Evaluation of non-small cell lung cancer treatment strategies in a region of China with low-risk for COVID-19

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Research Article

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Abstract

Purpose: This study analyzed the morbidity and mortality associated with non-small cell lung cancer (NSCLC) and evaluated treatment strategies for it in a low-risk area of COVID-19 in China.

Materials and methods: We selected patients admitted to Sichuan Science City Hospital from September 2019 to February 2020 and divided them into experimental and control groups. The treatment strategy was evaluated by patients' prognosis.

Results: 9,010 patients were hospitalized. The total morbidity was 0.699%, of which 0.504% was observed in the control group and 0.991% in the experimental group (P=0.024). The total mortality was 0.999/10^3, of which 0.630/10^3 was observed in the control group and 1.413/10^3 in the experimental group (P=0.322). Therapy discontinuation and cancer progression in the experimental group were significantly higher than the control group (P<0.001, P=0.007). The treatment methods and prognosis were not significantly different for early-stage patients between the two groups. Late-stage patients in the experimental group experienced significantly lower percentages of non-surgical treatments (P<0.001), higher percentages of discontinued therapies (P<0.001), lower percentages for prognosis of wellness (P<0.001), and higher percentages of cancer progression (P<0.001) than the control group.

Conclusion: NSCLC exhibited significantly higher morbidities during the COVID-19 pandemic. The mortality in the experimental group was slightly higher than the control group, while the difference in cancer progression was significant. It is feasible to perform surgery for early-stage NSCLC patients, and treatment should not be suspended for late-stage patients in regions with low-risk for COVID-19 infection.

Introduction

The Wuhan Municipal Health Commission first reported the existence of COVID-19 on December 8, 2019, and subsequently confirmed that it emerged as early as December 1, 2019[1]. Since the outbreak of COVID-19, the Chinese government has executed high standard testing methods, including chest CT imaging and viral nucleic acid detection[2,3]. When individuals are admitted to a hospital in China, they are required to undergo a chest CT scan and be tested for the presence of respiratory virus nucleic acid[3] to detect whether they are infected with COVID-19 at the time of admittance. When carrying out a chest CT scan, the physician may discover the presence of lung space-occupying lesions (LSOLs) unexpectedly, including ground-glass nodules (GGNs), solid nodules, and partially solid nodules or pulmonary masses, which might have been undetected previously.

There is no evidence that proves any direct relationship between COVID-19 and non-small cell lung cancer (NSCLC). However, the potential for such a relationship is possible in that the number of histologically confirmed NSCLC cases diagnosed could increase due to the increased number of CT scans that are being performed. Therefore, the need to screen for COVID-19 infections could indirectly impact the number of NSCLC cases found and treated.
Cancer patients constitute a specific subgroup of patients in this pandemic due to their typically advanced age, complex health conditions, and low immune function, increasing the risk of adverse and more severe consequences from COVID-19 infection\cite{4}. For cancer patients undergoing active treatment or continued observation, lymphopenia, an independent indicator for a poor prognosis in COVID-19 patients, is common, and their immune response is impaired in cancer patients\cite{5,6}. Thus, cancer patients exhibit a higher mortality rate compared to the general population.

Rogado J et al.\cite{7} reported a significant increase in the mortality rate in lung cancer patients with Covid-19 compared to all Covid-19 patients, which may be due to a greater predisposition to respiratory infections and a previous diagnosis of COPD and metastatic disease in lung cancer patients. Therefore, providing care to patients with lung cancer has been challenging\cite{8}. Many researchers have proposed guidelines to manage this vulnerable population. Kumar S et al.\cite{9} suggested that in the case of limited surgical resources or high risks associated with perioperative care, NSCLC patients who presented with advanced yet localized disease that was resectable could be treated with specific, non-surgical management, including chemotherapy, chemoimmunotherapy, radiation therapy, and immunotherapy. A previous consensus statement suggested that during the COVID-19 pandemic, the annual screening exam and treatment of clinical stage I NSCLC should be delayed\cite{10}. The statement also concluded that it could be acceptable to delay the surveillance CT scan for approximately three to six months for patients with an incidentally detected pure GGN of any size, a partially solid lung nodule with a solid component of 6 to 8 mm, or a solid nodule that was less than 8 mm in diameter\cite{10}. Raskin J et al.\cite{11} recommended delaying surgery for up to three months in cases of small-size NSCLC that did not appear to grow rapidly, and the growth rate should be followed with chest CT scans. These guidelines propose potential approaches to reduce the risk of COVID-19 infections in NSCLC patients. However, problems with these guidelines are apparent. First, did these guidelines apply to all NSCLC patients? Do NSCLC patients in areas that were low-risk for COVID-19 infections benefit equally from these guidelines? To our knowledge, no studies have addressed these questions. Therefore, we carried out a retrospective study that analyzed the morbidity and mortality of NSCLC and evaluated treatment strategies for NSCLC patients in a region of China where COVID-19 infection was determined to be low-risk.

**Materials And Methods**

1. Patients

We selected patients admitted to the Sichuan Science City Hospital from September 2019 to February 2020 and divided them into an experimental group and a control group. Patients in the control group were hospitalized from September 2019 to November 2019, and the experimental group consisted of individuals hospitalized from December 2019 to February 2020. Individuals in the control group who followed their medication protocol through the whole observation period without changing treatment methods were further subdivided. However, if they experienced neoadjuvant therapy during the control period but underwent surgery during the experimental period or continued treatment during the control
period and discontinued the treatment during the experimental period, the individual was placed in the experimental group. All hospitalized patients were included except for pediatric and obstetric patients, and patients younger than 18 years old and were admitted only for routine follow-up examinations.

2. Treatment strategy

Any patient with an unclear diagnosis or a malignant LSOL discovered on CT was encouraged to undergo a definitive diagnosis through biopsy with permission from the patient or their family members. The treatment strategies in the control group followed the guides of the Chinese Society of Clinical Oncology (CSCO). We chose patients in stages I and II and resectable stages IIIA and IIIB for surgical treatment. Non-surgical treatments, including chemotherapy, targeted therapy, radiation therapy, and immunotherapy, were performed for postoperative, locally advanced NSCLC patients and patients not suitable for surgical treatment.

During the pandemic, we generated our own treatment strategies after consulting several guidelines. Therefore, in the experimental group, patients in stages I and II were advised to undergo surgery, while patients in stages III and IV were told to delay any therapy, including surgery, chemotherapy, radiation therapy, and immunotherapy. However, targeted therapy was not delayed because it occurred at outpatient locations. All patients treated during the pandemic underwent a chest CT scan and a respiratory virus nucleic acid test for COVID-19. All treatments were suspended if a patient was suspected to be infected.

3. Treatment strategy evaluation

Treatment strategies were evaluated based on the prognosis of the different treatment methods, including surgical and non-surgical treatments and discontinued therapies. If someone stopped therapy for more than one month, they were considered to have discontinued therapy. The prognosis was classified into one of three levels: well, progression, and death. The well prognosis was defined as no recurrence or metastasis present. Progression was designated when any sign and symptom of recurrence was present or metastasis and tumor growth was discovered during reexamination. The definitions of morbidity and mortality included newly confirmed or deceased NSCLC patients from the hospitalized patients observed during the study period. Patients in early-stage NSCLC included atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (Ais), and stages I and II. Late-stage patients included stages III and IV. The deadline for following up on patients was July 2020.

4. Statistical analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses. Measured data were expressed as means ± standard deviation or as medians. The t-test was used to compare normally distributed data with equal variances. The Mann-Whitney U test was used to compare non-normally distributed data sets. Countable data were expressed as absolute values and percentages.
Comparisons between groups were performed using the chi-square test or Fisher's exact probability test. A difference was considered to be statistically significant if P was less than 0.05.

Results

1. Morbidity and mortality associated with NSCLC

9,010 patients hospitalized in Sichuan Science City Hospital between September 2019 and February 2020 participated in this study, including 4,518 men and 4,492 women. 196 NSCLC patients were confirmed by pathology and treated in our hospital, including 133 previously confirmed late-stage patients who received non-surgical treatment and 63 newly confirmed patients. The total morbidity was 0.699% (63/9,010). Morbidity in the control group was 0.504% (24/4,764) and 0.919% (39/4,246) in the experimental group (P=0.024). The clinical characteristics of the 9,010 patients are shown in Table 1. The clinical characteristics of the 63 newly confirmed patients are shown in Table 2.

All nine deaths were cancer-specific. The total mortality was 0.999 /10^3 (9/9,010). The mortality in the control group was 0.630/10^3 (3/4,764) and 1.413/10^3 (6/4,246) in the experimental group. The mortality rates between the two groups were not significantly different (P=0.322). Among the 196 NSCLC patients, the age of patients in the control group was significantly higher than the experimental group (P=0.024). The number of patients who discontinued therapy and patients with cancer progression was significantly lower than the experimental group (P<0.001, P=0.007). The clinical characteristics of the 196 NSCLC patients are shown in Table 3.

2. Treatment strategy evaluation

62 of the 196 NSCLC patients were early-stage cases, and the treatment methods and prognosis among them did not differ significantly. There were no significant differences among the 134 late-stage patients in surgical treatment (P=0.995). However, there were significant differences in non-surgical treatments (P<0.001) and discontinuation of therapy (P<0.001) between the two groups. Also, the number of patients who exhibited a well prognosis in the control group was significantly higher than the experimental group (P<0.001). Whereas a significantly lower number of patients exhibited cancer progression in the control group compared to the experimental group (P<0.001). The mortality in both early and late stages was not significantly different between the two groups. The comparison of different treatment methods and prognosis of the 196 NSCLC patients are seen in Table 4.

Discussion

The city in which our hospital is located had a population of more than 5.3 million, and 22 cases of COVID-19 were confirmed at the end of February 2020. All 22 patients were cured and discharged, and no new cases have been reported. Therefore, the city was a genuinely low-risk area for COVID-19, and there were no COVID-19-infected patients in our hospital. Also, we developed a series of prevention programs in the operating room, including checking body temperature, wearing medical face masks or protective
clothing, and utilizing laminar airflow in the surgery rooms. Treatments were suspended, and quarantine action was taken if a patient was suspected of being infected with COVID-19 before being hospitalized. During the pandemic, we used a surgical treatment strategy for early-stage NSCLC patients and a non-surgical strategy for patients in late-stage NSCLC. This strategy was employed because early-stage patients exhibited less respiratory disease and trauma during surgery; these patients could recover and be discharged more quickly. On the other hand, late-stage patients routinely exhibited complex health conditions and low immune function, which easily led to complications such as longer in-hospital stays and increased risk of infection. Therefore, we conducted this study to determine a reasonable strategy to treat NSCLC.

The total morbidity for NSCLC among the 9,010 patients was 0.699%, which was dramatically higher than that reported from 2009 to 2011\textsuperscript{[12-14]} in China. This may be because this study included hospitalized patients with a relatively high prevalence rate, in contrast to the general population. On the other hand, patients in hospitals have a high probability of undergoing CT imaging, which could result in finding additional LSOLs. Therefore, the observed higher morbidity was reasonable. As seen in Table 1, the number of patients with unclear diagnoses and malignant LSOLs in the experimental group was significantly higher than the control group (P\textless{}0.001). This might have occurred due to a significant difference between the two groups in patient CT imaging (P\textless{}0.001) and the number of LSOLs observed (P\textless{}0.001). Therefore, the morbidity in the experimental group was significantly higher than the control group (P=0.024). It is known that chest CT imaging is of considerable importance in lung cancer screening. The National Lung Screening Trial Research of America found that 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false-positive results; and the rate of death from any cause was reduced in the low-dose CT group\textsuperscript{[15]}. An Early Lung Cancer Action Project study showed that 85% of the CT-detected cancers were stage I, and the rate of cure for these malignancies was in excess of 80\%\textsuperscript{[16]}. Table 2 illustrates that most of the newly confirmed NSCLC cases were early stage, which is a beneficial result of performing CT imaging widely. Table 3 also demonstrates a significant difference between the two groups for cancer progression patients (P=0.007). This result occurred because patients discontinued therapy in the experimental group at a significantly higher rate than the control group (P\textless{}0.001). Therefore, this study indicated that some high-risk patients delayed further examination and treatment. This observation illustrates the importance of developing rational treatment strategies for NSCLC patients during adverse situations such as the COVID-19 pandemic. Even though there was no significant difference in the mortality between the two groups (P=0.322), it might become significant over time.

In the context of COVID-19, it is critical to control the spread of infection during the pandemic, but managing cancer patients also is vital. Currently, researchers have proposed several recommendations to address this problem. The European Society of Medical Oncology (ESMO)\textsuperscript{[17]} described principles that classified three levels, high, medium, and low, of priorities for cancer care management. It is important to note that ESMO recommended high priority for advanced NSCLC cases and applying neoadjuvant treatment in potentially resectable stage IIIA cases. Table 4 reveals that late-stage patients in the
experimental group experienced a significantly lower number of non-surgical treatments (P<0.001) and a higher percentage of discontinued therapies (P<0.001) than the control group. This implied that most patients who experienced delayed treatment were in a late stage of NSCLC and received non-surgical treatments. This might be the reason why late-stage patients in the experimental group exhibited a significantly lower prognosis for wellness (P<0.001) and a higher percentage of cancer progression (P<0.001) than the control group. Therefore, an effective non-surgical strategy should be used with advanced NSCLC patients.

However, the ESMO recommendations were not based on risk classifications and recommended surgery be delayed in cases of early-stage NSCLC. On the other hand, Cafarotti[18] suggested using a surgical treatment for NSCLC stages I to IIa, when there was a low risk of infection. The latter treatment plan was nearly identical to the strategy we proposed. Table 4 demonstrates that the treatment methods and prognosis among early-stage patients were not significantly different between the two groups. These results suggested that a definitive surgical strategy was feasible and could achieve a well prognosis for early-stage patients in low-risk areas when strict testing and prevention measures were utilized. We also see in Table 4 that patients in the control group were significantly older than the experimental group. This might have occurred because older patients in the experimental group experienced a delay in treatment due to complex health conditions and low immune function.

We also observed a significantly higher number of late-stage patients in Tables 3 and 4. This might be due to an accumulation of previously confirmed late-stage patients who underwent ancillary therapies in the observation period, which resulted in the presence of several unavoidable extreme results that are seen in Table 3.

This was a retrospective study, which was critical to conduct before constructing a valid prospective study. It is critical to develop treatment strategies according to the actual levels of risk that take place. The information gained from this study will allow improvement in future treatment strategies.

Conclusion

The morbidity associated with NSCLC during the COVID-19 pandemic increased significantly due to the expanded use of chest CT imaging. The mortality in the experimental group was slightly higher than the control group, while the difference in cancer progression was significant. Thus, for patients in areas with low-risk for COVID-19 infections, it is preferred to perform surgery for early-stage NSCLC patients and undesirable to suspend treatment for late-stage NSCLC patients when strict testing and prevention measures are utilized.

Declarations

Compliance with Ethical Standards
Disclosure of potential conflicts of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Research involving Human Participants: The study protocol was approved by the Ethics Committee of the Sichuan Science City Hospital.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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### Tables

Table 1 Clinical characteristics of the 9010 hospitalized patients

| ns               | Control group (%) | Experimental group (%) | P Value |
|------------------|-------------------|------------------------|---------|
| Male             | 2364 (26.24%)     | 2154 (23.91%)          | 0.301   |
| Female           | 2400 (26.64%)     | 2092 (23.22%)          |         |
| (years)          | 60.85±17.65       | 61.49±17.40            | 0.080   |
| Patients test CT scan | 1694 (18.80%) | 2729 (30.29%)          | 0.001   |
| al LSOLs         | 713 (7.91%)       | 1743 (19.35%)          | 0.001   |
|lear diagnosis LSOLs | 77 (0.85%)     | 174 (1.93%)            | 0.001   |
|ignant LSOLs     | 49 (0.54%)        | 76 (0.84%)             |         |
| Confirmed NSCLC  | 24 (0.27%)        | 39 (0.43%)             | 0.024   |

Abbreviation: LSOLs: lung space-occupying lesions; NSCLC: non-small cell lung cancer.
Table 2 Clinical characteristics of the 63 newly confirmed NSCLC patients

| Items          | Control group (%) | Experimental group (%) | P Value |
|----------------|-------------------|------------------------|---------|
| Sex            |                   |                        |         |
| Male           | 11 (17.46%)       | 20 (31.75%)            | 0.797   |
| Female         | 13 (20.63%)       | 19 (30.16%)            |         |
| Age (years)    | 68.83±11.02       | 68.56±15.50            | 0.936   |
| Tumor types    |                   |                        |         |
| AAH            | 1 (1.59%)         | 1 (1.59%)              | 0.842   |
| Ais            | 1 (1.59%)         | 1 (1.59%)              |         |
| ADC            | 19 (30.16%)       | 29 (46.03%)            |         |
| SCC            | 3 (4.76%)         | 8 (12.70%)             |         |
| Stage          |                   |                        |         |
| AAH            | 1 (1.59%)         | 1 (1.59%)              |         |
| Ais            | 1 (1.59%)         | 1 (1.59%)              |         |
| I              | 13 (20.63%)       | 29 (46.03%)            | 0.443   |
| II             | 8 (12.70%)        | 8 (12.70%)             |         |
| III            | 0 (0%)            | 0 (0%)                 |         |
| IV             | 1 (1.59%)         | 0 (0%)                 |         |

Abbreviation: AAH, atypical adenomatous pyperplasia; Ais, adenocarcinoma in situ; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Table 3 Clinical characteristics of the 196 NSCLC patients
| Items            | Control group (%) | Experimental group (%) | P Value |
|------------------|-------------------|------------------------|---------|
| **Sex**          |                   |                        |         |
| Male             | 66 (33.67%)       | 47 (23.98%)            | 0.393   |
| Female           | 46 (23.47%)       | 37 (18.88%)            |         |
| **Age (years)**  | 66.75±11.14       | 63.04±11.53            | 0.024   |
| **Tumor types**  |                   |                        |         |
| AAH              | 1 (0.51%)         | 1 (0.51%)              |         |
| Ais              | 1 (0.51%)         | 1 (0.51%)              | 0.971   |
| ADC              | 93 (47.45%)       | 71 (36.22%)            |         |
| SCC              | 17 (8.67%)        | 11 (5.61%)             |         |
| **Stage**        |                   |                        |         |
| AAH              | 1 (0.51%)         | 1 (0.51%)              |         |
| Ais              | 1 (0.51%)         | 1 (0.51%)              |         |
| I                | 13 (6.63%)        | 29 (14.80%)            | 0.004   |
| II               | 8 (4.08%)         | 8 (4.08%)              |         |
| III              | 55 (28.06%)       | 25 (12.76%)            |         |
| IV               | 34 (17.35%)       | 20 (10.20%)            |         |
| Therapy discontinuance | 17 (8.67%)       | 38 (19.39%)           | 0.001   |
| Cancer progression | 9 (4.59%)        | 18 (9.18%)             | 0.007   |
| Dead             | 3 (0.630/10³)     | 6 (1.413/10³)          | 0.322   |

Abbreviation: AAH, atypical adenomatous pyperplasia; Ais, adenocarcinoma in situ; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Table 4 Comparison of different treatment methods and prognosis of the 196 NSCLC patients
| ns                      | Control group (%) | Experimental group (%) | P Value |
|-------------------------|-------------------|------------------------|---------|
| Ly stage                | 23 (11.73%)       | 39 (19.90%)            | 0.755   |
| Surgical treatment      | 17 (8.67%)        | 31 (15.82%)            |         |
| On-surgical treatment   | 0 (0%)            | 1 (0.51%)              | 0.999   |
| Therapy discontinuance  | 6 (3.06%)         | 7 (3.57%)              | 0.525   |
| Prognosis               |                   |                        |         |
| Well                    | 21 (10.71%)       | 35 (17.86%)            | 0.998   |
| Progression             | 2 (1.02%)         | 3 (1.53%)              | 0.999   |
| Dead                    | 0 (0%)            | 1 (0.236/10³)          | 0.997   |
| Ae stage                | 89 (45.41%)       | 45 (23.00%)            |         |
| Surgical treatment      | 7 (3.57%)         | 4 (2.04%)              | 0.995   |
| On-surgical treatment   | 71 (36.22%)       | 10 (5.10%)             | 0.001   |
| Therapy discontinuance  | 11 (5.61%)        | 31 (15.82%)            | 0.001   |
| Prognosis               |                   |                        |         |
| Well                    | 79 (40.31%)       | 25 (12.76%)            | 0.001   |
| Progression             | 7 (3.57%)         | 15 (7.65%)             | 0.001   |
| Dead                    | 3 (0.630/10³)     | 5 (1.178/10³)          | 0.118   |