Evaluating Treatment strategies for Non-small Cell Lung Cancer during COVID-19: A Propensity Scores Matching Analysis

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Research Article

Keywords: non-small cell lung cancer, COVID-19, therapy discontinuance, prognosis

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-78352/v3>

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Version of Record: A version of this preprint was published at Medicine on August 12th, 2022. See the published version at <https://doi.org/10.1097/MD.00000000000030051>.

Abstract

Background

We had different understanding of treatment strategies to which we preferred conduct surgery for early-stage patients and delay treatment for late-stage non-small cell lung cancer patients at beginning of the COVID-19 pandemic. However, as we learned more about other guidelines, we were not sure whether our strategies have caused adverse results.

Methods

We divided patients hospitalized from September 2019 to February 2020 into experimental and control groups, and evaluated treatment strategies by patients' prognosis. Propensity scores matching was used to adjust selection bias.

Results

Therapy discontinuation in the experimental group were significantly higher than the control group ($P = 0.001$). The differences of cancer progression and the number of deaths between the two groups were not significant ($P = 0.376, 0.128$, respectively). There were significant differences in non-surgical treatment and discontinued therapy for late-stage patients ($P = 0.001, 0.001$, respectively), while the differences of surgical treatment and therapy discontinuance for early-stage patients were not significant ($P = 0.243, 0.243$, respectively). The cancer progression and death toll differences in both early and late stage between the two groups were not significant ($P = 0.608, 0.489, 0.197, 0.197$, respectively). Multivariate analysis revealed therapy discontinuation did not predicted progress-free survival independently (hazard ratio = 1.007, 95% confidence interval: 0.653–1.552, $P = 0.976$).

Conclusions

For patients in regions with low risk for COVID-19 infections, surgery should not be delayed for early-stage patients if the hospital has adequate medical resources and strict testing and prevention measures are utilized. Delaying treatment less than three months can not significantly impact the prognosis of late-stage non-small cell lung cancer patients.

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 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.

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.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.^{5,6} Thus, cancer patients exhibit a higher mortality rate compared to the general population.

Rogado J et al.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 chronic obstructive pulmonary disease (COPD) and metastatic disease in lung cancer patients. Therefore, providing care to patients with lung cancer has been challenging.⁸ Many researchers have proposed guidelines to manage this vulnerable population. Kumar S et al.⁹ suggested that in the case of limited surgical resources or high risks associated with perioperative care, non-small cell lung cancer (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.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.¹⁰ Raskin J et al.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, at the beginning of the pandemic, we mainly used a surgical treatment strategy for early-stage NSCLC patients and non-surgical treatment and therapy discontinuance strategies for patients in late-stage NSCLC, which was different from most guidelines. These strategies were employed because, in our opinion, early-stage patients exhibited less respiratory disease and trauma during surgery; these patients could recover and be discharged more quickly. Besides, 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. Furthermore, as more and more people have recognized the fact that the pandemic will not end soon, we may have to deal with its effects over the long term, and conservative strategies may not be suitable for most areas, especially in regions with low

risk for COVID-19. Therefore, we carried out a retrospective study to determine whether our treatment strategies were reasonable.

Methods

Patients

We selected patients admitted to our 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 entire observation period without changing treatment methods were further subdivided. However, when evaluating treatment strategy, 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. The study was approved by the Ethics Committee of the Sichuan Science City Hospital (NO.: 2020007) and informed consent was obtained from all patients and their legal guardians.

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.

At the beginning of the pandemic, we generated our own treatment strategies. 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 for three months, including surgery, chemotherapy, radiation therapy, and immunotherapy. However, targeted therapy was not delayed because it occurred at outpatient locations. There were two main principles for therapy discontinuation, namely doctor's suggestion and patient factors. Doctors suggested patients to temporarily delay therapy mainly for those in late stage. Patient factors include those refused to treatment and tentatively discontinue therapy for the reason of physical weakness and toxic and side effect. 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.

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: stable, progression, and death. The stable disease 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. 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. We followed up with patients via medical records and telephone interviews, and the deadline was April 2021.

Statistical analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses. Continuous data were expressed as means $\pm$ 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. Categorical data were expressed as counts and percentages. Comparisons between groups were performed using the chi-square test and Fisher's exact probability test. Survival curves were analyzed by the Kaplan–Meier method. Indicators with statistically significant results were incorporated into a Cox regression analysis for multivariate analysis of risk factors for progress-free survival (PFS). Propensity scores matching (PSM) was used to adjust selection bias. A difference was considered to be statistically significant if the P-value was less than 0.05.

Results

Patient characteristics

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 classified as early-stage cases, except one late-stage case who chose non-surgical treatment and was included in the experimental group. A flow chart diagramming the patient selection process is presented in Figure 1. 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.

The twelve deaths that occurred during this study were cancer-specific, and the total mortality was 0.133% (12/9,010). Among the 196 NSCLC patients, the difference of cancer progression between the two groups was not significant ($P=0.058$), while the number of deaths in the control group was significantly lower than the experimental group ($P=0.032$) before PSM. After PSM, we found both cancer progression and the number of deaths were not significantly different between the two groups. The clinical characteristics of the 196 NSCLC patients are shown in Table 3.

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 before and after PSM. There were no significant differences among the late-stage patients in surgical treatment. However, there were significant differences in non-surgical treatments ($P = 0.001$) and discontinuation of therapy ($P = 0.001$) between the two groups before and after PSM. The prognosis of the late-stage patients was not significantly different after PSM. The comparison of different treatment methods and prognosis of the 196 NSCLC patients are seen in Table 4. Of all the 55 therapy discontinuance cases, only 18 late-stage patients returned to treatment after discontinuing therapy three months later. There were not cases delay therapy due to COVID-19 infection or worry about infection. The reasons for the discontinuation of therapy are shown in Table 5.

Risk factor analysis for cancer progression

We first analyzed the 12-month PFS using Kaplan-Meier curves and discovered that stage and discontinuation of therapy were significant predictors of poor survival, while age and sex were not after PSM, as seen in Figure 3. We then used Cox multivariate regression analysis to estimate the significantly associated variables listed above and determined that stage was an independent predictor of PFS, while discontinuation of therapy was not (Table 6).

Discussion

The city in which the 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 recovered and were discharged, and no new cases have been reported. The city was a low-risk area for COVID-19, and there were no COVID-19-infected patients in this hospital up to February 2020. 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. At the beginning of the pandemic, we conducted progressive strategies for early-stage patients and conservative strategies for late-stage patients. As we learned more about other guidelines, we realized that our previous strategies had some differences from most recommendations, and we were not sure if it has caused adverse results. Therefore, we conducted this study to verify it in a region of China where COVID-19 infection was determined to be low-risk.

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 ($P = 0.001$), which is a result of performing CT imaging widely. 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.¹² 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%.¹³ Table 2 illustrates that most of the newly confirmed NSCLC cases were early stage, which also is a beneficial result of performing CT imaging widely.

After PSM, patients discontinuing therapy in the experimental group was significantly higher than the control group, and the difference was particularly obvious in late-stage patients (Table 3, 4). However, the Table 4 shows that the difference of cancer progression and the number of deaths in both early and late-stage patients between the two groups were not significant ($P=0.608, 0.489, 0.197, 0.197$, respectively). The reason may be that, on the one hand, some unexpectedly detected LSOLs were cured radically via surgery, and on the other hand, some late-stage patients returned to treatment within three months after therapy discontinuation so that it could not distinctly influence patients' prognosis. This is why the discontinuation of therapy was not an independent predictor of PFS, as noted in Figure 3 and Table 6.

The European Society of Medical Oncology (ESMO)¹⁴ 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, which is opposite to our strategies. The recommendation is advisable, and now we firmly believe that it is unadvisable to suspend treatment for late-stage patients. However, as information obtained from our study, it is also optional to delaying treatment less than three months and it can not significantly impact the prognosis of late-stage NSCLC patients.

Besides, the ESMO recommendations were not based on risk classifications and recommended surgery be delayed in cases of early-stage NSCLC, while Cafarotti¹⁵ suggested using surgical treatment for NSCLC stages I to IIA when the infection risk was low. The latter treatment plan was nearly identical to the strategy we proposed. Table 4 demonstrates that the prognosis among early-stage patients was not significantly different, which might be because there were no significant differences in treatment methods between the two groups. Some studies reported that LSOLs may double time in nodule size and progress from localized to regional or distant disease after a 3-month delay^{16,17}, and the probability of doubling in size of nodule was 0.14¹⁷. Maren E et al. also thought that the patient's NSCLC has progressed to a more advanced stage owing to delay treatment, and immediate surgical biopsy of lung nodules suspicious for cancer in hospitals with low COVID-19 prevalence likely results in improved 5-year survival¹⁸. Therefore, we preferred not to delay surgery for early-stage patients if the hospital has adequate medical resources and safe security or transfer system.

We 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, Figure 2 and Figure 3.

This was a retrospective study, which was critical to conduct before constructing a valid prospective study. It is clear that the current pandemic will not end soon, and we should be prepared to deal with its

effects over the long term. The study of Zhou et al.¹⁹ demonstrated the significant impact of the COVID-19 crisis on oncological care, and they suggested appropriate change of treatment decisions and continued follow-up and psycho-oncological support of NSCLC patients during this pandemic. The information gained from this study will offer additional guidance and provide some experience to doctors.

Conclusions

For patients in regions with low risk for COVID-19 infections, we should not deliberately delay surgery for early-stage patients if the hospital has adequate medical resources and strict testing and prevention measures are utilized. Even though it is unadvisable to suspend treatment for late-stage patients, if necessary, it is optional to delaying treatment less than three months and it can not significantly impact the prognosis of late-stage NSCLC patients.

Declarations

Acknowledgements: The authors would like to express their gratitude to EditSprings (<https://www.editsprings.com/>) for the expert linguistic services provided.

Author contributions: (I) Conception and design: M.Y. and L.Z. (II) Literature search: M.Y. (III) Provision of study materials or patients: L.Z. (IV) Collection and assembly of data: Y.C. (V) Statistical analysis: M.Y. and Y.C. (VI) Manuscript preparation: M.Y. and Y.C. (VII) Manuscript review: L.Z.

Additional Information

Competing interests: The authors declare no competing interests.

Data Availability Statement: The data that support the findings of this study are openly available in *Harvard Dataverse* at <https://doi.org/10.7910/DVN/LJBH8D>

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Tables

Table 1 Clinical characteristics of the 9,010 hospitalized patients

Items	Control group (%)	Experimental group (%)	P Value
Sex			
Male	2364 (26.24%)	2154 (23.91%)	0.301
Female	2400 (26.64%)	2092 (23.22%)	
Age (years)	60.85±17.65	61.49±17.40	0.080
Patients test CT scan	1694 (18.80%)	2729 (30.29%)	0.001
Total LSOLs	713 (7.91%)	1743 (19.35%)	0.001
Unclear diagnosis LSOLs	77 (0.85%)	174 (1.93%)	0.001
Malignant LSOLs	49 (0.54%)	76 (0.84%)	0.001

Abbreviations: 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
New confirmed NSCLC	24 (38.10%)	39 (61.90%)	
Sex			
Male	10(15.87%)	19 (30.16%)	0.613
Female	14 (22.22%)	20 (31.75%)	
Age (years)	65.46±11.10	61.67±13.40	0.250
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%)	0.443
Ais	1 (1.59%)	1 (1.59%)	
I	13 (20.63%)	29 (46.03%)	
II	8 (12.70%)	8 (12.70%)	
III	0 (0%)	0 (0%)	
IV	1 (1.59%)	0 (0%)	

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

Table 3 Clinical characteristics of the 196 NSCLC patients pre- and post-PSM

Items	Pre-PSM			Post-PSM		
	Control group (%)	Experimental group (%)	P Value	Control group (%)	Experimental group (%)	P Value
Sex			0.770			0.225
Male	66 (33.67%)	47 (23.98%)		32 (23.89%)	40 (29.85%)	
Female	46 (23.47%)	37 (18.88%)		35 (23.12%)	27 (20.15%)	
Age (years)	65.68±10.51	63.45±11.66	0.163	65.21±10.87	64.84±11.06	0.803
Tumor types			0.971			0.505
AAH	1 (0.51%)	1 (0.51%)		1 (0.75%)	0 (0%)	
Ais	1 (0.51%)	1 (0.51%)		1 (0.75%)	1 (0.75%)	
ADC	93 (47.45%)	71 (36.22%)		15 (11.20%)	10 (7.46%)	
SCC	17 (8.67%)	11 (5.61%)		50 (37.31%)	56 (41.79%)	
Stage			0.004			0.860
AAH	1 (0.51%)	1 (0.51%)		1(0.75%)	0 (0%)	
Ais	1 (0.51%)	1 (0.51%)		1(0.75%)	1(0.75%)	
I	13 (6.63%)	29 (14.80%)		13 (9.70%)	13 (9.70%)	
II	8 (4.08%)	8 (4.08%)		8 (5.97%)	8 (5.97%)	
III	55 (28.06%)	25 (12.76%)		20 (14.93%)	25 (18.66%)	
IV	34 (17.35%)	20 (10.20%)		24 (17.91%)	20 (14.93%)	
Therapy discontinuance	17 (8.67%)	38 (19.39%)	0.001	6 (4.48%)	33 (24.63%)	0.001
Cancer progression	71 (36.22%)	41 (20.92%)	0.058	44 (32.84%)	38 (28.36%)	0.376
Dead	3 (1.53%)	9 (4.60%)	0.032	3 (2.24%)	9 (6.72%)	0.128

Abbreviations: AAH, atypical adenomatous hyperplasia; Ais, adenocarcinoma in situ; ADC, adenocarcinoma; SCC, squamous cell carcinoma; PSM, propensity score matching.

Table 4 Comparison of different treatment methods and prognosis of the 196 NSCLC patients pre- and post-PSM

Items	Pre-PSM			Post-PSM		
	Control group (%)	Experimental group (%)	P Value	Control group (%)	Experimental group (%)	P Value
Early stage						
Surgical treatment	17 (73.91%)	31 (79.49%)	0.755	17	20	0.243
Non-surgical treatment	0 (0%)	1 (2.56%)	1.000	0	0	
Therapy discontinuance	6 (26.09%)	7 (17.95%)	0.525	6	2	0.243
Prognosis						
Stable	20 (86.96%)	34 (87.18%)	1.000	20	20	1.000
Progression	3 (13.04%)	4 (10.26%)	1.000	3	1	0.608
Dead	0 (0%)	1 (2.56%)	1.000	0	1	0.489
Late stage						
Surgical treatment	7 (7.87%)	4 (8.89%)	1.000	0	4	0.117
Non-surgical treatment	71 (79.78%)	10 (22.22%)	0.001	34	10	0.001
Therapy discontinuance	11 (12.36%)	31 (68.89%)	0.001	0	31	0.001
Prognosis						
Stable	18 (20.22%)	0 (0%)	0.001	0	0	
Progression	68 (76.40%)	37 (82.22%)	0.510	41	37	0.197
Dead	3 (3.37%)	8 (17.78%)	0.007	3	8	0.197

Abbreviations: PSM, propensity score matching.

Table 5 Reasons for discontinuation of therapy

Items	Control group (%)	Experimental group (%)
Early stage		
Patient refusal	5 (9.10%)	7 (12.73%)
Doctor's suggestion	0 (0%)	0 (0%)
Physical weakness	1 (1.81%)	0 (0%)
COVID-19 infection	0 (0%)	0 (0%)
Late stage		
Patient refusal	4 (7.27%)	5 (9.10%)
Doctor's suggestion	0 (0%)	20 (36.36)
Toxicity	4 (7.27%)	4 (7.27%)
Physical weakness	3 (5.45%)	2 (3.64%)
COVID-19 infection	0 (0%)	0 (0%)

Table 6. Multivariate analysis of risk variables for cancer progression pre- and post-PSM

	Pre-PSM		Post-PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Therapy discontinuance (Yes vs. No)	1.424 (0.987-2.074)	0.065	1.007 (0.653-1.552)	0.976
Age (≥60 years old vs. 60 years old)	1.231 (0.820-1.850)	0.316		
Stage (Late vs. Early)	10.281 (5.170-20.447)	0.001	22.502 (8.949-56.584)	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

Figures

Figure 1

The flow chart of diagraming the patient selection process

Figure 2

The PFS of sex(a), age(b), stage(c) and therapy discontinuance(d) pre-PSM

Figure 3

The PFS of sex(a), age(b), stage(c) and therapy discontinuance(d) post-PSM