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Neoadjuvant treatment in stage III NSCLC: comparison with NADIM 2 trial as a gold standard

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Background and Objective

- It exists scientific controversy about equivalence in overall survival (OS) between neoadjuvant (NT) radiation plus chemotherapy (NTChRT) versus NT chemotherapy alone (NTCh) in resectable stage III (rsIII) NSCLC. The most important phase III trials published about these different type of NT, Thomas et al.**(1)** and Pless et al**.(2)** do not compare "true "concurrent NTChRT vs NTCH instead NTCh followed by RT+ Ch vs. NTCh.

- We showed the results of a multicenter protocol where both arms, **"true" NTChRT (60 Gy in 30 fractions) and NTCh, was used as a comparison with both arms results of NADIM2** trial **(3)** as gold standard in rsIII (AJCC, 8th).

Materials and Methods

- We analyzed consecutive 67 patients who received NT per protocol in four centers (2013-2020). NTChRT or NTCh strategy was chosen in each Multidisciplinar Lung Cancer Committee. Both NT strategies were considered as equivalent induction treatments .

- We showed comparison between Clinical Characteristics of NADIM2 vs. our multicenter group patients (Table 1).

- Single-center surgery and Pathological Response (PR) evaluation by 2 pathologists was made (Hospital Clínic) (Table 2) **(4)**.

- Categorical variables were compared using the Fisher's exact test and chi-square. Normally-distributed continuous variables were compared using two sample-t-tests. P values of < 0.05 were considered statistically significant.

Table 2. Comparison between pathological response to NTchRT vs NTCh in multicenter retrospective study

Table 5. Pathological response.

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

*According to the percentage of viable cells in the histological study.

Results

40 patients received NTChRT and 27 NTCh. The NTChRT arm had a higher proportion of stage IIIB (12 vs. 6), higher multinodal disease (7 vs 0), and one stage IV (treated after resected M1 CNS). NADIM2 reported similar characteristics in the immunotherapy + Ch arm (ICh), more stage IIIB (14 vs 11) and multinodal disease (22 vs 11) vs. control NTCh arm (table 1).

A 14,1% of patients in NADIM2 NTCh arm and a 14,8% in our NTCh arm had local progression vs. no one in NADIM2 Ich arm and a 2,5% in NTChRT arm (1 distant progression).

Our result showed that maximum PR (≤ 10% viable cells) was 54.5% vs. 9.5% (p= 0.001), favoring NTChRT. Complete PR (cPR) was 17.1% vs 4.8% (p= 0.23) in NTChRT vs NTCh, respectively (Table 2). In NADIM2 Major PR (<15% viable cells) were 53% vs. 14% in favor of Ich, and cPR showed a statistically significant improvement in the Ich arm (37% vs.7%).

Progression free survival (PFS) at 24 months was non-significantly different between NTChRT vs NTCh (41 vs 31%). ICh PFS was significantly better in NADIM2 (67.2% vs. 40.9%).

OS at 24 months was significantly improved in the NTChRT vs. NTCh arm (77% vs 45 % (p<0.02) in our group (Figure 1). In the NADIM2 OS was 85.0% and 63.6% favoring ICh.

Table 1 . Comparison between Clinical characteristics of NADIM 2 trial and our multicenter retrospective study. Left: NADIM2. Right: H. Clinic Barcelona

Characteristic	Nivolumab plus Chemotherapy (N=57)	Chemotherapy Alone (N=29)
Median age (IQR) — yr	65 (58–70)	63 (57–66)
Body-mass index — no. (%)†		
≤25	15 (26)	10 (34)
>25	42 (74)	19 (66)
Female sex — no. (%)	21 (37)	13 (45)
History of tobacco use — no. (%)		
Never smoked	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
ECOG performance-status score — no. (%)‡		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Histologic type — no. (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous-cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
TNM classification — no. (%)§		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)
Median tumor size (range) — mm	50 (15–155)	52 (15–166)
Node stage — no. (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)

	RTCh (n= 40)	Ch (n= 27)	*p value*
Age	60 (54-67)	67 (62-73)	0.32
Gender			
Male	26 (65%)	21 (77.8%)	0.29
Performance status			
ECOG 0	7 (17.5%)	5 (18.5%)	
ECOG 1	33 (82.5%)	20 (74.1%)	0.21
ECOG 2	0	2 (7.4%)	
Smoking habit			
Yes	20 (50%)	15 (55.6%)	
No	2 (5%)	3 (11.1%)	0.48
Former smoker	18 (45%)	9 (33.3%)	
Tumor localization			
Apex	7 (17.5%)	1 (3.7%)	
Right upper lobe	13 (32.5%)	13 (48.1%)	
Right lower lobe	6 (15%)	2 (7.4%)	0.33
Left upper lobe	12 (30%)	9 (33.3%)	
Left lower lobe	2 (5%)	2 (7.4%)	
Histology			
Adenocarcinoma	25 (62.5%)	20 (74.1%)	
Squamous	13 (32.5%)	6 (22.2%)	0.28
NSCLC*	0	1 (3.7%)	
Large cell	2 (5%)	0	
Stage			
IIIA	27 (67.5%)	21 (77.8%)	0.52
IIIB	12 (30%)	6 (22.2%)	
IV	1 (2.5%)	0	
T			
T1	4 (10%)	9 (33.3%)	
T2	16 (40%)	9 (33.3%)	0.08
T3	10 (25%)	7 (25.9%)	
T4	10 (25%)	2 (7.4%)	
N			
0	5 (12.5%)	0	**0.04**
2	34 (85%)	27 (100%)	
3	1 (2.5%)	0	
Metastasis	1 (2.5%)	0	0.59
Nodal station distribution			
N0	6 (15%)	0	
1N2	12 (30%)	19 (70.4%)	
2N2	2 (5%)	1 (3.7%)	**0.012**
1N2+1N1	13 (32.5%)	7 (25.9%)	
2N2+1N1	5 (12.5%)	0	
1N1+1N2+1N3	2 (5%)	0	

Conclusions

- This is the first study on NT for rsIII NSCLC with a **true comparison** between concurrent **NTChRT** vs. NTCh in rsIII (AJCC, 8th), performed by highly specialized oncologist team.

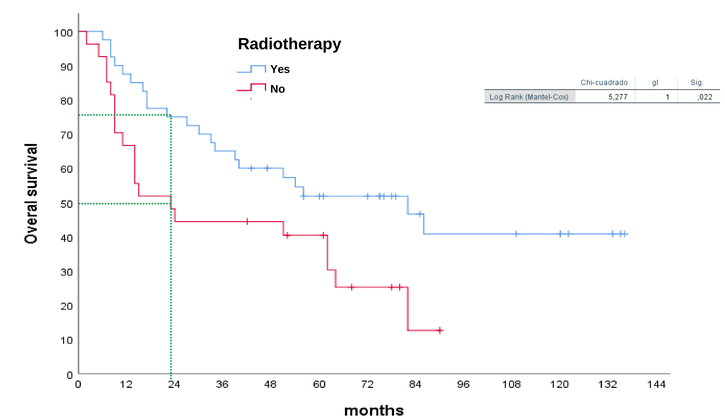
- Our results offer real-world NT data for rsIII patients. Compared with NADIM2 they show similar results for local progression, cPR, Maximum/Major PR and OS in both NTCh arms. And the NTChRT arm showed better overall results, with the abscence of local progression, superior PR and better OS compared to both NTCh arms (H. Clinic and NADIM2).

- Compared to sequential ChRT, concurrent ChRT has shown significant better outcomes in locally advanced NSCLC (phase III trials) (5). In the NT setting, this improvement has not been assessed. We report an improvement of OS and PR with "true" NTChRT compared to NTCh alone.

References

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Figure 1. Overall survival comparison at 2 years (as NADIM2 trial) between both arms (NTChRT vs NTCh) in our multicenter study



Disclosures & Correspondence

First author and presenter has nothing to declare.

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