Cancer Treatment and Research Communications 43 (2025) 100910

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Analysis of operability parameter changes in neoadjuvant treatment with chemotherapy and anti-PD-1/PD-L1

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ARTICLE INFO

Keywords:
Neoadjuvant
Operability
DLCO
Chemo-inmunotherapy

ABSTRACT

Background: The adoption of combined chemotherapy (CT) and immunotherapy (IO) has advanced neoadjuvant therapy (NA) for non-small cell lung cancer (NSCLC), but data on functional impacts are limited. This multicenter retrospective study evaluates respiratory function in NSCLC patients undergoing NA.

Methods: From 2020 to 2024, 186 patients treated with CT or CT-IO (anti-PD-1/PD-L1) were analyzed. Respiratory tests (DLCO, FEV1, FVC) pre- and post-NA were compared, alongside clinical, pathological, and surgical variables.

Results: Median age: 68; 66.6 % male; 93 % smokers/ex-smokers, histologies: Squamous and adenocarcinoma (46 % each), DLCO decline was greater in CT-IO vs. CT (-12.6 % vs. -7.8 %, $p = 0.007$) and CT-IO showed increased FEV1 (+3.8 % vs. -2.5 %, $p = 0.001$) and FVC (+3.7 % vs. -0.7 %, $p = 0.003$), surgery rate: 85.7 % (lobectomy

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https://doi.org/10.1016/j.ctarc.2025.100910

Available online 3 April 2025

most common at 83.3 %) and no differences in complications were found except for 9 immune-mediated events in CT-IO.
Conclusions: CT-IO impacts DLCO more but improves FEV1 and FVC compared to CT. These findings warrant further validation in prospective studies.

Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1,2]. Around 30 % of NSCLC are considered resectable at diagnoses, including stages I and II and a selective proportion of stages IIIA and IIIB. For a long period of time chemotherapy (CT) had been the standard of care in the adjuvant and neoadjuvant setting in resectable NSCLC, with modest results, increasing OS by 4–5 % at 5 years [3].

After many years without any advances in the field, the promising results of the neoadjuvant (NA) chemo-immunotherapy (CT-IO) has dramatically changed the landscape of locally advanced non-small cell lung cancer (NSCLC). With the initial results of NADIM and Checkmate-816 trials, NA CT-IO has become the standard of care for potentially resectable, locally advanced NSCLC [4–6]

Recent results of NA trials also support the use of perioperative CT-IO for the management of locally advanced NSCLC, even though the characteristics of the patients that can benefit more from this schema remain unclear [7–10].

For years, it has been known that the administration of chemotherapy alters pulmonary diffusion (DLCO), causing its deterioration in most cases. This is especially true for particularly pneumotoxic drugs such as bleomycin (Bleomycin), gemcitabine, fluorouracil, taxanes, and certain TKIs, which are associated with pulmonary toxicity. Often, this toxicity is subclinical, with the only manifestation being a greater deterioration of DLCO after treatment compared to baseline values [11].

A priori, the addition of immunotherapy (IO) to chemotherapy (CT) could lead to an increase in potential toxicity and a greater impact on the reduction of pulmonary diffusion after NA treatment. Imunotherapy, specifically PD-1/PD-L1 inhibitors, would be associated with an increase in alveolar damage caused by the dysregulation of T lymphocytes and other immune system cells. This is due to the immune activation induced by these drugs through the blockade of the PD-1/PD-L1 axis [12].

However, there is very few evidence in the literature about the real impact of NA treatments with CT-IO on the respiratory functional parameters that determine the operability of patients. The alteration of DLCO during preoperative treatment could, in some cases, affect surgery in patients with values <50 % before starting NA. Additionally, the deterioration of this parameter is one of the main factors associated with a higher probability of postoperative complications [13].

In this multicenter study, we will retrospectively analyze the impact of NA treatment with CT or CT-IO, comparing the effect on DLCO decline between the two groups, as well as the impact on FEV1 and FVC. Similarly, we will correlate the pre- and post-NA changes in these parameters with various clinical variables.

Patients and methods

Patients

This study is an observational, retrospective non-randomized and non-controlled study. It was approved by the Ethics Committee of Hospital Clinico San Carlos, Madrid (23/628-O_M_SP). All clinical information regarding the included patients was extracted from electronic medical records. Patients diagnosed with non-small cell lung cancer (NSCLC) stage II-IIIA-IIIB candidates treated with neoadjuvant treatment (CT alone vs CT-IO) and candidates to surgery were included. Inclusion criteria: patients with stage II-III non-small cell lung cancer who are candidates for surgery and neoadjuvant treatment, and who have respiratory function tests available before starting preoperative treatment and after it, prior to surgery (% predicted values of DLCO, FEV1, and FVC). Exclusion criteria: patients with non-small cell lung cancer who are not candidates for surgery or neoadjuvant treatment. All included patients signed informed consent before participating in the study.

Pulmonary function testing

Pulmonary function tests (PFTs) were performed before and after the last cycle of neoadjuvant therapy (3rd or 4th cycle). PFT parameters collected included predicted forced vital capacity (FVC), predicted forced expiratory volume at 1 s (FEV1), predicted diffusion capacity of the lung for carbon monoxide (DLCO). The overall mean of each parameter pre- and post-NA was calculated in the chemotherapy vs chemotherapy-immunotherapy arm, and the percentage variation of these parameters was analyzed in each patient and in each arm, comparing the differences between the two groups.

Surgery after neoadjuvant treatment

Surgery was performed after the completion of neoadjuvant therapy (3–4 courses). The surgery was carried out in the Thoracic Surgery departments of the participating centers. After evaluating the response to neoadjuvant treatment in each center's tumor boards, as well as operability parameters, patients underwent surgery. Preoperative mediastinal reevaluation was performed using EBUS or mediastinoscopy. Surgery consisted in anatomical lung resection (segmentectomy, lobectomy, bi-lobectomy or pneumonectomy) and systematic lymph node dissection. We analyzed the percentage of conversions to thoracotomies due to intraoperative complications. We collected pathological results of the resection, both at the nodal level and the primary tumor. All postoperative complications (respiratory, cardiovascular, and others) were recorded and graded according to the Clavien-Dindo classification (I-V). We also analyzed other parameters such as average hospital stay and the need for reoperation within the first 30 days after surgery. Mortality was defined as death before discharge or within 30 days of the operation

Statistical analysis

The statistical analysis was conducted at the Department of Methodology and Biostatistics of the European University of Madrid. Initially, a descriptive analysis of the variables collected in the study was performed, and normalization of respiratory variables was performed considering the normality parameters of the Functional Respiratory Exploration Department at Hospital Infanta Sofía.considering normalized parameters. Subsequently, a comparative analysis of the same variables between the groups of patients who received CT versus those who received CT-IO was carried out (Ficher test, Chi Cuadrado, U-Mann Withney). Finally, a logistic regression analysis was performed for the variables DLCO, FEV1, and FVC, considering all the variables included in the analysis.

Results

Patient demographic and clinical characteristics

From January 2020 to April 2024, 198 patients from 14 hospitals were recruited and 186 patients met the inclusion criteria and were deemed eligible for the study. Twelve patients, did not have a complete

respiratory evaluation (pre- and post-NA) and were not evaluable. Thus, 186 patients were included in the analysis and underwent NA treatment with CT or CTIO (anti-PD-1 or anti-PD-L1, in clinical trial, compassive use authorized by the pharmacy of each center for unapproved combinations or routine clinical practice setting). All different treatments received by all patients included were collected in Table 1. Data on clinical, pathological, and surgical variables were described in Tables 2 and 3. Median age was 68, with 66,6 % men, 60 %/38 % ECOG 0/1 and 93 % smokers or ex-smokers. Squamous and adenocarcinoma histology were most common (46 % in both groups) and PD-L1 expression was balanced. Non-G12C KRAS mutation remains as the most prevalent molecular alteration (15 %).

Neoadjuvant protocols

The preoperative treatment protocols received are included in *Table A*.

- *Neoadjuvant CT*. Most of the included patients who received neoadjuvant chemotherapy were given platinum-based combination regimens: carboplatin 5 AUC and paclitaxel 175 mg/m^2 every 21 days, or the RENO regimen with cisplatin 80 mg/m^2 and carboplatin 5 AUC on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8 every 21 days [14]. None of these patients received neoadjuvant radiotherapy.
- *Neoadjuvant CT-IO*. All complications, inmune-related or no, were registered

Changes in pulmonary function

All patients included PFTs before CT-IO and after 3 cycles during preoperation assessment. Ten patients were ineligible for surgery, with functional deterioration more prominent in the CT-IO subgroup (6/10), without statistical significance (p 0.1). In preoperative setting, we did not find differences in PFTs between both groups (CT vs CT-IO): DLCO 88 % vs 82 %, p 0,29; FEV1: 85 % vs 84 %, CVF: p 0,4; 94 % vs 96 %, p 0,2. However, we did find significant differences in the predicted DLCO percentage after NA between the 2 p.m. (CT vs. CT-IO): DLCO 77 % vs. 69 %, p 0.03; FEV1 81 % vs. 88 %, p 0.02; FVC 91 % vs. 100 %, p 0.02 (Fig. 1). We observed that while the predicted DLCO showed a more pronounced decrease in patients with CT-IO compared to CT, there was a significant increase in FEV1 and FVC compared to levels prior to the start of treatment. When we analyzed the percentage change in DLCO in patients treated with CT vs. CT-IO, we again found significant differences with a more marked reduction in the CT-IO arm (12.6 % vs. CT 7.8 %, p 0.007) (Fig. 2*)*. Additionally, we observed a significant increase in FEV1 (3.8 % vs. CT −2.5 %, p 0.001) and FVC (3.7 % vs. CT −0.7 %, p 0.003).

Table 1
Preoperative treatment protocols received by all participants.

Regimen	N
CT-IO	**126**
Carboplatin-Paclitaxel-Pembrolizumab	18
Carboplatin-Paclitaxel- Nivolumab	90
Carboplatin-Paclitaxel-Atezolizumab-Bevacizumab	1
Carboplatin-Pemetrexed-Pembrolizumab	12
Cisplatin-pemetrexed-Pembrolizumab	1
Cisplatin-Pemetrexed-Nivolumab	2
Carboplatin-Pemetrexedl-Durvalumab	1
Carboplatin-Paclitaxel-Atezolizumab	1
CT-Double IO	**6**
Carboplatin-Paclitaxel-Monalizumab-Durvalumab	2
Carboplatin-Paclitaxel-Tiroglobumab-Atezolizumab	3
Carboplatin-Paclitaxel-Duravalumab-Oleclumab	1
CT	**54**
Carboplatin-Pacltaxel	17
Cisplatin-Vinorelbine	10
Carboplatin-Vinorelbine	6
Cisplatin-Gemcitabine	4
Cisplatin-Pemetrexed	10
Carboplatin-Pemetrexed	4
Cisplatin-Docetaxel	3

Table 2
Baseline characteristics of all patients included.

Variable	N 186 (%)
Age (median)	68
Gender	
Men	124 (66,4)
Women	62 (33,3)
ECOG at diagnosis	
0	112 (60,2)
1	72 (38,7)
2	2 (1,08)
Comorbidities	
CPDO	51 (27,4))
Cerebrovascular	23 (12,37))
Cardiovascular	28 (15,6)
Renal	15 (8,06)
Liver	8 (4,3)
Neuromuscular	2 (1,08)
Autoimune	14 (7,5)
Smoking status	
Never	11 (5,9)
Former	102 (54)
Current	73 (39,2)
TNM at diagnosis (8th IASLC classification)	
IB	2 (0,1)
IIA	2 (0,1)
IIB	45 (24,1)
IIIA	120 (64,5)
IIIB	17 (9,1)
Histology	
Squamous	86 (45,7)
Adenocarcinoma	87(46,7)
NOS	13 (6,9)
PDL1 expression	
<1	62 (36)
1–49	49 (28,6)
>50	60 (35,5)
NGS	28 (15 %)
K-RAS (12c/no 12C)	11 (39 %): 2(7); 9 (32)
EGFR	8 (28,5)
ROS-1	2 (7,1)
MET	1 (3,5)
HER2	1 (3,5)
BRAF	1 (3,5)
OTHERS (TP53, BRCA2, SMARC4)	4 (14,2)

Complications during NA treatment

Relating to NA treatment, CT compared to the previous analysis, with it being 29 % versus 25 % previously, although the proportion of CT-IO remained higher (70 %). Complications during NA showed no significant differences, with the exception of the 10 immune-mediated adverse events, 9 in CT-IO (p 0,28).

Postoperative pathological analysis

The pathological re-staging of the mediastinum was carried out in 113 out of 186 patients included in the study, with no differences between the two groups (CT 63 % vs. CT-IO 60 %, p= 0.78). Regarding the re-evaluation technique, the most common was mediastinoscopy (84/113), followed by EBUS (28/113). By groups, we observed that in the CT arm, 42 % underwent EBUS and 57 % underwent mediastinoscopy, while in the CT-IO arm, 17 % underwent EBUS and 82 % underwent mediastinoscopy (p 0.006).

Table 3
Comparative surgical outcomes and pathological results from all patients included.

Variable	CT N 39 (%)	CT-IO N 117 (%)	p
Surgery			
No	11 (20,4)	15 (11,6)	0122
Yes	43 (79,6)	114 (88,4)	
Mediastinal Evaluation			
EBUS	14 (42,4)	14 (17,7)	**0006**
Mediastinoscopy	19 (57)	65 (82,3)	
Downstaging	20 (51)	72 (62,1)	0,23
Type of surgery			0,8
Lobectomy	32 (74,4)	97 (86,6)	
Bilobectomy	4 (9,3)	9 (8)	
Neumonectomy	7 (16,3)	6 (5,4)	
VATS-Toracotomy conversion	9 (17,6)	13 (10,5)	0,19
Pathological responses			
CPR	15 (34)	67 (58,7)	**0009**
MPR	4 (9,3)	34 (29,8)	
ICU admission	4 (7,8)	6 (5)	1,00
Complications after surgery			
Respiratory	13(25,2)	29 (24)	0,8
Cardiovascular	6 (11,8)	5 (4,2)	0,08
Others	2 (3,9)	6 (5)	1,00
Complications C-D > 3	7 (16,2)	23 (20,1)	0,08
Re-operation within 90 days	2 (3,9)	5 (4,2)	1,00
Re-admission within 90 days	4 (7,8)	7 (5,8)	0,7
Inoperability rate (FRT)	4 (7,4)	6 (4,7)	0,48
Hospital stay			
<7 days	30 (61,2)	88 (73,9)	**0003**
7–21 days	10 (20,4)	28 (23,5)	
>21 days	9 (18,2)	3 (2,5)	
Mortality rate 90 days	3 (6,9)	1 (0,8)	0,06
Exitus			
No	40 (74,1)	126 (95,5)	**0001**
Yes	14 (25,9)	6 (4,5)	

Complications and postoperative events

Table 3 lists the main surgical events and complications. Surgery was performed in 157/186 (84 %) of the patients included in the study. We did not find differences between the two arms, with a non-significant higher percentage in the CT-IO arm: CT 79 % vs. CT-IO 88 %, p 0.1. Ten patients were inoperable after NA, with a higher number of cases in the CT group (4/54, 7.4 %) compared to the CT-IO group (6/128, 4.7 %), no significant differences. Respiratory test deterioration was main explanation. Regarding the type of surgery, lobectomy was the most frequent surgery overall and in both groups, followed by segmentectomy, with no differences between the two groups. Overall, there was a 32 % rate of post-surgery complications with no differences between the two arms. Conversions to thoracotomy were more common in CT group vs CT-IO (17 % vs 10 %, p 0.19). *Re*-interventions within the first 90 days were more common in CT-IO, but without significance (4.2 % vs 3.9 %, p 1.0).

There were also no differences in ICU admissions after surgery nor in readmissions within the first 90 days (CT 7.8 % vs. CT-IO 5.8 %, p 0.7), with a higher and statistically significant percentage in admissions longer than 3 weeks in the CT group vs. CT-IO (CT 18.4 % vs. CT-IO 2.5 %, p 0.003). Regarding 90-day postoperative mortality, we found 3 deaths in the CT arm (6.9 %) versus 1 death in the CT-IO arm (0.08 %), approaching statistical significance (p= 0.06).

Univariate analysis

Univariate regression analysis revealed a significant relationship with DLCO decline, smoking (0.037), and treatment with CT-IO (P = 0.03), and a trend with COPD (p 0.058). Also we found a significant relationship between and an increase of FVC rate and absence of renal (p 0013) and hepatic failure (p 0,04) and type of treatment (CT-IO vs CT) with a higher increase in combination treatment with a trend to statistical significance (p 0,07). In univariate analysis for FEV1 increase, again, no liver disease was related with an improvement with this parameter (p 0019) as well as IMC 17–25 (p 0001). Again, the type of treatment (CT-IO vs CT) was associated to a higher increase of FEV1 (p 0,01).

Discussion

As we have previously discussed in several sections, this study aims to examine the impact of different NA treatments on the operability of patients with lung cancer and locally advanced disease. To date, this aspect has been scarcely evaluated in the literature. Most studies focus on the impact of chemotherapy or chemoradiotherapy on DLCO as a neoadjuvant treatment, not only for lung cancer but also for breast or esophageal cancer [14,15].

In the context of lung cancer, Connolly JG et al. highlighted the importance of repeated pulmonary function testing to identify patients at higher risk of morbidity or mortality after neoadjuvant chemotherapy in a retrospective analysis of 1001 patients with resectable lung cancer. They categorized pulmonary function based on the American College of Surgeons Oncology Group major criteria: DLCO ≥50 % as normal and DLCO <50 % as impaired. Patients were divided into five subgroups based on combined pre- and post-induction DLCO status: normal-normal, normal-impaired, impaired-normal, impaired-impaired, and preinduction only. Multivariable analysis revealed that patients with normal-impaired DLCO status had a higher risk of respiratory complications (odds ratio, 2.29 [95 % CI, 1.12–4.49]; P= 0.02) and in-hospital complications (odds ratio, 2.83 [95 % CI, 1.55–5.26]; P< 0.001). The type of neoadjuvant chemotherapy was not linked to an increased risk of complications or changes in DLCO [16].

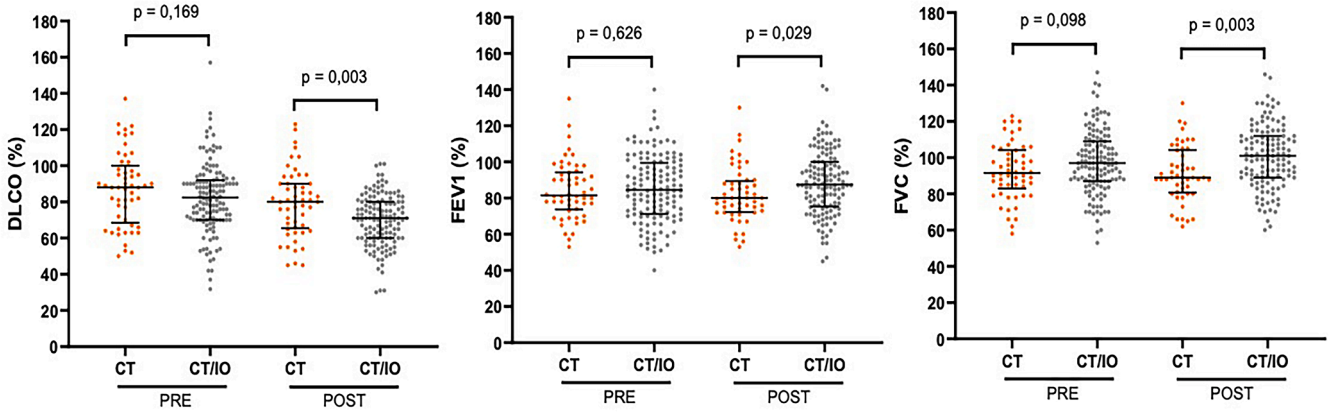

Fig. 1. Global differences among pre- and post-respiratory test in both groups in pre-NA and post-NA setting.

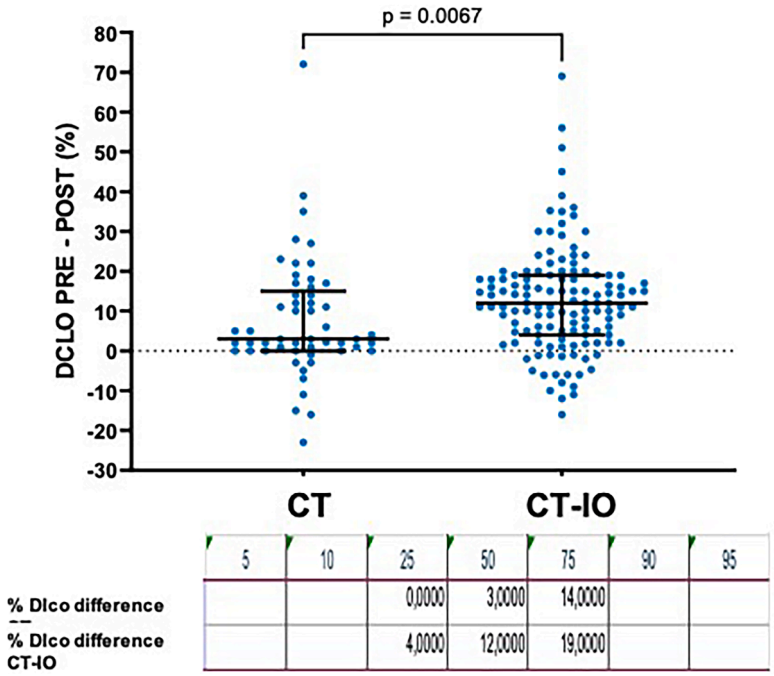

Fig. 2. Percentage of reduction in predicted DLCO value between pre- and post- NA in CT-IO vs CT.

These days, the neoadjuvant strategy based on the combination of chemotherapy and immunotherapy (anti-PD-1/PD-L1) has become the standard therapy for patients in stage IIIa, with potential benefits extendable to patients with earlier stages (stage II) and stage IIIB.

However, there are no published studies evaluating the impact of the combination of CT-IO vs. CT on pulmonary function tests, particularly DLCO, in the context of resectable lung cancer. Gao Y et al. analyzed the impact of NA with CT-IO in a retrospective series of 220 Asian patients with locally advanced esophageal cancer who received CT-IO. They compared the changes in FEV1 %, FVC %, and FEV1/FVC % in pulmonary function before and after NA. Similar to our study, they found a significant increase in the predicted pre- and post-NA values of FEV1 % (p= 0.018) and FVC % (p= 0.005). However, in contrast, there was a significant decline in DLCO % predicted (102.97 ± 26.22 % before CT-IO vs. 90.18 ± 25.04 % after CT-IO; P< 0.05) [13].

A similar analysis was conducted by Zhu Y et al. In their retrospective study, they analyzed the impact of NA based on CT-IO (anti-PD-1/PD-L1) on DLCO, FEV1, and FVC in 30 patients with locally advanced lung cancer. They found a significant increase in predicted FEV1 % compared to before NA (85.27 % ± 15.86 %, P= 0.013, 0.022, respectively). On the other hand, the predicted FVC % value before and after treatment was not significantly different (P= 0.084). Regarding the predicted DLCO value, there was again a significant decrease between before and after CT-IO (83.61 % ± 13.10 % to 78.69 % ± 13.85 %, P= 0.023). Similar to Gao's study, they did not find respiratory complications between the DLCO % pred decreased group and the non-decreased group (P= 0.546) [17].

These both studies, however, do not compare the findings of the impact of CT-IO with CT, as all patients in this study received the combination.

Our study, although a retrospective series with 2 p.m. not balanced in terms of the number of patients included in each (CT-IO 132 vs. CT 54 patients), is the first comparative analysis of the impact on respiratory function produced by CT-IO vs. CT. We analyzed the pre- and post-NA variations in both groups. As previously mentioned, we found significant differences with a more marked reduction in DLCO in the CT-IO arm (12.6 % vs. CT 7.8 %, p= 0.007) along with a significant increase in FEV1 (3.8 % vs. CT −2.5 %, p= 0.001) and FVC (3.7 % vs. CT −0.7 %, p= 0.003). This means that the combination of CT-IO would produce a greater deterioration in DLCO compared to CT, potentially rendering those patients with pre-NA DLCO values around 50 % from operable to inoperable. In our study, only 10 patients were ineligible for surgery, 6 out of 132 of whom were due to a drop in DLCO after NA that rendered them inoperable, while this occurred in 4 out of 54 patients in the CT group, without significant differences (p= 0.1).

Various authors explain the impact of different NA treatments with CT on pulmonary diffusion by the development of toxicity mediated by varied pathophysiology. This is based on direct endothelial damage to the alveolar capillaries due to the recruitment of inflammatory cells; cytokine release syndrome, inducing endothelial dysfunction, capillary leak syndrome, and non-cardiogenic pulmonary edema, as in the case of gemcitabine; alveolar damage induced by the activation of lymphocytes and alveolar macrophages; and the accumulation of free radicals causing oxidative damage, as seen with bleomycin (Bleomycin). The addition of PD-1/PD-L1 inhibitors to CT could increase alveolar damage by causing T lymphocyte dysregulation and affecting other immune cells due to the blockade these drugs exert on the immune checkpoint. Additionally, potential immune-mediated pneumonitis could further contribute to increased lung damage compared to CT alone. In most cases, this toxicity is subclinical, reflected by a drop in DLCO, which can sometimes be clinically relevant, affecting the operability of certain patients [12, 18–20].

The increase in the percentage values of predicted FEV1 and FVC is related to the fact that patients in the CT-IO arm had more local responses compared to the CT arm, improving lung ventilation independently of the effect on DLCO.

Regarding the pathological reevaluation, we found more videomediastinoscopies in the CT-IO arm (p= 0.006). A possible explanation could be the persistence of significantly sized and FDG-avid lymph nodes on imaging tests (CT and PET-CT), which might have led to the use of videomediastinoscopies to confirm mediastinal staging in the CT-IO group. The biological explanation involves the lymphocytic infiltration underlying the immune response induced by the combination, not only in the primary tumor but also in the locoregional lymph nodes. This finding has also been observed in the previously mentioned pivotal studies [6].

As expected and consistent with the results of the main pivotal studies, the percentage of pathological responses in the operated patients (113/186, 60.7 %) was higher in the CT-IO arm compared to the CT arm, with 58.7 % CPR and 29.8 % MPR in the CT-IO arm versus 34 % CPR and 9.3 % MPR in the CT arm (p 009). However, while the results in the CT-IO arm align with those published in various NA and perioperative CT-IO studies (NADIM, CM 816, CM77-T), the control arm results in our series are somewhat higher than expected. A possible explanation could be the greater use of cisplatin in this group, which is known to be associated with higher local response rates compared to carboplatin [20–22]. Similarly to the other previously mentioned studies, we did not find differences in postoperative complications or 90-day mortality between the two arms.

However, as expected, we observed a higher percentage of immune-mediated complications in the CT-IO arm both before and after surgery (10 cases in the CT-IO arm, primarily hypothyroidism, transaminitis, and mild, self-limiting pneumonitis) [5,6].

However, we did find differences in the average length of stay exceeding 21 days, which was higher in the CT arm compared to the CT-IO arm (18.2 % vs. 2.5 %, $p= 0.03$). Since we did not find differences in the percentage of postoperative complications, mortality, reoperations, or ICU stays, one possible explanation for these differences could be the patient profile (the CT-IO arm included patients with a more favorable ECOG performance status). Another possible explanation could be the responses to the NA treatment, which were poorer in the CT arm, indicating patients with a higher tumor burden and greater fragility. Although not statistically significant, there is a slightly higher incidence of conversions to thoracotomy and pneumonectomies in the CT cohort, which are factors associated with a prolonged length of stay, the former because of pain control and the latter to prevent late onset of cardio-respiratory complications [23].

Similarly, a trend toward higher perioperative mortality at 90 days of 6.9 % in the CT arm versus 0.8 % in the CT-IO arm ($p= 0.06$) could also justify the longer stay in the CT arm Since we did not find differences in readmissions (7.8 % CT vs. 5.8 % CT-IO, $p= 1.00$), reoperations (3.9 % CT vs. 4.2 % CT-IO, $p= 0.7$), or the percentage of patients admitted to the intensive care unit (7.8 % CT vs. 5 % CT-IO, $p= 1.00$), it is likely that patients in the CT arm had other intermediate-severity medical-surgical complications that contributed to a longer hospital stay compared to the CT-IO group.

However, given the differences in sample size between each arm, a more solid understanding of this finding would require a prospective analysis with balanced arms to obtain more conclusive and reliable results.

In the univariate analysis, we found that the main factors independently associated with the decrease in DLCO were smoking ($p= 0.037$), treatment with CT-IO ($p= 0.03$), and a trend toward statistical significance for the presence of COPD ($p= 0.058$). These findings are consistent with the multivariate analysis conducted by other authors who evaluated the impact of CT-IO on DLCO in different contexts. In the univariate analysis, the presence of *exitus* was also significantly and independently associated with the variation in FEV1 in both groups. As described, we found more cases of *exitus* in the CT group compared to the CT-IO group (24.9 % vs. 4.5 %, $p= 0.06$). Although we did not find differences in perioperative mortality, at the time of patient inclusion in our study, there were more patients who had progressed in the CT group compared to the CT-IO group, with a higher burden of thoracic disease and greater ventilatory limitation [13,16].

The results suggest the advisability of repeating pulmonary function tests after administering NA treatment, especially with CT-IO, particularly in patients with DLCO close to 50 %. According to our findings, these patients could experience a drop of around 13 % (the average value obtained in our analysis), affecting their operability. While we did not find differences in the operability of the patients included in our retrospective analysis, it is likely that these findings could be confirmed in a prospective study with balanced treatment arms. However, it is unlikely that such a study could be conducted today, given that the combination of CT-IO has become the standard therapy.

We must highlight as a strength of this study that it is the first comparative analysis of the impact of CT-IO versus CT on operability in a considerable sample of patients with locally advanced NSCLC (186 patients) who received NA treatment. Despite being a retrospective analysis, we found significant differences in the deleterious effect of CT-IO on pulmonary diffusion, a finding not previously described in this context or in a comparative analysis.

The main limitations are the retrospective design and the differences in the number of patients in each arm, which could have influenced the results, especially in the comparative subgroup analysis.

Conclusions

In this retrospective study, we found a greater deleterious effect of NA treatment with CT-IO compared to CT on DLCO, a parameter closely related to operability and postoperative complications in the context of surgical treatment for localized or locally advanced NSCLC. This is particularly important for patients with predicted DLCO values on the borderline of operability. Therefore, it is crucial to assess DLCO values before and after NA in patients undergoing CT-IO, especially in smokers and those diagnosed with COPD. Prospective studies are needed to confirm these findings and to identify more precise markers to pinpoint vulnerable patients.

Glossary

CT: Chemotherapy
IO: Inmunotherapy
CT-IO: Chemo-Inmunotherapy
NSCLC: Non-small cell lung cancer
NA: Neoadjuvant treatment
DLCO: Diffusing capacity for carbon monoxide
PD-1/PD-L1: Programme Death-Ligand 1
FEV1: Forced Expiratory Volume in 1 s
FVC: Forced Vital Capacity
PFTs: Pulmonary function tests
COPD: Chronic Obstructive Pulmonary Disease

CRediT authorship contribution statement

M Sereno: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A Collazo-Lorduy:** Writing – original draft, Supervision, Data curation. **Y Garitaonaindia:** Supervision, Data curation. **D Gómez de Antonio:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **J Baena Espinar:** Writing – review & editing, Supervision, Data curation. **C Aguado de la Rosa:** Writing – review & editing, Data curation. **P Cruz Castellanos:** Writing – review & editing, Data curation. **S Falagán Martínez:** Writing – review & editing. **LE Chara Valverde:** Data curation. **R López-Castro:** Writing – review & editing, Data curation. **A López-Martin:** Writing – review & editing, Data curation. **J Rubio-Pérez:** Writing – review & editing, Data curation. **A Gómez Rueda:** Data curation. **C Traseira Puchol:** Data curation. **X Mielgo Rubio:** Data curation. **B Losada Vila:** Data curation. **J Rogado:** Data curation. **E Bernal Hertfelder:** Data curation. **L Gutiérrez Sainz:** Data curation. **JL Campo-Cañaveral:** Data curation. **I Romano:** Formal analysis, Data curation, Conceptualization. **I. Thuissard:** Software, Methodology, Formal analysis. **G Rubio Romero:** Writing – review & editing. **E Casado Sáenz:** Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We thank all the patients and their families who participated in this study, allowing us access to their medical history. We also thank the statistical methodology team at UEM for their support in the analysis and interpretation of the data reviewed within the study.

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