European Review for Medical and Pharmacological Sciences 2020; 24: 11445-11454

New models of care and multidimensional solutions for oncological patients in the post-acute SARS-COV-2 period: a "Second Phase" also for cancer patients

F. CONSOLI[1], C. CRISTINI[2], M.G. GUARINONI[3], R. LEVAGGI[4], N.F. LOPOMO[5], R. MAROLDI[6], M. MELCHIORI[5], P.C. MOTTA[3], E. SARDINI[5], A. BERRUTI[1], P. BOSSI[1]

[1]Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Medical Oncology, University of Brescia, at ASST-Spedali Civili, Brescia, Italy
[2]Department of Clinical and Experimental Sciences, Division of Neurosciences, Unit of General Psychology, University of Brescia, Brescia, Italy; Interdipartimental University Center of Research "Adaption and Regeneration of Tissues and Organs - (ARTO)", University of Brescia, Brescia, Italy
[3]Department of Medical and Surgical Specialties, Radiological Science and Public Health, University of Brescia, Brescia, Italy
[4]Department of Economics and Management, University of Brescia, Brescia, Italy
[5]Department of Information Engineering, University of Brescia, Brescia, Italy
[6]Department of Radiology, University of Brescia, at ASST-Spedali Civili Brescia, Italy

Abstract. – In Italy, SARS-CoV-2 outbreak registered a high transmission and disease rates. During the acute phase, oncologists provided to re-organize services and prioritize treatments, in order to limit viral spread and to protect cancer patients.

The progressive reduction of the number of infections has prompted Italian government to gradually loosen the national confinement measures and to start the "Second phase" of measures to contain the pandemic. The issue on how to organize cancer care during this post-acute SARS-CoV-2 phase appears crucial and a reassessment of healthcare services is needed requiring new models of care for oncological patients. In order to address major challenges in cancer setting during post-acute SARS-CoV-2 phase, this work offers multidimensional solutions aimed to provide a new way to take care of cancer patients.

Key Words:
SARS-CoV-2, COVID-19, Public Health, Telemedicine, Cancer Care.

Introduction

During the acute phase of SARS-CoV-2 outbreak, oncologists had to make quick choices in several fields: selection of patients for treatments, re-organizing outpatient visits, triaging patients at the entrance and limiting the access of caregivers and re-prioritizing the agenda[1-3]. In Italy, the Italian Association of Medical Oncology (AIOM) provided recommendations about the management of cancer patients in active treatments or in follow-up. Decisions about oncological treatments continuation should consider symptoms, tumors features, treatment characteristics, disease response and potential risk of SARS-CoV2 infection; patients in follow-up had to delay visits so to limit patients access in hospital except for cases with signs or symptoms related to a progressive disease[4].

The effect of social distancing and lockdown are showing their efficacy in Italy so far, with a progressive reduction of number of infections and need of intensive care unit for high-risk patients[5,6]. This effect prompted Italian government to gradually allow return to work, travelling and social activities, with the use of personal protective equipment. The Italian government has defined the "Second Phase" of the nationwide lockdown as "living with the virus". This means that the suppression strategy adopted in Italy and other countries led to a consistent decrease of the proportion of infected people, but the number of COVID positive people still remain relevant.

Solutions to this pandemic outbreak of SARS-CoV-2 are required for cancer patients: a re-as-

Corresponding Author: Francesca Consoli, MD; e-mail: francesca.consoli@asst-spedalicivili.it

sessment of the public healthcare service is needed to protect cancer frail patients, potentially vulnerable to infections[7]. Nowadays, major issues are identifying infected and uninfected patients as accurately as possible, adopting all measures to prevent infection and designing specific protocols for cancer care for SARS-CoV2 positive patients[7]. Accordingly, the "Second Phase" is requiring new models of care also for oncological patients: it cannot be defined too simplistically as a return to the status quo ante. We have the enormous chance to use the lessons learnt from the emergency phase and to translate them into new opportunities to improve our delivery of care.

Hereafter, we present some of the major challenges the Second phase will pursue and the possible changes we may adopt leveraging on the information collected during the acute phase and within a multidimensional context.

Challenges and Multidimensional Solutions

Triage and Test for SARS-CoV-2

An anamnestic assessment to classify patients as SARS-CoV-2 free or suspect is needed. A hospital and a telephonic triage protocol aim at an early identification of infections symptoms, also identifying possible positive contacts[8]. Testing anyone who has symptoms compatible with SARS-CoV-2 should be considered. However, symptom-based screening alone fails to detect a high proportion of infectious cases that are totally asymptomatic. A key factor in the transmissibility of SARS-CoV-2 is the high level of viral SARS-CoV-2 shedding in the upper respiratory tract[9]. Contrary to classical influenza, transmission of SARS-CoV-2 from asymptomatic has also been documented[10,11].

Testing asymptomatic patients is of utmost importance for cancer patients. The IDSA recommends SARS-CoV-2 testing for asymptomatic immunocompromised patients who require hospitalization and for asymptomatic individuals prior to receiving immunosuppressive therapy[12].

The current literature findings shows a sensitivity of 56 to 83% for the SARS-CoV-2 PCR and the Negative Predictive Value decreases with increasing prevalence of the infection[13]. During a pandemic, false negative results can produce serious consequences in the management of cancer patients. The limited sensitivity could be compensated by repeated measures[14,15].

New diagnostic strategies are needed in order to optimize the medical care of our patients. Serological assays based on recombinant antigens derived from both S and N proteins are becoming widely used in laboratory diagnostics[16-23]. Development of an antibody response to infection, however, takes time and is host dependent. In the case of SARS-coV-2, early studies[18,20,23,24] suggest that the majority of patients seroconvert between 7 and 11 days postexposure to the virus. As a result of this delay, antibody testing is not useful in the setting of an acute illness[20,22,23]. These tests allow identification of patients who have been infected and this information may be useful for a surveillance of the virus spread within the oncology patients and may identify patients that have achieved a protective immunity and could be submitted to antineoplastic therapies without risk.

In this respect ELISA tests reacting with the complete or partial N protein have been found highly sensitive and could be useful for epidemiological purposes, conversely testing reactivity of SARS-CoV2 patient sera with S protein was found to be less sensitive, but, since the S protein is responsible for virus-cell receptor interactions, laboratory tests revealing S protein in sera could potentially identify a patient subset who has developed immunity against the virus[17,20,24]. Therefore, the identification of cases that may have contracted the infection is currently based on the combination of several parameters, such as triage, upper respiratory tract swabs, radiological findings and serology[2,3,14,18,20,25,26].

During the phase two, as oncologists working in a public hospital, we decided to continue the systematic triage of clinical conditions for all patients, before entering in the Oncology Department, limiting the access of caregivers. Surgical masks and hand washing were always recommended and provided to all patients. Regarding hospital admissions, upper respiratory tract swabs and radiological exams (Chest X-ray) were performed.

How to Deal with SARS-COV-2 Positive Patients

The data surrounding the biology, epidemiology, clinical characteristics and treatments about SARS-CoV-2 virus have been growing daily in the last 3 months. Meanwhile, the clinical spectrum of disease severity continues to be defined[3,20,27-31]. Specifically, in a report from the Chinese Center of Disease control on 44,500 SARS-CoV-2 confirmed infections, 81% of pa-

tients had mild symptoms (no or mild pneumonia), 14% had severe respiratory symptoms (dyspnea, hypoxia, or >50% lung involvement on imaging) and 5% were critical (respiratory failure, shock, or multiorgan system dysfunction). The overall case fatality rate was 2.3%, while it was 49% in critical illness patients[32].

So far, limited retrospective experiences explored the incidence of SARS-CoV-2 in cancer patients: conflicting results emerged from these reports, mainly due to confounding variables, such as small number of cases, cancer types, anti-cancer treatments and underling health conditions[33-35]. Older patients seemed to be more vulnerable and susceptible to a severe SARS-CoV-2 course[33]. In a Chinese report, mortality rate in hospitalized cancer patients was 28%[36]. More recently, two large studies[37,38] from China and New York showed increased odds of death in cancer patients, after contracting COVID-19. Moreover, it is still unclear how chemotherapy, target agents or immune-checkpoint inhibitors may affect patients' susceptibility to viral infection and complications[2,8]. Accordingly, the current mitigation of SARS-CoV-2 outbreak will make necessary to further strengthen the collaboration between oncologists and SARS-CoV-2 task force to re-organize healthcare system.

As depicted in the WHO algorithm for SARS-CoV-2 patients, the triage pathway is the first step to screen symptoms and to estimate disease severity, guiding clinicians in management and patients' referral[39]. In neoplastic patients, an evidence-based assessment of both cancer outcome and risk/benefit ratio of systemic treatments should be achieved, when SARS-CoV-2 disease has been diagnosed[3]. Mild cases may be referred to community care and isolated, while severe cases will be referred to specific wards, within each hospital, such as intensive care units (ICU)[39].

In patients suffering for life-limiting neoplastic illness and SARS-CoV2 infection, a supportive care program may be provided by palliative care specialists. Home management could be appropriate for patients with mild infection and symptoms, who can be adequately isolated in the outpatients setting approach. Symptomatic patients should be referred to a palliative care center[40].

Recently, European Society of Medical Oncologist (ESMO) and American Society of Clinical Oncology (ASCO) have suggested some recommendations in order to improve the management of cancer patients, during SARS-CoV-2 pandemic[41,42]. Clinicians should balance the cost-benefit ratio of cancer therapies according to treatment setting, disease prognosis, patients' comorbidities and preferences, probability and risk from viral infection[7]. Three levels of priorities have been identified in the approach of cancer patients. ESMO encourages to prioritize oncological treatment in patients with symptomatic disease and/or when the magnitude of the intervention is considered high (i.e., adjuvant therapies)[41]. Palliative cancer treatments need to be discussed, envisaging potential alternative regimens: short-term approaches (i.e., symptomatic radiotherapy) or supportive care should be considered as strategies to palliate symptoms[3].

Home-Care Based Management of Oncological Therapies: a "Bridge" Between Hospital and Home-Care

Since the beginning of the SARS-CoV-2 emergency, traditional hospital-centered health management appeared to be incapable of adequately dealing with the increasing number of patients and diseases[43]. Overcrowded hospital became carriers of infection and pragmatic actions had to be required to preserve more vulnerable cancer patients[2].

The current Second Phase period is revealing considerable room for the development of new strategies to optimize cancer patients' management: so far, many challenges are emerging to minimize patients' exposure. Efforts are necessary to draw up new models to deliver cancer care. Accordingly, we are exploring new perspectives to provide comprehensive care to cancer patients. The "Home-Care Project" has been designed during the SARS-CoV-2 emergency, as an opportunity to warrant oncological treatments directly at patients' home. Bridging hospital to home care, a cancer team, consisting of an oncologist, a nurse and a pharmacist will be relocated to deliver oral or intramuscular cancer treatments directly at patients' home. Noteworthy, many cancer patients are elderly with comorbidities and their frailty needs to be preserved from hospital-acquired infection. Another important challenge of this project will be to improve the therapeutic relationship between patients and clinicians, handling their concerns and potentially optimizing the adherence to treatments[44-46]. Nurses will have an established connection to patients to build a good-quality patient-nurse relationship: this program will also include educational strategies, that will play an important

role in achieving patients' medications adherence and tailoring their needs[47,48]. Nurses will provide a link and support through home visit, telephone call[49].

The "Home Care Project" will also provide the integration of multidisciplinary team consultation, during patients' disease re-assessment. Timely and appropriate medical services will be accessed when needed using the smart healthcare technology[50,51]. Teleconsultation will allow to optimize patients' journey, reaching more personalized strategic solutions. Moreover, the use of mobile device, such as portable ultrasound tools could enable the assessment of SARS-CoV2-related pneumonia signs, as well as being a first imaging screening in case of treatment adverse events or disease-related signs and symptoms[25,52,53].

Home-Care Based Support for Treatment-Related Adverse Events and Disease-Induced Symptoms

Prevention and treatment of adverse events due to oncological therapies and disease will be changing thanks to the lessons learned during the acute pandemic phase. From one hand, the need to reduce hospital access to cancer patients may put them at higher risk of delayed recognition and treatment of toxicities; on the other, it offers new opportunities for alternative ways to offer supportive care. In fact, some symptoms need to be promptly identified to receive an adequate treatment, as timely approach is essential, just thinking to some immunotherapy-induced toxicities which can benefit from early steroidal therapy.

Therefore, strict adherence to preventative suggestions, prompt identification and early, home-based treatment of toxicities may be the key points in reshaping supportive care for cancer patients.

Guidelines for most of the treatment or disease-related adverse events put emphasis in measures to be adopted for prevention: this message should be strongly reinforced in the Second Phase period, before starting any oncological treatment. Moreover, identification of the subjects at highest risk of developing toxicities could help increasing preventative measures and defining closer follow up in-between visits or home access. There are algorithms and reviews useful to identify patients at higher risk of chemotherapy-induced nausea and vomiting[54], infections[55] and mucositis[56]. Less is known about targeted and about immunotherapy-related adverse events, except for patients having autoimmune diseases.

The systematic use of patient-reported outcome (PRO) tools has been shown to be a reliable method to better estimate patients' needs and anticipate solutions. Through PROs use, the oncological team may improve pain management, and overall symptom detection and control; moreover, the use of supportive care itself is increased[57]. Integrating PRO tools into the routine assessment of patients at home may ameliorate the management of symptoms, by an anticipated diagnosis and better evaluation of the impact of the toxicity on the patients.

Another strategy could be implemented is the scheduled nurse phone call, to support patients during oncological treatment, through a more precise assessment of patient's status and suggested interventions according to pre-specified protocols[49].

Home-based approach to supportive care is feasible, similarly to what described before in delivering oncological treatments. The use of bisphosphonate, hydration, antibiotic/antiviral/antifungine intravenous therapies, intravenous painkillers and other supportive treatments during active anticancer therapy may be provided within the same model of the "Home Care Project", thus delivering a simultaneous care model closer to patient's everyday life.

Therefore, to implement the best management in a home-care based setting, one should at least be able to: create a team; follow up periodically the patients by phone call and telemonitoring; encourage a close connection with the general practitioner; use PRO to assess symptoms and promptly take action against them.

Multidimensional Solutions: Think Out of the Box

New health management models require multidimensional solutions, exploiting the novel and enabling technologies that are present even outside the healthcare system. This includes, for instance, the introduction of "smart" healthcare services. eHealth approaches should be indeed integrated as a standard part with ubiquitous access to the diagnosis, treatment and care processes[58]. The multidimensional approach – focusing above all oncological subjects in the actual pandemic context – addresses the multiple possibility of: (1) remotely communicating and acquiring real-time information from the patients by means of mobile, wearable and environmental technologies; (2) collecting, safely transmitting and digitally managing patients records; (3) performing ad hoc analytics and providing user-defined systems for clinical decision support.

Telemedicine can allow patients and cancer team to communicate remotely with a high level of specialist support with the benefit to compliance with the requirement of this pandemic context, limiting patients and staff exposure to infections, as well. Telehealth visits allow a patient-centered health management, emphasizing a real-time self-monitoring of patients, immediate feedback of health data, and timely intervention of medical behavior. Wearable technologies allow enabling the continuous monitoring of physiological parameters, such as heart rate, blood pressure, blood oxygen saturation, electrocardiograph (ECG) and body temperature. Mobile technologies and actual smartphones collect information and transmit it to remote server for storage and analysis using also wearable devices.

The oncological treatment can benefit by improving monitoring of symptoms and toxicities, through the support of software applications and wearables. A digital platform composed of a web application, sensors and communication infrastructure increases the efficacy of a home-care therapy by integrating the action between the care team and the patient. The general objective of the web application is to support clinical and nursing workflows, both for the hospital oncologists and for the home-care team (oncologists and nurses) performing therapeutic and diagnostic tasks at the patient's home. Furthermore, telemedicine offers an active involvement of patients and caregivers into the oncological care process[59]. The remote care digital platform may address an active collaboration between patients and cancer-team promoting an innovative approach, even focusing on cancer patients management during the current COVID-19 context[51]. Within this network we can provide proper responses to both clinical (e.g., at home blood tests booking, on-line functional assessments, control of medications taking, real-time ECG monitoring, home clinical trial management, etc.), socio-clinical (e.g., automatic delivery of prescribed medications, contact with the general practitioner, etc.) and social (e.g., psychological support, company keeping and consolation providers, delivery of food, aids, etc.) needs, that characterize multifactorial pathologies, such as the oncological ones. "Virtual" nursing was reported to be indeed effective in improving health-related quality of life during rehabilitation phase[60] and the use of telepresence was reported to be feasible even in palliative home care, by enhancing feelings of security and safety among the patients[61]. Furthermore, the telehealth approach can well stress the possibility of education and engagement provided at a distance. In particular, the patient represents indeed the focus of the healthcare system, but he/she is not only a passive element; actually, the proposed approach aims to stress the capacity of the novel technologies to awaken awareness of his/her role in the process, providing motivation, participation and engagement. In this perspective, the "gamification" of specific assessment – including PROs – and/or rehabilitation strategies seem to be an optimal solution, even in oncological patients[62].

Finally, in a close future, the integration of "enhanced" multiparametric information will allow us to both define and support a possible tailored approach for each specific patient (i.e., "personalized medicine"), and to provide solution in a predictive and prospective fashion.

The Need to Prove Cost-Effectiveness

Expanding home-care program faces important challenges. One of this is the lack of evidence about cost-effectiveness of this model of care, apart from some specific programs[63]. The cost per year of life saved (adjusted for the quality of life) may be a useful indicator in this context since it allows to incorporate both the costs of care, the improvements in quality of life deriving from a more personalized care, and the increase in life expectancy derived from an increase in compliance and appropriateness[64]. Given the heterogeneity in patients' needs and characteristics, the analysis should be stratified by patients characteristics (age being one of the most important aspects, but also the presence of comorbidities may be a useful indicator)[65] and oncological care needed. This may allow to identify which patients will receive the maximum benefit from home care and should be prioritized in its use.

In this regard, in our center, a pilot study has just started, comparing home-care with traditional approach, in patients receiving oral, subcutaneous and intramuscular oncological therapies: the main objective is to conduct a cost-effectiveness analysis to assess costs and health-related effects (in term of Quality Adjusted Life Years) in both setting, comparing each other to estimate the possible advantage of the experimental approach.

Clinical Trials

Enrolment of patients within clinical trials has been greatly reduced or even stopped during the acute phase; however, the second phase will require innovative ways to proceed with clinical

research, so not to preclude the completion of ongoing studies and the design of new ones[66].

Suggestions about interventions for risk mitigation and for selection of which patient offer participation into clinical trials have been recently reported[67]. Guidance from national regulatory agencies for clinical trials during the SARS-COV-2 pandemic have been released. After this acute phase we will have to also reshape the way to propose clinical trials to patients. We should insert also the risks linked to SARS-COV-2 infection as superimposable factor which could impact on trial results and balance the possible benefit in participating to that clinical trial with the possible harms, considering also the risks with standard of care treatments. This requires a careful discussion with patient's associations and Ethical Committees, to receive inputs and to allow patient access to new drugs, without jeopardizing safety.

Follow Up in Cancer Patients

During the first phase of the Italian SARS-CoV-2 outbreak, hospitals represented one of the main carriers of infection, especially in highly endemic regions as Lombardy. Follow-up outpatient program has been re-scheduled to reduce access to hospitals and to preserve patients' health[7,8]. During the second phase of the mitigation of SARS-CoV-2 infection, efforts will be required to develop new surveillance programs for cancer patients, who completed oncological treatments. The traditional doctor-centred health management will be replaced by a patient-centred model. This approach will leverage on the creation of a network between oncologists, family doctors and patients. The implementation of telemedicine service will allow patients to easily access to health services, while physicians will dynamically manage patients' assessments.

Moreover, a remote follow-up using PROs tools may represent a strategy to assess patients' health as a part of usual outpatients' visit, thus optimizing the frequency of hospital consultations.

Consequences of Fear of Infection in Oncological Patients

Need to Triage Also the Psychological Impact on Patients

Fear and anxiety arise from the perception of danger, presumed or real[68,69] and can develop in various ways. We often fear what is unknown, which appears uncertain and obscure. We fear the dark and the unknown, which can happen with the threat of a pandemic[70].

Generally, we experience a state of anxiety or anguish when we lose our stable references, there is uncertainty about the future, we foresee a condition of forced solitude and isolation, when our lives or those of our loved ones are affected by a challenging chronic or disabling disease, which are already the prevailing fears of the elderly[71].

The most fragile among us, such as those who suffer from cancer, feel more exposed to events that can threaten their precarious state of health and sometimes also independence.

The recent and current pandemic situation caused by SARS-CoV-2 can generate a particular state of worry and anxiety[72], especially in cancer patients. During this serious pandemic, cancer patients are frightened to be unable to complete the necessary treatment, the planned therapies, the periodic checks already scheduled for their cancer.

The fear of contagion and the uncertainty of treatment lead to anxious "expectation"[69], which is added to and intensification of the anxiety linked to the same specific disease[73].

Every fear or anxiety needs to be heard with sensitivity, attentiveness and interest, individually or in a group, in order to offer greater understanding and support, including through the use of telematic supports[74]. In this very delicate period, cancer patients, perhaps more than others, require specific psychological intervention to be best reassured, accompanied, supported, particularly if they are alone, without an adequate family or social network.

In this second phase, we can better identify cancer patients who need psychological treatment by a screening including: a) a semi-structured interview by a specific questionnaire; b) appropriate scales of evaluation of anxiety and depression, for instance DASS-21 (Depression anxiety stress scale)[75].

Alertness for Possible Second Outbreak

In case of second outbreak, the greater awareness gained during the first phase will guide clinicians on how to deal cancer patients. Our multidimensional model would suggest how to manage cancer patients' needs, limiting their hospital exposure and personalizing their journey. The re-assessment of the public health services would become the "scaffold" to develop new models of care to warrant an adequate standard of care to cancer patients during a potential second outbreak.

Table I. Practical multidimensional solutions to approach cancer patients during post-acute SARS-CoV2 period.

Issues	Solutions
Early detection of SARS-COV-2 positive patients	Triaging patients before entering in Oncological Department Using surgical mask and hand washing Limiting the access of caregivers Upper respiratory tract swab, serological radiological exams before hospital admission
How to deal with SARS-COV-2 positive patients	Mild cases should be referred to community care, while severe cases should be referred to specific wards, within each hospital Patients suffering for life-limiting neoplastic illness and SARS-CoV2 infection should be referred to a supportive care program To strengthen the collaboration between oncologists and SARS-CoV-2 task force
How to optimize the management of cancer patients, to guarantee a continuum of care	Integration between hospital and territory Home care assistance creating a cancer team Follow up by phone call Close connection with general practitioner (GP) Use of PRO to assess symptoms and promptly take action against them Telemonitoring patients through web-app and wearable devices
How to deal with psychological impact of	Offering psychological supports to patients
How to deal with clinical trials cancer and SARS-Cov-2	Optimizing selection and telemonitoring of patients participating to clinical trials
How to deal with the follow-up in cancer patients	Close connection with general practitioner (GP)

Conclusions

Every crisis could be considered as a limit or as an opportunity to depict new ways to organize the work and improve the management of care we offer to our patients.

Thinking out of the box and involving different experts with a multidimensional view could allow a better management of oncological patients (Table I). We believe that the hospital-centered model should leave room for a patient-centered model, through a close interaction between hospital and territory.

The reshape of cancer care after the SARS-CoV-2 pandemic will be a priority for oncologists, embracing new models and opening new scenarios, so taken advantages of difficult periods. Nowadays, the message of the Chicago Mayor Raham Emanuel to Barack Obama could be read with a contemporary new meaning: "You never want a serious crisis to go to waste. And what I mean by that is an opportunity to do things that you think you could not do before".

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Authors' Contribution

FC, AB and PB designed the idea of the manuscript. All the Authors contributed to the writing and reviewed the final paper.

References

1) Schrag D, Hershman DL, Balsh E. Oncology practice during the COVID-19 pandemic. JAMA 2020. doi: 10.1001/jama.2020.6236 [Epub ahead of print 2020 Apr 13].
2) Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. Nat Rev Clin Oncol 2020; 17: 268-270.
3) Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and cancer: a comprehensive review. Curr Oncol Rep 2020; 22: 53.
4) Rischio Infettivo da Coronavirus COVID 19: Indicazioniper l'Oncologia del Presidente Eletto AIOM, del Presidente CIPOMO e del Presidente COMU. Available at: https://www.aiom.it/wp-content/uploads/2020/03/20200313_COVID- 19_indicazioni_AIOM-CIPOMO-COMU.pdf.

5) Chintalapudi N, Battineni G, Amenta F. COVID-19 virus outbreak forecasting of registered and recovered cases after sixty day lockdown in Italy: a data driven model approach. J Microbiol Immunol Infect 2020; 53: 396-403.

6) Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225-1228.

7) Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. Nat Cancer 2020, 1: 565-567.

8) van de Haar J, Hoes LR, Coles CE, Seamon K, Fröhling S, Jäger D, Valenza F, de Barud F, De Petris L, Bergh J, Ernberg I, Besse B, Barlesi F, Garralda E, Piris-Gimenez A, Baumann M, Apolone G, Soria JC, Tabernero J, Caldas C, Voest EE. Caring for patients with cancer in the COVID-19 era. Nat Med 2020; 26: 665-671.

9) Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA Niemeyer D, Jones TC, Vollmar P, Rothe C, Hoelscher M, Bleicker T, Brünink S, Schneider J, Ehmann R, Zwiglmaier K, Drosten C, Wendtner C. Virological assessment of hospitalized patients with COVID-2019. Nature 2020; 581: 465-469.

10) Zhou R, Li F, Chen F, Liu H, Zheng J, Lei C, Wu X. Viral dynamics in asymptomatic patients with COVID-19. Int J Infect Dis 2020; 96: 288: 290.

11) Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirglmaier K, Zange S, Wolfen R, Hoelscher M. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020; 382: 970-971.

12) Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19, 2020. Available at: https://www.idsociety.org/practice-guideline/covid.

13. Kokkinakis I, Selby K, Favrat B, Genton B, Cornuz J. Covid-19 diagnosis: clinical recommendations and performance of nasopharyngeal swab-PCR. Rev Med Suisse 2020; 16: 699-701.

14) Zitek T. The appropriate use of testing for COVID-19. West J Emerg Med 2020; 21: 470-472.

15) Lee TH, Lin RJ, Lin RTP, Barkham T, Rao P, Leo Y-S, Lye DC, Young B, National Centre for infectious disease Covid-19 outbreak research team. Testing for SARS-CoV-2: can we stop at two? Clin Infect Dis 2020. doi: 10.1093/cid/ciaa459. [Epub ahead of print 2020 Apr 19].

16) Infantino M, Grossi V, Lari B, Bambi R, Perri A, Manneschi M, Terenzi G, Liotti I, Ciotta G, Taddei C, Benucci M, Casprini P, Veneziani F, Fabbri S, Pompetti A, Manfredi M. Diagnostic accuracy of an automated chemiluminescent immunoassay for anti-SARS-CoV-2 IgM and IgG antibodies: an Italian experience. J Med Virol 2020. doi: 10.1002/jmv.25932. [Epub ahead of print 2020 Apr 24].

17) Stadlbauer D, Amanat F, Chromikova V, Jiang K, Strohmeier S, Arunkumar GA, Tan J, Bhavsar D, Capuano C, Kirkpatrick E, Meade P, Brito RN, Teo C, McMahon M, Simon V, Krammer F. SARS-CoV-2 seroconversion in humans: a detailed protocol for a serological assay, antigen production, and test setup. Curr Protoc Microbiol 2020; 57: e100.

18) Xiang F, Wang X, He X, Peng Z, Yang B, Zhang J, Zou Q, Hong Y, Ma Y, Hui L, Wei X, Cai P, Ma WL. Antibody detection and dynamic characteristics in patients with COVID-19. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa461. [Epub ahead of print 2020 Apr 19].

19) Zainol Rashid Z, Othman SN, Abdul Samat MN, Ali UK, Wong KK. Diagnostic performance of COVID-19 serology assays. Malays J Pathol 2020; 42: 13-21.

20) Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK Liao P, Qiu JF, Lin Y, Cai XF, Wang DQ, Hu Y, Ren XL, Tang N, Xu YY, Yu LH, Mo Z, Gong F, Zhang JL, Tian WG, Hu L, Zhang XX, Xiang JL, Du, HX, Liu HW, Lang CH, Luo XH, Wu SB, Cui XP, Zhou Z, Zhu MM, Wang J, Xue CJ, Li XF, Wang L, Li ZJ, Wang K, Niu CC, Yang QJ, Tang XJ, Zhang Y, Liu XH, Li JJ, Zhang DC, Zhang F, Liu P, Yuan J, Li Q, Hu JL, Chen J, Huang AL. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020; 26: 845-848.

21) Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, Sun R, Wang Y, Hu B, Chen W, Zhang Y, Wang J, Huang B, Lin Y, Yang J, Cai W, Wang X, Cheng J, Chen Z, Sun K, Pan W, Zhan Z, Chen L, Ye F. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020. doi: 10.1002/jmv.25727. [Epub ahead of print 2020 Apr 29].

22) Qu J, Wu C, Li X, Zhang G, Jiang Z, Li X, Zhu Q, Liu L. Profile of IgG and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. doi: 10.1093/cid/ciaa489. [Epub ahead of print 2020 Apr 27].

23) Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang Q, Xu S, Zhu H, Xu Y, Jin Q, Sharma L, Wang L, Wang J. Profiling early humoral response to diagnose novel Coronavirus disease (COVID-19). Clin Infect Dis 2020. doi: 10.1093/cid/ciaa310. [Epub ahead of print 2020 Mar 21].

24) Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Fu Y, Ge S, Liu L, Zhang J, Xia N, Zhang Z. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa344. [Epub ahead of print 2020 Mar 28].

25) Tung-Chen Y. Lung ultrasound in the monitoring of COVID-19 infection. Clin Med 2020; 20: e62-e65.

26) Zhao X, Liu B, Yu Y, Wang X, Du Y, Gu J, Wu X. The characteristics and clinical value of chest CT images of novel coronavirus pneumonia. Clin Radiol. 2020; 75: 335-340.

27) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course

and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.

28) Del Rio C, Malani PN. COVID-19 - new insights on a rapidly changing epidemic. JAMA 2020. doi: 10.1001/jama.2020.3072. [Epub ahead of print 2020 Feb 28].

29) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Chen Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.

30) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W , Li H, Liu M, Xiao Y, Gao H, Guo, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

31) Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481.

32) Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-1242.

33) Liang W, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335-337.

34) Ma J, Yin J, Quian Y, Wu Y. Clinical characteristics and prognosis in cancer patients with covid-19: a single center's retrospective study. J Infect 2020; 81: 318-356.

35) Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. Lancet Oncol 2020; 21: e180.

36) Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, Jia P, Guan HQ, Peng L, Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu, SY, Zhao JP, Zhou M. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31: 894-901.

37) Dai MY, Liu D, Liu M, Zhou FX, Li GL, Chen Z, Zhang Z, You H, Wu M, Zheng Q, Xiong Y, Xiong H, Wang C, Chen C, Xiong F, Zhang Y, Peng Y, Ge S, Zhen B, Yu T, Wang L, Wang H, Liu Y, Chen Y, Mei J, Gao X, Li Z, Gan L, He C, Li Z, Shi Y, Qi Y, Yang J, Tenen DG, Chai L, Mucci LA, Santillana M, Cai H. Patients with cancer appear more vulnerable to SARS-CoV-2: a multi-center study during the COVID-19 outbreak. Cancer Discov 2020; 10: 783-791.

38) Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA, Gartrell BA, Smith RV, Ohri N, Garg M, Racine AD, Kalnicki S, Perez-Soler R, Halmos B, Verma A. Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. Cancer Discov 2020; 10: 935-941.

39) WHO. Algorithm for COVID-19 triage and referral, 2020; (22 March): 1-6.

40) Chidiac C, Feuer D, Naismith J, Flatley M, Preston N. Emergency palliative care planning and support in a COVID-19 pandemic. J Palliat Med 2020; 23: 752-753.

41) ESMO. Cancer Patient Management During the COVID-19 Pandemic. Esmo Guideline. Available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic

42) ASCO. ASCO Coronavirus Resources. Available at: https://www.asco.org/asco-coronavirus-information

43) Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gali NK, Sun L, Duan Y, Cai J, Westerdahl D, Liu X, Xu K, Ho KF, Kan H, Fu Q, Lan K. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature 2020; 582: 557-560.

44) Jacobs JM, Pensak NA, Sporn NJ, MacDonals JJ, Lennes IT, Safren SA, Pirl WP, Temel JS, Greer JA. Treatment satisfaction and adherence to oral chemotherapy in patients with cancer. J Oncol Pract 2017; 13: e474-e485.

45) Paolella GA, Boyd AD, Wirth SM, Cuellar S, Venepalli NK, Crawford SY. Adherence to oral anticancer medications: evolving interprofessional roles and pharmacist workforce considerations. Pharmacy (Basel) 2018; 6: 23.

46) Bassan F, Peter F, Houbre B, Brennstuhl MJ, Costantini M, Speyer E, Tarquinio C. Adherence to oral antineoplastic agents by cancer patients: definition and literature review. Eur J Cancer Care 2014; 23: 22-35.

47) Fennimore LA, Ginex PK. Oral agents for cancer treatment: effective strategies to assess and enhance medication adherence. Nurs Clin North Am 2017; 52: 115-131.

48) Prip A, Pii KH, Møller KA, Nielsen DL, Thorne SE, Jarden M. Observations of the communication practices between nurses and patients in an oncology outpatient clinic. Eur J Oncol Nurs 2019; 40: 120-125.

49) Compaci G, Ysebaert L, Obéric L, Derumeaux H, Laurent G. Effectiveness of telephone support during chemotherapy in patients with diffuse large B cell lymphoma: the Ambulatory Medical Assistance (AMA) experience. Int J Nurs Stud 2011; 48: 926-932.

50) Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. N Engl J Med 2020; 382: 1679-1681.

51) Mei H, Dong X, Wang Y, Tang L, Hu Y. Managing patients with cancer during the COVID-19 pandemic: frontline experience from Wuhan. Lancet Oncol 2020; 21: 634-636.

52) Vetrugno L, Bove T, Orso D, Barbariol F, Bassi F, Boero E, Ferrari G, Kong R. Our Italian experience using lung ultrasound for identification, grading and

serial follow-up of severity of lung involvement for management of patients with COVID-19. Echocardiography 2020; 37: 625-627.

53) Chernack B, Knowlton SE, Kohler MJ. The use of ultrasound in palliative care and hospice. Am J Hosp Palliat Care 2017; 34: 385-391.

54) Dranitsaris G, Molassiotis A, Clemons M, Roeland E, Schwartzberg L, Dielenseger P, Jordan K, Young A, Aapro M. The development of a prediction tool to identify cancer patients at high risk for chemotherapy induced nausea and vomiting. Ann Oncol 2017; 28: 1260-1267.

55) Rolston KV. Infections in cancer patients with solid tumors: a review. Infect Dis Ther 2017; 6: 69-83.

56) Bowen JM, Gibson RJ, Coller JK, Blijlevens N, Bossi P, Al-Dasooqi N, Bateman EH, Chiang K, de Mooij C, Mayo B, Stringer AM, Tissing W, Wardill HR, van Sebille YZA, Ranna V, Vaddi A, Keefe DM, Lalla RV, Cheng KKF, Elad S, (MASCC/ISOO). Systematic review of agents for the management of cancer treatment-related gastrointestinal mucositis and clinical practice guidelines. Support Care Cancer 2019; 27: 4011-4022.

57) Licqurish SM, Cook OY, Pattuwage LP, Saunders C, Jefford M, Koczwara B, Johnson CE, Emery JD. Tools to facilitate communication during physician-patient consultations in cancer care: an overview of systematic reviews. CA Cancer J Clin 2019; 69: 497-520.

58) Penedo FJ, Oswald LB, Kronenfeld JP, Garcia SF, Cella D, Yanez B. The increasing value of eHealth in the delivery of patient-centred cancer care. Lancet Oncol 2020; 21: e240-e251.

59) Liao Y, Thompson C, Peterson S, Mandrola J, Beg MS. The future of wearable technologies and remote monitoring in health care. Am Soc Clin Oncol Educ Book 2019; 39: 115-121.

60) Zhou K, Wang W, Zhao W, Li L, Zhang M, Guo P, Can Z, Li M, An J, Li J, Li X. Benefits of a WeChat-based multimodal nursing program on early rehabilitation in postoperative women with breast cancer: a clinical randomized controlled trial. Int J Nurs Stud 2020; 106: 103565.

61) Steindal SA, Nes AAG, Godskesen T, Dihle A, Lind S, Winger A, Klarare A. Patients' experiences of telehealth in palliative home care: a scoping review. J Med Internet Res 2020; 22: e16218.

62) Navarro-Alamán J, Lacuesta R, Garcia-Magariño I, Gallardo J. A methodology for the design and development of gamified mobile apps for monitoring cancer survivors. J Biomed Inform 2020; 106: 103439.

63) Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev 2013; 6: CD007760.

64) Tan-Torres TE, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, Murray CJL. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization. WHO, 2003.

65) Coyle D, Buxton MJ, O'Brien BJ. Stratified cost-effectiveness analysis: a framework for establishing efficient limited use criteria. Heal Econ 2003; 12: 421-427.

66) Borno HT, Small EJ. Does the COVID-19 outbreak identify a broader need for an urgent transformation of cancer clinical trials research? Contemp Clin Trials 2020; 92: 105997.

67) de Paula BHR, Araújo I, Bandeira L, Barreto NMPB, Doherty GJ. Recommendations from national regulatory agencies for ongoing cancer trials during the COVID-19 pandemic. Lancet Oncol 2020; 21: 624-627.

68) Freud S. Vorlesungen zur Einführung in die Psychoanalyse (Lektion 25). S. Fischer Verlag, Frankfurt am Main. 1915-17.

69) Freud S. Jenseits des Lustprinzips. Internationaler Psychoanalytischer Verlag. Leipzig, Wien, Zürich. 1920.

70) Taylor S. The psychology of pandemics: preparing for the next global outbreak of infectious disease. Newcastle upon Tyne: Cambridge Scholars Publishing, 2019.

71) Cristini C. Elderly women and their fears: a pilot investigation, Eur Geriatr Med 2018; 9 (suppl 1): S129.

72) Horesh D, Brown AD. Traumatic stress in the age of Covid-19: a call to close crtitical gaps and adapt to new realities. Psychol Trauma 2020; 12: 331-335.

73) Markfelder T, Pauli P. Fear of pain and pain intensity: meta-analysis and systematic review. Psychol Bull 2020; 146: 411-450.

74) Bao Y, Sun Y, Meng S, Shi J, Lu L. 2019-nCoV epidemic: address mental health care to empower society. Lancet 2020; 395: e37-e38.

75) Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995; 33: 335-343.