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Original Research

## Organisational challenges, volumes of oncological activity and patients' perception during the severe acute respiratory syndrome coronavirus 2 epidemic



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## KEYWORDS

SARS-CoV-2;  
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measures

**Abstract** *Background:* On February 23rd, the 1st case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed at the University Hospital Trust of Verona, Italy. On March 13th, the Oncology Section was converted into a 22-inpatient bed coronavirus disease (COVID) Unit, and we reshaped our organisation to face the SARS-CoV-2 epidemic, while maintaining oncological activities.

*Methods:* We tracked down (i) volumes of oncological activities (January 1st - March 31st, 2020 versus the same period of 2019), (ii) patients' and caregivers' perception and (iii) SARS-CoV-2 infection rate in oncology health professionals and SARS-CoV-2 infection-related hospital admissions of "active" oncological patients.

*Results:* As compared with the same trimester in 2019, the overall reduction in total numbers of inpatient admissions, chemotherapy administrations and specialist visits in January–March 2020 was 8%, 6% and 3%, respectively; based on the weekly average of daily accesses, reduction in some of the oncological activities became statistically significant from week 11. The overall acceptance of adopted measures, as measured by targeted questionnaires administered to a sample of 241 outpatients, was high (>70%). Overall, 8 of 85 oncology health professionals tested positive for SARS-CoV-2 infection (all but one employed in the COVID Unit, no hospital admissions and no treatment required); among 471 patients admitted for SARS-CoV-2 infection, 7 had an "active" oncological disease (2 died of infection-related complications).

*Conclusions:* A slight, but statistically significant reduction in oncology activity was registered during the SARS-CoV-2 epidemic peak in Verona, Italy. Organisational and protective measures adopted appear to have contributed to keep infections in both oncological patients and health professionals to a minimum.

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## 1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak has caused more than 8,242,000 cases and 445,535 deaths worldwide [1], translating into previously unseen challenges for healthcare systems, hospital resource overload and impairment of routine medical care [2–4].

Patients with cancer are felt to be particularly vulnerable, both in terms of risks of infection [5–7] and need to avoid undue delays in cancer treatment [3,8,9]. For patients with cancer, the fear that measures adopted to limit the spread of infection and strained

hospital resources might negatively affect their disease management and prognosis overwhelms fears related to the new pandemic, generating mistrust and lack of compliance towards protective measures. In that respect, the current lack of structured, real-life data on the impact of containment measures on volumes and quality of oncology activities fuels patients' and caregivers' fears and disappointment. A recent survey conducted by the 'Codice Viola' patients' association on 484 patients with cancer depicts drastic and important reductions in cancer care-related activities in Italy, especially with regard to delays in cancer surgery [10].

To address the actual changes in oncological activity volumes in relationship to the organisational changes implemented, we tracked down protective/organisational measures, oncological activity, patient perception of adopted measures and confirmed SARS-CoV-2 cases among our healthcare professionals and patients with cancer during the peak of SARS-CoV-2 epidemics at the Verona University Hospital Trust (Italy).

## 2. Methods

### 2.1. Study design and data collection

We retrospectively analysed the activity of our Section of Oncology at the University Hospital Trust of Verona (Italy) from January 1st to March 31st, 2020, to investigate how organisational changes related to the SARS-CoV-2 epidemics impacted on (i) volumes of oncological activity (in comparison with the same period in 2019), (ii) cases of SARS-CoV-2 infections observed in oncology health professionals and (iii) hospital admissions of ‘active’ oncological patients for SARS-CoV-2 infection.

Oncology healthcare professionals were routinely screened for SARS-CoV-2 infection by multiplex reverse transcription polymerase chain reaction (RT-PCR) based research of SARS-CoV-2 genomic sequences on naso- and oro-pharyngeal swab-derived samples (NPSs) [11], according to a structured periodic screening strategy (Supplementary Methods).

Patients with cancer admitted to the Verona University Hospital Trust for SARS-CoV-2 infection were identified by reviewing medical charts of all patients admitted to the institutional coronavirus disease (COVID) Units (including intensive care unit - ICUs) from February 1st (21 days before the first confirmed SARS-CoV-2-positive case) to April 14th, 2020 (14 days after the end of the observation period chosen to monitor oncological activity) (Supplementary Methods). The last follow-up date was April 30th, 2020.

### 2.2. Patient-reported perception of organisational measures

To assess patients’ perception of risks and their acceptance of protective/organisational measures, anonymous questionnaires (Supplementary Methods), developed by our Psycho-Oncology Service, were administered at triage to all patients accessing our outpatient facilities, over a 21-day period; questionnaires were returned on a voluntary basis.

### 2.3. Statistical analysis

For oncological activity volumes, total numbers and daily average numbers  $\pm$  standard deviation were reported for the January–March trimester of 2019 and

2020; variations in daily average activity volumes (calculated on a monthly or weekly bases, as indicated) between the two periods were compared using a two-tailed Student’s *t*-test for unpaired samples with unequal variance. The percentage of relevant answers to relevant questionnaire items is reported with 95% confidence intervals (95% CI).

## 3. Results

### 3.1. SARS-CoV-2-related events and organisational protective measures

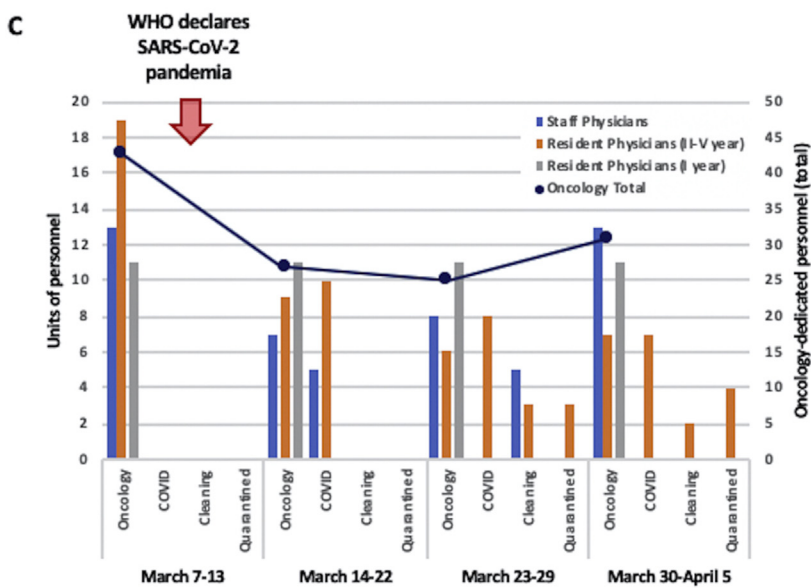
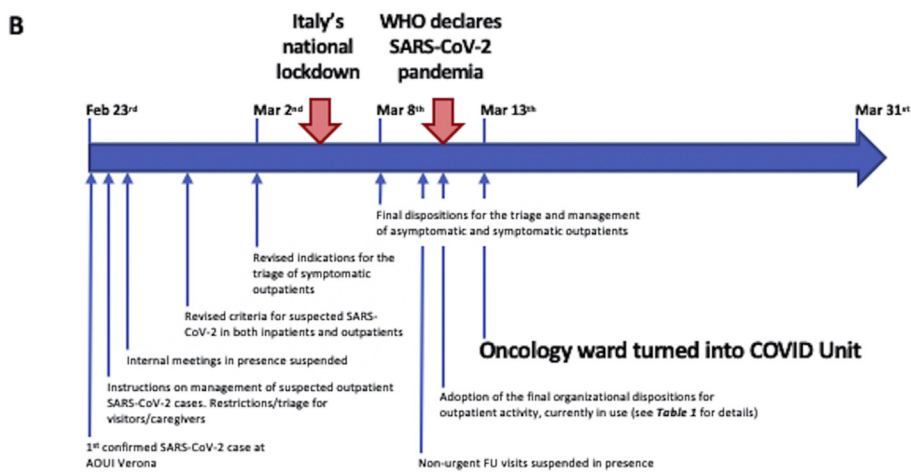
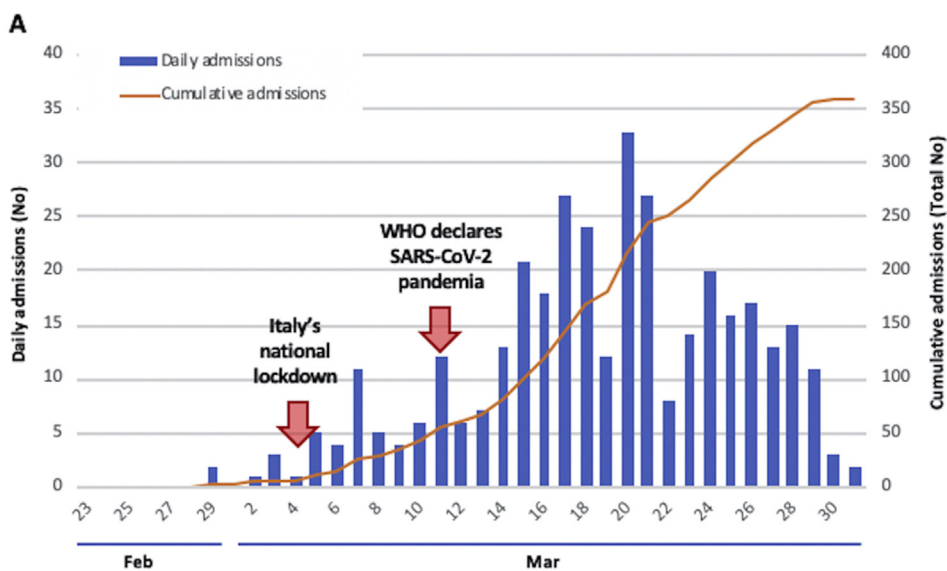
On February 23rd, 2020, the first confirmed case of SARS-CoV-2 infection was diagnosed at the Verona University Hospital Trust. Daily and cumulative hospital admissions for SARS-CoV-2 infection are shown in Fig. 1A; a peak of 33 daily admissions was reached on March 20th, 16 days after the national lockdown on March 4th, and a plateau at 360 hospital admissions was reached as of March 30th. During the epidemiological peak, inpatient and ICU beds were increased to a total of 199 SARS-CoV-2-dedicated beds.

Our Oncology Section adopted progressive restrictions to hospital access to visitors/caregivers and organisational measures, according to the timelines shown in Fig. 1B. Final dispositions regulating outpatient oncology activity issued on March 11th are shown in Table 1, in comparison with cancer-specific indications by the Italian Ministry of Health and scientific societies.

On March 13th, the Oncology Ward was converted into a 22-bed COVID Unit, initially staffed by Oncology personnel on a voluntary basis, and oncological inpatients were transferred to a surgical ward, where they were followed by Oncology physicians. Segregated personnel teams were created, one dedicated to the COVID unit and a “clean” one dedicated to oncological patients (Supplementary Methods). Such organisation resulted in an overall 40% and 43% reduction in oncology-dedicated medical and nursing/auxiliary staff, respectively; over subsequent weeks, Oncology personnel were gradually substituted for by other specialists, returning to a full Oncology staffing by the end of April (Fig. 1C).

### 3.2. Overall volumes of oncology activities

We tracked down volumes of oncological activities from January 1st to March 31st, 2020, in comparison with the same period in 2019. Priority was given to avoiding ongoing systemic treatment interruptions; activation of new systemic treatments was subjected to a structured waiting list, designed to allow for the initiation of treatment within a maximum of 14 days, according to priorities described in Supplementary results. Total



hospital admissions for oncological procedures during the first trimester of 2020 showed an overall 8% reduction as compared with 2019; average weekly admissions, calculated on a monthly basis, showed a 40% reduction in March ( $p = 0.08$ , Fig. 2A). Changes in total and daily average chemotherapy administrations (calculated on a weekly basis) are shown in Fig. 2B: a 6% reduction in total chemotherapy administrations was observed; an average 14% reduction in daily average chemotherapy administrations over weeks 11–13 was also observed, reaching statistical significance on weeks 11 and 13 ( $p = 0.03$  and  $p = 0.04$ , respectively). Total specialist visits were reduced by 3%; changes in daily average specialist visits (calculated on a weekly basis) showed a more pronounced decline in weeks 11–13, with an average 35% reduction, which was statistically significant ( $p < 0.03$ ) for weeks 11, 12 and 13 (Fig. 2C). Variations in disease-specific specialist, chemotherapy and follow-up visits are shown in Supplementary Fig. 1. Follow-up evaluations were conducted remotely (phone calls, e-mails and transmission of diagnostic tests and exams), except for those patients who needed an urgent evaluation in presence.

### 3.3. Patient-reported perception of risks and acceptance of protective and organisational measures

We surveyed our population of oncological outpatients to understand their perception of risks and their acceptance of the adopted organisational measures. Among 241 respondents (demographics described in Supplementary Fig. 2A), fear of accessing hospital facilities and fear that chemotherapy treatment could increase the risk of contracting SARS-CoV-2 infection was reported as quite high or high in 34% (95% CI: 29–41%) and 27% (95% CI: 21–33%), respectively (Fig. 3 top). Awareness of disease-related risks of infection and strategies to reduce such risks was reported as ‘very’ or ‘quite clear’ by the vast majority [83% (95% CI: 78–88%) and 93% (95% CI: 90–96%), respectively] of respondents (Fig. 3 bottom). Interestingly, almost all patients felt that the organisational measures adopted to minimise the risk of SARS-CoV-2 infection were clearly expressed (98%, 95% CI: 96–100%) and mostly derived by information received at the triage point (73%, 95% CI: 67–79%; Supplementary Fig. 2B). Overall acceptance of organisational and social distancing measures was very high

(Supplementary Fig. 2C); the only notable exception was acceptance of phone-based follow-ups and restaging visits, which were perceived as ‘not very adequate’ or ‘not adequate at all’ by 17% (95% CI: 12–22%) and 18% (95% CI: 13–23%) of respondents, respectively.

### 3.4. SARS-CoV-2 infection in oncology healthcare professionals

Among a total of 85 Oncology healthcare professionals (Fig. 4), 40 were at least temporarily employed in the newly created COVID Unit.

Up to April 12th, 8 Oncology healthcare professionals (9%) tested positive for SARS-CoV-2 infection (Fig. 4). Although 7 of 8 positive cases were observed among personnel who had been employed in the COVID Unit, none of these cases could be tracked down to inappropriate personal protective equipment use or intra-hospital contagion.

In all but one asymptomatic infected oncology healthcare professional, SARS-CoV-2 infection presented with phenotype 1 (mild symptoms, refer Supplementary Methods) [12] and did not require hospitalisation or specific treatment; infection resolved after a median of 25.5 days (Fig. 4).

### 3.5. SARS-CoV-2 infection in active oncological patients

Among 471 patients admitted to the hospital’s COVID units as of April 14th, 2020, a total of 75 patients had a history of cancer diagnosis; of these, 15 were classified as ‘active’ according to the definition given in Supplementary methods. Among a total of 525 patients who had accessed our Section of Oncology in the period February 1st–April 14th, 2020, 7 ‘active’ oncological patients were admitted for SARS-CoV-2 infection (1.3%); the remaining 8 active oncological patients retrieved in the database were followed for their oncological disease at other institutions. Characteristics of the underlying oncological disease of the 7 patients analysed are reported in Supplementary Table 1. The most common symptom at onset was fever (5/7), followed by dyspnoea (4/7); the most common COVID phenotype at onset was phenotype 2 and two patients progressed to a worse phenotype during hospitalisation (Supplementary Table 2). Five patients received oxygen therapy (1 requiring noninvasive ventilation - NIV and 1 requiring mechanical

Fig. 1. Timelines during the peak of SARS-CoV-2 epidemics at the Verona University Hospital Trust (Italy). (A) Daily (histograms) and cumulative (orange line) SARS-CoV-2-related admissions to the Verona University Hospital Trust between February and March 2020. (B) Timeline of organisational and protective measures adopted by the Section of Oncology (Table 1). (C) Deployment of medical personnel (staff physicians, II/V-year resident physicians, I-year resident physicians) after the creation of the COVID unit: total units used in different areas (Oncology or COVID unit) or undergoing cleaning or quarantine periods (if SARS-CoV-2 positive) for each category of personnel are shown in colour-coded histograms; the dotted line represents total oncology-dedicated personnel at each time point. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.) SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1

Cancer-specific protective measures adopted at the Verona University Hospital Trust (Italy).

	Italian MoH	AIOM-CIPOMO-COMU	ESMO	Oncology section, Verona
Date	Mar 10, 2020	Mar 13, 2020	April 01, 2020	Mar 08–11, 2020
Triage	No indications were given about triage	No access allowed to oncology facilities before evaluation by healthcare professionals if the patient has fever and/or respiratory symptoms (cough, sore throat, dyspnoea). Symptomatic oncological patient at home should contact the Oncology Department before access and follow a personalised path.	'Previous day' telephone triage recommended to identify flu-like symptoms in patients with cancer so that appropriate measures can be taken.	'Previous day' telephone triage to identify flu-like symptoms and/or contact with a confirmed or suspected case of SARS-CoV-2. Triage at oncology facilities' entrance (performed by a healthcare professional): symptomatic patients are immediately referred to ER for evaluation; patients with clinical suspicion of infection follow a personalised, "protected" path.
Patients undergoing active treatment	Local health authorities and each hospital should identify and apply an efficient way to guarantee the essential oncological treatment to maintain dose intensity without interfering with patient prognosis.	Phone-based triage of patients scheduled for treatment. Consider risk/benefit ratio of delaying anticancer treatment (tumour biological hallmarks, patient clinical features, risks of SARS-CoV-2 infection)	Discuss the benefits and risks of present cancer therapy in the setting of the SARS-CoV-2 pandemic: treatment setting, disease prognosis, patients comorbidities, patients preferences, risks from SARS-CoV-2 infection. Evaluate if the planned local treatment is a priority or can be postponed ("wait and see" approach). Re-evaluate treatment schedules to reduce the number of visits (three or two-weekly as opposed to weekly, oral or subcutaneous alternatives as opposed to intravenous administration); prioritise adjuvant therapies.	No interruption or delay of planned treatment (unless mandated by clinical conditions); phone-based triage of scheduled patients; prior day remote laboratory check to avoid access in case of non-permissive exams. Social distancing between patients in waiting areas and in therapy areas (time-scheduled access). Prioritisation of new treatments: (1) treatment-emergent conditions, neoadjuvant/adjuvant, clinical trial; (2) first-line palliative therapy; (3) second- or further line palliative therapies.
Follow-up	To postpone, where possible and in accordance with the specialists, follow-ups, to limit the time spent in health facilities (both to limit the risk of exposure to SARS-CoV-2 and to reduce the amount of work of structures already partially overloaded).	Delay physical examination of patient unless urgent clinical reasons. Where possible telematical contact to allow examination of laboratory/imaging exams.	Routine blood tests may be carried out at local healthcare centres rather than in hospitals. Essential imaging assessments to check on the progress of cancer will still go ahead, but these may be reduced in frequency, especially if you are in remission or have stable or slowly progressing cancer.	Non-urgent FU visits suspended in presence. E-mail and phone contact with patients to allow examination of laboratory and imaging exams.
Caregiver	No indication about caregiver	No caregiver allowed for outpatients scheduled for treatment, except in the case of documented need of continuous assistance. Maximum	No indication about caregiver	No caregiver allowed for outpatients scheduled for treatment, except in the case of documented need of continuous assistance. Maximum

Table 1 (continued)

	Italian MoH	AIOM-CIPOMO-COMU	ESMO	Oncology section, Verona
PPE	Surgical mask outside home, particularly when patients need to go to the hospital for exams, visits or treatments.	one caregiver allowed (after triage) for every inpatient. Surgical masks provided to all patients and caregivers at entrance. Surgical mask and gloves for healthcare personnel. If possible use FFP2-FFP3 mask.	Patients should wear PPE when they attend hospitals for visits and treatments. Clinical staff responsible for the checkpoint area should be trained and wear PPE.	one caregiver allowed (after triage) for every inpatient. Surgical masks and gloves provided to all patients and caregivers at entrance. Surgical mask and gloves for healthcare personnel. Additional FFP2-FFP3 mask and waterproof coat for healthcare professionals who evaluate clinically suspicious patients.

MoH, Ministry of Health; AIOM, Italian Association of Medical Oncology; CIPOMO, Board of Directors of Hospital-based Medical Oncologies; COMU, Board of University-based Medical Oncologists; ESMO, European Society of Medical Oncology; PPE, personal protective equipment; ER, emergency room; FU, follow-up.

ventilation); all but one patient received hydroxychloroquine and 5 of 7 received lopinavir/ritonavir (Supplementary Table 2). Two patients died of SARS-CoV-2-related complications, 5 of 7 were discharged (all but one after at least one negative NPS) and 3 have resumed their oncological treatment.

#### 4. Discussion

Although approximately half of our Oncology Section was temporarily involved in SARS-CoV-2 patient care, careful organisational measures allowed for a minimal reduction in the volumes of oncological activities (3–8%). Implementation of telephone and in

presence triage, access reduction, social distancing policies and remote consultation activities were largely accepted by patients and minimally interfered with the effective delivery of cancer care. Although data collected on SARS-CoV-2 infection in healthcare professionals and SARS-CoV-2-related hospital admissions of ‘active’ cancer have no epidemiological value, the numbers are low, suggesting that thoughtful organisational and protective measures might keep the risk of infection to a minimum while allowing to maintain the usual volumes of cancer care activities.

Cancer-specific protective measures endorsed by scientific societies (including restrictions to hospital access and telephone or web-based consultations, refer Table 1)

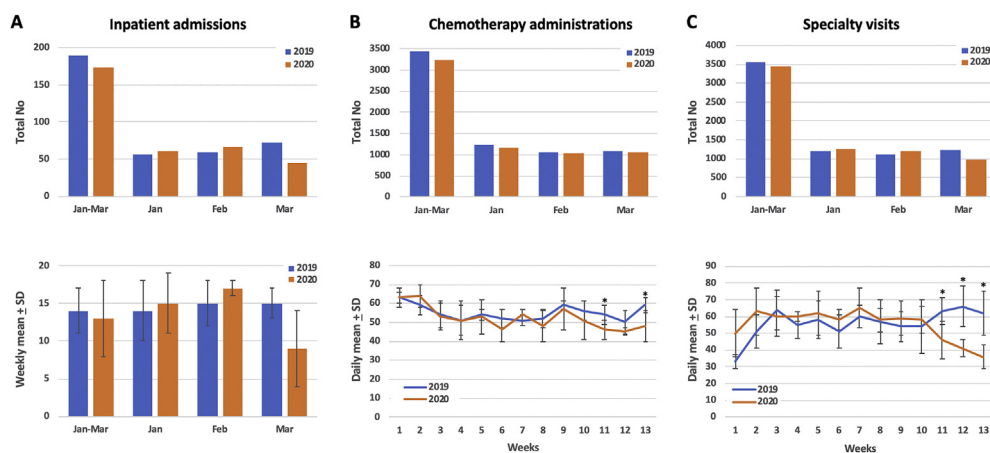


Fig. 2. Changes in overall volumes of oncology activities during the first trimester of 2020, as compared with the same period of 2019. (A) Total (top panel) and average weekly numbers (calculated over the entire trimester – leftmost histograms – or over each single month)  $\pm$  standard deviation (SD, bottom panel) of hospital admissions for oncological procedures; differences in average weekly admissions between 2019 and 2020 were not statistically significant by Student’s *t*-test. (B) Total (top panel) and average daily numbers (calculated over each single week)  $\pm$  standard deviation (SD, bottom panel) of chemotherapy administrations;  $*p < 0.04$  by Student’s *t*-test. (C) Total (top panel) and average daily numbers (calculated over each single week)  $\pm$  standard deviation (SD, bottom panel) of speciality visits;  $*p < 0.03$  by Student’s *t*-test.



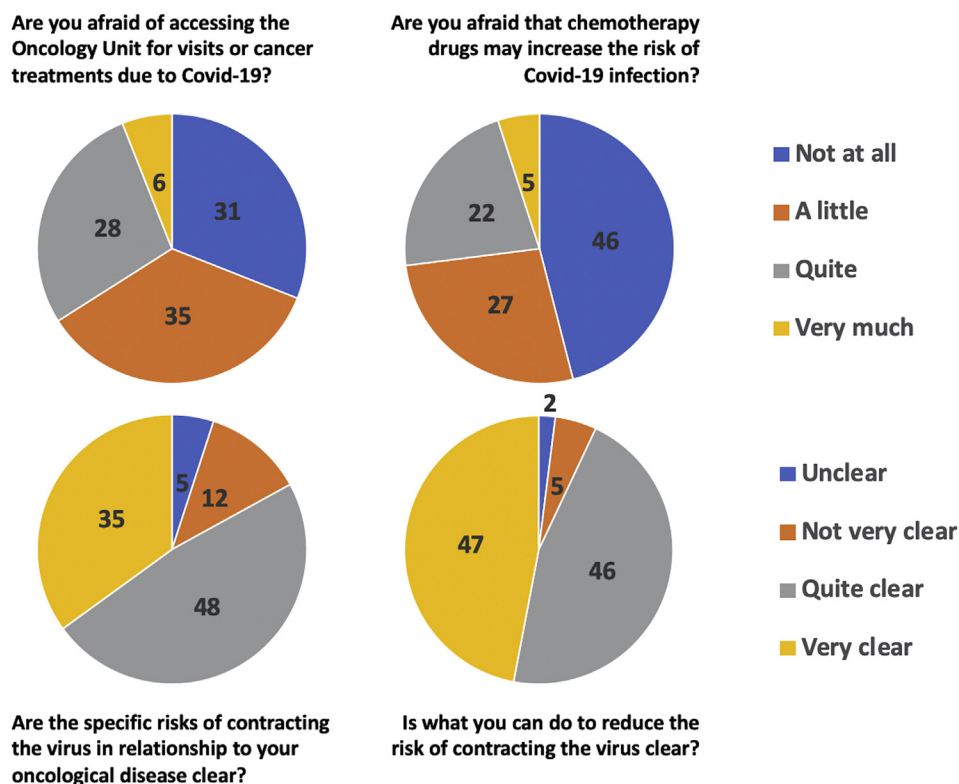


Fig. 3. Patient-reported fears and awareness of risks. Distribution of answers (numbers indicate percentages of total respondents,  $n = 241$ ) to the indicated questions regarding fears of contracting the SARS-CoV-2 infection (top) and awareness of cancer-related risks of infection and strategies to reduce them (bottom) are shown in pie charts. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[13,14] were adopted early during the course of the epidemic; oncological treatment prioritisation was established based on a structured waiting list (Supplementary Results), and we maintained virtual multidisciplinary meetings on a weekly basis, as per our standard clinical practice [15,16]. Considering the lack of clear data supporting the notion that oncological treatment-related adverse events may imply a higher risk of SARS-CoV-2 infection or predict a worse disease course, systemic treatments were not de-escalated and/or postponed [8,17].

Reduction in the overall volumes of oncological activity in the first trimester of 2020, as compared with the same period in 2019, was limited. These data are difficult to compare with the few other reported experiences, which have estimated a cumulative reduction in the overall number of patients with cancer admitted to hospitals ranging from 20 to 30% [17,18]; such reductions are, however, similar to the statistically significant differences observed in some of our activities during the most acute epidemic phase (weeks 11–13). Discrepancy maybe due, in part, to the fact that we have included in the analysis specialist visits (~40%) and follow-up consultations (90%) which were carried out by telephone. A more prominent reduction was observed in the gap between chemotherapy visits and actual chemotherapy infusions (Supplementary Fig. 1), likely due to previous day telephone triage, which prevented

patients with symptoms and/or laboratory abnormalities from unnecessarily accessing the hospital.

Reporting of real-world data should be encouraged to paint a clear picture of how the SARS-CoV-2 pandemic is impacting on cancer care in Italy and worldwide. Uncertainty may cause patients to feel abandoned, aggravate disease-related distress and lead patients to abandon life-saving treatments, as recently reported in 15–20% of cases [19]. Moreover, fear that restrictive measures may negatively affect cancer management and prognosis may fuel patients' anger and mistrust, leading to low compliance to such measures: in a moment of extreme vulnerability, the patient mind activates coping mechanisms that focus on their primary objective, cancer treatment, confining the fear of the infection in the background [20]. Adequate and timely information, an effective doctor-patient relationship and prompt psychological support are critical to transcend the new physical barriers represented by masks and remote assistance [21–23]. This conclusion is supported by our data on patients' reported perception of restrictive measures: even though approximately 30% of patients still feared the risk of contracting SARS-CoV-2, the vast majority felt well informed and acceptance of the adopted measures was very high (>80%).

Data reported on SARS-CoV-2 infections in Oncology healthcare professionals and oncological

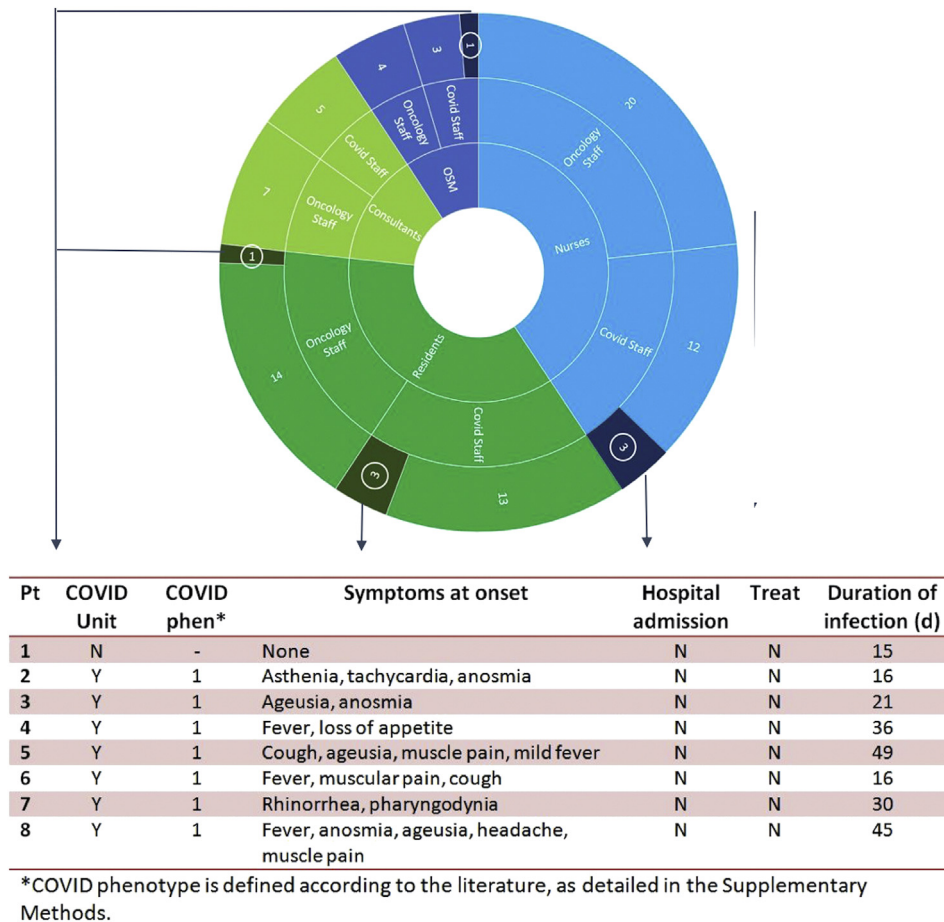


Fig. 4. SARS-CoV-2 infection in oncology healthcare professionals. Distribution of oncology personnel is depicted in the pie chart (top): inner circle indicates the type of personnel considered (consultants, residents, nurses, auxiliary personnel – OSM); middle circle indicates the allocation of each type of personnel (Oncology or COVID unit); outer circle indicates the numbers of each type of personnel allocated to each activity; numbers of SARS-CoV-2–infected personnel for each category are highlighted and infection details exploded in the accompanying table (bottom). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients are meant to be purely descriptive and have no epidemiological value. The Wuhan Union Hospital reported a 1.7% infection rate among healthcare workers [24], and in Italy, more than 28,900 healthcare workers were confirmed as infected [25]. However, epidemiological conclusions cannot be presently drawn, as testing strategies vary widely across different hospitals and within the same hospital; in addition, close contacts of positive oncology healthcare professionals were aggressively tracked down and none tested positive. Importantly, only 1 of the positive health professionals was actually in contact with oncological patients and colleagues in charge of ‘clean’ oncological activity, supporting the effectiveness of a segregated-team model in containing infection risks [18]. With regard to cases of infection in our patient population with cancer, we elected to collect and analyse only cases requiring hospital admission, for whom we had a reliable source of information and a precise reference population. A recent epidemiological study conducted in the Veneto region indicates a 0.3% prevalence of SARS-CoV-2 infection

among male patients with cancer, with a slightly but significantly higher odds ratio (OR), as compared with the general population [OR: 1.79 (1.62–1.98),  $P < 0.0001$ ] [26]; however, these data should be interpreted with caution because neither all cancer patients nor the general population has been systematically tested and NPSs may not detect a resolved past infection, thus potentially underestimating the actual prevalence of SARS-CoV-2 exposure. Whether incidence and clinical severity of SARS-CoV-2 infection in oncological patients is different from those in the general population remains to be answered. Currently available series are limited and convey conflicting results [5–7,27–29]; larger, well-designed, epidemiological studies will need to be conducted, perhaps using serological approaches [30], to definitively address these questions. Nevertheless, the number of severe cases requiring hospital admission appears to be low in our experience, with a 1.3% (7/525) rate of severe infection in the population of patients who accessed Oncology facilities during the epidemics peak (February 1st–April 14th).

Potential long-term impact of infection containment measures on oncology care should be considered. Suspension of screening programs, diagnostic procedures, follow-up visits and the inadequate timing of supportive care are predicted to lead to a 5–10% decrease in survival in high-income countries [31,32]; such figures could be even worse, if we also consider the possible slow down of oncology clinical trials and cancer research, education and collaboration [33]. However, the experience we report herein suggests that timely and thoughtful adoption of organisational and protective measures, coordinated efforts of all the figures involved in modern cancer care (physicians, psychologists, nurses, auxiliary and support personnel) and effective communication strategies to frankly share risks and needed sacrifices with patients/caregivers [22] can lead to effective protection of healthcare workers and patients with cancer alike, while minimally disrupting adequate cancer care.

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### Author contributions

S.Z., I.Z., D.T., S.P. and M.M. were involved in the study conception and design. S.Z., I.Z., D.T., M.C., A.C., A.F., S.M., S.T.R., A.R., F.Z., E.Z., S.P. and M.M. participated in literature search, data collection, analysis and interpretation and design of figures and tables. M.M. was responsible for the statistical analysis. S.Z., I.Z., D.T., S.P. and M.M. had full access to all the study data, wrote the initial draft of the manuscript and had the final responsibility for the decision to submit for publication. All authors participated in drafting, reviewing and approval of the final manuscript.

### Conflict of interest statement

M.M. reports receiving personal fees from Pfizer, EUSA Pharma and Astra Zeneca, outside the submitted manuscript. S.P. reports receiving honoraria or speakers' fee from Astra Zeneca, Eli-Lilly, BMS, Boehringer Ingelheim, MSD and Roche, outside the submitted manuscript. All remaining authors have declared no conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.05.029>.

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