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Symptom Management and Supportive Care

Prevalence and Clinical Impact of SARS-CoV-2 Silent Carriers Among Actively Treated Patients with Cancer During the COVID-19 Pandemic

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cancer • COVID-19 • SARS-CoV-2 • Coronavirus • Silent carriers

Abstract

Introduction. In Europe, the SARS-CoV-2 pandemic had its first epicenter in Italy. Despite a significant mortality rate, the severity of most cases of COVID-19 infection ranges from asymptomatic to mildly symptomatic, and silent infection affects a still-unknown proportion of the general population. No information is available on the prevalence and clinical impact of SARS-CoV-2 silent infection among patients with cancer receiving anticancer treatment during the pandemic.

Materials and Methods. From April 1, 2020, to the end of the same month, 560 consecutive patients with cancer, asymptomatic for COVID-19 and on anticancer treatment at Papa Giovanni XXIII Hospital in Bergamo, were evaluated and tested for SARS-CoV-2. We implemented a two-step diagnostics, including the rapid serological immunoassay for anti–SARS-CoV-2 immunoglobulin (Ig) G/IgM and the nasopharyngeal swab reverse transcriptase-polymerase chain reaction (RT-PCR) test in case of seropositivity to identify SARS-CoV-2 silent carriers.

Results. In 560 patients, 172 (31%) resulted positive for anti–SARS-CoV-2 IgM/IgG antibodies, regardless of different type of cancer, stage, and treatment. The Ig-seropositive patients were then tested with RT-PCR nasopharyngeal swabs, and 38% proved to be SARS-CoV-2 silent carriers. At an early follow-up, in the 97 SARS-CoV-2–seropositive/RT-PCR–negative patients who continued their anticancer therapies, only one developed symptomatic COVID-19 illness.

Conclusion. Among patients with cancer, the two-step diagnostics is feasible and effective for SARS-CoV-2 silent carriers detection and might support optimal cancer treatment strategies at both the individual and the population level. The early safety profile of the different anticancer therapies, in patients previously exposed to SARS-CoV-2, supports the recommendation to continue the active treatment, at least in cases of RT-PCR–negative patients. ***The Oncologist*** 2021;26:341–347

Implications for Practice: This is the first study evaluating the prevalence and clinical impact of SARS-CoV-2 silent infection in actively treated patients with cancer, during the epidemic peak in one of the worst areas of the COVID-19 pandemic. Lacking national and international recommendations for the detection of asymptomatic SARS-CoV-2 infection, a pragmatic and effective two-step diagnostics was implemented to ascertain SARS-CoV-2 silent carriers. In this series, consisting of consecutive and unselected patients with cancer, the prevalence of both SARS-CoV-2–seropositive patients and silent carriers is substantial (31% and 10%, respectively). The early safety profile of the different anticancer therapies, in patients previously exposed to SARS-CoV-2, supports the recommendation to continue the active treatment, at least in case of RT-PCR–negative patients.

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Introduction

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing the coronavirus disease (COVID-19) pandemic in 2020 was first identified in China in December 2019. By May 30, 2020, it had affected more than 6 million people in 170 countries and resulted in 370,000 deaths globally [1]. In Europe, the SARS-CoV-2 pandemic had its first epicenter in Italy, particularly in the northern region of Lombardy, and the city of Bergamo registered internationally the worst increase in the odds of death, with a 463% increase above expected levels [2].

Although this pandemic appears particularly dangerous for elderly patients [3–5], other subgroups might be susceptible to critical illness and death, including patients with cancer [6]. Preliminary evidence from Chinese investigators showed that patients with cancer affected by COVID-19 had a risk of the composite endpoint of invasive ventilation, admission to the intensive care unit, and death that was five times higher than in patients without cancer [7]. However, despite a significant mortality rate, most cases of COVID-19 range from asymptomatic to mildly symptomatic infection, and SARS-CoV-2 silent infection is predicted to be widespread in the population [8].

Although the clinical course of symptomatic COVID-19 in patients with cancer has been recently described [9–11], information is still unavailable about the prevalence and the possible clinical impact of SARS-CoV-2 silent infection among patients with cancer receiving anticancer treatment during the pandemic.

Subjects, Materials, and Methods

In February and March 2020, during the pandemic peak, a total of 1,037 patients with cancer were actively on cancer treatment at the Papa Giovanni XXIII Hospital in Bergamo. Of these patients, 397 (38%) experienced an overt and/or severe symptomatic COVID-19 illness and were home-treated (276 cases) and/or hospitalized (121 cases). These patients are not part of the present analysis. From April 1, 2020, to the end of the same month, 560 consecutive and unselected of the remaining patients with cancer, who were scheduled for an anticancer treatment in the outpatient facility of our hospital and who remained asymptomatic or had been previously only mildly symptomatic for COVID-19 and who were not receiving any anti-COVID-19 therapy, were evaluated and tested for SARS-CoV-2 infection when accessing the hospital for their scheduled cancer treatment. All eligible patients signed a dedicated informed consent form, approved by the local ethical committee, and 528 of 560 completed a survey questionnaire about signs or symptoms of COVID-19 that had possibly occurred in the previous 2 months.

We implemented a two-step diagnostics of SARS-CoV-2 infection, including the use of rapid lateral flow chromatographic serological immunoassay for the qualitative detection of anti–SARS-CoV-2 immunoglobulin (Ig) G and M for all patients and the use of a nasopharyngeal swab RNA reverse transcriptase-polymerase chain reaction (RT-PCR) assay for the cases that showed IgM/IgG seropositivity.

The main clinical characteristics of the study population are reported in Table 1.

Detection of SARS-CoV-2 RNA by RT-PCR

Presence of SARS-CoV-2 on nasopharyngeal swab specimens was determined by means of real-time RT-PCR. GeneFinder COVID-19 Plus RealAmp Kit (Elitech, Milan, Italy) or Allplex 2019-nCoV Assay (Seegene, Inc., Seoul, South Korea) were used to detect SARS-CoV-2 by amplification of the *RdRp*, *E*, and *N* gene according to the recommendations and as previously described [12]. Overall, 198 specimens obtained from nasopharyngeal swab were tested by RT-PCR.

Detection of IgG and IgM against SARS-CoV-2

To evaluate the presence of IgG and IgM against SARS-CoV-2, all enrolled subjects were tested with the NADAL COVID-19 IgG/IgM Test (Moers, Germany), which is a qualitative membrane-based immunoassay for the detection of IgG and IgM antibodies to SARS-CoV-2 in whole blood, serum, or plasma specimens. For this purpose, blood was obtained from each subject by venipuncture at the time of blood tests for cancer treatment. Plasma was dispensed to the specimen well of the test cassette. Finally, two drops of diluent were added to the specimen well of the test cassette.

The NADAL COVID-19 IgG/IgM Test consists of an IgG component and an IgM component. In the IgG component, antihuman IgG is coated in the IgG test line region. During testing, the specimen reacts with SARS-CoV-2 antigen-coated particles in the test cassette. The mixture then migrates upward on the membrane chromatographically by capillarity and, if the specimen contains IgG antibodies, reacts with the antihuman IgG in the IgG test line region. Antihuman IgM is coated in the IgM test line region, and if specimen contains IgM antibodies, the conjugate-specimen complex reacts with antihuman IgM. If the specimen contains SARS-CoV-2 IgG antibodies, a colored line appears in the IgG test line region. Similarly, a colored line appears in IgM test line region if the specimen contains SARS-CoV-2 IgM antibodies. If the specimen does not contain antibodies, no colored line appears in either of the test line regions, indicating a negative result. To serve as a procedural control, a colored line always appears in the control line region, indicating that the proper volume of specimen has been added and membrane wicking has occurred.

Aim of the Study

Primary endpoints of the study were to estimate the prevalence SARS-CoV-2 silent carriers in consecutive and unselected patients with cancer on active treatment and to evaluate the clinical impact of the silent SARS-CoV-2 infection in this population.

Statistical Analysis

Descriptive statistics were used to analyze and report patients' characteristics. Clinical and biological variables were stratified into categories, to preserve statistical power and feasibility of data collection. Continuous variables are expressed as the median (interquartile range). Categorical variables are expressed as numbers and proportions (%) and were compared by Fisher's exact test or χ^2 test, as

Table 1. Patients' characteristics

Characteristics	(*n* = 560)
Age	
Median (range)	65 (19–89)
Age >75 yr, *n* (%)	89 (16)
Gender, *n* (%)	
Female	336 (60)
Male	224 (40)
Type of cancer, *n* (%)	
Breast	188 (34)
Pulmonary	95 (17)
Melanomas	89 (16)
GI	88 (16)
GU	61 (11)
Others	39 (6)
Stage, *n* (%)	
Advanced	422 (75)
Local	138 (25)
Type of treatment,[a] *n* (%)	
Chemotherapy	243 (43)
Targeted therapy	208 (37)
Immunotherapy	112 (20)
Endocrine therapy	95 (17)
Radiotherapy	9 (2)
Survey questionnaire clinical presentation, *n* (%)	528 (94)
Asymptomatic	231 (41)
Previously mildly symptomatic[a]	297 (53)
Dyspnea	25 (4)
Cough	71 (13)
Fever	72 (13)
Cold	49 (9)
Diarrhea	65 (12)
Loss of smell and taste	62 (11)
Thorax imaging exams	165 (30)
Pneumonia signs	16 (3)
Family member COVID-19 positive	45 (8)
Other contacts COVID-19 positive	21 (4)
Setting of care, *n* (%)	
Outpatients	560 (100)
Subsequent hospitalized	36 (6)
Inpatients	0 (0)
Anti–SARS-CoV-2 test, *n* (%)	560 (100)
IgM or IgG	172 (31)
IgM and IgG	114 (20)
IgM	44 (8)
IgG	14 (3)
RT-PCR test, *n* (%)	198 (35)
Positive	58 (10)
Negative	140 (25)

[a]Multiple options per patient are present.
Abbreviations: GI, gastrointestinal (stomach/colorectal/pancreatic); GU, genitourinary (prostate/kidney/bladder); IgG, immunoglobulin G; IgM, immunoglobulin M; NA, not applicable; RT-PCR, reverse transcriptase-polymerase chain reaction.

appropriate. All tests were performed two-sided at a significance level of $\alpha = 0.05$. Statistical analyses were performed using R (version 3.6.2).

Results

In 560 patients, 172 (31%) resulted positive for anti–SARS-CoV-2 IgM/IgG antibodies. Notably, 59 of 161 (37%) of those seropositive patients were completely asymptomatic, and 102 of 161 (63%) reported mild symptoms in the previous 8 weeks, including slight episodes of cough or cold in 22 of 102 (22%), self-limited fever in 11 of 102 (13%), and mild flu symptoms in 15 of 102 (15%). The proportion of seropositive patients was associated with the presence or absence of previous mildly symptomatic events (respectively, 34% vs. 26%, $p = .036$) and irrespective of the type of cancer, stage, and/or type of treatment (supplemental online Material 1–5).

According to the protocol, 155 of 172 (90%) anti–SARS-CoV-2 IgM/IgG seropositive patients were tested with RT-PCR nasopharyngeal swabs, and 58 of 155 (37%) proved to be SARS-CoV-2–positive carriers; most patients (40/52, 77%) had previously reported COVID-19 mild symptoms (Fig. 1B). All 58 SARS-CoV-2 active carriers were prescribed domiciliary quarantine and the anticancer treatment was suspended until two subsequent RT-PCR–negative tests could be obtained at weekly intervals; one exception was an elderly woman with advanced melanoma who received anti–programmed death-ligand 1 immunotherapy despite being a silent carrier but who developed an unexpected and fatal progressive pneumonia [13]. Eventually, 50 of 58 SARS-CoV-2 silent carriers cleared the virus within 8 weeks of follow-up, converting to an RT-PCR–negative test at a median time of 14 days (range, 6–45) with an anticancer treatment rescue at a median of 23 days (range 1–113 days). The silent carriers were mostly women (37 women vs. 21 men), with a median age of 65 years (range, 19–89 years), receiving chemotherapy or targeted therapy in the majority of cases (41 of 58). In line with the seroprevalence distribution, the rate of RT-PCR SARS-CoV-2 positivity was irrespective of the different type of cancer, stage, and/or type of treatment (supplemental online Material 2–5). Table 2 shows a comparative description of the main characteristics of two cohorts of RT-PCR SARS-CoV-2–positive patients, mildly symptomatic versus asymptomatic without significant differences in the clinicopathologic variables evaluated.

For prevention policy, mainly related to patients' hospitalization, 43 of 388 seronegative patients (11%) underwent an RT-PCR test outside the screening study, and notably, all were found to be RT-PCR SARS-CoV-2 negative.

During the 8 weeks of follow-up, 36 patients required hospitalization and 5 died (4 related to cancer progression and one due to SARS-CoV-2 infection). In the 97 asymptomatic seropositive/RT-PCR–negative patients receiving anticancer treatment, only one developed a mild symptomatic COVID-19 illness, eventually proving to have converted to RT-PCR positivity at a subsequent test.

Because of the wide heterogeneity of the study population, we limited the anticancer-drug safety profile evaluation to hematological toxicity only in chemotherapy-exposed patients, reporting an overall 11.5% of transitory grade 3–4

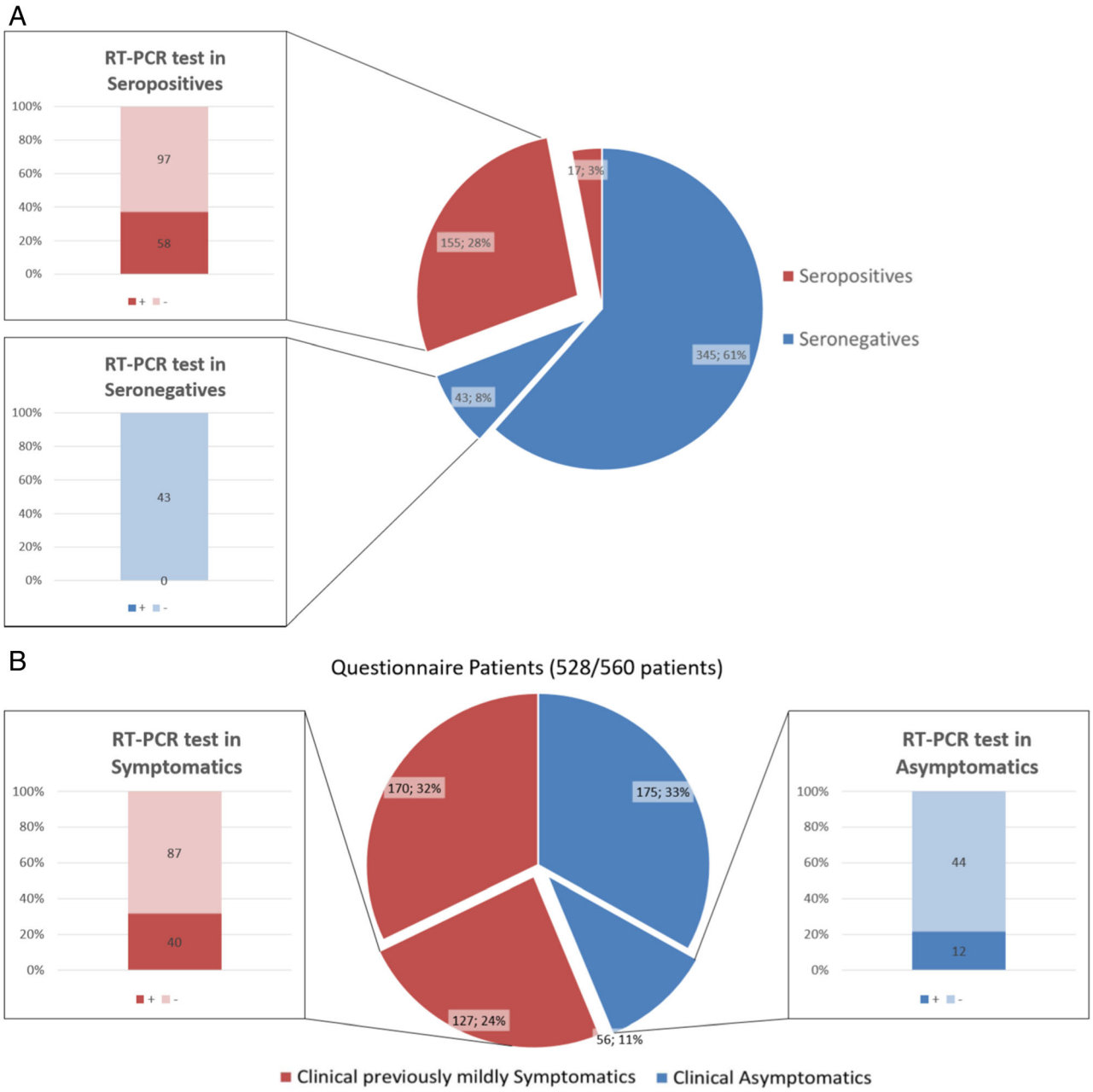

Figure 1. Proportion of SARS-CoV-2 silent carriers by seroprevalence selection **(A)** or by clinical selection **(B)**.
Abbreviation: RT-PCR, reverse transcriptase-polymerase chain reaction.

events (28 of 243), without any statistical differences between the two cohorts, whether asymptomatic or not. Because of the limited follow-up, any suggestion about the long-term safety profiles of the different anticancer treatments in previously (or not) SARS-CoV-2–exposed patients is currently precluded.

Discussion

To our knowledge, this is the first study on the prevalence and clinical impact of SARS-CoV-2 silent infection in actively treated patients with cancer during the pandemic peak in one of the worst areas of the COVID-19 outbreak.

In the countries with high COVID-19 incidence, the transmission of SARS-CoV-2 was either effectively prevented by standard infection control measures or might have remained undiagnosed because of asymptomatic or mildly symptomatic course. In the province of Bergamo, during the devastating overall COVID-19 crisis, SARS-CoV-2 silent infection went largely undetected, but the relevant role of the silent SARS-CoV-2 spreaders during the pandemic was eventually recognized [14]. Indeed, without information on the true rate of infection in the population, the predicted contagion trajectory long remained unclear, and the deriving data on morbidity and mortality stemming from COVID-19 were not fully appreciated. Considering this, identifying SARS-CoV-2 silent carriers, especially in vulnerable populations, should not be considered negligible.

It is reasonable to assume patients with cancer would be at least as susceptible to infection with SARS-CoV-2 as their

Table 2. Mildly symptomatic versus asymptomatic silent carriers

Characteristics	Mildly symptomatic silent carriers (*n* = 40), *n* %	Asymptomatic silent carriers (*n* = 12), %
Age		
Median (range)	61.5 (31–86)	67.5 (47–79)
Age >75 yr	2 (5)	2 (16)
Gender		
Female	24 (60)	8 (67)
Male	16 (40)	4 (33)
Type of cancer		
Breast	17 (42.5)	6 (50)
Pulmonary	3 (7.5)	0 (0)
Melanomas	5 (12.5)	3 (25)
GI	7 (17.5)	2 (17)
GU	7 (17.5)	0 (0)
Others	1 (2.5)	1 (8)
Stage		
Advanced	14 (35)	3 (25)
Local	26 (65)	9 (75)
Type of treatment		
Chemotherapy	12 (30)	3 (25)
Targeted therapy	10 (25)	2 (17)
Immunotherapy	6 (15)	0 (0)
Endocrine therapy	4 (10)	1 (8)
Radiotherapy	8 (20)	6 (50)
Mortality	2 (5)	1 (8)
Clearance virus	37 (92.5)	11 (92)
Median (range)	14 (6–45)	20 (7–32)
Therapy reprise	35 (87.5)	9 (75)
Median (range)	23 (1–113)	37 (1–59)

Abbreviations: GI, gastrointestinal; GU, genitourinary.

healthy peers, possibly with a higher risk of severe complications [15, 16]. During the pandemic, the need to protect fragile patients requires strategy of attentive surveillance, especially at the crucial time of progressively lifting social restrictions [17]. In this context, the focus on the SARS-CoV-2 silent carriers takes on particular importance [18]. Because of the weakness of the RT-PCR as a sole SARS-CoV-2 diagnostic method in surveillance has been described [19], owing to its inability to detect past infection [20, 21], we implemented a pragmatic two-step diagnostics, with the rapid serological test in all patients and a second step with an elective RT-PCR test limited to the seropositive patients.

Notwithstanding the debate on the immune-protective role of anti–SARS-CoV-2 IgM/IgG [22], the accuracy and the added diagnostic value of the serological testing has been recognized [23, 24]; if captured within the correct time frame, serological testing can detect both active and past infections, providing relevant information on the pandemic [25].

In our case series, 1 of 3 asymptomatic or mildly symptomatic patients had mounted an immune response to SARS-CoV-2, suggesting a previous virus exposure. Eventually, according to the two-step diagnostics, 1 of 10 patients was identified as a SARS-CoV-2 silent active carrier. Because E.U. recommendations at that time [26] suggested not to perform the SARS-CoV-2 diagnostics in asymptomatic cases, even in the vulnerable cancer population, all such silent carriers would have gone undetected, with potential harmful implications for the patient and for the contacts. Indeed, the identification of such silent carriers is of paramount importance at both the individual and the population level [27, 28]: at the individual level because of the opportunity to protect cancer patients from possible COVID-19 complications while on anticancer treatment and at the population level because of the opportunity to mitigate the pandemic evolution through the isolation of potential silent spreaders not otherwise detectable [29].

In areas of widespread infection, the identification of SARS-CoV-2 silent carriers can be predicted with both a serological and a clinical selection. In our experience, the seroprevalence selection allowed SARS-CoV-2 active carriers detection with a number-needed-to-test calculation of 2.6, versus 10 with no selection. Notably, clinical selection based on reported previous COVID-19 mild symptoms provided a comparable number-needed-to-test calculation of 3.2 but with a negative predictive value of 79% and, therefore, with the risk of losing a quote of SARS-CoV-2 silent active carriers.

According to the results of the present study, the overall clinical impact of SARS-CoV-2 silent infection in patients with cancer was limited and did not preclude the safe continuation of active cancer treatment whenever indicated, at least in cases of RT-PCR negativity. However, the risk of a severe infection in SARS-CoV-2 silent carriers while on anticancer therapies is predicted to be marginal but present, and it should be balanced with the risk of cancer evolution to determine optimal individual patient care.

We are aware that our study presents some limitations. We ran a pragmatic study, not intended to formally evaluate the sensitivity and specificity of the different SARS-CoV-2 diagnostic assays. However, a preliminary estimation of the post-test accuracy by predictive values was performed, shedding light on the two-step SARS-CoV-2 diagnostics approach. Even though we cannot exclude an undetected quote of silent carriers, in our series, the seroprevalence selection provided an encouraging negative predictive value of 100%, at least in the limited sample of 43 (11%) seronegative patients who were tested, suggesting the accuracy of the two-step strategy if further confirmed. Furthermore, we did not collect data about the long-term effect of SARS-CoV-2 silent infection or about the magnitude and duration of the immune response in the seropositive patients, nor about what antibody titer may be necessary to protect individuals from reinfection. Moreover, we did not have information about the long-term safety profile of anticancer treatments in previously virus-exposed patients. Finally, the presumed risk of contagion and clinical significance of SARS-CoV-2 silent carriers requires further evaluation.

Conclusion

Our data indicate the prevalence of the SARS-CoV-2 silent infection is substantial in a consecutive and unselected series of patients with cancer actively treated during the pandemic. The detection and tracking of these silent carriers could be relevant to protect vulnerable patients and control contagion. In our experience, the SARS-CoV-2 two-step diagnostics is feasible and effective for the detection of silent carriers and might inform about the infection trajectory both at the individual and the population levels. The early safe profile of the different anticancer therapies we observed in patients previously exposed to SARS-CoV-2 supports the recommendation to continue the active treatment, at least in cases of RT-PCR negative patients.

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The study was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent, approved by institutional review board and local Ethics Committee

All data generated or analyzed during this study are included in the published article. Additional supporting data are available from the corresponding author on reasonable request.

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Disclosures

Alberto Zambelli: Roche, Novartis, Pfizer, Eli Lilly & Co., AstraZeneca, Genomic Health (C/A, Other-speakers bureau), Novartis, Pfizer, Eli Lilly & Co. (Other-travel and accommodations); **Carlo Tondini:** Roche, Novartis, Pfizer, Eli Lilly & Co. (C/A, Other-speakers bureau). The other authors indicated no financial relationships.

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For Further Reading:
Gianpiero Fasola Giacomo Pelizzari Diego Zara et al. Feasibility and Predictive Performance of a Triage System for Patients with Cancer During the COVID-19 Pandemic. ***The Oncologist*** First published: 04 February 2021.

Implications for Practice:
This is the first study to provide data on the predictive performance of a triage system in the oncological setting during the coronavirus disease outbreak. A questionnaire-based triage has a low positive predictive value to triage patients with cancer and suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) symptoms, and a differential diagnosis with tumor- or treatment-related symptoms is mandatory to avoid unnecessary treatment delays. Consequently, adequate recourses should be reallocated for a triage implementation in the oncological setting. Of note, body temperature measurement improves the overall sensitivity of the triage process, and widespread testing for SARS-CoV-2 infection should be implemented to identify asymptomatic carriers.