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## Retrospective Study

# Pathological response to neoadjuvant therapy with chemotherapy vs chemoradiotherapy in stage III NSCLC-contribution of IASLC recommendations

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**Abstract**

**BACKGROUND**

Neoadjuvant treatment (NT) with chemotherapy (Ch) is a standard option for resectable stage III (N2) NSCLC. Several studies have suggested benefits with the addition of radiotherapy (RT) to NT Ch. The International Association for the Study of Lung Cancer (IASLC) published recommendations for the pathological response (PHR) of NSCLC resection specimens after NT.

**AIM**

To contribute to the IASLC recommendations showing our results of PHR to NT Ch *vs* NT chemoradiotherapy (ChRT).

**METHODS**

We analyzed 67 consecutive patients with resectable stage III NSCLC with positive mediastinal nodes treated with surgery after NT Ch or NT ChRT between 2013 and 2020. After NT, all patients were evaluated for radiological response (RR) according to Response Evaluation Criteria in Solid Tumours criteria and evaluated for surgery by a specialized group of thoracic surgeons. All histological samples were examined by the same two pathologists. PHR was evaluated by the percentage of viable cells in the tumor and the resected lymph nodes.

**RESULTS**

Forty patients underwent NT ChRT and 27 NT Ch. Fifty-six (83.6%) patients underwent surgery (35 ChRT and 21 Ch). The median time from ChRT to surgery was 6 wk (3-19) and 8 wk (3-21) for Ch patients. We observed significant differences in RR, with disease progression in 2.5% and 14.8% of patients with ChRT and Ch, respectively, and partial response in 62.5% ChRT *vs* 29.6% Ch ( $P = 0.025$ ). In PHR we observed  $\leq 10\%$  viable cells in the tumor in 19 (54.4%) and 2 cases (9.5%), and in the resected lymph nodes (RLN) 30 (85.7%) and 7 (33.3%) in ChRT and Ch, respectively ( $P = 0.001$ ). Downstaging was greater in the ChRT compared to the Ch group (80% *vs* 33.3%;  $P = 0.002$ ). In the univariate analysis, NT ChRT had a significant impact on partial RR [odds ratio (OR) 12.5; 95% confidence interval (CI): 1.21 - 128.61;  $P = 0.034$ ], a decreased risk of persistence of cancer cells in the tumor and RLN and an 87.5% increased probability for achieving downstaging (OR 8; 95%CI: 2.34-27.32;  $P = 0.001$ ).

**CONCLUSION**

We found significant benefits in RR and PHR by adding RT to Ch as NT. A longer follow-up is necessary to assess the impact on clinical outcomes.

**Key Words:** Non-small cell lung cancer; Chemotherapy; Chemoradiotherapy; Neoadjuvant treatment; Resectable stage III; Pathological response

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**Core Tip:** Preoperative chemotherapy (Ch) has become a standard treatment option, especially in resectable stage III (primarily N2) non-small cell lung cancer (NSCLC). Phase II and phase III studies have raised the question as to whether preoperative Ch plus radiotherapy provides any additional benefits to preoperative Ch. The objective of our retrospective study was to contribute (with an experienced team of medical oncologists, radiation oncologists, thoracic surgeons, and pathologists) to the International Association for the Study of Lung Cancer recommendations in relation to



differences in the pathological evaluation of tumors and mediastinal and hilar nodes in resectable stage III NSCLC, comparing neoadjuvant Ch *vs* chemoradiotherapy.

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## INTRODUCTION

The International Association for the Study of Lung Cancer (IASLC) recently published recommendations for the pathological evaluation of histological specimens from the resection of non-small cell lung cancer (NSCLC) after neoadjuvant therapy (NT)[1]. This article describes the lack of consensus in clinical practice regarding the evaluation of surgical specimens and in precise definitions of the degree of pathological response (PHR).

The seminal articles by both Junker *et al*[2] and Pataer *et al*[3] have been the main guide for the pathological evaluation of NT in recent decades. Although Junker *et al*[2] proposed that the lymph nodes of these patients be evaluated in the same way as the primary tumor (pT), the importance of the precise histological characteristics of these nodes has not been well established.

In relation to treatment, NT chemotherapy (Ch) has become a standard treatment option, especially in resectable stage III NSCLC[4]. However, later phase II and phase III studies raised the question as to whether NT Ch plus radiotherapy (RT) provides any additional benefit to NT Ch[5,6].

In 1996, the Lung Cancer Committee of our hospital (LCCHCB) initiated the first phase II trial of induction chemoradiotherapy (ChRT) in stage III NSCLC in Spain. We used the histological evaluation recommended by Junker *et al*[2] to describe the percentage of viable cells in resected neoplastic samples. The long follow-up of these results was presented at several international congresses[7].

In 2012, following the results of the Intergroup phase III trial[8], the LCCHCB and three other hospitals developed a new phase II trial with NT in resectable stage III NSCLC patients with exclusive lobectomy and a histologically proven single mediastinal lymph node level. In the Hospital Clínic de Barcelona (HCB), induction “per protocol” was with radical ChRT up to 60 Gy, and in the other hospitals the induction was performed with Ch alone (except for Pancoast tumors that also received induction of ChRT). After NT, all the patients were evaluated for radiological response (RR) according to Response Evaluation *Criteria* in Solid Tumours (RECIST) criteria and for surgery by a specialized group of thoracic surgeons. All the histological samples were examined by the same two pathologists.

The objective of this retrospective study was to contribute (with an experienced team of medical oncologists, radiation oncologists, thoracic surgeons, and pathologists) to the IASLC recommendations on differences in the pathological evaluation of tumor and mediastinal and hilar nodes in resectable stage III NSCLC comparing NT Ch *vs* ChRT.

## MATERIALS AND METHODS

### Patient selection

The population studied in this retrospective analysis were all patients consecutively diagnosed with resectable stage III NSCLC (AJCC, 8<sup>th</sup> edition) with pathologically proven single positive mediastinal lymph nodes treated between 2013 and 2020. NT treatment was followed by surgery with intention-to-cure according to the protocols of the four participating institutions and the decision of the respective Lung Cancer Committees. Some patients with N3 Level involvement and stage IV (single brain

metastasis previously treated with radiosurgery) were accepted for salvage thoracic surgery by decision of the LCCHCB. Patients with histologically demonstrated NSCLC but N2 Lymph nodes not accessible for biopsy were eligible, provided that the N2 node had a diameter greater than 1 cm and was positron emission tomography/computerized tomography (PET/CT) positive.

Patients who did not fully complete the curative treatment course were included in the study for intention-to-treat analysis.

### **Pre-treatment evaluation**

All patients were evaluated by the multidisciplinary Lung Cancer Committee in each hospital which was composed of pulmonologists, radiologists, nuclear radiologists, medical oncologists, radiation oncologists and thoracic surgeons. The initial diagnostic study included radiological evaluation by chest CT, PET/CT, brain imaging [CT or brain magnetic resonance imaging (MRI)], and cardiopulmonary tests. Mediastinal and hilar involvement was confirmed by mediastinoscopy, endobronchial ultrasound (EBUS) and/or esophageal ultrasound (EUS). Before surgery, all patients were reassessed by the committee using chest CT to assess response to NT, and patients not demonstrating progression were considered for thoracic surgery.

### **Treatment**

NT with ChRT or Ch was performed according to the protocol of each hospital and according to the clinical characteristics of each patient. All the patients included were considered for radical surgery by resection of the tumor and extensive resection of the hilar and mediastinal lymph nodes. RT was performed in the ChRT group concomitant with Ch, using 3 dimensional (D) conformal RT with standard fractionation of 2 Gy per fraction up to a total dose of 60 Gy (range 58-62 Gy). RT was administered to the pT and affected lymph nodes, with margins for microscopic disease and patient set up error. 4D assessment was not used, and involved-field of tumor and nodal treatment was exclusively adopted. Patients in both groups received platinum-based Ch without consolidation Ch after surgical resection. In the NT-Ch group, patients with R1 resection or persistence of viable cells in N2 Lymphadenectomy received postoperative RT (PORT) up to 54-60 Gy.

### **Post-NT evaluation and treatment**

Chest CT scan was used to assess RR between 3 wk and 4 wk after NT according to the RECIST criteria. Operable patients who did not progress during NT were considered for radical surgical treatment. All patients were operated centrally in the same hospital (HCB). After surgery, PHR was evaluated by the same team of pathologists. Patients not considered for surgery after NT were treated with radical ChRT.

### **Histological assessment of pT and lymph nodes**

PHR was defined according to the percentage of viable cells in the sample in both the pT and in the pathological lymph nodes (pN). It was categorized into five groups: 0%-10%; 11%-30%; 31%-50%, 51%-70%; > 70%, according to the literature. pN were taken into account to determine the downstaging rate.

Small volume samples (up to 2 cm) of pT and pN were completely sampled. In larger tumors, at least one paraffin block per cm of the largest diameter of the tumor was sampled in each specimen. The percentages of viable tumor cells, tumor necrosis, and fibrosis were evaluated in each slide, and the average of the percentages of viable tumor cells was reported for each patient. In specimens evaluated during 2020, PHR was evaluated following the IASCL recommendations[1]. In these cases, an entire cross-section of the tumor bed was sampled and photographed matching the areas on the specimen corresponding to the submitted blocks, and the percentage of necrosis, stromal tissue and viable tumor of the tumor bed was recorded. The components of the stromal tissue, fibrosis and inflammation were not specified.

### **Statistical analysis**

Data were retrospectively analyzed after previous approval by the institutional review board. Two cohorts of patients were analyzed: NT ChRT plus surgery and NT Ch plus surgery. The parameters analyzed and compared in each group were: Mean age, sex, performance status, stage at diagnosis, TNM description, lung tumor location, N2-N3 confirmation, pathological distribution of the affected lymph node level, Ch scheme based on platinum doublet, acute RT or Ch toxicity, RR according to RECIST, and the median time from the end of NT to surgery. The type of surgery and complications of the intervention, levels of systematic lymph node dissection, the presence of DS, the

percentage of histological tumor viability (HTV) and lymph node histological viability (HLNV) were also analyzed. Both HTV and HLNV were also analyzed according to the histological type (adenocarcinoma *vs* squamous carcinoma) and NT type (ChRT *vs* Ch).

We performed a descriptive analysis comparing variables related to demographic, clinical, treatment and response data. The student's *t* test was used for quantitative variables, while the chi-square and Fisher exact test were applied for qualitative variables. Univariate analysis was carried out to assess the impact of ChRT on response using a logistic regression model. The statistical analyses were performed by a radiation oncologist with expertise in the IBM SPSS© version 25.0.

## RESULTS

Between 2013 and 2020, 67 patients with resectable locally advanced NSCLC were evaluated (66 stage III and one stage IV with single brain metastasis, previously treated with radiosurgery); 65% were men, and the median age was 64 years (41-79). More than 90% of the patients had good functional status (ECOG PS  $\leq$  1). The most frequent histology was adenocarcinoma (62.5% ChRT and 74.1% Ch). Pathological nodal confirmation at diagnosis was made in most patients (87.5% ChRT and 92.6% Ch) by EBUS/EUS, mediastinoscopy or both. The clinical characteristics of the patients are summarized in [Table 1](#).

In the ChRT group 47.5% of the patients simultaneously received Ch with cisplatin plus VP16 *vs* 0% in the Ch group, while 37% of the Ch group received the carboplatin-based doublet (with vinorelbine, taxol or gemcitabine) *vs* 7.5% in ChRT (with vinorelbine) ([Table 2](#)). Of the 40 ChRT patients, 28 (70%) started concomitant treatment within less than 7 d, 9 (22.5%) patients started at between 7 d and 14 d, and in 3 (7.5%) concomitant treatment was initiated after more than 14 d.

A total of 10 patients required hospitalization secondary to NT; 8 (20%) in the ChRT group *vs* 2 (7.4%) in the Ch group. Grade 2-3 esophagitis was observed in 10 (14.5%) patients with ChRT (only 2 grade 3) compared with no esophagitis in the Ch group.

Five patients in the ChRT group presented toxicity after surgery; 2 presented atrial fibrillation that was treated pharmacologically, 2 cases required surgical management due to bronchio-pleural fistula and cerebrospinal fluid fistula, and one patient presented grade 5 toxicity due to complicated bronchio-pleural fistula five months after surgery. No case of surgical toxicity was observed in the Ch group.

The RR showed a statistically significant difference ( $P = 0.025$ ) in favor of NT with ChRT, with no case of local progression.

One patient (2.5%) in the ChRT group presented disease progression with brain metastases prior to surgery *vs* 4 patients (14.8%) in the Ch group who presented local progression during Ch.

Twenty-five (62.5%) ChRT patients showed partial RR compared to 8 (29.6%) in the Ch group ([Table 3](#)).

A total of 11 patients did not undergo surgery after committee reassessment. Of these, 5 (12.5%) were in the ChRT group, and surgery was not performed due to poor post-NT respiratory functionalism in 1, high risk of pneumonectomy in another, in 1 patient symptomatic brain metastasis was detected prior to surgery, 1 developed bilateral pneumonia secondary to influenza type A, and 1 patient presented poor respiratory functionalism prior to NT and stable radiological disease and suspicion of brain metastasis on MRI. The remaining 6 (22.2%) Ch patients did not undergo surgery: 1 for poor post-NT respiratory function and high risk of pneumonectomy, 3 for local disease progression during Ch, and 2 patients showed poor response after NT. The characteristics of the surgery according to NT group are shown in [Table 4](#).

Lobectomy was the most frequent type of surgery (60% ChRT and 76% Ch), although this was more complex (due to vascular reconstruction, rib resection and / or vertebrectomy) in 25.7% *vs* 9.6% of patients receiving ChRT compared to Ch, respectively.

The median time from the end of NT with ChRT to surgery was 6 wk (3-19), and the median time from the end of the NT Ch to surgery was 8 wk (3-21).

In relation to PHR there was a statistically significant difference in favor of the ChRT group ([Table 5](#)). Maximum response ( $\leq$  10% viable cells) was observed in the tumor in 54.5% *vs* 9.5% ( $P = 0.001$ ) and at the lymph node level in 85.5% *vs* 33.3% ( $P = 0.001$ ) with ChRT and Ch, respectively. Downstaging was achieved in 28 (80%) and 7 (33.3%) ChRT and Ch patients, respectively ( $P = 0.002$ ). Two patients in the ChRT group showed lymph node involvement outside the RT field after surgery, but with

**Table 1 Patient characteristics, n (%)**

	RTCh (n = 40)	Ch (n = 27)	P value
Age	60 (54-67)	67 (62-73)	0.32
Gender			0.29
Male	26 (65)	21 (77.8)	
Performance status			0.21
ECOG 0	7 (17.5)	5 (18.5)	
ECOG 1	33 (82.5)	20 (74.1)	
ECOG 2	0	2 (7.4)	
Smoking habit			0.48
Yes	20 (50)	15 (55.6)	
No	2 (5)	3 (11.1)	
Former smoker	18 (45)	9 (33.3)	
Tumor localization			0.33
Apex	7 (17.5)	1 (3.7)	
Right upper lobe	13 (32.5)	13 (48.1)	
Right lower lobe	6 (15)	2 (7.4)	
Left upper lobe	12 (30)	9 (33.3)	
Left lower lobe	2 (5)	2 (7.4)	
Histology			0.28
Adenocarcinoma	25 (62.5)	20 (74.1)	
Squamous	13 (32.5)	6 (22.2)	
NSCLC <sup>1</sup>	0	1 (3.7)	
Large cell	2 (5)	0	
Stage			0.52
IIIA	27 (67.5)	21 (77.8)	
IIIB	12 (30)	6 (22.2)	
IV	1 (2.5)	0	
T			0.08
T1	4 (10)	9 (33.3)	
T2	16 (40)	9 (33.3)	
T3	10 (25)	7 (25.9)	
T4	10 (25)	2 (7.4)	
N			0.04
0	5 (12.5)	0	
2	34 (85)	27 (100)	
3	1 (2.5)	0	
Metastasis	1 (2.5)	0	0.59
Nodal station distribution			0.012
N0	6 (15)	0	
1N2	12 (30)	19 (70.4)	
2N2	2 (5)	1 (3.7)	

1N2 + 1N1	13 (32.5)	7 (25.9)	
2N2 + 1N1	5 (12.5)	0	
1N1 + 1N2 + 1N3	2 (5)	0	
Nodal staging method			0.68
EBUS	24 (60)	14 (51.9)	
Mediastinoscopy	2 (5)	3 (11.1)	
EBUS and mediastinoscopy	8 (20)	6 (22.2)	
EUS	1 (2.5)	2 (7.4)	
None	5 (12.5)	2 (7.4)	

<sup>1</sup>Specific histology could not be determined in one patient. Ch: Chemotherapy. ECOG: Eastern Cooperative Group. NSCLC: Non-Small Cell Lung Cancer. RTCh: Radiochemotherapy; EUS: Endoscopic ultrasound; EBUS: Endobronchial ultrasound

**Table 2 Chemotherapy regimens, n (%)**

	RTCh	Ch
	(n = 40)	(n = 27)
Cisplatin-Etoposide	19 (47.5)	0
Cisplatin-Vinorelbine	14 (35)	6 (22.2)
Cisplatin-Pemetrexed	4 (10)	3 (11.1)
Cisplatin-Docetaxel	0	6 (22.2)
Cisplatin-Gemcitabine	0	2 (7.4)
Carboplatin-Vinorelbine	3 (7.5)	1 (3.7)
Carboplatin-Paclitaxel	0	6 (22.2)
Carboplatin-Pemetrexed	0	1 (3.7)
Carboplatin-Gemcitabine	0	2 (7.4)

Ch: Chemotherapy. RTCh: Radiochemotherapy.

**Table 3 Radiological response, n (%)**

	RTCh	Ch	P value
	(n = 40)	(n = 27)	
Disease progression	1 (2.5)	4 (14.8)	0.025
Stable disease	14 (35)	14 (51.9)	
Partial response	25 (62.5)	8 (29.6)	
Complete response	0	1 (3.7)	

Ch: Chemotherapy. RTCh: Radiochemotherapy.

maximum PHR in the nodes within the RT field. Numerical but not significant differences were found in complete PHR (17.1% ChRT *vs* 4.8% Ch;  $P = 0.23$ ).

In addition, the Ch group had a higher rate of "non-response" to NT in the tumor (> 70% viable cells pT) 38.1% *vs* 2.9% for ChRT ( $P = 0.001$ ), being 42.9% Ch *vs* 5.7% ChRT ( $P = 0.001$ ) at the lymph node level (> 70% viable pN cells).

In the univariate analysis, the use of NT ChRT had a significant impact on the RR with an increased probability of presenting partial response [odds ratio (OR) 12.5; 95% confidence interval (CI): 1.21-128.61;  $P = 0.034$ ]. In addition, NT ChRT patients presented a decreased risk of persistence of cancer cells in the tumor and resected

**Table 4 Surgery characteristics, n (%)**

	RTCh (n = 40)	Ch (n = 27)	P value
No surgery	5 (12.5)	6 (22.2)	
Type of surgery			0.48
Lobectomy	21 (60)	16 (76)	
Bilobectomy	3 (8.6)	1 (4.8)	
Pneumonectomy	2 (5.7)	1 (4.8)	
Lobectomy and vascular reconstruction	1 (2.8)	1 (4.8)	
Lobectomy and rib resection	5 (14.3)	1 (4.8)	
Lobectomy with rib resection and vertebrectomy	3 (8.6)	0	
Segmentectomy with rib resection and vertebrectomy	0	1 (4.8)	
Node level dissection			0.26
2N2 + 1N1	4 (11.4)	3 (14.3)	
3N2	2 (5.7)	5 (23.7)	
3N2 + 1N1	12 (34.3)	7 (33.3)	
3N2 + 2N1	5 (14.3)	3 (14.3)	
4N2 + 1N1	8 (22.9)	1 (4.8)	
4N2 + 2N1	0	1 (4.8)	
4N2 + 1N3	2 (5.7)	0	
5N2 + 1N1	2 (5.7)	1 (4.8)	

Ch: Chemotherapy. RTCh: Radiochemotherapy.

lymph nodes (Table 6). Patients in the ChRT group presented an 87.5% increased probability of presenting lymph node downstaging (OR 8; 95% CI: 2.34-27.32;  $P = 0.001$ ).

When analyzing both HTV and HLNv by histological (adenocarcinoma *vs* squamous carcinoma) and NT type, remarkable results were not obtained due to the limited number of patients in each group.

## DISCUSSION

In this retrospective multi-institutional phase II study we compared NT Ch *vs* NT ChRT and present the RR and PHR following NT in patients with stage III NSCLC treated by lung cancer specialists from 4 experienced university centers.

Several randomized clinical trials (RCT) have compared NT Ch to NT ChRT, but the results of some of these studies have only been reported in abstract form [9,10], which precludes a real scientific analysis, especially at the level of PHR. Another phase II RCT was published comparing NT Ch *vs* NT ChRT [11], but no relevant information was obtained due to the small number of patients included ( $n = 46$ ) which were further divided into three different groups. In addition, the main endpoint of this study was the feasibility of surgery, and PHR results were not provided.

Thomas *et al* [5] published a RCT that compared a control group undergoing induction Ch with 3 cycles of cisplatin and VP16 followed by surgery and PORT *vs* an intervention group that underwent NT Ch with the same regimen followed by twice-daily RT (45 Gy) concomitant with carboplatin and vindesine, followed by surgery. In the study, 54% and 59% of ChRT and Ch patients underwent surgery, respectively, and only 37% and 32% of each group, respectively achieved complete resection. This may be due to the inclusion of a proportion of locally advanced NSCLC not clearly resectable at first (15% with T4N2 and 22% with T4N3). It is also important to note that about 20% of the patients in each group progressed to induction Ch prior to NT ChRT

Table 5 Pathological response, *n* (%)

	RTCh	Ch	P value
	( <i>n</i> = 40)	( <i>n</i> = 27)	
No surgery	5 (12.5)	6 (22.2)	
Pathological complete response	6 (17.1)	1 (4.8)	0.23
Tumor response <sup>1</sup>			0.001
0%-10%	19 (54.4)	2 (9.5)	
11%-30%	9 (25.7)	2 (9.5)	
31%-50%	4 (11.4)	3 (14.3)	
51%-70%	2 (5.7)	6 (28.6)	
> 70%	1 (2.8)	8 (38.1)	
Nodal response <sup>1</sup>			0.001
0%-10%	30 (85.7)	7 (33.3)	
11%-30%	1 (2.8)	0	
31%-50%	2 (5.7)	3 (14.3)	
51%-70%	0	2 (9.5)	
> 70%	2 (5.7)	9 (42.9)	
Downstaging	28 (80)	7 (33.3)	0.002

<sup>1</sup>According to the percentage of viable cells in the histological study.

Ch: Chemotherapy. RTCh: Radiochemotherapy.

or surgery, and all patients with NT Ch received PORT.

Each endpoint favored NT ChRT with more complete resection (75% *vs* 60%;  $P = 0.008$ ), nodal downstaging from N2 to N0-1 (46% *vs* 29%,  $P = 0.02$ ) and PHR greater than 90% (60% *vs* 20%;  $P < 0.0001$ ). Patients with complete resection and mediastinal downstaging presented a greater overall survival (OS), with no differences in progression-free survival (PFS) or OS in relation to the different types of NT.

Katakami *et al*[12] published an RCT of 60 pathologically proven N2 patients randomized to receive induction Ch with docetaxel and carboplatin plus concurrent RT (40 Gy) followed by surgery or NT Ch followed by surgery. Nodal downstaging was described in 20.8% and 40% in Ch and ChRT, respectively. The median OS in patients with and without downstaging in the ChRT arm was 72.1 mo and 31.2 mo, respectively ( $P = 0.018$ ) and 32.6 mo and 29.0 mo, respectively ( $P = 0.542$ ) in the Ch arm. The median PFS and OS in each study arm were not statistically significant due to the small sample size.

The next RCT comparing NT Ch *vs* NT ChRT was performed by Pless *et al*[13]. Similar to the trial by Thomas *et al*[5], this study was not a true and strict comparison between NT Ch and NT ChRT. Patients were randomized to 3 cycles of NT Ch (cisplatin and docetaxel) plus sequential RT *vs* NT Ch. All patients were scheduled for surgery. An additional difference with the Thomas trial was that PORT was only administered in the case of microscopic (R1) or macroscopic (R2) tumor margins (16% of trial patients). Patients treated with sequential NT ChRT presented higher lymph node downstaging (64% *vs* 53%), albeit without statistically significant differences. In this study, it is also important to point out two things. First, all the patients were resectable and had low-bulky disease, and second, the trimodal therapy was not radical NT with concurrent ChRT, but rather NT Ch plus sequential RT and surgery. Sequential ChRT is far from being as effective as concurrent ChRT. To our knowledge no study has compared the differences in PHR of sequential *vs* concurrent ChRT, but there is a meta-analysis on the efficacy of these treatments[14].

A true trimodality phase II trial was published by the RTOG 02-29[15]. This trial evaluated downstaging rates in 57 patients with stage III NSCLC (pathologically proven N2 or N3) who received weekly carboplatin and paclitaxel with concurrent RT (50.4 Gy to mediastinal nodes and pT and 10.8 Gy boost to gross disease). The mediastinum was pathologically reassessed after completion of ChRT. Forty-three

**Table 6 Univariate analysis investigating the impact of neoadjuvant therapy radiochemotherapy on the response**

	OR	95%CI	P value
Radiological response			
Disease progression	Reference		
Stable disease	4	0.39-40.42	0.240
Partial response	12.5	1.21-128.61	0.035
Complete response	NA <sup>1</sup>		
Pathological tumor response			
0%-10%	Reference		
11%-30%	0.474	0.05-3.92	0.489
31%-50%	0.14	0.17-1.13	0.065
51%-70%	0.03	0.004-0.30	0.002
> 70%	0.01	0.001-0.16	0.001
Pathological nodal response			
0%-10%	Reference		
11%-30%	0.474	0.057-3.92	0.489
31%-50%	0.14	0.17-0.13	0.065
51%-70%	0.03	0.004-0.30	0.002
> 70%	0.01	0.001-0.16	0.001
Downstaging			
No	Reference		
Yes	8	2.34-27.32	0.001

<sup>1</sup>Not applicable: only one patient in the chemoradiotherapy group and none in the Chemotherapy group. CI: Confidence interval.

patients (75%) were evaluable for the primary endpoint. Twenty-seven patients achieved the primary endpoint of downstaging (63%). Thirty-seven patients underwent resection. The 2-year OS rate was 75% for those who achieved downstaging, 52% for those with residual nodal disease, and 23% for those who were not evaluable for the primary endpoint ( $P = 0.0002$ ).

Radical ChRT attempts to eliminate the possibility of administering a subtherapeutic dose of RT (45 Gy) and/or RT interruptions in patients who, for whatever reason, cannot undergo surgery. The rationale for combining NT Ch with full-dose RT was supported by a retrospective analysis of RT series in NSCLC in which a dose in the range of 58–77 Gy might be necessary to control 50% of gross tumors[16].

During the years of the RCTs comparing NT with Ch and ChRT in stage III NSCLC, other RCTs such as that of the EORTC 0894[17], INT 0139[8] and the ESPATUE trial [18], carried out another line of research on whether surgery adds any real benefits in OS compared to radical concurrent ChRT.

The EORTC 08941 RCT randomized patients to definitive RT *vs* surgery (with PORT in patients with R1 resection) in NSCLC with pathologically proven N2 responding to the initial Ch doublet. It should be noted that 39% of the 579 patients progressed or did not respond to NT Ch and only 61% of all patients were randomized to RT or surgery. There were no statistically significant differences in PFS or OS between the two groups.

In the INT 0139 trial, 396 patients with resectable stage IIIA N2 NSCLC were randomized to concurrent radical RT (61 Gy) with 2 cycles of cisplatin and VP16 *vs* concurrent RT (45 Gy) with the same Ch regimen and surgery. The median OS was not significantly improved with the addition of surgery. However, in an exploratory analysis, the median OS was significantly higher for patients undergoing lobectomy compared with definitive ChRT (33.6 *vs* 21.7 mo;  $P = 0.002$ ). Other factors related to an improvement in OS were pathologic N0 status (34.4 *vs* 26.4 mo;  $P \leq 0.0001$ ) and pathological complete response (PCR) (T0N0: 39.8 mo). Criticisms regarding the INT

0139 trial were the incomplete accrual rate, an under-powered subset analysis suggesting an advantage of trimodal therapy, and a very high mortality rate among patients who underwent pneumonectomy[19]. It should also be noted that the EORTC and the Intergroup trials were designed at a time when routine PET/CT scan had not yet been incorporated into usual clinical practice, and nodal staging using EBUS or EUS was not available in most hospitals.

The ESPATUE trial compared definitive treatment with ChRT *vs* trimodal therapy. Patients with stage IIIA (N2) and IIIB NSCLC underwent 3 cycles of NT Ch with cisplatin and paclitaxel. Patients who did not progress were treated with hyperfractionated RT (45 Gy in 30 fractions twice daily) plus Ch. The patients were reevaluated for operability during the last week of RT, and those eligible for surgery were randomized to completing RT or surgery. The study closed prematurely, with 246 patients being enrolled and 161 patients randomized. Seventy of 81 of the surgical patients underwent surgery, of which 66 underwent R0 resection. A total of 5 (7%) patients presented grade 5 toxicity after surgery. After a median follow-up of 78 mo, there were no differences in PFS or OS.

A cumulative meta-analysis of RCT comparing definitive ChRT *vs* NT therapy followed by surgery[20] in stage III NSCLC found no significant differences in OS in these patients after NT Ch and surgery. It is also noteworthy that the trials with concurrent NT ChRT and radical ChRT showed a better OS than the other trials with NT Ch alone before surgery.

Another line of research has been to combine ChRT with antibodies against epidermal growth factor receptors (EGFR) in stage III NSCLC. The NRG oncology RTOG 0839 study[21] was designed to test the hypothesis that adding an EGFR antibody to the standard ChRT could potentially improve the outcome in this group of patients. The endpoint was downstaging, but an unexpectedly high mortality rate was observed in the panitumumab group.

In addition, a phase II RCT with erlotinib *vs* gemcitabine plus cisplatin as NT was performed in patients with stage IIIA-N2 NSCLC with EGFR mutations in exon 19 or 21[22]. A total of 72 patients were randomized. No PCR was found in any of the arms. Three of 31 patients in the erlotinib arm and none of 23 Ch patients achieved maximal pathologic response (MPR).

A recent line of investigation of NT in stage III (N2) NSCLC has been the combination of concomitant Ch with immunotherapy. NADIM, a single-arm, phase II multicenter trial in resectable stage IIIA NSCLC, included 46 patients who received 3 cycles of NT Ch plus nivolumab followed by surgical resection, and then continued nivolumab for one year. At 24 mo, PFS was 77.1% (95%CI: 59.9-87.7). No patient presented disease progression during NT, and 34 (83%; 95%CI: 68-93) of 41 operated patients had MPR, 26 of whom (63%; 95%CI: 62-91) showed PCR. Thirty-seven (90%) of the 41 patients operated presented nodal downstaging (from N2 to N1-N0)[23].

For nearly three decades, PHR after NT has been correlated with survival[24]. According to Pisters *et al*[24] PCR predicts a higher OS, which is considered an important endpoint for Ch. However, the mean frequency of PCR after NT Ch is 4% to 7% (the PCR rate appears to be higher in squamous cell carcinomas). Due to the low proportion of PCR after NT Ch, another surrogate parameter of OS in relation to PHR was considered for NT Ch by Hellman *et al*[25] who proposed MPR, defined as a value < 10 % of viable cells in resected tumors, as a surrogate endpoint for OS. This proposal was based on a previous analysis by Pataer *et al*[3] in 192 resected stage I-IV NSCLC patients treated with NT Ch. The percentage of viable tumor cells after NT Ch was considered a categorical variable and analyzed in relation to the risk of death. A significant improvement in OS was demonstrated in those with 0-10% viable tumor cells compared to other groups (11%-30%, 31%-50%, 51%-70%, and 71%-100%).

This correlation between MPR and OS has not been validated in NT ChRT[5], although a positive association between lymph node downstaging and improved OS has been shown in pathological IIIA N2 NSCLC after NT ChRT and NT Ch[25]. Even if the degree of PHR is a predictor of OS, only a few studies have described a detailed pathological assessment (percentage of viable cells) at the pT and metastatic node level. The PHR to NT can significantly vary between the tumor and metastatic lymph nodes. The extent of lymphadenectomy may vary between centers and may depend on the methodological approach of the surgeons and pathologists at each hospital. Furthermore, the minimum number of lymph nodes or lymph node levels that must be resected has not been defined. This last fact is directly related to the experience of thoracic surgeons in tumor resection and / or in the extension of radical complementary lymphadenectomy with a minimum of nodal stations evaluated.

There is little consensus on the precise definition of what is considered as "resectable" T4 or N2-N3 disease, and there is no universally accepted definition of "potentially resectable N2" disease. Surgical treatment largely depends on the experience of the hospital and the expertise of the thoracic surgeons involved. T4 disease involves a locally aggressive tumor with invasion of nearby mediastinal structures, such as the carina, great vessels, and / or vertebrae. In these cases, it can be very difficult to achieve complete resection (R0) as defined by the IASLC[26].

The importance of the so-called "time window" recommended for performing surgery after NT ChRT has been reported. A retrospective study of 1623 patients with stage IIIA NSCLC treated with concurrent NT ChRT found a statistically significant decrease in OS when surgery was performed more than 6 wk after completion of RT [27]. OS was compared in patients operated at 0-3 wk, 3-6 wk, 6-9 wk and 9-12 wk after completing RT. The multivariate analysis demonstrated no significant difference in those who underwent surgery within 6 wk of NT ChRT. However, significant reductions in OS were observed in patients operated at more than 6 wk and  $\leq 9$  wk after NT [hazard ratio (HR) = 1.33, 95%CI: 1.01-1.76,  $P = 0.043$ ].

The optimal treatment strategy in resectable stage III (N2) NSCLC is debated, and different guidelines from the United Kingdom, Europe and the United States have made recommendations. The common recommendation is to administer multimodal treatment to prevent distant disease with systemic therapy and achieve local control by surgery, RT, or both. Furthermore, multimodal treatments require experienced multidisciplinary teams to minimize the secondary risks of the treatments and maximize their benefits[28].

The most recent guidelines are the National Institute for Health and Care Excellence guidelines[29]. On pages 33-34 of these guidelines, detailed recommendations for operable stage IIIA-N2 NSCLC are described: "... the available evidence showed that ChRT and surgery are more effective than ChRT alone in people well enough for surgery and when the disease is operable...There was an 89% chance that ChRT and surgery improved the mean OS time compared to ChRT...".

The authors of this recent English guideline do not recognize as methodologically true or scientific some meta-analyses and/or systematic reviews of different articles of supposed NT comparisons reporting the absence of benefits in OS with the addition of RT to Ch as NT in stage III (N2) NSCLC[30-34].

Our phase II study is the first study in the scientific literature on NT in patients with stage III NSCLC, in which a true comparison is made between NT ChRT *vs* NT Ch prior to surgery performed by specialists with lengthy experience and a centralized group of thoracic surgeons and pathologists. This latter fact avoids biases due to different surgical skills and reduces the probability of morbidity and mortality in stage III patients after NT[35]. The evidence supports the association between the experience of thoracic surgeons and lower mortality and improvement in long-term OS after lung resection[36]. In addition, histological evaluation by the same two pathologists with experience in lung cancer reduces interobserver variability, achieving greater homogeneity in the results. To our knowledge, this is the first study in the literature in which the same two pathologists made an exhaustive description of the percentage of viable cells in the tumor and in all lymph nodes resected after NT, actually comparing the response to Ch *vs* ChRT. Two other factors of our study must be highlighted. A detailed description of the lymph node stations (mediastinal and hilar) affected prior to NT was made as well as the lymph node levels resected by lymphadenectomy. To our knowledge, this has never been reported in any other NT study, and both could be considered as a factor of surgical quality and may have a positive prognostic role in the evolution of the disease. This pathological description of the resected nodes is being studied in order to better differentiate surgically treated patients into different stages[37].

The main limitation of our study is that it is not an RCT. However, there were no significant differences in the characteristics of the patients, such as gender, performance status, tumor location or histology (Table 1). Nevertheless, the median age was slightly higher in the NT Ch group compared to the NT ChRT group (67 *vs* 60 years), and we also observed a higher proportion of apical / Pancoast tumors (7 *vs* 1) and stages IIIB (16 *vs* 7) in the NT ChRT group compared to the NT Ch patients. There was a significant difference in the Ch schemes used (Table 2) in NT ChRT compared to NT Ch, with 55.6% of ChRT patients being treated with cisplatin-VP16 compared to 0% in the NT Ch group. There is no evidence in the literature that one cisplatin doublet-based regimen is better than another. There is perhaps more experience with concurrent cisplatin-VP16 treatment with RT, and therefore the data could support this scheme in favor to others[19].

Furthermore, in relation to the evaluation of the RR, it should be noted that 4 NT Ch patients (14.8%) progressed locally to NT compared to none in the NT ChRT group. Of these patients who progressed, 2 did not undergo surgery and the other 2 were considered by the Lung Committee for salvage surgery. Both underwent R1 resection, and were therefore considered for PORT, and 1 developed multiple metastases during PORT planning. This evolution with local progression of the tumor during Ch is consistent with the results (between 20% and 30%) of the previously commented studies of induction Ch (EORTC, ESPATUE and the study of Thomas *et al*[5]). In relation to PHR, more than 38% of the NT Ch patients did not respond to Ch, with persistence of 70% or more of viable cells in the tumor and/or the nodes. In contrast, local progression and unresponsiveness after concurrent NT ChRT was 0% and 2.8%, respectively, being very similar to NT with Ch and immunotherapy in the NADIM trial. Indeed, the limited response to NT Ch in approximately 50% of the patients has not been adequately addressed in any previous study to assess whether this could be detrimental to long-term outcomes, and studies are needed to determine the impact of this treatment on PFS and OS.

Regarding the type of surgery, we observed more complex interventions in the NT ChRT group, according to the more advanced stages (*e.g.*, T4) in 27.5% compared to 7.4% in the NT Ch group. The first group included patients with locally advanced NSCLC, which was not easily amenable to primary resection, and in whom treatment with definitive ChRT could have been a valid option. These patients could be stratified into high-volume nodal disease (bulky, multilevel N2 or N3) or locally invasive pT (T4 N0-1 or superior sulcus tumor). According to the literature, in these patients only the experience of the thoracic surgeon provides greater local control and perhaps greater PFS and OS compared to definitive ChRT[19]. In our opinion, locally advanced tumors were the main cause of greater post-surgical morbidity and complications in the NT ChRT (3) compared to NT Ch (0), with two broncho-pleural fistulas and one cerebrospinal fluid fistula. The last case was a Pancoast tumor treated with lobectomy and vertebrectomy. The remaining NT ChRT patients and all the NT Ch patients could be considered as low volume N2 disease (IIIA) in which total resection could be achieved.

The median time between the end of RT and surgery was 6 wk (3-19). This is slightly longer than the recommended time of 3 w to 4 wk for resection after NT ChRT [27]. The median time between the last cycle of Ch and surgery was 8 wk (3-21). The recommended time between NT Ch and the intervention is unknown, which may explain why our treatment interval was so long. Cases with a longer interval (*e.g.*, 19 wk and 21 wk) were patients requiring salvage surgery.

There was also a significant difference in favor of the NT ChRT group in the PHR in the tumor and lymph nodes (Table 5). It should be noted that the NT Ch patients obtained 4.8% PCR at the tumor level, which is in line with what was observed by Pataer *et al*[3].

In the analysis of lymph node downstaging, we found significant differences between the patients receiving NT ChRT and those with NT Ch. In the ChRT group, 2 patients had positive nodes outside the initially diagnosed nodes. This is probably due to the volume of radiation treatment in these patients being limited to gross disease, and thus, these "out-of-field" nodes did not receive RT, and no local effect should be expected at this level. The involvement of these nodes was limited to intracapsular microscopic disease, which was diagnosed in the detailed pathological study after radical lymphadenectomy.

When comparing the PHR of our results of the NT ChRT group with that of the NADIM trial (the study with the best results published to date in this type of patients), the results are slightly better in the NADIM[23] study, with MPR in the tumor of 83% and 90% downstaging compared to an MPR of 54.5% in the tumor and 80% downstaging in our NT ChRT group, and 9.5 % and 33.3% in the NT Ch group, respectively. A longer follow-up will show whether these differences in PHR between NT ChRT and NT Ch have any impact on the PFS and OS of our patients.

When most of our patients were treated, the interim results of the LungART trial on the role of PORT had not yet been published[38]. Our NT Ch patients with persistent pN2 after surgery received PORT (54 Gy) following the LungART recommendations.

After the results published by the NADIM[23] trial, it is unlikely that an RCT will be conducted comparing NT Ch *vs* NT ChRT with robust results. In our opinion, the current line of research that should be followed in patients with stage III NSCLC is the combination of NT with immunotherapy and Ch or RT, concomitantly or in consolidation, as in the PACIFIC study[39].

We therefore believe that despite not being a RCT or prospective study, the results of our study may be useful to guide NT in patients with resectable stage III (N2) NSCLC, according to the experience in multimodal treatment and the surgical skills of each center in this type of patient.

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## CONCLUSION

Neoadjuvant treatment with ChRT provides significant benefits in both radiological and PHR in patients with resectable stage III NSCLC. However, a longer follow-up is necessary to assess the impact on clinical outcomes.

## ARTICLE HIGHLIGHTS

### **Research background**

There is no standardized clinical consensus for the evaluation of the surgical specimen in patients with non-small cell lung cancer (NSCLC) who have received neoadjuvant treatment with chemotherapy, radiotherapy, or a combination of both.

### **Research motivation**

Following the recently published recommendations by the International Association for the Study of Lung Cancer (IASLC) for the pathological evaluation of tumors and lymph nodes, we analyzed the radiological and pathological response of patients treated with neoadjuvant chemotherapy or chemoradiotherapy.

### **Research objectives**

Our intention was to contribute to the IASLC recommendations with clinical results that reflect the differences in the response to neoadjuvant therapy with chemoradiotherapy *vs* chemotherapy.

### **Research methods**

We performed a retrospective analysis of patients with resectable stage III NSCLC treated with chemotherapy or chemoradiotherapy as neoadjuvant treatment followed by surgery. All histological samples were examined to assess pathological response by the percentage of viable cells in the tumor and the resected lymph nodes.

### **Research results**

We observed better results in the chemoradiotherapy group for both radiological and pathological response, with a lower risk of persistence of cancer cells in the tumor and resected lymph nodes, and with a greater probability of achieving downstaging.

### **Research conclusions**

In this study we observed a greater response to neoadjuvant treatment when adding radiotherapy to chemotherapy. We believe that this could contribute to improving the management of this group of patients.

### **Research perspectives**

Longer follow-up of these patients is necessary to establish a relationship between pathological response and clinical outcomes.

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