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Efficacy and Surgical Complexity of Neoadjuvant Chemo-Immunotherapy for Locally Advanced Non-Small Cell Lung Cancer

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Abstract

Introduction: The efficacy of immune checkpoint inhibitors (ICIs) in combination with platinum-based chemotherapy before surgery in patients with locally advanced resectable non-small cell lung cancer has been shown. However, cases of unresectability due to progression of disease or adverse events have been reported, as well as cases of conversion to open thoracotomy, often due to hilar inflammation and fibrosis.

Methods: Patients with locally advanced non-small cell lung cancer who received preoperative therapy between 2013 to 2025 were retrospectively studied. We analyzed the course of preoperative therapy, operative findings, and pathological responses.

Results: There was no significant difference in the proportion of open thoracotomy (62.5% vs 60.8%) or postoperative complications (50% *vs* 42%) between the chemo-immunotherapy (CIT) group and the non-ICIs group, whereas adhesion or fibrosis around lesions tended to be higher in the CIT group (62.5% *vs* 43.4%). In patients with neoadjuvant therapy, a major pathological response was significantly more frequent in squamous cell carcinoma (SCC) than in non-SCC (29% vs 0%), and in SCC treated by chemoradiotherapy (40% *vs* 0%). Furthermore, the frequency of a complete pathological response tended to be higher in SCC (36% *vs* 12%) and in SCC treated by CIT (50% *vs* 0%).

Conclusion: Although CIT might increase the surgical complexity, its surgical outcomes are similar to those in patients without ICIs. CIT and chemoradiotherapy may have a therapeutic effect in patients with locally advanced SCC, whereas CIT might not be appropriate for patients with locally advanced non-SCC.

Trial registration: The Institutional Review Board of Kanazawa Medical University approved the protocol of this retrospective study (approval number: I392), and written informed consent was obtained from all patients.

Keywords: Neoadjuvant therapy; Chemo-immunotherapy; Surgical complexity; Non-small cell lung cancer

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Introduction

The efficacy of immune checkpoint inhibitors (ICIs) in combination with platinum-based chemotherapy before surgery in patients with locally advanced resectable non-small cell lung cancer (NSCLC) has been shown in several recent trials [1-3]. In these trials, neoadjuvant chemotherapy with ICIs, including antibodies against programmed death-1 and programmed death-ligand 1, showed the potential to improve progression-free survival and overall survival. Neoadjuvant ICI therapy has the potential advantage of exposure to the whole tumor–antigen repertoire, which leads to a broader and more diverse immune response. Although the immune response has potentially improved micro-metastases and the outcome, there may be a delay to resection and an increase in intraoperative complexity and postoperative morbidity or mortality [4]. The rate of intraoperative unresectability due to progression of disease in trials have been reported to be 0% to 5% for neoadjuvant ICI therapy and 0% to 10% for neoadjuvant chemotherapy with ICIs [5]. The rate of conversion from video-assisted thoracic surgery to open thoracotomy, often because of hilar inflammation and fibrosis, ranges from 17% to 54% [6-8]. Furthermore, 1- and 3-year survival analyses showed that a longer delay to surgery increased mortality compared with a shorter delay, and the overall oncological outcome may be affected by the timing of surgery after neoadjuvant treatment [9].

In a previous report, clinical responses, such as a complete response and a partial response (PR) on response evaluation criteria in solid tumor (RECIST) were better in the neoadjuvant chemo-immunotherapy (CIT) group than in the neoadjuvant chemotherapy group [10]. Additionally, pathological responses, including a major pathological response (MPR) and complete pathological response (CPR), were better in the CIT group than in the neoadjuvant chemotherapy group. Neoadjuvant CIT significantly improved the MPR and CPR in lung adenocarcinoma in another report [11]. However, an MPR was higher in patients with lung squamous cell carcinoma (SCC) who received neoadjuvant ICI therapy than in those with lung adenocarcinoma [12]. In another study, chemoradiotherapy (CRT) resulted in a higher MPR rate than neoadjuvant CIT in patients with locally advanced NSCLC, whereas the CPR rate and survival outcome were not significantly different between these therapies [13]. These studies suggest that the therapeutic effect varies depending on the histological type or type of neoadjuvant therapy, including CIT and CRT.

In this study, we retrospectively evaluated the efficacy and safety of neoadjuvant CIT in patients with locally advanced NSCLC.

Materials and Methods

Patients

Among 1345 patients with NSCLC who underwent pulmonary resection at Kanazawa Medical University between 2013 and 2025, 34 who received preoperative therapy were enrolled in this retrospective study. This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review committee of Kanazawa Medical University approved the study protocol (approval number: I392), and all patients gave written informed consent.

Data of clinical factors, such as sex, age, smoking history, carcinoembryonic antigen concentrations, prognostic nutrition index (PNI), neutrophil-to-lymphocyte ratio (NLR), cancer inflammation prognostic index (CIPI), maximum standardized uptake value (SUVmax) on [14] F-fluorodeoxyglucose positron emission tomography/computed tomography of the main tumor or metastatic lymph nodes, and lobe involvement, were collected. The smoking history was assessed using the Brinkman index, which was calculated by multiplying the number of cigarettes smoked per day by the number of years that the patients smoked [14]. The PNI was calculated by combining serum albumin concentrations with the total peripheral lymphocyte count in peripheral blood. Previous studies have reported that the preoperative PNI is a prognostic factor in patients with NSCLC [15,16]. Although the NLR is defined as the ratio of neutrophils to lymphocytes and is a parameter of systemic inflammation and stress in critically ill surgical and medical patients [17], it is also a prognostic factor for patients with NSCLC who have undergone pulmonary resection [18,19]. The CIPI was calculated as carcinoembryonic antigen concentrations × the NLR, and has been reported to be a prognostic factor for patients with NSCLC treated by pulmonary resection [20,21].

Preoperative factors

Data of the regimen of preoperative CIT, types of preoperative therapy (neoadjuvant or salvage), completeness rate of preoperative therapy, surgical procedure rate after preoperative therapy, clinical stage (cStage), status of the clinical T factor (cT), status of clinical lymph node metastasis (cN), tumor reduction rate after preoperative therapy, RECIST on computed tomography (CT), status of cStage yield to treatment (ycStage), status of cT yield to treatment (ycT), and status of cN yield to treatment (ycN) were collected.

Perioperative factors

Data of the operative procedures, approach of operative procedures (video-assisted thoracic surgery or open thoracotomy), length of the operation time (min), diameter of surgical incision (mm), amount of bleeding (ml), presence of adhesion or fibrosis around the tumor or metastatic lymph nodes, and operative complications were collected. The operating procedure was divided into the following eight categories: lobectomy, sleeve lobectomy, lobectomy combined with reconstruction of the pulmonary artery, lobectomy combined with segmentectomy, lobectomy combined with chest wall resection, lobectomy combined with segmentectomy and chest wall resection, bi-lobectomy, and pneumonectomy. Postoperative complications were categorized into five grades according to the Clavien–Dindo classification system [22]. This revised version has defined five grades of severity with subgrades (grade I, II, IIIa, IIIb, IVa, IVb, and V), and the suffix “d” (for “disability”) is used to denote any postoperative impairment.

Pathological factors

Data of the histological type, lymphatic invasion (Ly), vascular invasion (V), grade of differentiation (G), pathological stage yield to treatment (ypStage), status of pathological T factor yield to treatment (ypT), status of pathological lymph node metastasis yield to treatment (ypN), efficacy of preoperative therapy (Ef), and the pathological response were collected. Ef was evaluated as the rate of a residual viable tumor and categorized into the following three categories: residual viable tumor more than one third (Ef 1), residual viable tumor less than one third (Ef 2), and no residual viable tumor (Ef 3). The pathological response was categorized as an MPR or a CPR. An MPR was defined as a residual viable tumor less than 10%, and a CPR was defined as no residual viable tumor. Furthermore, the relationships between cStage, ycStage, and ypStage or cN, ycN, and ypN were evaluated.

Statistical analyses

Continuous variables are shown as the median and range. We used Pearson’s chi-square test of independence to compare the frequencies of the variables. Cumulative survival was calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. The cut-off values for factors associated with recurrence were calculated using receiver operating characteristic curve analysis, and prognostic analyses were performed using these cut-off values. Risk factors of a pathological response were analyzed using a logistic regression analysis. A multivariate analysis was performed for the factors that showed significant differences in a univariate analysis. All statistical analyses were two-sided, with statistical significance set at $P<0.05$. Statistical analyses were performed using JMP software v13.2 (SAS Institute Inc., Cary, NC, USA).

Results

Preoperative data

The relationships between the characteristics of the 34 patients with NSCLC who received preoperative therapy with and without ICI therapy are shown in Table 1. Eleven (32%) patients received CIT and

Table 1: Comparison of preoperative data between ICIs therapy and non-ICIs therapy.

	ICIs group (n = 11)	Non-ICIs group (n=23)	P-value
Neoadjuvant / Salvage	7-8	2-21	0.04
Gender (male / female)	1-10	8-15	0.11
Age, median, range (y)	65 (44 - 78)	68 (54 - 77)	0.83
Brinkman index, median, range	820 (0 - 1800)	840 (100 - 1920)	0.73
CEA, median, range (ng/ml)	5.5 (2.3 – 1779.1)	2.5 (1.0 – 73.0)	0.02
PNI, median, range	49.2 (41.9 – 59.3)	46.2 (39.3 – 54.4)	0.02
NLR, median, range	3.29 (1.17 – 4.71)	2.94 (1.58 – 11.54)	0.47
CIPI, median, range	22.27 (3.62-6674.66)	8.52 (2.98-214.62)	0.2
SUV_{max}, median, range	21.44 (2.53 – 26.70)	12.13 (6.8 – 46.8)	0.02
SUV_{max} of LN, median, range	5.98 (0-28.17)	3.97 (0-19.0)	0.25
cStage (IIB / IIIA / IIIB / IV)	2/7/2/0	5/17/0/1	0.18
cT (1b / 1c / 2a / 2b / 3 / 4)	2 / 0 / 2 / 0 / 2 / 5	0 / 2 / 10 / 1 / 4 / 6	0.16
cN (0 / 1 / 2)	02-03-2006	04-10-2009	0.63
Tumor reduction rate on CT, median, range (%)	45 (-10-70)	34 (5-70)	0.12
ycStage (IA1 / IA2 / IA3 / IB / IIA / IIB / IIIA)	1/2/4/1/2/0/1	0/5/6/2/1/5/4	0.34
ycT (1a / 1b / 1c / 2a / 2b / 3 / 4)	1 / 2/ 4 / 1 / 2 / 0 / 1	0 / 5 / 10 / 2 / 1 / 3 / 2	0.5
ycN (0 / 1 / 2)	11 / 0 / 0	18-03-2002	0.24
Down-stage from cStage to ycStage	7 (87.5%)	17 (73.9%)	0.42
Down-stage from cT to ycT	9 (81.8%)	21 (91.3%)	0.42
Down-stage from cN to ycN	9 (81.8%)	14 (60.8%)	0.22
RECIST (PR / SD)	3-8	8-13	0.36
PR on RECIST (%)	72.7	43.3	0.36
Lobe of tumor (RU / RM / RL / LU / LL)	6 / 0 / 1 / 4 / 0	13 / 1 / 2 / 4 / 3	0.54
Hilar type	4 (36.3%)	13 (56.5%)	0.27
Discontinued cases of ICIs therapy	4 (36.3%)	NA	NA
Preoperative therapy followed by surgery	8 (72.7%)	23 (100%)	<0.01

ICIs: Immune-Checkpoint Inhibitors; CEA: Carcinoembryonic Antigen; PNI: Prognostic Nutrition Index; NLR: Neutrophil-to-Lymphocyte Ratio; CIPI: Cancer Inflammation Prognostic Index; SUVmax: Maximum of Standardized Uptake Value; LN: Lymph Node; cStage: Clinical Stage; cT: Status of Clinical T Factor; cN: Status of Clinical Lymph Node Metastasis; CT: Computed Tomography; y: Yield to Treatment; RECIST: Response Evaluation Criteria in Solid Tumor; PR: Partial Response; SD: Stable Disease; RU: Right Upper; RM: Right Middle; RL: Right Lower; LU: Left Upper; LL: Left Lower; NA: Not Available

23 (68%) patients did not have ICI therapy. The proportion of patients who received neoadjuvant therapy was significantly lower in the CIT group than in the non-ICI group (P=0.04). In patients in the CIT group, carcinoembryonic antigen concentrations (5.5 ng/ml *vs* 2.5 ng/ml, P=0.02), the PNI (49.2 *vs* 46.2, P=0.02), and SUVmax (21.44 *vs* 12.13, P=0.02) were significantly higher than those in patients in the ICI group. Furthermore, the proportions of the tumor reduction rate on CT after preoperative therapy (45% *vs* 34%, P=0.12), down-staging from cStage to ycStage (88% *vs* 74%, P=0.42), down-staging from cN to ycN (82% *vs* 61%, P=0.22), and a PR on RECIST (73% *vs* 43%, P=0.36) tended to be higher in the CIT group than in the ICI group. Four (36.3%) patients discontinued CIT because of radiation pneumonitis, liver disfunction, hyponatremia, or exacerbation of diabetes mellitus, and three (27.3%) patients could not receive surgery because of radiation pneumonitis, progression of disease, or exacerbation of interstitial pneumonitis in the CIT group. Although all patients had surgery performed after preoperative therapy in the non-ICI group, there was likely to be selection bias because patients who were considered ineligible for surgery by internal medicine were not included.

Perioperative data

A comparison of perioperative data between the CIT and non-ICI groups is shown in Table 2. There were no significant differences in the frequency of open thoracotomy, number of operative procedures (lobectomy/sleeve lobectomy/lobectomy combined with reconstruction of pulmonary artery/lobectomy combined with segmentectomy/lobectomy combined with chest wall resection/lobectomy combined with segmentectomy and chest wall resection/bi-lobectomy/pneumonectomy), length of the operation time, diameter of the surgical incision, amount of bleeding, or rate of postoperative complications between the two groups However, adhesion or fibrosis around tumor or metastatic lymph node tended to be higher in the CIT group than in the ICI group (P=0.35).

Pathological data

A comparison of pathological data between the CIT and non-ICI groups is shown in Table 3. Three patients who did not receive surgery in the CIT group were excluded. There were no significant differences in the histological type (adenocarcinoma/SCC/pleomorphic carcinoma), ypT, or pN between the two groups. However, the proportion of ypStage 0 to IA1 tended to be lower in the CIT group than in the ICI group (P=0.25). Ef was significantly different between the two groups (P=0.01), and the frequency of Ef 1 tended to be higher in the CIT group than in the ICI group (P=0.12).

Table 2: Comparison of perioperative data between ICIs group and non-ICIs therapy group.

	ICIs group (n=11)	Non-ICIs group (n=23)	P-value
Operative approach (VATS / Open)	3-3	9-14	0.91
Open thoracotomy	5 (62.5%)	14 (60.8%)	0.94
Operative procedure (Lob/Sleeve Lob / Lob+PA plasty / Lob+Seg / Lob+CWR / Lob+Seg+CWR / Bilob / Pneumo)	4 / 0 / 1 / 1 / 1 / 0 / 0 / 1	13 / 4 / 0 / 0 / 1 / 1 / 3 / 1	0.2
Resection more than lobectomy	4 (36.3%)	10 (43.4%)	0.69
Length of operation time, median, range (min)	168 (126-315)	169 (107-437)	0.89
Diameter of surgical incision, median, range (mm)	13.5 (4-20)	12 (5-22)	0.59
Amount of bleeding, median, range (mL)	60 (5-300)	60 (5-365)	0.99
Adhesion or fibrosis around tumor or metastatic lymph node	5 (62.5%)	10 (43.4%)	0.35
Postoperative complications	4 (50%)	9 (42%)	0.72
Clavien-Dindo grade (0 / 2 / 3a / 3b / 4 / 5)	4 / 1 / 3 / 0 / 0 / 0	14 / 2 / 5 / 1 / 0 / 1	0.83

ICIs: Immune-Checkpoint Inhibitors; VATS: Video-Assisted Thoracic Surgery; Open: Open Thoracotomy; Lob: Lobectomy; PA plasty: reconstruction of Pulmonary Artery; Seg: Segmentectomy; CWR: Chest Wall Resection; Bilob: Bi-lobectomy; Pneumo: Pneumonectomy

Table 3: Comparison of pathological data between ICIs group and non-ICIs group.

	ICIs group (n=8)*	Non-ICIs group (n=23)	P-value
Histological type (Ad / SCC / Pleo)	04-04-2000	12-10-2001	0.81
ypStage (0 / IA1 / IA2 / IA3 / IB / IIA / IIB / IIIA)	3 / 0 / 1 / 0 / 2 / 1 / 0 / 1	7 / 7 / 3 / 0 / 0 / 0 / 3 / 3	0.05
ypStage IIB or IIIA	1 (12.5%)	6 (26.8%)	0.42
ypStage 0 or IA1	3 (37.5%)	14 (60.9%)	0.25
ypT (0 / 1mi / 1a / 1b / 1c / 2a / 2b / 3 / 4)	2 / 0 / 0 / 2 / 0 / 2 / 0 / 1 / 1	5 / 4 / 4 / 5 / 0 / 1 / 2 / 0 / 2	0.24
ypN (0 / 1 / 2)	07-01-2000	18-03-2002	0.68
Ef (1a / 1b / 2 / 3)	1 / 3 / 2 / 2	5 / 0 / 13 / 5	0.01
Ef 1	4 (50.0%)	5 (21.7%)	0.12
Ef2	2 (25.0%)	13 (56.5%)	0.12
Ef 3	2 (25.0%)	5 (21.7%)	0.84
Ef ≥ 2	4 (50.0%)	18 (78.2%)	0.12
Major pathological response (MPR)	0 (0%)	4 (17.4%)	0.2
Complete pathological response (PCR)	2 (25%)	5 (21.7%)	0.84
MPR and PCR	2 (25%)	9 (39.1%)	0.47
Down-stage from cStage to ypStage	7 (87.5%)	19 (82.6%)	0.74
Down-stage from ycStage to ypStage	3 (37.5%)	17 (73.9%)	0.06
Down-stage from cT to ypT	6 (75.0%)	19 (82.6%)	0.63
Down-stage from ycT to ypT	3 (37.5%)	17 (73.9%)	0.06
Down-stage from cN to ypN	6 (75.0%)	16 (69.5%)	0.77
Down-stage from ycN to ypN	0 (0%)	2 (8.7%)	0.38
Ly (present / absent / unknown)	0 / 8/ 0	4 / 18 / 1	0.35
V (present / absent / unknown)	03-05-2000	8 / 14/ 1	0.83
G (1 / 2 / 3 / 4 / unknown)	0 / 4 / 2 / 0 / 2	3 / 13 / 3 / 1 / 3	0.61

ICIs: Immune-Checkpoint Inhibitors; *Excluded the inoperable cases in ICIs group; Ad: Adenocarcinoma; SCC: Squamous Cell Carcinoma; Pleo: Pleomorphic Carcinoma; y: Yield To Treatment; pStage: Pathological Stage; pT: Status of Pathological T Factor; pN: Status of Pathological Lymph Node; Ef: Efficacy of Preoperative Therapy; cStage: Clinical Stage; cT: Status of Clinical T Factor; cN: Status of Clinical Lymph Node Metastasis; Ly: Lymphatic Invasion; V: Vascular Invasion; G: Grade of Differentiation

Furthermore, down-staging from ycStage to ypStage (P=0.06) and down-staging from ycT to ypT (P=0.06) tended to be lower in the CIT group than in the ICI group.

A comparison of pathological responses by the histological type or neoadjuvant therapies with exclusion of patients who had salvage surgery performed or inoperable cases are shown in Table 4. The frequency of an MPR was significantly higher in patients with SCC than in those without SCC (P=0.01) and in patients with SCC treated by CRT (P=0.02). However, the frequency of a CPR tended to be higher in patients with SCC than in those without SCC (P=0.11) and in those with SCC treated by CIT (P=0.10). The frequency of Ef 1 was 75% in patients who had CIT *versus* 30% in those with CRT in patients who did not have SCC.

Univariate and multivariate analyses

A univariate analysis of prognostic factors related to Ef 2 or 3 was performed (Table 5). The cut-off values of the factors associated

Table 4: Comparison of pathological responses by histological types or neoadjuvant therapies*.

	Ef 1	P-value	Ef 2	P-value	Ef 3	P-value	MPR	P-value	CPR	P-value
Histological type (N=31)										
SCC (N=14)	1 (7%)	0.01	8 (57%)	0.37	5 (36%)	0.11	4 (29%)	0.01	5 (36%)	0.11
Non-SCC (N=17)	8 (47%)		7 (41%)		2 (12%)		0 (0%)		2 (12%)	
Chemo-ICIs (N=8)										
SCC (N=4)	1 (25%)	0.15	1 (25%)	NS	2 (50%)	0.12	0 (0%)	NS	2 (50%)	0.1
Non-SCC (N=4)	3 (75%)		1 (25%)		0 (0%)		0 (0%)		0 (0%)	
Chemoradiotherapy (N=20)										
SCC (N=10)	0 (0%)	0.06	7 (70%)	0.36	3 (30%)	0.6	4 (40%)	0.02	3 (30%)	0.6
Non-SCC (N=10)	3 (30%)		5 (50%)		2 (20%)		0 (0%)		2 (20%)	

*Excluded the cases performed salvage surgery and inoperable cases.
Ef: Efficacy of Preoperative Therapy; N: Number of Patients; SCC: Squamous Cell Carcinoma; Chemo: Chemotherapy; ICIs: Immune-Checkpoint Inhibitors; MPR: Major Pathological Response; CPR: Complete Pathological Response; NS: Not Significant

Table 5: Univariate analysis of prognostic factors related Ef 2 or 3.

Univariate analysis				
Variables		Odds ratio	95% CI	P-value
Gender	male	0.61	0.100-3.73	0.59
Age (y)	< 70	2.18	0.452-10.575	0.33
Smoking status	Brinkman index ≥ 600	1.7	0.308-9.374	0.54
CEA (ng/mL)	> 5	0.23	0.045-1.225	0.08
PNI	< 47.60	2.88	0.568-14.681	0.2
NLR	> 2.39	2.18	0.452-10.575	0.3
CIPI	> 49.45	NA	NA	NA
SUV_{max}	≥ 26.3	0.16	0.013-2.130	0.16
LN SUVmax	>4.3	2.88	0.568-14.681	0.2
ICIs	present	0.27	0.050-1.526	0.14
Tumor reduction rate on CT (%)	≥ 45	5.53	0.586-52.331	0.13
Down-stage from cStage to ycStage	present	0.97	0.151-6.247	0.97
Down-stage from cT to ycT	present	2.87	0.335-24.299	0.33
Down-stage from cN to ycN	present	3.33	0.662-16.763	0.14
PR on RECIST	present	1.15	0.241-5.529	0.85
Histological type	SCC	11.55	1.222-109.185	0.03

Ef: Efficacy of Preoperative Therapy; CEA: Carcinoembryonic Antigen; PNI: Prognostic Nutrition Index; NLR: Neutrophil-to-Lymphocyte Ratio; CIPI: Cancer Inflammation Prognostic Index; SUV_{max}: Maximum of Standardized Uptake Value; LN: Lymph Node; ICIs: Immune-Checkpoint Inhibitors; CT: Computed Tomography; cStage: Clinical Stage: y: Yield to Treatment; cT: status of Clinical T Factor; cN: Status of Clinical Lymph Node Metastasis; RECIST: Response Evaluation Criteria in Solid Tumor; PR: Partial Response; SCC: Squamous Cell Carcinoma

with Ef 2 or 3 were calculated using a receiver operating characteristic curve analysis. The following cut-off values were determined: age, 70 years; PNI, 47.60; NLR, 2.39; CIPI, 49.45; SUVmax, 26.3; SUVmax of metastatic lymph nodes, 4.3; and tumor reduction rate on CT, 45%. The univariate analysis showed that only SCC (odds ratio [OR]: 11.55, 95% confidence interval [95%CI]: 1.222–109.185, P=0.03) was a significant prognostic factor for Ef 2 or 3. Furthermore, a univariate analysis of prognostic factors related to an MPR or CPR was performed (Table 6). The cut-off values of factors associated with an MPR or CPR were calculated using a receiver operating characteristic curve analysis. The following cut-off values were determined: age, 75 years; PNI, 44.20; NLR, 3.31; CIPI, 15.51; SUVmax, 21.44; SUVmax of metastatic lymph nodes, 4.0; and tumor reduction rate on CT, 25%. The univariate analysis showed that the PNI (OR: 15.83, 95% CI: 1.532–163.548, P=0.02), SUVmax of metastatic lymph nodes (OR: 8.35, 95% CI: 1.400–49.883, P=0.01), and SCC (OR: 13.50, 95% CI: 2.152–84.688, P<0.01) were significant prognostic factors for an MPR or CPR. However, none of these factors were significant prognostic factors for an MPR or CPR in the multivariate analysis.

Discussion

In this study, we evaluated the efficacy of neoadjuvant CIT in patients with locally advanced NSCLC. The proportions of the tumor reduction rate on CT after preoperative therapy, down-staging from cStage to ycStage, down-staging from cN to ycN, and a PR on RECIST tended to be higher in the CIT group than in the ICI group. Furthermore, Ef 1 tended to be higher in the CIT group, while down-staging from ycStage to ypStage and down-staging from ycT to ypT tended to be lower in the CIT group than in the ICI group. A previous report showed that clinical responses, such as a complete response and PR on RECIST, were significantly better in the adjuvant CIT group than in the adjuvant chemotherapy group [10]. Additionally,

Table 6: Univariate analysis of prognostic factors related MPR or CPR.

		Univariate analysis			Multivariate analysis		
Variables		Odds ratio	95% CI	P value	Odds ratio	95%CI	P value
Gender	male	2.42	0.405-14.463	0.33			
Age (y)	< 75	5.38	0.566-51.171	0.14			
Smoking status	BI ≥ 600	5.38	0.566-51.171	0.14			
CEA (ng/mL)	≤ 5	8.18	0.874-76.581	0.06			
PNI	< 44.2	15.83	1.532-163.548	0.02	NA		
NLR	> 3.31	2.8	0.609-12.856	0.18			
CIPI	> 15.51	0.56	0.113-2.786	0.48			
SUV_{max}	≥ 21.44	0.66	0.106-4.182	0.66			
LN SUV_{max}	>4.0	8.35	1.400-49.883	0.01	NA		
ICIs	present	0.51	0.085-3.156	0.47			
Tumor reduction rate on CT (%)	≥ 25	0.21	0.038-1.167	0.07			
Down-stage from cStage to ycStage	present	0.66	0.119-3.725	0.64			
Down-stage from cT to ycT	present	2.87	0.335-24.299	0.33			
Down-stage from cN to ycN	present	1.76	0.161-19.339	0.64			
PR on RECIST	present	1.77	0.358-8.808	0.48			
Histological type	SCC	13.5	2.152-84.688	<0.01	7.92	0.634-99.072	0.1

MPR: Major Pathological Response; CPR: Complete Pathological Response; CI: Confidence Interval; BI: Brinkman Index; CEA: Carcinoembryonic Antigen; PNI: Prognostic Nutrition Index; NA: Not Available; NLR: Neutrophil-to-Lymphocyte Ratio; CIPI: Cancer Inflammation Prognostic Index; SUVmax: Maximum of Standardized Uptake Value; LN: Lymph Node; ICIs: Immune-Checkpoint Inhibitors; CT: Computed Tomography; Cstage: Clinical Stage; y: Yield to Treatment; cT: Status of Clinical T Factor, cN; Status of Clinical Lymph Node Metastasis; RECIST: Response Evaluation Criteria in Solid Tumor; PR: Partial Response; SCC: Squamous Cell Carcinoma

pathological responses, including an MPR and CPR were significantly better in the CIT group than in the adjuvant chemotherapy group. Furthermore, neoadjuvant CIT significantly improved the MPR and CPR in lung adenocarcinoma in another report [11]. The rate of an MPR was significantly higher in patients with SCC than in those without SCC treated by CRT in this study. A previous report showed that neoadjuvant CRT resulted in a higher MPR rate than neoadjuvant CIT in patients with locally advanced NSCLC, whereas the CPR rate and survival outcome were not significantly different between these therapies [13]. Similarly, in another study, neoadjuvant CRT resulted in higher MPR and CPR rates than neoadjuvant CIT in patients with esophageal SCC [23]. Neoadjuvant CIT and CRT may have a therapeutic effect in patients with locally advanced SCC, whereas neoadjuvant CIT might not be appropriate for patients without locally advanced SCC.

In the phase 3 KEYNOTE-671 study, 6/325 (1.8%) participants in the pembrolizumab arm died at ≤30 days after surgery, whereas 2/317 (0.6%) participants in the placebo arm died at ≤30 days after surgery from surgery-related adverse events [24]. In a previous report, CIT was associated with a higher absolute risk of surgery cancellation-related adverse events, whereas the incidence of surgery cancellations was low in those who had CIT (3.14%) and in those without ICIs (1.80%) [25]. This study showed that 35% of patients required conversion from a minimally invasive to open approach, often because of hilar inflammation and fibrosis, and this percentage is comparable to a similar recent trial of neoadjuvant chemotherapy [26]. Furthermore, the addition of ICIs to chemotherapy was not associated with a delay in surgery due to toxicity, an increased rate of conversion from the minimally invasive to open approach, or to changes in the extent or completeness of resection in the CheckMate 816 study [27]. In this study, the rate of open thoracotomy and postoperative complications were not significantly different between the CIT and non-ICI groups, whereas the rate of adhesion or fibrosis around the tumor or metastatic lymph nodes tended to be high in the CIT group. Although neoadjuvant ICI therapy might lead to increase surgical challenges, neoadjuvant CIT should be implemented in patients with locally advanced NSCLC because of its therapeutic effect.

This study has several limitations. First, this was a retrospective study, and it potentially involved unobserved cofounding and selection biases. Second, this study was performed at a single institution, and the study population was small. Third, the possibility cannot be ruled out that some patients were not included in this study because of insufficient data, resulting in selection bias.

Conclusion

In summary, our findings suggest that neoadjuvant CIT and CRT have a therapeutic effect in patients with locally advanced SCC, whereas neoadjuvant CIT might not be appropriate for patients without locally advanced SCC. Furthermore, neoadjuvant CIT should be implemented in patients with locally advanced NSCLC because of the therapeutic effect, whereas neoadjuvant ICI therapy might lead to increased surgical challenges.

Declarations of Interest

Acknowledgment

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Ethics approval and consent to participate

The present study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Boards of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all of the patients.

Consent to publish

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to [our institutional restrictions e.g., them containing information that could compromise research participant privacy/consent], but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

N. M. performed the research, collected and analyzed the data and wrote the paper. M.I., S. I., and Y.I. contributed to sample collection. H. U. contributed to supervision of this study and revision of the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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