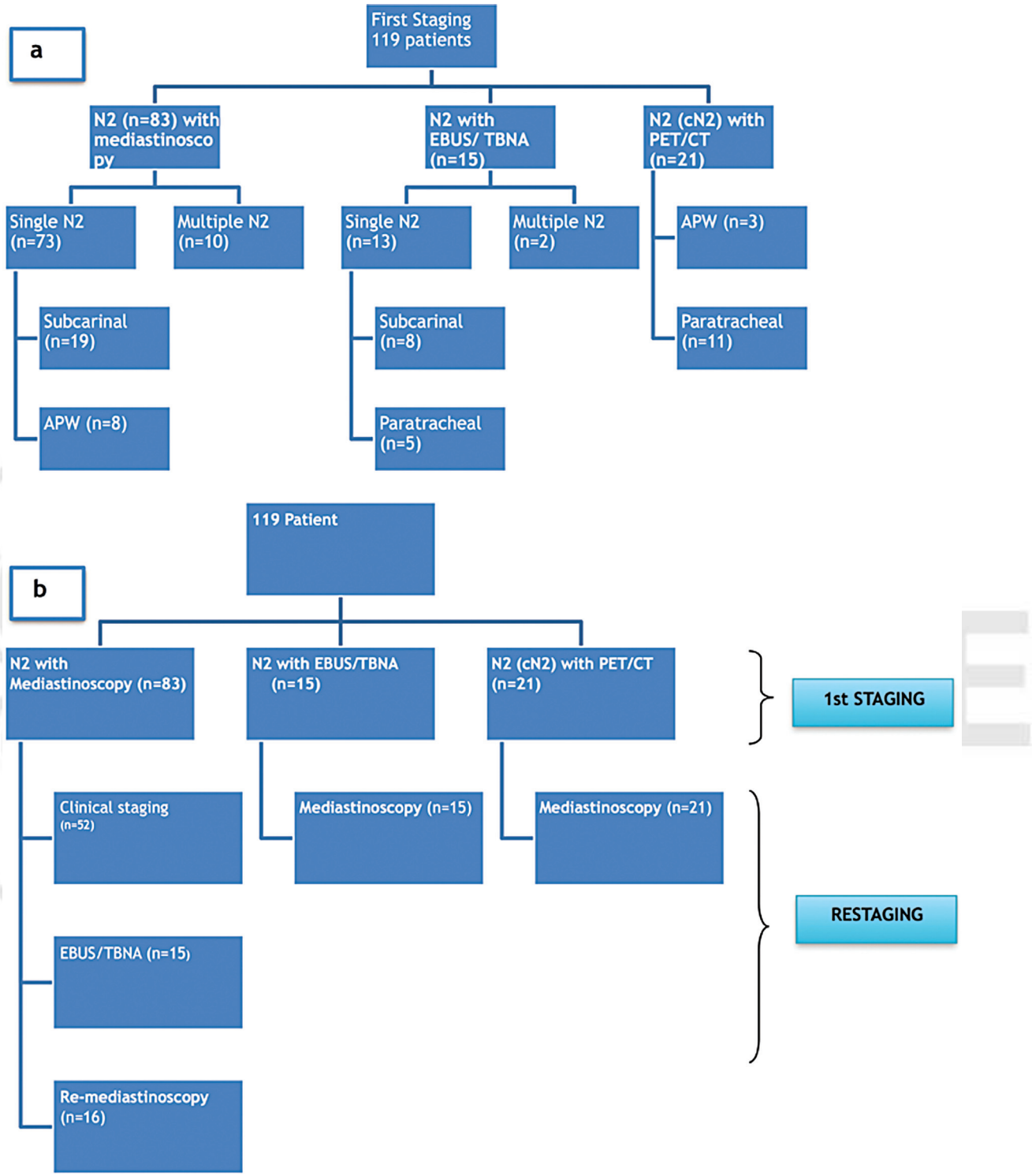

Fig. 1 (**a**) Diagnostic methods and details of the involved N2 zone in the first staging. (**b**) Diagnostic methods of restaging. APW, aortopulmonary window; EBUS/TBNA, endobronchial ultrasound/transbronchial needle aspiration; PET-CT, positron emission tomography–computed tomography.

Response Evaluation Criteria In Solid Tumors guidelines.[13] Patients with partial response ($n = 92$) or stable disease ($n = 27$) were discussed at a weekly multidisciplinary oncological meeting, and 67 patients underwent invasive restaging, whereas 52 of them underwent clinical restaging (►**Fig. 1b**). Forty-seven patients had PET scans after neoadjuvant therapy. Remediastinoscopy was performed on 16 patients.

Surgery

All patients in the study group were completely resected. In the excluded patient group, microscopic incomplete or

Table 1 Baseline clinical characteristics

		n (%)
Total number		119 (100%)
Age (y)		54.9 ± 8.3
Gender	Male	111 (93.2%)
	Female	9 (6.7%)
Smoking status	Never smoked	11 (9.2%)
	Ex-smoker	92 (77.3%)
	Active smoker	16 (13.4%)
Tumor side	Left	44 (36.9%)
	Right	75 (63%)
Histological subtype	Squamous cell carcinoma	50 (42%)
	Adenocarcinoma	48 (40.3%)
	Adenosquamous carcinoma	19 (15.9%)
	Large cell carcinoma	2 (1.6%)
Radiological T-stage	1	2 (1.6%)
	2	67 (56.3%)
	3	28 (23.5%)
	4	22 (18.4%)
Baseline mediastinal staging	Mediastinoscopy N2	83 (69.7%)
	Transbronchial (EBUS/TBNA) N2	15 (12.6%)
	Clinical (PET-CT) N2	21 (17.6%)
Baseline mediastinal lymph node involvement zone	Paratracheal	62 (52.1%)
	Subcarinal	34 (28.5%)
	Aortopulmonary	11 (9.2%)
	Paratracheal + subcarinal	12 (10%)

Abbreviations: EBUS/TBNA, endobronchial ultrasound/transbronchial needle aspiration; PET-CT, positron emission tomography–computed tomography.

Table 2 Resection type and definitive pathology

		n (%)
Type of resection	Lobectomy	77 (64.7%)
	Bilobectomy	19 (15.9%)
	Pneumonectomy	23 (19.3%)
Standard or extended	Standard resection	98 (82%)
	Extended resection (sleeve, atrium or thoracic wall resection, etc.)	21 (17.6%)
Pathological stage (ypTNM)	T0N0M0	35
	T0N2M0	2
	T1N0M0	17
	T1N1M0	8
	T1N2M0	10
	T2N0M0	13
	T2N1M0	7
	T2N2M0	16
	T3N0M0	1
	T3N1M0	2
	T3N2M0	5
	T4N0M0	1
	T4N1M0	1
	T4N2M0	1
ypN2 involvement	Single	25 (21%)
	Multiple	9 (7.5%)
Adjuvant therapy	Yes	38 (31.9%)

indeterminate resection (R1) was performed in five patients (3.7%) and macroscopic incomplete resection (R2) in one patient (1%). Ninety-six of the patients underwent lobectomy (bilobectomy was performed in 19 of them), and the remaining 23 underwent pneumonectomy. Eight of the patients who underwent pneumonectomy were right sided, and 15 were left sided. Partial chest wall resection was performed in addition to a right-side pneumonectomy case. Bronchial stump was covered in 72 of the patients who had lobectomy or pneumonectomy. The intercostal muscle was used in 2 patients, pericardial fat was used in 7 patients, and the pleural flap was used in 51 patients.

Pathology

Downstaging of mediastinal lymph nodes ypN0 and ypN1 was found in 56.3% ($n = 67$) and 15.1% ($n = 18$) of the cases, respectively, whereas persistent ypN2 was detected in 28.5% ($n = 34$) of all patients (►**Table 2**). Complete pathological response (ypT0N0) was found in 29.4% ($n = 35$) of patients. In the subgroup of patients with persistent mediastinal lymph node disease, 21% ($n = 25$) of them had single level ypN2, whereas 7.5% ($n = 9$) of them had multilevel ypN2 disease. Adjuvant treatment was applied to 38 cases (31.9%). Of these, 19 were ypN2, 7 were ypN1, and 4 were ypN0.

Mortality and Morbidity

Surgical mortality rate was 5% ($n = 6$). Three patients developed pneumonia, and one patient developed acute respiratory distress syndrome (ARDS) following bronchopleural fistula. Additionally, mortality developed in one patient after pulmonary embolism and another after myocardial infarction. Right-side pneumonectomy was performed in one of these cases, partial chest wall resection in addition to right upper lobectomy was performed in another, and standard lobectomy was performed in the other four patients. Complication rate was calculated as 39.4% ($n = 47$) (►**Table 3**). The most frequent complications were persistent air leaks and airspace (11.7%). Bronchopleural fistula developed in eight cases. Pneumonectomy was, therefore, performed in four of those cases (two left and two right), whereas bilobectomy was performed in the other four. No fistula was seen in any standard lobectomy. Bronchopleural fistula developed

Table 3 Postoperative morbidity after resection

Complication	*n*	%
Persistent air leak, space	14	11.7
Bronchopleural fistula	8	6.7
Pneumonia	8	6.7
Arrhythmia	5	4.2
Wound site infection	3	2.5
Hoarseness	2	1.6
Chylothorax	2	1.6
Pulmonary embolism	1	0.8
Cerebrovascular accident	1	0.8
Respiratory failure	1	0.8
Renal failure	1	0.8
Hemorrhage	1	0.8
Total	47	39.4

after right lower bilobectomy in one case resulted in mortality following ARDS.

Recurrence

Recurrence was detected in 25.2% ($n = 30$) of the patients during follow-up. The most common ones were brain metastasis and local recurrence, each was seen at a rate of 7.5% (►**Table 4**). The risk factors affecting recurrence were to have a nonsquamous cell histological tumor ($p = 0.006$) and to receive chemotherapy only ($p = 0.04$). Besides, the type of operation ($p = 0.881$) and presence of persistent N2 ($p = 0.693$) did not affect the development of recurrence.

Survival

Overall 5YS rate was 47.2% (median 57 ± 9.5 months), while it was 23.4% (median 36 ± 9.3 months) for persistent N2s. The factors that adversely affect survival were presence of nonsquamous cell histological type ($p = 0.006$), high ypT stage ($p = 0.001$), persistent N2 ($p = 0.02$), and recurrence in follow-up ($p < 0.001$), while cT stage ($p = 0.294$), subcarinal metastatic lymph node, neoadjuvant cause ($p = 0.694$), the type of operation ($p = 0.942$), and the staging method ($p = 0.325$) had no effect on survival. It was observed that in the ypN2 group, subcarinal compared with other zones (median: 57 vs. 16 months, $p = 0.08$) and multiple versus single involvement (23 vs. 0%, $p = 0.412$) were found to have a negative but not statistically significant effect on survival (►**Fig. 2**; ►**Table 5**).

Discussion

Stage IIIA-N2 NSCLC patients constitute a heterogeneous group with a spectrum ranging from microscopic single level to multilevel unresectable mediastinal lymph node involvement. Therefore, there is no consensus on its optimal treatment. A possible approach to patients with resectable stage IIIA-N2 NSCLC is resection following the neoadjuvant therapy.[7,8,14,15] In the intergroup lung study,[16] overall 5YS was better in the surgical group at a rate of 27%, but not significantly different from the nonsurgical group at a rate of 20%. European Organisation for Research and Treatment of Cancer study[17] randomized patients with pathologically proven N2 disease. Initially, all patients were judged to have an unresectable disease and were subjected to induction chemotherapy. Those who responded to chemotherapy were randomized into radiotherapy and surgery groups. The 50% incomplete resection rate in the surgical group and the 15% 5YS rate were disappointingly low.

Table 4 Recurrences detected during postoperative follow-up

Recurrence	*n*	%
Brain	9	7.5
Local	9	7.5
Contralateral lung	4	3.3
Bone	4	3.3
Liver	2	1.6
Adrenal	2	1.6
Total	30	25.2

Studies over the years have shown that adding radiotherapy to chemotherapy does not improve survival compared with chemotherapy alone, even if pathological complete response (pCR) rates are higher.[18,19] In our study, the frequency of CRT application decreased over the years, and the rate of neoadjuvant chemotherapy only increased.

The total 5YS was 47.2 and 23.4% after general and persistent N2 resection, respectively. However, all patients who were treatable and who had stable disease after neoadjuvant therapy were included in the study. In the current study, following surgical multimodality treatment of NSCLC, the morbidity rate was found to be 39.5%. The mortality rate in our study was 5% ($n = 6$), which was higher than the literature.[6–8]

It was determined that our mortality rate was high especially in the early period of our series, and this rate decreased over time. The most important factor in mortality was pneumonia ($n = 3$). Immunosuppression after neoadjuvant therapy increases complications. We think that immunosuppression is more effective in the formation of infective complications in our patient population with a low–intermediate socioeconomic level. Preoperative patient preparation and evaluation is very important in these cases. We think that our mortality rate has decreased with our patient preparation methods that have developed over the years. It was observed that the type of resection did not affect survival, and therefore, pneumonectomy, which is the subject of discussion, can be safely performed after neoadjuvant therapy. Bronchopleural fistula developed in eight cases. Pneumonectomy was, therefore, performed in four of those cases (two left and two right), whereas bilobectomy was performed in the other four. One of the most important complications after neoadjuvant therapy is bronchopleural

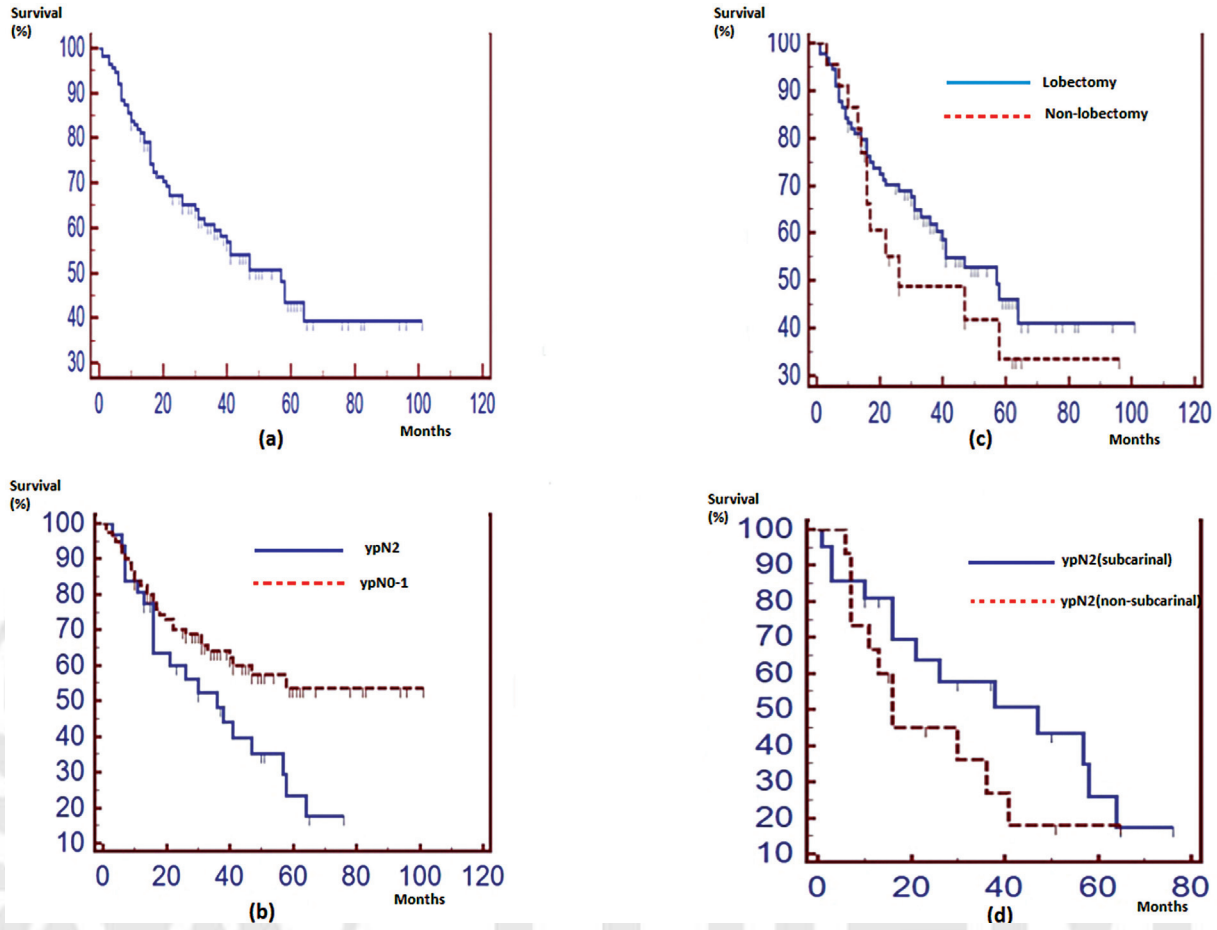

Fig. 2 Survival graph (**a**: overall survival; 47.2%, **b**: survival by N-downstaging status; 53.5% for ypN0–1, 23.4% for ypN2, $p = 0.02$, **c**: survival by resection type; 33% for lobectomy, 46% for pneumonectomy, $p = 0.942$, and **d**: survival by ypN2 involvement zone; 34% for subcarinal, 43% for nonsubcarinal, $p = 0.694$).

fistula. In pneumonectomy cases performed after neoadjuvant therapy, tissue support is placed and increased care is taken to prevent this complication. This surgical approach should also be demonstrated after lower bilobectomies after neoadjuvant therapy. Okuda et al also concluded that neoadjuvant therapy and a right lower lobe location were risk factors after a lobectomy, while a right-side and complete pneumonectomies were risk factors after a pneumonectomy.[20] In the study conducted by Mansour et al, it was reported that pneumonectomy performed in patients even with persistent N2 status is safe.[21] Persistent N2 status is the most obvious and worst prognostic factor. 5YS in published series of patients with persistent N2 disease after neoadjuvant therapy is poor compared with patients with pN0 disease (5YS <20 vs. 30–40%, respectively).[3,15,22–25]

In our study, the risk factors affecting recurrence were to have a nonsquamous cell histological tumor ($p = 0.006$) and to receive chemotherapy only ($p = 0.04$). Similarly, in the study of Montemuiño et al, locoregional recurrence was significantly lower in the CRT group (8.5 vs. 13.5%; $p = 0.047$), but distant recurrence rates were similar in the two groups.[26]

In the present retrospective series, patients with persistent N2 disease had 5YS with a rate of 23.4%, while patients with mediastinal nodal downstaging had a trend of better 5YS with a rate of 53.5% ($p = 0.02$). This subgroup of 35 patients with persistent N2 was a heterogeneous group. There was a significant difference between single and multilevel persistent N2 at 5YS during resection (23 vs. 0%, $p = 0.412$). This result was consistent with data published by the IASLC Lung Cancer Staging Project (34 vs. 20%, $p < 0.0001$). Subcarinal persistent N2 (median: 57 vs. 16 months, $p = 0.08$) was determined as a poor prognostic factor. Sufficient restaging is paramount. These results also confirm the finding that there are insufficient data to exclude all resectable patients with persistent N2 disease from surgery, as some of those can be treated with favorable outcomes.[27]

Considering patients with persistent nonmultiple mediastinal LN disease as a separate subgroup after neoadjuvant therapy, a better than predicted 20 to 34% 5YS was observed.[3,4,15,28,29] Nowadays, first staging is performed more accurately, as PET/CT, EBUS/EUS, and/or mediastinoscopy opportunities are becoming widespread.[30] Indeed, although many experiences have shown a poor prognosis in persistent N2 patients,[9,11,31] some authors have reported encouraging results in some subsets of these patients and provided evidence about the large variability of N2

Table 5 Five-year survival analysis

	%	*p*-Value
Histological type		
Squamous	22	0.06
Nonsquamous (adenocarcinoma, large cell, adenosquamous cell)	51	
First staging in N2 zone		
Subcarinal	34	0.694
Nonsubcarinal (paratracheal, aortopulmonary)	43	
Staging method		
Invasive	55	0.01
Clinic	32	
Operation type		
Lobectomy	33	0.942
Pneumonectomy	46	
YpT		
ypT0–1	27	0.001
ypT3–4	56	
N downstaging		
ypN0–1	53.5	0.02
ypN2	23.4	
ypN2 zone		
Subcarinal	28	0.08
Nonsubcarinal (paratracheal, aortopulmonary, paraesophageal)	61	
ypN2 involvement		
Single	66	0.412
Multiple	37	
Recurrence		
Yes	0	0.001
No	23.2	

disease.[32–35] In particular, Bueno et al[23] and Vansteenkiste et al[36] reported a 5YS rate of 9, 0, and 14%, respectively. In contrast, Cerfolio et al[37] reported a 5YS rate as 42% for a highly selected group of persistent N2 patients who underwent R0 resection after CT. Especially, Decaluwé et al[38] focused on the number of lymph nodes as a predictor of survival, showing that patients with single lymph node disease have a better prognosis compared with patients with multiple nodal involvements ($p = 0.03$). Moreover, Decaluwé et al[38] found a significant difference in 5YS between persistent single and multilevel N2 at resection (37 vs. 7.1%; $p < 0.005$).

In the current study, a trend toward a shorter survival was observed when the ypN2 zone was subcarinal versus other zones, but did not reach statistical significance ($p = 0.08$). In addition, a trend toward a shorter survival of patients with multiple N2 involvement ($p = 0.412$) was observed.

Conclusion

Pulmonary resection after neoadjuvant therapy has been increasingly used in patients with N2 causes. Poor long-term survival was especially found in the persistent N2 group. This situation points to the importance that should be given to restaging. In the persistent N2 group, relatively good survival was detected with the exclusion of multiple involvement or subcarinal involvement.

Conflict of Interest
None declared.

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