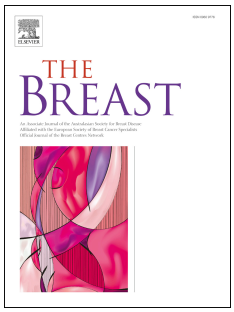
Journal Pre-proof



Recommendations for Triage, Prioritization and Treatment of Breast Cancer Patients During the COVID-19 Pandemic

Giuseppe Curigliano, Maria Joao Cardoso, Philip Poortmans, Oreste Gentilini, Gabriella Pravettoni, Ketti Mazzocco, Nehmat Houssami, Olivia Pagani, Elzbieta Senkus, Fatima Cardoso, editorial board of The Breast

PII: S0960-9776(20)30093-X

DOI: https://doi.org/10.1016/j.breast.2020.04.006

Reference: YBRST 3034

To appear in: *The Breast*

Received Date: 6 April 2020

Revised Date: 9 April 2020

Accepted Date: 9 April 2020

Please cite this article as: Curigliano G, Cardoso MJ, Poortmans P, Gentilini O, Pravettoni G, Mazzocco K, Houssami N, Pagani O, Senkus E, Cardoso F, editorial board of The Breast, Recommendations for Triage, Prioritization and Treatment of Breast Cancer Patients During the COVID-19 Pandemic, *The Breast*, https://doi.org/10.1016/j.breast.2020.04.006.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 The Author(s). Published by Elsevier Ltd.

Journal Pre-proof

Recommendations for Triage, Prioritization and Treatment of Breast Cancer Patients During the COVID-19 Pandemic

Giuseppe Curigliano [1,2*§], Maria Joao Cardoso [3,4], Philip Poortmans[5], Oreste Gentilini [6], Gabriella Pravettoni [1,2], Ketti Mazzocco[1,2], Nehmat Houssami [7], Olivia Pagani [8], Elzbieta Senkus [9] and Fatima Cardoso[3], on behalf of the editorial board of The Breast.

[1]Istituto Europeo di Oncologia, IRCCS, Department of Early Drug Development; [2]University of Milano, Milano, Italy; [3]Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation; [4]Nova Medical School, Lisbon, Portugal; [5]Paris Sciences & Lettres - PSL University; Paris, France; [6]Breast Surgery, San Raffaele University and Research Hospital, Milano, Italy; [7]Faculty of Medicine and Health, Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; [8]Oncology Institute of Southern Switzerland and Breast Unit of Southern Switzerland, Geneva University Hospitals, Swiss Group for Clinical Cancer Research (SAKK), Bellinzona, Switzerland; [9]Medical University of Gdansk, Gdansk, Poland.

*All authors equally contributed to the design, manuscript writing, editing and final approval of the current manuscript

[§]Corresponding author:
Giuseppe Curigliano, MD, PhD, Prof
Division of Early Drug Development for Innovative Therapies
European Institute of Oncology IRCCS
University of Milan, Department of Oncology and Haemato-Oncology
Via Giuseppe Ripamonti n. 435, 20141, Milan, Italy
e-mail: giuseppe.curigliano@ieo.it

Journal Pre-proof

Journal Pre-proof

Recommendations for Triage, Prioritization and Treatment of Breast Cancer Patients During the COVID-19 Pandemic

Giuseppe Curigliano [1,2*§], Maria Joao Cardoso [3,4], Philip Poortmans[5,6], Oreste Gentilini [7], Gabriella Pravettoni [1,2], Ketti Mazzocco[1,2], Nehmat Houssami [8], Olivia Pagani [9], Elzbieta Senkus [10] and Fatima Cardoso[3], on behalf of the editorial board of The Breast.

[1]Istituto Europeo di Oncologia, IRCCS, Department of Early Drug Development; [2]University of Milano, Milano, Italy; [3]Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation; [4]Nova Medical School, Lisbon, Portugal; [5]Iridium Kankernetwerk, Department of radiation oncology, Wilrijk-Antwerp, Belgium; [6] University of Antwerp, Faculty of Medicine and Health Sciences, Wilrijk-Antwerp, Belgium; [7]Breast Surgery, San Raffaele University and Research Hospital, Milano, Italy; [8]Faculty of Medicine and Health, Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; [9] Service Interdisciplinaire de Cancérologie, Hopital Riviera-Chablais, Rennaz, Vaud, Geneva University Hospitals, Swiss Group for Clinical Cancer Research (SAKK), Switzerland; [10]Medical University of Gdansk, Gdansk, Poland.

*All authors equally contributed to the design, manuscript writing, editing and final approval of the current manuscript

[§]Corresponding author:
Giuseppe Curigliano, MD, PhD, Prof
Division of Early Drug Development for Innovative Therapies
European Institute of Oncology IRCCS
University of Milan, Department of Oncology and Haemato-Oncology
Via Giuseppe Ripamonti n. 435, 20141, Milan, Italy
e-mail: giuseppe.curigliano@ieo.it

Abstract

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) associated disease (COVID-19) outbreak seriously challenges globally all health care systems and professionals. Expert projections estimate that despite social distancing and lockdown being practiced, we have yet to feel the full impact of COVID-19. In this manuscript we provide guidance to prepare for the impact of COVID-19 pandemic on breast cancer patients and advise on how to triage, prioritize and organize diagnostic procedures, surgical, radiation and medical treatments.

Journal Pre-proof

Introduction

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated disease (COVID-19) has rapidly escalated to pandemic proportions. By the beginning of April 2020, over 1,000,000 cases of confirmed infections and over 66,000 deaths from COVID-19 were reported worldwide [www.worldometers.info/coronavirus]. The most common symptoms of COVID-19 are new onset of a continuous cough and/or temperature ≥37.8˚C [1]. Ageusia and anosmia are also frequent symptoms at the early phase of diagnosis [1]. While most patients have no or mild symptoms, about a quarter of patients develop severe symptoms and 5% will have critical symptoms. The clinical manifestations, as well as case fatality rates have been higher in the elderly, those with comorbidities such as respiratory and cardiovascular disease, males and smokers [2]. There is currently no approved nor proven effective treatment or vaccine available for COVID-19, but there are several ongoing trials of potential therapies.

COVID-19 has led to a severe overloading of hospital systems in most affected regions and countries [3]. Healthcare resources (human as well as material) have been rearranged to manage the influx of a large number of patients requiring intensive monitoring, artificial ventilation, and in selected cases extracorporeal membrane oxygenation [4]. Even in countries where COVID19 has not attained very high incidence rates, containment measures are recommended and are being implemented, to prevent infections both of patients and healthcare professionals. The response to this pandemic has led to a sudden disruption of routine medical care, including the treatment of cancer patients, an especially vulnerable population, whose outcomes are dependent on timely and high-quality multidisciplinary interventions [5]. Travel restrictions have made it difficult for some cancer patients to reach the hospital and the fear of infection while visiting the hospital has caused many others to cancel their appointments. Staffing gaps within the oncology departments have arisen as a result of redeployment and sequestering of medical and supporting staff to other areas of critical need – such as respiratory units, emergency departments, and intensive care units (ICUs), as well as self-isolation or quarantine of staff members with suspicious symptoms and/or positive SARS-CoV-2 test [6]. Consequently, many routine visits to the outpatient clinics have been either replaced by telephone/video consultation or deferred.

Independently of whether in a general hospital or in an oncology facility, measures need to be put in place to protect patients and health professionals, and to create a safe circuit to treat or transfer (according to country/regional directives) SARS-CoV-2 infected patients with cancer. These actions have also a strong impact on available resources and routine processes that need to be considered to avoid system disruption. As breast cancer specialists, our main goal is to take care of breast cancer patients within a multidisciplinary environment, able to provide high level treatment within the shortest period of time and according to established quality indicators. However, the current extraordinary worldwide situation requires an urgent re-organization and adapted allocation of healthcare resources, staff as well as infrastructures without compromising patients' outcomes.

Journal Pre-proof

The aim of the present recommendations is to provide guidelines, including selection criteria to service provision and prioritization of treatments, according to the pandemic scenario in each country/region (Table 1), for breast cancer patients care during this critical moment when benefits and risks are influenced by a serious external health threat. This necessitates that all current medical decisions must be carefully weighed taking into account unusual parameters and be balanced not only for the safety of individual patients but also for the community. The PDCA (plan–do–check–act or plan–do–check–adjust) approach is aimed at continuously following, monitoring and improving the organization based on the obtained results in every single hospital and/or department (Figure 1).

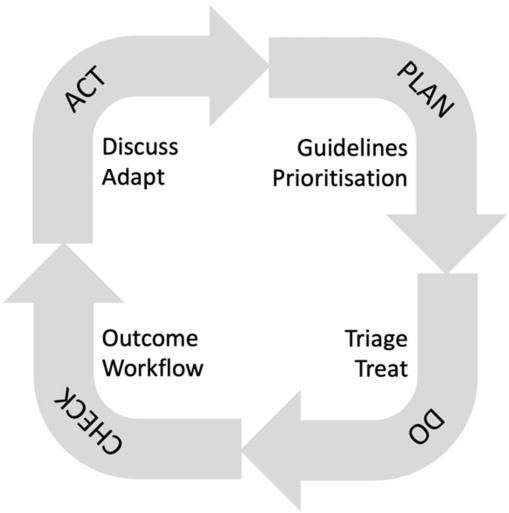


Figure 1: PDCA is an iterative four-step management method aimed at continuous improvement of processes [7]

Therefore, the following proposals must be interpreted as extraordinary, limited to the duration of the contingent pandemic situation, and should be adapted to national/regional circumstances taking into account existing public health regulations. We highlight that these considerations do not overcome the individual physician judgment or available treatment guidelines but represent an expert-opinion-based guidance for optimal allocation of resources during an unprecedented critical period, drawing on current knowledge in a rapidly emerging and evolving situation.

Proposed risk stratifications [8,9]:

I) Breast cancer patients recently suspected or recently diagnosed

II) Breast cancer patients on active treatment (i.e. chemotherapy, immunotherapy, anti-HER2 therapy, endocrine therapy with or without targeted therapies)

III) Breast cancer patients in follow-up (non-active treatment) or on adjuvant endocrine therapy alone

Supplementary risk factors: age over 60 / pre-existing cardiovascular disease/ pre-existing respiratory disease/ smokers / males

Journal Pre-proof

General recommendations (Table 2)

1. Patients should be informed and guided to follow all measures of social distancing and wearing personal protective equipment (i.e. mask) when travelling to the hospital, always in compliance with each country public health regulations.
2. Early identification of symptoms suspicious of SARS-CoV-2 infection is crucial, as well as of symptoms or adverse events caused by the malignancy or antitumor treatments. This pre-screening can be done by phone before each appointment at the hospital and/or at the entry of the hospital. Body temperature should be measured at the entry of the hospital. Patients with symptoms suspicious of SARS-CoV-2 infection, should be tested and managed in a COVID-19 hospital or in the COVID-19-dedicated departments/areas of the cancer center.
3. Patients who need to be hospitalized for cancer treatment should be treated in COVID-19-free hospitals or COVID-19-free departments/areas of the hospital and be, as much as possible, shielded from potential SARS-CoV-2 infection, with a dedicated diagnostic and therapeutic internal pathway.
4. No visits should be allowed in the inpatient facilities and no accompanying care giver should enter the hospital with the patient for appointments or treatments.
5. Staff should be organized by shifts, limiting the number of people working simultaneously to the minimum required.
6. The multidisciplinary tumour boards (MDM) should be continued but performed via web meetings or restricted to one element of each discipline of the core team [10]. All decisions of the MDM should continue to be discussed with the patient and the final decision must account for the patients' preferences.
7. Due to different availability of tests and different public health measures taken in each country, we recommend that testing guidelines of the national health authorities are followed. If tests are available, patients should be tested for SARS-CoV-2 before surgery or any invasive procedure and before initiating immunosuppressive therapies, independently of symptoms. If positive, the procedure and/or treatment should be postponed and resumed only after the patient is considered recovered. However, it is important to realize that even with this approach, some cases will be missed in view of the false negative rate of the PCR test on pharyngeal swabs.

Screening and Diagnosis (Table 2)

1. Due to the foreseeable reduction of resources and to ensure the safety of patients and staff, population mammographic screening should be suspended until the pandemic has subsided [4,5,11,12] .

2. Diagnostic procedures in symptomatic patients should be scheduled according to local availability and resources. However, all efforts should be made to avoid delayed diagnosis in those with suspicious

Journal Pre-proof

symptoms or clinical or imaging findings [BIRADS 5 (high priority) or BIRADS 4 (medium priority)] and its potential impact on cancer outcomes [4,5,11,12].

Locoregional Treatment in Early Breast Cancer (EBC)

Surgery versus primary systemic treatment (Table 3)

Under normal circumstances, primary systemic therapy (PST) is increasingly used and preferred over upfront surgery, not only for locally advanced disease but also in the EBC setting, both within and outside clinical trials. This is due to the established benefits of this approach in terms of surgical de-escalation and more recently to optimize further adjuvant treatments. PST includes both neo-adjuvant/primary chemotherapy ± anti-HER2 therapy (NAC) and neo-adjuvant/primary endocrine therapy (PET).

During the COVID-19 pandemic, PST indications in EBC patients may be temporarily reconsidered taking into account the availability of facilities and healthcare resources, the number of required hospital visits and the risks of compromising the immune system associated with different type of treatments [9,12-14]. The situation might widely vary according to different countries but also in different cities and different hospitals. Therefore, it is even more critical that indications for treatment are taken in a multidisciplinary setting, in light of what is deemed to be the best option for each patient in that specific time and place. A crucial balance is needed between maintaining a high quality of breast cancer care, not jeopardizing cancer outcomes, and minimizing both the risks of infection by SARS-CoV-2 and the risks of complications of anticancer treatments. The decision between primary surgery or PST should also take into account the pandemic scenario (Table 1) in each centre (i.e. early stages vs mitigation phase vs recovery phase). For instance, some patients with EBC who under normal circumstances would receive PST might be treated with primary surgery especially when a limited procedure is feasible in an outpatient setting. In contrast, some patients who, under normal circumstances, could be treated with primary surgery, such as postmenopausal women with limited luminal A/B disease, might be treated with primary endocrine therapy in order to delay invasive procedures and hospitalization.

Surgery (Table 3)

At this point in time, when surgery is indicated, preference should be given to the most effective minimal surgical procedure with the fastest recovery time, that lower risks for the individual patient and reduce the need of healthcare resources. These general recommendations should be applied even in countries where the outbreak has not yet dramatically affected the health system and the surgical activity is still maintained with a reduction that is less than half the usual production[13,15-17].

Journal Pre-proof

1. Defer all benign, cosmetic, and risk-reducing procedures.
2. Offer outpatient surgery whenever possible.
3. Postpone all delayed breast reconstructions.
4. Minimize the use of oncoplastic procedures if they require prolonged hospitalization and/or have a high risk for complications.
5. In case immediate breast reconstruction is considered, recommend simpler (less intensive) procedures with fast recovery (microsurgery should not be undertaken – high resources needed).

The following is meant to be a grid of priority in order to minimize the possible detrimental effect of treatment delay in a worst-case scenario when the availability of surgical slots is highly reduced (e.g. 10-20% of the usual activity). We propose to prioritize patients with diagnosed malignancy into 4 categories. 1) Urgent: surgery within 2 weeks; 2) High priority: surgery within 4 weeks; 3) Medium priority: surgery within 8 weeks; 4) Low priority: surgery after 8 weeks allowed.

1. Urgent:
    a. Patients with significant tumour burden, not responding or progressing under PST.
    b. Pregnant patients, if surgery upfront was decided by the multidisciplinary tumour board.
    c. Patients with complicated locally advanced tumours not otherwise manageable.
2. High Priority
    a. Patients with early isolated loco-regional recurrence (within 48 months from primary treatment).
    b. High-risk patients with contraindications to PST, or node positive, or with disease showing biological features of aggressiveness.
3. Intermediate Priority
    a. Patients treated with PST (ideally at a maximum of 4-6 weeks after treatment completion).
    b. Pre-menopausal patients with ER+ tumours and without indication for preoperative chemotherapy (since neoadjuvant endocrine therapy is not recommended for these patients outside of clinical trials).
4. Low Priority
    a. Ductal carcinoma in situ (however, high grade ER negative or very extensive DCIS and/or with palpable lump or extensive microcalcifications might fall into the intermediate priority category based on case by case considerations).
    b. Post-menopausal patients with Luminal A-like cancer. In these women primary endocrine therapy could be initiated, and surgery could be postponed.

Radiation therapy (Table 4)

Early breast cancer (EBC)

Radiation therapy (RT) for breast cancer is most often delivered after completion of other treatments, including surgery and chemotherapy. Conventional treatment duration is between 3 and 7 weeks. During the COVID-19 pandemic, we need to contribute to the statement of the World Health Organisation (WHO) "to stop, contain, control, delay and reduce the impact of this virus at every opportunity". This translates into minimising exposure and burden to both patients and healthcare personnel without compromising oncological outcome, by minimising the number of hospital visits and limiting the complexity of RT planning/treatment [18]. A useful approach during the pandemic is to give preference, to the least resource-intensive treatment regimen, provided that there are data supporting the use of this type of regimen.

The following recommendations can be considered and discussed with the patients, based on the particular circumstances that may be influenced by social restrictions to contain viral spread, the proportion of the population that is affected, the percentage of the personnel that is present and the pre-existing treatment capacity:

1. Postpone RT up to 3 months for high-risk and up to 6 months for low-risk patients [19].

   In the past, protocols were based on the common position that RT should start as soon as possible following surgery in order to increase treatment efficacy. Following population-based data from a more recent cohort of breast cancer patients, starting RT shortly after surgery does not seem to be associated with a better long-term outcome [19].

2. Moderate hypofractionation should be used for all breast/chest wall and nodal RT, e.g. 40Gy in 15 fractions over 3 weeks [19-21].

   The use of moderate hypofractionation is already the standard of care in many countries and in the altered risk-benefit context of a pandemic should be strongly considered for all patients, including those after breast reconstruction.

3. Deliver RT in 5 fractions for all patients requiring RT with node negative tumours that do not require a boost. Options include 28-30Gy in one weekly fraction over 5 weeks or 26Gy in 5 daily fractions over 1 week as per the FAST and FAST Forward trials, respectively [22-24].

   Five-year local relapse data for FAST Forward will be published soon but data on 3-year normal tissue toxicity has already been demonstrated to be equivalent with 40Gy in 15 fractions.

4. Boost RT should be omitted to reduce fractions and/or complexity in the vast majority of patients unless those 40 years old and under, or over 40 years with significant risk factors for local relapse [25]

   Boost RT reduces the local recurrence risk without improving survival. An example of a significant risk factor is the presence of involved resection margins where further surgery is not possible. Any boost should be with a minimum supplementary number of fractions or given concurrently with the treatment fractions.

Journal Pre-proof

5. Accelerated partial breast RT can also be considered for selected low-risk patients [26-29].
   Accumulating data support the use of partial breast irradiation. An accelerated schedule like in the Florence trial, using 30Gy in 5 fractions over 2 weeks, suits very well. The duration could be further reduced by condensing the schedule into a 1-week fractionation schedule (reducing the total dose) or delivery of intraoperative electron-based RT that is delivered as a one-step procedure together with the lumpectomy.
6. Omission of RT might be considered in elderly patients at low risk of recurrence [30].
   The elderly constitutes the population at higher risk to develop severe consequences from COVID-19 and at the same time the population of patients who derive the less benefits, in absolute terms, from postoperative RT. This indication, however, should be evaluated in the light of the local situation and reconsidered for the individual patient every 4 weeks.

Trials investigating safe omission of RT can be considered if they do not impact on patient visits and resources are available. Centres may also consider omitting RT for low-risk ductal carcinoma in-situ (DCIS) depending on individual risk and benefit.

Advanced breast cancer (ABC)

For ABC, radiation therapy is urgent for the following situations:

1. Treatment of spinal cord compression.
2. Treatment of brain and leptomeningeal metastases.
3. Palliative treatments (e.g. of bone metastases) not responding to pharmaceutical interventions

Systemic therapy (Table 5)

Early breast cancer (EBC)

Early breast cancer can be a fatal disease if left untreated - adequate surgery combined with appropriate perioperative therapies are essential to increase the probability of cure. For this reason, treatment of EBC patients should, as much as possible, follow high quality international clinical guidelines [31]. However, some of the adjuvant systemic therapies have a significant risk of immunosuppression that can have detrimental effects during the COVID-19 pandemic. Some measures can be taken to decrease this potential detrimental effect:

- When utilizing chemotherapy regimens with intermediate/high risk of immunosuppression, such as anthracyclines, 3-weekly docetaxel or 3 weekly platinum, hematopoietic growth factors can be used to decrease the risk of neutropenia and febrile neutropenia.
- Steroids use should be limited to the indispensable, to avoid increasing the risk of immunosuppression.

Journal Pre-proof

- To decrease the number of visits to the hospital, 2-weekly (dose-dense) or 3-weekly regimens should be preferred. However, in patients above the age of 65 years, the number of visits should be balanced with the substantially better tolerability of weekly paclitaxel when compared to 3-weekly docetaxel. Dose-dense regimens allow for the shortest duration of treatment.
- For triple negative EBC, when deciding on the addition of platinum to anthracyclines and taxanes, the higher haematological toxicity and consequent risk of immunosuppression of these agents must be taken into account during this pandemic, in particular, considering that the potential additional benefit of these agents is still controversial.
- For HER2+ EBC, the use of anti-HER2 agents is highly recommended, as per guidelines, in view of the substantial survival benefit and the absence of data suggesting any detrimental effect of their use during this pandemic. In lower risk patients shortening trastuzumab administration to half year may be considered[32], except for those treated with the APT (weekly paclitaxel and trastuzumab) regimen. Trastuzumab subcutaneous formulation is preferred and, when resources allow it, home administration can be used.
- For ER+/HER2 negative EBC, the most difficult decision is related to the use of adjuvant chemotherapy. In cases where the benefit of this treatment is uncertain, the risk/benefit balance, during this pandemic, might more often be in favour of not administering chemotherapy. As for all decision-making process in oncology, the ultimate decision must be taken by the patient, after adequate information, since the attitude towards risks and benefits is highly variable according to individuals' values and preferences and may be different in the current pandemic situation. Genomic tests may be used to help treatment decision-making in doubtful cases.
- Adjuvant endocrine therapy, including the use of ovarian function suppression in pre-menopausal women, should follow the usual international guidelines, since no additional risk is foreseen from these agents. In selected cases, 3-monthly administration of LHRH agonist can be used, provided that confirmation of ovarian suppression is done; however, in very young women and/or women taking an aromatase inhibitor, the risk of inadequate ovarian suppression with the 3-monthly administration is higher. In addition, the administration of an LHRH agonist can be performed at home, if resources allow it.
- For adjuvant bisphosphonates, oral formulations can be preferred during this pandemic. Possible delay of administration or moving the administration earlier, when resources are still available may also be considered, in particular considering that the interval of administration of i.v. formulations is every 6 months.

Advanced breast cancer (ABC)

Journal Pre-proof

Advanced/metastatic breast cancer is an incurable disease, with a median survival of about 3 years, varying according to the breast cancer subtype. In addition, metastatic disease carries in itself some level of immunosuppression. It is therefore essential that all ABC patients remain under adequate treatment, according to high quality international guidelines [33], and close surveillance during the COVID-19 pandemic. Notwithstanding these facts, some measures may be taken to decrease the risk of complications and allow for adequate treatment of these patients.

- Even under normal (non-pandemic) circumstances, the balance between quantity and quality of life is crucial in the management of ABC. This holds equally in the COVID-19 pandemic and more so where treatment options are being cautiously considered, underscoring the need for shared decisions with patients. Dose reductions and dose interruptions should be considered, whenever the side effects are important. In some cases of prolonged treatments and stable disease, treatment holidays may be considered but require active and tight surveillance.
- For ER+/HER2 negative ABC, endocrine-based therapy is the preferred choice for the vast majority of patients and should follow the usual international guidelines, including the mandatory use of ovarian function suppression in pre-menopausal women.
- One of the most difficult decisions during the COVID-19 pandemic relates to the addition of CDK 4/6 inhibitors, in view of their immunosuppressive effect. These agents are now considered the standard of care for this subtype of breast cancer but can be used in either 1st or 2nd line. During this pandemic, the decision to add a CDK 4/6 inhibitor to endocrine therapy should take into account the burden of metastatic disease, the pace of disease progression and the possibility of using these agents later in the course of the disease (situation variable in different countries).
- The addition of an mTOR inhibitor or a Pi3KCA inhibitor to endocrine therapy must also take into account their immunosuppressive effect and the risk of pneumonitis/interstitial lung disease and other serious side effects, as well as the lack of survival benefit seen so far from the use of these agents. Decision should be made on a case-by-case basis, considering the burden of metastatic disease, the pace of disease progression, the possibility of using these agents later in the course of the disease, and the availability of other therapeutic options.
- When utilizing chemotherapy, preference should be given to oral agents and agents with lower risk of immunosuppression, such as capecitabine, including for triple negative or HER2+ ABC. Vinorelbine can be used in its oral formulation and a dose reduction can be considered to avoid haematological toxicity.
- In cases where the use of i.v. agents and/or agents with higher risk of immunosuppression is needed, preference should be given to liposomal formulations of anthracyclines and 3-weekly regimens of taxanes or platinum compounds. Once again, the number of visits should be balanced with the substantially better tolerability of weekly paclitaxel when compared to 3-weekly docetaxel, in particular for older and/or less fit patients. Use of prophylactic hematopoietic growth factors should also be considered.

Journal Pre-proof

- For HER2+ ABC, the use of anti-HER2 agents is highly recommended, as per guidelines, in view of the substantial survival benefit and the absence of data suggesting any detrimental effect of their use during this pandemic.
- The use of bone modulating agents should be discussed on a case-by-cases basis, depending on the burden of bone disease and the presence/absence of symptoms. In many circumstances, it is possible to increase the interval of administration of i.v. bisphosphonates, limiting the number of visits to the hospital while maintaining a good control of bone metastases. Furthermore, the administration of s.c. denosumab can be performed at home, if resources allow it.

The Psychological Management of Cancer Patients during the COVID-19 outbreak

The rapid spread of SARS-CoV-2 epidemics and the increased risk of clinical severe events in cancer patients occur alongside psychological side effects that worsen patients' situation. The significant psychological impact on oncological patients is compounded by multiple factors during the pandemic – knowledge that the individual is at higher risk of serious complication if infected by Covid-19, loneliness and isolation as a result of social distancing, and the underlying constant fear of the cancer. Loneliness is associated with higher risk of mortality in cancer patients [34,35]. Social distancing is known to have negative health consequences and increase risk for premature mortality during normal times [36], but it also enhances patients' feelings of uncertainty associated with their prognosis. It is now well documented that perceived uncertainty increases individual emotional distress and this in turn has negative effects on clinical outcomes in cancer patients [37,38]. Three main aspects explain such uncertainty: patients' perception of the impact of social isolation and of the healthcare crisis to access the cancer center to continue treatments; the risk of being infected when accessing the cancer center; and the need to change daily habits, especially those recommended by health professionals as affecting well-being and clinical outcomes, such as physical activity. The need to be isolated to contain the epidemics is a stark contrast to what is normally recommended for cancer patients including the importance of outdoor physical exercise and of maximizing social supports.

To deal with the increased risk of distress and psychological disorders and the obligation to adhere to social isolation, telemedicine has been used also by psychologists and psychiatrists to guarantee psychological individual and group support for patients while limiting visits to the cancer center. In order to propose the adequate support to patients, psychological status and associated contributing factors should be monitored at different time points of the care pathway. Hospital Anxiety and Depression Scale (HADS) is an easy to use questionnaire and has a good accuracy in assessing anxiety and depression in cancer patients[39]. Furthermore, even in presence of low levels of depression and anxiety it will be crucial to identify critical

levels of intolerance of uncertainty and feelings of loneliness in order to implement interventions to decrease the risk of further distress and psychopathological complications.

Journal Pre-proof

Journal Pre-proof

Conclusions

In the context of the COVID-19 pandemic, we recommended that routine breast screening be suspended, and that patients with early and advanced breast cancer be treated as outpatients as much as possible at the nearest medical center. Exams and appointments of patients on follow-up or under adjuvant endocrine therapy should either be postponed or managed through telemedicine. Treatment should follow international guidelines, as much as possible, but efforts should be made to minimize the number of hospital visits. All treatment decisions should be taken in the context of a multidisciplinary tumour board, which may take place virtually. All treatment decision-making should balance risk and benefits of treatment in the context of the specific pandemic level, on a case by case discussion, always including patients' preferences.

Journal Pre-proof

Disclosures of interest statement

GC reports grants from Roche, advisory role for Daichii Sankyo, Astra Zeneca Macrogenics, BMS and Ellipsis, personal fees from MSD, Astra Zeneca, travel grants from Pfizer, personal fees from Daichii Sankyo, outside the submitted work;

MJC, OG have no financial disclosures

PP is a medical advisor for Sordina IORT Technologies spa

GP reports no conflicts of interest

KM reports no conflicts of interest

NH receives funding via a National Breast Cancer Foundation (NBCF Australia) Breast Cancer Research Leadership Fellowship.

OP reports no conflicts of interest

ES reports honoraria: Amgen, AstraZeneca, Clinigen, Egis, Eli Lilly, Genomic Health, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, TLC Biopharmaceuticals. Travel support: Amgen, AstraZeneca, Egis, Novartis, Pfizer, Roche. Clinical research: Amgen, AstraZeneca, Boehringer, Eli Lilly, Merck, Novartis, Pfizer, Roche, Samsung

FC has consultancy role for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seattle Genetics, Teva.

Journal Pre-proof

References

1. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA.* 2020.

2. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA.* 2020.

3. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *The Lancet.* 2020.

4. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. *New England Journal of Medicine.* 2020.

5. Ueda M, Martins R, Hendrie P, et al. Managing Cancer Care During COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. *J Natl Compr Canc Netw.* 2020;18(4).

6. Extance A. Covid-19 and long term conditions: what if you have cancer, diabetes, or chronic kidney disease?

BMJ. 2020;368:m1174.

7. Deming WE. *Out of the crisis.* 1986.

8. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21(3):335-337.

9. NHS. Clinical guide for the management of cancer patients during the coronavirus pandemic. 2020; https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/Specialty-guide_Cancer-and-coronavirus_17-March.pdf.

10. Biganzoli L, Cardoso F, Beishon M, et al. The requirements of a specialist breast centre. *Breast.* 2020;51:65-84.

11. ASBrS, ACR. ASBrS and ACR Joint Statement on Breast Screening Exams During the COVID-19 Pandemic. 2020.

12. ASCO. Care of Individuals with Cancer During COVID-19. 2020; https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19.

13. ASBrS. Recommendations for Prioritization, Treatment and Triage of Breast Cancer Patients During the COVID-19 Pandemic: Executive Summary. 2020; https://www.breastsurgeons.org/docs/news/The_COVID-19_Pandemic_Breast_Cancer_Consortium_Recommendations_EXECUTIVE_SUMMARY.pdf?01.

14. ECCO. Statement on COVID-19 from the European Cancer Organisation's Board of Directors. 2020; https://www.ecco-org.eu/Global/News/Latest-News/2020/03/NEWS-Statement-on-COVID-19-from-the-European-Cancer-Organisation-Board-of-Directors.

15. ACS. COVID-19: Guidance for Triage of Non-Emergent Surgical Procedures. 2020; https://www.facs.org/about-acs/covid-19/information-for-surgeons/triage.

16. ACS. COVID-19: Recommendations for Management of Elective Surgical Procedures. 2020; https://www.facs.org/about-acs/covid-19/information-for-surgeons/elective-surgery.

17. ASPS. ASPS Statement on Breast Reconstruction in the face of COVID-19 Pandemic. 2020; https://www.plasticsurgery.org/documents/medical-professionals/COVID19-Breast-Reconstruction-Statement.pdf.

18. Coles CE, Aristei C, Bliss J, et al. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic. *Clinical Oncology.* 2020;32(5):279-281.

19. van Maaren MC, Bretveld RW, Jobsen JJ, et al. The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival. *British Journal of Cancer.* 2017;117(2):179-188.

20. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *The Lancet Oncology.* 2013;14(11):1086-1094.

21. Whelan TJ, Pignol J-P, Levine MN, et al. Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer. *New England Journal of Medicine.* 2010;362(6):513-520.

22. Brunt AM, Haviland J, Sydenham M, et al. FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results (CRUKE/04/015). *International Journal of Radiation Oncology • Biology • Physics.* 2018;102(5):1603-1604.

23. Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol.* 2016;120(1):114-118.

24. Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivotto IA. Hypofractionated Nodal Radiation Therapy for Breast Cancer Was Not Associated With Increased Patient-Reported Arm or Brachial Plexopathy Symptoms. *International Journal of Radiation Oncology • Biology • Physics.* 2017;99(5):1166-1172.

25. Brunt AM, Haviland J, Sydenham M, et al. OC-0595: FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy:3-year normal tissue effects. *Radiotherapy and Oncology.* 2018;127:S311-S312.

26. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients

treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol.* 2015;16(1):47-56.

27. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet.* 2017;390(10099):1048-1060.

28. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer.* 2015;51(4):451-463.

29. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy

Journal Pre-proof

for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013;14(13):1269-1277.

30. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *The Lancet Oncology.* 2015;16(3):266-273.

31. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis,

treatment and follow-up. *Annals of Oncology.* 2019;30(10):1674.

32. Earl HM, Hiller L, Vallier A-L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *The Lancet.* 2019;393(10191):2599-2612.

33. Cardoso F, Senkus E, Costa A, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Annals of Oncology.* 2018;29(8):1634-1657.

34. D'Ippolito S, Shams M, Ambrosini E, Calì G, Pastorelli D. R1 - The effect of loneliness on cancer mortality. Annals of Oncology. 2017;28:vi82.

35. Hill EM, Hamm A. Intolerance of uncertainty, social support, and loneliness in relation to anxiety and depressive symptoms among women diagnosed with ovarian cancer. Psychooncology. 2019;28(3):553-560.

36. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and Social Isolation as Risk Factors for Mortality: A Meta-Analytic Review. *Perspectives on Psychological Science.* 2015;10(2):227-237.

37 Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: The many biobehavioral pathways driving tumor progression. *Cancer Treat Rev.* 2017;52:58-70.

38. Reis JC, Antoni MH, Travado L. Emotional distress, brain functioning, and biobehavioral processes in cancer patients: a neuroimaging review and future directions. *CNS Spectr.* 2020;25(1):79-100.

39. Annunziata MA, Muzzatti B, Bidoli E, et al. Hospital Anxiety and Depression Scale (HADS) accuracy in cancer patients. *Supportive Care in Cancer.* 2019.

Journal Pre-proof

Table 1

	Scenarios to describe progression of COVID-19 outbreaks - according to ECDC
Scenario 1	Multiple introductions but limited local transmission in the country. Despite the introductions there is no apparent sustained transmission (only second generation cases observed or transmission within sporadic contained clusters with known epidemiological links). In this situation, the objective is containment by blocking transmission opportunities, through early detection of imported and locally-transmitted COVID-19 cases in order to try to avoid or at least delay the spread of infection and theassociated burden on healthcare systems
Scenario 2	Increasing number of introductions and of more widespread reports of localised human-to-human transmission in the country. In this situation, the objective remains to contain where practicable and otherwise slow down the transmission of the infection. This will increase the time available for development, production and distribution of PPE and effective therapeutic options, and would play a crucial role in reducing the burden on the healthcare system.
Scenario 3	Localised outbreaks, which start to merge becoming indistinct. In this scenario, there is sustained human-to-human transmission in the country (more than two generations of cases outside of sporadic clusters with known epidemiological links) and an increasing pressure on healthcare systems. The objective at this stage is to mitigate the impact of the outbreak by decreasing the burden on healthcare systems and protect populations at risk of severe disease.
Scenario 4	Widespread sustained transmission where healthcare systems are overburdened due to a large demand for emergency healthcare services, a strained ICU capacity, overworked healthcare workers and reduced staff availability due to illness, lack of PPE and lack of diagnostic testing capacity. The objective at this stage is still to mitigate the impact of the outbreak, decrease the burden on healthcare services, protect populations at risk of severe disease and reduce excess mortality.
European center disease control scenarios description https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic	

Table 2

Modality	Pandemic Scenario	Urgent	High Priority	Medium Priority	Low Priority
Outpatient visits	**Scenario 1 and 2**	Infection	Post-operative visits for complications	Follow-up visits of mutation carriers	Follow-up visits: low risk patients
Replace as much as possible by telemedicine (phone/video)		Haematoma if acute or progressive	Patients on treatment with symptoms	Follow-up visits of high-risk patients	Benign and low risk lesions
		Newly diagnosed invasive cancer	Established patients with new problems	Psychological support visits	
			New diagnostic of invasive cancer		
	Scenario 3 and 4	Infection and haematoma if acute or progressive	None	Post-operative visits for complications	Newly diagnosed non-invasive cancer
				Patients on treatment with symptoms	Follow-up visits of mutation carriers
				Established patients with new problems	Follow-up visits of high-risk patients
					Psychological support visits
Diagnostics and Screening	Scenario 1 and 2	None	Diagnostic imaging BIRADS 4b,c and 5	None	Routine screening deferred
			Signs or symptoms that are suspicous of recurrence		Screening of mutation carriers
	Scenario 3 and 4	None	None	Diagnostic imaging BIRADS 4b,c and 5	Routine screening suspended
				Signs or symptoms that are suspicous of recurrence	Screening of mutation carriers
				Newly diagnosed non-invasive cancer	

Journal Pre-proof

Table 3

Modality	Pandemic Scenario	Urgent	High Priority	Medium Priority	Low Priority
Surgery	Scenario 1 and 2	Incision and drainage of abcesses and haematomas	Early isolated loco-regional recurrence (within 48 months from primary treatment)	Pre-menopausal patients stage I invasive	DCIS low and intermediate or small high grade
				DCIS high grade ER negative extensive or palpable	
		LABC not responding to PST	High risk patients with contra-indications to PST, younger than 40, or node positive or biologically agressive		Post menopausal Luminal A like non LABC - endocrine therapy can be initiated
		Pregnant patients	Patients treated with PST (ideally at a maximum 4-6 weeks after treatment completion		
		Complicated LABC not otherwise manageable			
Replace as much as possible by telemedicine (phone/video)	**Scenario 3 and 4**	incision and drainage of abcesses and hematomas	LABC not responding to PST	Early isolated loco-regional recurrence (within 48 months from primary treatment)	DCIS low and intermediate or small size high grade
			Pregnant patients		Post menopausal Luminal A like non LABC - endocrine therapy can be initiated
			Complicated LABC not otherwise manageable	High risk patients with contra-indications to PST, younger than 40, or node positive or biologically agressive	
					Pre-menopausal patients stage I invasive
				Patients treated with PST (ideally at a maximum 4-6 weeks after treatment completion	DCIS high grade ER negative extensive or palpable

Table 4

Radiation therapy	Scenario 1 and 2	Continuation of already started treatments (consider shortening by hypofractionation)	Postoperative radiation therapy for high-risk patients	Postoperative radiation therapy for intermediate-risk patients	Postoperative radiation therapy for low-risk patients
			Patients on treatment with symptoms	Post-treatment visits for complications	
		Palliative treatments not responding to pharmaceutical interventions		Palliative treatments responding to pharmaceutical interventions (for example brain metastases)	Follow-up visits of high-risk patients
		Acute spinal cord compression and brain/leptomeningeal metastases			
Replace as much as possible by telemedicine (phone/video)	**Scenario 3 and 4**	Acute spinal cord compression and brain/leptomeningeal metastases	Continuation of already started treatments (consider shortening by hypofractionation)	Postoperative radiation therapy for high-risk patients	Postoperative radiation therapy for intermediate-risk patients
			Palliative treatments not responding to pharmaceutical interventions	Patients on treatment with symptoms	Palliative treatments responding to pharmaceutical interventions
					Post-treatment visits for complications
					Follow-up visits of high-risk patients

Table 5

Modality	Pandemic Scenario	Urgent	High Priority	Medium Priority	Low Priority
Systemic therapy EBC	Scenario 1 and 2	NAC/AC and biological therapy for triple negative and HER2 + BC	Use of endocrine therapy to enable delayed surgery in clinical stage I or II luminal non locally advanced breast cancers.	For postmenopausal women with stage I cancers, with low-intermediate grade tumors, lobular breast cancers, low risk genomic signatures, prefer endocrine therapy and delay surgery.	Follow up imaging, restaging studies, echocardiograms, ECGs and bone density scans can be delayed if clinically asymptomatic
		Completion of NAC (with or without anti-HER2 therapy) that has already been initiated	For selected HER2 + BC, elderly patients with cardiovascular or other comorbidities: duration of adjuvant anti HER2 treatment for may reasonabe for 6 instead of 12 months		
Replace as much as possible by telemedicine (phone/video)		Adjuvant chemotherapy for patients with high risk Luminal cancers	Continuation of standard adjuvant endocrine therapy (including LH-RH analogue in premenopausal)		
		Chemotherapy schedules may be modified so as to reduce clinical visits (for instance, using 2 or 3 week dosing instead of weekly). Patients should receive G-CSF growth factor support so as to minimize neutropenia, while dexamethasone use should be limited as appropriate to reduce immunosuppression.	Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adaptation of procedures (e.g. abandining research biopsies)		
	Scenario 3 and 4	NAC/AC and biological therapy for triple negative and HER2+ BC	Use of endocrine therapy to enable delayed surgery in clinical stage I or II luminal non locally advanced breast cancers	For postmenopausal women with stage I cancers, with low-intermediate grade tumors, lobular breast cancers, low OncotypeDX@ scores (<25), or low risk signatures prefer endocrine therapy and delay surgery.	Follow up imaging, restaging studies, echocardiograms, ECGs and bone density scans can be delayed if clinically asymptomatic
		Completion of NAC/AC (with or without anti-HER2 therapy) that has already been initiated	For selected HER2 positive breast cancer, elderly patients with cardiovascular or other comorbidities: Adjuvant anti HER2 treatment for may reasonably be curtailed after 7 months instead of 12 months of treatment	Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adaptation of procedures (e.g. abandining research biopsies)	
		Chemotherapy schedules may be modified so as to reduce clinical visits (for instance, using 2 or 3 week dosing instead of weekly). Patients should receive G-CSF growth factor support so as to minimize neutropenia, while dexamethasone use should be limited as appropriate to reduce immunosuppression.	Adjuvant chemotherapy for patients with Luminal cancers		
			Continuation of standard adjuvant endocrine therapy (including LH-RH analogue in PM)		
Systemic therapy MBC	Scenario 1 and 2	Visceral crisis	For patients for whom chemotherapy is recommended prefer oral treatments in order to reduce access to hospital. Consider dose reductions as needed to minimize side effects.	Consider delaying addition mTOR, or PIK3CA inhibitors to endocrine therapy, particularly in elderly patients with comorbidities	If clinically asymptomatic follow up imaging, restaging studies and some echocardiograms and ECGs can be delayed or done at lengthened intervals if clinically stable
		anti-HER2 agents for HER2+ ABC	Chemotherapy schedules may be modified to reduce clinical visits (for instance, using 2/3 week dosing instead of weekly). Patients should receive G-CSF support to minimize neutropenia, while dexamethasone use should be limited as appropriate to reduce immunosuppression.		
			Careful balance benfit/risk before initiating 1st line CDK4/6 inhibitors (ER+) or 1st line immunotherapy (TNBC		
			Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adaptation of procedures (e.g. abandining research biopsies)		
	Scenario 3 and 4	Visceral crisis	For patients for whom chemotherapy is recommended prefer oral treatments in order to reduce access to hospital.Consider dose reductions as needed to minimize side effects.	Consider delaying addition mTOR, or PIK3CA inhibitors to endocrine therapy, particularly in elderly patients with comorbidities	If clinically asymptomatic follow up imaging, restaging studies and some echocardiograms and ECGs can be delayed or done at lengthened intervals if clinically stable
		Anti-HER2 agents for HER2+ ABC	Chemotherapy schedules may be modified to reduce clinical visits (for instance, using 2 or 3 week dosing instead of weekly). Patients should receive G-CSF growth factor support to minimize neutropenia, while dexamethasone use should be limited as appropriate to reduce immunosuppression.	Careful balance benfit/risk before initiating 1st line CDK4/6 inhibitors (ER+) or 1st line immunotherapy (TNBC)	
Replace as much as possible by telemedicine (phone/video)				Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adaptation of procedures (e.g. abandoning research biopsies)	

Scenarios to describe progression of COVID-19 outbreaks - according to ECDC

Scenario 1	Multiple introductions but limited local transmission in the country. Despite the introductions there is no apparent sustained transmission (only second generation cases observed or transmission within sporadic contained clusters with known epidemiological links). In this situation, the objective is containment by blocking transmission opportunities, through early detection of imported and locally-transmitted COVID-19 cases in order to try to avoid or at least delay the spread of infection and theassociated burden on healthcare systems
Scenario 2	Increasing number of introductions and of more widespread reports of localised human-to-human transmission in the country. In this situation, the objective remains to contain where practicable and otherwise slow down the transmission of the infection. This will increase the time available for development, production and distribution of PPE and effective therapeutic options, and would play a crucial role in reducing the burden on the healthcare system.
Scenario 3	Localised outbreaks, which start to merge becoming indistinct. In this scenario, there is sustained human-to-human transmission in the country (more than two generations of cases outside of sporadic clusters with known epidemiological links) and an increasing pressure on healthcare systems. The objective at this stage is to mitigate the impact of the outbreak by decreasing the burden on healthcare systems and protect populations at risk of severe disease.
Scenario 4	Widespread sustained transmission where healthcare systems are overburdened due to a large demand for emergency healthcare services, a strained ICU capacity, overworked healthcare workers and reduced staff availability due to illness, lack of PPE and lack of

	diagnostic testing capacity. The objective at this stage is still to mitigate the impact of the outbreak, decrease the burden on healthcare services, protect populations at risk of severe disease and reduce excess mortality.	
	European center disease control scenarios description https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic	

Journal Pre-proof