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Postoperative cerebral infarction risk is related to lobectomy site in lung cancer: a retrospective cohort study of nationwide data in Japan

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ABSTRACT

Objectives To determine the incidence of cerebral infarction after lobectomy at different sites using inpatient data from a diagnosis procedure combination database.
Design Retrospective cohort study.
Setting Data were retrieved from the Japanese diagnosis procedure combination inpatient database for patients who underwent lobectomies for lung cancer between April 2018 and March 2020.
Participants The analysis included 37 352 patients from 556 institutions who underwent lobectomies for lung cancer.
Main outcomes and measures The occurrence of cerebral infarction after lobectomy during hospitalisation was estimated using multilevel logistic regression models adjusted for sex, age, body mass index, smoking history, activity of daily living, surgical approach (thoracotomy or video-assisted), clinical cancer stage, comorbidities and hospital-level factors to describe the association between cerebral infarction and different lobectomy sites.
Results Overall cerebral infarction after lobectomy occurred in 99 patients (0.27%): 29 with left upper lobectomy (0.39%), 19 with left lower lobectomy (0.34%), 32 with right upper lobectomy (0.24%), 6 with right middle lobectomy (0.21%) and 13 with right lower lobectomy (0.16%). The multilevel multivariate logistic regression analysis revealed high ORs for the left upper lobectomy and left lower lobectomy groups. In both univariate and multivariate analyses, left upper lobectomy had the highest OR for the occurrence of cerebral infarction compared with lobectomies at other sites.
Conclusions and relevance Left upper lobectomy had the highest OR for the occurrence of cerebral infarction after lung cancer lobectomy during hospitalisation. There is an urgent need to investigate the specific mechanisms underlying postoperative cerebral infarction after left upper lobectomy and to establish preventive measures such as altering surgical methods, using radiological examinations for early detection and better use of anticoagulants.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Cerebral infarction after lobectomy is an irreversible and sometimes life-threatening complication.
- ⇒ Previous studies have reported that left upper lobectomy contributes to a higher risk of developing cerebral infarction compared with lobectomies at other sites, but these studies have been case reports or small-scale case-control studies.
- ⇒ The relationship between the site of lobectomy and incidence of cerebral infarction after surgery still requires confirmation with large-scale clinical data.

WHAT THIS STUDY ADDS

- ⇒ Among all sites of lobectomies, the left upper lobectomy was found to have the highest OR for postoperative cerebral infarction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The findings of this study highlight the urgent need for new interventional research to define the specific mechanisms underlying postoperative cerebral infarction after left upper lobectomy and to establish preventive measures.

INTRODUCTION

In Japan, lung cancer has the third highest morbidity and the highest mortality rate among all malignancies.[1] Depending on the tumour node metastasis (TNM) stage, different therapies are used as treatment, including surgery, radiation and chemotherapy. In general, patients with stage 0–3A lung cancer undergo surgery, with lobectomy being the standard procedure. The reported postoperative complications are bronchopleural fistula, arrhythmias, including atrial fibrillation and more serious complications such as acute exacerbation of interstitial pneumonia, infections, including pneumonia and fistulous empyema and thromboembolic disease such as cerebral infarction.[2]

Cerebral infarction after lobectomy is an irreversible and sometimes life-threatening complication. The risk factors for cerebral infarction after lung resection are cardiac thromboembolism due to postoperative atrial fibrillation,[3] cancer-associated hypercoagulability (Trousseau syndrome),[4] postoperative dehydration[5] and other common risks such as diabetes, smoking and prolonged bed rest.[6] Previous studies have reported that left upper lobectomy contributes to a higher risk of developing cerebral infarction compared with lobectomies at other sites.[7–13] However, because cerebral infarction is such a rare complication of pulmonary resection, with rates as low as 0.2%–0.8%, almost all of these studies were case reports or small-scale case-control studies.[14 15] The relationship between the site of lobectomy and incidence of cerebral infarction after surgery still requires confirmation with large-scale clinical data.

The aim of this study was to identify the incidence of cerebral infarction after lobectomies performed at different sites by using a Japanese nationwide database from the diagnosis procedure combination (DPC) system. We hypothesised that left upper lobectomy would have the highest risk of causing postoperative cerebral infarction compared with lobectomies at other sites.

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted using data from the Japanese DPC inpatient database from April 2018 to March 2020. The DPC system was introduced in 2003 in Japanese medical hospitals authorised to treat patients enrolled in a health insurance plan. As of 2020 in Japan, over 1600 hospitals have adopted the DPC system.[16] The system determines the per-diem hospital reimbursement based on patient diagnosis and the procedures made available to them during their hospital stay to regulate diagnostic and therapeutic approaches. DPC data consist of medical procedures such as surgeries and treatments performed, medications and disease names with the dates of onset or which are indexed in the original Japanese codes.[16 17] Of the over 1600 hospitals participating in DPC, we constructed our database by analysing DPC data from 1291 hospitals, which covers approximately 90% of all acute care beds in Japan. We analysed 16 001 612 inpatient cases from these hospitals between 1 April 2018 and 31 March 2020.

Case selection

We identified patients who had undergone lobectomies based on the codes of the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10 code) and the Japanese medical intervention classification master codes (treatment code).[18] These were then used to unify information entered into the DPC database. Hospitalised patients who had undergone a lobectomy for primary lung cancer (ICD-10 code: C34) and patients who had undergone a lobectomy (treatment codes: K5143, 514-23) were included in the study. Exclusion criteria included missing information (body mass index (BMI), activity of daily living (ADL), smoking history and clinical TNM classification), failure to identify

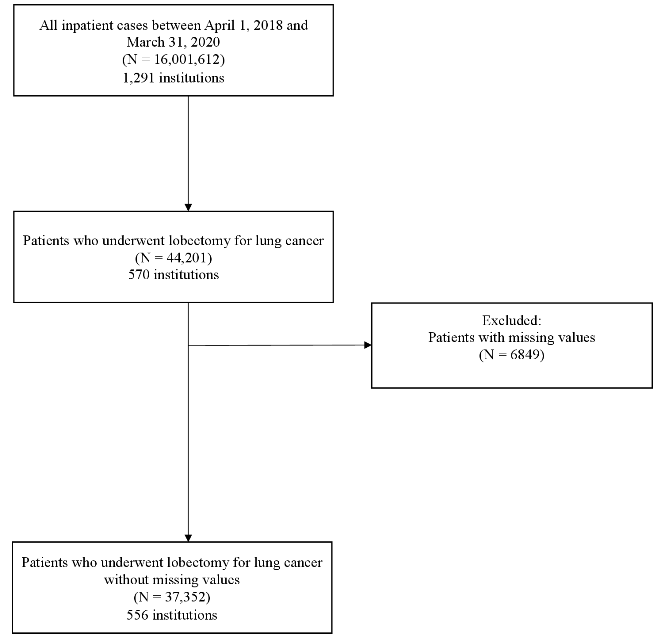

Figure 1 Flow chart of inclusion and exclusion criteria for the study. From the data of 16 001 612 hospitalised patients, 37 352 cases of lobectomy for lung cancer were extracted.

the resected lobe or more than once surgical procedure for lung cancer (treatment code; K514: lung malignant tumour surgery, or K514-2: video-assisted lung malignant tumour surgery) during the same hospitalisation period. A flow chart of the case selection process is presented in figure 1.

Evaluation of the resected lobe

Each patient's resected lobe was labelled with the appropriate ICD-10 code (C341: upper lobe, C342: middle lobe, C343: lower lobe) and by the surgical information in the DPC database as right-sided or left-sided.

Evaluation of postoperative cerebral infarctions

From the DPC records of ICD-10 codes for postoperative complications during hospitalisation, we identified 'I63' as a postoperative cerebral infarction.[16]

Covariates variables

The following confounding factors were extracted from the information contained in the DPC data: patients' characteristics (age,[19] sex, BMI, smoking history and ADL[6]), clinical cancer TNM stage,[4 20] surgical approach (thoracotomy or video-assisted) and underlying comorbidities as risks for thrombosis. BMI was divided into the following quaternary groups: <18.5 (underweight), 18.5–25 (normal range) and ≥25 (obese), according to the guidelines of the Japan Society for the Study of Obesity.[21] Smoking history was categorised into 'never' and 'current or former', and ADL was categorised into fully ambulatory, use of a cane, wheelchair users and total assistance. We classified cancer TNM stage as follows: stage 0 (T0–Tis, N0, M0), stage 1 (T1–T2a, N0, M0), stage 2 (T2b–T3, N0, M0 or T1–T2, N1, M0), stage 3 (T4, N0, M0 or T3–T4, N1, M0 or any T, N2–N3, M0) and stage 4 (any T, any N, M1), according to WHO standards.[22] Underlying comorbidities used as covariates included atrial fibrillation,[3] diabetes, hypertension,[23] history of cerebral infarction,[24 25] heart failure,[26] hypertrophic cardiomyopathy,[27 28] chronic kidney disease (stage 3–5)[29] and vascular disease (history of myocardial infarction,[30] arterial plaque[31] and venous thrombosis[32]) according to previous studies and clinical experience.

Statistical analysis

The ORs with 95% CIs were estimated using a multilevel logistic model nested in each hospital. In the multivariate analysis, the model included age, sex, BMI, smoking history, ADL, clinical cancer TNM stage, surgical approach, operative time, underlying comorbidities and number of surgeries for lobectomy as the hospital-level factor, dividing them into quartiles. P<0.05 was considered statistically significant. Statistical analyses were performed using commercial software (Stata Statistical Software: Release 16; StataCorp, College Station, Texas, USA).

RESULTS

Patient characteristics

This study included 37 352 patients from 556 institutions who underwent lobectomies for lung cancer. In this cohort, 7462 (20.0%) underwent left upper lobectomies, 5593 (15.0%) underwent left lower lobectomies, 13 075 (35.0%) underwent right upper lobectomies, 2912 (7.8%) underwent right middle lobectomies and 8310 (22.3%) underwent right lower lobectomies (table 1).

ORs for the occurrence of cerebral infarction

In this population, cerebral infarction after lobectomy occurred in 99 of 37 352 patients (0.27%); 29 with left upper lobectomies (0.39%), 19 with left lower lobectomies (0.34%), 32 with right upper lobectomies (0.24%), 6 with right middle lobectomies (0.21%) and 13 with right lower lobectomies (0.16%) (table 2). Multivariate analysis identified the highest ORs for the left upper lobectomy (OR 2.66, 95% CI 1.37 to 5.16, p=0.004) and left lower lobectomy (OR 2.20, 95% CI 1.08 to 4.49, p=0.03) groups.

In the post hoc analysis, we found that the existence of postoperative atrial fibrillation was significantly associated with cerebral infarction (adjusted OR 7.69, 95% CI 4.14 to 14.29, p<0.001), but there was less change in ORs in the resected lobe for the occurrence of cerebral infarction after adding postoperative atrial fibrillation as a covariate in the statistical model.

DISCUSSION

We examined the incidence of cerebral infarction in relation to different lobectomy sites. We found that left upper and left lower lobectomies were risk factors for cerebral infarction occurrence, with left upper lobectomies showing the highest OR among all other types of lobectomies.

We demonstrated that left upper lobectomy for cancer is a significant risk factor for postoperative cerebral infarction using a large, real-world dataset as opposed to case-control studies of smaller populations. Similar to the findings of our study, the incidence of postoperative cerebral infarction was reported to be higher in patients undergoing left upper lobectomy in a retrospective case-control study that collected data from 1670 patients' medical records between 2008 and 2015.[11] Resection of the left upper lobe was also reported to increase the risk of cerebral infarction in a multicentre, retrospective case-control study that used data of 610 patients collected from 153 institutions of the Japanese Association for Chest Surgery between 2004 and 2013.[10]

We suggest one major possible mechanism underlying the occurrence of postoperative cerebral infarction after left upper lobectomy. It is thrombosis in the long pulmonary vein stump, which has been reported previously.[7–9 12 13] Long pulmonary vein stumps are more likely to remain after a left upper lobectomy, which may cause thrombosis in the left atrium after lung resection, as shown using contrast-enhanced CT.[7 8 13] The median length of the pulmonary vein stump after left upper lobectomy was reported to be significantly longer than that of the other pulmonary vein stumps.[8] Furthermore, blood flow evaluation using intraoperative ultrasonography showing the presence of spontaneous echo contrast in the left superior pulmonary vein stump has been reported to be predictive of thrombosis that could cause arterial infarction.[9] In addition, the mechanism of thrombus formation in the vein stump was explainable by Virchow's triad (ie, blood stasis, endothelial injury and hypercoagulability).[12] These reports revealed congestion and blood flow turbulence in the long pulmonary vein stump, which may contribute to cerebral infarction after a left upper lobectomy.

On the contrary, we suggest atrial fibrillation as one minor possible mechanism underlying the occurrence of postoperative cerebral infarction after left upper lobectomy. Although only one article analysing the relationship between lobectomy and atrial fibrillation was found in our search, left lobectomy (including lower lobectomy) was suggested as a risk factor for atrial fibrillation after lobectomy in a single-centre retrospective cohort study that used data of 186 patients between 2005 and 2010,[3] citing vagal stimulation associated with lobectomy

Table 1 Basic characteristics of the patients

	Total	Left upper lobectomy	Left lower lobectomy	Right upper lobectomy	Right middle lobectomy	Right lower lobectomy
	N=37 352	N=7462	N=5593	N=13 075	N=2912	N=8310
		20.0%	15.0%	35.0%	7.80%	22.3%
Variables						
Age, mean (SD)	70.0 (9.1)	69.6 (9.0)	70.3 (9.1)	69.9 (9.0)	69.8 (10.0)	70.4 (8.9)
Sex, men	22 377 (59.9%)	4495 (60.2%)	3276 (58.6%)	7946 (60.8%)	1487 (51.1%)	5173 (62.3%)
Body mass index						
<18 kg/m^2	1443 (3.9%)	257 (3.4%)	210 (3.8%)	492 (3.8%)	132 (4.5%)	352 (4.2%)
18–24.9 kg/m^2	24 416 (65.4%)	4874 (65.3%)	3696 (66.1%)	8502 (65.0%)	1888 (64.8%)	5456 (65.7%)
>25 kg/m^2	11 493 (30.8%)	2331 (31.2%)	1687 (30.2%)	4081 (31.2%)	892 (30.6%)	2502 (30.1%)
Smoking history (current or former)	22 604 (60.5%)	4512 (60.5%)	3325 (59.4%)	8011 (61.3%)	1459 (50.1%)	5297 (63.7%)
Activity of daily living						
Self-reliant	36 727 (98.3%)	7345 (98.4%)	5503 (98.4%)	12 875 (98.5%)	2847 (97.8%)	8157 (98.2%)
Use of a cane	377 (1.0%)	63 (0.8%)	60 (1.1%)	125 (1.0%)	42 (1.4%)	87 (1.0%)
Wheelchair user	144 (0.4%)	33 (0.4%)	17 (0.3%)	38 (0.3%)	13 (0.4%)	43 (0.5%)
Total assistance	104 (0.3%)	21 (0.3%)	13 (0.2%)	37 (0.3%)	10 (0.3%)	23 (0.3%)
Cancer TNM stage						
0	1757 (4.7%)	302 (4.0%)	210 (3.8%)	703 (5.4%)	205 (7.0%)	337 (4.1%)
I	26 765 (71.7%)	5332 (71.5%)	3908 (69.9%)	9749 (74.6%)	2254 (77.4%)	5522 (66.5%)
II	5303 (14.2%)	1067 (14.3%)	955 (17.1%)	1582 (12.1%)	255 (8.8%)	1444 (17.4%)
III	3188 (8.5%)	691 (9.3%)	454 (8.1%)	943 (7.2%)	169 (5.8%)	931 (11.2%)
IV	339 (0.9%)	70 (0.9%)	66 (1.2%)	98 (0.7%)	29 (1.0%)	76 (0.9%)
Comorbidities						
Any of the following applies	16 183 (43.3%)	3240 (43.4%)	2377 (42.5%)	5649 (43.2%)	1215 (41.7%)	3702 (44.5%)
Chronic kidney disease	276 (0.7%)	39 (0.5%)	46 (0.8%)	110 (0.8%)	21 (0.7%)	60 (0.7%)
Vascular disease	1034 (2.8%)	230 (3.1%)	181 (3.2%)	326 (2.5%)	64 (2.2%)	233 (2.8%)
Hypertrophic cardiomyopathy	47 (0.1%)	7 (0.1%)	8 (0.1%)	19 (0.1%)	7 (0.2%)	6 (0.1%)
Heart failure	1409 (3.8%)	289 (3.9%)	208 (3.7%)	482 (3.7%)	102 (3.5%)	328 (3.9%)
Hypertension	9664 (25.9%)	1963 (26.3%)	1374 (24.6%)	3440 (26.3%)	761 (26.1%)	2126 (25.6%)
Diabetes	7380 (19.8%)	1438 (19.3%)	1097 (19.6%)	2530 (19.3%)	504 (17.3%)	1811 (21.8%)
Cerebral infarction or haemorrhage	394 (1.1%)	72 (1.0%)	56 (1.0%)	140 (1.1%)	34 (1.2%)	92 (1.1%)
Atrial fibrillation	1473 (3.9%)	300 (4.0%)	209 (3.7%)	554 (4.2%)	127 (4.4%)	283 (3.4%)

Continued

Table 1 Continued

	Total	Left upper lobectomy	Left lower lobectomy	Right upper lobectomy	Right middle lobectomy	Right lower lobectomy
	N=37 352	N=7462	N=5593	N=13 075	N=2912	N=8310
		20.0%	15.0%	35.0%	7.80%	22.3%
Surgical approach						
Thoracotomy	5625 (15.1%)	1292 (17.3%)	828 (14.8%)	1696 (13.0%)	388 (13.3%)	1421 (17.1%)
Video-assisted	31 727 (84.9%)	6170 (82.7%)	4765 (85.2%)	11 379 (87.0%)	2524 (86.7%)	6889 (82.9%)
Hospital-level factor: number of lobectomies in the observation period						
1–72	9436 (25.3%)	1778 (23.8%)	1453 (26.0%)	3313 (25.3%)	761 (26.1%)	2131 (25.6%)
73–117	9266 (24.8%)	1915 (25.7%)	1405 (25.1%)	3235 (24.7%)	711 (24.4%)	2000 (24.1%)
120–182	9714 (26.0%)	1966 (26.3%)	1440 (25.7%)	3335 (25.5%)	749 (25.7%)	2224 (26.8%)
184–482	8936 (23.9%)	1803 (24.2%)	1295 (23.2%)	3192 (24.4%)	691 (23.7%)	1955 (23.5%)

TNM, tumour node metastasis.

and cutting vagal cardiac branches during the superior mediastinal lymph node dissection. Atrial fibrillation is a well-known cause of thrombosis in the left atrium,[33] and this study provides additional evidence for the frequency of postoperative cerebral infarction after lobectomy. In addition, it may be one possible reason for the high OR for left lower lobectomy in this study. However, this was not demonstrated to be a strong mechanism in the present cohort, as the post hoc analysis including postoperative atrial fibrillation showed less OR variation. This suggestion should be clarified in subsequent interventional studies.

It is important, but challenging, to establish methods to decrease the risk of postoperative cerebral infarction for patients undergoing a left upper lobectomy for lung cancer. One suggested solution is ensuring that the pulmonary vein stumps are as short as possible during the lobectomy process, because the pulmonary vein stump after left upper lobectomy remains long in many cases.[7–9 12 13] Although almost all pulmonary veins are resected with linear staplers, care should be taken to move the linear stapler to the mediastinal side when the pulmonary veins are resected to ensure that the vein stumps are short. In addition, radiological examinations, especially contrast-enhanced CT in the early postoperative period, should be considered for the early detection of blood clots. The reported median postoperative period interval before the detection of thrombus is reported to be 3 months (range, 2–19 months),[8] but the onset was within 24–48 hours in some cases.[34] As for medication, the use of anticoagulants (ie, heparin, warfarin or other direct oral anticoagulants) should be considered in accordance with the treatment of left atrial thrombosis. Indeed, several reports have stated that starting anticoagulant therapy immediately after surgery for pulmonary vein thrombosis led to the prevention of thrombosis and elimination of thrombus.[12 35 36] The dosage and duration of treatment need to be adjusted for each patient, but the length of treatment is unknown, and the risk of bleeding needs to be considered. We hope that further research will reveal a reliable method to prevent this complication.

There are inherent limitations in the present study. First, owing to the nature of the DPC system, only data during hospitalisation could be analysed, which made it difficult to track cerebral infarctions that were related to lobectomies but occurred after discharge from the hospital. Second, data that could not be entered into the DPC database (eg, laboratory data and detailed radiological findings) and preoperative treatment for comorbidities before admission (eg, surgery or other procedures for arrhythmias such as pacemaker implantation and atrial Maze procedure) were not included in this analysis. Although some of this information can be inferred to some extent from the codes that were added when abnormal values are reported, more specific content that could be used as variables by extraction methods from sources other than the DPC system would improve the overall analysis. Third, this study is an epidemiological

Table 2 OR for the occurrence of cerebral infarction

% of events	Number of events (n=99)	Patients (n=37 352)	Sites of lobectomy	Univariate OR	Univariate 95% CI	Univariate P value	Multivariate* Adjusted OR	Multivariate* 95% CI	Multivariate* P value
Left upper lobectomy	7462	29	0.39%	2.49	1.29 to 4.80	0.006	2.66	1.37 to 5.16	0.004
Left lower lobectomy	5593	19	0.34%	2.17	1.07 to 4.41	0.032	2.20	1.08 to 4.49	0.030
Right upper lobectomy	13 075	32	0.24%	1.57	0.82 to 3.00	0.171	1.60	0.83 to 3.07	0.158
Right middle lobectomy	2912	6	0.21%	1.33	0.50 to 3.52	0.562	1.29	0.48 to 3.45	0.607
Right lower lobectomy	8310	13	0.16%	Reference			Reference		

*Adjusted for sex, age, body mass index, smoking, activity of daily living, surgical approach (thoracotomy or video-assisted), stage, comorbidities and hospital-level factors.

study and has not led to specific verification of the previously mentioned causes and preventive measures. These mentions of causes and measures were only supported by case reports or small-scale case-control studies in previous reports. Thus, it is necessary to conduct further interventional research to detect certain causes and construct treatment strategies.

CONCLUSIONS

In this nationwide DPC study conducted in Japan, we identified the incidence of cerebral infarction associated with each type of lobectomy used to surgically treat patients with lung cancer. We found that the left upper lobectomy had the highest OR for postoperative cerebral infarction among all sites of lobectomies. The findings of this study have demonstrated the urgent need for new studies to investigate the specific mechanisms underlying postoperative cerebral infarction after left upper lobectomy and to establish preventive measures.

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Contributors NN, MM and YF conceived and designed the study. MO, YF, SM and KF acquired, linked and cleaned the data. MO and YF were responsible for statistical analysis. All authors interpreted the results, prepared the manuscript and approved the final version. YF, SM, KF and FT are the guarantors. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committee of Medical Care and Research at the University of Occupational and Environmental Health, Japan (approval no. R2-007).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data for this study were derived from the database maintained by the Ministry of Health, Labour, and Welfare, Japan.

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