Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Incidence and outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients with metastatic castration-resistant prostate cancer

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Abstract ***Background:*** Patients with cancer are at increased risk of complicated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, but it is still unclear if the risk of mortality is influenced by cancer type or ongoing anti-cancer treatments. An interesting debate concerning the potential relationship between androgen deprivation therapy (ADT) and SARS-CoV-2 infection has recently been opened in the case of prostate cancer (PC), and the aim of this multi-centre cohort study was to investigate the incidence and outcomes of SARS-CoV-2 infection in patients with metastatic castration-resistant prostrate cancer (mCRPC).

Patients and methods: We retrospectively reviewed the clinical records of patients with mCRPC who developed SARS-CoV-2 infection, and recorded their baseline clinical characteristics, their history of PC and SARS-CoV-2 infection, and their oncological status and treatment at the time of infection. The primary study end point was the death rate and the possible impact of the patients' PC-related history and treatments on mortality.

Results: Thirty-four of the 1433 patients with mCRPC attending the participating centres (2.3%) developed SARS-CoV-2 infection, 22 (64.7%) of whom were hospitalised. Most of the patients were symptomatic, the most frequent symptoms being fever (70.6%), dyspnoea (61.8%), cough (52.9%) and fatigue (38.2%). After a median follow-up of 21 days (interquartile range: 13–41), 13 patients had died (38.2%), 17 recovered (50.0%) and four (11.7%) were still infected. The number of treatments previously administered for mCRPC had a significant impact on mortality ($p = 0.004$).

Conclusions: Our findings contribute additional data to the current debate concerning the postulated protective role of ADT, which seems to be less in patients with metastatic PC.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, a novel betacoronavirus) has been rapidly spreading throughout the world since the beginning of 2020 and, by 3 June 2020, had caused 6,477,456 cases of coronavirus disease 2019 (COVID-19) and 383,011 deaths [1].

The first study of a small cohort of patients in China found that patients with cancer were at increased risk of complications [2] and, since then, larger studies have confirmed that mortality is high in patients with cancer and that it is associated with general risk factors [3,4]. Although it has been observed that 30-day mortality is higher in patients with active cancer than in those in remission [3], it is still unclear whether specific systemic treatments for active cancer affect susceptibility to SARS-CoV-2 infection or the risk of complications: for example, it is not known whether chemotherapy-related immunodepression affects the probability of being infected or of developing complications, or whether lung complications may be exacerbated by immunotherapy.

An interesting debate concerning the potential relationship between one specific anti-cancer treatment and SARS-CoV-2 infection has recently been opened in the field of prostate cancer (PC) as it has been hypothesised that androgen deprivation therapy (ADT) may interfere with cell penetration [5]. The expression of type II transmembrane serine proteases (TMPRSS2), which plays a central role in the cell penetration of SARS-CoV-2 [6], depends on androgen machinery [7] and, as ADT downregulates TMPRSS2 expression [8], patients with PC receiving ADT may be more protected against infection. Furthermore, this may be sufficient to counterbalance the other risk factors known to increase the risk of complications insofar as such patients have cancer, are men and, as they are usually older, are more likely to have multiple comorbidities.

A population-based study of patients with PC treated with ADT found a 0.07% incidence of SARS-CoV-2 infection, which indicates a significantly lower risk of

infection in comparison with patients not receiving ADT [9] and seems to support the existence of possible interactions between androgen machinery and SARS-CoV-2 infection [5].

The aim of this multi-centre cohort study was to confirm these findings in a homogeneous population of patients with metastatic castration-resistant prostrate cancer (mCRPC) by investigating the incidence, characteristics and outcomes of SARS-CoV-2 infection among such patients.

2. Patients and methods

We retrospectively reviewed the clinical records of patients with mCRPC attending 20 Italian oncological centres who developed SARS-CoV-2 infection between 1 February and 3 June 2020 and recorded their baseline clinical characteristics (pre-existing comorbidities and concomitant medications), their history of PC (Gleason score, local treatments, systemic treatments), their oncological status and treatment at the time of SARS-CoV-2 infection (disease diffusion, ongoing treatments, treatment response) and the history of the infection itself (symptoms, method of diagnosis, laboratory and radiological features, complications, treatments, outcomes).

The diagnosis of SARS-CoV-2 infection was made on the basis of the results of nucleic acid amplification tests of nasopharyngeal swabs, enzyme-linked immunosorbent assays and chemiluminescent immune-assays of blood samples, or the presence of unequivocal symptoms and radiological findings of COVID-19.

The clinical phenotypes of the infection were classified as type I (fever, headache, mild respiratory symptoms, sore throat, no hypoxaemia, normal chest radiography), type II (fever with infiltrates revealed by chest radiography or mild hypoxaemia), type III (fever, moderate/severe hypoxaemia, and multiple infiltrates revealed by chest radiography), type IV (severe hypoxaemia requiring mechanical ventilation, normal lung compliance), type V (severe hypoxaemia requiring mechanical ventilation, typical acute respiratory distress syndrome).

The study was approved by a central Institutional Review Board on 7 April 2020, and by the local IRBs of the participating centres in line with their institutional policy, and respected the principles of the Declaration of Helsinki.

The primary study end point was the death rate and the possible impact of the patients' PC-related history and treatments on mortality. The considered variables were the presence of metastases at the time of PC diagnosis (yes *vs* no), the time between the diagnosis of PC and infection onset, the length of ADT exposure, the presence of visceral metastases at the time of infection onset (yes *vs* no), the ongoing administration of steroids at the time of infection onset (yes *vs* no), the number of previously administered treatments for mCRPC (0–1 *vs* $\geq$ 2), and the type of ongoing mCRPC treatment at the time of infection onset (none *vs* chemotherapy *vs* a new hormonal agent). We also considered the patients' age and the number of pre-existing comorbidities (0 *vs* 1–2 *vs* $\geq$ 3).

The continuous variables are expressed as median values and interquartile ranges (IQRs), and the categorical variables as absolute numbers and percentages. The impact of the variables on the death rate was calculated using the chi-squared test (categorical variables) or univariate analysis of the mean values (continuous variables).

The statistical analyses were made using IBM SPSS Statistics software, version 21.0.

3. Results

Thirty-four of the 1433 patients with mCRPC attending the 20 participating centres (2.3%) developed SARS-CoV-2 infection. Their median age was 75 years (IQR = 69–82).

Table 1 shows the patients' main pre-existing comorbidities, and Table 2 shows their PC-related characteristics. The median time between the diagnosis of PC and infection onset was 64 months (IQR = 27–103), with 20 patients (58.8%) presenting localised disease at the time of the diagnosis of PC, and 29 (85.3%) having bone metastases, 22 (64.7%) nodal metastases, and seven (20.5%) visceral metastases at the time of the diagnosis of SARS-CoV-2 infection. All of the patients were receiving ADT, the median duration of which was 50 months (IQR = 19–66), and all but six were receiving additional treatment with chemotherapy (n = 9) or an androgen receptor-targeting agent (n = 19). About half of the patients were receiving these agents as first-line treatment for mCRPC. Concomitant steroid administration was recorded in the charts of 16 patients (47%).

Table 1
Comorbidities.

Pre-existing comorbidities	
Hypertension	20 (58.8%)
Ischaemic cardiac disease	3 (8.8%)
Atrial fibrillation	7 (20.6%)
Cardiac failure	2 (5.9%)
Diabetes	4 (11.8%)
Chronic renal failure	2 (5.9%)
COPD	3 (8.8%)
Number of pre-existing comorbidities	
0	4 (11.7%)
1–2	14 (41.2%)
≥3	16 (47.1%)

COPD: chronic obstructive pulmonary disease.

Table 2
Prostate cancer-related characteristics.

Status at the time of prostate cancer diagnosis	
Localised disease	20 (58.8%)
Metastatic disease	14 (41.2%)
Gleason score	
6–7	5 (14.7%)
8–10	27 (79.4%)
Unknown	2 (5.9%)
Time between PC diagnosis and SARS-CoV-2 infection (months)	
Median	64
Interquartile range	27–103
Exposure to androgen deprivation therapy (months)	
Median	50
IQR	19–66
Number of previous treatments for mCRPC	
0	16 (47.1%)
1	11 (32.3%)
≥2	7 (20.6%)
Metastases	
Bone	29 (85.3%)
Lymph node	22 (64.7%)
Visceral (lung, liver)	7 (20.6%)
Ongoing treatment for mCRPC	
ARTA	19 (55.9%)
Chemotherapy	9 (26.5%)
None	6 (17.6%)
Ongoing steroid administration	
Yes	16 (47.1%)
No	18 (52.9%)

ARTA = androgen receptor-targeting agent; mCRPC = metastatic castration-resistant prostate cancer; SARS-CoV-2 = severe acute respiratory syndrome corona virus 2.

Table 3 shows the characteristics of the SARS-CoV-2 infection. Most of the patients (n = 31) were symptomatic at the time of infection onset: the most frequent symptoms were fever (70.6%), dyspnoea (61.8%), cough (52.9%), and fatigue (38.2%). The diagnosis of these 31 patients was confirmed by a nasopharyngeal swab (n = 24), a serological examination (n = 2), or clinically (n = 5). The diagnosis of the three asymptomatic patients was made during screening procedures by means of a nasopharyngeal swab or serological examination. The most frequent COVID-19 clinical phenotypes were 1, 2 and 3, which were observed in respectively 26.5%, 23.5% and 20.6% of cases, and the most frequent complications were pneumonitis, which occurred in 16 patients (47.1%), and acute respiratory distress syndrome, which occurred in nine patients (26.5%). Twenty-two patients (64.7%) were hospitalised; the other 12 patients were managed at home. Five of the hospitalised patients were admitted to an intensive care unit (after developing massive pneumonitis and concurrent acute respiratory distress syndrome), four to a subintensive care unit, and 13 to an ordinary care unit.

The most frequent radiological features were areas of consolidation (44.1%) and interstitial abnormalities (38.2%), which were nearly always bilateral. The most frequently used treatments were antibiotics (76.5%), chloroquine (50.0%), steroids (35.3%) and heparin (20.6%). One patient also received tocilizumab.

Table 4 shows the relationships between mortality and selected variables. After a median follow-up of 21 days (IQR: 13–41), 13 patients had died (38.2%), 17 had recovered (50.0%) and four (11.7%) were still infected. Most of the deceased patients (11/13) were receiving ADT plus additional PC treatment: enzalutamide (n = 5), docetaxel (n = 3), abiraterone (n = 2) and cabazitaxel (n = 1). All were symptomatic at the time of diagnosis, and most (10/13) were hospitalised. The

Table 3
Characteristics of SARS-CoV-2 infection.

Symptoms	
Dyspnoea	21 (61.8%)
Dry cough	18 (52.9%)
Fever >37.5 °C	24 (70.6%)
Conjunctival congestion	1 (2.9%)
Diarrhoea	4 (11.8%)
Myalgia	6 (17.6%)
Otitis	1 (2.9%)
Dysgeusia	1 (2.9%)
Headache	3 (8.8%)
Fatigue	13 (38.2%)
Diagnosis	
Nasopharyngeal swab	26 (76.5%)
Serology	3 (8.8%)
Clinical	5 (14.7%)
Clinical phenotype of SARS-CoV-2 infection	
1	9 (26.5%)
2	8 (23.5%)
3	7 (20.6%)
4	2 (5.9%)
5	3 (8.8%)
Not defined	5 (14.7%)
Radiological findings	
Ground glass opacities/bilateral	9/9 (26.5%)
Consolidation/bilateral	15/14 (44.1%)
Interstitial abnormalities/bilateral	13/13 (38.2%)
Vascular thickening/bilateral	4/3 (8.8%)
Not available	6 (17.6%)
Complications	
Pneumonitis	16 (47.1%)
ARDS	9 (26.5%)
Sepsis	3 (8.8%)
Cardiac failure	2 (5.9%)
Arrhythmia	1 (2.9%)
Treatment	
Antibiotics	26 (76.5%)
Antifungals	1 (2.9%)
Chloroquine	17 (50.0%)
Non-invasive ventilation	10 (29.4%)
Antivirals	12 (35.3%)
Steroids	12 (35.3%)
Anti-IL-6 drugs	3 (8.8%)
Invasive ventilation	4 (11.8%)
Heparin	7 (20.6%)

ARDS = acute respiratory distress syndrome; SARS-CoV-2 = severe acute respiratory syndrome corona virus 2.

Table 4
Relationships between mortality and selected variables.

Variable	Alive # (%)	Dead # (%)	P value
Status at the prostate cancer diagnosis			
Localised disease	13 (65.0%)	7 (35.0%)	NS
Metastatic disease	8 (57.1%)	6 (42.9%)	
Presence of visceral metastases			
Yes	4 (57.1%)	3 (42.9%)	NS
No	17 (63.0%)	10 (37.0%)	
Ongoing administration of steroids			
Yes	10 (62.5%)	6 (37.5%)	NS
No	11 (61.1%)	7 (38.9%)	
No. of previously administered treatments for mCRPC			
0–1	20 (74.1%)	7 (25.9%)	0.004
≥2	1 (14.3%)	6 (85.7%)	
Ongoing treatment for mCRPC			
None	4 (66.7%)	2 (33.3%)	NS
ARTA	12 (63.2%)	7 (36.8%)	
Chemotherapy	5 (55.6%)	4 (44.4%)	
Pre-existing comorbidities			
0	7 (77.8%)	2 (22.2%)	NS
1–2	12 (60.0%)	8 (40.0%)	
≥2	2 (40.0%)	3 (60.0%)	
	Alive median (IQR)	Dead median (IQR)	P value
Age (years)	75 (68–81)	75 (69–83)	NS
Time between PC diagnosis and infection onset (months)	62 (20–107)	69 (43–139)	NS
Length of ADT exposure (months)	39 (17–62)	57 (34–115)	NS

ADT = androgen deprivation therapy; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; NS = not significant; PC = prostate cancer; COVID = coronavirus disease 2019.

deaths occurred a median of nine days (IQR: 4–20) after the diagnosis of COVID-19.

Median ADT exposure of the patients who died was longer than that of the patients who lived (57 *vs* 39 months), although the difference was not statistically significant. However, the number of previous mCRPC treatments had a significant impact on the mortality rate, which was 25.9% among the patients who had previously received 0–1 treatment, and 85.7% among those who had previously received more than one treatment ($p = 0.004$). Mortality also progressively increased with the number of pre-existing comorbidities, but this was not statistically significant.

4. Discussion

This is the first study of the outcomes of SARS-CoV-2 infection in patients with mCRPC; it also assessed the impact of PC-related variables on mortality due to the infection.

Since the start of the COVID-19 pandemic, the outcomes of patients with cancer have received considerable attention as they are considered to be at greater risk of a poor prognosis. The first studies involved only small cohorts of patients with cancer, but cumulative analyses have confirmed the higher risk of complications [10]. More recently, two larger studies have been published: one involving 920 patients with cancer in the COVID-19 and Cancer Consortium (CCC19) database, and the other involving 800 patients with cancer in the UK Coronavirus Cancer Monitoring Project (UKCCMP) [3,4]. These respectively reported mortality rates of 13% and 28% and showed relationships between higher death rates and older age, male sex and a number of comorbidities (the difference in mortality rates between the two studies is presumably related to the difference in the percentage of patients with active cancer: 49% in the CCC19 study and 100% in the UKCCMP study). It is also worth noting that the preliminary findings of the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) study of 428 patients with advanced thoracic cancers, most (>80%) of whom were treated with chemotherapy, immunotherapy or targeted therapies, indicate a mortality rate of 35.5% [11].

Although the kind of treatment received by the patients in the CCC19 and UKCCMP cohorts seems to have had no effect on mortality due to the infection, it has been suggested that ADT may have a protective effect on patients with PC [5] because of the potential relationship between androgen machinery and cell penetration by SARS-CoV-2, which depends on the gateway function of the angiotensin-converting enzyme 2 (ACE2) receptor and the priming of viral spike proteins by TMPRSS2 [6]. As TMPRSS2 transcription is regulated by androgenic ligands and the androgen receptor [7], the reduction in the expression of TMPRSS2 induced by ADT [8] may have a protective effect against SARS-CoV-2 infection. Consequently, patients with advanced PC treated with ADT may reflect a unique clinical scenario in which protective and risk factors coexist insofar as their clinical profiles usually include all of the factors related to a poor prognosis: they have cancer, they are men and, as they are usually older, they often having multiple comorbidities.

Unfortunately, there is very little information about the outcomes of SARS-CoV-2 infection in patients with PC. PC was the second most frequent solid tumour in the CCC19 study (15%), but the 152 patients with PC were not evaluated separately, and there are no data concerning their disease stage or treatment [3]. Furthermore, although the UKCCMP study included 78 patients with male genital organ cancers, they were not specifically analysed [4].

So far, only one registry-based study has evaluated patients with PC with SARS-CoV-2 infection [9]. It found 118 cases of patients with PC with laboratory-confirmed SARS-CoV-2 infection attending 68

hospitals in Italy's Veneto region and, by matching these cases to the Regional Cancer Registry data, the authors showed that only four of 5273 patients with PC receiving ADT (0.07%) developed the infection. As these patients were at significantly lower risk of developing SARS-CoV-2 infection than the patients who did not receive ADT or who had other types of cancer, the authors concluded that ADT may reduce sensitivity to the virus. Furthermore, none of the four patients died.

However, the results of our study of exclusively patients with mCRPC do not confirm these findings as the rate of infection was 2.3% and the mortality rate was 38.2%. The difference is clearly related to the differences in patient selection between the two studies. We selected a homogenous population of patients with metastatic PC, most of whom had been receiving ADT for a long time, whereas Montopoli *et al.* evaluated a cohort that probably also included patients receiving ADT because of a biochemical relapse in the absence of any clinically detectable signs of disease [9].

It is worth noting that our analysis was not limited to patients admitted to hospital (which would *per se* indicate complicated SARS-CoV-2 infection), but included all of the patients with mCRPC attending the participating centres who developed SARS-CoV-2 infection, regardless of hospitalisation. It is also interesting to note that the death rate observed in our study is similar to that observed in the TERAVOLT study, which only selected patients with advanced thoracic cancers receiving active anti-cancer treatment [11]. A high mortality rate can be expected in patients with thoracic tumours who develop SARS-COV-2–related respiratory complications but not in patients with mCRPC; however, this surprising finding may be partially related to the long-term disease history of our patients and the older median age of our mCRPC population (75 years) in comparison with the median age of the TERAVOLT cohort (68 years).

Conversely, the death rate observed in our study was higher than that observed in other series that included a relatively high proportion of patients in remission or treated with curative intent [12,13].

We found that the number of previous mCRPC treatments was the only factor that negatively affected the death rate. The patients who had recently developed castration resistance and had not yet been treated for the disease and those receiving first-line treatment had a mortality rate of 25.9%, which was significantly lower than the 85.7% mortality rate observed in the patients receiving a second or more advanced treatment line at the time they developed the infection. It is worth noting that the median ADT exposure of the patients who died was 18 months longer than that observed in those who were still alive, although this difference was not significant.

It should also be pointed out that, as in most other parts of the world, subjects in Italy were only tested for SARS-CoV-2 during the pandemic crisis if they presented suspected symptoms of infection or had been in contact with other subjects with proven infection. It is therefore clearly difficult to assess the real incidence of SARS-CoV-2 infection in our patients with mCRPC. However, in comparison with other series screened on the basis of the same policy, our findings support the view that patients with more advanced PC who develop SARS-CoV-2 infection have a poor prognosis. As has recently been postulated [14,15], it can be argued that heavily pre-treated patients with PC with metastatic involvement are at higher risk of developing SARS-CoV-2 infection and its complication regardless of ADT, whereas ADT may play a protective role in the early stages of the disease.

5. Conclusions

The power of the present study is clearly limited by the small number of patients, but it has the advantage that it is the first study assessing a homogeneous population of patients with PC with detailed histories of cancer and SARS-CoV-2 infection and the related treatments. Our findings therefore contribute additional data to the debate concerning the postulated protective role of ADT, which seems to be less in patients with metastatic PC. Further investigations in longitudinal prospective studies are warranted to clarify the relationship between ADT and the severity of SARS-CoV-2 infection in patients with PC, and the potential therapeutic role of ADT in managing this infection.

Credit author statement

Orazio Caffo: Conceptualization, Methodology, Formal analysis, Resources, Data Curation, Writing- Original draft preparation, Writing - Reviewing and Editing; Supervision; Donatello Gasparro: Investigation; Writing - Review & Editing; Giuseppe Di Lorenzo: Investigation; Writing - Review & Editing; Alberto Dalla Volta: Investigation; Writing - Review & Editing; Pamela Guglielmini: Investigation; Writing - Review & Editing; Paolo Zucali: Investigation; Writing - Review & Editing; Roberto Bortolus: Investigation; Writing - Review & Editing; Alessia Cavo: Investigation; Writing - Review & Editing; Giovanni Ceresoli: Investigation; Writing - Review & Editing; Rita Chiari: Investigation; Writing - Review & Editing; Giuseppe Fornarini: Investigation; Writing - Review & Editing; Lucia Fratino: Investigation; Writing - Review & Editing; Alessandro Iaculli: Investigation; Writing - Review & Editing; Marco Maruzzo: Investigation; Writing - Review & Editing; Cristina Masini: Investigation; Writing - Review & Editing; Franco Morelli: Investigation; Writing - Review & Editing; Claudia Mucciarini: Investigation; Writing - Review & Editing; Giuseppe

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Conflict of interest statement

O. C. reports receiving honoraria as speaker or advisor for Astra Zeneca, Astellas, Janssen and Pfizer. The other authors have no conflicts of interest to be declared.

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