



Real-world evidence of safety and influence for lung cancer surgery under COVID-19 pandemic in Japan

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Background: The COVID-19 pandemic has affected the clinical practice of lung cancer surgery in Japan, but few studies have revealed the real situation of surgical practice for lung cancer in this country. This latest information will help us to decide the future direction of lung cancer surgery under pandemic circumstances.

Methods: We collected data from patients with primary lung cancer who underwent thoracic surgery between 2018 and 2021. To investigate the impact of the COVID-19 pandemic on lung cancer surgery, we compared between 2018–2019 (prepandemic group) and 2020–2021 (pandemic group) in the respect of patient characteristics, pathological findings, and short-term outcome after lung cancer resection by Mann-Whitney and Fisher's exact tests. Moreover, the monthly number of surgeries for lung cancer in our institution during 2020–2021 was compared with the number of newly diagnosed COVID-19 patients in Japan by Spearman correlation analysis.

Results: From 2018 through 2021, 936 patients with primary lung cancer underwent surgical intervention in our institute and were included in this study. The number of surgeries did not decrease in the pandemic group (n=443) compared with that in the prepandemic group (n=493). Tumor and invasive size in stage I which was measured by pathologist were significantly larger in the pandemic group than in the prepandemic group (tumor size: $P=0.031$, invasive size: $P<0.001$). In terms of postoperative short-term outcome, the median hospital stay was 6 days, 30-day mortality was 2, and morbidity was around 20% in both groups. Only one patient suffered from COVID-19 infection 5 months after right upper lobectomy. An increased ratio of newly diagnosed COVID-19 cases in Japan was negatively correlated with the number of surgeries for lung cancer in our institution in the next month ($r=-0.393$, $P=0.007$), although there was no correlation in the present or the month after next.

Conclusions: Even during the COVID-19 pandemic period, lung cancer surgery could be performed safely and in a sustainable manner. However, pathological findings of lung cancer tended to be progressive in early-stage lung cancer.

Keywords: COVID-19; pandemic; lung cancer surgery; tumor enlargement; short-term outcome

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Introduction

The COVID-19 pandemic is anticipated to continue causing damage on society and economies around the world by imposing substantial burdens on morbidity and mortality (1). As a result of the ensuing lockdown, most non-COVID-19 health services have decreased, and there is growing concern about the impact on other patient groups, especially cancer patients, for whom prompt diagnosis and treatment initiation are essential for achieving optimal results (2-4). The COVID-19 pandemic requires immediate staff and capacity relocation, and nonemergency clinical services, such as elective specialized surgery for cancer, must be postponed because of the unrecognized pressure on hospital wards and the intensive care unit (ICU) (5). Some studies have revealed a substantial increase in the number of avoidable cancer deaths estimated as a result of diagnostic and therapeutic delays due to the COVID-19 pandemic (6,7). Although recent studies showed non-inferiority of surgical outcome during the COVID-19 pandemic, one particular subset of cancer patients who might be at high risk includes those who require surgery for lung cancer, as many of these cases occur in older people who have respiratory comorbidities (8,9). The risk-to-benefit ratio for lung cancer treatment must be carefully weighed in the pandemic era, but only few studies have demonstrated the real situation of surgical practice for lung cancer in Japan.

In this study, we collected data from patients with primary lung cancer who underwent surgery from 2018 to 2021. To investigate the impact of the COVID-19 pandemic on lung cancer surgery, we compared real-world data from our hospital including patient background, surgical procedure and approach, histology, pathological

stage, and short-term outcome after lung cancer resection between 2018–2019 and 2020–2021. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1289/rc>).

Methods

Patients

The inclusion criterion for this study was all pulmonary resections for primary lung cancer performed between 2018 and 2021 in our institution. Lung metastases and benign tumors were excluded. We retrospectively collected patient demographic, clinical, and pathological data for those who fulfilled the inclusion criteria from a review of the medical records. Consequently, 936 patients with lung cancer were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Nagoya University Hospital approved this retrospective study (approval No. 2016-0507), and individual consent for this retrospective analysis was waived.

Design and assessments

Patients were divided into two groups: the pre-pandemic group, which included patients who underwent surgery between 2018 and 2019, and the pandemic group, which included patients who underwent surgery between 2020 and 2021. Patient and tumor characteristics, including gender, age, surgical procedure and approach, TNM stage, histological type, postoperative complications by Clavien-Dindo classification, 30-day mortality, 90-day mortality, first-visit date to our department, and operation date, were collected from medical records. The number of patients diagnosed each day with COVID-19 in Japan was also collected from the website of the Ministry of Health, Labour and Welfare (10).

Patient screening for COVID-19 infection

During 2020–2021, the practice of preoperative COVID-19 screening and isolation was implemented in line with the patient admission protocol at Nagoya University. The admission date was 24 hours preoperatively both before and after the outbreak. During the COVID-19 pandemic, patients were advised to be isolated for 14 days and record

Highlight box

Key findings

- Even during the COVID-19 pandemic period, lung cancer surgery was performed safely in Japan.

What is known and what is new?

- Pathological findings of lung cancer tended to be progressive under the COVID-19 pandemic.
- When the newly diagnosed COVID-19 cases increased, the number of surgeries for lung cancer decreased in a delayed fashion.

What is the implication, and what should change now?

- The hospitals should remain open even during future COVID waves and continue to use efficient screening methods and conduct proper vaccination.

their symptoms and body temperature for 20 days before admission. In addition, a nasopharyngeal COVID-19 antigen test was performed on admission. Surgical activity was maintained, and the surgical department was not shut down during the pandemic period. As a postoperative screening protocol, a follow-up was performed once in 3 months during the first 2 years and once in 6 months during 2–5 years. COVID-19 screening test was only conducted for patients who displayed any infectious diseases symptoms postoperatively.

Statistical analysis

Variables were represented as the median and interquartile range, and categorical data were described as counts and percentages. We performed the Mann-Whitney test and Fisher's exact test to compare the distributions of the continuous and categorical variables between the prepandemic and pandemic groups, respectively. To understand the relationship between pandemic waves and surgery volume, Spearman analysis was applied for correlation analysis between the increased ratio of COVID-19 patients in Japan and the volume of operation in our hospital. An increase in the ratio of COVID-19 patients was calculated as follows: in a given month, the anterior and posterior half-month cumulative total daily number of patients diagnosed with COVID-19 in Japan was calculated, and the present half-month cumulative total was divided by the previous value and multiplied by 100. To calculate the correlation, this increase ratio was compared with the number of surgeries conducted in the current month or the following month (Figure S1). Values of $P < 0.05$ were considered to be statistically significant. Statistical analysis was performed using EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (11).

Results

Patient characteristics

We included in this study 936 patients with primary lung cancer who underwent surgical intervention in our institute from 2018 through 2021. Of the patients, 62.2% were male. Most patients had a smoking history, and 19.1% of patients suffered from chronic obstructive pulmonary disease. Lobectomy or bilobectomy were the most common surgical procedures in this period. In terms of pathological

characteristics, a large majority of patients were diagnosed with stage I lung adenocarcinoma.

Comparison of clinicopathological features before and after the COVID-19 outbreak

Table 1 compares the characteristics of patients in 2018–2019 (prepandemic) and in 2020–2021 (pandemic). The number of patients did not decrease in the pandemic group ($n=443$) in comparison with the prepandemic group ($n=493$). Patient background characteristics, including age, body mass index, sex, smoking, and comorbidities, were not different between the two groups. In the prepandemic group, the proportion of patients who received video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery (RATS) approaches was significantly higher compared with the pandemic group ($P < 0.001$). With respect to pathological findings, stage I cases showed the highest increase in the pandemic period compared with the prepandemic period, although other stages were similar between two groups. The distribution of stage I diseases indicated that only stage IA1 was decreased and that IB had the greatest increase after the pandemic (Figure 1A). In particular, stage IA3 and IB tumors had a higher increase in 2021 compared with the other years (Figure 1B). When tumor and invasive size in stage I were compared between the two groups, the pandemic group showed significantly larger sizes compared with the prepandemic group (tumor size: $P=0.031$, invasive size: $P < 0.001$, Figure 2).

Short-term outcome after surgery

Table 2 displays the outcomes after surgery. The median hospital stay after surgery was 6 days, and the 30- and 90-day mortality rates were similar in both groups. Complications were seen in 92 of 443 (20.8%) patients in the prepandemic group and 108 of 493 (21.9%) patients in the pandemic group. A total of 42 of 443 (9.4%) patients in the prepandemic group and 54 of 493 (10.9%) patients in the pandemic group were classified as Clavien-Dindo grades 3–4, which comprises prolonged air leakage requiring chemical pleurodesis or surgical treatment, bronchopleural fistula, atelectasis, empyema, bleeding, and cerebral infarction; there was no significant difference in the proportion of these complications between the two groups. As a severe complication, only one patient had COVID-19 infection after lung cancer resection. The patient developed COVID-19 pneumonia and bronchopleural fistula

Table 1 The comparison of patient background and procedural demographics between prepandemic and pandemic periods

Variables	Year 2018–2019 (n=443)	Year 2020–2021 (n=493)	P value
Age, years, median [IQR]	71 [66–75]	72 [65–76]	0.444
BMI, kg/m ² , median [IQR]	22.5 [20.3–24.8]	22.7 [20.7–24.95]	0.192
Sex (male), n (%)	272 (61.4)	314 (63.7)	0.499
Smoking, n (%)			0.071
Non-smoker	155 (35.0)	143 (29.0)	
Ex-smoker	227 (51.2)	289 (58.6)	
Current smoker	61 (13.8)	61 (12.4)	
Comorbidity, n (%)			
Hypertension	128 (28.9)	192 (38.9)	0.001
Diabetes mellitus	61 (13.8)	87 (17.6)	0.107
COPD (FEV1.0% <70)	178 (40.2)	209 (42.4)	0.507
Interstitial pneumonia	30 (6.8)	39 (7.9)	0.533
Ischemic heart disease	10 (2.3)	6 (1.2)	0.313
Cerebrovascular disease	4 (0.9)	7 (1.4)	0.553
Other malignant disease	30 (6.8)	42 (8.5)	0.329
Procedure, n (%)			0.632
Lobectomy/bilobectomy	330 (74.5)	370 (75.1)	
Segmentectomy/sublobar	88 (19.9)	105 (21.3)	
Pneumonectomy	2 (0.5)	2 (0.4)	
Lung resection + chest wall	16 (3.6)	12 (2.4)	
Others	7 (1.5)	4 (0.8)	
Approach, n (%)			<0.001
Open	247 (55.8)	143 (29.0)	
VATS	126 (28.4)	207 (42.0)	
RATS	70 (15.8)	143 (29.0)	
Pathology, n (%)			0.411
LUAD	318 (71.8)	361 (73.2)	
LUSQ	81 (18.3)	95 (19.3)	
Others	44 (9.9)	37 (7.5)	
Pathological stage, n (%)			0.334
0	11 (2.5)	12 (2.4)	
I	291 (65.7)	354 (71.8)	
II	72 (16.3)	65 (13.2)	
III	60 (13.5)	55 (11.2)	
IV	9 (2.0)	7 (1.4)	

IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1.0%, forced expiratory volume % in one second; VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery; LUAD, lung adenocarcinoma; LUSQ, lung squamous cell carcinoma.

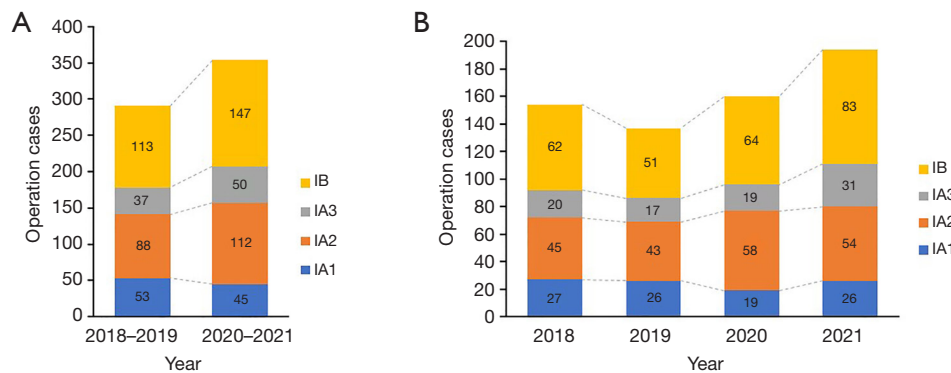


Figure 1 Bar graphs showing the distribution of pathological stage I lung cancer. (A) The counts of stage I diseases are compared between 2018–2019 and 2020–2021. After the pandemic, a decrease was observed only in stage IA1, with the largest increase seen in stage IB. (B) An annual comparison of stage I disease shows that stage IA3 and IB tumors were notably increased in 2021.

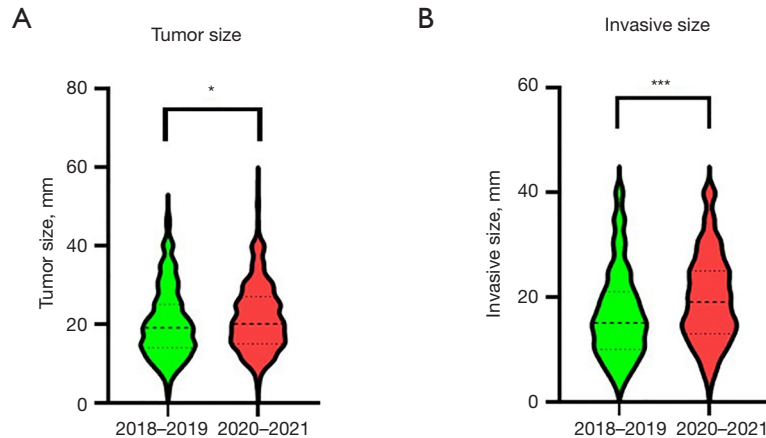


Figure 2 Tumor and invasive sizes of stage I lung cancers are compared between 2018–2019 and 2020–2021. The sizes in the pandemic group were significantly larger than those in the prepandemic group (tumor size: $P=0.031$, invasive size: $P<0.001$). Median tumor and invasive sizes and interquartile range were summarized by violin plot. *, $P<0.05$; ***, $P<0.001$.

5 months after right upper lobectomy for lung cancer. Pleural drainage was performed and antibiotic treatment was administered in the ICU. Two weeks after treatment initiation, we identified negative conversion of SARS-CoV-2 antigen and spontaneous closure of the bronchopleural fistula.

Impact of COVID-19 pandemic on the volume of lung cancer operations

We investigated the effect of the COVID-19 pandemic on the volume of lung cancer operations performed in our department (Figure 3). The first case of Japanese SARS-CoV-2 infection was detected in January 2020, and the

first wave of the pandemic occurred in April of the same year. The number of newly diagnosed COVID-19 cases in Aichi prefecture was highly correlated with that in Japan. Operation cases decreased around April. Under the third and fourth waves, operation cases decreased again in a delayed fashion. These distributions of operation cases contained no correlation with those of 2018–2019 ($r=-0.010$, Figure S2). When the increase ratio of new COVID-19 cases in Japan was compared with the volume of lung cancer operations, a negative correlation was detected with the number of surgeries performed in the next month, although no correlation was found in the present month and the month after next (present month: $r=-0.139$, $P=0.347$, next month: $r=-0.393$, $P=0.007$, month after next: $r=-0.224$,

Table 2 Short term outcome after surgery

Variables	Year 2018–2019 (n=443)	Year 2020–2021 (n=493)	P value
Length of stay after operation, median [IQR]	6 [5–7]	6 [5–8]	0.426
30-day mortality, n (%)	2 (0.45)	0 (0)	0.244
90-day mortality, n (%)	2 (0.45)	3 (0.81)	1
Complication, n (%)			0.762
Clavien-Dindo grade 1–2	50 (11.2)	54 (10.9)	
Clavien-Dindo grade 3–4	42 (9.4)	54 (10.9)	
Detail of Clavien-Dindo grade 3–4, n (%)			
Prolonged air leakage	29 (6.5)	37 (7.5)	0.554
Bronchopleural fistula	2 (0.45)	2 (0.40)	1
Pneumonia	10 (2.3)	9 (1.8)	0.652
Atelectasis	6 (1.4)	1 (0.20)	0.057
Chylothorax	5 (1.1)	2 (0.40)	0.265
Empyema	5 (1.1)	7 (1.4)	0.777
Bleeding	3 (0.68)	4 (0.81)	1
Cerebral infarction	0 (0)	2 (0.40)	0.501

IQR, interquartile range.

$P=0.143$, *Figure 4*). The same relationship was investigated using 2022 data and we realized that no negative correlation was observed for this dataset (*Figure S3*). Additionally, number of surgeries around the COVID waves gradually increased from the first to the fifth wave (*Figure S4*). On the other hand, the median time from the first visit to surgery (TFS) was 32 days for the pre-pandemic group and 31 days for the pandemic group, and no significant difference in TFS was found between the two groups ($P=0.150$). This finding indicated that in our institution, surgical activity was maintained and no shutdown of the surgical department occurred during the pandemic period.

Discussion

During the COVID-19 pandemic, secondary effects such as limited health care service availability should be considered. In recent years, estimates of the impact of cancer treatment delays on survival have been reported (5,12,13). Several guidelines and recommendations for cancer diagnosis and therapy under a pandemic situation have been provided based on expert opinions (14). However, evidence regarding the safety and influence of surgical treatment on lung cancer remain limited in this field under the COVID-19

pandemic. In this study, we evaluated the volume of surgery, clinicopathological features, and short-term outcomes of patients with lung cancer by comparing the real-world data in our department between pre-pandemic and pandemic periods.

As shown in *Figures 3,4*, new COVID-19 cases belatedly affected the volume of lung cancer surgery. Indeed, when the World Health Organization declared COVID-19 to be a global pandemic in March 2020, the problem of delayed surgical therapy worsened (15,16). The effects of COVID-19 also have had an impact on cancer diagnoses around the world. In the United Kingdom, referrals for cancer-suspected cases decreased by about 80% (7,17). The potential causes of these delays in diagnosis and treatment are the limitations in hospital resources and the hesitancy of patients to receive necessary health care services during the COVID-19 pandemic (18,19). According to a study of lung cancer patients who participated in clinical trials during the SARS outbreak, 64% of patients were hesitant to visit a hospital due to fear of infection, and 4% of patients decided to cease all treatment because of infection issues. In another study using the United States National Cancer Database, when the interval between the cancer diagnosis and surgical therapy was greater than 12 weeks, patients

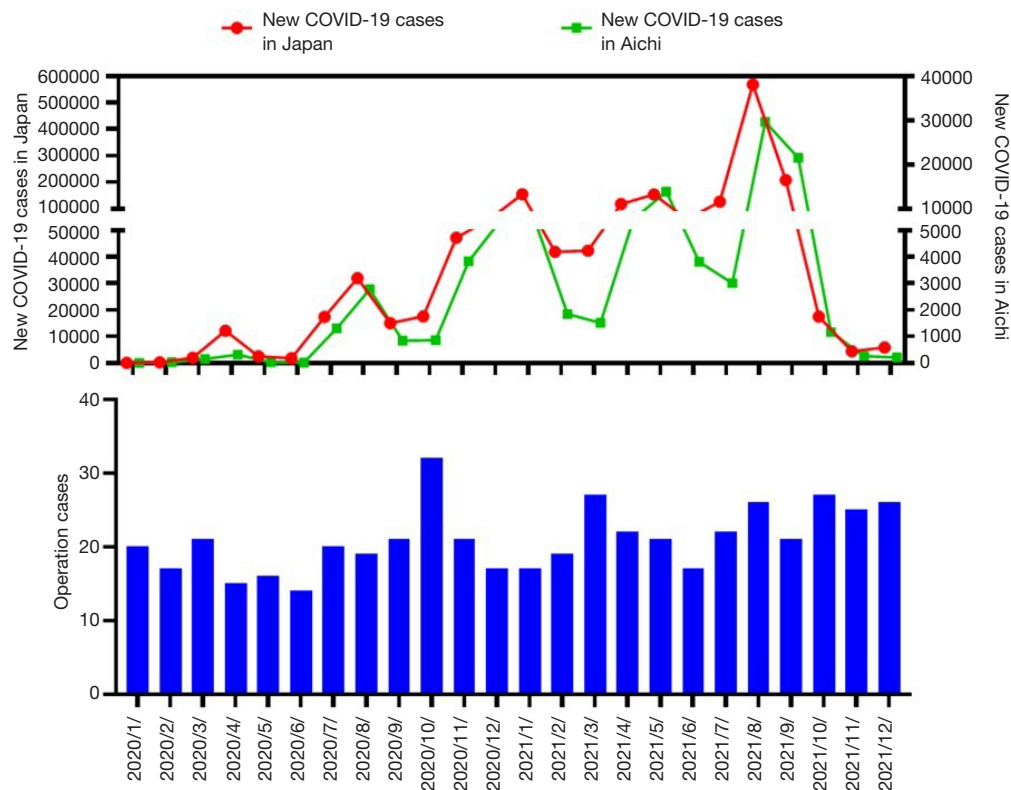


Figure 3 Comparison of the volume of lung cancer surgery in our department with new COVID-19 cases in Japan and Aichi during the pandemic period. The first pandemic wave occurred in April 2020. The number of cases undergoing operation decreased around April. Under the third and fourth waves, the number of cases receiving an operation decreased again in a delayed fashion.

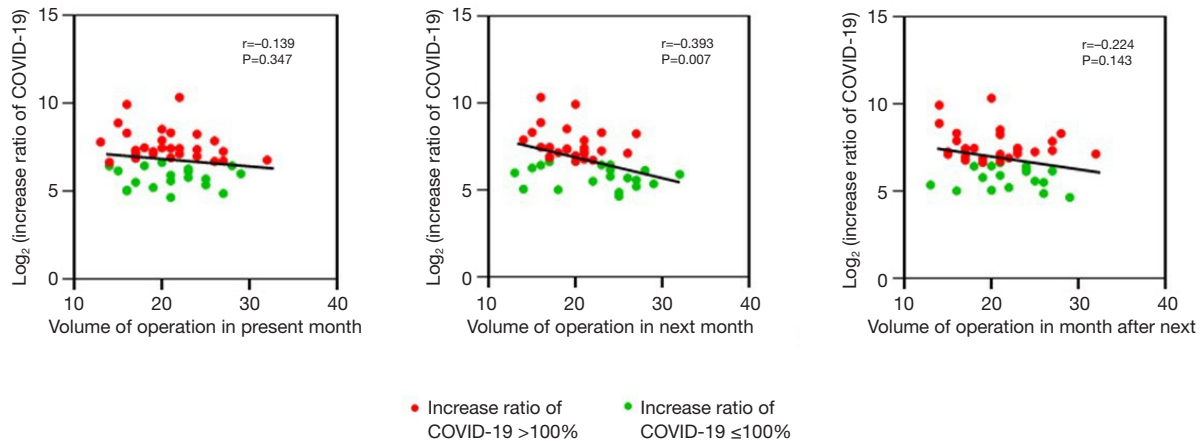


Figure 4 Scatter plots showing the relationship between the increase ratio of new COVID-19 cases in Japan and operation volume in the present month, next month, and the month after next. A significant negative correlation was detected between the increase ratio of COVID-19 and operation volume in the next month ($r=-0.393$, $P=0.007$). Red plots indicate that the increase ratio of COVID-19 cases was $>100\%$, and green plots indicate that the increase ratio of COVID-19 was $\leq 100\%$.

with clinical stage I non-small cell lung cancer were found to have a higher risk of upstaging and a worse rate of overall survival (20). In our study, the pathological outcome of patients with stage I cancer tended to be larger in tumor and invasive size during the pandemic period (Figures 1,2). This is probably due to the delay in surgical treatment and the selection of surgical indication for lung cancer of higher malignancy. However, there was no significant delay in TFS during the pandemic period compared with the pre-pandemic period. No shutdown or limitation in the surgical department occurred in our hospital after the COVID-19 outbreak, although many institutions stopped performing elective surgery for non-cancer cases in other countries (21). Even if hospital activity was maintained, the waves of COVID-19 affected the volume of diagnosis and surgery for lung cancer in a delayed fashion, likely because of patient hesitancy to receive necessary health care services. Recently, patient hesitancy seemed to have decreased because the number of surgeries was minimally almost affected by the latest COVID wave as shown in Figures S3,S4. One of the reasons for this change is prevalence of vaccines and other therapies including Paxlovid (22). Therefore, the hospitals should remain open even during future COVID waves and continue to use efficient screening methods and conduct proper vaccination.

Retrospective studies reported COVID-19 infection mortality rates of upward of 50% in patients with lung cancer even without lung resection (23). In terms of patients who received lung cancer surgery, the mortality rate was extremely high among those positive for COVID-19 within 30 days postoperatively (24). This vulnerable group might be particularly susceptible to subsequent pulmonary complications due to immunosuppressive responses to surgery as well as immune-suppressive mediators from the tumor (25,26). Although there is little information regarding the perioperative safety of patients with lung cancer, a recent study conducted in the United States showed that the postoperative COVID-19 infection rate was 7.3%, and there was no difference in major complications after surgery between the pre-pandemic and pandemic groups (8). In our study, only one patient developed COVID-19 five months after lung cancer resection, with no difference observed in the postoperative complication rate between the two groups (Table 2). To maintain the safety of surgery, we should continue to preoperatively screen all patients for SARS-CoV-2 infection by nasopharyngeal swab and provide careful postdischarge follow-up and isolation from the risk of COVID-19 infection, especially within the first month

after surgery.

Numerous studies have already reported the benefits of both VATS and RATS compared with open surgery in terms of less invasiveness for patients (27-30), and recently RATS was suggested to provide safe and equivalent surgical efficacy compared with VATS (31,32). From the trends in surgical approach, the application of VATS and RATS could successfully be extended without an increase of major complications during this coronavirus pandemic era. Specifically, frequency of RATS recently increased in our department. In our opinion, the reason for the increase in minimally invasive surgery is that it can be safely performed even during the COVID-19 pandemic. However, the number of minimally invasive surgeries have gradually increased from 2019. We speculate that the reason for this is probably institutional, and not an effect of the pandemic.

Our study has several potential limitations. This was a retrospective study conducted at a single institution on a rather small number of patients. To assess a patient's prognosis, particularly during a pandemic, long-term follow-up is necessary. Systematic COVID-19 screening was performed only for preoperative patients. Postoperative information regarding COVID-19 was obtained from patient declaration or screening at the time of hospital readmission.

Conclusions

We were able to safely perform lung cancer surgery in a sustainable manner during the COVID-19 pandemic. However, among patients who received surgical treatment, we observed enlargement of the tumor in early-stage lung cancer during the COVID-19 pandemic period.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1289/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Institutional Review Board of Nagoya University Hospital (approval No. 2016-0507) and individual consent for this retrospective analysis was waived.

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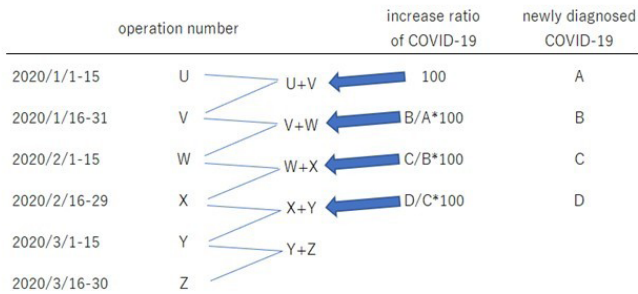
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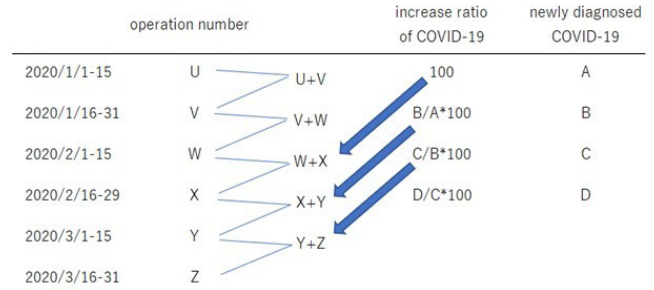
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Correlation between increase ratio of COVID-19 and number of operation in present month



Correlation between increase ratio of COVID-19 and number of operation in next month



Pairing of correlation in present month

U+V	100
V+W	B/A*100
W+X	C/B*100
X+Y	D/C*100
⋮	⋮

Pairing of correlation in next month

W+X	100
X+Y	B/A*100
Y+Z	C/B*100
⋮	D/C*100
⋮	⋮

Figure S1 Calculation method for the correlation between the increase ratio of COVID-19 patients and volume of operation in our hospital. The increase ratio of COVID-19 patients was calculated as follows. In a given month, the anterior and posterior half-month cumulative total number of patients diagnosed each day with COVID-19 in Japan was calculated, and the present half-month cumulative total was divided by the previous value and multiplied by 100. To calculate the Spearman correlation, this increase ratio was compared with the number of surgeries conducted in the current month or the following month.

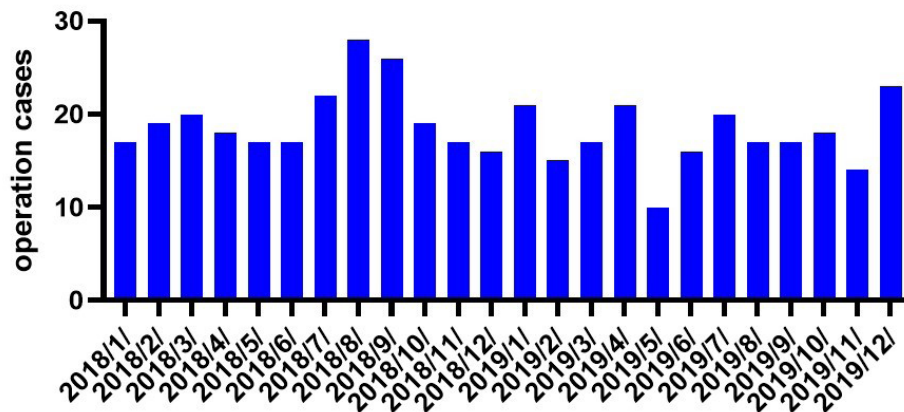


Figure S2 Bar graph showing the volume of lung cancer surgery in the pre-pandemic period.

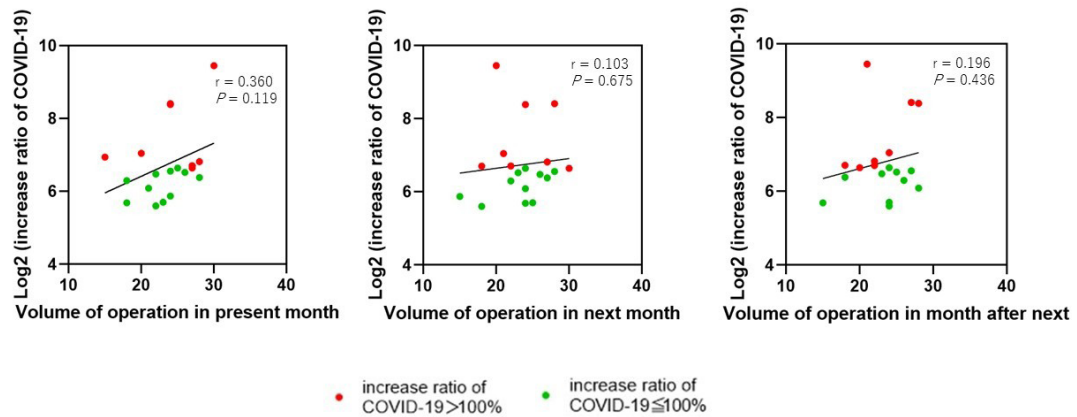


Figure S3 Scatter plots showing the relationship between the increased ratio of new COVID-19 cases in Japan and the operation volume in the present month, next month, and the month after next. The data were derived from January to October 2022.

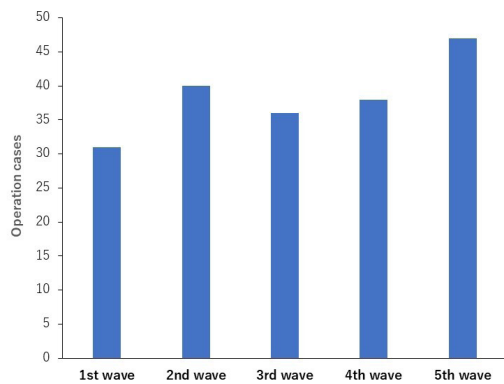


Figure S4 Bar graph showing the lung cancer surgery volume for each COVID-19 wave. The number of surgical cases shows the sum of the cases for the continuous 2 months which include the month on top of the wave and the succeeding month.