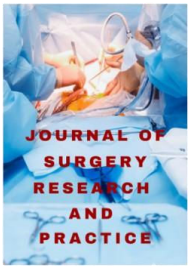

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Research Article

Chemoimmunotherapy for Patients with Resectable Non-Small Cell Lung Carcinoma: Real-World Data Analysis from a Surgical Point of View

Niels Michael Dörr-Jerat[1,2*], Miriam Möller[3], Stanislav Hajduch[1], Claus Jürgen May[1], Stephan Eisenmann[4], Wolfgang Schütte[3], Kevin Rudolph[5], Marcus Krüger[1,2]

[1]Department of Thoracic Surgery, Martha - Maria Hospital Halle - Dölau, Halle (Saale), Germany
[2]University Hospital Halle. Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[3]Department of Pneumology, Martha - Maria Hospital Halle - Dölau, Halle (Saale), Germany
[4]Department of Pneumology, University Hospital Halle, Halle (Saale), Germany
[5]Department of Neurosurgery, BG Klinikum Bergmannstrost, Halle, Halle (Saale), Germany

***Correspondence author:** Niels Michael Dörr-Jerat, Department of Thoracic Surgery, Martha - Maria Hospital Halle - Dölau, Halle (Saale), Germany and University Hospital Halle. Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; Email: nielsdoerr@gmail.com

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Abstract

Background: Neoadjuvant treatment with Chemoimmunotherapy (CIT) for patients with Non-Small Cell Lung Carcinoma (NSCLC) is a rapidly growing area of interest. Currently, several ongoing trials with varying designs are in progress, and the first immune checkpoint inhibitors are approved by the European Medicines Agency. Moreover, surgeons are facing new challenges associated with this innovative approach.

Methods: We retrospectively reviewed the medical records of 18 patients who underwent neoadjuvant CIT before surgery for NSCLC between September 2019 and June 2024 at our institution. We ensured a minimum follow-up of 90 days.

Results: Neoadjuvant CIT and oncological resection of NSCLC were administered to eight women and ten men. The median age was 65 years (range: 52-80 years). A total of 56% (n=10) of the patients had adenocarcinoma, and 44% had squamous cell carcinoma. A total of 56% of the patients presented with UICC stage IIIA disease (n=10), while 33% had stage >IIIA disease (n=6). The mean initial tumor size was 55 mm. Nivolumab (plus platin-based chemotherapy) was administered to 61% of the patients (n=11), 28% received pembrolizumab, 6% received cemiplimab, and 6% received atezolizumab. Restaging of the chest via computed tomography revealed stable disease in 56% of the patients, a partial response in 33%, and progressive disease in 11%. The mean surgical delay was 117 days. In 67% of the patients, the surgical approach was thoracotomy (n=12), while 33% underwent VATS (n=6). Five patients (28%) were converted; thus, the conversion ratio of the minimal approach was 45%. Sixteen patients (89%) had tumor-free margins (R0). The median hospital stay was 9 days (range: 7-77). Pathologists confirmed downstaging in 61% (n=11) of the patients. A complete pathological response was achieved in 33%, a major pathological response in 22%, and a pathological response in 33%. Based on the Clavien–Dindo classification, 28% of the patients had no surgical complications (n=5). Grade I occurred in 28%, grade II in 33%, grade III in 6%, and grade IV in 6% of the patients. No patients died within 90 days after surgery. All patients were alive according to the latest follow-up.

Conclusion: Oncologic lung resection after neoadjuvant CIT may be challenging but feasible. As visualization of the CIT response is still very limited, our data support surgical exploration after neoadjuvant CIT.

Keywords: Surgery; Lung Cancer; Immunotherapy; Resectability; Response

Abbreviations

AE: Adverse Events; CIT: Chemoimmunotherapy; COVID-19: Coronavirus Disease; cPR: Complete Pathological Response; CT: Computed Tomography; ctDNA: Circulating Tumor DNA; EMA: European Medicines Agency; IASLC: International Association for the Study of Lung Cancer; IT: Immunotherapy; mPR: Major Pathological Response; NSCLC: Non-Small Cell Lung Carcinoma; OS: Overall Survival; PD: Progressive Disease; PD-1: Programmed Death 1; PD-L1: Programmed Death-Ligand 1; pPR: Partial Pathological Response; PR: Partial Response; RECIST: Response Evaluation Criteria in Solid Tumors; RFS: Recurrence-Free Survival; SD: Stable Disease; SR: Survival Rate; UICC: Union for International Cancer Control; VATS: Video-Assisted Thoracoscopy

Introduction

The global burden of cancer has a dramatic impact and is dynamic. According to the Global Burden of Disease 2019 Cancer Collaboration, cancer was second only to cardiovascular diseases in terms of the number of deaths, years of life lost, and cancer-related disability-adjusted life years in 2019 [1]. In Germany, lung cancer is the third most common malignancy in women and the second most common malignancy in men. The 5-year Survival Rate (SR) is comparatively poor. Only 25% of females and 21% of males survive the first 5 years after diagnosis of lung cancer [2]. Approximately 80% of all malignant lung tumors are Non-Small Cell Lung Cancer (NSCLC) [3].

NSCLC is the leading cause of cancer-related mortality [4]. However, compared with rapidly developing therapeutic options, early-stage NSCLC has a lower impact on the SR. According to Pignon et al., the 5-year SR of patients with NSCLC improves by only 5% with standard-of-care platin-based chemotherapy [5]. Due to the high burden of NSCLC and the poor improvement in survival outcomes, efforts to develop novel strategies are warranted. Thus, multiple neoadjuvant trials of immunotherapy, either alone or in combination with platin-based chemotherapy, have been launched.

Neoadjuvant immunotherapy (IT) can improve the SR for both early and advanced NSCLC [6, 7]. Systemic therapy before surgery offers in vivo assessment, improved delivery of drugs to tumors, earlier treatment of micrometastatic disease, and downstaging before local therapy [8]. Additionally, patients are more likely to receive planned systemic therapy and may be in better physical and mental condition than are those who have undergone upfront oncologic lung surgery [9, 10].

Studies in breast [11] and skin cancer [12] suggest that treating treatment-naive cancers with neoadjuvant IT elicits a better immune response than adjuvant therapy once the tumor is removed. These findings are supported by research that specifically examines the use of neoadjuvant IT for NSCLC [13]. Additionally, neoadjuvant IT has the potential to enhance the immune system's ability to combat tumors in resectable NSCLC by modifying T cells and B cells in the vicinity of the tumor. This could have a noteworthy effect on Recurrence-Free Survival (RFS) [14].

CheckMate 816 (Bristol Myers Squibb; NCT02998528) is a randomized phase III trial that includes patients with resectable NSCLC (stage IB-IIIA). The study compared neoadjuvant therapy with the Programmed Death 1 (PD-1) monoclonal antibody nivolumab plus platinum-based chemotherapy to neoadjuvant therapy with platinum-based chemotherapy alone. Patients who underwent neoadjuvant treatment with nivolumab plus platinum-based chemotherapy had significantly longer event-free survival and a more frequent complete Pathological Response (cPR). Treatment did not result in a considerable increase in inoperability or any therapy-related complications [15]. Based on the findings of CheckMate 816, nivolumab was approved by the European Medicines Agency (EMA) for the neoadjuvant therapy of resectable NSCLC patients with a high risk of recurrence (size ≥5 cm; N+ status) and PD-L1 expression ≥1%. In addition, based on the positive results of the Keynote 671 study (Merck Sharp & Dohme LLC; NCT03425643), perioperative therapy with pembrolizumab was approved in 2024 for the treatment of resectable NSCLC patients with a high risk of recurrence. This means that two neoadjuvant treatment options with chemoimmunotherapy (CIT) for resectable NSCLC are currently available outside of clinical trials [16].

Several other ongoing trials with varying designs are currently in progress, as shown in Table 1. Their conclusive findings are eagerly anticipated. Moreover, surgeons are currently contending issues seemingly linked to the use of IT. Our study examined these aspects in a case series of patients who underwent oncologic lung resection for NSCLC after neoadjuvant CIT at our institution.

Methodology

We retrospectively reviewed the medical records of 18 patients who underwent neoadjuvant chemoimmunotherapy before surgery for NSCLC between September 2019 and June 2024 at our institution. We performed a minimum follow-up of 90 days. We closed inclusion in September 2024. The inclusion criteria were as follows: (1) Patients between 18 and 99 years of age who received preoperative CIT prior to resection of NSCLC.

Treatment decisions were made on the basis of an interdisciplinary tumor conference before and after CIT, as well as after surgery. The Clavien–Dindo classification was used to rank postoperative complications in an objective and reproducible manner.

Radiological responses to CIT were evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). The longest diameter of each target lesion was manually measured by radiologists on an axial CT image plane using calipers, a PACS measurement tool. According to the International Association for the Study of Lung Cancer (IASLC), a major pathological response was defined as less than or equal to 10% of viable tumor, and a complete pathological response was defined as no viable tumor [17].

RFS was defined as the time from the day of tumor surgery to the date of the first documented disease recurrence. Overall Survival (OS) was defined as the time from the date of cancer diagnosis to the date of death, irrespective of the cause of death. The minimum follow-up time was 90 days after surgery.

Results

Patient Characteristics

A total of 18 patients (8 women and 10 men) underwent both neoadjuvant CIT and oncological lung resection for NSCLC. The median age at the time of surgery was 65 (range: 52-80) years. Eight (44%) tumors were right-sided, and ten (56%) were left-sided. Based on the 8th edition of the TNM classification, ten (56%) patients presented initially with UICC stage IIIA disease. Six (33%) patients had advanced NSCLC (stage >IIIA), two (11%) had UICC stage IIIB NSCLC and four (22%) had UICC VI (evidence of metastases). The average tumor size before CIT was 58 mm (σ 25.89). Overall, ten (56%) patients presented with adenocarcinoma, and eight (44%) had squamous cell carcinoma. Eleven (61%) patients received nivolumab (plus platinum-based chemotherapy), one (6%) patient received atezolizumab, one (6%) patient received cemiplimab, and five (28%) patients received pembrolizumab. A total of 78% of the patients received the planned CIT. The mean time between the diagnosis of NSCLC and surgery was 117 days (σ 23.91). A radiological response according to computed tomography (CT) after CIT was documented in 33% of the patients. In six (33%) patients, video-assisted thoracoscopy (VATS) was performed. An open approach per thoracotomy was needed in twelve (67%) patients. The conversion ratio of the minimal approach was 45%. Lobectomy, bilobectomy, atypical resection and additional chest wall resection (including rip dissection) were performed for 15 (83%), 2 (11%), 1 (6%), and 3 (17%) patients, respectively. Pneumonectomy was not performed. In four (22%) patients, atypical resection was necessary in addition to lobectomy. The median length of hospital stay was 9 days (range: 7-77). The baseline characteristics are shown in Table 2.

Efficacy

According to the results of restaging, upon initial ICI treatment, six (33%) patients achieved partial response (PR), and ten (56%) achieved Stable Disease (SD). Two patients (11%) presented with Progressive Disease (PD). cPR was achieved in six patients (33%), major pathological response (mPR) was achieved in four patients (22%), and partial Pathological Response (pPR) was achieved in six patients (33%). Two patients (11%) were nonresponders (Fig. 1). According to the RECIST and UICC criteria, both patients had stable stage IIIA adenocarcinoma after nivolumab-based CIT. According to the pathological examination, both patients with clinical progressive disease had pseudoprogression. One of those patients with pseudoprogressive disease had pancost tumors >10 cm in diameter. This patient achieved a pPR without downstaging according to the UICC. Downstaging was achieved in 11 patients (61%). Interestingly, all included patients (n=7) with clinical N2-status presented with ypN0-status afterwards. Tumor-free margins were achieved in all but two patients (89%). The R1-margin was at the chest wall resection in both patients. Thus, adjuvant radiation was recommended.

The mean follow-up was 413 days (σ 448.31). Two patients experienced recurrence approximately 6 months after lung surgery despite adjuvant therapy. One of these patients experienced cerebral recurrence of her resected metastasis. A female patient with

adenocarcinoma of the left upper lobe of the lung with solitary cerebral metastases received neurosurgical treatment and 2 cycles of neoadjuvant CIT (pembrolizumab, pemetrexed and carboplatin). SD was achieved by neoadjuvant therapy. Lung resection was performed 4 months after diagnosis. The patient was treated with adjuvant CIT, which was discontinued due to CIT-induced adverse events. Cerebral recurrence was diagnosed 6 months after lung surgery and 10 months after diagnosis.

The other female patient with central T4 adenocarcinoma of the right upper lobe of the lung underwent postoperative radiotherapy due to ypN2 disease after neoadjuvant CIT (nivolumab, pemetrexed and carboplatin) and extensive surgery, including upper bilobectomy. She was diagnosed with contralateral recurrence with numerous metastases (M1a) 6.5 months after lung surgery (Fig. 2). All included patients were alive at the time of the latest follow-up.

Safety

CIT-induced Adverse Events (AEs) (intestitial lung disease, enterocolitis, polyneuropathy, thyroiditis, pruritus, herpes genitalis, etc.) are relevant issues. However, AEs (such as anemia, pancytopenia, granocytemia, mucositis, etc.) were more frequently attributable to platin-based chemotherapy than to IT. Therefore, a change in the planned procedure (e.g., number of cycles) cannot automatically be attributed to IT. However, 78% (n=14) of the patients received the planned CIT.

The mean duration of surgery was 262 minutes (σ 99,73). Conversion from VATS to an open approach via thoracotomy was needed in five patients (26%), for a conversion ratio of 45%. However, eight patients (53%) underwent initial thoracotomy because of tumor size or local infiltration. Common surgical complications were hemorrhage or anemia (with need for blood transfusion), pneumonia, prolonged air leakage, delirium and pain. Five patients (33%) were treated without any complications. According to the Clavien–Dindo classification, Grade I, II, III, and IV surgical complications were recorded in 27%, 27%, 7%, and 7%, respectively. One patient with a Grade IV complication needed retransfer to the ICU because of nosocomial COVID-19 infection and the need for reintubation. In the course of the disease, recurrent pleural effusion required thoracic drainage; unfortunately, surgical revision was subsequently performed due to a hematothorax. A Grad III complication was considered a prolonged air leakage. After pleurodesis with doxycycline, the air leakage persisted, and surgical revision was mandatory. The median length of stay was 8.5 days (range 7-77). However, due to COVID-19 infection, the maximum length of stay was 77 days. No patient died during inpatient treatment. The 90-day survival rate was 100%.

Patient 1 - PD-L1 neg. NSCLC

However, we observed a complete pathological response in PD-L1-negative NSCLC patients treated with nivolumab-based CIT. In our study, we included one female patient with a PD-L1-negative high-grade adenocarcinoma of the right upper lobe of the lung. After a remarkable delay of 7 months due to nivolumab-based CIT, immune-related AEs (hyperthyroidism) and hyperthyroidism treatment, despite poor radiological response, right upper VATS lobectomy was performed without perioperative complications. The patient was discharged from the hospital on the 7th postoperative day. A complete pathological response was achieved; furthermore, all the resected nodes (n=17) lacked evidence of vital tumor tissue. The patient is alive without evidence of recurrence (follow-up 420 days). All (n=10) but two included patients with major (n=1) or complete pathological response (n=1) were also PD-L1 positive/TPS >5% ($\chi^2(1) = 2.80$, $p = 0.094$, $\varphi = 0.45$). Two patients with recurrent disease thus far were PD-L1 negative (TPS <5%), and pathological examination revealed a minor response to CIT.

Patient 2 - distant lymph node metastases

One of our patients had PD-L1 positivity. advanced squamous cell carcinoma of the left upper lobe of the lung. The patient presented with evidence of mediastinal and abdominal lymph node metastases as well as synchronous colon carcinoma. After hemicolectomy, he was treated with 3 cycles of neoadjuvant CIT before VATS lobectomy. Leukopenia and enterocolitis with ulceration occurred within the CIT. However, the patient was discharged 7 days after lung surgery. A complete pathological response was reported. The patient is alive without evidence of recurrence (follow-up 378 days).

Patient 3 - Downstaging

One of our cases illustrates the challenge of resectability assessment very well. A female patient with a large, nodal positive adenocarcinoma of the right lower lobe with suspected pericardial and chest wall infiltration received 3 cycles of CIT (pembrolizumab, carboplatin, pemetrexed). The restaging after CIT showed SDs in the CT scan. We decided to treat the otherwise young and healthy patient. Extended lobectomy of the left upper lobe with extrapleural chest wall release, additional atypical resection of segment VI, intrapericardial vascular preparation and partial resection of the pericardium were performed via

thoracotomy. Pathological examination revealed pPR, tumor-free margins and downstaging from clinical UICC stage IIIA to pathological IB. After 8 days, the patient was discharged and was alive without recurrence (follow-up 762 days).

Patients 4 and 5 - Response evaluation

A patient with a large right-sided T4 pancost tumor (max diameter 105 mm) with UICC stage IIIA who received nivolumab-based CIT. After two cycles, a CT scan was performed. Due to progressive disease (max. diameter 150 mm), tumor mass reduction was mandatory (Fig. 3). Thoracotomy with lobectomy and advanced chest wall resection was performed. Pathological examination revealed tumor-free margins and a PR. The patient is alive without evidence of recurrence (follow-up 680 days).

In comparison, another patient with a right-sided T4 tumor in the lower lobe (max. diameter 112 mm) with UICC stage IIIA disease received 3 cycles of nivolumab-based CIT. Restaging resulted in stable disease. Thoracotomy via bilobectomy, intrapericardial vascular preparation, partial resection of the pericardium, including removal of mediastinal fatty tissue and resection of the phrenic nerve as well as the azygos vein, was needed to achieve tumor-free margins. However, pathological assessment revealed UICC IIIB disease due to ypN2 status (4/15) without a pathological response to CIT. After 6.5 months, contralateral metastasis was diagnosed (follow-up 270 days). The patient received second-line therapy with sorafenib (Fig. 2). Both patients were relatively young (<65 years) and healthy and underwent high-risk surgery because of formally resectable NSCLC.

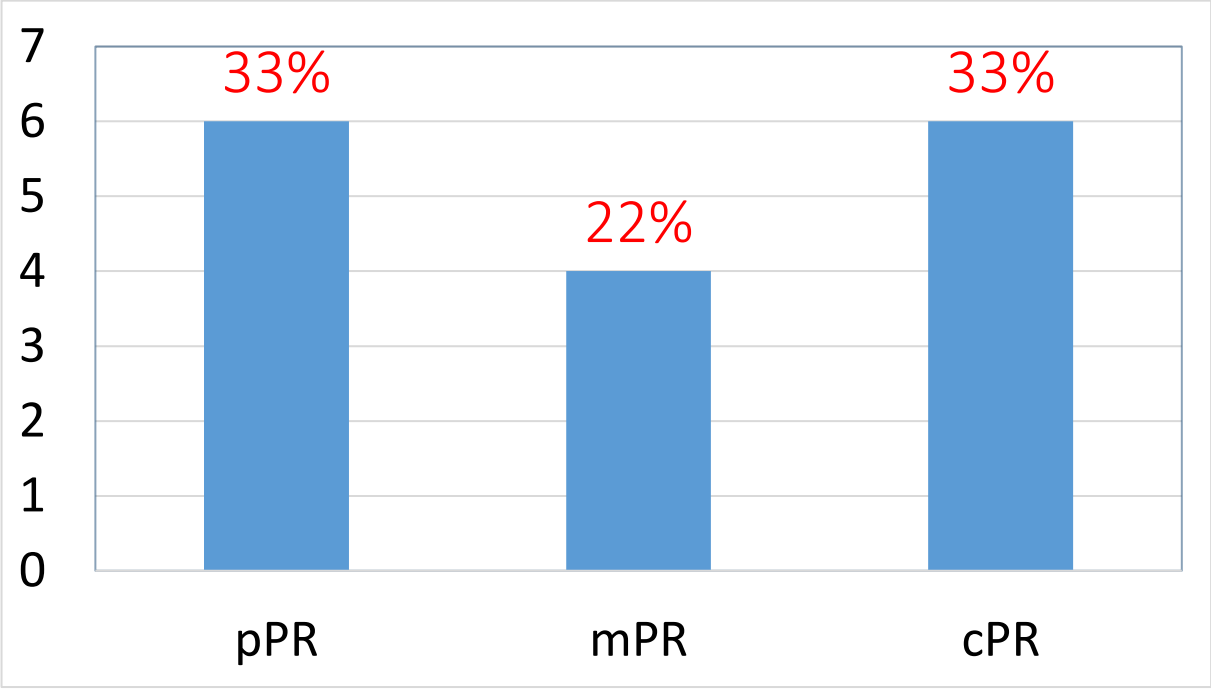

Figure 1: Regression grading according to the IASLC. pPR: partial Pathological Regression; mPR: major Pathological Regression; cPR: complete Pathological Regression; IASLC: International Association for the Study of Lung Cancer.

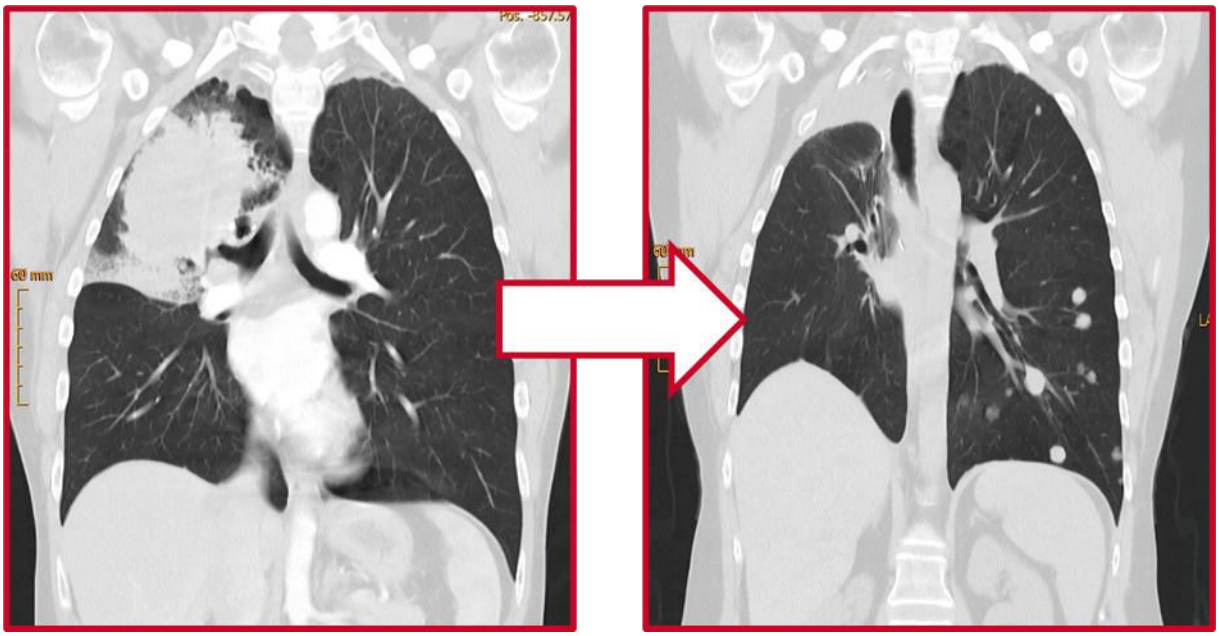

Figure 2: Recurrence after upper bilobectomy. CT scans before oncologic lung resection for NSCLC and of 1st follow- up showing contralateral recurrence 6.5 months after multimodal approach with neoadjuvant nivolumab-based CIT, advanced right-sided upper bilobectomy and adjuvant mediastinal radiation.

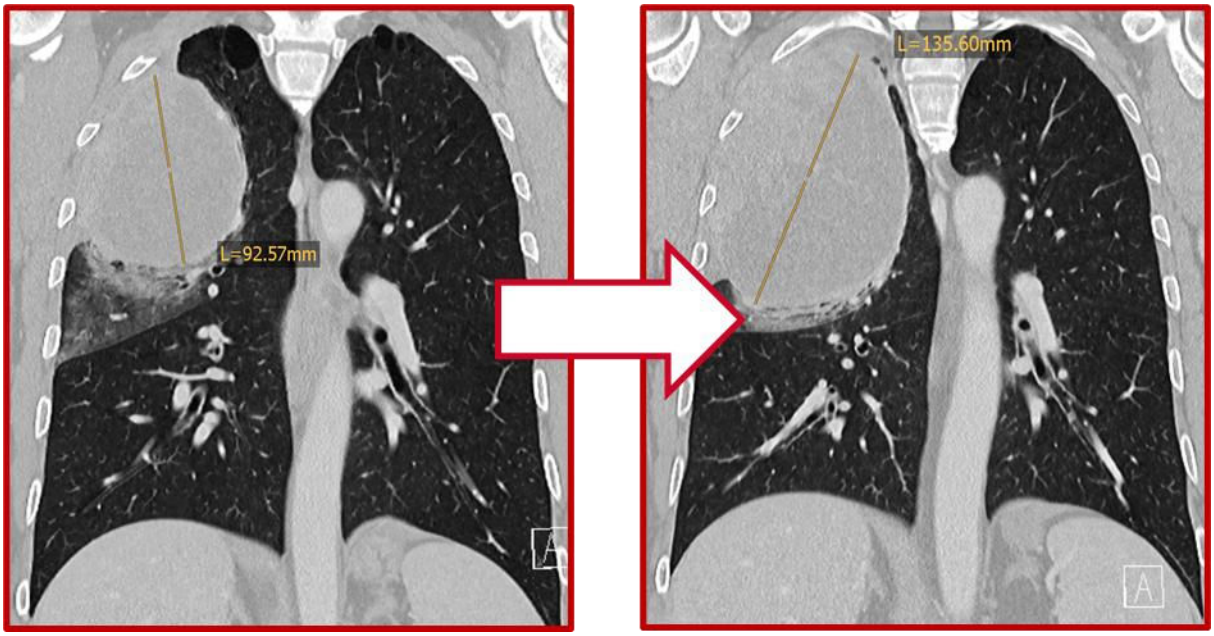

Figure 3: Pseudoprogression. CT scan before CIT with evidence of a T4- NSCLC of the right upper lobe. According to the RECIST 1.1 criteria, the CT scan shows progressive disease after two cycles of nivolumab-based CIT. The pathological examination reveals a pseudoprogression.

Trail	Phase	Enrollment	Neoadjuvant Agents	No.	Reference
CheckMate 816	3	505	Nivolumab + platinum-based chemotherapy	NCT02998528	Forbe 2022 N Engl J Med.
LCMC3	2	181	Atezolizumab monotherapy	NCT02927301	Chaft 2022 Nat Med.
NEOSTAR	2	82	Camrelizumab + platinum-	NCT04379739	Liu 2023 Cancer

			based chemotherapy		Immunol Immnother
Keynote-671	3	786	Pembrolizumab + platinum-based chemotherapy (Neoadjuvant/Adjuvant)	NCT03425643	Wekelee 2023 N Engl J Med.
AEGEAN	3	826	Durvalumab + platinum-based chemotherapy (Neoadjuvant/Adjuvant)	NCT03800134	Hejmach 2023 N Engl J Med.
Neotorch	3	501	Toripalimab + platinum-based chemotherapy	NCT04158440	Shun Lu 2023 ASCO
Empower- Lunge 1	3	712	Cemiplimab monotherapy	NCT03088540	Sezer 2021 Lancat

Table 1: Clinical trials on perioperative chemoimmunotherapy.

Characteristics	
Age, years Median (range)	65 (52-80)
Age groups, n (%) < 65 ≥ 65	 8 (44) 10 (56)
Sex, n (%) female	 8 (44)
ECOG score, n (%) 0 1 2	 14 (78) 2 (11) 2 (11)
Histological subtypes, n (%) Adenocarcinoma Squamous cell carcinoma	 10 (56) 8 (44)
Staging, n (%) ≤ IIIA > IIIA	 12 (67) 6 (33)
PD-L1 expression, n (%) < 1% 1-49% ≥ 50% unknown	 4 (22) 6 (33) 4 (22) 4 (22)
IT, n (%) Nivolumab Atezolizumab Cemiplimab Pembrolizumab	 11 (61) 1 (6) 1 (6) 5(28)
Chemotherapy, n (%)	
Carboplatin	17 (94)
Cisplatin	1 (6)
Clinical response, n (%) PD SD	2 (11) 10 (56) 6 (33)

PR CR	0
Surgical approach, n (%) VATS Thoracotomy	 7 (29) 11 (61)
Surgical extent, n (%) Only atypical resection Lobectomy Bilobectomy Additional atypical resection Chest wall resection	 1 (6) 15 (83) 2 (11) 4 (22) 3 (26)
CR: Complete Response; ECOG: Eastern Cooperative Oncology Group; IT: Immunotherapy; PD: Progressive Disease; PD-L1: Programmed Death-Ligand 1; PR: Partial Response; SD: Stable Disease; VATS: Video-Assisted Thoracoscopic Surgery.	

Table 2: Baseline characteristics.

Complete Response (CR)	Disappearance of all lesions and pathologic lymph nodes
Partial Response (PR)	≥ 30 % decrease in the sum of the longest diameter
Stable Disease (SD)	Neither PR nor PD
Progressive Disease (PD)	≥ 20 % increase in the sum of longest diameters with an absolute increase of ≥ 5 mm, or new lesions

Table 3: Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Discussion

PD-L1 Status

Nivolumab is the first immune checkpoint inhibitor approved by the European Medicines Agency (EMA) for the neoadjuvant therapy of resectable NSCLC patients with a high risk of recurrence (size ≥5 cm; N+ status) and a tumoral PD-L1 expression ≥1%. The approval for PD-L1-positive NSCLC patients was based on subgroup analysis of the Checkmate816 trial. Across the PD-L1 subgroups, CIT was shown to be beneficial. Moreover, the use of PD-L1 expression as an immune checkpoint inhibitor biomarker is particularly controversial. Indeed, numerous trials have demonstrated the efficacy of IT in patients with PD-L1-negative tumors [18]. According to the Danish cohort study published 2021 by Cronin-Fenton et al., tumoral PD-L1 expression in stage III unresected NSCLC tumors was not associated with OS or disease progression. However, PD-L1 expression in tumor-infiltrating immune cells and the extent of PD-L1 expression in tumors are associated with survival benefit [19]. Other authors argue that the combination of immunotherapy with platinum-based chemotherapy in the first-line setting is beneficial regardless of the tumoral PD-L1 status [20]. For example, in 2024, Sorin et al published a systemic review and meta-analysis that included 8 randomized clinical trials. The author's findings suggest that even patients with resectable NSCLC with tumor PD-L1 levels <1% may have an event-free survival benefit from neoadjuvant chemoimmunotherapy [21]. Even true, the methods and assays used for the assessment of PD-L1 expression via immunohistochemistry are variable, and tumoral PD-L1 expression appears to be highly heterogeneous. Some studies have shown higher PD-L1 expression in immune cells than in tumor cells, even in the same tumor region [22]. Treatment-related adverse events and treatment discontinuation are related to CIT. Thus, indications for CIT need further research addressing biomarkers other than the tumoral PD-L1 status. From a surgical perspective, we recommend safe decision-making at the individual patient level. Consequently, since numerous publications [23, 24] have shown the safety of immunotherapy in the neoadjuvant setting, indications, such as the tumoral PD-L1 status, should not be made on a currently uncertain basis. In addition to other biomarkers, further treatment individualization in the sense of multimodal neoadjuvant therapy could also improve patient outcomes. Since 2024, perioperative pembrolizumab has been approved by the EMA for resectable NSCLC without limitations based on PD-L1 expression (16). However, Peng et al. emphasized the benefits of nivolumab plus ipilimumab plus chemotherapy for NSCLC patients with PD-L1-negative expression, and nivolumab plus chemotherapy plus bevacizumab both appear to be the most effective therapeutic strategies for this population [25]. However, further research comparing treatment options in PD-L1-negative patients is needed.

Assessment of Resectability

Advanced tumors are more likely to need thoracotomy than smaller localized tumors are. The median tumor size in the VATS subgroup was 53 cm (range 26-71) versus 63 cm (range 9-112) in the thoracotomy subgroup. We included six patients with advanced NSCLC (≥ UICC stadium IIIA). Three patients presented with distant metastases (pulmonal and cerebral), one with abdominal lymph node metastasis. Two patients had UICC stage IIIB disease because of cN2 disease. All patients with distant metastases underwent local metastasectomy before thoracic surgery. Despite adjuvant IC with pembrolizumab, one of these patients presented with local recurrence of cerebral metastasis 12 months after diagnosis of NSCLC and 6 months after lung surgery. Consequently, three other patients are alive without recurrence despite having advanced disease. One of those patients had PD-L1 positivity. advanced squamous cell carcinoma of the left upper lobe of the lung. The patient presented with evidence of mediastinal and abdominal lymph node metastases as well as synchronous colon carcinoma. After hemicolectomy, he was treated with 3 cycles of neoadjuvant CIT before VATS lobectomy. Leukopenia and enterocolitis with ulceration occurred within the CIT. However, the patient was discharged 7 days after lung surgery. A complete pathological response was reported.

A total of 39% (n=7) of our patients had a cN2 status. Patients with traditionally advanced NSCLC with distant metastases or contralateral lymph node metastases (cN3 status) were excluded from curative resection. According to Raman et al., surgery as part of a multimodal approach in clinical N3-stage NSCLC is associated with similar or worse short-term but improved long-term survival compared with chemoradiation. Thus, in a selected group of patients with N3-stage NSCLC, surgery may be useful in a multimodal therapy setting [26]. No patients with N3 carcinoma were included in our study. However, all included clinical N2-stage NSCLC patients had pathological ypN0-carcinoma ($\chi^2(4) = 3.49$, $p = 0.479$, $\varphi = 0.44$) with at least a major pathological response ($\chi^2(2) = 4.55$, $p = 0.103$, $\varphi = 0.50$).

Our findings demonstrated that CIT in patients with locally advanced potentially resectable NSCLC, followed by major oncologic lung resection, may be a beneficial approach. Peer et al. emphasized that preneoadjuvant bulky mediastinal disease (lymph nodes > 20 mm), persistent postoperative N2 disease, R1 resection, preoperative N2 multistation disease and postoperative stage IIIA emerged as negative predictive factors for patients with major oncologic lung resection after neoadjuvant chemotherapy or chemoradiation in potentially resectable stage III NSCLC [27]. However, further research is needed to determine the relevance of preneoadjuvant bulky mediastinal disease, preoperative clinical N2 multistation disease and N3-stage NSCLC after neoadjuvant CIT. However, the variability of patients included in randomized trials limits the ability to combine results across studies and thus limits the strength of recommendations in many ways [28]. Patient safety should be considered when deciding on indications. Although the statement is arbitrary, Daly et al. recommend oncologic lung resection in the context of multimodal treatment approaches for advanced stage III NSCLC only in departments with perioperative mortality ≤5% [29]. Early evidence suggested that surgery after neoadjuvant CIT is feasible and can be performed safely [6], although surgery may be more complex and challenging than usual, and we do not yet know the impact of a general change in the indication for surgery in the CIT setting beyond stage IIIA NSCLC.

Response Evaluation

Changes in tumor burden after CIT were termed the response. The radiological response criterion (called the Response Evaluation Criteria in Solid Tumors [RECIST]) before surgery (Table 3) obtained by CT scans was distinguished from the pathological response achieved by the pathological examination of the tumor itself. Treatment-induced response is used as a surrogate of survival [30]. Thus, criteria for defining response to treatment are crucial. Thoracic surgeons need to know how to address the discordance between postoperative pathological and preoperative radiological responses obtained via CT scans. The challenge is to find a priori features that can distinguish pseudoprogression from progressive disease. Thus, we are able to determine whether the risk of extensive tumor resection is justified and which patients may not benefit from surgery.

During CIT, lesions may present a large spectrum of heterogeneous responses that vary in terms of form, timing, and duration. If the tumor enlarges before shrinking, this process is known as pseudoprogression (pPD). pPD is typically associated with the activation of tumor-infiltrating lymphocytes [31]. Another described effect, called “nodal immune flare”, also results in pPD. This radiological nodal progression is based on immune cell infiltration and granulomas, without evidence of malignancy on pathological examination [32]. Thus, the RECIST criteria are limited in their ability to predict patient response [33] and might underestimate the benefit of CIT [34].

According to the 2019 meta-analysis published by Lu et al., tissue assessment of PD-L1 was the best response biomarker for predicting response to checkpoint blockade [35]. Currently, we know that the expression of a biomarker is heterogeneous, comprising only a part of the whole population, and provides a snapshot, which therefore does not correspond to reality or tumor biology. Furthermore, tissue biopsy is an invasive diagnostic test with inherent risk. Research on biomarkers such as circulating tumor DNA (ctDNA), circulating HLA-DRlow monocytes or dendritic cells and radiomics are promising features for overcoming this gap [36-38]. Yue et al. emphasized the high concordance between ctDNA and pathological response. The authors also set out to determine the prognostic value of perioperative ctDNA levels in predicting recurrence [36]. An alternative approach to predicting response is to analyze the patient's microbiome to monitor the response to CIT [39]. We included a male patient in our series who needed lower bilobectomy with chest wall resection for right-sided central NSCLC despite a partial response to CIT (ca. 30% increase in tumor size). According to the pathological assessment, there was evidence of a complete pathological response (no vital tumor). The patient is alive without recurrence after almost 5 years of follow-up. We currently do not know whether these patients or comparable patients would have an equivalent oncological outcome with a less extensive surgical procedure. Currently, surgery is indispensable. An ambitious goal will be to identify patients with NSCLC who will benefit entirely from avoiding local therapy.

Conclusion

Until the total neoadjuvant CIT for NSCLC in selected patients is part of clinical practice, surgery remains a prerequisite for improving the prediction and meaning of response rates as an endpoint of upcoming research. Thus, we recommend exploration whenever feasible and safe. Because operations after CIT are often more challenging than upfront surgery, oncologic lung resection should be performed by an experienced thoracic surgeon in high-volume departments with low perioperative mortality.

Conflict of Interest

The authors declare no conflict of interest.

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Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The ethics committee of the medical chamber of the state of Saxony-Anhalt (Headquarter Dessau-Rosslau) approved the study protocol (approval number: 66/23). Written and informed consent was obtained for the conduct of the study with anonymous clinical data analysis.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author's Contribution

NMDJ analyzed and interpreted the patient data and wrote the manuscript; MM analyzed and interpreted the patient data and wrote the manuscript; SH and CJM operated on the patients and supervised the perioperative course; SE and WS supervised and indicated immunotherapy; and KR advised on the preparation of the statistics. MK supervised the whole interpretation and writing process, operated the patients and supervised the perioperative course.

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