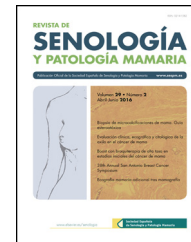




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## SPECIAL ARTICLE

# Diagnosis and locoregional treatment of patients with breast cancer during the COVID-19 pandemic



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**Abstract** We are facing a pandemic that is going to affect a significant part of the population. At the end of April in the world there are about 3,000,000 cases, with 205,000 deaths and 860,000 patients recovered.

The response to this pandemic has in many cases led to a significant change in the daily work of caring for cancer patients, the good results of which depend largely on time-adjusted protocols and multidisciplinary treatments.

We present a review of local, surgical and radiotherapy treatment together with authors' recommendations made from personal experience on ways to act in the diagnosis and surgical treatment of breast cancer during the COVID-19 pandemic.

The multidisciplinary Breast Committees must continue to meet weekly in videoconference format. All surgical actions and irradiations must be carried out with maximum safety for both the patients and the participating teams. Hypofractionation in radiation therapy should be the

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**PALABRAS CLAVE**

Cáncer de mama;  
 COVID-19;  
 Tratamiento  
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 Cirugía y radioterapia

standard treatment. Sometimes it is recommended to apply a primary systemic treatment or even a primary irradiation. Great coordination between the surgical and oncology teams, both medical and radiotherapeutic, is essential.

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**Diagnóstico y tratamiento locorregional de las pacientes con cáncer de mama durante la pandemia de la COVID-19**

**Resumen** Nos enfrentamos a una pandemia que afecta a una parte importante de la población. A finales de abril de 2020, en el mundo hay cerca de 3.000.000 de casos, con 205.000 muertes y 860.000 pacientes recuperados.

La respuesta a esta pandemia en muchos casos ha supuesto modificaciones importantes en el cuidado diario de las pacientes con cáncer, dependiendo el buen resultado en buena parte del ajuste de los protocolos a las circunstancias especiales y a los tratamientos multidisciplinarios.

Presentamos una revisión del tratamiento quirúrgico y de radioterapia junto con las recomendaciones de los autores basadas en su experiencia personal a la hora del diagnóstico y tratamiento locorregional del cáncer de mama durante la pandemia del COVID-19.

Los comités multidisciplinarios deben seguir reuniéndose semanalmente en formato de videoconferencia. Todas las intervenciones quirúrgicas e irradiaciones deben ser llevadas a cabo con la máxima seguridad tanto para las pacientes como para el personal sanitario que participa.

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## Introduction

The current outbreak of the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2; ‘‘COVID-19’’) has spread worldwide from an epicenter in the Hubei Province of the People’s Republic of China. By the end of April 2020, there were more than 3,000,000 cases with 205,000 deaths and 860,000 recovered patients was recognized as a pandemic by the World Health Organisation (WHO). COVID-19 was recognized on the 11<sup>th</sup> of March 2020 and had led to worldwide repercussions in healthcare delivery.

Early data from China has shown that up to 10% of hospitalized patients require critical care, usually in the intensive care unit (ICU) and hospitals have had to reorganize their services to attend to this severe increase in demand. Men are more likely to be affected than women, with 69.2% of mortality recorded in men. In women, the average age of mortality was demonstrated to be more advanced; 82 years vs 78 years respectively.<sup>1</sup>

During the weeks after the appearance of COVID-19, there have been considerable repercussions to cancer care, including breast cancer services. Specialist surgical and oncological evaluation of breast cancer patients has faced multiple issues, impacting on the diagnosis and treatment of patients with breast cancer.

Patients with diagnosed cancer have an increased risk of infection when compared to the general population as they are immunocompromised by the malignancy and indeed by oncological therapy and surgical procedures.<sup>2</sup> Additionally, should they develop an infection, the overall prognosis is worse, with higher ICU admission, mechanical ventilation requirements and mortality.<sup>3</sup>

The response necessitated by this novel situation has resulted in modification of the routine care of breast cancer patients. The success of this will depend largely on the appropriate use of multidisciplinary diagnostic pathways and treatment protocols, and the adjustment of turnaround times in every hospital to these special circumstances.<sup>4</sup>

In those breast units housed in independent buildings outside of the main hospital, no outstanding measures were needed as the premises were COVID-19 free. However, most hospitals have had to adapt to the special circumstances, including lack of resources, operating theater capacity rooms (respirators moved to ICU units), and staff being affected by the disease. This presented a difficult situation without a clear deadline.

Indeed multidisciplinary team (MDT) meetings had to occur regularly, abiding to the physical current restrictions, with only one person per specialty, maintaining a safe distance and wearing surgical masks. As physical MDT meetings have been difficult to organize in the majority of hospitals, the use of cloud platforms for video and audio conferences were utilized.

In this manuscript we present a review of locoregional treatment of breast cancer; surgery and radiotherapy. This comprises authors personal recommendations based on own experiences during the COVID-19 outbreak in accordance with international proposals.

## Breast cancer diagnosis

The patient should ideally only attend a single appointment when there is a suspicion of breast cancer that needs to be evaluated or when the diagnosis has been confirmed.

This would likely result in an agreed management plan after explaining the MDT decision, with either inclusion onto the surgical 'waiting list' following signed informed consent, or referred onto medical oncology services for primary/neoadjuvant treatment.

Patients with benign biopsy results should be contacted by phone to arrange an appointment for possible follow up or discharge from the Unit. Many patients feel overwhelmed by the situation and are weary of attending face-to-face appointments at the Hospital, which should be respected. If the biopsy results are non-conclusive and further complementary or interventional investigations are needed they will be requested. If these further studies yield benign results, they should be given by telephone.

Elderly and frail patients, especially those in nursing homes, with a breast lump are at highest risk of COVID-19, and it is recommended that they would not be evaluated at the hospital until the situation is over. Should a face-to-face appointment be required, ideally no accompanying care giver should be in attendance.

It is very important to minimize the contagion. All the staff must wear appropriate personal protective equipment (PPE) according to local protocol (i.e. surgical masks, gowns and eye protection) and maintain social distancing. If physical examination is needed, it should be performed with gloves followed by hand wash with soap for 20s. Staff and patient safety should be a priority at all times.<sup>5</sup>

In order to ensure patient and staff safety, breast screening programs and genetics counseling clinics/family history screening should be deferred until the end of the pandemic.<sup>6</sup>

All efforts should be made to avoid delayed diagnosis in those patients with suspicious clinical symptoms or imaging findings BIRADS 5 (high priority) or BIRADS 4 (medium priority) as these potentially impact cancer outcomes.<sup>7</sup>

In the current situation, it is strongly recommended that a clip is placed in any suspicious breast lesion during the first core biopsy, whether it is palpable or not, in order to avoid repeating this invasive procedure once the final pathology report is obtained.<sup>8</sup>

Breast MRI should only be used for special cases in non-infected patients in order to primarily protect the patient from infection, and also to reduce the tedious disinfecting process of the MRI Units.<sup>9</sup>

## Locoregional treatment: surgery

Every hospital, health system and breast surgeon should review their activity to organize, postpone or cancel planned breast operations or invasive procedures.

If SARS-CoV-2 tests are available, as they should always be, all patients should be tested 48h before the operation by PCR. If PCR is positive, the operation will be cancelled, and PCR will be repeated again depending on local protocols. The surgery will be planned accordingly when a negative SARS-CoV-2 test result has been achieved. Only a complete surgical team (anesthetists, surgeons, nurses, auxiliary nurses and porters) who are not symptomatic or have been in contact with an infected individual will perform the operation, ensuring patient safety.

If the surgical procedure can be deferred without compromising oncological outcomes, this should be considered.

It is essential to bear in mind that the immunosuppressive nature of both surgery and chemotherapy, may confer onto the patient an increased risk of infection compared to those without treatment.

Difficult decisions are taken daily, not only from oncological but also from ethical perspectives about which patients should have immediate surgery or which patients should have deferred surgery. One of the primary challenges of this situation is to organize and to adapt the breast units to the evolving situation without knowing when it will come to an end.

It may be taken into consideration when organizing treatment, that a 60-day delay in surgical treatment in stage I and II breast cancer has no impact on the prognosis of the patient, from the oncological point of view.<sup>10</sup>

## Surgical phases during the COVID-19 pandemic<sup>11</sup>

### PHASE I: few COVID-19 admitted patients and most hospital resources available

Surgery should be considered to patients likely to have decreased survival if surgery is not performed within 3 months:

- Patients completing neoadjuvant treatment
- Patients with tumours that are T2 or N1 Estrogen Receptor positive (ER)/Progesterone Receptor positive (PR) Human epidermal growth factor receptor 2 negative (HER2-)
- Patients with Triple negative or HER2 positive cancer
- Discordant radiology-pathology
- Patients with local recurrence
- For patients with triple negative/HER2 positive cancer, T1N0M0 should be considered as high priority for surgical intervention. The MDT should decide if T1 patients can receive neoadjuvant therapy

### After neoadjuvant chemotherapy

1. Hormone receptor positive invasive carcinoma
  - If partial or complete response is obtained, hormonal therapy can be continued to delay surgery by 4-8 weeks. Assess for progression every 2 weeks by telephone follow-up.
  - If ER positive and HER2 positive, hormonal therapy can be added to and anti-HER2 targeted therapy to defer surgery by 4-8 weeks with telephone follow-up every two weeks to assess for progression
2. Triple negative/HER2 + invasive
  - Defer surgery 4-8 weeks. It will be considered priority surgery when the situation returns to normal
3. Reconstruction with autologous tissue should be deferred. If immediate reconstruction needs to be done, direct prosthesis or expander should be the surgery of choice.
4. Encourage use of breast conserving surgery whenever possible, taking onto account availability/applicability of adjuvant radiotherapy.

**Patients that may have deferred surgery include**

- Excision of benign lesions
  - Discordant radiology–pathology lesions likely to be benign
  - High risk lesions – atypia, papilloma.
  - Prophylactic mastectomy, risk-reducing surgery, and second stage of two-stage reconstructions should be deferred to a minimum of three months
  - Sentinel node biopsy for incidental infiltrative cancer identified on excisional biopsy
  - cTisN0 lesions – whether ER positive or negative
  - DCIS
1. ER positive DCIS can be treated with hormone therapy (Tamoxifen or Aromatase inhibitors) with telephone follow-up every 4 weeks to assess for progression
  2. Small volume of ER negative DCIS without radiological suspicion of infiltrative disease can have deferred treatment and be followed up every 4 months
  3. Large volume DCIS, which is ER negative, high grade or palpable can be deferred with a strict MDT follow up every 4 weeks to detect new lumps or nipple discharge. These patients will be considered as high priority for surgery when the situation return to normal
    - Surgery for re-excision of margins
    - Tumors responding to neoadjuvant hormonal treatment
    - T1N0 ER positive PR positive/HER2 negative cancers
    - Inflammatory and locally advanced breast cancer having neoadjuvant therapy

**Non-surgical treatment to be considered, if resources are available**

1. Patients with T1N0 ER positive PR positive HER2 negative cancer can receive hormonal therapy.
2. Patients with Triple negative and HER2 positive cancer can undergo neoadjuvant therapy
3. Inflammatory carcinomas and locally advanced tumors should receive neoadjuvant therapy

**PHASE II: rapidly escalating phase. Large volume of hospital admissions due to COVID-19, requiring ICU care. Ventilators in limited capacity and shortage of theater facility**

Surgery should be restricted to patients with compromised overall survival if the procedure is not performed within the next few days.

Autologous reconstruction should be deferred.

Patients to have surgery as soon as possible:

- Drainage of breast abscess
- Evacuation of hematomas
- Review of an ischemic mastectomy flap
- Revascularization/review of an autologous tissue flap

The rest of breast procedures should be deferred.

Alternative treatments recommended if resources available:

- Consider neoadjuvant therapy for eligible patients as defined above
- Observation for the remaining cases with telephone follow-up every two weeks

**PHASE III: all hospital resources dedicated to COVID, only emergency surgery theatre capacity available**

Surgery should only be performed when patient survival is compromised if not operated within hours:

- Drainage of breast abscess
- Evacuation of hematomas
- Revision of an ischemic mastectomy flap
- Revascularization/revision of an autologous tissue flap

Emergency cases that should be considered for surgery in this phase:

- Disease that has progressed during primary treatment
- Angiosarcomas
- Malignant Phyllodes

**Locoregional treatment: radiotherapy**

Radiotherapy provision during the COVID-19 pandemic faces two main challenges. Firstly, to minimize patient contagion without compromising oncology results, as patients undergoing radiotherapy have an increased risk of infection. The second issue is related to the limitation of resources, which in a large number of hospitals have been dedicated to COVID-19 control. Deferring of surgical procedures will result in patients presenting to radiotherapy services potentially with a two- or three-month delay. This is an important management problem as patients with breast cancer represent 30% of those having radiotherapy.<sup>12</sup>

Measures during the pandemic and post pandemic have been anticipated. The European (ESTRO)<sup>13</sup> and the American societies (ASTRO) have designed different strategies that span from deferring to avoiding radiation in selected cases and the use of ultra-short irradiation schemes or even preoperative irradiation.

**Avoiding radiotherapy**

International guidelines recommend omission of radiotherapy after an informed consent in patients when<sup>14</sup>:

- Patients are older than 70
- Tumor is less than 20 mm
- Tumor is Grade I
- There is no angio-lymphatic or perineural invasion
- ER positive PR positive HER2 negative
- Ki67 < 10%
- The patient must be aware that there can be an increase in local recurrence.
- The patient will always receive hormone therapy

Radiotherapy can also be omitted in patients with low or medium grade DCIS including non-palpable tumors, less than 25 mm in size and with free margins. Special attention will be considered in patients younger than 40 years old as they have an increased risk of recurrence.<sup>15</sup>

## Delay radiotherapy

The irradiation can be deferred as much as 12 weeks in new patients after surgery.<sup>15</sup>

## Hypofractionated radiotherapy scheme (15–16 fractions)

Despite there being a variability in the treatment choice,<sup>16</sup> hypo-fractionated radiotherapy is a standard method<sup>17,18</sup> in many Spanish centers. Therefore, it should be considered as the first-choice treatment for any breast cancer,<sup>19</sup> including post-mastectomy, nodal irradiation<sup>20</sup> or even after immediate reconstruction.

In the same way, it is advisable to perform boost with hypofractionation<sup>21</sup> or even integrated with whole breast irradiation protocol and complete the treatment in 15 fractions.

## Ultra-short schedules (5–7 fractions)

The Spanish Group of Oncology Radiotherapy (GEORM) recommends the implementation of ultra-short schedules without skipping irradiation to any patient that should receive it in the original protocols.

## Whole breast and node irradiation

This group has elaborated the RHEMA protocol based in results obtained from UK FAST Trial,<sup>22,23</sup> UK FAST\_FORWARD trial<sup>24,25</sup> and HAI-5.<sup>26</sup> A 26Gy dose is given in a 5 daily fractions scheme of 5.2Gy and 29Gy at the tumor bed with a integrated boost dose of 5.8Gy. This protocol is initially considered for Tis-T3N0 tumors, but it can be also considered for node irradiation. It is important to highlight that this ultra-short schemes require special techniques as high conformational radiotherapy including IMRT (Intensity modulated radiotherapy) or VMAT (Volumetric Intensity-Modulated Arc Therapy) and IGRT (Image Guided Radiotherapy) that will verify daily position of the patient before every session.

## Partial irradiation of the breast

In selected patients and according to the criteria defined by cooperative groups GEC-ESTRO and ABS-ESTRO partial irradiation of the breast can be considered intraoperatively after tumorectomy/quadrantectomy with external radiotherapy<sup>27,28</sup> with a five 6Gy fractions for a 30Gy dose or 37.5Gy in 3.75Gy per fraction delivered twice daily<sup>29</sup> on the tumor bed with negative margin.

Conditions to be met are:

- Patient age over 50 years
- Tumor less than 3 cm
- Clear excision margins
- No positive nodes
- Grade I-II
- Luminal A biological type breast cancer

Brachiotherapy can also be an alternative but it is not available in all centers during the pandemic.

## Preoperative irradiation

Delay in surgery secondary to the pandemic will result in a delay in local treatment, which is essential for disease control. Preoperative radiotherapy emerges as an interesting alternative based in published research studies. Pathological response may be obtained with preoperative irradiation.<sup>30,31</sup> It will allow an oncologically-safer delay in surgery, improve prognosis and facilitate systemic treatment combination. The GEORM preoperative irradiation protocol is named RAPOCAMA, where 40.5 Gy are delivered in 2.7 Gy fractions in the breast with 54 Gy concomitant boost delivered 3.6 Gy daily.

This protocol can be used concomitantly with taxanes, anti-HER2 or hormonal therapy. It cannot be concomitant with anthracyclines. If they are required, the suggested protocol is radiotherapy first, and then taxanes and anthracyclines. In selected cases it can be shortened to 26Gy in breast in five 2.6 Gy fractions and concomitant 29–30 Gy boost in 5.7–5.8 Gy fractions at the tumor bed with concomitant hormonal therapy. With this preoperative alternative, surgery can be deferred for 20 weeks.

Finally, for elderly patients<sup>32</sup> without indication for surgery a hypofractionated radiotherapy scheme is proposed with weekly 6.5Gy dose delivered for 5 weeks for a total of 32.5Gy. A boost of two 6.5Gy fractions can be added to the scheme. In this case and if axillary nodes are to be included 5.5Gy fractions will be delivered up to a total dose of 27.5 Gy.

## Conclusions

Breast units are facing new scenarios and unprecedented situations during the pandemic. Protocols have been adapted to the changing situation, placing patient safety and oncological care of paramount importance. These patients not only have a diagnosis of breast cancer but also suffer a lockdown with restrictions to communicate and to move freely, adding an increase of anxiety.

Multidisciplinary team meetings should be continued and performed 'virtually' or restricted to one member by specialty if videoconferencing facilities are not available. The patient should be informed accordingly about the COVID situation and the decisions taken.

All surgical and radiotherapy procedures must be performed with the highest level of patient and staff safety.

Many breast units may have to change their protocols, and we should not ignore the future impact that those changes will have on our patients. Notwithstanding, our duty is to minimize this impact as much as possible. We have to be proactive and to learn from positive consequences that can be applied to future protocols.

During these months the importance of local and national leadership in every specialty has been raised as an essential measure to reorganize the activity to achieve optimal safety and efficiency.

Looking toward the future, many research lines are now open not only focusing on the impact of COVID-19 in the

diagnosis and treatment of breast cancer, but also on the opinion of how patients have experienced this extreme situation. Study of PREMS (Patient Reported Experience Measure) and PROMS (Patient Reports Outcome Measure) will be determinant to prepare for future actions and improve patient cancer care.

Additionally, two important questions remain to be answered by our future research work:

- Will there ever be a return back to normality?
- Will protocol modification remain after the pandemic as standard treatments?

## Conflict of interest

Ricardo Pardo, Manel Algara and Angel Montero are associated editors at the Journal. Antonio Piñero is co-editor in chief at the Journal.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.senol.2020.04.002](https://doi.org/10.1016/j.senol.2020.04.002)

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