Pneumonectomy in Stage IIIA-N2 NSCLC: Should It Be Considered After Neoadjuvant Chemotherapy?

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Abstract

This study aims to analyze the outcome of patients with stage IIIA-N2 non–small-cell lung cancer who underwent pneumonectomy to prove its safety and feasibility, in particular after induction chemotherapy. Based on the acceptable morbidity and mortality rate and the long-term survival, pneumonectomy should not be excluded for selected patients as a matter of principle.

Background: Owing to the expected poor long-term outcomes and high postoperative morbidity and mortality, patients with stage IIIA-N2 tumors candidate to pneumonectomy (PN) are usually excluded from surgery. This study aims to analyze the outcome of patients who underwent PN to prove its safety and feasibility. **Patients and Methods:** We retrospectively analyzed data from 233 patients who underwent PN for N2 non–small-cell lung cancer (NSCLC) between 1998 and 2015. Eighty-five patients were occult N2 disease (group 1), whereas 148 patients underwent induction therapy (IT) for stage IIIA-N2 (group 2). **Results:** Overall morbidity, postoperative mortality, and 90-day mortality rates were 46.8%, 2.6%, and 8.6%, respectively. The 2 groups (group 1 vs. 2) had similar postoperative and 90-day mortality rates: 2.4% versus 2.7% ($P = 1.00$), and 9.4% versus 8.1% ($P = .81$), respectively. The incidence of major morbidity was higher and statistically significant in group 2 compared with group 1: 23% versus 12.9% ($P = .1$). Postoperative bronchopleural fistula occurred in 4.7% (4/85) of patients with occult N2 (group 1) and in 10.1% (15/148) of patients undergoing IT (group 2) ($P = .10$). Median overall survival (OS) was 2.2 years, with a 3 and 5-year OS of 43.4% and 31.6%, respectively. Disease-free survival (DFS) was 1.5 years, with 3 and 5-year DFS of 41.6% and 32%, respectively; no difference in OS and DFS between the 2 groups was found. **Conclusions:** Considering the acceptable morbidity and mortality rate and the long-term survival, PN should not be excluded for selected patients with stage IIIA-N2 NSCLC as a matter of principle.

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Introduction

Stage IIIA-N2 non–small-cell lung cancer (NSCLC) comprises a very heterogeneous group of patients subjected to different therapeutic strategies and prognosis. Even if there is no clear consensus on the management of operable N2 disease, it is a matter of fact that patients with "potentially" resectable N2 disease, stable or respondent to induction therapy (IT), could be referred for surgery with a good long-term survival.[1-3] However, surgeons usually choose different therapeutic strategies for patients with IIIA-N2 NSCLC, and there are conflicting evidences about the efficacy of IT, above all when pneumonectomy (PN) is to be performed.

This means a lack of consensus regarding the management of stage IIIA and the role of PN.

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Table 1 Patients Pre- and Post-surgical Characteristics Stratified by the 2 Groups

	Total	Group 1 Occult pN2	Group 2 IT	*P* Value
		N (%)	N (%)	
Total	233 (100)	85 (100)	148 (100)	
Age, y				
<50	21 (9.0)	8 (9.4)	13 (8.8)	
50-59	62 (26.6)	13 (15.3)	49 (33.1)	
60-69	100 (42.9)	35 (41.2)	65 (43.9)	
70+	50 (21.5)	29 (34.1)	21 (14.2)	**.0009**
Gender				
Male	169 (72.5)	65 (76.5)	104 (70.3)	
Female	64 (27.5)	20 (23.5)	44 (29.7)	.31
cT				
1	21 (9.0)	9 (10.6)	12 (8.1)	
2	133 (57.1)	53 (62.4)	80 (54.1)	
3	58 (24.9)	17 (20.0)	41 (27.7)	
4	21 (9.0)	6 (7.1)	15 (10.1)	.12
cN				
0	36 (15.5)	36 (42.4)	–	
1	49 (21.0)	49 (57.6)	–	
2	148 (63.5)	–	148 (100)	
Clinical stage				
IA	1 (0.4)	1 (1.2)	–	
IB	15 (6.4)	15 (17.7)	–	
IIA	36 (15.5)	36 (42.4)	–	
IIB	18 (7.7)	18 (21.2)	–	
IIIA	148 (63.5)	15 (17.7)	133 (89.9)	
IIIB	15 (6.4)	–	15 (10.1)	
Pre-surgical treatment				
Chemotherapy	134 (90.5)	–	134 (90.5)	
Chemo-radiotherapy	9 (6.1)	–	9 (6.1)	
Radiotherapy	5 (3.4)	–	5 (3.4)	
Pneumonectomy				
Standard	133 (57.1)	60 (70.6)	73 (49.3)	
Extended	100 (42.9)	25 (29.4)	75 (50.7)	**.002**
Side				
Left	103 (44.2)	43 (50.6)	60 (40.5)	
Right	130 (55.8)	42 (49.4)	88 (59.5)	.14
pT				
0	12 (5.2)	–	12 (8.1)	
1	21 (9.0)	2 (2.4)	19 (12.8)	
2	104 (44.6)	46 (54.2)	58 (39.2)	
3	59 (25.3)	25 (29.4)	34 (23.0)	
4	37 (15.9)	12 (14.1)	25 (16.9)	**.002**
pN				
0	27 (11.6)	–	27 (18.2)	
1	37 (15.9)	–	37 (25.0)	
2	169 (72.5)	85 (100)	84 (56.8)	**<.0001**
pN2 stations (post-surgery)				
None	65 (27.9)	–	65 (43.9)	
Single	89 (38.2)	55 (64.7)	34 (23.0)	
Multiple	79 (33.9)	30 (35.3)	49 (33.1)	**<.0001**

Table 1 Continued

	Total	Group 1 Occult pN2	Group 2 IT	*P* Value
		N (%)	N (%)	
Pathologic stage				
Complete response (T0N0)	9 (3.9)	–	9 (6.1)	
IA	5 (2.2)	–	5 (3.4)	
IB	6 (2.6)	–	6 (4.1)	
IIA	16 (6.9)	–	16 (10.8)	
IIB	9 (3.9)	–	9 (6.1)	
IIIA	157 (67.4)	73 (85.9)	84 (56.8)	
IIIB	31 (13.3)	12 (14.1)	19 (12.8)	**<.0001**
Extent of surgery				
R0	227 (97.4)	85 (100)	142 (95.9)	
R1	5 (2.1)	–	5 (3.4)	
R2	1 (0.4)	–	1 (0.7)	.07
Histology				
NSCLC	6 (2.6)	–	6 (4.1)	
Squamous carcinoma	89 (38.2)	33 (38.2)	56 (37.8)	
Adenocarcinoma	117 (50.2)	45 (52.9)	72 (48.7)	
Large cell carcinoma	3 (1.3)	1 (1.2)	2 (1.4)	
Adenosquamous carcinoma	8 (3.4)	2 (2.4)	6 (4.1)	
Pleomorphic carcinoma	9 (3.9)	4 (4.7)	5 (3.4)	
Carcino-sarcoma	1 (0.4)	–	1 (0.7)	.55
Adjuvant treatment				
None	106 (45.5)	23 (27.1)	83 (56.1)	
Chemotherapy	25 (10.7)	21 (24.7)	4 (2.7)	
Radiotherapy	66 (28.3)	19 (22.4)	47 (31.8)	
Chemo-radiotherapy	15 (6.4)	11 (12.9)	4 (2.7)	
Unknown	21 (9.0)	11 (12.9)	10 (6.7)	**<.0001**

Bold text indicates a statistically significant correlation with a *P*-value less than .05.
Abbreviations: IT = induction therapy; NSCLC = non–small-cell lung cancer.

To date, patients with stage IIIA-N2 tumors candidate to PN are often excluded from surgery owing to the expected low long-term outcome and high postoperative morbidity and mortality.

Although in the past decades, the morbidity and mortality following PN dropped sharply owing to progresses in surgical technique and postoperative care,[4,5] the role of PN in N2 disease still remains controversial, especially considering the implemented use of the multimodality approach in advanced stage lung cancer and the increased risk of surgical complications after induction treatments.

This study aims to analyze the perioperative and long-term outcomes of PN performed in patients with stage IIIA-N2 NSCLC, and to assess its safety and feasibility when performed in selected patients.

Patients and Methods

Prospectively collected data of 4308 patients who underwent anatomical lung resections for NSCLC in our institution between 1998 and 2015 were analyzed retrospectively. Two hundred sixty-one patients (6.1%) underwent segmentectomies, 3047 (70.7%) lobectomies/bilobectomies, 279 (6.5%) bronchial and/or vascular sleeve lobectomy, and 721(16.7%) PNs.

Two hundred thirty-three (32.3%) of 721 patients who underwent PN were stage IIIA-N2.

Eighty-five (36.5%) patients were preoperative N0, and occult N2 disease was discovered after surgery (group 1); 148 (63.5%) patients were clinical or pathologic stage IIIA-N2 at diagnosis and underwent PN after IT (group 2).

Variables extracted from our database included: patients' general characteristics, preoperative diagnosis and stage, IT, operative findings, postoperative complications, pathologic findings, postoperative therapy, and outcomes. At the time of admission to hospital, before surgery was performed, patients provided written consent to use their personal data for clinical purpose and a separate one for epidemiologic research studies. Clinical charts were retrospectively reviewed to obtain information that are not routinely entered into the surgical database. Patients' follow-up was prospectively updated by contacting all those patients known to be alive at the time of their most recent visit to our institute. Information of patients lost at follow-up was retrieved through the General Register Office.

We excluded from the study all patients with incomplete or unknown pretreatment or preoperative staging, patients without systematic mediastinal lymph node dissection, and patients who underwent PN after IT for T4N0 NSCLC.

Table 2 Complications and Early Outcome

	Total	Group 1 Occult pN2	Group 2 IT	
	N (%)	N (%)	N (%)	*P* Value
Patients	233	85	148	
Median follow-up, y (range)	2.0 (0-18.2)	2.2 (0-18.2)	1.8 (0-17.4)	
Person-years of observation	717	263	454	
Post-operative complications[a]				
None	124 (53.2)	52 (61.2)	72 (48.6)	
Only minor	64 (27.5)	22 (25.9)	42 (28.4)	
Major[a]	45 (19.3)	11 (12.9)	34 (23.0)	.10
Atrial rupture	1 (0.4)	—	1 (0.7)	1.00
Cardiac dislocation	3 (1.3)	—	3 (2.0)	.56
Hemothorax	19 (8.2)	5 (5.9)	14 (9.5)	.46
Bronchopleural fistula	19 (8.2)	4 (4.7)	15 (10.1)	.21
Esophageal fistula	1 (0.4)	—	1 (0.7)	1.00
ARDS/pneumonia	11 (4.7)	3 (3.5)	8 (5.4)	.75
Fistula				
None	212 (91.0)	81 (95.3)	131 (88.5)	
Postoperative[b]	19 (8.2)	4 (4.7)	15 (10.1)	
After 90 days	2 (0.9)	0 (0.0)	2 (1.4)	.44
Early mortality				
Death within 90 days	20 (8.6)	8 (9.4)	12 (8.1)	.81
Death within 30 days	6 (2.6)	2 (2.4)	4 (2.7)	1.00

Abbreviations: ARDS = acute respiratory distress syndrome; IT = induction therapy.
[a]Thirteen patients had both minor and major complications; some patients have more than 1 major complication.
[b]Including early, intermediate, and late fistula.

All patients were studied with a total body computed tomography (CT) scan and, since 2003, all patients received positron emission tomography (PET) with fluorodeoxyglucose. Whenever possible, mediastinal lymph node involvement was verified with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) (since 2011), mediastinoscopy, or video-assisted thoracic surgery. All patients with N2 (cN2 or pN2) disease underwent cisplatin-based IT, based on the patient's performance status and medical oncologist's decision.

Thoracic surgeons and oncologists confirmed patients' resectability and induction treatment plans during a multidisciplinary meeting. The patient was excluded from surgery and was not included in the analysis if the tumor progressed, becoming unresectable, or if distant metastases were identified; instead, the patient was offered PN in case of stable disease or if responded to IT.

All patients undergoing IT were restaged with total body CT scan, and PET with fluorodeoxyglucose when available (after 2003).

A senior surgeon performed 106 (45%) PNs, whereas 12 surgeons performed all the other cases, with a mean number of 10 PN (range, 1-36) per surgeon.

All patients underwent PN and radical lymphadenectomy via muscle-sparing lateral thoracotomy. Systematic lymph nodal dissection according to the classification of the American Thoracic Society was performed in all patients, removing all lymphatic tissue from stations 2R, 4R, 7, and 10R for right-sided tumors and from stations 5, 6, 7, and 10L for left-sided tumors. In case of macroscopic evidence of multi-station lymph nodal involvement, frozen sections of the lymph nodes were usually performed to decide whether to continue with the planned surgery. The bronchial stump was covered with a vascularized flap in 106 (71.6%) of 148 patients who underwent IT. Whenever feasible, before proceeding with PN, a lung-sparing procedure was always attempted, otherwise a PN was performed according to the patient condition and tumor status.

TNM stage as per TNM 7[6] and the histologic subtype were obtained from pathologic reports. The definition of complete or incomplete resection followed the International Association for the Study of Lung Cancer (IASLC) criteria.[7]

Postoperative complications were classified as minor or major as reported in the literature.[8,9]

Postoperative bronchopleural fistulas were classified according to the time of onset after the operation: early (1-7 days), intermediate (8-30 days), and late (more than 30 days).[10] Bronchopleural fistulas occurring more than 90 days from surgery were not considered as postoperative complications.

Postoperative mortality was defined as deaths occurring within 30 days after surgery or during in-hospital stay.

Statistical Analysis

Differences in the distribution of pre- and post-surgical characteristics, postoperative complications, and early mortality across patients' groups were assessed with the Fisher exact test. Overall survival (OS) was defined from the date of surgery to the date of last contact or death. Disease-free survival (DFS) was defined from the date of surgery to the date of progression, last contact, or death. OS

Table 3 Univariable and Multivariable Analysis

	Overall Survival		Progression-free Survival		Progression-free Survival	
	Univariable HR (95% CI)	*P* Value	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Group						
Group 1 (Occult N2)	1.00		1.00			
Group 2 (IT)	1.02 (0.75-1.40)	.89	0.98 (0.67-1.42)	.89		
Age						
< 50	1.00		1.00			
50-59	1.12 (0.62-2.02)	.70	1.38 (0.72-2.64)	.34		
60-69	1.13 (0.65-1.98)	.67	0.73 (0.38-1.38)	.33		
70+	1.77 (0.98-3.20)	.06	1.33 (0.66-2.68)	.42		
Gender						
Males	1.00		1.00			
Females	1.18 (0.84-1.66)	.34	1.23 (0.82-1.84)	.31		
Clinical Stage						
I	1.00		1.00			
II	1.31 (0.67-2.56)	.44	1.16 (0.54-2.53)	.70		
III	1.45 (0.78-2.69)	.24	1.12 (0.54-2.33)	.75		
Pneumonectomy						
Standard	1.00		1.00		1.00	
Extended	1.29 (0.95-1.75)	.10	1.64 (1.14-2.38)	**.008**	1.47 (1.01-2.14)	**.046**
Extent of surgery						
R0	1.00		1.00			
R1/2	1.14 (0.47-2.78)	.78	1.47 (0.60-3.61)	.40		
Side						
Right	1.00		1.00			
Left	0.98 (0.72-1.33)	.89	0.87 (0.60-1.26)	.45		
pT						
0	1.00		1.00			
1	2.98 (0.97-9.18)	**.06**	3.93 (0.83-18.6)	**.08**		
2	4.83 (1.76-13.3)	**.002**	6.46 (1.57-26.6)	**.01**		
3	4.96 (1.78-13.8)	**.002**	5.49 (1.30-23.3)	**.02**		
4	4.71 (1.64-13.6)	**.004**	3.72 (1.57-28.8)	**.01**		
pN						
0	1.00		1.00			
1	2.56 (1.40-4.69)	**.02**	4.01 (1.64-9.83)	**.002**		
2	1.76 (1.06-2.94)	**.03**	3.12 (1.45-6.75)	**.004**		
N2 stations (pathologic)						
None	1.00		1.00		1.00	
Single	0.98 (0.67-1.43)	.90	1.27 (0.77-2.12)	.34	0.88 (0.50-1.56)	.67
Multiple	1.21 (0.83-1.78)	.32	1.74 (1.06-2.86)	.03	1.14 (0.66-1.99)	.63
Pathologic stage						
II-III	1.00		1.00		1.00	
I	0.66 (0.33-1.36)	.26	0.53 (0.22-1.30)	.17	0.53 (0.19-1.44)	.21
Complete response (pT0pN0)	0.21 (0.07-0.66)	**.008**	0.11 (0.02-0.80)	**.03**	0.13 (0.02-0.97)	**.047**
Histology						
Adenocarcinoma	1.00		1.00			
Squamous carcinoma	1.03 (0.75-1.43)	.85	0.88 (0.59-1.32)	.53		
Other histologies	1.08 (0.66-1.80)	.74	1.16 (0.66-2.05)	.61		

Table 3 Continued

	Overall Survival		Progression-free Survival		Progression-free Survival	
	Univariable HR (95% CI)	*P* Value	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Adjuvant treatment						
None	1.00		1.00			
Chemotherapy	0.77 (0.44-1.37)	.38	1.01 (0.55-1.87)	.97		
Radiotherapy	1.02 (0.72-1.45)	.91	1.03 (0.67-1.59)	.90		
Chemo-radiotherapy	1.08 (0.59-1.99)	.80	1.25 (0.59-2.65)	.56		
Unknown	0.79 (0.46-1.36)	.40	0.74 (0.37-1.52)	.41		

Bold text indicates a statistically significant correlation with a *P*-value less than .05.
Abbreviations: CI = confidence interval; HR = hazard ratio; IT = induction therapy.

and progression-free survival (PFS) curves were plotted using the Kaplan-Meier method, and the log-rank test was used to assess the difference in survival between groups. Univariate and multivariable Cox proportional hazards regression models were used to assess the association between various patients' characteristics, DFS, and OS. Only variables significantly associated with outcome at univariate analysis were retained in the multivariable models. All analyses were performed with SAS software (version 9.2, Cary, NC). All *P*-values were 2-sided, and $P < .05$ were considered statistically significant.

Results

Patients' pre and post-surgical characteristics, stratified by the 2 groups, are shown in Table 1.

In group 1, all patients were staged with CT scan and 63 (74%) patients with PET scan. In 45 patients, there was no evidence of mediastinal lymph node involvement; in 18 patients, the clinical doubt of mediastinal involvement was pathologically excluded by EBUS-TBNA and mediastinoscopy in 15 cases, and video-assisted thoracic surgery in 3 patients.

In group 2, the mediastinal lymph node involvement was pathologically confirmed before starting IT in 46 (31.1%) of 148 patients, in 11 cases with EBUS-TBNA, and in 35 patients with mediastinoscopy. One hundred two (68.9%) of 148 patients had only a clinical staging, based on the evidence of lymph nodal enlargement with short axis larger than 15 mm at CT scan and/or an increased pathologic uptake evident at PET scan. Those patients were staged and managed for a multimodal approach in other centers, and only subsequently referred to our institute for surgery. Instead, all patients treated in our institute had a mediastinal lymph nodal involvement pathologically confirmed through EBUS-TBNA or mediastinoscopy.

Most of group 2 patients (n = 82/148; 55.4%) underwent at least 3 cycles of cisplatin-based chemotherapy; 59 (39.9%) patients had more than 3 cycles of chemotherapy based on the oncologist evaluation after restaging, whereas 7 (4.7%) patients had only 1 or 2 cycles of chemotherapy owing to acute toxicity. Induction chemotherapy consisted mainly of a platinum/gemcitabine combination in 99 (66.9%) of 148 patients. Nine (6.1%) patients underwent induction chemo-radiotherapy, whereas 5 (3.4%) patients underwent only radiotherapy.

All patients who underwent PN after IT responded to or had a stable disease. Patients with progression of disease after IT were addressed with definitive chemo-radiotherapy treatment.

Right PN was performed in 130 (55.8%) patients. Extended PN was performed in 100 (42.9%) patients including: intrapericardial PN in 74 patients, pericardial resection in 15, atrial resection in 8, chest wall + vertebrae resection in 1, diaphragm resection in 1, and tracheal sleeve and resection/reconstruction of superior vena cava in 1. Bronchial stump was always sutured through a mechanical stapler except for 1 patient, and it was covered with a vascularized flap in 155 (66.5%) patients (mediastinal fat flap in 104, pleural flap in 33 cases, pericardial flap in 10 patients, and muscular flap in 8). Surgical glues were applied in 109 (46.8%) cases, whereas additional reinforcement stitches with Prolene 3.0 were used in 16 (6.8%) cases.

Two hundred twenty-seven (97.4%) of 233 patients had a radical resection (R0), 5 (2.1%) a microscopic incomplete resection (R1), and 1 (0.5%) a macroscopic incomplete resection (R2).

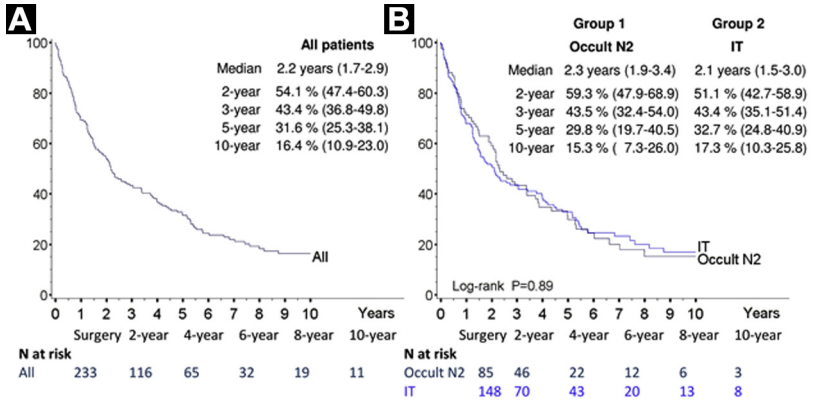
In group 2, persistent pN2 was found in 84 (56.7%) patients, incomplete down staging pN1 in 37 (25%) patients, and pathologic down-staging pN0 in 18 (12.2%) patients. Nine (6.1%) patients had a pathologic complete response (pT0N0).

Adjuvant treatments were administered in 51 (60%) of 85 patients in group 1 and 55 (37.2%) of 148 patients in group 2. In group 1, within the majority of patients that underwent adjuvant chemotherapy (n = 33/51; 37.6%), 11 had chemotherapy combined with radiotherapy, whereas 19 patients had only radiant treatment; in 23 (27%) patients, adjuvant treatments were not administered owing to poor postoperative physical condition of the patient or because they were refused by the patient. In group 2, the most frequent adjuvant treatment was radiotherapy, which was administered in 51 (34.5%) patients, whereas only 8 patients had a second line of chemotherapy (in 4 patients combined with radiotherapy).

Postoperative complications and early outcomes after PN, stratified by the 2 groups, are listed in Table 2. Minor complications occurred in 77 (33%) patients, and the most frequent complication was atrial fibrillation (n = 40; 17.2%), followed by anemia requiring blood transfusion (n = 34; 14.6%). Major complications after surgery were observed in 45 (19.3%) patients. Re-thoracotomy was performed owing to hemothorax in 18 (7.7%) cases, cardiac dislocation in 1 (0.4%), and empyema without fistula in 1 (0.4%).

Postoperative bronchopleural fistula was observed in 19 (8.2%) patients: 8 patients were treated with thoracostomy, 6 with direct suture of the fistula, and 5 with conservative treatment (chest tube and

Figure 1 Overall Survival of All Patients (A) With N2 Lung Cancer And According to Both Groups of Patients (Occult N2 Vs. IT) (B)



Abbreviation: IT = induction therapy.

antibiotic therapy). Factors associated with the development of bronchopleural fistula are listed in Table 3.

Two patients (0.8%) developed bronchopleural fistula after 90 days: 1 after 4 months and another after 9 months from surgery; both of them had IT and postoperative RT. One patient was treated with thoracostomy, and the other one with chest tube; both patients survived the complication and died of disease after 50 and 60 months, respectively.

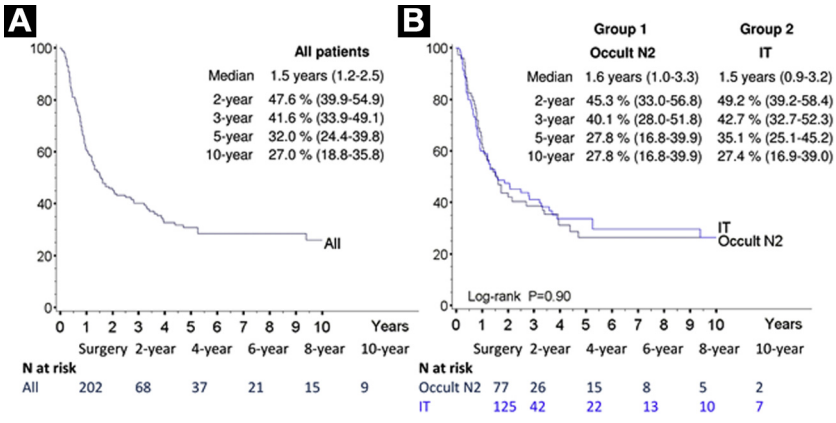
Fourteen (6%) patients died from postoperative complications: 6 (2.6%) patients died within 30 days after surgery or during hospital stay and 8 (3.4%) died within 90 days. Six (2.6%) patients died within 90 days for other causes. Mainly, the cause of postoperative death for complications was respiratory failure (8 patients), bronchopleural fistula (4 patients), sepsis (1 patient), and massive bleeding owing to atrial rupture (1 patient).

The overall morbidity, postoperative mortality, and 90-day mortality rates were 46.8%, 2.6%, and 8.6%, respectively (Table 2).

The median OS was 2.2 years, with a 3-, 5-, and 10-year OS of 43.4%, 31.6%, and 16.4%, respectively (Figure 1A). The DFS was 1.5 years, with a 3-, 5-, and 10-year PFS of 41.6%, 32%, and 27%, respectively (Figure 2A). There was not difference both in OS and in DFS between the 2 groups (Log-rank $P = .89$ and $P = .9$, respectively) (Figure 1B and 2B).

Univariate analysis and multivariate analysis are described in Table 4. The IT and laterality did not influence survival. The comparison of median OS time between single N2 station and multiple N2 stations showed a significant difference at univariate analysis ($P = .03$) but was not confirmed in the multivariate setting ($P = .63$). Both the univariate and multivariate analysis showed that extended resection had a significantly poorer prognosis (hazard ratio, 1.47; 95%

Figure 2 Disease-Free Survival of All Patients (A) With N2 Lung Cancer And According to Both Group of Patients (Occult N2 Vs. IT) (B)



Abbreviation: IT = induction therapy.

Table 4 Factors Associated With the Development of Bronchopleural Fistula

	All	No Fistula	Fistula	
	N	N (%)	N (%)	*P* Value
All patients	233	212 (91.0)	21 (9.0)	
Side				
Right	130	114 (87.7)	16 (12.3)	
Left	103	98 (95.1)	5 (4.9)	.06
Pre-surgical treatment				
None (occult pN2)	85	81 (95.3)	4 (4.7)	
Chemotherapy	134	121 (90.3)	13 (9.7)	
Chemo-radiotherapy	5	3 (60.0)	2[b] (40.0)	
Radiotherapy	9	7 (77.8)	2[b] (22.2)	**.03**
Type of pneumonectomy				
Standard	133	119 (89.5)	14 (10.5)	
Extended	100	93 (93.0)	7 (7.0)	.49
Type of bronchial suture[a]				
Endo GIA	55	49 (89.1)	6 (10.9)	
Covidien TA	173	158 (91.3)	15 (8.7)	
Manual suture	1	1 (100)	–	.64
Type of bronchial stump reinforcement				
None	42	36 (85.7)	6 (14.3)	
Vascularized flap	155	144 (92.9)	11 (7.1)	.22
Adjuvant treatment	**All**	**No Fistula**	**Within 30 days**	**After 30 days**
None	106	100 (86.8)	12 (11.3)	2 (1.9)
Chemotherapy	25	25 (100)	0 (0.0)	0 (0.0)
Radiotherapy	66	61 (92.4)	1 (1.5)	4 (6.1)
Chemo-radiotherapy	15	14 (93.3)	0 (0.0)	1 (6.7)
Unknown	21	20 (95.2)	1 (4.8)	0 (0.0)

Bold text indicates a statistically significant correlation with a *P*-value less than .05.
[a]Type of suture missing for 4 patients.
[b]One early and 1 late fistula.

confidence interval, 1.01-2.14; $P = .046$), whereas patients with a complete pathologic response to IT had a significantly better survival (hazard ratio, 0.13; 95% confidence interval, 0.02-0.97; $P = .047$).

The incidence of major morbidity was higher but not statistically significant in group 2 compared with group 1: 23% versus 12.9% ($P = .1$). The incidence of postoperative bronchopleural fistula was 8.2%, and it was not statistically significant ($P = .10$) when comparing the 2 groups, although it occurred more frequently in patients who had IT (10.1% vs. 4.7%). Furthermore, 5 (71.4%) of 7 patients who developed a fistula after 30 days from surgery underwent postoperative radiotherapy ($P = .10$), and 16 (76.1%) of 21 patients had a right PN ($P = .06$). The related mortality was 26% (n = 5/19).

Postoperative and 90-day mortality rates were similar between the 2 groups (group 1 vs. 2): 2.4% versus 2.7%; ($P = 1.00$), and 9.5% versus 8.1% ($P = .78$), respectively. No differences in morbidity and mortality were observed between right and left PN.

Discussion

By many, PN is considered a challenging procedure, and a multimodal treatment strategy has been increasingly implemented owing to the related high postoperative morbidity. In particular, taking into consideration both the high postoperative risk and the low long-term survival, the role of PN in patients with advanced lung cancer with stage IIIA-N2 is much debated.

To date, the postoperative risk has been found to be significantly increased, with a postoperative mortality ranging between 14% and 43% in patients undergoing PN following IT.[11-14]

Different randomized trials have been reported in literature comparing the outcome of PN in patients with and without chemotherapy,[15,16] but with different results. The European trials, such as the French Thoracic Cooperative Group[15] and the MRC LU22 (Medical Research Council (MRC LU22)/Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose)/NVALT 2 (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose)/EORTC 08012 (European Organisation for Research and Treatment of Cancer) multicenter randomized trial,[16] did not find a significant increase in mortality rates after IT. In the surgery arm of the EORTC 08941 trial, a 30-day mortality rate of 7% after 3 cycles of platinum-based chemotherapy in advanced-stage diseases was shown.[17] Also, in the most recent French general thoracic surgery database (EPITHOR [Register of Patients Operated On By

A Thoracic Surgeon]), the observed operative mortality after induction chemotherapy was 5.7%, paradoxically lower than the postoperative mortality of naive patients (8.6%), who did not have IT before surgery.[18] The German Lung Cancer Cooperative Group reported a treatment-related mortality of 6% in patients receiving PN after 3 cycles of cisplatin and etoposide compared with 14% to those patients who were treated with preoperative chemo-radiation therapy.[19]

On the contrary, the Southwest Oncology Group trial published in 2009 reported a 16.7% mortality rate in the PN group after induction chemotherapy in comparison with no mortality in the surgery-alone group, and worse results were observed when preoperative radiotherapy was combined.[12] In the Society of Thoracic Surgeons General Thoracic Surgery Database,[20] even if it was not statistically significant, chemotherapy was related to an increased risk of major morbidity and mortality, whereas induction chemo-radiation therapy was shown as an independent risk factor for major adverse events after PN. Also in the INT 0139 trial, patients with stage IIIA-N2 undergoing PN after platinum-based induction chemotherapy plus radiotherapy had a 25.9% 30-day mortality rate.[11]

This variability was probably because of the different neoadjuvant therapies rather than the treatment strategy itself. American groups mostly performed chemo-radiation therapy (58.7% according to the last available date of the Society of Thoracic Surgeons General Thoracic Surgery Database) compared with the only chemotherapy treatment of the European groups (8.2% according to the most recent French general thoracic surgery database - EPHITOR).[18,20]

In this study, patients who underwent PN with or without IT had similar 30-day and 90-day mortality rates (2.4% vs. 2.7% and 9.5% vs. 8.1%, respectively), showing a relative impact of IT on survival. This is probably owing to the fact the most of the patients underwent only chemotherapy as IT, whereas only 6.1% had concomitant chemo-radiation therapy.

In our previous studies conducted by Leo in 2006[21] and Borri in 2007,[22] it was shown that mortality after a standard PN (performed after IT) remained below 5%, even if the risk of respiratory complications was significantly increased; mortality was instead up to 10% after extended PN, owing to a higher rate of surgical (bronchopleural fistula) and respiratory complications.

In this study too, the incidence of major morbidity in patients who underwent PN after IT was higher but not statistically significant. Respiratory complications such as acute respiratory distress syndrome and pneumonia occurred more frequently in patients who underwent IT (5.4% vs. 3.5%); furthermore, the incidence of postoperative bronchopleural fistula, even if it was not statistically significant when comparing the 2 groups, occurred more frequently in patients who had IT (10.1% vs. 4.7%). In particular, 71.4% (5/7) of the patients who developed a fistula after 30 days from surgery underwent postoperative radiotherapy, showing that it was probably related to the postoperative treatment and not to the surgery itself.

To date, the supposed increased incidence of bronchial stump fistula following PN after IT is usually reduced by the systematic use of vascularized flaps.[11,13] For this reason, to reduce the anastomotic dehiscence rate, in most of our patients, we usually protect the bronchial stump with a vascularized flap (n = 155/233; 66.5%), particularly in those patients who underwent IT (n = 10/148; 71.6%). However, even if in line with the available literature (0.8%-15%),[23] the incidence of our postoperative bronchopleural fistula was high (8.2%) and probably related to: (1) the radical lymphadenectomy performed in all patients; (2) most of the PNs were performed on the right side. Although laterality did not influence long-term survival in our patients, most of the patients (16/21; 76.1%) with postoperative bronchopleural fistula underwent a right PN, despite the bronchial stump protection. This was probably because most of the right PNs included extended resections, procedures with higher morbidity and mortality rates, and were associated with a higher number of lymph nodes resected, leading to a greater devascularization of the bronchial stump.

The 3- and 5-year OS rates of this study were 43.4% and 31.6%, respectively, with no difference in survival between patients undergoing IT and patients who did not. The IT and laterality did not influence long-term survival, whereas both the number of N2 stations and the extended resection showed a significantly poorer prognosis, suggesting the importance of a correct patient selection. Even adjuvant treatments were not statistically related to the patients' survival both in univariate and multivariate analysis; however, based on the performance status of the patients, we perform adjuvant chemotherapy in case of occult N2 disease or adjuvant radiotherapy in case of persistent N2 disease after induction chemotherapy.

Some earlier retrospective studies comparing lobectomy with PN reported a poorer outcome after PN, even without an IT,[24-27] which could be related to the worse prognosis of centrally located tumors and, at the same time, to the higher physiological impact of a PN (increased early mortality after the resection).[28] In fact, in our previous study conducted on patients who underwent a lung resection (lobectomy and PN) following IT for stage IIIA-pN2, we evidenced a reasonable mortality and morbidity (major) rates of 3.4% and 9.9%, respectively, especially as most cases were patients who underwent PN,[29] with a slightly better survival in the lobectomy group, even if not statistically significant (see Supplemental Figure 1 in the online version).

Our study has few limitations. The most important bias is its retrospective nature, which probably limits and influences all of the variables included in the analysis. Also, most of our patients were pre- and/or postoperatively followed in other hospitals, thus the treatment strategy and preoperative staging were not uniform. The preoperative staging was mainly performed by imaging, and N2 disease was not routinely pathologically proven in all patients before starting the treatment; therefore, we compared patients with cN2 disease with patients with pN2 who received IT before PN, showing that there was no difference in OS (see Supplemental Figure 2 in the online version).

To date, analysis of patients with stage IIIA-N2 NSCLC with 1 pathologic nodal station (included in 2 prospective trials), treated with chemo-radiotherapy showed a median actuarial OS of 26 months with a 3- and 5-year estimate OS of 37% and 24%, respectively, and a low morbidity rate although usually associated with high rates of loco-regional and distant relapse.[30]

Conclusion

Although several studies favor a definitive chemo-radiotherapy treatment in patients with IIIA-pN2 NSCLC, through our results, we showed that PN is a valid surgical option in fit patients

considering the acceptable long-term survival and the low rate of posttreatment morbidity; however, patients who underwent extended resections with multiple N2 involvement had a poorer prognosis, emphasizing that an accurate patient selection is a prerequisite to extended surgery.

Clinical Practice Points

- A definitive chemo-radiotherapy treatment is often considered the treatment of choice by most surgeons and oncologists for patients with IIIA-pN2 NSCLC based on poor survival and high risk of postoperative complications when PN is required.
- However, we have shown in our study that PN could be a valid surgical option in fit patients considering the acceptable long-term survival and the low rate of posttreatment morbidity.
- PN should not be excluded for selected patients with stage IIIA-N2 NSCLC as a matter of principle, but a careful selection of the patients must be a prerequisite for this surgery, excluding extended resections and multiple N2 involvement, which were related to a poorer prognosis.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.10.005.

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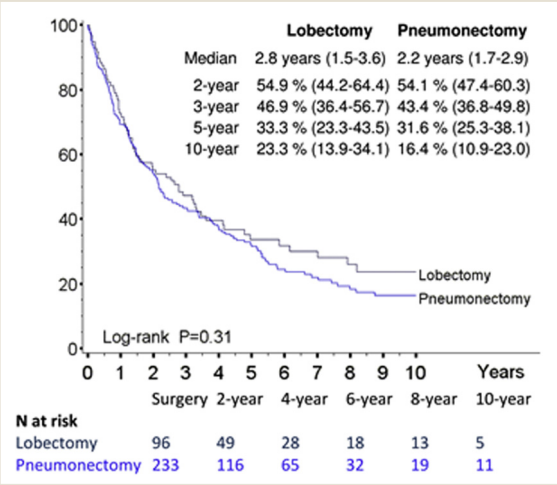
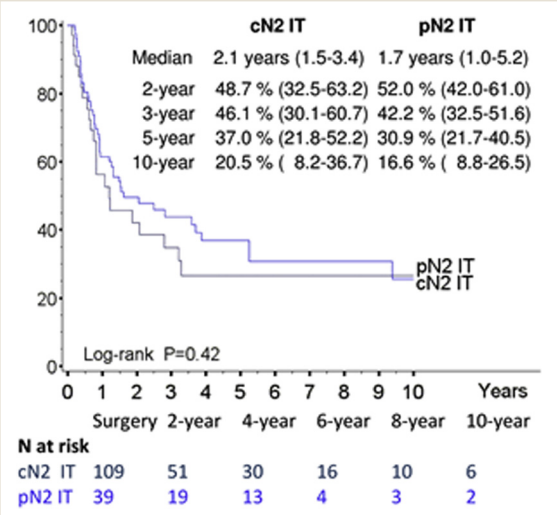
Supplemental Data

Supplemental Figure 1 Overall Survival According to the Type of Surgery



Supplemental Figure 2 Overall Survival of Patients With cN2 or pN2 Who Received IT



Abbreviation: IT = induction therapy.