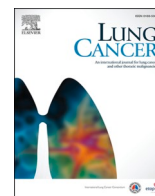




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Impact of COVID-19 on the management of patients with thoracic cancers in a tertiary referral center

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 has spread worldwide in 2020 leading the World Health Organization to declare a pandemic. Patients with thoracic cancers have been reported at higher risk to develop severe disease, and die from COVID-19. In this setting, clinical practice recommendations for the management of patients were published. We report here how these guidelines were implemented in a routine practice setting.

Methods: We retrospectively collected the characteristics, treatment regimen and modification, as well as COVID-19 status and death for all patients with thoracic malignancies scheduled for an appointment at Institute Curie from March 23rd to April 17th 2020.

Results: A total of 339 patients were included. Treatment strategy was modified for a total of 110 (32 %) patients because of COVID-19; these modifications were in accordance with guidelines for 92 % of patients. The majority of dose modifications were related to immune checkpoint inhibitors, for which switch to flat dosing every 4–6 weeks was made. A total of 5 (1.5 %) patients were diagnosed with COVID-19 disease, 1 of whom died from disease complication.

Conclusion: Our study provides a unique insight in the decision making for patients with thoracic malignancies in the setting of COVID-19 outbreak, showing how guidelines were implemented in the clinic, and what may be optimized in the clinical practice of thoracic oncology in the future.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is caused by a novel beta-coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The first cases of pneumonia were reported in Wuhan City, China, in December 2019 [2] and were rapidly followed by a worldwide dissemination. The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern [3]. COVID-19 has affected more than 30 million people all over the world and has been responsible for more than 900,000 deaths [4]. France has the 9th highest number of cases of COVID-19 cases in the world, with more than 354,000 confirmed cases and almost 30,000 deaths as of September 2020 [4]. The French hospital emergency response (“Plan Blanc”) and a nation-wide lockdown were implemented from March 16th to May 11th, 2020. The Paris area (Ile-de-France) remained the epicenter of the epidemic in France at this period.

[reference suppression]

Cancer patients could represent a high-risk population. Wu et al. reported a 2.3 % death rate in the general population *versus* 5.6 % among cancer patients, based on 44,672 confirmed cases in China [5]. Patients with thoracic cancers are at even higher risk to develop severe disease and die from COVID-19; mortality rate was 36 % in the largest series reported. Besides landmark prognostic factors such as performance status, age, disease progression, prior administration of chemotherapy, as unique modality or in combination with immune checkpoint inhibitors, was associated with increased risk of death; admission of patients in intensive care units was lower compared to other tumor types [6].

In this setting, clinical practice recommendations for the management of patients with thoracic malignancies based on expert consensus were published by several groups, including the European Society for Medical Oncology [7,8]; the Oncology group of the French Society for

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Respiratory Medicine released national guidelines on March 23th 2020 [9]. Here we report how these guidelines were implemented at the beginning of the pandemic, at the level of a tertiary referral center for thoracic cancers, analyzing the clinical situation, the modification of the management, and the outcome of patients over the month following the publication of the national guidelines. Ultimately, we provide a unique insight in the actual decision making for patients with thoracic malignancies in the setting of COVID-19 outbreak.

2. Material and methods

2.1. Patient care at Institute Curie

Located in Paris, Institute Curie is a comprehensive cancer center founded by Marie Curie in 1921 and one of the leading hospitals dedicated to the treatment of patient with cancer. Overall, more than 1000 patients with thoracic cancer have been treated at Institute Curie every year since 2017, making Institute Curie one of the most dynamic cancer center for the management of thoracic tumors in France. Five full-time thoracic oncologists are dedicated to the management of those patients. Since 2019, Institute Curie implemented virtual consultation *via* webcam and phone calls, to enable physicians to contact patients for follow-ups and planning of cancer treatment administration in the outpatient clinic.

2.2. Clinical practice guidelines during COVID-19 pandemic

National clinical practice guidelines for the management of patients with thoracic malignancies under the auspices of the Oncology group of the French Society for Respiratory Medicine are presented in Table 1. The key points are the following: 1) avoid the appointment of patients at cancer treatment facilities where patients could be infected by COVID-19 and encourage virtual consultation whenever possible; 2) to postpone surgery for early-stage tumors whenever applicable; 3) adapt cancer treatment regimens for patients with advanced, metastatic tumors, through modifying dose scheduling and discontinuing immune checkpoint inhibitors, especially in patients with durable disease control.

2.3. Data collection

Inclusion criteria for this analysis were the following: 1) histologically-confirmed thoracic malignancy, including lung cancer, mesothelioma, and thymic tumors, 2) with scheduled appointment for a consultation and/or administration of cancer treatment and/or hospitalized in the inpatient clinic, 3) from March 23rd to April 17th 2020 in the month following the publication of the clinical practice recommendations for the management of patients with thoracic malignancies in the context of the pandemic. This retrospective study was approved by the Institutional Data Review Committee of Institute Curie; all patients gave consent at the initiation of their care for the retrieving of healthcare information from their electronic medical record. Clinical data were then retrospectively collected, including patients baseline characteristics, histology, stage, treatment regimen, dates of treatment, and treatment modification, as well as COVID-19 status and death.

3. Results

3.1. Patients' characteristics

During the study period, a total of 343 patients with thoracic malignancies had been scheduled for an appointment at Institute Curie (Fig. 1). Three patients were not able to actually attend because of quarantine, and one patient without cancer was excluded from the analysis. Overall, 288 patients (85 %) had Non-Small Cell Lung Cancer (NSCLC), 26 had Small-Cell Lung Cancer (8%), 11 had mesothelioma

Table 1

French national guidelines concerning thoracic tumors and COVID-19, according to the SPLF (Société de Pneumologie de Langue Française), published on March 18th 2020.

NSCLC	Surgery	Radiotherapy	Systemic treatment
Non metastatic		-stereotaxic radiation whenever possible	Chemotherapy -continuation of treatment with a maximum of 3 cycles of platine-based chemotherapy -CARBOPLATINE preferred to CISPLATINE
Early stage (I -> IIIA)	-postponing or cancelation of surgery	-no adjuvant radiotherapy -continuation of adjuvant treatment if already started	- cancellation of day 8 injection -systematic G-CSF to avoid hospitalization for neutropenia Chemotherapy -CARBOPLATINE preferred to CISPLATINE
Locally-advanced		-continuation of treatment if already started	Immunotherapy - DURVALUMAB administered at the dose of 1500 mg every 4 weeks
Metastatic Targetable			Targeted therapy -continuation of treatment -preference for teleconsultation -after first tumor assessment showing disease control, follow-up every 4 months 1st line -continuation of chemotherapy plus immunotherapy until 4 cycles if already started -systematic discussion before the initiation of maintenance -single-agent immunotherapy with PEMBROLIZUMAB : if treatment started for less than 1 year, possibility to double the dose and the delay the time between injections (PEMBROLIZUMAB 400 mg every 6 weeks). If stable disease and treatment for more than 1 year, discussion of discontinuation ≥2 lines -systematic discussion before the initiation of a chemotherapy -single-agent immunotherapy : if treatment started for less than 1 year, possibility to double the dose and the delay the time between injections (NIVOLUMAB 480 mg every 4 weeks, PEMBROLIZUMAB 400 mg every 6 weeks,
alteration			
Absence of targetable			
alteration			

(continued on next page)

Table 1 (continued)

NSCLC	Surgery	Radiotherapy	Systemic treatment
			ATEZOLIZUMAB 1200 mg every 3 weeks). If stable disease and treatment for more than 1 year, discussion of discontinuation
			-chemotherapy : discussion of cancelation of day 8 and day 15 (PACLITAXEL, VINORELBINE)
			-systematic G-CSF prophylaxis to avoid neutropenia
Small-cell lung cancer		-continuation of treatment if already started	-continuation of treatment -CARBOPLATIN preferred to CISPLATIN -systematic G-CSF prophylaxis to avoid neutropenia
MESOTHELIOMA			-systematic discussion before the initiation of treatment in advanced disease -single-agent immunotherapy : if treatment started for less than 1 year, possibility to double the dose and the delay the time between injections (NIVOLUMAB 480 mg every 4 weeks). If stable disease and treatment for more than 1 year, discussion of discontinuation -systematic discussion to discontinue BEVACIZUMAB maintenance
THYMIC TUMOR	-postponing of surgery whenever possible		

Legend : G-CSF = Granulocyte-Colony Stimulating Factor; NSCLC = Non Small Cell Lung Cancer; SCLC = Small Cell Lung Cancer.

(3%), and 14 had a thymic tumor (4%). Among NSCLC patients, 23 patients had early-stage/localized disease (8%), 48 had a locally advanced disease (17 %), and 217 metastatic disease (75 %) (Table 2).

A total of 25 patients were new patients and had their first appointment during the period; 127 (37 %) patients were seen through virtual consultation, and 228 (67 %) were physically seen by a physician at Institute Curie, and 16 (5%) had both types of appointment (virtual and physical appointments) during the period.

3.2. Treatment adaptations

During the study period, 110 (32 %) patients had the treatment strategy adapted because of COVID-19.

A total of 34 (31 %) of those patients were receiving immune checkpoint inhibitors (ICI), including durvalumab for locally advanced NSCLC, and pembrolizumab for metastatic NSCLC, with a switch to flat

dosing every 4–6 weeks (Table 3). Additional 55 (50 %) patients received primary G-CSF prophylactic treatment after chemotherapy, among whom 30 were receiving a combination of chemotherapy plus immune checkpoint inhibitors. We did not notice any uncommon nor relevant adverse event related to the administration of G-CSF concomitantly to immunotherapy. Oral, instead of intravenous, vinorelbine was administered to 8 (7%) patients at home after blood test control.

Treatment was suspended for 12 patients (3.5 % of the cohort) because of the COVID-19 context, including early discontinuation of chemotherapy or immunotherapy in 7 patients with controlled disease; 1 additional patient with SCLC had altered general status discontinued chemotherapy, and finally died from cancer; 1 patient had a delayed initiation of radiotherapy for locally-advanced disease, because of COVID-19 disease suspicion (he finally was tested negative).

Through the important use of virtual consultation, no impact was observed for the 18 patients under surveillance after surgical resection of early-stage NSCLC, and for the 46 patients with oncogene-addicted NSCLC, especially those receiving targeted agents.

3.3. Concordance with guidelines

Of the 110 modifications of treatment strategies, 101 (92 %) were in accordance with the recently published guidelines; for 9 patients, treatment modification had not been stated in the guidelines: cancellation of the fourth cycle of adjuvant chemotherapy (n = 2), cancellation of the fourth cycle of chemotherapy during concomitant chemoradiotherapy (n = 2), no initiation or early discontinuation of durvalumab before one year in patient with controlled disease (n = 2), 3 patients did not received the planned treatment: one patient did not receive post-operative radiotherapy – an option highly debated and ultimately known as potentially deleterious -, and 2 elderly patients were directed to palliative care because of their age and poor performance status.

3.4. Death related to COVID-19

A total of 5 (1.5 %) patients were diagnosed with COVID-19 disease, 1 of whom (with mesothelioma) died from disease complications; 11 (3.2 %) additional patients died from cancer during the study period.

4. Discussion

Our report is the first study, to our knowledge, to analyze how treatment strategies for thoracic malignancies were adapted during the COVID-19 outbreak in early 2020 in a tertiary referral center, after guidelines were implemented. Our data show only 32 % of patients had the treatment strategy adapted during the study period; the vast majority of those adaptations were done in accordance with guidelines. Only 5 patients were infected with COVID-19.

Our data indicate that 68 % of patients experienced no change in the treatment strategy during the COVID-19 outbreak; this may be explained by 1/ the French health authorities recommendation to continue cancer care at cancer centers such Institute Curie, and sparing these centers from the referral by emergency units of non-cancer patients with COVID-19, 2/ the early organization of our center to avoid COVID-19 positive patients to come to the hospital, through systematic call the day before their appointment, and to orientate such patients presenting with symptoms potentially related to COVID-19 in a dedicated pathway within the hospital, thus securing non-COVID-19 patients regarding the safety of outpatient visits at Institute Curie, and 3/ the high proportion of patients in the setting of surveillance, or treated with targeted agents not requiring such adaptations. Through such organization, as well as systematic delivery of neutropenia prophylaxis, only few patients in our cohort presented with COVID-19 infection. The combination of G-CSF and immunotherapy was never described before in thoracic oncology, but no relevant adverse event was described for patients receiving G-CSF after a combination of chemotherapy and

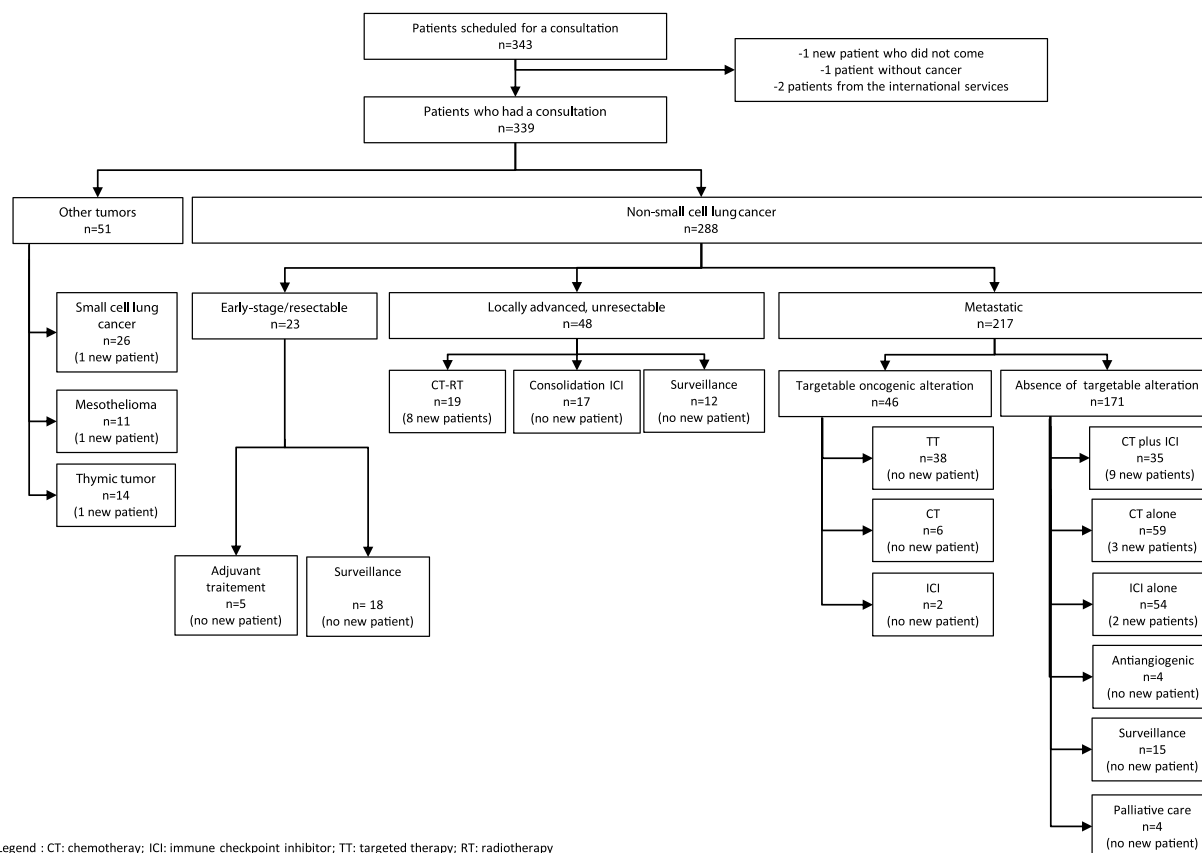


Fig. 1. Flow-chart.

Table 2
Patients' characteristics.

Characteristics	n (%)
Total	339 (100 %)
Age	
Median [range]	68 [23–91]
Sex	
Male	182 (54 %)
Female	157 (46 %)
ECOG performance status	
0–1	286 (84 %)
2	41 (12 %)
3–4	12 (4%)
Histology	
Non-Small Cell Lung Cancer	288 (85 %)
Small-cell lung cancer	26 (8%)
Mesothelioma	11 (3%)
Thymic tumor	14 (4%)
Stage of Non-Small Cell Lung Cancer	
Total	288 (100 %)
Early-stage/resectable	23 (8%)
Locally-advanced, unresectable	48 (17 %)
Metastatic	217 (75 %)

*Khi-2 square test.

immunotherapy. Other manuscripts highlight the importance to revisit patients' treatment and management during the pandemic [10]. Still 1 (0,2%) patient with mesothelioma died from the disease, showing the high fragility of these patients among patients with thoracic tumors. The death rate was in line with previous studies focusing on the mortality of

COVID-19 in patients with thoracic malignancies.

Meanwhile, the high proportion of patients receiving ICI allowed us to reduce the number of patients visit at the hospital through adaptation of dosing regimens, in line of the guidelines based on pharmacokinetics studies and dosing modification released after the approval of those agents.

At Institut Curie we decided to keep ICI flat dose regimens for patients with good tolerance of these therapeutic schemes: durvalumab 1500 mg every 4 weeks after chemo-radiotherapy for locally advanced NSCLC, and pembrolizumab 600 mg every 6 weeks.

After the COVID-19 outbreak, when patients preferred this option, we kept the use of telemedicine for surveillance every other appointment, alternating with a physical appointment. And we implemented more widely the web-based application MOOVICARE to collect in real-time patients' relevant symptoms that may lead to a faster clinical appointment at the center.

Whether such adaptations will be continued beyond the COVID-19 outbreak remains to be evaluated.

In the future, at national and/or international level, redefining patient pathways in the setting of ICI treatment may also include virtual consultation the day before treatment delivery, the wider use of web-based application for follow-up and capture of patient-related outcomes or side effects, or the at-home administration of treatment.

Ultimately, our data validate the guidelines released in an emergency setting at the beginning of the COVID-19 outbreak in early 2020, as 92 % of treatment adaptations actually done were in accordance with those guidelines [9]; only 8% of treatment modifications were not anticipated by the guidelines, but were actually based on standard clinical practice.

To conclude, our study provides a unique insight in the decision making for patients with thoracic malignancies in the setting of COVID-19 outbreak, showing how guidelines were implemented in the clinic. This work also describes what may be optimize in clinical practice of

Table 3
Impact of COVID-19 pandemia on patient management.

Population (n)	Impact on management (n)		COVID-19 infection n	Deaths	
	n	Treatment modifications		n	Cause of death
TOTAL (n = 339)	110		5	12	
Non-small cell lung cancer (n = 288)	109		3	0	
Early-stage/ resectable (n = 23)	3		0	0	
Adjuvant (n = 5)	3	-n = 2: Platine based chemotherapy received (3 cycles), cancelation of 4th cycle -n = 1: cancelation of PORT	0	0	
Surveillance (n = 18)	0		0	0	
Locally advanced (n = 48)	20		0	0	
Chemo-radiotherapy (n = 19)	4	-n = 1: delay before initiation of radiotherapy because of suspected COVID-19 infection -n = 2: cancelation of 4th cycle of chemotherapy -n = 1: no initiation of durvalumab in an elderly patient -n = 15: switch to durvalumab flat dose 1500 mg/4w -n = 1: discontinuation of durvalumab after 10 months	0	0	
Consolidation ICI (n = 17)	16		0	0	
Surveillance (n = 12)	0		0	0	
Metastatic (n = 217)	86		3	6	
Absence of targetable alteration (n = 171)	86		0	0	
Chemotherapy plus ICI (n = 35)	30	-n = 30 : primary G-CSF prophylaxis -n = 25 : primary G-CSF prophylaxis -n = 8 : switch to oral chemotherapy	0	0	
Chemotherapy (n = 59)	34	-n = 1: temporary discontinuation because of COVID-19 infection -n = 17: switch to pembrolizumab 400 mg/6 w. For 1 patient the dose was then re-administered at 200 mg/3 w because of increased asthenia	1	2	cancer
ICI (n = 54)	22	-n = 1: discontinuation of pembrolizumab because of age (elderly) -n = 2: switch to nivolumab at 480 mg/4w	0		

Table 3 (continued)

Population (n)	Impact on management (n)		COVID-19 infection n	Deaths	
	n	Treatment modifications		n	Cause of death
		-n = 2: discontinuation of nivolumab after 20 months in the setting of stable disease			
Antiangiogenic agent (n = 4)	0		0	0	
Surveillance (n = 15)	0		1	0	
Palliative care (n = 4)	0		0	4	cancer
With targetable oncogenic alteration (n = 46)	0		0	0	
Targeted therapy (n = 38)	0		1	0	
Chemotherapy (n = 6)	0		0	0	
ICI (n = 2)	0		0	0	
Other tumors (n = 51)	1		2	6	
Small-Cell Lung Cancer (n = 26)	1	-n = 1: palliative care due to general state degradation along with late diagnosis	0	4	cancer
Mesothelioma (n = 11)	0		2	1	COVID-19
Thymic tumors (n = 14)	0		0	1	cancer

Legend: G-CSF = Granulocyte-Colony Stimulating Factor; ICI: immune checkpoint inhibitor; PORT = Post-Operative Radiotherapy.

thoracic oncology in the future to reduce the number of physical appointments to the hospital. The COVID-19 pandemia may have been a triggering event for the development of virtual medicine.

CRedit authorship contribution statement

Clémence Basse: Investigation, Formal analysis, Writing - original draft, Visualization. **Catherine Daniel:** Conceptualization, Writing - review & editing. **Alain Livartowski:** Conceptualization, Writing - review & editing. **Sophie Beaucaire-Danel:** Conceptualization, Writing - review & editing. **Nicolas Girard:** Conceptualization, Methodology, Writing - original draft, Visualization, Supervision.

Declaration of Competing Interest

The authors have no conflict of interest to declare

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