

## Research Article

# Incidence of COVID-19 Infection in Advanced Lung Cancer Patients Treated with Chemotherapy and or Immunotherapy

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## Abstract

**Background:** The standard treatment for advanced non-small cell lung cancer without driver mutations is represented by chemotherapy and/or immunotherapy. Few data regarding the incidence of Coronavirus Disease 19 (COVID 19) in these patients are available, compared to the general population and it is not known whether this incidence is higher among patients receiving chemotherapy rather than immunotherapy.

**Methods:** We retrospectively collected data from advanced lung-cancer patients treated with chemotherapy and/or immune-checkpoint inhibitors consecutively from 1<sup>st</sup> April 2020 to 31<sup>st</sup> December 2020. We performed an oral-nasopharyngeal swab within 48 from the start of the treatment and we repeated it every other cycle. A swab was also required in case of the appearance of symptoms suspected of COVID. In the present work, we evaluated both the correlation between COVID and type of anticancer treatment and the incidence of positive swabs in patients with lung cancer and in the general population of our province.

**Results:** The rate of COVID in our patients with lung cancer was 8.4% (4 out of 43). In the same period, the percentage of positive swabs in the resident population of our province was 1.3% (range 0.08-3.2). All but one lung cancer patients recovered without specific therapy and without need for hospitalization. The molecular swab was negative after a median period of 36 days (range 21-46). One chemotherapy-treated patient died of COVID at home. We grouped cancer patients in two categories: those receiving chemotherapy only and those treated with chemotherapy + immune-checkpoint inhibitor or immune-checkpoint inhibitor alone. We observed no statistical differences in the incidence of COVID.

**Conclusion:** Our data suggest that patients with advanced lung cancer were at higher risk of COVID compared to the general population and there was no difference in the incidence of infections between patients treated with chemotherapy and those receiving immunotherapy.

**Keywords:** COVID-19, Advanced NSCLC, Immune checkpoints inhibitor

## Introduction

Lung cancer is the leading cause of cancer-related deaths in Western countries. Non-Small-Cell Lung Cancer (NSCLC) accounts for more than 85% of primary lung cancers and approximately two-thirds of NSCLC patients are diagnosed at an advanced stage and their prognosis remains poor [1].

The discovery of driver oncogene alterations such as Epidermal Growth Factor Receptor (EGFR) mutations and Anaplastic Lymphoma Kinase (ALK) rearrangements, as well as the identification of their targeted inhibitors, has dramatically improved the outcomes in highly selected patients [2,3]. In parallel, the improvements in the knowledge of cancer immune editing and the discovery of immune-checkpoint inhibitors have provided important new treatment opportunities for driver mutation negative NSCLC [4,5]. So far, immune-checkpoint inhibitors (administered alone or in combination with chemotherapy)

have become the standard of care in metastatic disease and they gained the role of maintenance therapy after chemo-radiation in locally advanced disease [6]. A recent report highlights a mortality reduction in patients with advanced driver mutation negative NSCLC, probably due to the introduction of these new strategies in daily clinical practice [7]. So far, chemotherapy alone remains the treatment reserved for those patients without a driver mutation and with specific contraindications for immunotherapy (i.e. autoimmune disorders).

COVID-19, a respiratory tract infection disease caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV-2), has been spreading worldwide since late 2019 [8]. The rapid circulation of the virus and the hypothesis that patients with cancer could be particularly at risk if infected, has led many scientific societies to recommend on the one hand to minimize hospital admissions (to prevent infection) and on the other to study

strategies to be able to maintain therapeutic standard for patients with cancer [9,10]. Evidences that patients with a history of cancer have a higher mortality rate due to COVID-19 compared with the general population have been established over time [11-15]. Patients with lung cancer may be more susceptible to infection by SARS-CoV-2. This finding is probably multifactorial and could be due to the systemic immunosuppression caused either by the tumour itself or the anticancer treatments, either by the older age of lung cancer patients than those with other type of cancer and also to most prevalence of chronic lung diseases, cardiovascular comorbidities and smoking exposure in this population [16].

We paid particular attention to immune checkpoint inhibitors whose pulmonary adverse events were thought to potentially, and theoretically, complicate and/or hide a SARS-COV-2 infection, even if in the absence of scientific evidence [17].

The purpose of the present study is twofold: to evaluate whether the incidence of SARS-COV-2 infection in patients with NSCLC is higher than in the general population of our province (Lucca) and to assess the incidence of SARS-COV-2 in patients receiving immunotherapy compared to patients treated with chemotherapy.

### Patients and Methods

This is a retrospective study carried out at the Medical Oncology Unit of Lucca, Tuscany region, in Italy. Each investigator identified patients through a database. The election criteria were: documented stage IV NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) <2 and treatment with an immune-checkpoint inhibitor, a chemotherapy or both, as indicated in daily clinical practice. An adequate bone marrow reserve and good liver and renal functions were required. The exclusion criteria were: EGFR, ALK or ROS-1 aberrations, active or suspected autoimmune disease requiring systemic steroid administration (>10 mg daily, prednisone-equivalent) or other immunosuppressive medications, medical history of active hepatitis B or C, positive test of Human Immunodeficiency Virus (HIV). We included all eligible patients treated consecutively in the period from 1<sup>st</sup> April 2020 to 31<sup>st</sup> December 2020. Patient data were collected retrospectively from medical records and included: demographics, histological and molecular characteristics, number of metastatic sites, number and presence of comorbidities. Data of SARS COV2 positivity rate in our province were collected by Health Ministry reports [18] and are summarized them in Tables 1 and 2.

**Table 1:** Distribution of oral-nasopharyngeal swabs and COVID-positive cases in Lucca province.

	April		May		June		July		August		Septemb		October		Novem		Dicemb	
Day	ONS	NP	ONS	NP	ONS	NP	ONS	NP	ONS	NP	ONS	NP	ONS	NP	ONS	NP	ONS	NP
1	771	42	1289	13	1362	1	1351	0	1385	1	1536	0	1832	11	4650	177	10480	73
2	802	31	1295	6	1363	1	1351	0	1388	3	1538	2	1874	42	4763	113	10548	68
3	843	41	1304	9	1364	1	1351	0	1391	3	1551	13	1893	19	4871	108	10640	92
4	855	12	1308	4	1364	0	1351	0	1392	1	1559	8	1911	18	5038	167	10776	136
5	872	17	1310	2	1364	0	1351	0	1398	6	1572	13	1937	26	5281	243	10860	84
6	888	16	1314	4	1364	0	1351	0	1402	4	1583	11	1957	20	5505	224	10949	89
7	920	32	1316	2	1364	0	1362	11	1405	3	1589	6	1988	31	5739	234	11049	100
8	954	34	1319	3	1364	0	1362	0	1407	2	1595	6	2015	27	6001	262	11072	23
9	979	25	1324	5	1364	0	1362	0	1414	7	1596	1	2078	63	6157	156	11130	58
10	988	9	1328	4	1365	1	1362	0	1417	3	1602	6	2141	63	6328	171	11200	70
11	1006	18	1329	1	1366	1	1362	0	1419	2	1621	19	2194	53	6585	257	11285	85
12	1020	14	1329	0	1366	0	1362	0	1423	4	1636	15	2235	41	6739	154	11349	64
13	1060	40	1331	2	1366	0	1364	2	1429	6	1642	6	2268	33	6944	205	11424	75
14	1061	1	1335	4	1366	0	1365	1	1430	1	1642	0	2305	37	7178	234	11484	60
15	1073	12	1336	1	1366	0	1365	0	1440	10	1644	2	2362	57	7397	219	11532	48
16	1134	61	1338	2	1366	0	1366	1	1444	4	1645	1	2464	102	7707	310	11612	80
17	1158	24	1348	10	1367	1	1367	1	1451	7	1668	23	2531	67	8061	354	11692	80
18	1165	7	1352	4	1367	0	1367	0	1455	4	1678	10	2609	78	8490	429	11756	64
19	1197	32	1352	0	1369	2	1367	0	1457	2	1697	19	2649	40	8674	184	11835	79
20	1213	16	1352	0	1369	0	1367	0	1472	15	1721	24	2679	30	8914	240	11902	67
21	1215	2	1352	0	1369	0	1371	4	1479	7	1732	11	2746	67	9143	229	11973	71
22	1221	6	1356	4	1369	0	1371	0	1485	6	1745	13	2841	95	9376	233	12011	38
23	1225	4	1357	1	1370	1	1371	0	1490	5	1752	7	3022	181	9501	125	12074	63
24	1230	5	1360	3	1351	0	1374	3	1496	6	1773	21	3212	190	9577	76	12149	75
25	1244	14	1360	0	1351	147	1376	2	1497	1	1784	11	3402	190	9710	133	12229	80
26	1256	12	1360	0	1351	0	1377	1	1498	1	1788	4	3583	181	9866	156	12307	78
27	1265	9	1361	1	1351	0	1380	3	1504	6	1794	6	3693	110	10024	158	12325	18
28	1269	4	1361	0	1351	0	1380	0	1509	5	1811	17	3835	142	10172	148	12351	26
29	1273	4	1361	0	1351	0	1381	1	1513	4	1812	1	4007	172	10300	128	12408	57
30	1276	3	1361	0	1351	0	1384	3	1525	12	1821	9	4271	264	10407	107	12465	57
31	/	/	1361	0	/	/	1384	0	1536	11	/	/	4473	202	/	/	12546	81

ONS: Oral-nasopharyngeal swab; NP: Number of COVID-positive cases.

**Table 2:** Distribution by month of the COVID positivity rate in Lucca province.

Month	Total number of ONS	Total NP	Positivity rate%
April	32,433	547	1.68
May	41,459	85	0.20
June	40,871	156	0.37
July	42,355	33	0.08
August	44,951	152	0.34
September	50,127	285	0.57
October	83,007	2,652	3.20
November	229,098	5,934	2.60
December	359,413	2,139	0.59
Total	923,714	11,983	1.30

ONS: Oral-nasopharyngeal swab; NP: Number of COVID-positive cases.

The study was approved by the local ethics committee with Protocol Number 20412 and conducted according to the Good Clinical Practice Guidelines and to the World Medical Association Helsinki Declaration.

### Evaluation Criteria

Pre-treatment evaluation included medical history, physical examination, complete blood-cell count with routine chemistry and Computed-Tomography (CT) scan of chest and abdomen. All patients were asymptomatic at the baseline and we performed an oral-nasopharyngeal swab (PCR test) was performed within 48 hours before the start of the treatment and repeated it before each subsequent cycle of therapy. The oral-nasopharyngeal swab was also required in the presence of symptoms suspected for COVID 19.

### Statistical Analysis

This is a descriptive observational study for which a calculation of the population sample to be included is not necessary. We divided Patients into two groups: those who received chemotherapy only and those who received chemotherapy plus immunotherapy or immunotherapy alone. We assessed the correlation between the incidence of positive swabs in treated patients and in the general population as well as the correlation between positive swabs and patient groups using Fisher's exact test with 0.05 set as significance level of P-values.

### Results

From 1st April 2020 to 31 December 2020, we treated 43 patients, with the previously specified inclusion criteria. All patients tested negative for the molecular swab performed at baseline. Most were men (65.1%) with good performance status (ECOG-PS = 0 - 51.2%) and with adenocarcinoma (55.8%). The clinical characteristics of the patients are listed in Table 3. Eleven patients out of 31 did not have any comorbidity, 9 out of 31 presented one comorbidity and 11 patients had 2 or more comorbidity. The most frequent comorbidities were cardiovascular disease and chronic lung disease.

Most of our patients were treated in first line (64.1%): 18 patients received platinum-based chemotherapy alone, 1 received Gemcitabine only, 4 received platinum-based chemotherapy plus immune-

**Table 3:** Clinical characteristics.

Characteristics	Patients, n (%)
<b>No. Patients</b>	43
<b>Age, median yrs</b>	71
<i>Range</i>	39-84
<b>Sex</b>	
Male	28(65.1)
Female	15 (34.9)
<b>ECOG-PS</b>	
0	22 (51.2)
1	21 (48.8)
<b>Histology</b>	
Adenocarcinoma	24 (55.8)
Epidermoid	14 (32.6)
Large cells	2 (4.6)
SCLC	3 (7.0)
<b>Smoking status</b>	
Never	3 (7.0)
Former	29 (67.5)
Current	9 (20.9)
ND	2 (4.6)
<b>Stage</b>	
IIB	2 (4.6)
III	9 (21.0)
IV	32 (74.4)
<b>Comorbidities</b>	
0	13 (30.2%)
1	13 (30.2%)
2	14 (32.5%)
>3	3 (7.1%)
Cardiovascular or cerebrovascular disease	17
Lung diseases	13
Diabetes and other Endocrine disorders	9
Chronic Kidney Failure	1
Other malignancies	2
Depressive syndrome	3

ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; SCLC: Small-cell Lung Cancer; ND: Not Declared.

checkpoint inhibitors (all of these received Platinum-Pemetrexed-Pembrolizumab), 18 patients were treated with immune-checkpoint inhibitors alone (pembrolizumab, durvalumab, atezolizumab or nivolumab). Finally, 2 patients were included in clinical trials. Only one patient received platinum-based chemotherapy associated with radiotherapy for locally advanced inoperable disease (Table 4). Symptoms suspected of Covid-19 infection occurred in 5 patients, but only one tested positive at the molecular swab. On the contrary, 3 asymptomatic patients tested positive at screening swab for a total of 4 positive patients. Two of them were receiving immune-checkpoint inhibitors and 2 chemotherapy alone.

Table 4: Treatments.

Treatment line	N. (%)
1 line*	25 (64.1)
2 line*	11 (28.2)
> 3 line*	3 (7.7)
*for the metastatic disease: 39 patients.	
Treatment type	N. (%)
Platinum based Chemotherapy	18 (42%)
Monochemotherapy	1 (2%)
Chemotherapy+ immune checkpoint inhibitors	4 (9.5%)
Immune checkpoint inhibitors	18 (42%)
Clinical Trials	2 (4.5%)
Platinum-Gemcitabine	6
Platinum-Pemetrexed	4
Platinum-Paclitaxel	4
Platinum-Vinorelbine	2
Platinum-Etoposide	2
Gemcitabine	1
Platinum-Pemetrexed-Pembrolizumab	4
Pembrolizumab	7
Nivolumab	7
Durvalumab	3
Atezolizumab	1

We observed no correlation between number or type of comorbidities and incidence of COVID-19.

Therefore, in the period from 1st April 2020 to 31 December 2020 the rate of Sars-Cov 2 infections in our population of NSCLC patients was 8.4% (4 out of 43). No patient received any specific treatment; the molecular swab was negative after a median period of 36 days (21-46). A patient undergoing chemotherapy died of COVID-19 at home. We did not observe any statistical differences in terms of incidence of COVID 19 infection between patients receiving chemotherapy only and those treated with chemotherapy + immune-checkpoint inhibitor or immune-checkpoint inhibitor alone (Fisher's exact test;  $P=1$ ). In the same period, as reported by Health Ministry data [18], in our province (387,876 inhabitants) a total of 923,714 oral-nasopharyngeal swabs (PCR test) were performed and the total number of positive tests was 11,983, with a positivity rate of 1.3%, range 0.08-3.2 (Tables 1 and 2).

The incidence of COVID 19 infection among our lung cancer patients was statistically higher than in the general population (Fisher's exact test  $P= 0.0055$ ).

## Discussion

Maintaining cancer care during the pandemic has represented a challenge that has required new flexible strategies and a careful weighing between the COVID-19 risk and the optimal oncological therapeutic standard.

To date, there has been no standard-of-care approach for treating patients with lung cancer during the pandemic. Several organizations and groups of experts shared general recommendations for management of cancer patients [19-21]. The European Society of Medical Oncology (ESMO), for example, recommended prioritizing outpatient visits (for patients with) in case of a new diagnosis of lung cancer, in order to keep the standard work-up without undue delay [22,23].

However, early in the pandemic, it was clear that patients with chronic diseases, including cancer patients, presented a greater risk of severe COVID-19, with high mortality [24-29]. Moreover, patients with lung cancer seemed to be particularly vulnerable to lung infections compared to those with other cancers or to the general population [30]. This observation agreed with our data. In fact, in our series of lung cancer patients for whom the basal molecular swab and the subsequently periodic screening tests were mandatory, we registered a positivity rate of 7.8% in 9 months. This figure was significantly higher than that observed in the resident population in the same period, which was 1.3%;  $P=0.0055$  [18].

The higher rate of positivity could be partially explained by the median age of our patients at diagnosis (71 years) and by the fact that 65% of them had two or more comorbidities in addition to metastatic lung cancer. The report of Memorial Sloan Kettering Cancer Center (MSKCC) suggested that several baseline clinical features were associated with increased risk of COVID-19 severity, including age, obesity, smoking history, chronic lung disease, hypertension and congestive heart failure. On the contrary, cancer features, such as presence of active/metastatic lung cancer or history of prior thoracic radiation or thoracic surgery, PD-L1 immunohistochemistry did not appear to impact severity of COVID-19. The report concluded that patient-specific features, rather than cancer-specific characteristics and type of treatments, are the most significant determinants of severity of COVID-19 disease [31]. However, the multivariate analysis of TERAVOLT study showed that smoking history was the only feature associated with COVID death in lung cancer patients [32].

Although our sample size is too small to draw definitive conclusions, in our series the number and severity of comorbidities did not impact on COVID 19 severity.

One out of 4 lung cancer patients died of COVID, for a mortality rate of 25%.

Our data seemed to agree with those available in other reports [16,31-33] and suggested that patients with thoracic cancer have a higher risk of death than those with other type of cancers and then the general population. In addition, Spanish data showed that mortality rate might be higher in lung cancer patients (32.7 %) [16], in agreement with the meta-analysis of Saini and coll [28] and the meta-analysis of Tagliamento and coll [34]. Similar results were reported by the TERAVOLT registry in patients with thoracic malignancies [32] and by UK Coronavirus Cancer Monitoring Project (UKCCMP) [35]. On the contrary, in a Chinese meta-analysis, the authors did not show a significant difference in mortality between lung cancer patients and those with other types of tumors [36].

One of our patients died without being admitted to intensive care unit; as the life expectancy of patients with advanced lung cancer has increased with the introduction of new treatment options, their early access to the intensive care unit should be taken into account and decided in a multidisciplinary team [37]. In the COVID era, many of the lung cancer-related symptoms such as cough, fever, asthenia or some of the treatment-related adverse events can be misinterpreted and might complicate the management of clinical daily life. In addition, the pulmonary adverse events of immunotherapy may need a careful evaluation in order not to be confused with SARS-COV2 pneumonia. Moreover, radiographic findings of COVID-19 may be indistinguishable from pneumonitis caused by lung cancer treatment, including immunotherapy [38]. We observed that programmed death 1 (PD-1) blockade exposure was not associated with increased risk or severity of COVID-19; in fact, we did not report any differences in COVID infection rate between treatments with immune-checkpoint inhibitors and chemotherapy. We can hypothesize that immunotherapy does not increase susceptibility to COVID-19 infection, nor does increase mortality. Luo and coll [39] and Trapani and coll [40] suggested that there was no significant difference in COVID severity regardless of PD-1 blockade exposure. TERA-VOLT [32] and CCC19 studies [26] reached the same conclusions.

The main limitation of our study is the sample size, which affects the ability to perform adjustments for multiple potential confounding factors. Moreover, a control group of non-cancer patients or other-cancer patients is missing. Larger studies are needed in order to generalize these results.

## Conclusion

We suggest that patients with advanced lung cancer are very fragile and they seem to be at higher risk of Sars-Cov 2 infection and COVID-19 mortality compared to the general population. Moreover, we observed no differences in the incidence of COVID between patients treated with chemotherapy and those receiving immunotherapy. Finally, in the management of these fragile patients, the risk-benefit ratio of anticancer therapy must be carefully evaluated and should be considered an early and prompt COVID treatment in case of infection.

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