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Breast Cancer

Personalized Risk–Benefit Ratio Adaptation of Breast Cancer Care at the Epicenter of COVID-19 Outbreak

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Abstract

Northern Italy has been one of the European regions reporting the highest number of COVID-19 cases and deaths. The pandemic spread has challenged the National Health System, requiring reallocation of most of the available health care resources to treat COVID-19-positive patients, generating a competition with other health care needs, including cancer. Patients with cancer are at higher risk of developing critical illness after COVID-19 infection. Thus, mitigation strategies should be adopted to reduce the likelihood of infection in all patients with cancer. At the same time, suboptimal care and treatments may result in worse cancer-related outcome. In this article, we attempt to estimate the individual risk–benefit balance to define personalized strategies for optimal breast cancer management, avoiding as much as possible a general untailored approach. We discuss and report the strategies our Breast Unit adopted from the beginning of the COVID-19 outbreak to ensure the continuum of the best possible cancer care for our patients while mitigating the risk of infection, despite limited health care resources. ***The Oncologist*** 2020;25:e1013–e1020

Implications for Practice: Managing patients with breast cancer during the COVID-19 outbreak is challenging. The present work highlights the need to estimate the individual patient risk of infection, which depends on both epidemiological considerations and individual clinical characteristics. The management of patients with breast cancer should be adapted and personalized according to the balance between COVID-19-related risk and the expected benefit of treatments. This work also provides useful suggestions on the modality of patient triage, the conduct of clinical trials, the management of an oncologic team, and the approach to patients' and health workers' psychological distress.

Introduction

Italy was the first European country severely affected by the COVID-19 outbreak, and within the country, Lombardy reported the highest number of new cases and deaths. Lombardy has 10,088,484 inhabitants, with a reported number of 109,465 COVID-19 confirmed positive cases (incidence 1.085%) and 13,269 deaths, accounting for about one third of the total cases in Italy and half of the deaths as of April 27, 2020 [1]. Beyond the uncountable economic impact and unprecedented personal restrictions, the pandemic spread of COVID-19 resulted in a dramatic challenge for the National Health System (NHS). Indeed, NHS had to suddenly reallocate most of the available health care resources to treat COVID-19-positive patients, generating an unexpected and undue competition with other health care needs, including those of patients with cancer. The special population of patients with cancer is at higher risk of dismal outcome from COVID-19 infection owing to fragility, comorbidities, and treatment-induced immunosuppression; moreover, it is also at higher risk of infection

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because of the frequent hospital accesses for clinical evaluation, exams, and treatment administration. At the same time, the reduced health care resources, the possible adjustment of treatment schedule and administration, the difficulties in planning treatment strategies, and the restrictions in movements and accesses to the hospital may result in cancer-related short- and long-term dismal outcomes. In this context, mitigation of the risk of COVID-19 infection among oncologic patients represents an important challenge. Thus, the oncology community has to quickly react and reorganize, facing these new issues: the balance between treatments and potential COVID-19 exposure, the mitigation of possible care disruptions, and the allocation of limited health care resources.

Here, we discuss and report the strategies timely adopted by our Breast Unit at the San Raffaele Hospital in Milan, starting from the beginning of the COVID-19 outbreak, to ensure the continuum of the best possible cancer care for our patients while mitigating the risk of infection.

Estimate of the Risk of Infection

Although some general recommendations on the management of patients with cancer during the COVID-19 outbreak already exist, further efforts should be made to precisely estimate the actual risk of COVID-19 infection and the possible related health consequences. This quantitative risk estimate has to be considered as every other competitive risk in the decision-making process, as oncologists are already used to doing for comorbidities. The risk of infection depends on a combination of general and individual factors.

First, the general risk may vary according to the epidemiological phase of the pandemic in relation to the geographic location of the hospital as well as the area where patients live.

Moreover, the risk of infection depends on factors related to the capability of the institution to establish specific interventions to mitigate this risk, such as the realization of separated and independent accesses and paths for COVID-19-positive and -negative patients, the environment sanitation, and the optimal use of personal protective equipment (PPE) by both health care providers and patients.

Individual factors are patient related and include the observance of optimal social distancing outside the hospital, the possible cohabitation with individuals at higher risk of infection, the need of using public transportation, the number and duration of planned accesses to the hospital, and the type of possible invasive procedures.

The individual risk of developing severe and life-threatening consequences from COVID-19 infection seems overall increased in patients with cancer [2], probably owing to the disease-related comorbidity and immunosuppressive treatments. Age is the most relevant risk factor, followed by comorbidities such as hypertension, cardiovascular disorders, hypercholesterolemia, and diabetes [3]. Moreover, it should be considered that women have a significantly lower risk of developing a critical illness from the infection compared with men [3], and this observation has obvious implications for patients with breast cancer. For explicative purposes, Table 1 proposes a possible evaluation to estimate the individual risk of developing a potential critical illness from COVID-19 infection, taking into account general and individual factors. This is an empiric, nonquantifiable risk stratification, based on epidemiologic data and on a large cohort of cases admitted in intensive care units in Lombardy [3, 4]. Although arbitrary, it represents our attempt to provide a pragmatic and operative definition of the risk.

In summary, we believe that a precise and individualized estimate of the risk of infection, which should be continuously revised over time with the epidemiologic evolution, is the critical preliminary step before selecting strategies for breast cancer management. During the spread of the COVID-19 outbreak, the emotional impact generated by both the overall number of disease-related deaths and the effects of social restrictions may lead to an overestimation of the individual risks with potential serious consequences on the outcomes of patients with cancer.

Indeed, despite the fact that COVID-19 is an unquestionable serious threat on the public health scale, cancer still remains one of the first causes of death in high-income countries [5]. Arbitrarily postponing and modifying treatment strategies including surgery, radiation therapy, and medical therapy without properly balancing the risk–benefit ratio may lead to significantly worse outcomes than keeping the best standard practice during the pandemic spread, which may largely outweigh the increased risk of infection [6, 7].

Mitigation of the Risk of Infection

One of the key interventions needed to maximize the benefit–risk balance for each individual patient is to implement all the measures needed to minimize the risk of infection. The insidious onset of the infection, which may present with a long incubation period without any obvious clinical symptoms and even remain asymptomatic or with mild symptoms for its entire course, favors the diffusion of the infection because of the contagiousness of these patients [8]. The approach adopted in some countries, including Italy, of performing COVID-19 testing only for symptomatic patients or health care workers contributes to making hospitals places at higher risk of COVID-19 transmission.

Reduce Hospital Visits and Use Telemedicine

During the COVID-19 outbreak, all countries adopted strategies of social distancing and individual restrictions as the major interventions to reduce the spread of infection. Accordingly, staying home is also the safest precaution for patients with cancer. We immediately decided to limit outpatient visits to those strictly necessary for acute oncological issues and for patients with ongoing active treatments who need physical examination and clinical evaluation. For patients on oral treatment, provided recent blood tests are available, drugs may be collected in the hospital by a relative or delivered home and supplied for longer period (2–3 cycles). Patients are managed remotely by telemedicine consultation or by phone/e-mail to evaluate possible side effects and review lab tests. Patients may in turn notify the health care team of any new or concerning issue by telephone or e-mail.

Whenever possible, routine follow-up visits have been converted to telemedicine or, alternatively, postponed. We review blood tests and radiological scans and inquire about possible symptoms of recurrence and side effects of adjuvant treatments; we also provide follow-up indications and plan subsequent visits. Because locoregional recurrences

Table 1. Factors contributing to an individualized estimate of the risk of COVID-19 infection

	Risk of developing a serious illness		
Risk of infection[a]	**Age, years**	**Comorbitities[b]**	**Individual risk estimate[c]**
Low	<45	No	Low
		Yes	Low
	45–70	No	Low
		Yes	Intermediate
	>70	No	Low/Intermediate
		Yes	Intermediate/High
Moderate	<45	No	Low
		Yes	Intermediate
	45–70	No	Intermediate
		Yes	Intermediate/High
	>70	No	High
		Yes	High
High	<45	No	Intermediate
		Yes	High
	45–70	No	Intermediate/High
		Yes	High
	>70	No	High
		Yes	High

The table represents our empiric and pragmatic attempt for risk stratification based on epidemiological data.
[a]The risk of infection takes into account the epidemiological situation in the geographic area where the hospital is located and where the patient lives, personal risk of exposure related to different factors such as the use of public transportation, optimal social distancing outside the hospital, and possible cohabitation with an individual at higher risk. Moreover, mitigation procedures adopted in the hospitals should be considered.
[b]For the purpose of estimating the risk of patients with cancer, a diagnosis of early breast cancer or very low burden metastatic disease is not considered a comorbidity. Ongoing cancer treatments potentially inducing a severe immunosuppression are considered risk factors of developing a critical illness in case of COVID-19 infection.
[c]For some categories, we suggest considering additional factors for a more precise risk estimate.

are most likely curable if promptly diagnosed, we always recommend a physical examination as soon as the epidemiologic situation allows it, especially when mammography and breast ultrasound have not been performed recently. Despite the fact that physician–patient interactions may be challenging when managed remotely, the vast majority of patients appreciate the possibility of obtaining medical aid while minimizing hospital accesses and physical contacts. A new digital platform—currently in use—is being implemented in our institute for telemedicine, with possible benefits that may continue beyond the pandemic, allowing a wider use of telemedicine in clinical practice. For patients who need to come to the hospital, the accompanying family member has been limited to one person only, and unless strictly necessary because of patient limitations, relatives are allowed to stay in the waiting room only.

Delay of Medical Tests and Procedures

Many procedures and medical tests have been postponed. Routine screening for breast cancer has been deferred until the COVID-19 pandemic resolves. Breast ultrasound, mammography, and magnetic resonance imaging have been reserved for those people with abnormal clinical findings or highly suspicious symptoms/signs of recurrence. Disease assessment for advanced disease may be delayed and done at longer intervals if the patient is clinically stable or with radiologic disease response at the previous imaging evaluation. Cardiologic assessment is performed only for patients on treatment or for those who are about to start a new potentially cardiotoxic treatment. If baseline cardiologic evaluation must be delayed, postponing cardiotoxic agents (i.e., starting with taxane and postponing anthracyclines in the adjuvant setting) may be considered. Routine cardiologic assessment during human epidermal growth receptor 2 (HER2)-targeted treatment in clinically stable and asymptomatic patients may be delayed. Positioning of implantable vascular access for chemotherapy infusion is avoided or delayed whenever possible; in patients having a port-a-cath, flush can be performed every 12 weeks. Similarly, only necessary biopsies are performed, as in the case of a new diagnosis. Biopsies performed for redetermination of the biologic characteristics of the tumor or for research purposes are omitted or delayed in cases of moderate or high risk of infection.

Patient Triage, Dedicated Path, and Use of PPE

All patients and accompanying persons are screened the day before coming to the hospital through a telephonic triage with a checklist including investigation of suspicious clinical symptoms or strict contact during the previous 3 weeks with people having any symptoms of infection (having or not a diagnosis of COVID-19 disease). If the screening is negative, patients are requested to check their temperature at home before coming to the hospital and to access the hospital wearing a surgical mask and, if possible, gloves. If the screening is positive, an

immediate test for COVID-19 or quarantine is indicated, as needed. When deemed clinically indicated, patients on active ongoing treatment may have a nasopharyngeal swab at the hospital the day before oncologic evaluation/therapy administration. The nasopharyngeal swab is performed in a designed area by a dedicated staff in full PPE. Patients having fever, dyspnea, or respiratory symptoms highly suspicious for COVID-19 infection are required to stay home and contact the designated number for seeking appropriate medical support.

We arrange appointments and visits in order to minimize patients' stay in the waiting room as well as contact among patients. For the few patients accessing the oncology department without an appointment, a triage is performed by an adequately trained nurse in a separated room to evaluate the possible presence of suspicious symptoms. All paths in the hospital for COVID-19-negative patients are completely separated from those for COVID-19-positive ones.

For inpatients, no visitors are allowed. Patients stay in single rooms in order to limit possible interpatient infection transmission. Moreover, all patients are screened for COVID-19 infection with a nasopharyngeal swab before admission in the ward in the attempt to maintain the oncology department COVID-19-free. Should patients develop even mild symptoms while hospitalized, they undergo a new nasopharyngeal swab. In cases of confirmed COVID-19 infection, patients are immediately transferred to a specific dedicated division.

Personalizing Breast Cancer Management According to Individual Risk Estimate

General Considerations

Recommendations on the management of patients with cancer during the pandemic outbreak have been proposed by medical societies and relevant institutions [9–12]. In Northern Italy, the first case of COVID-19 infection was reported at the end of February, followed by the rapid spread of the disease, prior to its worldwide diffusion and the subsequent release of such recommendations. Here, we report our current institutional guidelines, which have been progressively implemented over time, taking into account our own direct experience along with expertise from other Italian centers. From the very beginning, we emphasized the need to avoid an overestimation of the risk of COVID-19 infection and the key role of adapting treatment recommendations according to the individual risk estimate (Table 1). We acknowledge that the strategies and measures taken in each hospital and clinic may depend on the individual organization, the institution's resources, and the epidemiologic situation. Our institution is a general hospital and a research institute, taking care of about 1.5 million patients yearly and performing 30,000 surgical procedures per year. During the COVID-19 pandemic, many departments have been converted into COVID-19 wards and most of the intensive care capability dedicated to COVID-19 patients. During this period, surgeries have been limited to urgent procedures, and regular nonurgent outpatients have been deferred or managed in other hospitals (see below, Hub and Spoke system).

Adapting Treatment Administration

For patients with ongoing treatment, the decision of maintaining the correct schedule of administration or, conversely, of modifying the schedule and route of administration was taken evaluating the individual risk estimate and the expected benefit of maintaining the standard therapy (Table 2). For instance, the benefit expected from a (neo) adjuvant treatment with curative intent in a high-risk patient with early breast cancer almost certainly outweighs the risk of infection, with the possible exception of frail patients with a high individual risk. However, for selected patients on (neo)adjuvant treatment, the shift to three-weekly administration instead of the weekly administration may be considered. Instead, a treatment in the advanced setting in a clinically stable patient may be adapted even in cases of moderate risk. When a new treatment has to be started, the choice of the regimen among those of comparable efficacy is based on the possibility of minimizing the risk of infection. Oral therapies should be preferred whenever possible, as they are manageable with a reduced number of accesses to the hospital. Indeed, we provide patients with drug supply for two or three cycles, assessing by teleconsultation clinical condition, laboratory exams, and tolerability. For frail patients or those with logistic restrictions, we offer the possibility of drug home delivery or collection by a relative from the hospital.

In cases of serious logistic problems as a result of the shutdown of public transportation, we suggested patients with ongoing infusional therapies to engage the hospital nearest home.

At our hospital, we are continuing to administer chemotherapies, biological treatments, targeted agents, and immunotherapies, as there is no definitive evidence demonstrating that risks outweigh benefits. However, some concerns exist on the possible increased risk due to chemotherapy-induced neutropenia. To minimize this risk, we are discussing case by case the prescription of prophylactic granulocyte colony-stimulating factors for patients on chemotherapy regimens, even if not recommended by current guidelines. No definitive evidence exists on the putative correlation between immunotherapy administration and dismal outcome in cases of infection. The use of dexamethasone should be limited to avoid immunosuppression.

Managing Surgery

Restrictions to breast cancer surgery during the outbreak are mainly due to the reduction of the institution's resources (intensive care, anesthesiologists, and operating rooms) and—to a lesser extent—are decided in order to reduce the risk of infection during the hospitalization in centers with a high number of COVID-19-positive patients as well as to avoid the risk of postsurgery complications and visits. However, delayed oncologic surgery might lead to disease progression and compromise tumor resectability, possibly resulting in worse survival outcomes [13, 14]. Decision on priority for surgery is mainly based on clinical factors including patient condition, putative aggressiveness of

Table 2. Managing cancer treatment administration and visit schedule according to individual risk estimate (as described in Table 1)

Treatments/visits	Individual risk estimate		
	Low	Medium	High
Low priority			
Bisphosphonates/denosumab (unless urgently needed for hypercalcemia)	Delay	Delay	Delay
Dual anti-HER2 blockade maintenance therapy for HER2+ mBC beyond 2 years and optimal remission	As standard practice (consider delay)	Delay	Delay
Follow-up visit (without concern for recurrence)	Delay (telemedicine)	Delay (telemedicine)	Delay (telemedicine)
Visit of patients with mBC on ET alone for >6 months (without concern for progression)	In-person visit (case by case)	Delay (telemedicine)	Delay (telemedicine)
Intermediate priority			
Follow-up visit (with concern for recurrence)	As standard practice	As standard practice	Delay
Start postsurgical adjuvant CT in intermediate-risk patients	As standard practice	Delay 1–2 months	Delay 2–3 months
Duration of adjuvant trastuzumab in low-risk HER2+ patients	As standard practice	As standard practice	Consider shortening to 6 months
Addition of CDK4/6, mTOR, or PIK3CA inhibitors to ET	As standard practice	Consider delay or telemedicine	Consider delay or telemedicine
Reschedule timing of CDK4/6, mTOR, or PIK3CA inhibitors administration for stable/responding patients with mBC	As standard practice or telemedicine	Personalized delay	Delay
Start CT (± HER2-targeted agents) for clinically stable patients with mBC with low tumor burden	As standard practice	Personalized delay	Personalized delay
Reschedule timing of CT administration in patients with mBC with clinically and radiologically stable disease	As standard practice	Consider adjustments	Adjustments recommended
High priority			
Neo/adjuvant CT for TN, HER2+ and high-risk ER+/HER2− disease (consider prophylactic G-CSF to reduce neutropenia)[a]	As standard practice	As standard practice	Only minimal delay allowed
Follow-up visit (in case of high suspicion of recurrence or moderate/severe symptoms)	As standard practice	As standard practice	Only minimal delay allowed
Management of serious treatment AE (e.g., neutropenic fever, stomatitis, bleeding)	As standard practice	As standard practice	As standard practice
Patients with visceral crisis and symptomatic progression	As standard practice	As standard practice	As standard practice (minimal delay)

[a]In cases of new diagnosis of luminal-B breast cancer at high risk of recurrence and the impossibility of starting a neoadjuvant chemotherapy or performing surgery, neoadjuvant endocrine therapy could be considered, with careful monitoring. Chemotherapy and surgery will be administered later on.

Abbreviations: AE, adverse event; G-CSF, granulocyte colony-stimulating factor; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth receptor 2; mBC, metastatic breast cancer; TN, triple negative.

the disease, and available therapeutic options (Table 3). In all cases, excision of benign lesions and prophylactic surgery are postponed. In most of the cases, surgery for ductal carcinoma in situ is postponed, and administration of endocrine therapy for hormone receptor-positive (HR+) cases could be considered if a long delay is expected [15, 16]. Re-excision surgery for positive margins could be postponed at the end of adjuvant chemotherapy or delayed (endocrine therapy should be started if indicated). Patients with low- or intermediate-risk HR+/HER2-negative breast cancer, who are not candidates for chemotherapy, could be offered primary endocrine treatment, regardless of menopausal status, allowing surgery deferral for 8–12 weeks. Patients finishing neoadjuvant treatment should undergo surgery

Table 3. Prioritization of breast surgical procedures to optimize limited health care resources during COVID-19 infection spread

Degree of surgery priority	Clinical conditions
High priority (surgery within 4 weeks)	Progression under PST
	TN or HER2+ breast cancer without response after PST (unless low tumor burden)
	Breast cancer with high-risk features (N+, symptomatic disease) or locally advanced tumors not eligible for PST
	Postsurgical complications (revision of ischemic mastectomy flap, periprosthetic infection)
	Isolated locoregional recurrence (unless eligible for systemic treatment)
Intermediate priority (surgery within 8 weeks)	TN disease with response after PST (ideally no more than 6 weeks)
	HER2+ disease with response after PST (continuing HER2 targeted agents ± ET)
	TN or HER2+ breast cancer not candidate for PST without high-risk features
	ER+/HER2− breast cancer with high-risk features (case by case)
	Patients with isolated locoregional recurrence without high-risk biological features
Low priority (surgery after 8 weeks allowed)	DCIS (however, high-risk features like high grade, ER negativity, or very extensive disease might fall into the intermediate priority category based on a case-by-case decision)
	ER+/HER2− breast cancer when primary endocrine therapy could be considered
	ER+ patients after PST with ongoing "bridge" ET
Very low priority	Benign breast lesions
	Reconstructive and prophylactic surgery

Abbreviations: DCIS, ductal carcinoma in situ; ET, endocrine therapy; ER, estrogen receptor; HER2, human epidermal growth receptor 2; N+, node positive; PST, primary systemic therapy; TN, triple negative.

within the correct timeframe, especially patients with HER2+ and triple-negative breast cancer; however, if no surgical capacity is available, some delay may be considered acceptable in a few selected cases (i.e., patients achieving a clinical complete response or patients with partial response who can continue HER2-targeted agents). In HR+ disease, an endocrine treatment could be given (continuing HER2 targeted agents in HR+/HER2+ disease) allowing a slightly longer delay of surgery [17].

To guarantee the fair allocation of medical resources in response to the growing demand during the emergency, the health care system in Lombardy has adopted the "hub-and-spoke" hospital model. The regional government has established a network consisting of a main (hub) institution and one or more satellite (spoke) institutions for each specific service. According to this model, patients requiring undeferrable procedures are referred to the reference hospitals. Hub hospitals have realized separated and independent accesses and paths for COVID-19-positive and -negative patients; the provision of their services is also guaranteed through collaboration with medical teams from other institutions.

The resources available for breast surgery at our hospital have been defined by our institutional Crisis Unit, which continuously monitors the health care resources needed to manage COVID-19-positive patients and those left for the other clinical activities including breast cancer surgery. Starting from the beginning of the COVID-19 outbreak in Italy, with the first case reported on February 21, regular surgical activity was carried out until the end of February. Since the beginning of March, as the number of infections increased, demanding more health care resources (especially intensive care units), the surgical activity was reduced, starting from very low priority procedures (with the interruption of all the benign lesions excisions and reconstructive and prophylactic surgery). Since April 1, our surgical team has carried out all the surgical procedures at the European Institute of Oncology, the “oncological hub” hospital; thus, more careful patient selection and prioritization of surgical procedures has been necessary.

Although the definition of the priority for surgery may be informed by some general rules summarized in Table 3, the multidisciplinary approach is more important than ever to guarantee the best possible care for patients with cancer, providing personalized recommendations on the individual estimate risk and identifying the best treatment strategies even in the context of reduced health care resources. For this reason, despite the efforts to generate guidelines and recommendations, given the enormous number of variables that should be considered and the lack of evidence-based indication, we believe that every decision is mostly based on expert opinions in the multidisciplinary board.

Managing Radiation Therapy

Radiation therapies, including breast radiotherapy, require repeated accesses to the hospital and multiple contacts between patients and staff; moreover, the equipment may often be difficult to clean or sanitize, and this increases the risk of exposure for both patients and staff. It is therefore advisable to limit patients’ access to the radiation therapy department if not strictly necessary; thus, follow-up visits have been postponed or replaced with telematic consultations. Telephonic triage before admission to the hospital is also performed for patients who are candidates for radiotherapy.

As for surgery, prioritizing specific treatments and postponing nonessential procedures is crucial for the proper management of patients with breast cancer requiring radiation therapy. Many adjuvant radiation therapies may be delayed taking into account the risk of recurrence, expected benefit, and individual risk estimate, similarly to medical treatments.

Use of palliative medical treatments instead of radiation therapy is preferred, when expected to be of similar efficacy. Whenever possible, adoption of hypofractionated regimens should be considered to reduce the duration and the number of accesses to the radiotherapy department.

Managing the Medical Team During the Pandemic

We have cancelled the weekly multidisciplinary board of the Breast Unit, as well as all the other planned meetings, and moved them online to ensure staff safety without stopping research and educational activities. The administrative staff was recommended to operate in smart working modality whenever possible; the same was applied to physics in the radiation therapy department. In addition, our breast oncology team has been split into two groups to reduce the risk of cross infection and the consequences of a possible quarantine. The medical team wears appropriate PPE for the whole working day. According to the National Health System guidelines, the nasopharyngeal swab is not routinely offered to asymptomatic physicians.

To ensure the safety of patients with cancer and avoid cross infections, the breast oncology team has not been engaged for the treatment of COVID-19-positive patients.

Other Challenges During COVID-19 Spread

Managing Psychological Distress

An epidemic outbreak may have negative effects at both the individual and society level owing to a wide range of psychosocial distress. COVID-19 is the first serious threat to the worldwide population after the Spanish flu in 1918, which has not been experienced by this generation. The pandemic threat, the isolation resulting from the measures of social distancing, and the concern about the consequences of an unprecedented stop in economic activities are triggering emotional reactions such as anxiety, depression, pessimism, and panic.

Patients with cancer are at higher risk of psychological distress. Their perception of being weaker and more fragile increases the fear of falling sick and eventually dying in case of COVID-19 infection. Patients with cancer are also worried that the immunosuppression and side effects of their treatments might increase the likelihood of serious consequences in case of infection. Also, patients may be frightened to go to the hospital, as this may increase the likelihood of being infected. Conversely, patients with cancer might be afraid that modifications of their original treatment plan (delays, omissions, changes) would result in a suboptimal treatment, which could eventually compromise their outcome.

Not only patients but also health care workers are at higher risk of developing psychological distress [18].

In response to the psychological disorders of both patients and health care workers, our institution is providing psychological counselling services by remote consultation for all people who may need/wish it.

Clinical Trials

The effects of COVID-19 are not limited to the delivery of standard treatment to patients with cancer—they also have serious impact on the conduct of clinical trials. We recognize that the main goal when treating patients with breast cancer during the COVID-19 outbreak is continuing to offer the best available treatment options balancing individual risks and benefits. Enrolling patients in clinical trials is a way to allow early access to promising investigational treatments; hence, it should be guaranteed. However, during the COVID-19 pandemic, many challenges in the conduct of clinical trials may arise. Some challenges are related to patients (e.g., infection, self-isolation, quarantine, and travel limitations), some others are related to the infrastructures (e.g., interruptions in the supply chain for the investigational product or kits with delay in central lab service), and some others are related to the institutional resources (e.g., reduction of the personnel, delay in filling electronic case report forms, impossibility to organize remote site visits). These challenges may seriously affect the proper conduct of studies including adhering to protocol mandatory procedures, visits, and laboratory/diagnostic testing as well as the external monitoring of the study safety. Despite all these limitations, it is critical to adopt all adjustments and countermeasures to ensure that patients keep receiving the experimental treatment in the safest way, while maintaining the scientific integrity of the trial.

Regarding the management of clinical trials during the COVID-19 emergency in Italy, the Italian Medicines Agency (AIFA) provided general indications on the management of patients enrolled in clinical trials to minimize their risk of infection while maintaining trial integrity [19]. AIFA has invited trial sponsors to draw up a risk evaluation plan and to implement measures to minimize patients' risk while maintaining them on treatment. Given the emergency situation, in agreement with the European Good Clinical Practice Inspectors Working Group [20], AIFA has considered it acceptable to carry out some clinical trial procedures in a center nearest home, to dispense a larger supply of experimental treatment, to home-deliver such treatments, to use telephone and/or video calls to inform patients, and to delay some clinical evaluations planned per protocol. These strategies should be applied according to the individual center resources and organization. Sponsors provided specific indications for each protocol.

Research and Education

During the present phase of the COVID-19 outbreak, all the preclinical and translational research activities have been largely interrupted or delayed. The overall impact of such limitations on research will depend on the duration of this emergency. In the short term, there is also a serious risk to face a reduced availability of economic resources devoted to cancer research from charities and government due to the economic crisis and competitive demands of resources. The university has quickly moved all lessons to a remote mode.

Upcoming Scenarios

At the moment, the ultimate course of COVID-19 spread is still uncertain. Hopefully, the stringent measures of social distancing adopted in all developed countries will lower the number of new daily diagnosed cases of infection to none or few. However, without an efficacious vaccine, the risk of

a new outbreak of COVID-19 infection will remain consistently high, thus requiring maintaining risk-reducing precautions for a long period. This means that, even in the best desirable scenario of having only a low level of local circulation of the virus corresponding to an individual low risk of infection, many of the measures currently adopted should be maintained. For instance, careful triage of patients before being admitted to the oncology department should be continued. In addition, an increase and optimized use of telemedicine resources should be adopted not only to reduce unnecessary accesses to the hospitals during the COVID-19 epidemic but also as an occasion to rethink the way to provide a more convenient, efficient, and effective health care service for patients with cancer.

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Disclosures

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