



# Breast Cancer Management Guidelines During COVID-19 Pandemic

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## Abstract

The coronavirus disease (COVID-19) pandemic in 2020 has brought about complex challenges in healthcare delivery. With the new rules of lockdown and social distancing and with resources diverted to the management of COVID-19, there are difficulties in continuing usual cancer care. Patients are at risk of contracting COVID-19 with a high chance of patient to healthcare transmission and vice versa. Hospital visits, investigations and all modalities of treatment have potential complications that put patients at risk, some more than others. In this situation, there is a need to change our approach in the management of breast cancer to deliver it safely. We present modified guidelines based on the available consensus statements and evidence.

**Keywords** COVID-19 · Breast cancer · Radiotherapy · Chemotherapy · Breast surgery

## Introduction

COVID-19 (coronavirus disease) is a new global threat, and all healthcare systems have assessed resource allocation as part of their pandemic plans [1]. At the time of writing this article, there are 4,593,395 confirmed COVID-19 infections and 306,371 deaths globally [2]. There are many challenges as we face this pandemic in 2020; one of the most significant is to ensure the safety of patients and healthcare workers and, at the same time, deliver effective cancer management. A report from China has shown that patients with cancer are at higher risk of contracting COVID-19 and have shown poorer outcomes if they do [3]. Any modification to treatment protocols

should be scientifically and ethically justified [4]. There is a need for individual triaging of patients and new adaptable methods to provide safe and effective care.

The main objective of this article is to provide guidelines during the pandemic which are based on available scientific evidence, online recommendations via certified sites and our collective experience [5–7]. The article is divided into four sections: general logistics and diagnostics, surgical, neoadjuvant and adjuvant treatment guidelines. These guidelines should be considered by the local multidisciplinary team (MDT) and modified according to the availability of resources and the severity of the pandemic in their location.

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## General Logistics and Diagnostics

Triaging patients attending the outpatients' department should be done prior to the day of clinic. Phone or video consultations should be conducted where feasible and appropriate. Patients should be advised to attend clinics with limited attendants. Local infection control policies for COVID-19 should be maintained throughout the pathway. Diagnostic modalities should not be modified. A marker clip should be inserted in the tumour especially if neoadjuvant therapy is planned. It is advisable to conduct MDT meetings with only the core members present and virtual where possible. Treatment decisions should take into account patient factors, tumour factors, hospital factors including COVID-19 severity, and, therefore, benefits and risks of treatment.

1. Patient factors: Individuals with long-term health conditions are at a higher risk of morbidity and mortality if they get infected by COVID-19. Treatment modifications should be considered in this group [8–10]:
  - a. Body mass index (BMI) of 40 or above
  - b. Medical or cancer treatment that decreases immune competence
  - c. Comorbidities such as diabetes mellitus, cardiovascular disease and chronic liver and kidney disease
  - d. Respiratory conditions such as chronic obstructive pulmonary disease, bronchitis and asthma
  - e. Age over 65 years
2. Tumour factors:
  - a. Size
  - b. Grade
  - c. Axillary nodal status
  - d. Oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor-2 (HER-2) status
3. Local COVID-19 severity and the facilities to cope with it together with the capacity to manage other conditions such as cancer at the same time.
4. Benefits and risks of treatment: When considering the non-standard treatment due to the COVID-19 pandemic, the risks and benefits should be discussed and documented.
  - a. Patients should be treated in COVID-19 free areas if feasible.
  - b. All patients attending the hospital should be made aware of the risk of contracting COVID-19 infection.
  - c. Those planned for surgery should be checked for specific symptomatology of COVID-19 and history of contact.
  - d. Preoperative COVID-19 testing should be done in accordance with local guidelines.
  - e. The role and modality of imaging in COVID-19 is controversial. Although a few centres are undertaking preoperative chest X-rays or CT of the thorax in all patients undergoing surgery, this is not supported by evidence.
  - f. Personal protective equipment (PPE) should be used by all staff members as per the WHO guidelines.
  - g. While using electrocautery intraoperatively, adjust to the lowest power settings to reduce the volume of diathermy plumes and the concomitant use of a smoke evacuator is strongly recommended.
  - h. All modifications to standard plans should be documented and audited.
2. Breast cancer-specific guidelines: Choice of breast surgery should be based on the optimal theatre time, minimal morbidity and hospital stay. Pandemic-modified recommendations are [6, 7, 14–16]:
  - a. Breast conservation surgery (BCS):
    - i. Consider breast conservation surgery, without the requirement for reconstructive procedures. Level I oncoplastic procedures can be continued as before pandemic.
    - ii. Consider routine margin excision with a frozen section of the margins to reduce rates of re-excision.
    - iii. Localisation for impalpable lesions should be continued according to local protocols.
    - iv. Therapeutic mastoplasty and autologous flap reconstructions should be avoided.
  - b. Mastectomy:
    - i. Consider simple mastectomy.
    - ii. Immediate reconstruction, either implant-based or autologous, should be avoided.
    - iii. Axillary surgery: Sentinel node biopsy and axillary clearance should continue according to local protocol.
  - c. General considerations:
    - i. No additional cosmetic procedures or corrective surgery should be undertaken (lipomodelling, nipple reconstruction, symmetrisation procedures).

## Surgical Guidelines

The surgical guidelines are divided into general surgical, breast cancer-specific and surgical prioritisation.

1. The general surgical guidelines apply to all patients planned for cancer surgery [6, 7, 11–13]:

- ii. Subcuticular suturing is preferable to interrupted sutures as it avoids the need for additional postoperative visits.
  - iii. Avoid drains where possible.
  - iv. Day case surgery is preferable using specific pain management pathways and anaesthetic considerations.
  - v. Prophylactic antibiotics and preoperative MRSA (methicillin-resistant *Staphylococcus aureus*) screening may reduce postoperative infections and return to hospital.
3. Surgical prioritisation categories are shown in Table 1 [5–7].

### Neoadjuvant Treatment Guidelines

The neoadjuvant treatment guidelines are for endocrine therapy, systemic anticancer therapy (SACT) and radiotherapy.

1. Neoadjuvant endocrine therapy (NAET): NAET has been used as an alternative to surgery in unfit patients. Various studies have compared primary endocrine therapy to surgery or surgery followed by adjuvant tamoxifen. A study conducted by Robertson et al. [17] compared tamoxifen alone to mastectomy in elderly postmenopausal women with operable breast cancer. There was no difference in overall survival (OS) at a median follow-up of 24 months. Similarly, Phase III GRETA trial did not show any significant difference in the OS between the primary endocrine therapy arm and surgery arm [18].
  - a. Patient selection: Hormonal treatment can be considered in all ER-positive patients unfit or unwilling to undergo surgery during the pandemic.
  - b. Drug of choice: Aromatase inhibitors (AI) have been shown to be effective in neoadjuvant setting, leading

- to significantly higher response rates for letrozole than for tamoxifen and comparable ones for anastrozole [19–21].
- c. Duration of treatment: We recommend the use of NAET for at least 3 months and beyond that based on the local COVID-19 situation. This recommendation is based on a study conducted by Dixon et al. which showed a median reduction in tumour volume of about 50% between 3 and 6 months and a continued benefit of 33% between 12 and 24 months [22].
- d. Monitoring of response: It is advisable to assess response to NAET at 3 months.

2. Neoadjuvant systemic anticancer therapy (NA-SACT): NA-SACT should only be considered for downstaging and not to aid breast-conserving treatment. If appropriate, consider biological treatments on their own, such as aromatase inhibitors (with or without gonadotropin-releasing hormone (GnRH) analogues for pre-menopausal women) along with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors for oestrogen receptor-positive disease or anti-HER2 combination treatment with trastuzumab and pertuzumab for HER2-positive disease. If chemotherapy is essential, consider weekly paclitaxel as opposed to 3 weekly docetaxel. Neoadjuvant therapy can be discontinued once the desired response has been achieved if it is felt to be safer to proceed to surgery rather than continuing with SACT. Further details regarding the general considerations while giving SACT, prioritisation and modifications during COVID-19 will be discussed in the adjuvant SACT section.
3. Neoadjuvant radiotherapy: Breast radiotherapy is used as primary local therapy in patients who are not fit for surgery due to comorbidities or inoperable cancers after systemic treatment. With the advent of newer techniques and regimens for delivering radiotherapy and a greater understanding of the radiobiology, preoperative radiotherapy is being investigated in the trial setting, and early results are

**Table 1** Surgical prioritisation

Stratification level	Description	Examples
A - Action required immediately	Urgent surgery is indicated in life-threatening and/or clinically unstable scenarios	<ul style="list-style-type: none"> <li>• Bleeding/fungating tumour</li> <li>• Haematoma or bleeding after surgery</li> <li>• Flap necrosis</li> </ul>
B - Be on list for surgery	Delay in surgery beyond 6–8 weeks will have a negative outcome	<ul style="list-style-type: none"> <li>• Patients completing neoadjuvant chemotherapy</li> <li>• Triple-negative breast cancer (TNBC)</li> <li>• HER2-positive cancers</li> <li>• Node-positive cancers</li> </ul>
C - Consider alternate treatment options	Elective surgery carries a higher risk when local COVID-19 cases are high	<ul style="list-style-type: none"> <li>• Neoadjuvant endocrine therapy (NAET) for ER-positive cancers</li> <li>• Neoadjuvant radiotherapy (NART) in ER-negative cancers</li> </ul>
D - Defer surgery	Elective surgery can be delayed until the pandemic is over without potential negative outcome	<ul style="list-style-type: none"> <li>• Ductal carcinoma in situ</li> <li>• Pleomorphic lobular carcinoma in situ</li> <li>• High-risk lesions with atypia</li> <li>• Risk-reducing surgery</li> </ul>

positive about its adverse effects [23]. PAPBI (preoperative accelerated partial breast irradiation) is a phase II trial which investigated 40 Gy in 10 fractions then 30 Gy in 5 fractions over 1 week to the partial breast in 133 patients. It has recently reported 92% good or excellent cosmetic outcome and 3% local recurrence at 5 years [24]. The Royal College of Radiologists, UK, has issued ‘Emergency guidelines for pre-operative breast radiotherapy during the COVID-19 pandemic’ with British and Indian authors [25]. We have based our recommendations on this document which is available on the reference link.

- a. Patient selection: Patient selection for preoperative radiotherapy should be based on resource availability and requires flexibility to react to fluctuations during the COVID-19 pandemic. Preoperative radiotherapy can be considered for the following categories of patients:
  - i. Newly diagnosed invasive breast cancer with no systemic therapy option (chemotherapy or endocrine), such as a patient with ER-negative breast cancer considered unsuitable for chemotherapy due to significantly increased risk of COVID-19 mortality.
  - ii. Completion of all neoadjuvant therapy with no option of endocrine and/or HER2-directed therapy, i.e. triple-negative breast cancer
  - iii. Loco-regional cancer progression/poor response despite the use of all available neoadjuvant therapies, including HER2-directed and/or endocrine therapy.
- b. Radiotherapy technique and dose fractionation: Dose/fractionation regimens suggested are based on a combination of clinical experience within clinical trials in the adjuvant setting and radiobiological modelling. Since the guideline was produced and placed online, the FAST-Forward trial has published the 5-year data [26], Table 2

## Adjuvant Treatment Guidelines

1. Adjuvant hormonal treatment: Standard adjuvant hormonal treatment should be continued. Aromatase inhibitors are the preferred standard option in postmenopausal ER-positive women. Tamoxifen can also be used for treatment but is known to increase the risk of thromboembolism. Although COVID-19 has been shown to be associated with hypercoagulability [27], currently there is no evidence to suggest contraindication of tamoxifen during COVID-19 pandemic.

2. Adjuvant systemic anticancer therapy (A-SACT) guidelines: SACT should not be delivered to patients who have active COVID-19 infection or have index symptoms of COVID-19 infection.

- a. The general principles of A-SACT during the COVID-19 pandemic include:
  - i. Communication with patients to reassure and advise.
  - ii. Minimise face-to-face contact.
  - iii. Prioritise treatment, as discussed below.
  - iv. Phone or video consultation.
  - v. Local blood tests to minimise footfall in the hospital.
  - vi. Oral treatment, if suitable, is preferable to parenteral treatment.
  - vii. Remote delivery of oral SACT by post or courier if possible.
  - viii. If remote delivery is not possible, then consider ‘no-contact’ drug-collection areas.
  - ix. Modified treatment regimens as discussed below.
  - x. Routine G-CSF (granulocyte-colony stimulating factor) for 5 to 7 days for 3 weekly regimens or 3 days for weekly regimens.

It is also important to consider the level of immunosuppression associated with individual treatments and cancer types and other patient-specific risk factors such as frailty and comorbidities. Practical considerations include capacity issues, such as limited resources (workforce, facilities, intensive care, equipment). Finally, oncologists should balance the risk of cancer not being treated optimally versus the risk of the patient being immunosuppressed and becoming seriously ill or dying due to COVID-19.

- b. Prioritisation categories: In the UK, the National Institute for Health and Care Excellence (NICE) has published peer-reviewed treatment prioritisation categories which are available from the NICE website (Table 3) [28]. The NICE prioritisation categories have been interpreted by the Christie Breast Cancer Oncologists taking into account the published efficacy data from adjuvant and neoadjuvant studies in breast cancer. Clinical teams should discuss and categorise patients according to the type of disease they have, the aim of treatment and the expected benefit.

Most breast neoadjuvant and adjuvant breast cancer treatments fall in category 2 or 3, while most treatments for advanced cancers in the first- or second-line setting fall into category 4. Treatment beyond the second line for advanced disease is mostly category 6.

**Table 2** A suggested approach for emergency preoperative radiotherapy [25]

Patient and tumour characteristics	Emergency preoperative radiotherapy	
	Breast	Nodes
Clinical/radiological complete response following primary systemic therapy or impalpable tumour	26 Gy/5F/1 week to breast	
Palpable tumour	26 Gy/5F/1 week to breast with boost Boost: SIB (simultaneous integrated boost) 32 Gy/5F/1 week (additional 6 Gy/5F boost) or sequential boost	
Clinically/radiologically negative axilla		None or consider 26 Gy/5F/1 week to levels 1–4 if node-positive at presentation prior to primary systemic therapy
Clinically/radiologically positive axilla: N1		26 Gy/5F/1 week to levels 1–4
Clinically/radiologically positive axilla: N2–3		40 Gy/15F/3 weeks or 26 Gy/5F/1 week to axilla levels 1–4 and internal mammary nodes

- c. Modification of treatment: A-SACT should be used only when the benefit is significant; we consider at least 5% benefit according to PREDICT [29] to be a level of clinical significance to consider offering therapy. Use of genomic tests should be discussed by the MDT and only requested where there is genuine equipoise about the risk-benefit of A-SACT. For HER-2 positive breast cancers, adjuvant treatment with weekly paclitaxel and trastuzumab only should be considered for the node-negative disease. Also, for such patients, adjuvant trastuzumab should be advised for 6 months only in line with the findings of the PERSEPHONE trial [30].
- d. Palliative SACT guidelines: The general principles remain the same as for treatment of early breast cancer; however, the risk-benefit ratio needs to be carefully assessed on an individualised basis, considering the following factors:
- Has there been a response to treatment?
  - Is the treatment time critical?
  - Is the treatment necessary for symptom control?
- These factors are especially relevant for treatments in priority category 6. It is perfectly reasonable to consider short treatment breaks for patients already on treatment with evidence of response to treatment. Excellent communication with patients is essential to advise and reassure them during what seems to be a challenging and frightening time for patients with advanced cancer.
3. Adjuvant radiotherapy guidelines: Our advice is based on Coles et al. [31] but with modification because the FAST-Forward trial [26] has been published since the guidelines were released. During the pandemic, the need to reduce footfall in cancer centres drives the recommendations. Four measures are suggested, and these are shown in Table 4. Each patient who fulfils the criteria should be discussed in the MDT and then have the options discussed openly with the patient. If the decision is to proceed with radiotherapy, there is also the option to consider delaying the planning and treatment with the radiotherapy.
- Consider omitting radiotherapy from the lowest risk cases with invasive carcinoma and use the criteria in the PRIME II trial [32]. Cases of in situ carcinoma can also be considered.
  - Consider the FAST-Forward 26 Gy in 5 fractions daily schedule [26] or FAST (5 fractions once weekly) for a frail patient who would struggle to attend daily [33] for a patient requiring breast or partial breast radiotherapy. Many centres will introduce the FAST-Forward regimen as standard for patients irrespective of the pandemic given the happy coincidence of publication of the primary endpoint at this time. To reduce time in the department, try and avoid a deep breath hold technique as cardiac protection; a partial breast technique may suffice for some patients to offer cardiac protection. The number of patients in FAST-Forward was 6–7% of the total, but there is no intrinsic reason why chest wall radiotherapy cannot use the same dose-fraction schedule.
  - Boost radiotherapy does not offer a survival advantage and consider omission except in the highest risk cases. Where used consider hypofractionation such as 10 Gy in 2 fractions [25] or 13.35 Gy in 5 fractions.

**Table 3** Prioritisation categories of patients planned for SACT

Level	Treatment
1	Curative treatment with a high (more than 50%) chance of success. Adjuvant or neoadjuvant treatment which adds at least 50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
2	Curative treatment with an intermediate (20 to 50%) chance of success. Adjuvant or neoadjuvant treatment which adds 20 to 50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
3	Curative treatment with a low (10 to 20%) chance of success Adjuvant or neoadjuvant treatment which adds 10 to 20% chance of cure to surgery or radiotherapy alone or treatment given at relapse
4	Non-curative treatment with a high (more than 50%) chance of more than 1-year extension to life
5	Curative treatment with a very low (0 to 10%) chance of success. Adjuvant or neoadjuvant treatment which adds less than 10% chance of cure to surgery or radiotherapy alone or treatment given at relapse
6	Non-curative treatment with an intermediate (15 to 50%) chance of more than 1-year extension to life

- d. Consider omitting nodal radiotherapy for patients with biologically low-grade cancers with one or two macro metastases in the axilla which would allow a 5-fraction schedule to be employed to the breast.

We would also consider the 5-fraction schedule for nodal radiotherapy based on the adverse effect data from both FAST-Forward and FAST. For nodal radiotherapy, 40 Gy in 15 fractions over 3 weeks remains the standard regimen. We have not included this as a recommendation, but centres and countries may wish to debate this policy dependent upon the

effect that the COVID-19 pandemic has on their resources and balancing patient risk from the virus. If a patient has COVID-19, then radiotherapy should be omitted until recovery.

## Conclusion

The COVID-19 pandemic has posed a significant challenge in the management of breast cancer. The modifications presented

**Table 4** Adjuvant radiotherapy guidelines for breast cancer during COVID-19 pandemic [31]

Suggestion no.	Action	Conditions
1	Omit radiotherapy	Age $\geq$ 65 years (younger with comorbidities) + invasive breast cancer < 3 cm with clear margins + grade 1/2 + ER-positive and HER2-negative + node-negative + planned for endocrine therapy
2	Deliver radiotherapy in 5 fractions. 26 Gy in 5 daily fractions over 1 week or 28–30 Gy in once weekly fractions over 5 weeks [26]	For all patients requiring radiotherapy to the whole or partial breast or chest wall
3	Omit boost radiotherapy to reduce fractions or hypofractionation	Except in patients < 40 years age and those with a high risk of local recurrence
4	Omit nodal radiotherapy	Postmenopausal women with T1, grade 1–2, ER-positive, HER2-negative tumour with 1–2 macro metastases requiring whole breast radiotherapy following BCS and sentinel node biopsy [34]

in the manuscript can be a useful resource to tailor individualised treatment decisions.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Abbreviations** COVID-19, Coronavirus disease 2019; MDT, Multidisciplinary team; BMI, Body mass index; ER, Oestrogen receptor; PR, Progesterone receptor; HER 2, Human epidermal growth factor-2; CT, Computed tomography; PPE, Personal protective equipment; WHO, World Health Organization; BCS, Breast conservation surgery; MRSA, Methicillin-resistant *Staphylococcus aureus*; TNBC, Triple-negative breast cancer; NAET, Neoadjuvant endocrine therapy; NART, Neoadjuvant radiotherapy; NA-SACT, Neoadjuvant systemic anticancer therapy; GnRH, Gonadotropin-releasing hormone; CDK4/6, Cyclin-dependent kinase 4/6; SACT, Systemic anticancer therapy; PAPBI, Preoperative accelerated partial breast irradiation; Gy, Gray; F, Fraction; SIB, Simultaneous integrated boost; DVT, Deep vein thrombosis; A-SACT, Adjuvant systemic anticancer therapy; G-CSF, Granulocyte-colony stimulating factor; NICE, National Institute for Health and Care Excellence

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