

ORIGINAL ARTICLE

Treatment Patterns and Outcomes in Patients with Resectable Early-stage NSCLC in Japan

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Abstract

We conducted an analysis using the Medical Data Vision (MDV) database from 2008 to 2022 to evaluate real-world evidence on perioperative treatment strategies for patients with early-stage non-small cell lung cancer (NSCLC). Among 5107 patients with clinical stage I to III A NSCLC, 3457 (67.7%) underwent surgery only, 72 (1.4%) received neoadjuvant therapy (NeoAdj) followed by surgery, 1479 (29.0%) received adjuvant therapy (Adj) after surgery, and 99 (1.9%) underwent NeoAdj plus surgery plus Adj. The most commonly used agents were tegafur/uracil in 791 patients (50.1%) and platinum-based chemotherapy in 571 patients (36.2%). The median follow-up period was 44.4 months (range 0.1-139.2), with a median real-world disease-free survival (rwDFS) of 64.1 months (95% CI, 61.0-68.7). Median overall survival (OS) was not reached during the study period. This study highlights the significance of perioperative treatment strategies in early-stage NSCLC over a maximum follow-up of 11 years. The findings underscore the need for continued accumulation of real-world evidence to optimize treatment approaches in clinical practice.

Introduction

Lung cancer is responsible for an estimated 1.8 million deaths worldwide¹⁾. In Japan, the prevalence of lung cancer is 97.1 cases per 100000 people making it the third most common cancer ; it is also the third most common cause of death due to cancer in Japan²⁾. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer which accounts for 80-85% of all lung cancer cases³⁾. With the exception of stage III B and III C, the National Cancer Center Network and Japan Lung Cancer Society treatment guidelines recommend surgical resection as first line therapy for earlier-stage lung cancer when medically feasible (e.g., patient condition, location of tumor)⁴⁾⁵⁾. According to Japan Lung Cancer Society treatment guidelines 2023, for stage II B/III A (American Joint Committee on Cancer : AJCC staging version 8.0)⁶⁾, neoadjuvant therapy (platinum combination or chemoradiotherapy) is recommended depending on resectability of the cancer. Contrastingly, patients with postoperative pathologic stage I - III A (AJCC staging version 8.0) NSCLC with completed resection are highly recommended to be treated with adjuvant therapy. The recommended adjuvant therapy options prioritize tegafur/uracil combination therapy for stage I - II A or platinum therapy for stage II - III A⁴⁾⁵⁾. The proposed stages for the ninth edition Tumor, Node, Metastasis Classification (TNM)⁷⁾ were implemented in 2025, aim to improve the granularity of nomenclature regarding tumors which may lead to the change of TNM staging, treatment decisions, approaches and outcome of survival rate in future⁸⁾.

The evidence is somewhat inconclusive about the efficacy of neoadjuvant (i.e., pre-operative) and adjuvant (i.e., post-operative) chemotherapies in the treatment of early NSCLC⁹⁾. However, new trials using immune checkpoint inhibitors have shown promise in improving clinical outcomes for patients with resected early-stage NSCLC, for example, nivolumab (trial name : CheckMate816), atezolizumab (IMpower010) and durvalumab (AEGEAN)¹⁰⁾. Pembrolizumab combination with chemotherapy as neoadjuvant plus adjuvant therapy in patients with stage II B-III A disease (KEYNOTE671- resectable Stage II , III A, or III B [T3-4N2] [AJCC staging version 8.0]¹¹⁾). The results of these trials changed treatment system in early-stage NSCLC, however, there is still a lack of real-world evidence on pre- and post-operative therapies for early-stage NSCLC in Japan. Understanding the patient profiles, treatment patterns and clinical outcomes of patients treated for early-stage NSCLC may provide insights into unmet medical needs in pre- and post-operative treatment in Japan for healthcare providers.

I Methods

1. Data source

This was an observational retrospective database analysis using claims data from a hospital-based database (Medical Data Vision Co., Ltd. ; MDV). The MDV database is an anonymized database of hospital-based health claims and Diagnosis Procedure Combination (DPC) data covering 38 million patients in Japan¹²⁾. The database contains inpatient and outpatient medical care data from approximately 23% of the advanced

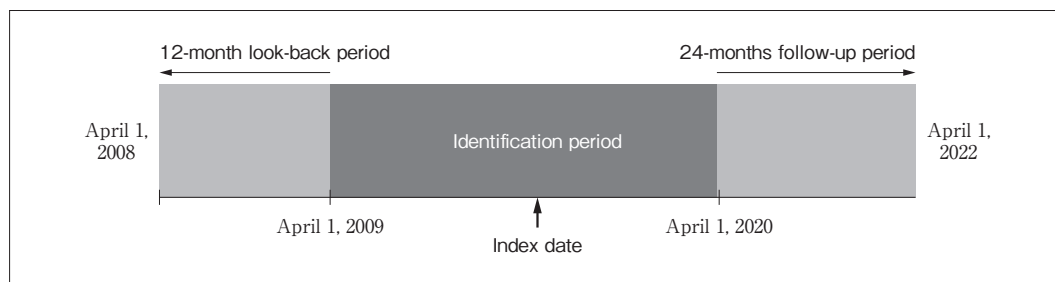


Figure 1 Definition of identification period, index date, look-back and follow-up period

treatment hospitals across Japan. Medical claims data are collected from all insurance types and approximately 48% of data are from patients aged 65 years and above¹³⁾. These claims can also be used to follow patients over time within the same institution. This database contains patient level information on demographics, clinical diagnoses (International Statistical Classification of Diseases and Related Health Problems, 10th Revision : ICD-10), procedures, prescriptions, as well as laboratory test values.

2. Study population

In the MDV database, the study population was defined as patients with NSCLC who had undergone surgical resection. The index date was defined as the first claim for resection to treat NSCLC within the identification period (April 1, 2009–April 1, 2020 ; **Figure 1**) to ensure a sufficiently large real-world sample while maintaining a structured follow-up period. The follow-up period was defined as a minimum of 24 months from the index date to capture post-surgical treatment patterns, and ended on April 1, 2022 (the latest available data cut-off in the MDV database), death, or the end of patient record (whichever occurs first). This approach ensured that all included patients had an equal opportunity for longitudinal follow-up and that study findings

were representative of contemporary real-world practice in Japan.

Patients who met all of the following criteria were included in the study : 1) patient was aged ≥ 20 on index date. ; 2) patient had at least one claim for a confirmed diagnosis of NSCLC (stage I, II or IIIA according to Union for International Cancer Control [UICC]) within the identification period ; 3) patient had at least one claim for surgical resection (lobectomy or pneumonectomy) within the identification period. Patients who met any of the following criteria were excluded from the study : 1) patients who had at least one claim for any other primary cancer during their patient record prior to index date ; 2) patients who had less than four claims in the database within the 24-month follow-up period (one claim every six months) from index date, except those who died within the 24-month follow-up period.

3. Variables and epidemiological measurements

1) Outcomes

The clinical outcome of overall survival (OS) and real-world disease-free survival (rwDFS) are analyzed. OS was defined as the number of days and months between the index date and whichever date comes first : end of patients' data, a claim for death

or a claim for death where NSCLC was the main disease. RwDFS was defined as the number of days and months between the index date and whichever of the following comes first : claims for NSCLC with recurrence of cancer, next treatment (adjuvant patients counted only if therapy changed from adjuvant therapy), end of patient data or a claim for death. The Kaplan-Meier method was used to assess all clinical outcomes, of which, a 50% survival rate median was reached for only a few groups. Therefore in this analysis, mean (or median) OS and rwDFS in the results refer to the descriptive mean (or median) time from index date to the censoring data (event date) during the follow-up period (i.e., observed survival time), unless otherwise stated.

2) Primary endpoints

Treatment patterns were separated in two groups : those patients who received neoadjuvant therapy before surgery and adjuvant therapy following surgery. Neoadjuvant therapy was defined as chemotherapy or radiotherapy that a patient received closest to the index date, starting within 4 months prior to the index date referred to previous study¹⁴⁾. Adjuvant therapy referred to chemotherapy or radiotherapy that a patient received closest to the index date, starting within 4 months after surgery¹⁵⁾. The regimens of platinum-based therapies and radiation therapy were included in neoadjuvant therapy ; adjuvant therapy regimens consist of tegafur/uracil combination therapy, platinum-based therapies and radiation therapy.

3) Covariates

Baseline demographic characteristics were assessed for the entire patient population

and by stage at diagnosis (I , II , IIIA, both AJCC staging version 7 or 8 as available in the database). The covariates of age, sex, weight are examined as close as possible to the index date within the investigation period. Additionally, index year, Modified Charlson Comorbidity Index (CCI)¹⁶⁾ scored during the look-back period and cancer staging information are utilized to describe patient characteristics. Patients were further stratified by age, cancer staging status of receiving adjuvant and/or neoadjuvant therapy.

4. Data analysis

All data analyses were performed using SAS[®] version 9.4. Continuous variables that follow an approximately normal distribution were summarized using mean, standard deviation (S.D.), median, and range. Categorical variables were summarized using frequency and percentage. As this study was descriptive, no statistical testing was conducted. All analyses were performed in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and applicable sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹⁷⁾¹⁸⁾.

5. Ethical approval

This study only utilized anonymized data from patients who have previously provided consent to MDV database for provision of their data to a third party for the purpose of academic or pharmaceutical-related research. Therefore, this study will not require additional patient informed consent because only anonymized secondary data was used in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry

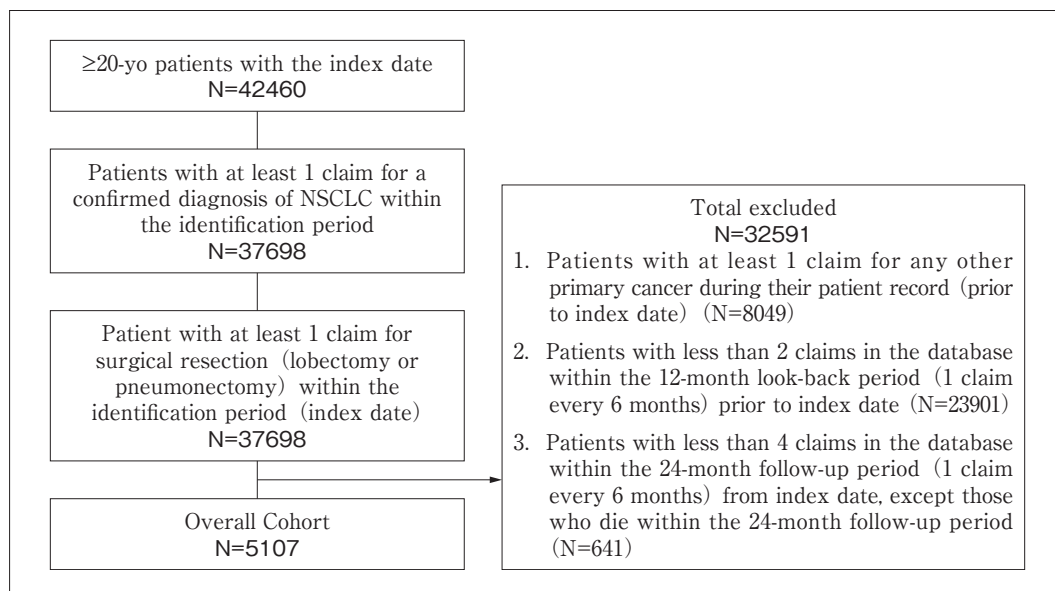


Figure 2 Selection of study population

of Health, Labour and Welfare of Japan¹⁹⁾. This study was approved by Medical Corporation Toukeikai Kitamachi Clinic Ethical Review Board approval number MSD09875.

II Results

1. General characteristics

In total, 5107 patients met the inclusion criteria (**Figure 2**). The median (range) age of the study population was 71.0 (20.0-92.0) years and 60.6% were male (**Table 1**). The mean (S.D.) Modified CCI score was 3.6 (1.7). Median (range) total follow-up time in the database was 44.4 (0.1-139.2) months. There were 3379 (66.2%) patients and 1454 (28.5%) patients described using the TNM 7th and 8th edition staging system, respectively. Stage I A was the most common 7th edition stage (1930, 37.8%) and 8th edition stage (911, 17.8%) ; Stage I A2 was the most common

substage for I A (400, 43.9%). Most eligible patients had 2019 as their index year (1026 patients, 20.1%), while only 1 eligible patient was identified in year of 2010.

2. Treatment Pattern

Of the eligible patient population, 3457 (67.7%) received surgery only, 72 (1.4%) neoadjuvant therapy and surgery, 1479 (29.0%) surgery and adjuvant chemotherapy, and 99 (1.9%) received neoadjuvant therapy, surgery and adjuvant therapy (**Table 2**). The median period of peri-operative treatment for the entire cohort (defined as total number of days with a claim for either neoadjuvant or adjuvant therapy) was 2.0 (range : 1.0-56.0) days for patients who received neoadjuvant therapy only, and 7.0 (1.0-70.0) days for patients who received adjuvant therapy only. The median (range) time to next therapy after adjuvant therapy (defined as the number of days between adjuvant therapy and first new line of therapy initiated

Table 1 Overall patient characteristics

Characteristics	Patients (n = 5107)
Age, years, Mean (S.D.)	70.3 (8.4)
Age, years, Median (Min-Max)	71.0 (20.0-92.0)
Male, n (%)	3095 (60.6)
Charlson comorbidity index, Mean (S.D.)	3.6 (1.7)
Charlson comorbidity index, Median (Min-Max)	3.0 (2.0-13.0)
Total follow-up time, month, Mean (S.D.)	48.2 (23.2)
Total follow-up time, month, Median (Min-Max)	44.4 (0.1-139.2)
Staging based on TNM 7 th edition, n (%)	
Stage I A	1930 (37.8)
Stage I B	733 (14.4)
Stage II A	328 (6.4)
Stage II B	145 (2.8)
Stage III A	243 (4.8)
Missing	1728 (33.8)
Staging based on TNM 8 th edition, n (%)	
Stage I A	911 (17.8)
Stage I A1	257 (28.2)
Stage I A2	400 (43.9)
Stage I A3	254 (27.9)
Stage I B	237 (4.6)
Stage II A	44 (0.9)
Stage II B	162 (3.2)
Stage III A	100 (2.0)
Missing	3653 (71.5)
Index year, n (%)	
2010	1 (0.0)
2011	3 (0.1)
2012	135 (2.6)
2013	251 (4.9)
2014	390 (7.6)
2015	606 (11.9)
2016	672 (13.2)
2017	789 (15.4)
2018	956 (18.7)
2019	1026 (20.1)
2020	278 (5.4)

S.D. : standard deviation

Table 2 Characteristics of treatment patterns of overall cohort (n = 5107)

Treatment pattern	
Patients receiving surgery only, n (%)	3457 (67.7)
Patients receiving neoadjuvant therapy and surgery, n (%)	72 (1.4)
Patients receiving surgery and adjuvant therapy, n (%)	1479 (29.0)
Patients receiving neoadjuvant therapy, surgery and adjuvant therapy, n (%)	99 (1.9)
Time to next therapy after adjuvant therapy, days, median (Min-Max)	14.0 (1.0-111.0)

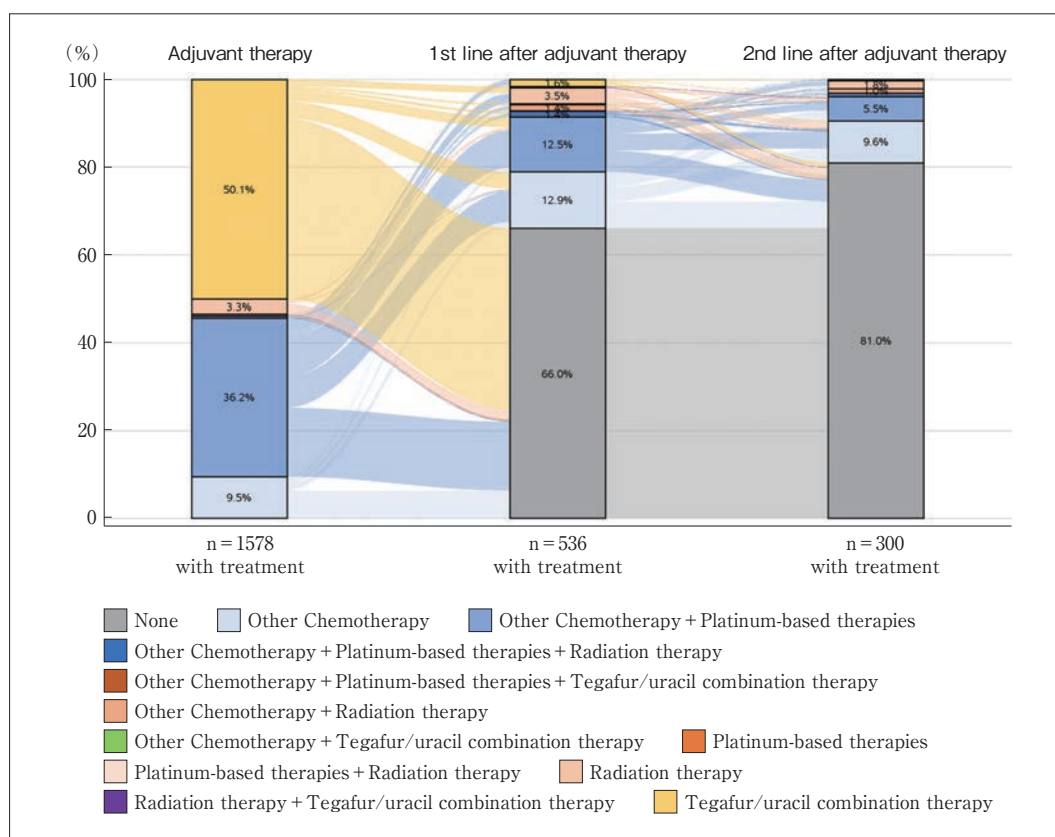


Figure 3 Treatment pattern in Sankey chart (overall)

after adjuvant therapy regimen) was 14.0 (1.0-111.0) days.

The transitions from adjuvant regimen to post-adjuvant regimens are described as treatment patterns in the Sankey chart (overall). As adjuvant, patients received

tegafur/uracil combination therapy 791 (50.1%), other chemotherapy with platinum-based therapies (571, 36.2%), or other chemotherapy only (150, 9.5%) (**Figure 3**). However, 536 and 300 patients had records of 1st and 2nd line after adjuvant therapy, and

66.0% and 81.0% did not receive any treatment, respectively. Overall, targeted therapeutic agents were used by 13.2% (n=206) of patients and consisted of EGFR inhibitor (184, 11.8%), ALK inhibitor (17, 1.1%), osimertinib (113, 7.3%) and VEGF inhibitor (157, 10.1% ; **Table 3**).

For treatment subgroups, surgery only patients (3457, 67.7%) were relatively older with a median (range) age of 72.0 (27.0-92.0) years old (**Table 4**). The proportion of TNM 7th Stage IIIA patients was relatively high among patient receiving neoadjuvant and surgery as well as those receiving neoadjuvant, surgery and adjuvant therapy (25.0% and 22.2%, respectively).

3. Clinical outcome

The clinical outcomes for the overall population were months of OS (**Figure 4**) and rwDFS (**Figure 5**). The Kaplan-Meier median for OS and rwDFS for the overall population was not reached and 64.1 (95% CI, 61.0-68.7) months, respectively. There were only enough events to calculate median rwDFS, and not OS, for the overall study population and all subgroups. The proportion of patients with an OS event were less than 10% in all groups whereas nearly 50% of patients in each group had an rwDFS event. The 5-year OS rate was 93.8% overall while the 5-year rwDFS rate was 51.9% and the 10-year rwDFS rate was 36.9%.

By age group, mean (S.D.) OS for patients <75 years was 49.9 (23.4) months and 44.6 (22.4) months for patients ≥75 years (**Table 5, Fig. S1A**). In cancer stage subgroups (**Fig. S2, 3**), OS fell considerably between stage I and stage II but remained similar between stage II and stage IIIA. For example, mean (S.D.) OS for stage I, II and IIIA

cancers using UICC version 7 staging was 57.1 (22.8), 47.8 (24.8) and 46.3 (25.7) months, respectively (**Table 5, Fig. S2A**). When compared among different treatment pattern subgroups, mean (S.D.) OS was over 40 months for all subgroups, with the longest being 48.8 (24.0) months among patients who received surgery and adjuvant therapy (**Table 5, Fig. S4A**). This duration was similar to mean (S.D.) OS for patients treated with surgery only 48.2 (22.7) months. The duration of mean (S.D.) OS in months was relatively shorter for patients who received neoadjuvant therapy before surgery 44.4 (25.0) months or neoadjuvant, surgery and adjuvant therapy at 41.2 (27.9) months.

The median rwDFS by age group were 74.1 (95% CI, 67.7-82.1) for patients <75 years and 50.1 (95% CI, 45.1-55.7) for patients ≥75 years (**Table 5, Fig. S1B**). However, mean rwDFS were similar regardless of age group at roughly 33 to 37 months. Patients with cancers staged using UICC version 7 had longer corresponding mean rwDFS than those staged using UICC version 8 (**Table 5, Fig. S2, 3**). Notable differences in rwDFS were found among four treatment pattern groups. The mean (S.D.) rwDFS for the neoadjuvant therapy and surgery group was relatively short at 20.8 (20.3) months compared to the neoadjuvant, surgery and adjuvant therapy group at 23.3 (25.8) months. Patients that received adjuvant therapy following surgery had a much longer rwDFS at 32.0 (26.9) months. The mean (S.D.) rwDFS was even higher at 38.3 (24.6) months among patients with surgery only. The median rwDFS followed a similar pattern among these subgroups however the duration for patients not requiring pre- or post-

Table 3 Characteristics of drug use in different treatment patterns of overall cohort

Regimens/therapy types	Patients, n (%)
Neoadjuvant therapy	N = 72
Chemotherapy (ATC code : L01)	62 (86.1)
Platinum-based therapies (L01F)	16 (22.2)
Radiation therapy	11 (15.3)
Both Chemotherapy and Radiation therapy	1 (1.4)
Adjuvant therapy*	N = 1578
Chemotherapy (L01)	1526 (96.7)
Platinum-based therapies (L01F)	586 (37.1)
Tegafur/uracil combination therapy	791 (50.1)
Radiation therapy	60 (3.8)
Both Chemotherapy and Radiation therapy	8 (0.5)
Number and percentage of patients receiving following drugs on and after the adjuvant therapy*	N = 1555
Chemotherapy Overall (L01)	1525 (98.1)
Platinum-Based Compounds Overall (L01f)	727 (46.8)
Carboplatin	460 (29.6)
Cisplatin	328 (21.1)
Nedaplatin	3 (0.2)
Others	55 (3.5)
Taxanes Overall (L1c2)	321 (20.6)
Docetaxel	128 (8.2)
Paclitaxel	227 (14.6)
Others	11 (0.7)
Other Chemotherapeutics (L01-[L1f+L1c2])	1431 (92.0)
Irinotecan	11 (0.7)
Gemcitabine	59 (3.8)
Pemetrexed	258 (16.6)
Vinorelbine	306 (19.7)
Tegafur/Gimeracil/Oteracil Potassium	123 (7.9)
Tegafur/Uracil	835 (53.7)
Others	357 (23.0)
Targeted Therapy Agents Overall (L1h)	206 (13.2)
EGFR Inhibitors Overall (L1h2)	184 (11.8)

(continued)

(Table 3 continued)

Regimens/therapy types	Patients, n (%)
Number and percentage of patients receiving following drugs on and after the adjuvant therapy*	N = 1555
Gefitinib	53 (3.4)
Erlotinib	35 (2.3)
Afatinib	46 (3.0)
Dacomitinib	1 (0.1)
Osimertinib	113 (7.3)
ALK Inhibitors Overall (L1h3)	17 (1.1)
Alectinib	16 (1.0)
Brigatinib	1 (0.1)
Lorlatinib	2 (0.1)
Ceritinib	1 (0.1)
Crizotinib	1 (0.1)
Others	1 (0.1)
BRAF/MEK Inhibitors Overall (L1h4)	1 (0.1)
Dabrafenib	1 (0.1)
Trametinib	1 (0.1)
Other Inhibitors	4 (0.3)
Tepotinib	1 (0.1)
Others	3 (0.2)
Monoclonal Antibodies Overall (L1g)	310 (19.9)
VEGF/VEGF Inhibitors Overall (L1g2)	157 (10.1)
Ramucirumab	67 (4.3)
Bevacizumab	111 (7.1)
Other Monoclonal Antibodies (L1g-[L1g2+l1g4])	242 (15.6)

* : including surgery and adjuvant (n = 1479) and neoadjuvant and surgery and adjuvant (n = 99)

operative treatment (i.e., surgery only) was highest at 79.8 (95% CI, 71.3-97.1) months (**Table 5, Fig. S4**). Trends for rwDFS by treatment pattern were much more discrete among patients with stage I NSCLC rather than higher stages (**Fig. S5B**).

III Discussion

Understanding the patient profiles, treatment patterns, and clinical outcomes of early-stage NSCLC is essential for identifying unmet medical needs in perioperative treatment strategies in Japan. Our study provides a

Table 4 Treatment pattern of neoadjuvant or/and adjuvant therapy in subgroups (n = 5107)

Subgroups	Surgery only N = 3457 (67.7%)	Neoadjuvant + surgery N = 72 (1.4%)	Surgery + adjuvant N = 1479 (29.0%)	Neoadjuvant + surgery + adjuvant N = 99 (1.9%)
Age, median (min-max)	72.0 (27.0-92.0)	69.0 (36.0-82.0)	69.0 (20.0-90.0)	66.0 (35.0-81.0)
Male, n (%)	2014 (58.3)	52 (72.2)	963 (65.1)	66 (66.7)
Charlson comorbidity index, median (min-max)	3.0 (2.0-5.0)	5.0 (2.0-10.0)	3.0 (2.0-12.0)	5.0 (2.0-11.0)
Stage I (UICC version 7)	1959 (56.7)	21 (29.2)	650 (43.9)	33 (33.3)
Stage II (UICC version 7)	208 (6.0)	14 (19.4)	238 (16.1)	13 (13.1)
Stage III A (UICC version 7)	91 (2.6)	18 (25.0)	112 (7.6)	22 (22.2)
Stage I (UICC version 8)	884 (25.6)	6 (8.3)	255 (17.2)	3 (3.0)
Stage II (UICC version 8)	109 (3.2)	3 (4.2)	89 (6.0)	5 (5.1)
Stage III A (UICC version 8)	32 (0.9)	3 (4.2)	57 (3.9)	8 (8.1)

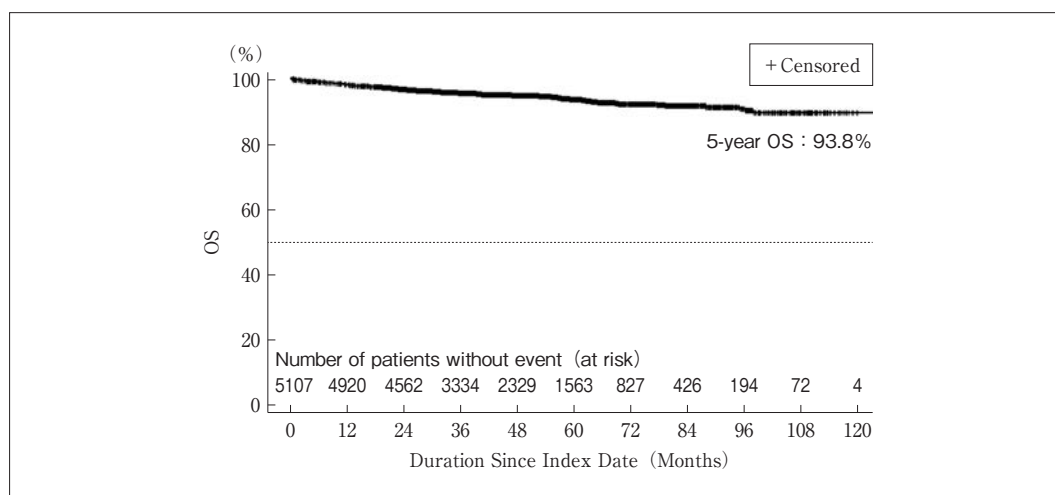


Figure 4 Kaplan-Meier curve for overall survival (overall)

comprehensive real-world analysis of more than 5000 patients, spanning up to 11 years, offering valuable insights into evolving treatment practices and their outcomes.

We observed similar OS among patients undergoing different treatment modalities for NSCLC, including surgery only, neoadjuvant

therapy and surgery, surgery and adjuvant therapy, and neoadjuvant therapy, surgery and adjuvant therapy. Notably, the Kaplan-Meier estimates suggest that surgery only may confer the best OS, consistent with findings by Snee et al.²⁰⁾, who reported superior outcomes with surgery only in

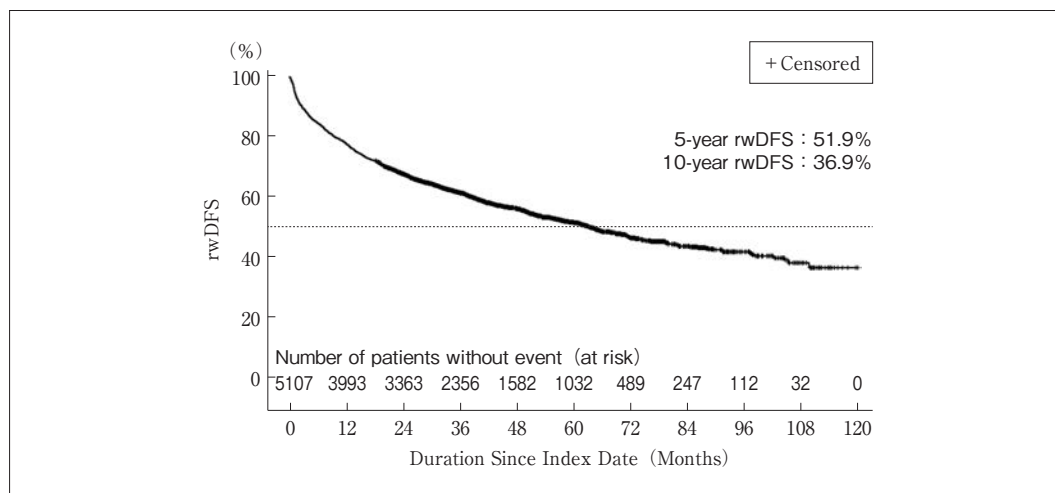


Figure 5 Kaplan-Meier curve for real-world disease-free duration (overall)

Table 5 Clinical outcomes in overall cohort and subgroups

Subgroups	Total patients, n	Time of OS, Month, Mean (S.D.)	Time of rwDFS, Month, Mean (S.D.)	Time of KM estimation rwDFS, Month, Median (95% CI)
Overall cohort	5107	48.2 (23.2)	35.9 (25.5)	64.1 (61.0-68.7)
Age : <75 years	3425	49.9 (23.4)	37.3 (26.5)	74.1 (67.7-82.1)
Age : ≥75 years	1682	44.6 (22.4)	33.1 (23.2)	50.1 (45.1-55.7)
Surgery only	3457	48.2 (22.7)	38.3 (24.6)	79.8 (71.3-97.1)
Neoadjuvant therapy and surgery	72	44.4 (25.0)	20.8 (20.3)	12.6 (8.2-19.6)
Surgery and adjuvant therapy	1479	48.8 (24.0)	32.0 (26.9)	41.3 (37.3-48.7)
Neoadjuvant therapy, surgery and adjuvant therapy	99	41.2 (27.9)	23.3 (25.8)	12.7 (5.8-24.2)
Stage I (UICC version 7)	2663	57.1 (22.8)	44.4 (27.1)	86.1 (76.2-102.1)
Stage II (UICC version 7)	473	47.8 (24.8)	27.5 (26.0)	19.5 (16.1-26.0)
Stage III A (UICC version 7)	243	46.3 (25.7)	25.3 (26.5)	14.6 (11.8-20.4)
Stage I (UICC version 8)	1148	32.3 (8.1)	26.8 (12.1)	NC
Stage II (UICC version 8)	206	29.7 (10.7)	18.4 (13.6)	18.3 (13.2-25.1)
Stage III A (UICC version 8)	100	28.1 (11.6)	15.8 (13.9)	10.6 (7.1-16.1)

KM, Kaplan-Meier ; NC, not calculated ; OS, overall survival ; rwDFS, real-world disease-free survival

early-stage NSCLC patients. However, it is important to consider that these findings are not statistically validated and could be influenced by unaccounted factors such as staging, age and comorbidities. The Kaplan-Meier curves for the groups that received treatments other than surgery were below that of the surgery-only group. The possible reasons are : The rate of stage I was higher in surgery only patients (UICC version 7 ; 56.7%), and the CCI was relatively higher in patients who took both neoadjuvant and adjuvant therapy (median ; 5.0). This observation aligns with Alexander et al.²¹⁾ who noted the presence of comorbidities may contribute to the prognosis. These patients' characteristics gaps among treatment patterns highlight the need for cautious interpretation of the data and underscore the potential for confounding factors to impact treatment outcomes.

Although adjuvant chemotherapy shows survival benefit in patients with completely resected NSCLC, the rate of those who undergo adjuvant chemotherapy remains low, 22-40% and this proportion aligns with our findings. The low uptake may be associated with concerns about toxicity and potentially lethal adverse events²²⁾.

The findings of this study also align with a growing body of literature that underscores the significant role of neoadjuvant and adjuvant therapies in the management of resectable NSCLC. Notably, the incorporation of immunotherapeutic agents such as nivolumab and pembrolizumab in combination with chemotherapy has been shown to enhance event-free survival and increase the rate of pathological complete response. For instance, Forde et al. demonstrated that

neoadjuvant nivolumab plus chemotherapy resulted in notably longer event-free survival compared to chemotherapy only in patients with stage I B to III A resectable NSCLC²³⁾. Similarly, Wakelee et al. found that the perioperative use of pembrolizumab with chemotherapy, followed by resection and continued pembrolizumab, significantly improved outcomes including OS and event-free survival compared to the traditional approach of chemotherapy followed by surgery¹¹⁾.

Moreover, the role of adjuvant therapy, particularly with targeted agents, continues to evolve. The ADAURA trial highlighted the efficacy of adjuvant osimertinib, which showed prolonged disease-free survival (DFS) benefits and a reduction in both local and distant recurrence rates for patients with resected EGFR-mutated NSCLC²⁴⁾. This is consistent with emerging trends suggesting that targeted therapies are reshaping the treatment landscape for patients with specific genetic profiles. Further supporting this trend, the IMpower010 study subgroup analysis of Japanese patients also observed a notable DFS improvement in those treated with adjuvant atezolizumab following cisplatin-based chemotherapy, especially in patients with specific tumor biomarkers²⁵⁾.

However, it is crucial to recognize the limitations inherent in the selection and application of these treatments. The study by Nagasaka and Gadgeel emphasizes the modest benefits of traditional adjuvant chemotherapy in early-stage NSCLC, suggesting a need for more refined criteria to determine which patients are most likely to benefit from such interventions²⁶⁾. Furthermore, Shukuya et al. point out the

specific conditions under which adjuvant chemotherapy with tegafur/uracil is recommended, noting that it may be beneficial only in patients with certain tumor characteristics, underscoring the importance of personalized medicine approaches in the era of molecularly targeted agents and immunotherapy²⁷⁾.

This study faced several limitations due to the constraints inherent with using a secondary database. Patients who sought care at non-participating centers were not tracked in the database. It included only patients who underwent surgery, preventing the identification of those who received neoadjuvant therapy without subsequent surgery. Additionally, stage information was missing for approximately one-third of patients, which reflects the nature of real-world claims data where documentation is driven by billing requirements rather than clinical trial standards. While our study only included patients with a confirmed NSCLC diagnosis, variations in coding practices may contribute to missing stage data.

Our study period ended in April 2022, with patient identification occurring between April 2009 and April 2020. As a result, our dataset does not capture the impact of more recent advancements in perioperative treatment strategies. However, our findings provide an essential historical baseline for understanding treatment patterns before these developments, offering valuable context for future studies evaluating their impact.

Furthermore, OS may be overestimated since the database captures only hospitalization-associated deaths, omitting those occurring in other settings. The definition of rwDFS was further complicated

by the inclusion of procedures and medical encounters linked with NSCLC disease codes, which do not necessarily indicate active disease and may not reflect genuine disease progression.

This analysis reveals considerable variations in treatment approaches across different patient demographics and NSCLC stages. Notably, the limited use of neoadjuvant therapy (1.4%) highlights a potential area for further optimization in preoperative management. Adjuvant therapy use varied across subgroups, influenced by patient age and disease stage, suggesting a need to refine treatment decision-making frameworks to ensure optimal patient selection. In conclusion, our study provides a robust real-world perspective on perioperative treatment trends and long-term outcomes in early-stage NSCLC in Japan. These findings emphasize the importance of ongoing monitoring and refinement of treatment strategies, highlighting the need for continued research on optimizing perioperative therapies to improve patient outcomes.

Acknowledgements

The authors would like to thank Real World Evidence team, Syneos Health Japan K.K. for medical writing support.

Disclosure

Funding

This study and the preparation of this manuscript were supported by funding from MSD K.K., Tokyo, Japan.

Conflict of interest

KI has received funding for lectures from MSD K.K. Tokyo, Japan, Takeda

Pharmaceutical, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, Ono Pharmaceutical, Pfizer, Novartis, Daiichi Sankyo, Amgen, Nihon Kasei, Janssen Pharmaceutical, and Taiho Pharmaceutical. NO and YI are employees of MSD K.K. Tokyo, Japan. YI holds stocks in Merck & Co., Inc., Rahway, NJ, USA. RM and FW are employees of Syneos Health.

Ethics Statement

The data used for the present study were retrospective and de-identified ; therefore, informed consent was not obtained.

The study was approved by the Institutional Ethical Review Board of the Kitamachi Clinic (Institutional Ethics Review Board No. MSD09875) on February 21, 2024, and conducted in accordance with the Declaration of Helsinki.

Informed Consent : N/A

Registry and the Registration No. of the study/trial : Medical Corporation Toukeikai Kitamachi Clinic Ethical Review Board approval number MSD09875

Animal studies : N/A

Author contributions

All authors contributed equally to the development of this study and the writing of this manuscript.

All authors meet ICMJE authorship criteria and have reviewed and approved the submitted version of the manuscript and agreed to be accountable for all parts of the work.

Data Availability Statement

The data used in this study were obtained

from MDV and are available for procurement through licensing. Access details can be found on MDV website (<https://en.mdv.co.jp/>).

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原著

切除可能な早期非小細胞肺癌日本人患者における 実臨床治療パターンとアウトカム

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要 旨

早期非小細胞肺癌（NSCLC）患者に対する外科切除の周術期治療戦略の実臨床でのエビデンスを検証するため、2008年から2022年までのMedical Data Vision（MDV）データベースを用いて解析を行った。対象となった臨床病期Ⅰ-ⅢA期NSCLC患者5107名のうち、3457名（67.7%）が手術のみ、72名（1.4%）が術前補助療法（NeoAdj）+手術、1479名（29.0%）が術後補助療法（Adj）+手術、99名（1.9%）がNeoAdj+手術+Adjを受けた。最も使用された薬剤はテガフル/ウラシル791名（50.1%）およびプラチナ製剤571名（36.2%）であった。フォローアップ期間中央値は44.4カ月（範囲0.1-139.2）、rwDFS中央値は64.1カ月（95% CI, 61.0-68.7）であり、OS中央値は未達であった。本研究は、最大11年間のフォローアップを通じ、周術期治療戦略の重要性を示した。さらなる実臨床でのエビデンスの蓄積が期待される。

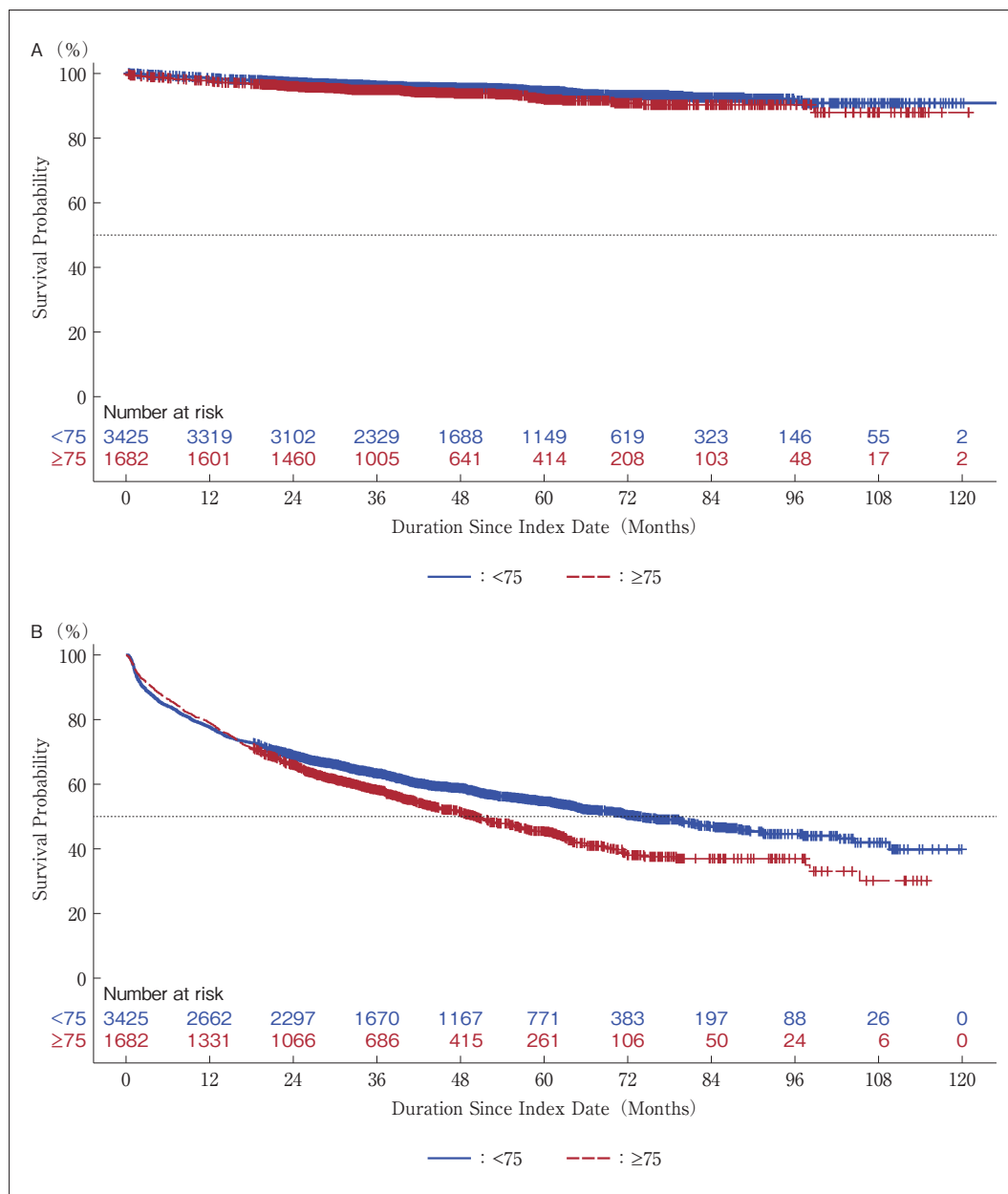


Fig. S1 Kaplan-Meier curves for (A) overall survival and (B) real world disease-free survival (age subgroup)

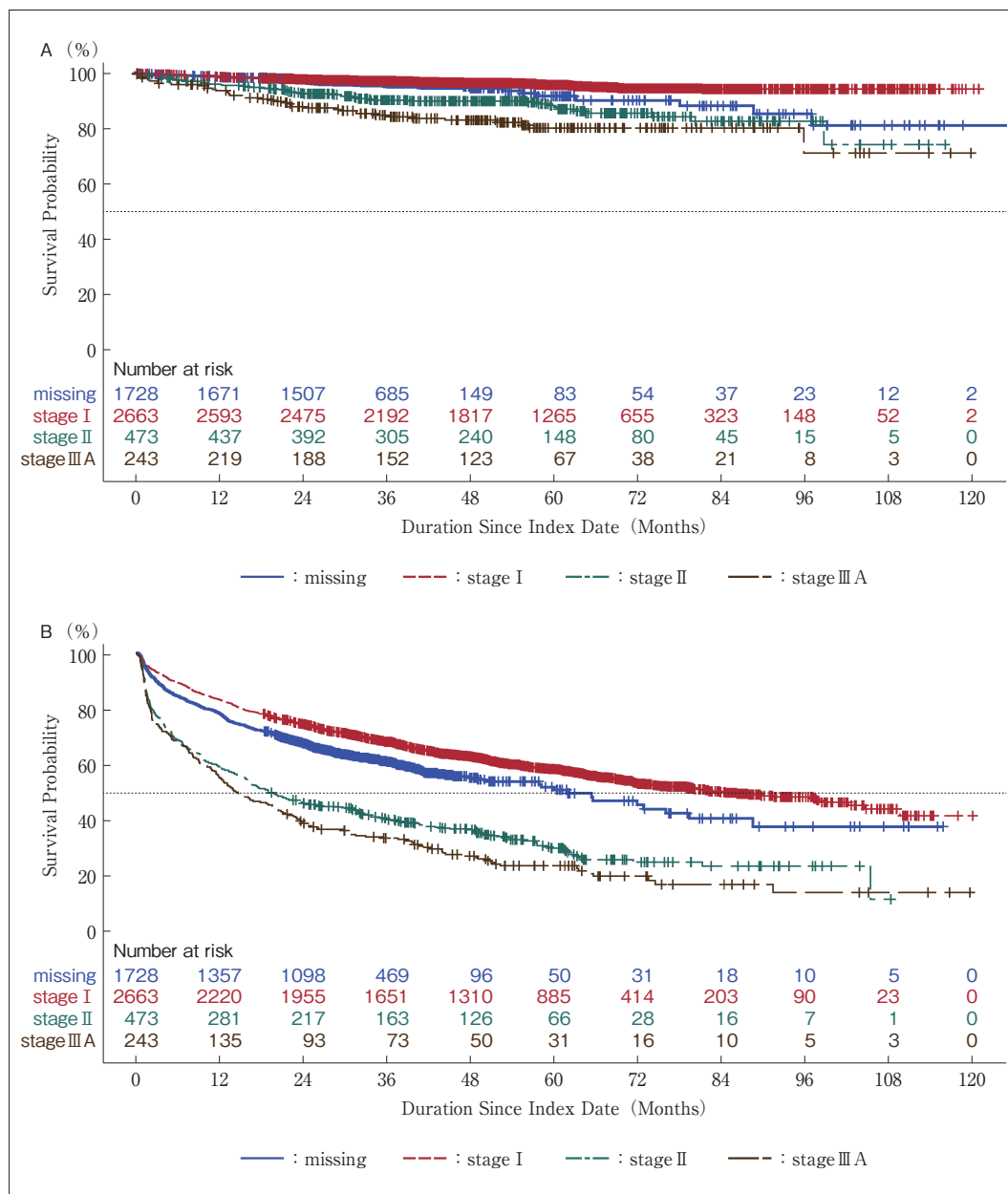


Fig. S2 Kaplan-Meier curves for (A) overall survival and (B) real world disease-free survival (UICC version 7 subgroup)

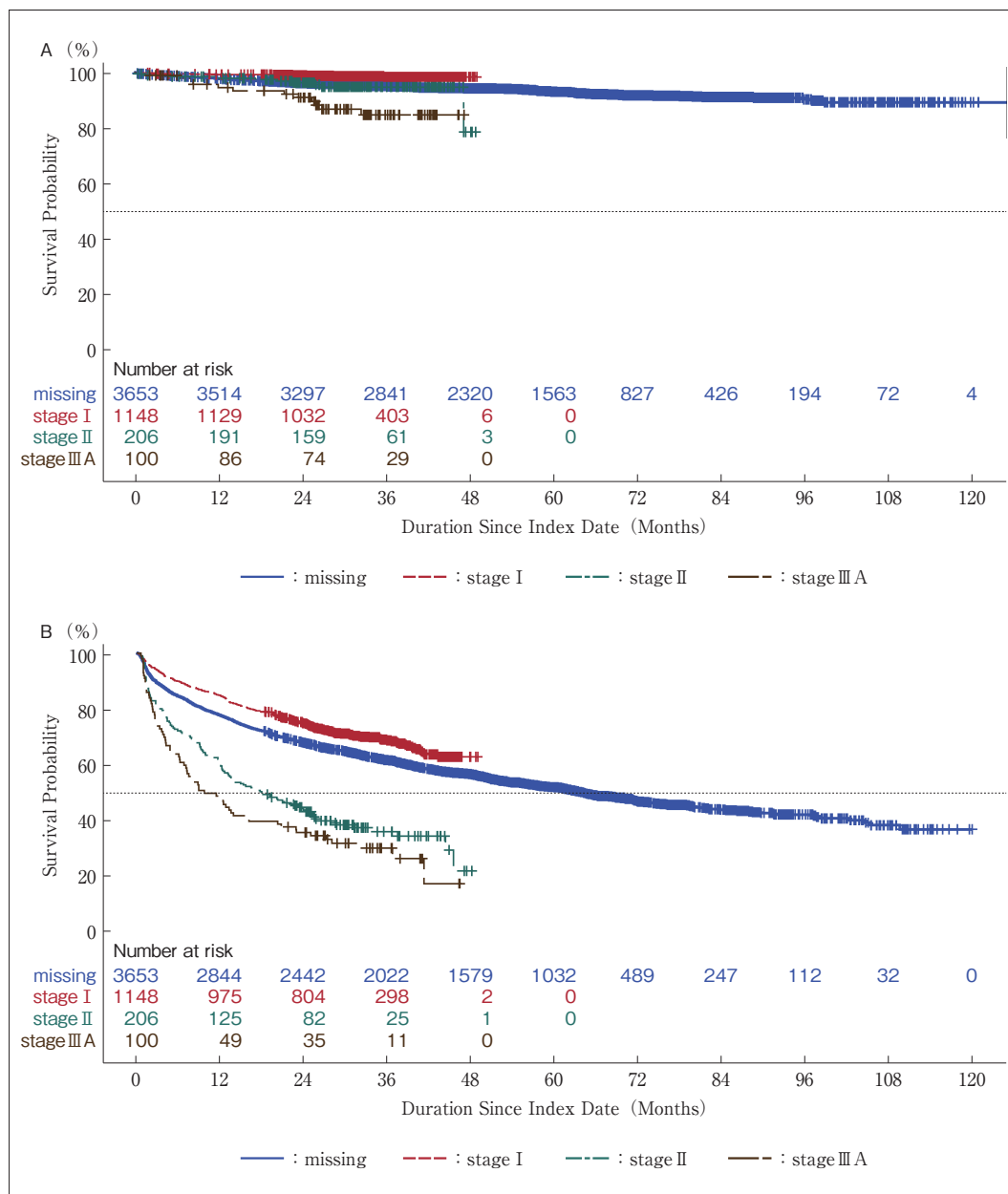


Fig. S3 Kaplan-Meier curves for (A) overall survival and (B) real world disease-free survival (UICC version 8 subgroup)

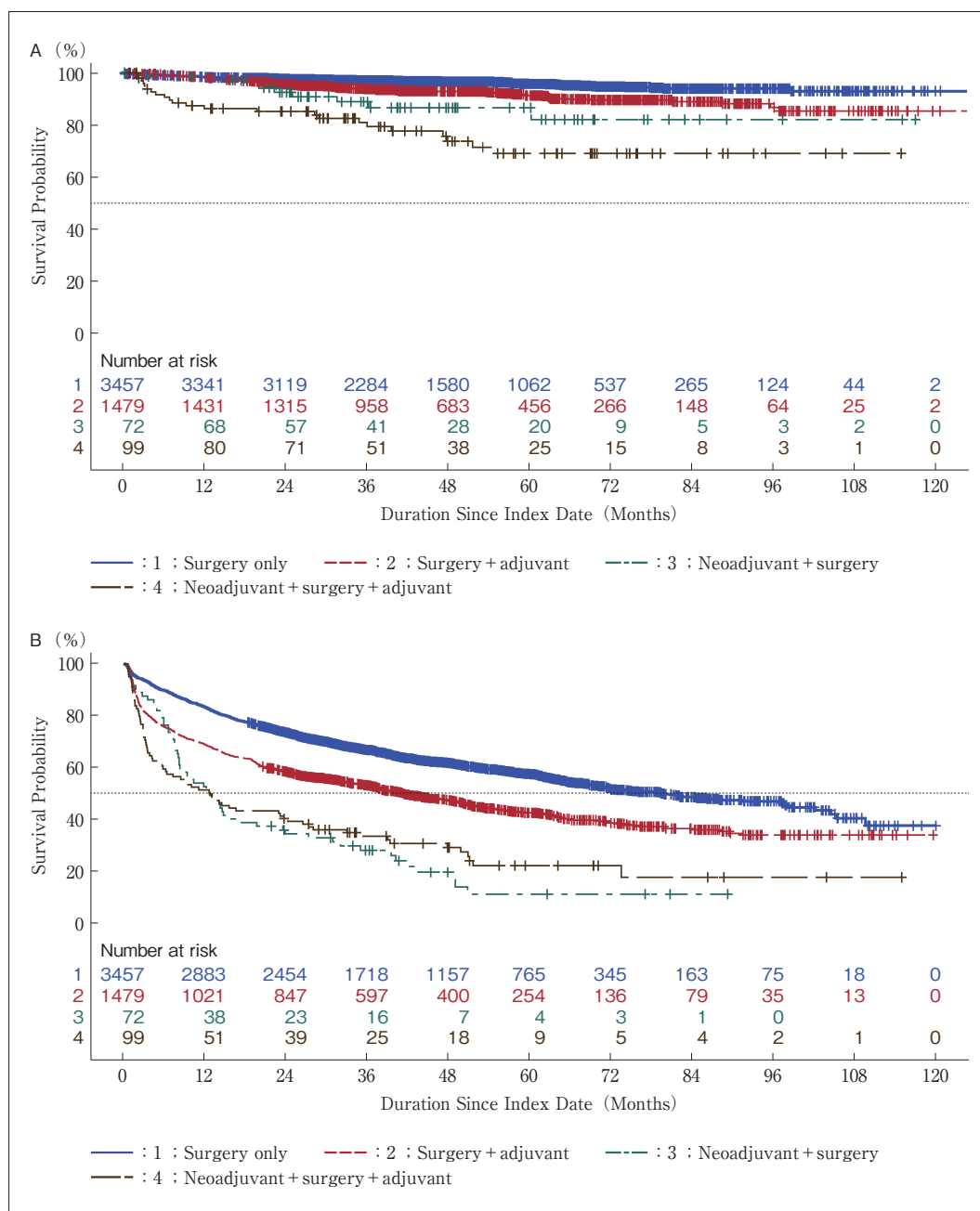


Fig. S4 Kaplan-Meier curves for (A) overall survival and (B) real world disease-free survival (treatment pattern subgroup)

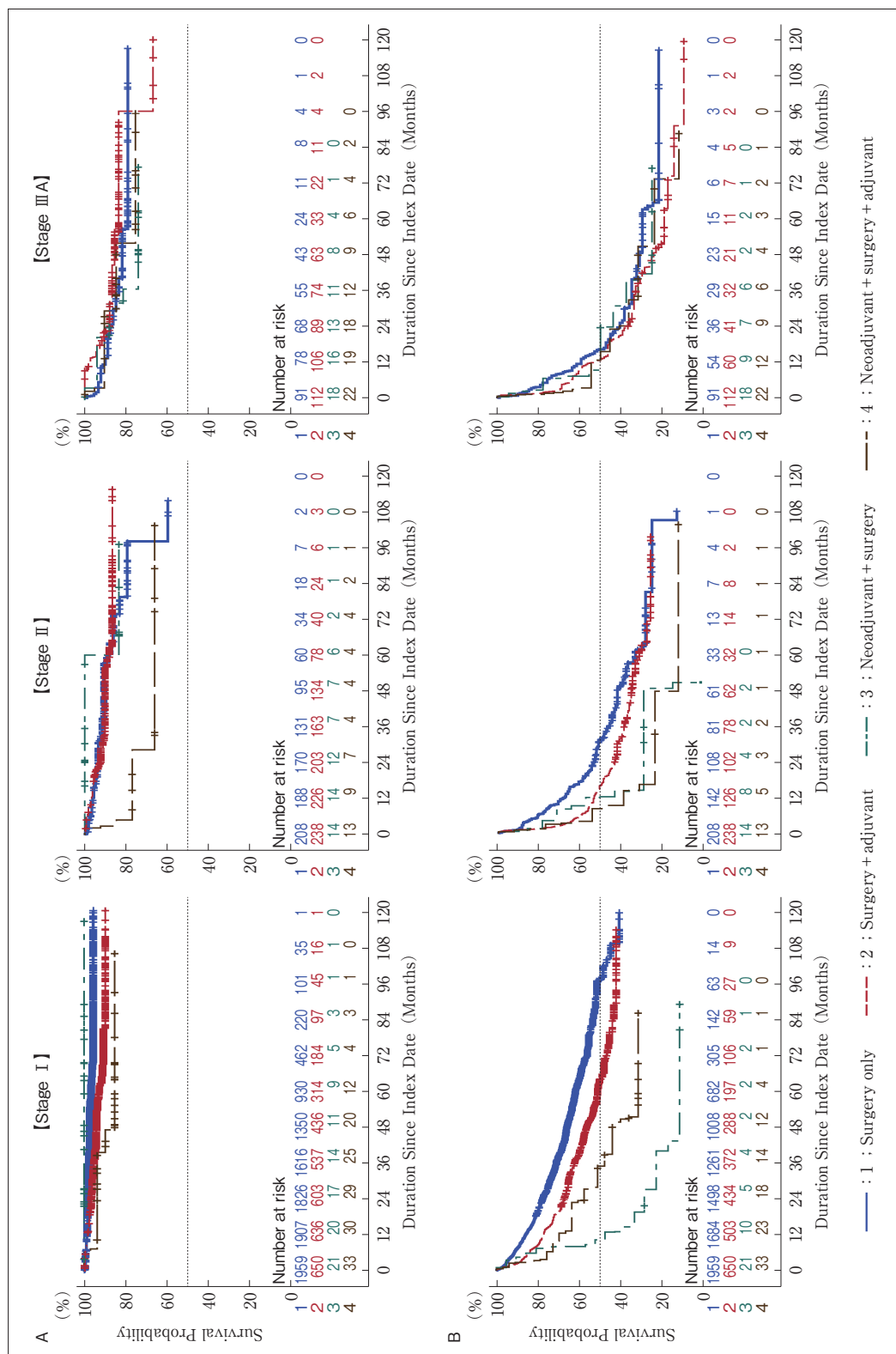


Fig. S5 Kaplan-Meier curves for (A) overall survival and (B) real world disease-free survival (staging [UICC version 7] and treatment pattern subgroup)

(Received for publication July 15, 2025)