

# Impact of COVID-19 Pandemic on Advanced Non-small Cell Lung Cancer Treatment at a Japanese Hospital

KUNIIHIKO MIYAZAKI<sup>1</sup>, TAKAHIDE KODAMA<sup>1</sup>, YUKA AIDA<sup>2,3</sup>, SHINYA SATO<sup>1</sup> and HIROAKI SATOH<sup>4</sup>

<sup>1</sup>Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan;

<sup>2</sup>Division of Respiratory Medicine, Faculty of Clinical Medicine, University of Tsukuba, Tsukuba, Japan;

<sup>3</sup>Division of Medical Oncology, Faculty of Clinical Medicine, University of Tsukuba, Tsukuba, Japan;

<sup>4</sup>Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito, Japan

**Abstract.** *Background/Aim:* The COVID-19 pandemic has forced medical institutions to scale back their practice. Changes in patient behavior seemed to be having an impact. We conducted a survey with the aim of reviewing lung cancer treatment during the pandemic period and identifying problems. *Patients and Methods:* We examined the medical records of all patients pathologically diagnosed with non-small cell lung cancer (NSCLC) in our hospital from 2017 to 2022. NSCLC patients were divided into two groups: those diagnosed between 2017 and 2019 (first period) and those diagnosed between 2020 and 2022 (second period). *Results:* Within the study period, 267 NSCLC patients (first period: 147 patients, second period: 121 patients) were diagnosed in our hospital. The patients in the two study periods did not differ significantly in age ( $p=0.613$ ), ECOG performance status ( $p=0.125$ ), and clinical stage ( $p=0.354$ ). Tumor size was significantly larger in the second period with a mean of  $5.88 \text{ cm} \pm 3.02$ , compared to  $4.24 \text{ cm} \pm 1.76$  in the first period ( $p<0.001$ ). In the standard treatment group, the median survival time was 457 days in the first period and 313 days in the second period ( $p=0.063$ ). In the best supportive care group, median survival time was 122 days in the first period

*and 57 days in the second period ( $p=0.004$ ). Conclusion:* Patients themselves refrained from seeking consultation for lung cancer treatment during the pandemic period. It is inconclusive how to reduce the delay due to the suppression of consultations, but this is an important issue for the future.

SARS-CoV 2 disease (COVID-19) has caused a global pandemic. Like other countries, Japan experienced the impact of COVID-19 on the population and associated deaths. The pandemic forced many hospitals to take measures to protect patients and medical staff, and some facilities had to limit services. Due to the COVID-19 epidemic in Japan, patients have been affected as health checkups were cancelled. Some medical institutions reported changes in the medical treatment system, such as postponement of surgery and treatment (1-7). During the pandemic, some medical facilities may not have provided adequate medical care. Moreover, changes in the behavior of patients seeking medical care, such as voluntary refraining from coming to the hospital, were also conceivable. In other words, it is suggested that changes in patient behavior may have made early diagnosis of lung cancer difficult, leading to an increase in advanced cases and poor prognosis. It is unknown and should be a subject of investigation whether adequate medical care was provided to lung cancer patients during the pandemic.

Our hospital is located in the suburbs of Tokyo, and while it is within commuting distance to the big city, it is considered a suburban hospital, which also attends patients from a large rural area. Our hospital cared for 436 inpatients and more than 5,000 outpatients due to COVID-19 in the three years from April 2020 to March 2023. In addition, our hospital has been responsible for and conducted over 13,000 SARS-CoV-2 vaccinations for local residents. At our hospital, we continued to practice without any restrictions throughout the pandemic. Nevertheless, a decrease in outpatient visits was noticeable. Furthermore, we had no

*Correspondence to:* Kunihiko Miyazaki, MD, Ph.D., Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki 3000854, Ibaraki, Japan. Tel: +81 2976371111, Fax: +81 297637163, e-mail: k.miyazaki@ryugasaki-hp.org

**Key Words:** Non-small cell lung cancer, COVID-19, delayed treatment, delayed diagnosis.

©2023 International Institute of Anticancer Research  
www.iiar-anticancer.org



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (<https://creativecommons.org/licenses/by-nc-nd/4.0>).

Table I. Characteristics of patients with non-small cell lung cancer.

	2017-2019 (first period)	2020-2022 (second period)	<i>p</i> -Value
Number of patients	148	121	
Sex (male, female)	108, 38	96, 25	0.315
Age (median, range)			
Male	77 (50-92)	77 (39-92)	0.467
Female	77 (54-95)	75 (49-74)	0.602
Clinical stage			
Stage IA-IIIa, PS0-2	63 (43.1%)	46 (38.0%)	
Stage IA-IIIa, PS3-4	1 (0.7%)	2 (1.7%)	0.354
Stage IIIB-IVB, PS0-2	71 (48.6%)	58 (47.9%)	
Stage IIIB-IVB, PS3-4	11 (7.5%)	15 (12.4%)	

choice but to temporarily suspend the health checkup service. In view of this background, this survey was carried out for the purpose of understanding this extraordinary situation and contributing to future medical care.

## Patients and Methods

In this study, we examined the medical records of all patients pathologically diagnosed with non-small cell lung cancer (NSCLC) in our hospital from 2017 to 2022.

Patients diagnosed between 2017 and 2019 (first period) and those diagnosed between 2020 and 2022 (second period) were divided into two groups for comparison. NSCLC was pathologically diagnosed according to the WHO classification. Prior to initiation of any anticancer treatment, all patients underwent TNM classification (8). For imaging, head computed tomography or magnetic resonance imaging, bone scans, and ultrasonography and/or computed tomography of the abdomen were performed. Suitable patients were identified in each hospital's clinical database, and information on patient demographics (age, sex, Eastern Cooperative Oncology Group performance status (PS), histology, clinical stage, etc.) was extracted from databases. Tumor response was assessed as complete response, partial response, stable disease, progressive disease, or not evaluable according to Response Evaluation Criteria in Solid Tumors (9).

For statistical comparison between two groups, the chi-squared test and Mann-Whitney *U*-test were used. Survival probability was estimated with the Kaplan-Meier method, and evaluated using the log-rank test and Cox's proportional hazard model. Multivariate analysis was performed using factors that obtained a  $p < 0.02$  by univariate analysis. A  $p$ -value of  $< 0.01$  was considered to indicate a significant difference.

This study was approved by the Institutional Review Boards of the Ryugasaki Saiseikai Hospital (No. 201502).

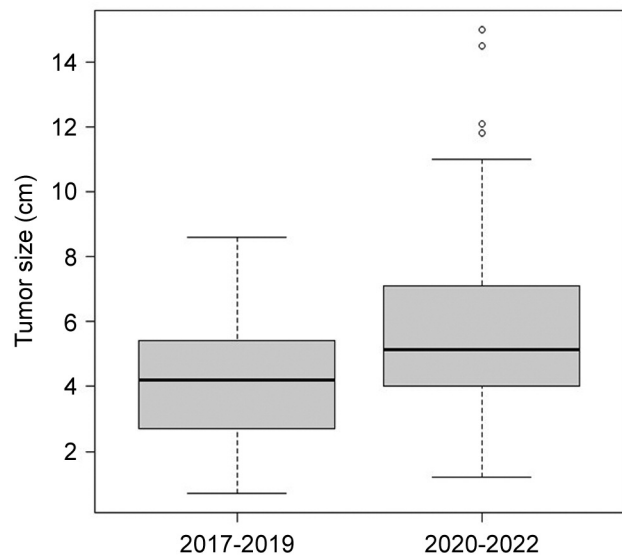


Figure 1. Tumor diameter in the advanced stage group in 2017-2019 and 2022-2022.

## Results

Patients diagnosed with NSCLC within the study period included 146 patients in the first and 121 in the second period. There were 108 male patients in the first period (50-92 years, median age 75 years) and 96 male patients in the second period (39-92 years, median 77 years). There were 38 female patients in the first period (54-95 years, median age 77 years) and 25 female patients in the second period (49-94 years, 75 years).

The clinical stages were divided into two groups: stage IA to IIIa (early-stage group) and IIIB to IVB (advance-stage group). Comparing the two groups in the first and second period, stage groups did not differ significantly ( $p = 0.354$ ) (Table I).

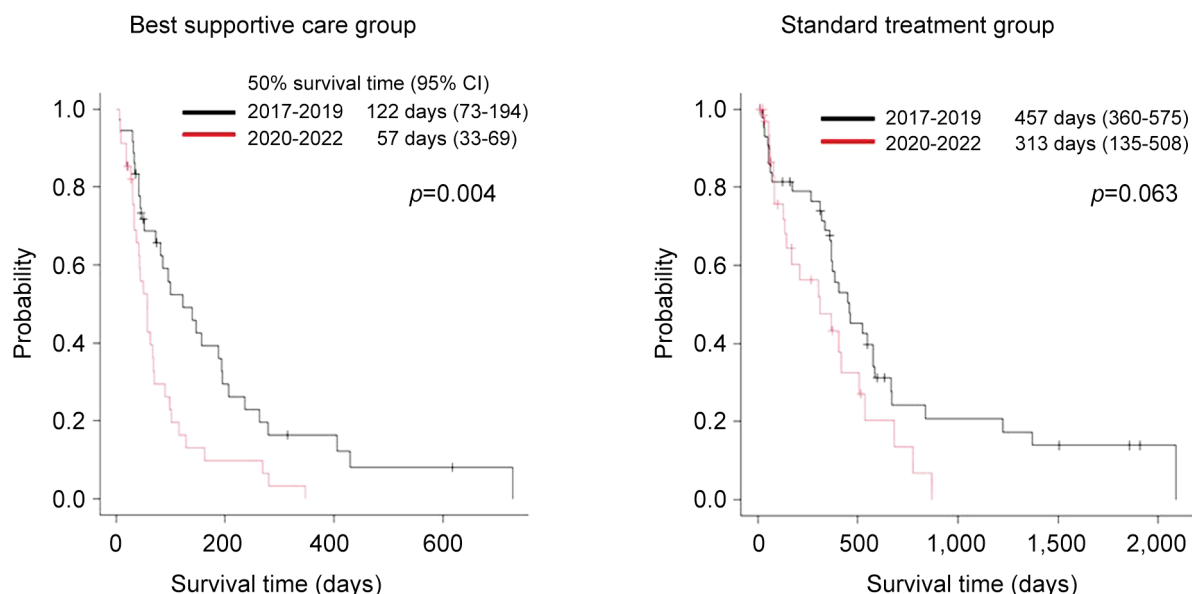


Figure 2. Survival curves of the best supportive care group and standard treatment group.

The PS were divided into two groups: PS 0-2 (good PS group) and PS 3-4 (poor PS group). Comparing these two PS groups in the first and second period, stage groups did not differ significantly ( $p=0.354$ ). In the early-stage group, 63 (43.1%) patients in the first period and 46 (38.0%) in the second period had good PS, 1 (0.7%) patient in the first period and 2 (1.7%) patients in the second period had poor PS at the time of diagnosis. In the advance-stage group, 71 (48.6%) patients in the first period and 58 (47.9%) in the second period had good PS, whereas 11 (7.5%) patients in the first period and 15 (12.7%) patients in the pandemic period had poor PS. No significant difference was found between them ( $p=0.354$ ). In patients with advanced-stage disease, age ( $p=0.613$ ) and PS ( $p=0.125$ ) did not differ significantly between 82 patients in the first period and 73 patients in the second period.

Because patient characteristics did not differ between the groups, we focused on tumor size as one of the factors that defined the 'T factor' of the TNM classification. The tumor diameter (mean  $\pm$  standard deviation) in patients from the first period was 4.24 cm  $\pm$  1.76 cm and 5.88 cm  $\pm$  3.02 cm in patients from the second period. The diameter of the primary NSCLC in patients from the second period was significantly larger than that in patients from the first period ( $p<0.001$ ) (Figure 1). The survival period was investigated separately for the best supportive care (BSC) group and for the standard treatment group, excluding the BSC group from all patients. There was no difference in proportions between the standard treatment group and the BSC group in the two periods ( $p>0.999$ ). In the standard treatment group, 50% survival time

was 457 days (95%CI=360-575 days) in the first period and tended to be shorter at 313 days (135-508 days) in the second period ( $p=0.063$ ) (Figure 2). In the BSC group, the 50% survival time was 122 days (95%CI=73-194 days) in the first period and 57 days (33-69 days) in the second period. The two periods differed significantly ( $p=0.004$ ) (Figure 2).

## Discussion

We detected no significant differences in patient characteristics, stage of NSCLC or the ratio of patients treated with standard therapy before and during the COVID-19 pandemic. However, the diameter of the primary NSCLC in patients during the pandemic period was significantly larger than that pre-pandemic. Although survival of patients treated with standard therapy was comparable, survival of patients with BSC in the pandemic period was shorter than that in the pre-pandemic period.

During the COVID-19 pandemic, medical institutions in many countries reported clinical practice restrictions and accompanying changes in patients' hospital visit behavior (10-13). In Japan as well, a decrease in the number of lung cancer screenings and surgeries has been reported (14). At our hospital, we had 121 advanced NSCLC patients, compared to 146 before the COVID-19 epidemic. We detected a slight decrease in the number of patients, despite the fact that the hospital had no restrictions to visits.

Enlargement of primary lesions and progression of cancers discovered during the COVID-19 epidemic have been confirmed (15-22). In breast cancer, for example, an increase

in tumor size (15-19) and the number of patients with advanced stage (17-19) has been reported. In patients with resectable NSCLC, there were some reports of increased primary tumor diameter during the COVID-19 pandemic, although no differences were found in clinical stage (20-22). To our best knowledge, however, no study has assessed tumor size in advanced NSCLC during the COVID-19 pandemic and confirmed that they were diagnosed with greater size. Therefore, this report is the first. There have been two interesting related studies. First, Zhao *et al.* reported that during the COVID-19 epidemic, lung cancers incidentally detected in all patients with screening CT were smaller than those in pre-COVID-19 patients (23). A second report from Japan stated that, unlike the number of surgeries for primary lung cancer, the number of surgeries for metastatic lung cancer had not declined (14). These findings suggested that patients who were incidentally diagnosed by active imaging or who were under medical surveillance were not affected by the COVID-19 epidemic.

We showed in this study that the diameter of the primary NSCLC in patients during the pandemic period was significantly larger than that before the pandemic. In addition, survival of patients with BSC in the pandemic period was shorter than that in the pre-pandemic period. It is highly possible that these results were related to the delay in the patients' visiting the hospital. It is important to strive to prevent delays in medical care even during a pandemic, but we were once again reminded of the importance of ensuring that there are no restrictions affecting the behavioral patterns of patients. It will be necessary not only for individual medical institutions to take action, but also for the entire society, including administrative agencies.

This study had some limitations. First, this study was a retrospective study with a very small number of patients at a single medical facility. It was a survey of patients with various backgrounds who received medical treatment, and we do not know whether our results could be generalized or whether universal information can be extracted from our results. Second, the period of this study overlapped with the general use of immune checkpoint inhibitors and chemotherapy. Although the prognosis of patients who received standard treatment during the pandemic tended to be short, it could not be denied that this might have led to the absence of a significant difference in the results. Despite these limitations, we do believe that at the end of the pandemic, clinical practice during the pandemic should be evaluated. Although this was a small study, it is expected that the actual presentation of the survey results may lead to a large-scale research. Delays in treatment due to shortcomings of medical providers should be avoided as much as possible. Verification of this point is necessary. In addition, it remains questionable how to reduce the delay in diagnosis and treatment due to patient-related factors, such as avoidance of consultations.

## Conflicts of Interest

All Authors have no conflicts of interest in relation to this study.

## Authors' Contributions

KM, TK, and SS designed the study. KM, TK, YA, and SS collected the data. KM, TK, SS and HS analyzed the data and prepared the manuscript. All Authors approved the final version of the article.

## References

- 1 Zhang J, Han Y, Zhang Y, Dong D, Cao Y, Chen X, Li H: Considerations for the surgical management of thoracic cancers during the COVID-19 pandemic: Rational strategies for thoracic surgeons. *Front Surg* 9: 742007, 2022. DOI: 10.3389/fsurg.2022.742007
- 2 Ömeroğlu Şimşek G: Lung cancer management in COVID-19 pandemic. *Turk Thorac J* 21(5): 340-344, 2020. DOI: 10.5152/TurkThoracJ.2020.20061
- 3 Petropoulou Z, Arkadopoulos N, Michalopoulos NV: Breast cancer and COVID-19: Challenges in surgical management. *Cancers (Basel)* 14(21): 5360, 2022. DOI: 10.3390/cancers14215360
- 4 Domper-Arnal MJ, Hijos-Mallada G, Lanás Á: The impact of COVID-19 pandemic in the diagnosis and management of colorectal cancer patients. *Therap Adv Gastroenterol* 15: 17562848221117636, 2022. DOI: 10.1177/17562848221117636
- 5 Nieder C, Haukland EC, Mannsaker B, Yobuta R: Palliative radiotherapy during the last month of life: Have COVID-19 recommendations led to reduced utilization? *In Vivo* 35(1): 649-652, 2021. DOI: 10.21873/invivo.12304
- 6 Pepe P, Pepe L, Pennisi M, Fraggetta F: Prostate cancer diagnosis and management during one year of the COVID-19 pandemic. *Anticancer Res* 41(6): 3127-3130, 2021. DOI: 10.21873/anticancer.15097
- 7 Vanni G, Pellicciaro M, Materazzo M, Pedini D, Portarena I, Buonomo C, Perretta T, Rizza S, Pistolesi CA, Buonomo OC: Advanced stages and increased need for adjuvant treatments in breast cancer patients: The effect of the one-year COVID-19 pandemic. *Anticancer Res* 41(5): 2689-2696, 2021. DOI: 10.21873/anticancer.15050
- 8 Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions: The IASLC Lung Cancer Staging Project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 11(1): 39-51, 2016. DOI: 10.1016/j.jtho.2015.09.009
- 9 Therasse P, Arbuck SG, Eisenhower EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. *Natl Cancer Inst* 92(3): 205-216, 2000. DOI: 10.1093/jnci/92.3.205
- 10 Yu JS, Rodrigues AJ, Bovonratwet P, Shen T, Premkumar A, Sehgal R, Carr Li JB, Dines JS, Ricci WM: Changes in orthopaedic

- diagnoses during the COVID-19 pandemic. *J Clin Orthop Trauma* 22: 101603, 2021. DOI: 10.1016/j.jcot.2021.101603
- 11 Jaswaney R, Davis A, Cadigan RJ, Waltz M, Brassfield ER, Forcier B, Joyner BL Jr: Hospital policies during COVID-19: an analysis of visitor restrictions. *J Public Health Manag Pract* 28(1): E299-E306, 2022. DOI: 10.1097/PHH.0000000000001320
  - 12 Xu S, Glenn S, Sy L, Qian L, Hong V, Ryan DS, Jacobsen S: Impact of the COVID-19 pandemic on health care utilization in a large integrated health care system: retrospective cohort study. *J Med Internet Res* 23(4): e26558, 2021. DOI: 10.2196/26558
  - 13 Taquechel K, Diwadkar AR, Sayed S, Dudley JW, Grundmeier RW, Kenyon CC, Henrickson SE, Himes BE, Hill DA: Pediatric asthma health care utilization, viral testing, and air pollution changes during the COVID-19 pandemic. *J Allergy Clin Immunol Pract* 8(10): 3378-3387.e11, 2020. DOI: 10.1016/j.jaip.2020.07.057
  - 14 Sato Y, Yamamoto H, Ikeda N, Konishi H, Endo S, Okada Y, Kondo H, Shintani Y, Toyooka S, Nakamura H, Hoshikawa Y, Chen-Yoshikawa TF, Yoshino I, Kakizoe T, Chida M: The impact of COVID-19 on thoracic surgical procedures in Japan: Analysis of data from the National Clinical Database. *Lung Cancer* 172: 127-135, 2022. DOI: 10.1016/j.lungcan.2022.08.011
  - 15 Gosset M, Gal J, Schiappa R, Helwig C, Bonomo I, Delpech Y, Barranger E: Breast cancer and SARS-Cov2: Lessons from a pandemic. *Anticancer Res* 43(5): 2235-2241, 2023. DOI: 10.21873/anticancer.16387
  - 16 Gürsoy M, Aslan Ö, Oktay Alfathı A, Zekioglu O, Göktepe B: Radiological and clinicopathological findings of breast cancer during the COVID-19 pandemic: a comparative study with the pre-pandemic era. *Diagn Interv Radio* 29(1): 53-58, 2023. DOI: 10.5152/dir.2022.21646
  - 17 Mason H, Friedrich AK, Niakan S, Jacobbe D, Casaubon J, Pérez Coulter A: The influence of screening mammography cessation and resumption on breast cancer presentation and treatment: a multi-hospital health system experience during the early COVID-19 pandemic. *Eur J Breast Health* 18(4): 306-314, 2022. DOI: 10.4274/ejbh.galenos.2022.2022-4-4
  - 18 İlğün AS, Özmen V: The impact of the COVID-19 pandemic on breast cancer patients. *Eur J Breast Health* 18(1): 85-90, 2021. DOI: 10.4274/ejbh.galenos.2021.2021-11-5
  - 19 Koca B, Yildirim M: Delay in breast cancer diagnosis and its clinical consequences during the coronavirus disease pandemic. *J Surg Oncol* 124(3): 261-267, 2021. DOI: 10.1002/jso.26581
  - 20 Kato T, Katsuya R, Okado S, Sato K, Noritake O, Nakanishi K, Noguchi M, Kadomatsu Y, Ueno H, Ozeki N, Nakamura S, Fukumoto K, Chen-Yoshikawa TF: Real-world evidence of safety and influence for lung cancer surgery under COVID-19 pandemic in Japan. *J Thorac Dis* 15(2): 542-551, 2023. DOI: 10.21037/jtd-22-1289
  - 21 Tomos I, Kapetanakis EI, Dimakopoulou K, Raptakis T, Kampoli K, Karakatsani A, Koumariou A, Papiris S, Tomos P: The impact of COVID-19 pandemic on surgical treatment of resectable non-small cell lung cancer in Greece. *Life (Basel)* 13(1): 218, 2023. DOI: 10.3390/life13010218
  - 22 Dolan DP, Lee DN, Polhemus E, Kucukak S, De León LE, Wiener D, Jaklitsch MT, Swanson SJ, White A: Report on lung cancer surgery during COVID-19 pandemic at a high volume US institution. *J Thorac Dis* 14(8): 2874-2879, 2022. DOI: 10.21037/jtd-22-5
  - 23 Zhao Y, Wang R, Shi F, Wu J, Jiang F, Song Q: Diagnostic efficacy of CT examination on early detection of lung cancer during pandemic of COVID-19. *Diagnostics (Basel)* 12(10): 2317, 2022. DOI: 10.3390/diagnostics12102317

*Received July 18, 2023*

*Revised August 21, 2023*

*Accepted September 4, 2023*