

Tor Vergata University-Hospital in the Beginning of COVID-19-Era: Experience and Recommendation for Breast Cancer Patients

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Abstract. *COVID-19 has been officially declared as a pandemic by the WHO. Italy was the first European country to be strongly affected by this outbreak. All elective and health promotion activities were reduced. Accordingly, Italian Breast Units and breast cancer (BC) screening programs scaled down significantly their activities. The aim of this study was to evaluate measures that could potentially reduce the clinical impact of COVID-19 on BC patients. Temporary recommendations are needed that could assist specialists in preventing COVID-19 infection and optimizing resources for diagnosis and treatment of BC patients.*

COVID-19 was officially declared as a pandemic by the WHO on March 11, 2020. Italy was the first European country to be involved. According to current data from the Ministry of Health, more than 120,000 people are or have been infected with the SARS-COV-2 virus and the fatality rate is greater than 11% (1). Therefore, most of the national health system's resources, especially with regard to intensive care, were reallocated for the management of these complex patients. In particular, all elective and health promotion activities were paused or profoundly reduced. Breast cancer units throughout Italy have suffered significant restrictions and abatements in their clinical activity (2). In Italy, approximately 5000 women are diagnosed early with breast cancer (EBC) (infiltrating cancer <1 cm or DCIS) every year

through organized national screening programs (2, 3). One in nine women will be diagnosed with Breast Cancer (BC) during their life time, and approximately more than 50,000 BC cases are diagnosed in Italy every year. These numbers indicate that BC is the primary tumor in the Italian population and in the female population, regardless of the age group (3).

Over the years, the national screening program improved significantly the prognosis of patients diagnosed with BC to approximately 87% at 5 years. The increase in EBC diagnoses during the first eight years of the screening program, resulted in the reduction of the rate of tumors in advanced stages by about 30%. It should be stressed that time is fundamental in achieving such results and indeed correlates to the duration of the screening program since its introduction (4). Early diagnosis primarily improves the patient's clinical outcome. It is important to underline that the incidence rate reduction represents a resource for our health system in terms of adjuvant therapy reduction, surgery duration, early return to work and improvement of life quality together with aesthetic result of our patients. In the pre-screening era, approximately 50% of patients had been diagnosed with locally advanced stage (5).

In recent years, awareness campaigns have made it possible to extend screenings to age groups excluded from the organized national screening program, as well as in regions where adherence to organized screening programs is difficult for various reasons. In this perspective, the interruption of elective or semi-elective clinical activities may also significantly impact the rate of radiographic and ultrasound examinations carried out independently. In the Lazio region, for example, not-invited screenings contribute to approximately 40% of total mammography screenings (Total mammography screening coverage in Lazio is 79.3%, organized mammography screening coverage 47.5%, and not-invited mammography screening coverage 31.5%) (3). Hence, considering and analyzing COVID-19 impact on not-invited screening is of paramount importance.

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The COVID-19 effect, in our opinion, should also be considered and discussed considering patients' psychological aspects. Some of our analyses currently being published, reflect how the fear of contagion can harm patients' adherence to core needle biopsy (CNB) procedures or even surgical procedures in hospitals that are increasingly being, partially or totally, redirected to the clinical management of COVID-19 patients. Despite the introduction of adjuvant and neoadjuvant chemotherapy, breast surgery is a mandatory treatment for all our patients; its refusal may have a severe impact on survival (6-8). Preliminary literature data demonstrate that in selected metastatic patients, primary tumor surgery can provide survival advantage (9, 10).

In the light of these data, the return to normal should be planned as soon as possible in order to avoid reversing the progress in clinical outcomes achieved in the past years. In the period following this emergency, the national and regional health systems will probably have the capacity to manage a greater number of patients with diagnoses of locally advanced BC (LABC), or even metastatic (11, 12). The estimated doubling time of BC ranges between 45 and 260 days (13). This variability along with the neoplasms' type of Gompertzian growth do not allow us to precisely estimate the number of patients who will progress during this period (14). Up to 50% of patients who would have benefited from screening in this emergency period, could presumably present with a tumor larger than one cm. These numbers may be worsened if the current situation extends for longer periods. Therefore, it is required, in our opinion, that organizations of specialists within the sector (Medical Oncologists, Oncological Surgeons, Radiotherapists, Breast Radiologists, Epidemiologists) produce general guidelines as has already been done by the Italian Society of Anesthesia Analgesia Resuscitation and Intensive Care (SIAARTI) (15) and by our Chinese colleagues in the main branches of surgical oncology (16-19). Additionally, guidelines issued by the Society of Surgical Oncology (SSO) on March 30, 2020 have been recently added to the aforementioned recommendations (20). Issuing specific guidelines for cancer patients is of even greater importance, since preliminary data show that a personal history of cancer is associated with higher rates of COVID-19 pathology as well as worse outcomes compared to the general population, with a greater risk when cancer treatment had been carried out in the last month (21). These guidelines could assist specialists in preventing COVID-19 infection as well as in optimizing resources for diagnosis and treatment of other diseases like BC. Specific guidelines could help physicians in the case of medical-legal issues. However, description of control measures taken in the hospital and nationwide to reduce the spread of COVID-19 is beyond the aim of this manuscript. Some examples of these measures are listed below.

1. General measures

- a. For patients:
 - i. Avoid crowded places (supermarkets, hospitals) as much as possible.
 - ii. Avoid contact with people who have been in direct contact with COVID-19 patients or patients at high risk of contagion.
 - iii. Maintain a separate space in the house paying special attention to ventilation.
 - iv. Frequent hand washing.
 - v. Use of appropriate personal protective equipment (PPE) when leaving the house.
 - vi. Measure body temperature daily.
 - vii. Adopt healthy lifestyles even during the lockdown period, avoiding excessive alcohol and food consumption, practicing moderate physical activity.
- b. Healthcare personnel:
 - i. Use of appropriate PPE during clinical visits, non-invasive tests and invasive diagnostic tests.

2. General measures:

- a. Punctual evaluation of the infection risk.
- b. Avoidance of evaluation of patients with fever of indeterminate origin except for oncological emergencies prior to exclusion of COVID-19.

3. Ambulatory surgical patients:

- a. Telehealth clinical activity for:
 - i. Second opinion.
 - ii. Postoperative outpatient visits in the absence of signs and symptoms or the need for minimally invasive procedures.
 - iii. Follow-up visits (evaluate delay of 1-3 months as well as pairing mammography screening).
- b. Principle of proximity: promoting the choice of hospital based on the proximity to BC patients' home in order to minimize travel.
- c. Screening of patients admitted to outpatient visits for COVID-19 symptoms and/or direct contact with COVID-19 patients.

4. Patients with surgical indication:

- a. Preoperative assessment/general recommendations:
 - i. All patients who are considered to have high surgical priority should be admitted to surgery when deemed safe by the reference health system/hospital.
 - ii. Enhance the one-stop approach (mammography, ultrasound, CNB in the same day) and perform all the exams for the preoperative assessment (anesthesiologic visit, blood test, chest x-ray, electrocardiogram when required).
 - iii. Usage of 8-gauge procedures for the histological diagnosis of neoplasia. In case of lesions that

- could be totally excised, proceed with systemic adjuvant therapy and re-evaluate the surgical options at the end of the outbreak (4-6 months) (22, 23).
- iv. Enforce enhanced recovery after surgery (ERAS) protocol to reduce as much as possible hospitalization, promote same day discharge and avoid the possible postoperative immune depression (*e.g.* awake surgery) (24-26) and promote conservative breast surgery when possible (25-27).
 - v. If technically not feasible to avoid mastectomy and the patient does not fall within the indications for neoadjuvant chemotherapy, consider pre-pectoral reconstruction (28).
- b. Risk reduction surgery/benign surgery:
 - i. Delay reconstructive surgeries by three months.
 - ii. Delay by three months all benign breast pathologies that require surgical re-excision after interventional procedures (*e.g.* CNB) (29, 30), except after conservative therapy failure (mastitis/abscess).
 - c. DCIS: test hormone receptors in all biopsies diagnosed with DCIS:
 - i. Estrogen receptor (ER) + DCIS could be treated with endocrine therapy for 3-5 months (aromatase *vs.* tamoxifen). Re-evaluation of patients every 8-12 weeks aimed to assess the onset of new symptoms.
 - ii. ER- DCIS treatment could be postponed in case of illness and re-evaluated through strict follow-up regime every 4 weeks.
 - iii. High grade DCIS/large dimensions ER- DCIS/palpable DCIS: decision regarding avoidance of surgery should be taken during multidisciplinary meeting (MDT). Telehealth evaluation every 4 weeks.
 - iv. Patients with ER- DCIS, micro-invasive ER+/ER- DCIS, high-grade DCIS, palpable DCIS, large ER- DCIS - should be considered high priority patients.
 - d. Invasive breast cancer (IBC):
 - i. Consider extensive use of neoadjuvant therapy (NAC) in order to reduce COVID-19 infection risk (31).
 - ii. ER+ IBC Stages I-II:
 - Start neoadjuvant chemotherapy if indicated.
 - Genetic test on CNB specimen to evaluate NAC (hormonal *vs.* standard chemotherapy).
 - Consider treatment with hormonal NAC up to a maximum of 3-5 months and reassessment every 4 weeks (ovarian suppression + tamoxifen *vs.* premenopausal aromatase inhibitors and aromatase inhibitors in post-menopausal patients).
 - In case of high-risk of adjuvant treatment after surgery, proceed with NAC.
 - iii. ER+ IBC Stages III-IV:
 - Evaluate hormonal NAC or NAC after MDT.
 - iv. IBC Triple Negative or Her2 Type:
 - T2N0M0 and T0-4N1M0: NAC.
 - T1N0M0: After MDT discussion, these patients should be considered to have high surgical priority. Eventual NAC should be discussed, especially in case of large lesion.
 - v. Surgery after NAC:
 - Consider using percutaneous biopsy techniques to verify the extent of the pathological response in order to stratify patients and to admit to urgent surgery [those who have not reached pathological complete response (pCR)] (32).
 - Evaluate continuation of the treatment with neoadjuvant intent by modifying the schedule according to the molecular subtype.
 - ER+ Tumors: Consider converting to hormonal NAC in the event of a complete or partial response to treatment in order to delay surgery by 4-8 weeks. Re-evaluate the patient every 2-4 weeks to assess any progression. In case of HER2+ patient, consider converting to target therapy treatment in the event of a complete or partial response in order to delay surgery by 4-8 weeks. Re-evaluate patients every 4 weeks to assess any progression. Delay the post-chemotherapy window by 4-8 weeks. These patients should be considered to have high surgical priority.
 - vi. Special cases:
 - Patients with progression disease during NAC, angiosarcomas and phyllodes malignant neoplasms should be considered as high surgical priority.

In our opinion, these suggestions could be utilized both, short term as temporal guidelines and long term as suggestions for the reorganization of health policies along with the clinical management of patients.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Oreste Claudio Buonomo, Marco Materazzo, Jonathan Caspi, Emilio Piccione, Gianluca Vanni contributed equally to this work: conception, design, drafting the work and final approval of the version to be published.

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