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Safety and Efficacy of Salvage Surgery after Treatment With Immune-Checkpoint Adjuvant Inhibitors for Advanced Non-Small Cell Lung Cancer: A Multicentric Study

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ABSTRACT

Objective: In advanced non-small cell lung cancer (NSCLC), immune-checkpoint inhibitors (ICIs) can achieve significant clinical responses. This raises the question of whether to consider salvage surgery as a curative treatment option. Few case series reported encouraging results in terms of pathological response. However, intraoperative risk and postoperative morbidity have been highlighted. This study aims to assess the safety and feasibility of surgery after ICIs administration and to evaluate its effectiveness on the final pathological examination.

Methods: We retrospectively identified stages III–IVA NSCLC consecutive patients who underwent surgery with radical intent after ICIs at three National Centers (2016–2022). Before treatment, all patients were considered unresectable by a multidisciplinary discussion. After surgery, pathological response was evaluated according to the International Association for the Study of Lung Cancer (IASLC) recommendation.

Results: Thirty-one patients were included; pretreatment clinical stage was: IIIA in 4 patients (10%), IIIB in 13 (42%), IIIC in 3 (13%), and IVA in 11 (35%). Median treatment duration was four cycles. Only anatomical resections were performed, with lobectomy that represent the main type of resection (22 patients, 74%). A minimally invasive approach was performed in 10 patients (32%), with a conversion rate of 0%. Postoperative complications were observed in eight patients (25%). Complete pathologic response (CPR) and major pathologic response (MPR) were 48% and 16%, respectively. Two and 3-years survival were 88%.

Conclusions: Based on our experience, salvage surgery of advanced NSCLC treated with ICIs confirm his feasibility and safety in responder patients. Moreover, it is associated with low morbidity, high CPR rate, and satisfying medium-term survival.

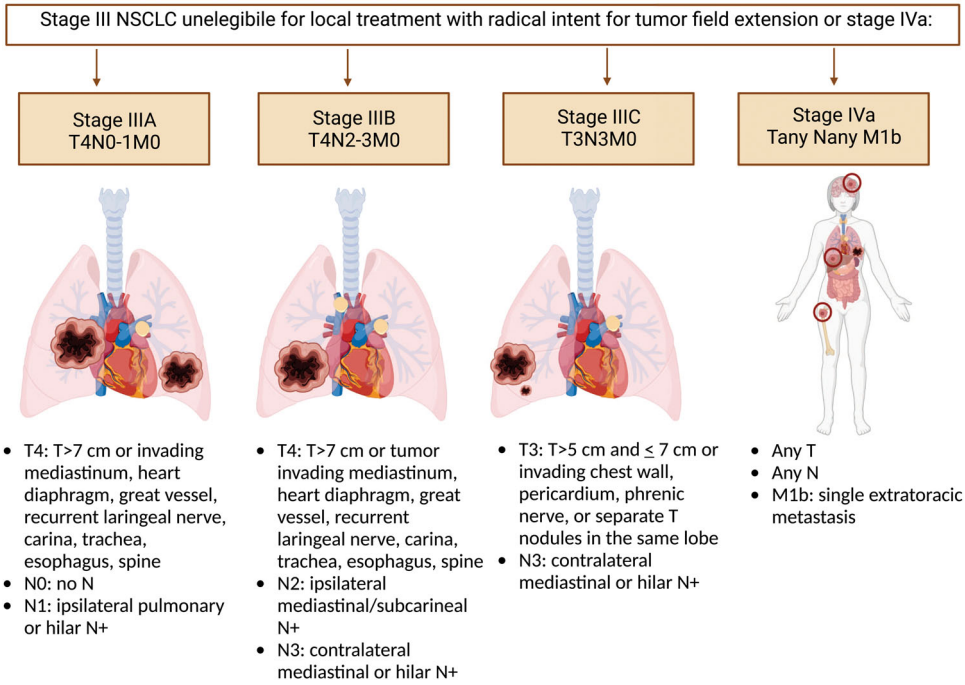

FIGURE 1 | Ineligibility to surgery or radiation therapy with radical intent for disease extension was discussed at multidisciplinary tumor board (MTB) and was related to: direct invasion of vital structures by the disease (heart, great vessels, esophagus) with or without lymph nodes involvement (Stage IIIA, IIIB, or IIIC) and metastatic disease with any T or N involvement (Stage IVA).

1 | Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Despite the recent implementation of screening programs, the diagnosis of non-small cell lung cancer (NSCLC) remains in advanced stages for nearly 80% of cases [2].

The discovery of the tumor immune microenvironment (TME) as a potential target for harnessing in NSCLC treatment has represented a groundbreaking advancement in thoracic oncology.

Nowadays, the optimal systemic treatment for advanced NSCLC patients who are ineligible for radical locoregional treatment depends on pathological and molecular characteristics. Specifically, in our country, NSCLC patients without actionable driver mutations are eligible for immune checkpoint inhibitors (ICIs) as single agents or in combination with chemotherapy, according to PDL1 expression level (greater than 50% or less than 50%, respectively) [3–7].

Recently, significant oncological and radiological responses to ICI have led to the possibility of reincorporating surgery as a curative treatment option. Few case reports and small case series have reported encouraging results in terms of major and complete pathological response (MPR and CPR), mainly in stage III tumors. However, several surgical challenges and potential perioperative risks have been highlighted [8, 9]. The surgical issues are strictly related to dense adhesions, hilar inflammation, and fibrosis of perivascular structures, depending on the hyperactivation of the inflammatory response [10].

In this study, we aim to analyze the safety and the feasibility of surgery following treatment with immunotherapy or chemoimmunotherapy in patients with locally advanced and oligometastatic NSCLC, initially deemed unresectable at a multidisciplinary tumor board evaluation.

2 | Methods

Thirty-one stages III–IVa NSCLC patients with no actionable driver mutations who underwent surgical resection with curative intent after ICI treatment were retrospectively identified from three different national cancer centers (Padua, Milan, and Rome) between October 2016 and June 2022. The study was performed in accordance with the Declaration of Helsinki; all patients signed an informed consent to and the Ethics Committee of our Institution approved the study (CESC IOV 2021/89), on November 23, 2021.

Inclusion criteria were:

- histologically confirmed diagnosis of NSCLC in Stage IIIa, IIIb, IIIc, and oligometastatic stage IV cases;
- oligometastatic disease, defined as the presence of five or fewer metastases in two or fewer organs [11];
- comprehensive molecular profiling and availability of PDL1 expression data;
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) ranging from 0 to 1;
- ineligibility to surgery or radiation therapy with radical intent for disease extension at Multidisciplinary Tumor Board (MTB) (Figure 1);
- functional suitability for ICI administration, either as monotherapy or in combination with chemotherapy.

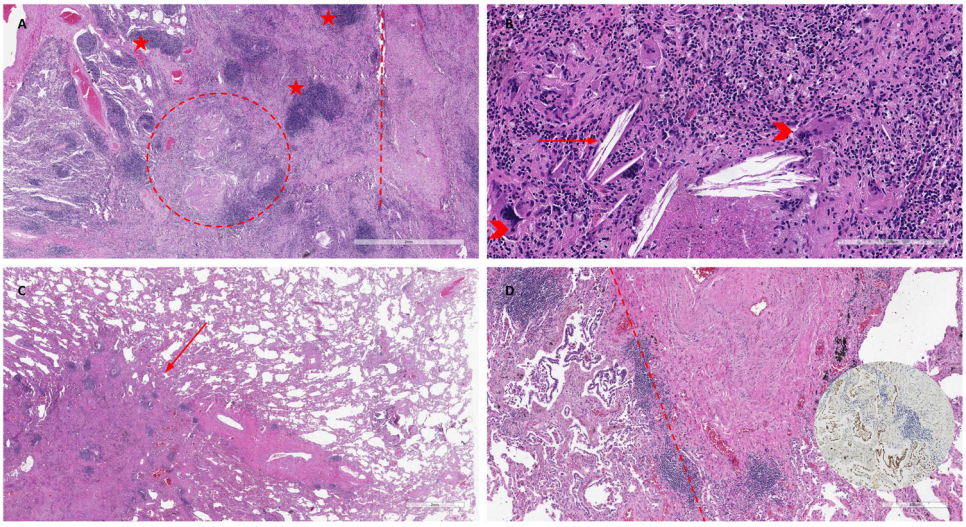

FIGURE 2 | Representative images of complete and major pathological responses. In complete pathological response, inflammation (stars on multiple nodular lymphoid aggregates), necrosis (dotted circle), and fibrosis (right side of the dotted lines) are detected in different percentages (A, hematoxylin and eosin, scale bar: 2 mm). At higher magnification, several multinucleated giant cells (red arrowhead) and macrophages with cholesterol clefts (red arrow) can be detected (B, hematoxylin and eosin, scale bar: 200 μm). In major pathological response, along with the distortion of the lung parenchyma (red arrow) (C, hematoxylin and eosin, scale bar: 2 mm), some residual viable tumor cells, constituting less than or equal to 10%, are visible (left side of the dotted lines) (D, hematoxylin and eosin, scale bar: 400 μm). Adenocarcinoma foci are highlighted in the inset, showing TTF1 positivity in the same area.

Patients with Stage IIIc and oligometastatic stage IV were treated according to the established standard therapy protocols (Figure 2).

ICI protocols included the anti-programmed death-1 (PD-1) agents (nivolumab 240 mg flat dose or 3 mg/kg every 2 weeks or pembrolizumab 200 mg flat dose or 2 mg/kg every 3 weeks), and anti-PD-L1 agent (atezolizumab dose) for four cycles; pembrolizumab was administered both as single agent and in combination with platinum-based chemotherapy according to PDL1 levels. Where the PDL1 level was not a selection criteria (e.g., nivolumab and atezolizumab in pretreated patients), the choice among different options was based on physician's preference, schedule of administration, drug access at the time of patients' inclusion in the study.

Patients who received ICIs as salvage therapy due to disease progression or early discontinuation due to chemotherapy-related toxicity were regarded as eligible for the study, provided they met the disease-related inclusion criteria. Safety profile of ICIs as well as chemotherapy was assessed in relation to adverse events (AEs), immune-related adverse events (irAEs), and serious adverse events (SAEs), based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After four cycles of systemic therapy, patients were re-evaluated at the MTB meeting. Surgery was then recommended in the following situations:

- a substantial clinical response that rendered the primary tumor amenable to resection;
- a control of distant metastases with residual intrathoracic disease.

All patients scheduled for lung resection underwent a comprehensive preoperative clinical and radiological assessment including physical examination, cardiac and pulmonary function tests. Clinical restaging was performed according to the VIII TNM edition by using chest, brain, abdomen CT scan, and PET-CT scan [12]. Mediastinal staging was performed to European Society of Thoracic Surgeons (ESTS) guidelines [13].

After surgery, perioperative mortality and morbidity were recorded. The follow-up was performed with a whole-body CT scan every 4 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter. The systemic treatment was continued after surgery as per physician's choice, according to a risk/benefit assessment including pathological staging and response, clinical features and patient's compliance. Clinical end-points were relapse free survival and overall survival. Relapse free survival was defined as the time between surgery to any progression of disease. Overall survival was intended as the time from the start of treatment to all-cause death.

2.1 | Pathological Assessment of the Tumor Bed

Following surgery, tumor samples were fixed in formalin, embedded in paraffin, and histologically classified in accordance with the 2021 WHO classification of lung tumors [14].

For small tumor bed samples with a maximum diameter of less than 3 cm, a comprehensive examination was conducted. Tumor bed samples exceeding 3 cm in diameter were assessed by evaluating at least one section for each centimeter of the greatest dimension of the tumor bed.

In accordance with the International Association for the Study of Lung Cancer (IASLC) recommendations [15], the evaluation of pathological response involved quantifying the presence of remaining tumor cells within the primary tumor. This was achieved by comparing the estimated cross-sectional area of viable tumor foci to the estimated cross-sectional areas of fibrosis and necrosis (tumor bed) on each slide. The tumor tissue samples were sectioned, and the percentage of viable tumor cells was documented for each slide. The average percentage of viable tumor cells was calculated for each patient. Tumors containing less than 10% viable cells were categorized as exhibiting MPR, whereas tumors with no viable tumor cells were considered to have achieved a CPR. For the assessment of treatment effect in lymph node metastases, a scoring system was applied in accordance with prior descriptions [15].

2.2 | Statistical Analysis

Descriptive statistics were reported as median (I and III quartiles) for continuous variables and percentages (absolute numbers) for categorical variables. Survival at follow-up was evaluated using the Kaplan–Meier method, while recurrence was evaluated using cumulative incidence functions (CIFs) to account for competing risks. The association between baseline variables of interest and events at follow-up were evaluated using Cox proportional hazard models. Results were reported as hazard ratio (HR), 95% confidence interval (CI), and p value. Analyses were performed using the R software.

3 | Results

The preoperative characteristics of these patients are summarized in Table 1. In particular, in our population, 18 (58%) patients were males and the median age was 64 years (IQR: 55–68). Adenocarcinoma was the histotype more represented (61%); according to clinical staging, Stage IIIa was observed in 4 patients (12%, 3 T4N0 and 1 T2bN2), IIIb in 13 (42%, 1 T2bN3, 7 T3N2, and 5 T4N2), IIIc in 3 (9.6%, 1 T3N3 and 2 T4N3), and IVa in 11 subjects (35%, all for metastatic disease, 7 in brain and 4 in bone).

3.1 | Therapeutic Pathway and Systemic Treatment Activity and Safety

Mean PD-L1 levels of our population was of 30% (IQR: 10–55). All patients received immunotherapy, as a single agent or in addition to platinum-based chemotherapy in 26% and 74% cases, respectively (Table 2). Pembrolizumab was the most used compound (74%). The median duration of treatment was four cycles (IQR: 4–7). Overall, five (16%) patients showed AEs and two (6%) irAEs, never severe forms. Grade > 3 AEs were reported in only one case.

In stage IV NSCLC, the treatment of the metastatic site was performed in all cases, by using surgery (50%), radiotherapy (40%), and their combination (10%).

From the comparison of the SUV values between pre- and posttreatment PET-CT scan, a median reduction of 7.8 for the

TABLE 1 | General characteristics of the patients.

Variable	31 patients
Age	64 (55–68)
Gender	
Male	18 (58%)
Female	13 (42%)
Smoking	
No	6 (19%)
Previous	13 (42%)
Current	12 (39%)
Pack year (P/Y)	37 (20–55)
Charlson Comorbidity Index (CCI)	4 (3–5)
PS-ECOG at diagnosis	
0	18 (59%)
1	13 (41%)
ASA score	
2	18 (58%)
3	12 (39%)
4	1 (3%)
FVC (%)	92% (82–105)
FEV1 (%)	91 (81–108)
DLCO (%)	68 (60–85)
Preoperative histology	
Adenocarcinoma	18 (58%)
Squamous cell carcinoma	9 (29%)
Adenosquamous carcinoma	1 (3.2%)
NOS carcinoma	3 (9.7%)
Mode of diagnosis	
Bronchoscopy	15 (48%)
CT-guided biopsy	12 (39%)
Mediastinoscopy	1 (3.2%)
Biopsy or resection of metastasis	3 (9.7%)
Median SUV_{max}	
T	15 (10–24)
N	5 (3–10)
Pretreatment clinical stage	
IIIA	4 (12%)
IIIB	13 (42%)
IIIC	3 (9.6%)
IVA	11 (35%)
Site of metastasis	
CNS	7 (58%)
Bone	4 (42%)

Note: Data are presented as median (IQR) or frequency.
Abbreviations: CNS, central nervous system; DLCO, diffusion lung carbon monoxide; FEV1, forced expiratory volume in the first second; NOS, not otherwise specified.

TABLE 2 | Treatment characteristics.

Variable	31 patients
Type of treatment	
Chemo-immunotherapy	23 (74%)
Immunotherapy	8 (26%)
Type of ICIs	
Atezolizumab	3 (9.7%)
Durvalumab	1 (3.2%)
Nivolumab	4 (13%)
Pembrolizumab	23 (74%)
Type of metastasis treatment	
Surgery	5 (50%)
RT	4 (40%)
RT + surgery	1 (10%)
No treatment	1 (10%)
Toxicity to standard chemotherapy	
Yes	9 (30%)
No	22 (70%)
Grade max of chemotherapy toxicity	
2	18 (59%)
3	12 (39%)
4	1 (3%)
Toxicity to immunotherapy	
Yes	4 (13%)
No	27 (87%)
Grade max of immunotherapy toxicity	
1	3 (75%)
2	1 (25%)
Best clinical response to treatment (RECIST 1.1 criteria)	
CR	4 (13%)
PR	22 (70%)
SD	5 (16%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

T parameter and 1.5 for the N parameter was noted. According to the RECIST criteria, 4 (13%), 22 (71%), and 5 (16%) patients showed complete, partial response, and stable disease, respectively.

Surgical resection was performed at the end of the systemic treatment with a median time from the end of the treatment to the day of surgery of 44 days (IQR: 32–56).

Relating to surgical procedure, 21 patients underwent open thoracotomy (68%) (Table 3) while a minimally invasive approach was performed in 10 patients (32%), by using VATS (6 patients, 19%) and robotic approach (4 cases,13%), without need for conversion and with a median operation time of 165 min (IQR: 127.5–182.5). Moreover we reported no intraoperative complications related to minor or major bleedings, with a mean estimated blood loss of 150 mL (IQR: 100–200). Intraoperative transfusion was required in one patient (3.2%) because of a preoperative hemoglobin level of 9.2 g/dL.

TABLE 3 | Surgical characteristics.

Variable	31 patients
Surgical approach	
Thoracotomy	21 (68%)
Minimally invasive surgery	10 (32%)
VATS	6 (19%)
RATS	4 (13%)
Conversion	
Yes	0
No	10 (100%)
Type of pulmonary resection	
Lobectomy	22 (71%)
Segmentectomy	2 (6.5%)
Lobectomy + segmentectomy	1 (3.2%)
Bilobectomy	2 (6.5%)
Pneumonectomy	4 (13%)
Intraoperative complications	
Yes (arrhythmias)	1 (3.2%)
No	30 (97.8%)
Postoperative complications	8 (25%)
Hemothorax	1 (12.5%)
Pneumonia	2 (25%)
PAL	2 (25%)
Others	3 (37%—2 dysphonia, 1 anemia)

Abbreviation: PAL, prolonged air leaks.

Lobectomy was the most common type of resection in 22 patients (74%), followed by pneumonectomy in 4 (13%), bilobectomy and segmental resections in 2 cases (6.5%). The median chest tube duration was of 6 days (IQR: 2.75–7.75), with a median length of stay (LOS) of 6.5 days (IQR: 4.25–10.75).

After surgery, seven patients (23%) experienced complications: one bleeding needing transfusions, one hemothorax (12%) requiring a surgical revision, two dysphonias (25%), two pneumonias (25%), and two prolonged air leaks (25%) resolved with conservative treatment. One patient reported a pneumonia in the contralateral lung after 17 days from discharging, that requires a rehospitalization for intravenous antibiotic treatment.

3.2 | Histological Examination of the Tumor Bed

At the pathological evaluation, the final histology was adenocarcinoma in 19 (61%) patients, squamous cell carcinoma in 9 (29%), adenosquamous carcinoma, sarcomatoid tumor and non-small cell cancer, not otherwise specified (NOS) (3.2%) subject

TABLE 4 | Pathological characteristics.

Variable	31 patients
Pathological stage	15 (48%)
0	
IA1	1 (3.2%)
IIB	3 (9.7%)
IIIA	8 (25%)
IIIB	1 (3.2%)
IIIC	1 (3.2%)
IVA	2 (6.4%)
Histology	
Adenocarcinoma	19 (61%)
Squamous cell carcinoma	9 (29%)
Adenosquamous carcinoma	1 (3.2%)
Sarcomatoid carcinoma	1 (3.2%)
NOS carcinoma	1 (3.2%)
Pathological response	
Major pathological response (MPR)	5 (16%)
Complete pathological response (CPR)	15 (48%)
Intraoperative complications	
Yes (arrhythmias)	1 (3.2%)
No	30 (97.8%)
Postoperative complications	8 (25%)
Hemothorax	1 (12.5%)
Pneumonia	2 (25%)
PAL	2 (25%)
Others	3 (37%—2 dysphonia, 1 anemia)

for each, respectively (Table 4). R0 resection was achieved in all cases.

Tumor bed was evaluated on several sections, ranging from 2 to 15 (median: 5; IQR: 5–6). CPR and MPR were diagnosed in 15 (48%) and 5 (16%) cases, respectively. For the remaining cases, a median of 80 (IQR: 60–80) was detected for viable tumor cells. While fibrosis and/or inflammation were always detected, necrosis was absent in 13 (42%) case. Concerning lymph-nodes, at final pathological examination, at least three lymph-nodes stations were examined. Metastases were described in 13 (42%) cases, in 6 (19.3%) involving N2 stations and in 3 (9.7%) showing extracapsular extension. In seven (22.5%), lymph-nodes signs of treatment were noted.

3.3 | Postoperative Therapeutic Pathway and Clinical Outcomes

According to the pathological staging, 13 (42%) patients underwent adjuvant systemic treatment with immunotherapy (10 pembrolizumab and 2 nivolumab) and in only 1 case with standard pemetrexed-based chemotherapy. Adjuvant radiotherapy was carried out in three patients, in one patient combined with ICIs (Table 5).

TABLE 5 | Post-discharge outcomes.

Variable	31 Patients
Adjuvant systemic therapy	13 (42%)
Chemotherapy	1 (9%)
Immunotherapy	12 (91%)
Type of adjuvant systemic therapy	13
Nivolumab	2 (15%)
Pembrolizumab	10 (77%)
Pemetrexed	1 7 (%)
Relapse	
Yes	6 (19%)
No	25 (81%)
Pattern of relapse	
Locoregional	3 (50%)
Distant	3 (50%)

The median follow-up was 19 months, with no 30 and 90 days mortality. The end-point of overall survival was not reached. Two and 3-years survival rate were 88%. Median relapse free survival was not reached; the cumulative incidence of relapse at 2 and 3 years was 25% and 34%, respectively. Totally, six relapses were observed in the follow-up period: three locoregional and three distant ones.

Although not statistically significant because of the lack of events, a slight trend toward a correlation between CPR and the reduction of mortality (HR: 0.59, 95% CI: 0.06–5.67; $p = 0.648$) and relapse (HR: 0.30, 95% CI: 0.03–2.59; $p = 0.271$) has been shown. Of the 15 patients with CPR, only one reported a locoregional relapse 2 years after surgery, that was treated with radiotherapy. All the 15 patients are still alive and free of disease at the end of follow up. No statistically significant correlation was found between MPR and relapse or survival and between the delta of the pre- and posttreatment PET-CT SUV and the percentage of viable cells in the tumor bed.

4 | Discussion

ICIs targeting the PD1/PDL1 axis have been introduced in the systemic treatment of advanced/metastatic NSCLC, both in pretreated and in naive patients. First-line immunotherapy as a single agent or in combination with platinum-based chemotherapy is currently approved in our country according to the PDL1 status, showing a clinically significant improvement in overall survival with long-term benefit in selected patients [5, 16].

This treatment option represents the best choice in oligometastatic or locally advanced NSCLC not eligible to locoregional therapy upfront. The peculiar mechanism of action of ICIs

lead to new and sometimes unpredictable response patterns, which reopen a window of opportunity for lung resection in selected cases.

This multicenter retrospective experience reports one of the largest consecutive series of surgery after immunotherapy in patients with advanced stage lung disease, deemed non resectable at a first multidisciplinary tumor board. Overall, systemic treatment was well tolerated, with mostly reported AEs and irAEs of low grade without any treatment interruption.

However, the use of this "rescue" surgery raises important issues in terms of surgical feasibility, safety, and outcomes. Some concerns about the use of these drugs before surgery are related to the great tumor response and inflammation that could make surgical procedures more challenging and technically demanding.

The activation of the inflammatory system that is the pivot of ICIs action, is also responsible for the substitution of tumor tissue with fibrotic scar tissue or necrosis, making some crucial surgical steps like vessel isolation and lymph node dissection from bronchovascular structures challenging. Chaft et al. [8] first described surgical problems during hilar dissection maneuvers due to dense fibrosis related to immunotherapy response. In their pioneering experience, two of the five patients were approached with minimally invasive surgery with one conversion to thoracotomy for dense hilar fibrosis.

Similarly, Bott et al. [9] in their experience of 20 cases, started with a minimally invasive approach in 13 patients (65%), but they had to convert to thoracotomy in 7 patients (54%) because of dense, vascularized adhesions with chest wall and great vessels. Conversely, Deng et al. [17] reported a series of 51 patients previously treated with PD-1 agents and standard chemotherapy. After treatment 31 patients received surgical therapy, conducted with a minimally invasive approach and no necessity of conversion.

Our experience confirmed the feasibility and safety of this surgery. Despite some technical difficulties, no intra and postoperative morbidity and mortality were recorded. In addition, in the minimally invasive group (10 patients), no conversions to open surgery were reported. We think that this result merits to be highlighted because minimally invasive surgery in patients previously treated with ICIs could be safe and effective in skilled surgeon hands, but a careful patient selection for this type of approach is recommended.

Although some studies included minor resections, in our study only anatomical resections were performed, thus justifying the median operation time reported, anyway in line with those previously presented in the literature [18].

Historically, there are some concerns about performing pneumonectomies after induction treatment, related to high mortality rates. In our study, among patients that underwent pneumonectomies, no 30- and 90-days mortality were reported with only one postoperative pneumonia, successfully treated with antibiotics. Interestingly, in a median follow up of 12 months, a single death for COVID-pneumonia was recorded. Shu et al. reported similar results with three pneumonectomies over 26 patients (12%) and no 30 days mortality [19]. Romero Romàn et al. reported a lower rate of pneumonectomies (three patients, 7.3%) in their surgical experience after chemoimmunotherapy in locally advanced NSCLC (Stage IIIA) [20]. The slight increase in pneumonectomies in our series may be probably explained by the advanced tumor stages (IIIB or IV in 90% of cases), implying a higher probability of adenopathies infiltrating the main bronchovascular structures.

Considering the anatomical resections, the postoperative course was mostly uneventful. Compared to the SWOG S9900 trial, our results are encouraging, especially analyzing the mortality (0% vs. 20%) and the rate of reintubation (0% vs. 7%), respiratory failure (0% vs. 7%), prolonged air leaks (6% vs. 9%), and pneumonias (3% vs. 7%) [21].

The assessment of the tumor bed following the administration of ICIs in prior clinical trials has yielded noteworthy outcomes. When ICIs were integrated with chemotherapy as compared to chemotherapy alone, a significant increase in both CPR (ranging from 4.5% to 33%) and MPR (ranging from 7% to 57%) was observed [22–24]. Notably, our reported CPR and MPR rates in the salvage setting are the most elevated on record. The notable variability in the rates of CPR and MPR may arise from several factors. Patient heterogeneity, including disease stage, tumor characteristics, and prior treatments, influences responses. Thus, interpreting CPR and MPR rates requires considering trial specifics and factors influencing response rates. From the pathological perspective, more efforts should be made toward the definition of standardized criteria and guidelines for evaluating the tumor bed that will take into account the intrinsic differences for each histotype. Moreover, it's important to consider the tumor bed's role as a dynamic entity, placing greater emphasis on the tumor microenvironment. Understanding the intricate relationship between the tumor bed microenvironment and treatment response is essential for optimizing therapeutic strategies and predicting patient outcomes in NSCLC and other cancers [25].

Our study presents several limitations: first the retrospective nature; secondly, although the study population is one of the greatest for this surgical experience, it still includes a "limited" number of patients to give definitive results. Finally, different type of systemic treatment was administered in our population. For this reason, future prospective trials are necessary to confirm our results.

5 | Conclusion

Immune checkpoint inhibitors as single agents or combined with chemotherapy represent the first line standard of care in patients without actionable driver mutations metastatic or locally advanced NSCLC without indication for locoregional treatment upfront. A salvage surgery in responder patients may be considered after a careful multidisciplinary team discussion. Our preliminary results provide support for the feasibility and safety of these therapeutic strategies. This "window of opportunity" represents the next logical step, building on recent findings regarding the use of immune checkpoint inhibitors in

the initial treatment of resectable NSCLC, and in line with upcoming clinical trials that will also include cases of borderline resectable disease.

Author Contributions

Conceptualization: Marco Schiavon, Giorgio Cannone, Giulia Pasello, and Federica Pezzuto. Data curation: Giorgio Cannone, Marco Schiavon, Giulia Pasello, Alessandra Ferro, Filippo Tommaso Gallina, Luca Bertolaccini, Federica Pezzuto, and Fares Shamshoum. Formal analysis: Giulia Lorenzoni and Dario Gregori. Funding acquisition: None. Investigation: Federico Rea, Marco Schiavon, Lorenzo Spaggiari, Francesco Facciolo, Giulia Pasello, Fiorella Calabrese, Federico Cappuzzo, Paolo Visca, Filippo De Marinis, and Valeria Midolo. Methodology: Marco Schiavon, Giulia Pasello, Federico Rea, Francesco Facciolo, Lorenzo Spaggiari, Giorgio Cannone, Filippo Tommaso Gallina, Luca Bertolaccini, Alessandra Ferro, and Fares Shamshoum. Project administration: Federico Rea, Marco Schiavon, Giulia Pasello, Lorenzo Spaggiari, Francesco Facciolo, Fiorella Calabrese, Federico Cappuzzo, Paolo Visca, Filippo De Marinis, and Valeria Midolo. Resources: None. Softwares: Giulia Lorenzoni and Dario Gregori. Supervision: Marco Schiavon, Giulia Pasello, Federico Rea, and Fiorella Calabrese. Validation: All the authors. Visualization: Marco Schiavon, Giulia Pasello, Giorgio Cannone, Luca Bertolaccini, Filippo Tommaso Gallina, and Federica Pezzuto. Writing–original draft: Marco Schiavon, Giulia Pasello, Giorgio Cannone, and Federica Pezzuto. Writing–review and editing: All the authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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