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# Clinical courses and outcomes of five patients with primary lung cancer surgically treated while affected by Severe acute respiratory syndrome coronavirus 2

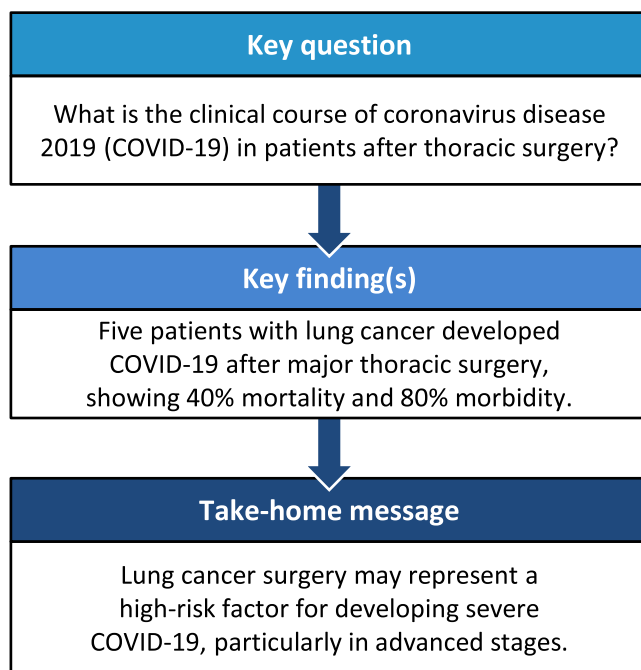
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## Abstract

**OBJECTIVES:** There is currently a lack of clinical data on the novel beta-coronavirus infection [caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] and concomitant primary lung cancer. Our goal was to report our experiences with 5 patients treated for lung cancer while infected with SARS-CoV-2.

**METHODS:** We retrospectively evaluated 5 adult patients infected with SARS-CoV-2 who were admitted to our thoracic surgery unit between 29 January 2020 and 4 March 2020 for surgical treatment of a primary lung cancer. Clinical data and outcomes are reported.

**RESULTS:** All patients were men with a mean age of 74.0 years (range 67–80). Four of the 5 patients (80%) reported chronic comorbidities. Surgery comprised minimally invasive lobectomy (2 patients) and segmentectomy (1 patient), lobectomy with *en bloc* chest wall resection (1 patient) and pneumonectomy (1 patient). Mean chest drain duration was 12.4 days (range 8–22); mean hospital stay was 33.8 days (range 21–60). SARS-CoV-2-related symptoms were fever (3 patients), persistent cough (3 patients), diarrhoea (2 patients) and syncope (2 patients); 1 patient reported no symptoms. Morbidity related to surgery was 60%; 30-day mortality was 40%. Two patients (1 with a right pneumonectomy, 74 years old; 1 with a lobectomy with chest wall resection and reconstruction, 70 years old), developed SARS-CoV-2-related lung failure leading to death 60 and 32 days after surgery, respectively.

**CONCLUSIONS:** Lung cancer surgery may represent a high-risk factor for developing a severe case of coronavirus disease 2019, particularly in patients with advanced stages of lung cancer. Additional strategies are needed to reduce the risk of morbidity and mortality from SARS-CoV-2 infection during treatment for lung cancer.

**Keywords:** Lung cancer • Thoracic surgery • Severe acute respiratory syndrome coronavirus 2 • Coronavirus disease 2019

**ABBREVIATIONS**

COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CT	Computed tomography
GGO	Ground-glass opacity
NSCLC	Non-small-cell lung cancer
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

**INTRODUCTION**

Since December 2019, the world health care community has faced a difficult challenge with the novel beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Because it is highly contagious, SARS-CoV-2 progressively spread from China to almost every country around the globe; Italy was the second country to be hit by the epidemic. Tuscany, in central Italy, has been massively involved after the regions of northern Italy (Lombardy and Veneto) [3]. The intense involvement of hospitals in the care of patients infected with SARS-CoV-2 and the extensive use of the intensive care required by patients with coronavirus disease 2019 (COVID-19) [2] limited elective surgical activity, including oncological surgery. Furthermore, cancer patients are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and the anticancer treatments [4–6]. Therefore, these patients may be at increased risk of contracting COVID-19 and have a poorer prognosis. In addition, a significant delay in surgical treatment may jeopardize their long-term survival and quality of life. There is also serious concern that some oncological diagnostic and therapeutic procedures, including bronchoscopy, double-lumen orotracheal intubation and lung resections in patients with a prolonged air leak may expose health care personnel to breath-borne viruses. Given these facts, thoracic surgeons must choose which patients should be considered as needing urgent treatment or at least which ones for whom treatment should not be postponed and which patients with lung cancer are more at risk of dying if they have a lung resection while being infected with SARS-CoV-2. Our goal was to report our experience with 5 patients surgically treated for a primary lung cancer while infected with SARS-CoV-2 at the beginning of the epidemic in Tuscany.

**MATERIALS AND METHODS**

At the onset of the SARS-CoV-2 epidemic in Italy, oncological surgical activity in the thoracic surgery unit was not interrupted. A total of 79 patients were operated on during this period. For this study, we retrospectively evaluated 5 adult patients infected with SARS-CoV-2 who were admitted to our thoracic surgery unit between 29 January 2020 and 4 March 2020 for surgical treatment of a primary lung cancer. When a patient in the early postoperative period of a video-assisted thoracic surgery segmentectomy for a non-small-cell lung cancer (NSCLC) had an unexplained persistent fever and dry cough, we performed a nasopharyngeal coronavirus swab test. The test result was positive for SARS-CoV-2. We then tested the other 11 patients in our unit for SARS-CoV-2; 4 of 11 patients who had undergone

surgery for lung cancer had positive test results. Of the 67 patients who had already been operated on and discharged, none developed symptoms related to SARS-CoV-2 infection. We performed nasopharyngeal coronavirus swab tests in 12 of these patients because of a positive family history of exposure; the results of all 12 tests were negative. Lymphopenia was defined as a count  $<0.4 \times 10^9/l$ . Chest drain management was standard: continuous aspiration (20 cm H<sub>2</sub>O) for the first 24 h; tube removal after 12 h with no air leak and liquid production  $<4 \text{ ml/kg/24 h}$ . Health care personnel who had been involved in patient management were also tested for SARS-CoV-2. The study was approved by the institutional SARS-CoV-2 scientific committee (ID:09, 17 April 2020).

**RESULTS**

Demographic and clinical data are shown in Table 1; postoperative computed tomography (CT) scans are exhibited in Fig. 1. All patients were men with a mean age of 74.0 years (range 67–80). Comorbidities were present in 80%; 3 (60%) patients were treated with a minimally invasive approach. Mean chest drain duration was 12.4 days (range 8–22); it was prolonged because of liquid production in 3 cases and air leak in 2. The mean hospital stay was 33.8 days (range 21–60). SARS-CoV-2-related symptoms were present in 4 patients (80%); lymphopenia was observed in 2 (40%) patients and anaemia requiring transfusions (haemoglobin  $<8 \text{ g/dl}$ ) was noted in 3 (60%) patients. postoperative morbidity related to the thoracic surgical procedure was 60%. The 30-day mortality was 40% (Table 1). Once the disease was diagnosed, treatment against SARS-CoV-2 was started, including antiviral medications, oxygenation, subcutaneous low-molecular-weight heparin (4.000 units/24 h) and other supportive care when needed (Table 1). For those patients who were discharged, low-molecular-weight heparin was continued for 2 weeks at home. A total of 150 health care workers who were identified as being at high risk of infection were given the nasopharyngeal coronavirus swab test: 3 (2%) of them had positive test results but none developed a severe case of COVID-19.

The following is a case by case description of the clinical reports.

**Case 1**

Case 1 was a male patient, 67 years of age, who was admitted for evaluation of an NSCLC of the lower lobe of the right lung (cT1aN0M0). He had a medical history of rheumatoid arthritis and of a squamous laryngeal tumour treated with surgery and adjuvant chemotherapy 10 years before; he was also a former smoker (40 pack/year, who stopped 2 years ago). Chest CT scans showed an irregular solid nodule in the lower lobe (S7) with no ground-glass opacities (GGOs) in the remaining lung. A trans-bronchial guided biopsy revealed a primary squamous cell carcinoma of the lung. The patient appeared well, with no fever or respiratory symptoms. On day 1 of hospitalization, he had a thoracoscopic resection of segment 7 associated with hilar and mediastinal lymphadenectomies, without incidence. On postoperative day 3, he had an intermittent fever (38.5°C) with peaks to 39.5°C. We started empirical antibiotic therapy (piperacillin and vancomycin). The results of a blood culture were negative. On postoperative day 7, the CT scans showed post-resection

changes in the right lower lobe (parenchymal opacity) with no distant GGO in the remaining lung areas. Blood and urinary cultures revealed no bacterial infections. The white blood cell count was  $13.5 \times 10^{12}/l$  on postoperative day 2 and progressively dropped to  $4.6 \times 10^{12}/l$  on postoperative day 10; the lymphocyte count was lowered to  $0.4 \times 10^9/l$  and the differential to 5%. The C-reactive protein level was always slightly high (about 300 ng/l) whereas the procalcitonin levels were normal. Based on the persistence of the fever and on the development of dyspnoea, chest tightness, wheezing and dry cough, on postoperative day 10 we performed another chest X-ray, which showed bilateral infiltrates in the lower lobes. The pharyngeal swab test for SARS-CoV-2 was performed. When the results of the test were positive, that same day the patient was transferred to the SARS-CoV-2 isolation ward for treatment as described. The patient's condition progressively improved; he was discharged on postoperative day 21 with no symptoms, no fever and no need for oxygen therapy.

### Case 2

Case 2 was a 74-year-old male ex-smoker (30 pack/year), with a history of chronic obstructive pulmonary disease (COPD). The patient was admitted for elective surgery for lung cancer (cT3N0M0). Three months before hospitalization, a CT scan showed a central hilar positron emission tomography positive lesion of the right lung. The results of invasive mediastinal staging were negative. A first surgical treatment comprising a right sleeve upper lobectomy extended to segment S6 was complicated by complete vein thromboses with parenchymal necrosis and infection so that he underwent a completion pneumonectomy on postoperative day 6. The subsequent period was characterized by progressive severe anaemia with no demonstration of any bleeding source that required transfusions on postoperative day 10, fever ( $38.2^\circ\text{C}$ ) and diarrhoea since postoperative day 8. Fever persisted despite broad-spectrum antibiotic therapy (piperacillin and vancomycin), as did coughing; progressive lymphopenia with lowered lymphocyte count appeared. Because the patient was exposed to case 1, a pharyngeal swab test for SARS-CoV-2 was performed; positive results were obtained on postoperative day 46. The patient was then transferred to the SARS-CoV-2 isolation ward for specific treatment. He gradually recovered until postoperative day 60, when he died of a pulmonary embolism.

### Case 3

Case 3 was an ex-smoker (40 pack/year), 70-year-old man with a history of COPD and hypothyroidism. The patient was diagnosed with a primary adenocarcinoma of the right upper lobe, involving the chest wall (2-3-4 ribs), cT3N0M0. After induction chemotherapy and radiotherapy (complicated by a urinary tract infection with left hydronephrosis, which needed a nephrostomy), the patient underwent a standard lobectomy with *en bloc* chest wall resection plus mediastinal lymph node radical dissection (R0 surgery). The postoperative period was uneventful but characterized by a slow functional recovery, ineffective cough, sputum retention and frequent episodes of atelectasis that required bronchoscopies. On postoperative day 10, the patient had fever ( $38.1^\circ\text{C}$ ), cough, diarrhoea, hypotension and anaemia without bleeding (haemoglobin 5.8 g/dl). Due to the presence in

the ward of patients infected with SARS-CoV-2, we performed the pharyngeal swab test; the results of the test were positive. The patient was then transferred to the SARS-CoV-2 isolation ward for specific treatment. Unfortunately, the patient's respiratory condition progressively deteriorated with the need for oxygen and respiratory support. The CT scan showed bilateral extended interstitial pneumonia. Because of further worsening of his clinical condition, the patient was transferred to the COVID-19 dedicated intensive care unit. After 24 h of non-invasive ventilation, mechanical ventilation was required. On postoperative day 25, the patient exhibited acute renal failure; the patient started continuous veno-venous haemodiafiltration (1000 U/h prefilter heparin, 10 mg/h post-filter protamine sulphate). Despite the treatment, his condition progressively worsened until he died on postoperative day 32 of multiple organ failure.

### Case 4

Case 4 was an 80-year-old male patient, admitted for elective surgery because of a middle lobe NSCLC (cT1bN0M0). He was a current smoker (10 pack/year), with a history of COPD and frequent exacerbations, hypertension and peripheral arterial occlusive disease. A CT scan showed a solitary nodule of the middle lobe; a transbronchial guided biopsy revealed a primary squamous cell carcinoma. The patient looked well, with no symptoms, so on day 1 of hospitalization, he had a robotic-assisted middle lobectomy with hilar and mediastinal lymphadenectomies. The postoperative period was characterized by a persistent air leak that prolonged chest drain duration and hospitalization. Broad-spectrum antibiotic (amoxicillin and clavulanate) therapy was started on postoperative day 5. On postoperative day 16 the patient suddenly had marked hypotension (blood pressure 85/50 mmHg) and tachycardia; the results of a blood test showed anaemia (haemoglobin 7.5 vs 11.70 g/dl the day before) and a slight increase in the white blood cell count ( $14.30$  vs  $11.70 \times 10^{12}/l$ ). Also on postoperative day 5, the patient had a contrast enhanced CT scan that showed neither GGO in the remaining lung nor active bleeding. The patient had no fever or respiratory symptoms. However, due to the presence in the ward of patients infected with SARS-CoV-2, we performed the pharyngeal swab test on postoperative day 17; the results of the test were positive. The same day he was moved to the SARS-CoV-2 isolation unit for specific treatment. The patient was discharged on postoperative day 30.

### Case 5

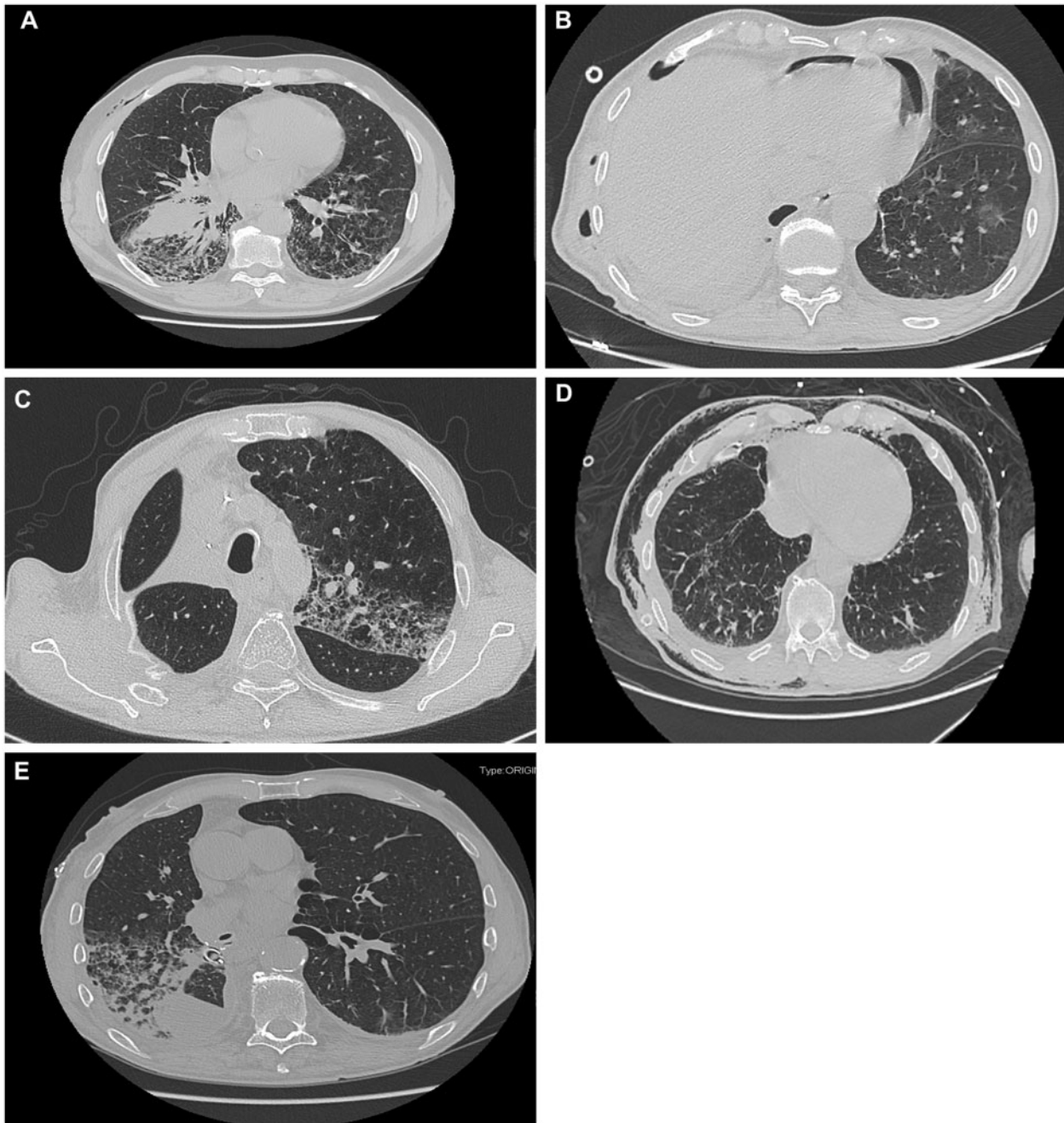
Case 5 was a 79-year-old male patient, current smoker (60 pack/year) and a history of alcohol abuse. He was admitted for evaluation of a lung cancer of the right lung, cT1N0M0 after complete staging. He had a medical history of psoriasis, bullous emphysema and peripheral arterial occlusive disease of the lower limbs. Because he had a persistent cough, we performed a chest CT scan. The scan showed a solid nodule in the right lower lobe. The subsequent CT-guided biopsy resulted in the diagnosis of a primary large-cell neuroendocrine carcinoma. His general condition was good, without symptoms. On day 1 of hospitalization, the patient had a thoracoscopic right lower lobectomy with hilar and mediastinal lymphadenectomies, without event. The postoperative period was characterized by a slow functional recovery, with the frequent

Table 1: Demographics and clinical characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Male	Male	Male	Male	Male
Age (years)	67	74	70	80	79
BMI (kg/m <sup>2</sup> )	26.4	22.1	19.1	22.7	19.4
Comorbidity	COPD, rheumatoid arthritis	No	COPD, hypothyroidism	COPD, systemic hypertension and PAOD	Psoriasis, bullous emphysema and PAOD
Previous cancer	Squamous laryngeal carcinoma	No	No	Urothelial carcinoma	No
FEV1 (%), n (%)	2.66 (89)	2.84 (94)	1.23 (86)	1.31 (50)	1.6 (69)
Induction treatment	No	No	Chemotherapy, radiotherapy	No	No
Surgical procedure	Segmentectomy	Sleeve lobectomy completion, pneumonectomy	Right upper lobectomy + chest wall resection	Middle lobectomy	Right lower lobectomy
pTNM	VATS T1bN0M0	Thoracotomy T2bN0M0	Thoracotomy yT3N0M0	RATS T1bN0M0	VATS T2aN0M0
Histological type	Squamous cell	Adenocarcinoma	Adenocarcinoma	Squamous cell	Small cell carcinoma
Chest drain duration (days)	12	18	8	22	17
Postoperative morbidity	No	Pulmonary vein thromboses	No	Prolonged air leak (>7 days)	Sputum retention, atelectasis and alcohol withdrawal
SARS-CoV-2-related symptoms	Fever, cough and dyspnoea	Fever, cough and diarrhoea	Fever, cough, diarrhoea and hypotension	Hypotension	No
Lymphopenia (<0.4 × 10 <sup>9</sup> /l)	Yes	Yes	No	No	No
Anaemia (Hb <8 g/dl)	No	Yes	Yes	Yes	No
Hospitalization after SARS-CoV-2 diagnosis (days)	10	14	18	13	6
SARS-CoV-2 treatment (days)	Lopinavir (10) Ritonavir (10) HCQ (10) LMWH (34)	Lopinavir (6) Ritonavir (6) HCQ (13) Darunavir (7) Cobicistat (7) LMWH (59)	Lopinavir (14) Ritonavir (14) HCQ (14) LMWH (31)	Lopinavir (9) Ritonavir (9) HCQ (9) LMWH (43)	Lopinavir (6) Ritonavir (6) HCQ (6) LMWH (39)
Intensive care unit stay (days)	No	8	25	No	No
Non-invasive ventilation (days)	No	No	1	No	8
Mechanical ventilation (days)	No	No	22	No	No
Postoperative hospital stay (days)	21	60	32	30	26
Outcome	Alive	Died	Died	Alive	Alive

BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in the first second; Hb: haemoglobin; HCQ: hydroxychloroquine; LMWH: low-molecular-weight heparin; PAOD: peripheral arterial occlusive disease; RATS: robotic-assisted thoracic surgery; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VATS: video-assisted thoracic surgery.





**Figure 1:** Postoperative chest computed tomography images: (A) case 1; (B) case 2; (C) case 3; (D) case 4; (E) case 5.

need of bronchoscopy for retained secretions with atelectasis and prolonged psychiatric treatment for alcohol withdrawal. Due to the presence of *Klebsiella oxytoca* on a bronchoalveolar aspiration culture, antibiotic treatment with vancomycin and meropenem was started on postoperative day 13. The patient never had a fever, and laboratory findings were normal. His general condition gradually improved. On postoperative day 17, a chest CT scan showed consolidation of the right upper lobe, associated with GGO in the same remaining lung. Because he was in the same room as a patient found to be infected with SARS-CoV-2, on postoperative day 20 he had the pharyngeal swab test, the results of which were positive. The same day he was transferred to the SARS-CoV-2 isolation ward for specific treatment. The patient's condition progressively improved, and he was discharged on

postoperative day 26. The final histological report revealed a pT2aN0M0 small cell lung cancer.

## DISCUSSION

On 11 March 2020, the World Health Organization declared the SARS-CoV-2 epidemic a pandemic [7]. Since then, elective cancer surgery has been disrupted around the world; surgeons have been faced with questions and considerations unimaginable in the pre-pandemic era. Should surgical treatment of lung cancer remain a priority? Which patients with lung cancer can wait for surgery and which ones would be placed at greater risk by a coronavirus infection and concomitant lung cancer treatment? Clearly, we do not

have a definitive answer, but we have made some recommendations based on our case series of 5 patients surgically treated and infected with SARS-CoV-2 during the perioperative period. In our 5 patients with lung cancer, the presence of SARS-CoV-2 was 'accidental', and surgical treatment was performed when the superimposed infection was not recognized. Liang *et al.* [8] recently suggested that patients with cancer are more likely to be infected with the virus because of their immune depressed state induced by the oncological treatment (chemotherapy or surgery) and by the cancer itself. This study was performed on 18 patients with cancer among a population of 2007 patients diagnosed with SARS-CoV-2, which is a small number. The authors emphasized that patients with cancer are at higher risk of developing severe disease (39% vs 8%). Also, patients who have been operated on or who have had anticancer chemotherapy in the month preceding the appearance of the virus had a higher risk (75%) of developing life-threatening disease than those who had not had surgery or chemotherapy (43%). The 5 patients with lung cancer included in our series showed a lower probability of severe events compared with patients with other types of cancers (1, 20% vs 8, 62%). Otherwise, Tian *et al.* [9] reported the results of the pathological examinations of 2 patients who had lobectomies performed for a primary adenocarcinoma and who retrospectively were found to have had COVID-19 at the time of surgery; they reported a mortality of 50% for those who had COVID-19.

The first consideration is that our patient outcomes were worse than those reported by Liang *et al.*: we actually observed 40% mortality in patients with severe COVID-19; the morbidity in 60% was associated with a long hospital stay (mean 33.8 days). An early stage lung cancer treated with a minimally invasive procedure is apparently associated with a better outcome. An immediate consequence of the presence of SARS-CoV-2-infected patients within the thoracic unit was that, since then, all patients scheduled for surgery, even those who were asymptomatic, have had a nasopharyngeal swab test 2 days before hospitalization. However, the clinical course and the pathological status of these cases can also be discussed for other reasons. All patients had primary lung cancer; thus, according to national rules, the surgical procedure was considered a high priority, meaning that the treatment must be performed 'within a month from diagnosis'. Because lung cancer surgery is considered as an 'urgent' surgery worldwide, 2 questions have become of fundamental importance for the thoracic surgeon: which lung cancer procedures can be delayed and which lung cancer patients are more at risk from in-hospital infection with SARS-CoV-2 during the postoperative period. In light of the continuing lack of resources, many institutions are negotiating a reduction in elective lung cancer procedures. So, the question is, what kind of surgery should be considered immediately 'necessary' and not to be delayed.

### Which lung cancer surgical procedures cannot be delayed?

The first answer may be surgical procedures for advanced stage lung cancer, because a delay of few months in this setting could mean progression towards inoperability. Another possible answer is patients undergoing multimodality treatment, at the end of their induction treatment, to be operated within 4–6 weeks after the end of neoadjuvant therapy.

Recently, the Thoracic Surgery Outcomes Research Network [10] provided a guide for triaging patients with thoracic malignancies during the COVID-19 pandemic. They defined 3 phases

of hospital status based on the prevalence of patients with COVID-19 within the hospital: the availability of hospital resources; the prevalence of infections; and the consequent resource depletion. Phase I is defined by the presence of few COVID-19 patients and intact hospital resources. Phase I can be considered to correspond to our scenario: The guideline in this setting is to consider that the surgical procedure should be performed as soon as feasible in the case of a solid or predominantly solid (>50%) lung cancer, lung cancer  $\geq 2$  cm, node-positive lung cancer and post induction therapy cancer. Although our case series met these indications, the results were not particularly satisfactory. In patients with stage IIIA lung cancer, a delay >3 months between the onset of neoadjuvant therapy and surgery has been associated with significantly reduced median survival [11, 12]. This situation describes the scenarios of our cases 2 and 3. Unfortunately, in these patients, infection with SARS-CoV-2 resulted in severe cases of COVID-19 that ended in death (not related to other infectious causes or complications). Moreover, surgical procedures for patients with advanced stages is more prone to postoperative complications, and the reduced availability of resources in intensive care units could jeopardize their management. On the other hand, patients with early stage lung cancer treated by minimally invasive surgery had a prolonged hospital stay (but outside intensive care) with successful outcomes. Moreover, in patients with stage I lung cancer, an interval between diagnosis and surgery greater than only 8 weeks has been reported to be associated with a significant reduction in the 5-year survival rate [13].

### Which patients are more at risk in case of in-hospital infection?

Phase II as defined by the Thoracic Surgery Outcomes Research Network [10] is characterized by the presence of many COVID-19 patients with the consequent major limitation of logistical and human resources. In this scenario, surgery should be restricted to patients whose survival is likely to be compromised if the surgery is delayed by a few days; all elective thoracic procedures should be deferred (3 months). Based on our case series, patients with early stage lung cancer treated with minimally invasive procedures had longer and more complicated recovery times mainly due to the co-existence of the symptoms and complications of COVID-19, but they were able to overcome the disease without the need for invasive ventilation. These results suggest that early stage lung cancer could be treated during the SARS-CoV-2 epidemic with moderate risk in patients with hospital-acquired infection. In contrast, patients with advanced stages of lung cancer and complex surgical procedures are prone to fatal complications from COVID-19, so they should be treated only if a completely SARS-CoV-2-free hospital pathway can be guaranteed or if the procedure cannot be postponed for urgent clinical reasons. In any case, the potential risks of postponing or proceeding with treatment should be accurately balanced on a case by case basis and discussed with the patient.

This case series has some obvious limitations due to the small sample size and to the different baseline characteristics, including comorbidities and preoperative pulmonary lung function. Moreover, due to the retrospective nature of the analysis, the date of exposure and the time of onset of the disease can only be presumed. Because of the shortage of nasopharyngeal coronavirus swab tests, its prescription at that time was allowed only by the department of public health and by the infectious disease specialists and in cases of persistent symptoms or exposure; this

situation limited the extension of the study to all the patients operated on during the same period.

## CONCLUSIONS

Based on our case series, surgery for lung cancer is a risk factor for developing severe COVID-19, particularly in patients with advanced stages of lung cancer. Therefore, in patients scheduled for lung cancer surgery during the SARS-CoV-2 outbreak, we suggest the following steps: (i) perform a preoperative SARS-CoV-2 nasopharyngeal swab test; if the test result is positive, consider postponing the surgical procedure; (ii) in endemic areas, consider intentional postponement of adjuvant chemotherapy or elective surgery for stable cancer in an advanced stage; (iii) provide the strongest protection possible for patients with lung cancer after their in-hospital admission; (iv) consider hospital surveillance or treatment in both the intensive care unit and the regular wards; and (v) have a multidisciplinary cancer board to guide the most appropriate therapeutic choice for each patient and consider alternative treatments.

**Conflict of interest:** none declared.

## Author contributions

**Alessandro Gonfiotti:** Conceptualization; Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing. **Lavinia Gatteschi:** Data curation; Investigation. **Alberto Salvicchi:** Data curation. **Stefano Bongiolatti:** Formal analysis; Methodology. **Federico Lavorini:** Supervision; Writing—review & editing. **Luca Voltolini:** Supervision; Writing—review & editing.

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