

Comparison between patients with or without perioperative rehabilitation on initiation of adjuvant chemotherapy for NSCLC

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Abstract

Introduction: Perioperative rehabilitation is recommended to prevent postoperative complications for patients with non-small cell lung cancer (NSCLC) who underwent surgery. However, the influence on the initiation of adjuvant chemotherapy for perioperative rehabilitation is unclear. This study aimed to investigate the impact of perioperative rehabilitation on the administration of adjuvant chemotherapy, in patients with stage II–IIIB NSCLC in Japan.

Methods: This observational study used a health claims database and included patients with resected stage II–IIIB NSCLC between 2017 and 2023. Perioperative rehabilitation was defined as rehabilitation starting within 7 days before or after surgery. The primary outcome was the proportion of patients who initiated adjuvant platinum-based chemotherapy within 90 days after surgery. Inverse probability of treatment weights (IPTW) based on propensity score were used to balance patient characteristics between patients with rehabilitation and without rehabilitation. Adjusted risk differences were estimated using IPTW weighted modified least squares regression. Subgroup analyses of NSCLC stages and comparative analyses of the rehabilitation subgroup versus patients without rehabilitation were performed. Additionally, a machine learning approach using a random forest model was applied to explore predictors for the delivery of perioperative rehabilitation and adjuvant chemotherapy. The shapley additive explanation (SHAP) values were summarized by a beeswarm plot, and the mean absolute SHAP value was calculated.

Results: A total of 8111 patients with stage II–IIIB NSCLC were included, of whom 5158 (median age: 73.0 years; 72.0% male) received perioperative rehabilitation and 2953 (72.0 years; 69.8% male) did not. Crude proportion of adjuvant chemotherapy initiation was 31.1% in patients with rehabilitation versus 29.1% in patients without rehabilitation. After IPTW weighting, the adjusted difference was 0.041 (95% CI 0.021, 0.062), equivalent to a difference of 4.1%, which was statistically significant ($P < .001$). In subgroup analyses, similar trends were observed. The top three features for perioperative rehabilitation of mean absolute SHAP value were type of hospital, hospital size and age. In addition, the top three features for adjuvant chemotherapy of mean absolute SHAP value were age, N factor and T factor according to the TNM. Perioperative rehabilitation was ranked seventh.

Conclusions: This nationwide cohort study showed that perioperative rehabilitation was associated with significantly more frequent initiation of adjuvant chemotherapy in patients with stage II–IIIB NSCLC. Additionally, our results showed that type of hospital and size contributed to implementation of perioperative rehabilitation. This suggests that hospital capacity and care-delivery system may be relevant for perioperative rehabilitation.

The study protocol was approved by the MINS research ethics committee (8 August 2024, approval number: MINS-REC-240223). This study was funded by AstraZeneca K.K.

Before IPTW weighting, patients in the perioperative rehabilitation group tended to be older, more likely to be male, and more frequently had poorer Hugh-Jones classification compared with those without perioperative rehabilitation; however, these imbalances were well balanced after weighting.

Table 1. Patients Characteristics and IPTW weighting

	Before weighting			After weighting		
	With perioperative rehabilitation	No perioperative rehabilitation	SMD	With perioperative rehabilitation	No perioperative rehabilitation	
Number of patients, n	5,158	2,953		7,500	7,552	
Age (years)	Mean [SD]	71.8 [8.7]	70.6 [9.3]	0.13	71.6 [8.8]	71.6 [9.0]
Gender, n (%)						
Male	3,716 (72.0)	2060 (69.8)	0.05	5286 (70.5)	5326 (70.5)	
Women	1442 (28.0)	893 (30.2)		2214 (29.5)	2226 (29.5)	
BMI (kg/m ²)	Mean [SD]	23.12 [3.43]	22.99 [3.47]	0.04	23.13 [3.42]	23.16 [3.49]
Hugh-Jones classification, n (%)						
0	145 (2.8)	108 (3.7)	0.05	235 (3.1)	237 (3.1)	
1	382 (7.4)	229 (7.5)	0.08	569 (7.5)	569 (7.5)	
2	769 (14.9)	396 (13.4)	0.04	1055 (14.1)	1048 (13.9)	
3	222 (4.3)	83 (2.8)	0.08	276 (3.7)	299 (4.0)	
4	134 (2.6)	55 (1.9)	0.05	176 (2.3)	205 (2.7)	
5	56 (1.1)	19 (0.6)	0.05	69 (0.9)	65 (0.9)	
Complications, n (%)						
ILD	678 (13.1)	352 (11.9)	0.04	971 (13.0)	1003 (13.3)	
COPD	2057 (39.9)	1235 (41.8)	0.04	3002 (40.0)	3021 (40.0)	
Stage, n (%)						
IIA	948 (18.4)	577 (19.5)	0.03	1,478 (19.7)	1460 (19.3)	
IIIB	2382 (46.2)	1317 (44.6)	0.03	3447 (46.0)	3458 (45.8)	
IIIA	1533 (29.7)	897 (30.4)	0.01	2171 (29.0)	2182 (28.9)	
IIIB	295 (5.7)	162 (5.5)	0.01	403 (5.4)	452 (6.0)	
Surgical procedure, n (%)						
Lobectomy	4346 (84.3)	2409 (81.6)	0.07	6,703 (89.4)	6721 (89.0)	
Total pneumonectomy	89 (1.7)	33 (1.1)	0.05	123 (1.6)	126 (1.7)	
Segmental resection	165 (3.2)	119 (4.0)	0.04	283 (3.8)	279 (3.7)	
Partial resection	237 (4.6)	160 (5.4)	0.04	391 (5.2)	426 (5.6)	

Background

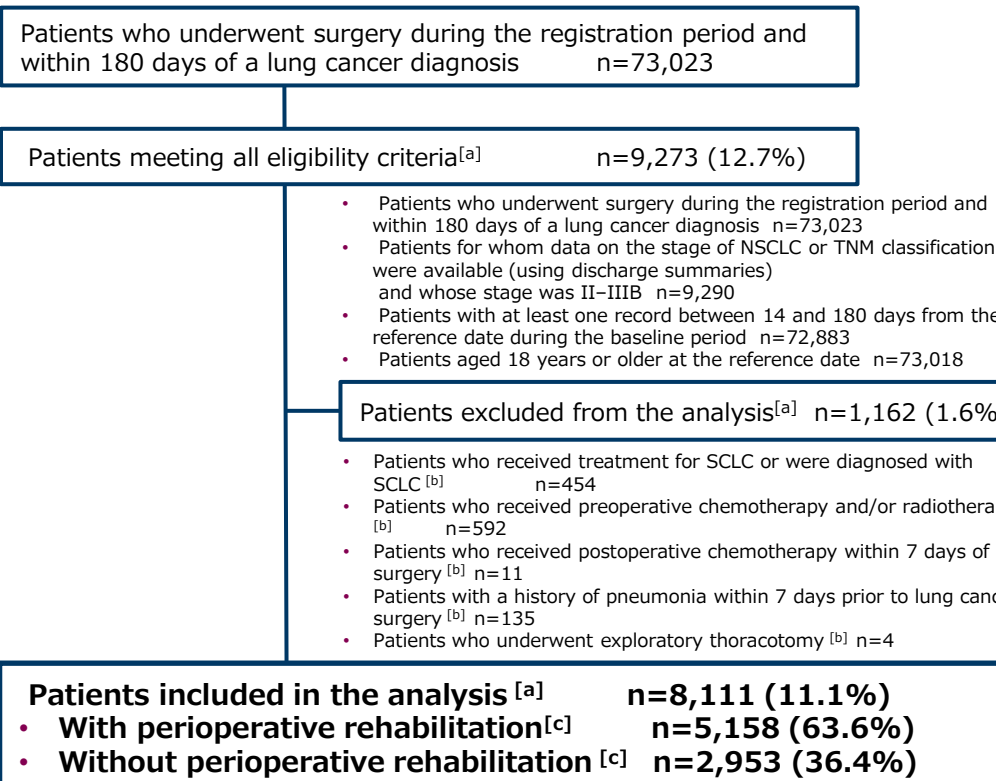
- Adjuvant platinum-based chemotherapy is recommended for patients with non–small cell lung cancer (NSCLC) who have undergone curative resection for pathological stage II–IIIB disease.¹
- The reported rates of administration of adjuvant chemotherapy are approximately 40% in stage II and 50% in stage IIIA, and its utilization is influenced by the patient's overall physical condition.²
- Perioperative rehabilitation is expected to reduce the risk of postoperative complications and promote recovery of physical function;³ however, its actual implementation rate has been reported to be approximately 50%.⁴
- Supporting patients' general condition through perioperative rehabilitation may improve tolerance to adjuvant chemotherapy in patients with NSCLC.

- Japanese Lung Cancer Society (ed.), Guidelines for the Diagnosis and Treatment of Lung Cancer, including Malignant Pleural Mesothelioma and Thymic Tumors, 2024 Edition, 2024. Kanahara Publishing
- Oya et al., 64th Annual Meeting of the Japanese Lung Cancer Society, 2023
- Japanese Society of Rehabilitation Medicine (ed.), Guidelines for Cancer Rehabilitation, 2nd Edition, 2019. Kanahara Publishing
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Results

Among 73,023 patients who underwent lung cancer surgery during the registration period, 8,111 met the eligibility criteria. Of these, 63.6% received perioperative rehabilitation as defined in this study.

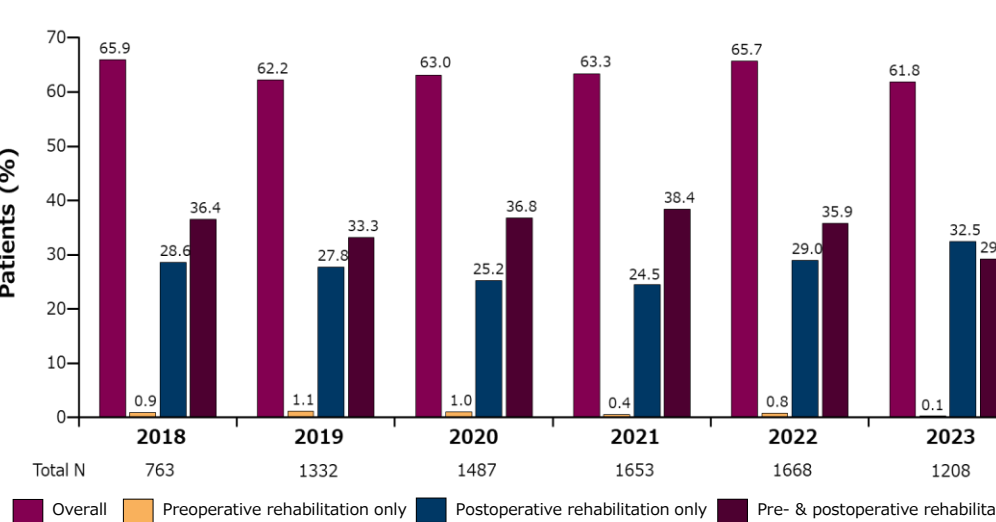
Figure 1. Study Diagram



*The earliest surgery date was used. [a] The denominator was the total number of patients in the cohort. [b] There is overlap in the counts between categories. [c] The denominator was the number of patients included in the analysis.

Regarding temporal trends in the implementation of perioperative rehabilitation, the proportion of patients receiving any perioperative rehabilitation remained slightly above 60% throughout the study period. No marked decline was observed even during the COVID-19 pandemic period.

Figure 2. Annual trends in %pts receiving perioperative rehabilitation



*No cases in 2017 were included because the DPC system was not yet aligned with the 8th edition of the UICC TNM classification.

Objectives / Study Design

Objective: To investigate the impact of **perioperative rehabilitation** on the **initiation of platinum-based adjuvant chemotherapy** in patients who have undergone surgery for stage II–IIIB non-small cell lung cancer.

Study Design: Retrospective cohort study using a claims database (Medical Data Vision, Inc.)

Patients: Patients who underwent surgery for Stage II–IIIB NSCLC

Exposure: Implementation of perioperative rehabilitation

Control: No perioperative rehabilitation

Outcome: Proportion of patients receiving pt-based adjuvant chemotherapy

Primary Outcome Measure: Proportion of patients receiving adjuvant chemotherapy within 90 days of lung cancer surgery

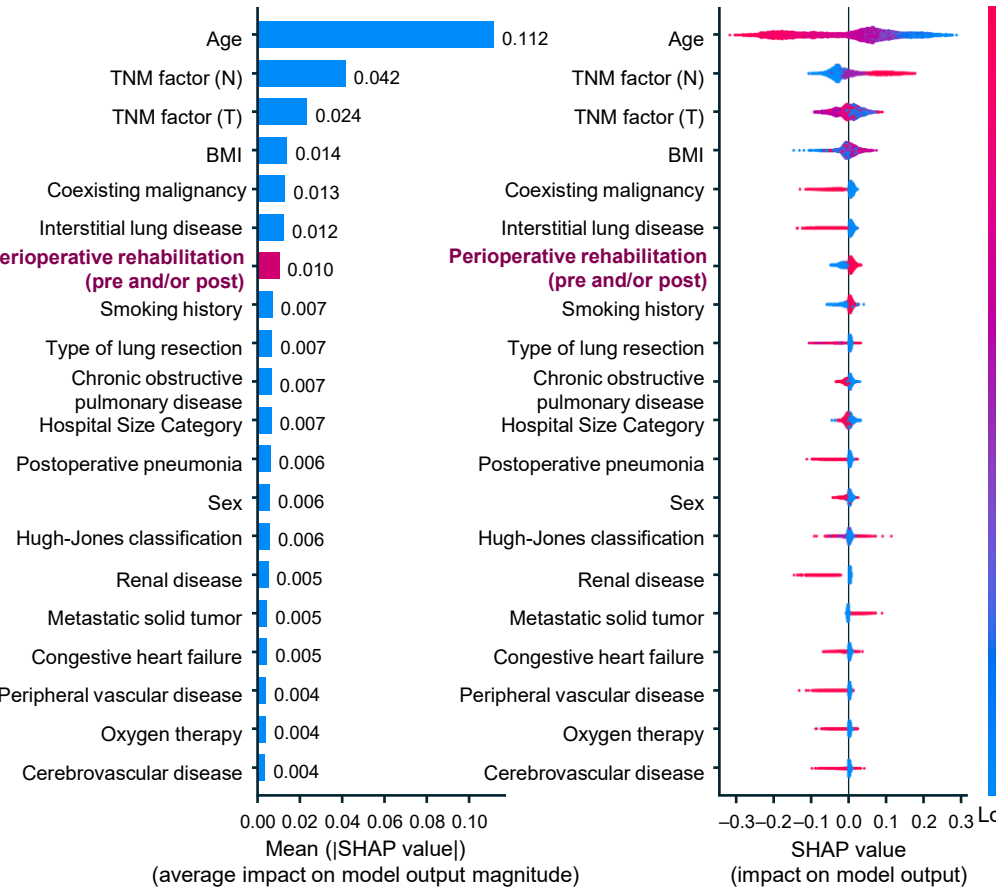
Key Secondary Outcomes: Subgroup analysis of the primary outcome (clinical stage, timing of rehabilitation), Status of perioperative rehabilitation

For the primary endpoint (Table 2: right), the initiation rate of platinum-based adjuvant chemotherapy was 4.1% higher in the perioperative rehabilitation group than in the no rehabilitation group.

In subgroup analyses by disease stage and timing of rehabilitation, although confidence intervals became wider due to reduced sample sizes, a consistent trend toward higher initiation rates of platinum-based adjuvant chemotherapy in the perioperative rehabilitation group was observed.

In the predictive model for the implementation of perioperative rehabilitation, the AUC was 0.654 (95%CI, 0.630–0.678), and hospital type, hospital size, and age were the top features based on mean absolute SHAP values. Regarding facility-related factors, general hospitals and those with larger bed capacity were more likely to provide perioperative rehabilitation, while among patient-related factors, older patients were more likely to receive perioperative rehabilitation. In the predictive model for the administration of adjuvant chemotherapy (Figure 3), the AUC was 0.757 (95% CI, 0.736–0.778), and the top three features based on mean absolute SHAP values were age, N factor, and T factor. The implementation of perioperative rehabilitation ranked seventh and represented the highest contributing factor among potentially modifiable variables within the model. Subgroup analyses stratified by perioperative rehabilitation status showed similar trends, indicating no significant interaction between perioperative rehabilitation and the major features associated with the use of adjuvant chemotherapy.

Figure 3. SHAP-Based Feature Importance Ranking and Effect Direction for Initiation of Adjuvant Chemotherapy



Eligibility Criteria

- Patients who underwent lung cancer surgery between January 2017 and September 2023
- Patients diagnosed with lung cancer within 180 days prior to lung cancer surgery
- Patients whose lung cancer was classified as stage II–IIIB according to the 8th edition of the UICC
- Patients aged 18 years or older on the reference date (7 days after lung cancer surgery)
- Patients with at least one record in the period from 180 days to 4 days prior to the reference date

Exclusion criteria

- Patients diagnosed with small cell lung cancer, or patients who have received etoposide or irinotecan
- Patients with a history of pneumonia within 7 days prior to lung cancer surgery
- Patients who received neoadjuvant therapy or preoperative radiotherapy
- Patients who received adjuvant chemotherapy within 7 days of lung cancer surgery
- Patients whose lung cancer surgery was performed via exploratory thoracotomy

Statistical Considerations

- Comparative analysis was performed using propensity score-weighted analysis (IPTW).
- Variables used in the propensity score model: Age, sex, smoking history, BMI, Barthel Index, Hugh-Jones classification, NSCLC stage, facility type, number of beds, surgical procedure, presence of pneumonia within 7 days post-surgery, concomitant ILD/COPD, Charlson Comorbidity Index
- We performed weighted least squares regression analysis using IPTW to estimate the difference in the proportion of patients receiving adjuvant chemotherapy according to the presence or absence of perioperative rehabilitation, along with its 95% confidence interval (CI).
- Subgroup analyses were performed by clinical stage and timing of perioperative rehabilitation.
- We explored predictors for perioperative rehabilitation and postoperative chemotherapy using a random forest model.
- SHAP values were used to quantify the contribution of each predictor to the outcome, and visualized with a bar plot of mean absolute SHAP values and a beeswarm plot.

Table 2. Initiation of adjuvant chemotherapy

Factors	No. of patients	Initiation of adjuvant chemotherapy, No. (%), unadjusted	Adjusted difference in initiation of adjuvant chemotherapy (95% CI)
All patients*			
With rehabilitation	4794	1489 (31.1)	0.041 (0.021, 0.062)**
Without rehabilitation	2708	788 (29.1)	**p<.001
Stage of NSCLC			
Stage IIA			
With rehabilitation	920	172 (18.7)	0.045 (0.006, 0.085)
Without rehabilitation	565	84 (14.9)	
Stage IIB			
With rehabilitation	2232	645 (28.9)	0.020 (–0.010, 0.050)
Without rehabilitation	1214	364 (30.0)	
Stage IIIA			
With rehabilitation	1379	569 (41.3)	0.075 (0.034, 0.116)
Without rehabilitation	790	287 (36.3)	
Stage IIIB			
With rehabilitation	263	103 (39.2)	0.015 (–0.080, 0.111)
Without rehabilitation	139	53 (38.1)	
Timing of rehabilitation			
Preoperative ± postoperative rehabilitation			
With preoperative rehabilitation	2697	796 (29.5)	0.029 (0.006, 0.051)
Without rehabilitation	2708	788 (29.1)	
Postoperative ± preoperative rehabilitation			
With postoperative rehabilitation	4737	1477 (31.2)	0.042 (0.022, 0.063)
Without rehabilitation	2708	788 (29.1)	
Preoperative + postoperative rehabilitation			
With pre- and postoperative rehabilitation	2640	784 (29.7)	0.030 (0.008, 0.053)
Without rehabilitation	2708	788 (29.1)	

* patients with incomplete data were excluded.

Conclusions

- This nationwide cohort study provides, to our knowledge, the first evidence that perioperative rehabilitation is associated with a significantly higher initiation rate of platinum-based adjuvant chemotherapy in patients with Stage II–IIIB NSCLC undergoing curative-intent resection, a finding consistently supported by subgroup analyses and machine learning models.
- Perioperative rehabilitation was also identified as one of the predictors of adjuvant chemotherapy initiation in the machine learning model, along with established clinical factors such as age and disease status. Further studies are warranted to explore strategies for broader implementation of perioperative rehabilitation and to validate its role in the evolving context of perioperative pharmacotherapy.