Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic

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A B S T R A C T
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.

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1. 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-

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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 reorganization and adapted allocation of healthcare resources, staff as well as infrastructures without compromising patients’ outcomes.

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 (Fig. 1).

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

![PDCA process diagram](https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic)

**Table 1**

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

| Scenario | Description |
|----------|-------------|
| **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 the associated 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 diase control scenarios description*

[https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic](https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic)
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.

1.1. 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.

1.2. 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 entrance 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 immuno-suppressive 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.

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

1.4. Locoregional treatment in early breast cancer (EBC)

1.4.1. 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 minimising 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 center (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 post-menopausal women with limited luminal A/B disease, might be treated with primary endocrine therapy in order to delay invasive procedures and hospitalization.

1.5. 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].

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.

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Table 2
Prioritization of outpatient, screening and diagnostic visits for patients with breast cancer.

| 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 |
|                |                   | 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 | |
|                | 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 Signs or symptoms that are suspicious of recurrence | None | Routine screening deferred |
|                |                   |                          |                                        |                                    | Screening of mutation carriers |
|                | Scenario 3 and 4  | None | Diagnostic imaging BIRADS 4b,c and 5 Signs or symptoms that are suspicious of recurrence | None | Routine screening suspended |

Table 3
Prioritization of surgery in patients with breast cancer.

| Modality    | Pandemic Scenario | Urgent                                      | High Priority                                      | Medium Priority                                      | Low Priority                                      |
|-------------|-------------------|---------------------------------------------|----------------------------------------------------|-----------------------------------------------------|---------------------------------------------------|
| Surgery     | Scenario 1 and 2  | Accidental and drainage of abscesses and haematoma | 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 |
|             |                   | ABC not responding to PST                   | ABC not responding to PST                          | ABC not responding to PST                            | ABC low and intermediate or small high grade |
|             |                   | Pregnant patients                           | Patients treated with PST ideally at a maximum 4-6 weeks after treatment completion |                         |                         |
|             | Scenario 3 and 4  | Complicated ABC not otherwise manageable  | Early isolated loco-regional recurrence (within 48 months from primary treatment) |                          |                          |
|             |                   | Pregnant patients                           | Complicated ABC not otherwise manageable          |                          |                          |
|             |                   | ABC not responding to PST                   | High-risk patients with contra indications to PST younger than 40 or node positive or biologically aggressive |                          |                          |
|             |                   | Pregnant patients                           | Patients treated with PST ideally at a maximum 4-6 weeks after treatment completion |                          |                          |

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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.

1.6. Radiation therapy (Table 4)

1.6.1. 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 Organization (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].

| Modality          | Pandemic Scenario | Urgent                                      | High Priority                        | Medium Priority                         | Low Priority                           |
|-------------------|-------------------|---------------------------------------------|--------------------------------------|----------------------------------------|----------------------------------------|
| 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         |                                       |                                        |                                        |
|                   |                   | Palliative treatments not responding to pharmacological interventions |                                    |                                       |                                        |
|                   |                   | Acute spinal cord compression without symptoms |                                    |                                       |                                        |
| Replace as much as possible by telemmedicine (phone/video) | Scenario 3 and 4 | Acute spinal cord compression with symptoms | Continuation of already started treatments (consider shortening by hypofractionation) | Postoperative radiation therapy for high-risk patients | Postoperative radiation therapy for intermediate-risk patients |
|                   |                   | Patients on treatment with symptoms         |                                      |                                       |                                        |
|                   |                   | Palliative treatments not responding to pharmacological interventions |                                      |                                       |                                        |
|                   |                   | Acute spinal cord compression without symptoms |                                      |                                       |                                        |

Table 4
Prioritization of radiotherapy in patients with breast cancer.
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.

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 Florencia trial, using 30 Gy 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 intra-operative 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.

1.7. 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

1.8. Systemic therapy (Table 5)

1.8.1. 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.
- 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.

1.9. Advanced breast cancer (ABC)

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
### Table 5
Prioritization of systemic treatment in patients with early and metastatic breast.

| Modality | Pandemic Scenario | Urgent | High Priority | Medium Priority | Low Priority |
|----------|------------------|--------|---------------|-----------------|-------------|
| **Systemic therapy HER2** | Scenario 1 and 2 | NAC/ABC and biological therapy for triple negative and HER2+ BC | Use of endocrine therapy to enable delayed surgery in clinical stage I or luminal non-lucrative advanced breast cancers. | For postmenopausal women with stage I cancers, with low-intermediate grade tumors, luminal breast cancers, low risk genetic signatures, prefer endocrine therapy and delay surgery. | Follow-up imaging, managing studies, echocardiograms, ECGs and bone density scans can be delayed if clinically asymptomatic. |
| | | Completion of NAC or without anti-HER2 therapy that has already been initiated | For selected HER2+ ABC eligible patients with cardiovascular or other comorbidities, duration of adjuvant anti-HER2 treatment for may be reasonable for 4 instead of 12 months. | | |
| | | Adjacent chemotherapy for patients with high risk luminal cancers | Continuation of standard adjuvant endocrine therapy (including AI-4N 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 docetaxel use should be limited so as to appropriate to reduce immunosuppression. | Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adoption of procedures (e.g. abbreviated research biopsy) | | |
| | Scenario 3 and 4 | NAC/ABC and biological therapy for triple negative and HER2+ BC | Use of endocrine therapy to enable delayed surgery in clinical stage I or luminal non-lucrative advanced breast cancer | For postmenopausal women with stage I cancers, with low-intermediate grade tumors, luminal breast cancers, low OncotypeDX score (<20), or low risk genetic signatures, prefer endocrine therapy and delay surgery. | Follow-up imaging, managing studies, echocardiograms, ECGs and bone density scans can be delayed if clinically asymptomatic. |
| | | Completion of NAC/ABC | For selected HER2+ positive breast cancer, CKD+ patients with cardiovascular or other comorbidities, adjuvant and HER2 treatment for may be reasonable for 4 instead of 12 months of treatment. | | |
| | | 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 docetaxel use should be limited so as to appropriate to reduce immunosuppression. | Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adoption of procedures (e.g. abbreviated research biopsy) | | |
| | | Adjacent chemotherapy for patients with luminal cancers | Continuation of standard adjuvant endocrine therapy (including AI-4N analogue in PM) | | |
| **Systemic therapy MBC** | Scenario 1 and 2 | Vitamin crisis | For patients for whom chemotherapy is recommended before treatments in order to reduce access to hospital. Consider dose reductions as needed to minimize side effects. | Consider delivering addition anti-HER2, or PRLCA inhibition to endocrine therapy, particularly in elderly patients with comorbidities | If clinically asymptomatic: follow up imaging, managing 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 so as to minimize neutropenia, while docetaxel use should be limited so as to appropriate to reduce immunosuppression. | | |
| | | Careful balance benefit/risk before initiating 1st line CDK4/6-inhibitors (PAM) or 1st line immunotherapy (IMC). | | |
| | | Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adoption of procedures (e.g. abbreviated research biopsy) | | |
| | Scenario 3 and 4 | Vitamin crisis | For patients for whom chemotherapy is recommended before treatments in order to reduce access to hospital. Consider dose reductions as needed to minimize side effects. | Consider delivering addition anti-HER2, or PRLCA inhibition to endocrine therapy, particularly in elderly patients with comorbidities | If clinically asymptomatic: follow up imaging, managing 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 so as to minimize neutropenia, while docetaxel use should be limited so as to appropriate to reduce immunosuppression. | Careful balance benefit/risk before initiating 1st line CDK4/6-inhibitors (PAM) or 1st line immunotherapy (IMC). | |
| | | | Continuation of treatment in the context of a clinical trial, provided patient benefits overweight risks, with possible adoption of procedures (e.g. abbreviated research biopsy) | | |

Replace as much as possible by telemedicine (phone/video)
1.10. 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.

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.

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References

[1] Livingston E, Bucker K. Coronavirus disease 2019 (COVID-19) in Italy. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.4344.

[2] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.4685.

[3] Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395(10231):1225–8. https://doi.org/10.1016/S0140-6736(20)30627-9.

[4] Hollander JE, Carr BG. Virtually perfect? Telemedicine for covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMp2003539.

[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;370: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):335–7.

[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. www.breastsurgeons.org/docs/news/The_COVID-19_Pandemic_Breast_Cancer_Consortium_Recommendations_EXECUTIVE_SUMMARY.pdf.

[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/tra
gue.

[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, Aritei C, Bliss J, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clin Oncol 2020;32(5):279–81.

[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. Br J Canc 2017;117(2):179–88.

[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. Lancet Oncol 2013;14(11):1086–94.

[21] Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362(6):513–20.

[22] Bruin AM, Haviland J, Sydenham M, et al. FAST phase III RCT of radiotherapy hypofractionation for treatment of early breast cancer: 10-year results (CRUISE/04/015). Int J Radiat Oncol Biol Phys 2018;102(5):1603–4.

[23] Bruin 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-Final Trial. Radiother Oncol 2016;120(1):114–8.

[24] Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivottio IA. Hypofractionated nodal radiation therapy for breast cancer was not associated with increased patient-reported arm or brachial plexopathy symptoms. Int J Radiat Oncol Biol Phys 2017;99(5):1166–72.

[25] Bruin AM, Haviland J, Sydenham M, et al. OC-0595: FAST-Fast phase 3 RCT of 1-week hypofractionated breast radiotherapy:3-year normal tissue effects. Radiother Oncol 2018;127:S311–2.

[26] Bartelink H, Maigong 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] Cole FC, 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(10109):1048–60.

[28] Livi I, 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 Canc 2015;51(4):451–63.

[29] Veronesi U, Orecchia R, Masonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (EILOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14(13):1269–77.

[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. Lancet Oncol 2015;16(3):266–73.

[31] Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 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. Lancet 2019;393(10191):2599–612.

[33] Cardoso F, Senikus E, Costa A, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ARC 4). Ann Oncol 2018;29(8):1634–57.

[34] D’Pilipoto S, Shams M, Ambrosini E, Calt G, Pastorelli D. RI - the effect of loneliness on cancer mortality. Ann Oncol 2017;28:vii82.

[35] Hill EM, Hamn A. Intolerance of uncertainty, social support, and loneliness in relation to anxiety and depressive symptoms among women diagnosed with ovarian cancer. Psycho Oncol 2019;28(3):553–60.

[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. Perspect Psychol Sci 2015;10(2):227–37.

[37] Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: the many biobehavioral pathways driving tumor progression. Canc Treat Rev 2017;52:58–70.

[38] Reis JG, 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. Support Care Canc 2019. https://doi.org/10.1007/s00520-019-05244-8.