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Lasting Impacts of the COVID-19 Pandemic on Breast Cancer Diagnosis and Treatment in the United States

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KEYWORDS

• Breast cancer • COVID-19 • Screening • Elective procedures
• Neoadjuvant endocrine therapy

KEY POINTS

- COVID-19 pandemic resulted in a decrease in the use of screening mammography in the early part of the pandemic.
- The moratorium on elective procedures early in the COVID-19 pandemic resulted in increased use of neoadjuvant endocrine therapy for hormone positive breast cancer delaying surgical resection until later in the pandemic.
- COVID-19 pandemic resulted in an increase in the utilization of telehealth and decreased enrollment in breast cancer clinical trials.
- There was an increase in same day discharge after all breast operations including mastectomy with or without reconstruction.
- Use of hypofractionated radiation regimens increased.

INTRODUCTION

Concern regarding a novel coronavirus first began in late fall of 2019 in China with the first human case of COVID-19 caused by SARS-CoV-2 reported in Wuhan City, China, in December 2019.[1] After more than 118,000 cases were reported in 114 counties and 4,291 deaths, escalation to the declaration of a worldwide pandemic by the World Health Organization (WHO)[1] occurred on March 11th, 2022.[2] Upon the declaration of a pandemic and surge of cases, countries began to close their borders to international travel and implemented stay-at-home orders. Social distancing and mask-wearing guidelines ensued in order to mitigate the spread of the novel virus.

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As the number of cases escalated, hospital systems became overwhelmed due to the shortage of essential medical equipment (especially PPE and ventilators), hospital beds, and health care workers. State of emergency declarations were made in order to reallocate and prioritize resources towards the COVID-19 pandemic. The reallocation of resources created unique challenges and downstream effects on many aspects of breast cancer diagnosis, treatment, and research efforts. Several medical societies collaborated in order to provide guidance on how to continue providing breast cancer care in unprecedented times. Due to the abrupt cessation of elective imaging and procedures, concern for continuing to provide appropriate screening, diagnosis, and treatment arose, especially in the oncology sector of health care. In addition, due to widespread concern about contracting the COVID-19 virus patients began to cancel or delay medical visits. In September 2020, the CDC released data in the *Morbidity and Mortality Weekly Report (MMWR)* that an estimated 41% of US adults had delayed or avoided seeking medical care due to concerns about exposure to COVID-19.[2]

IMPACT ON BREAST CANCER SCREENING

Modern modalities for breast cancer screening were developed in the late 1960s with the first official recommendations of screening mammography by the American College of Surgeons (ACS) in 1976.[3] The goal of screening is to detect and diagnose diseases at an early stage. At the time of the COVID-19 pandemic, the United States Preventive Services Task Force (USPSTF) recommended women aged 50-74 with an average risk of breast cancer have a screening mammogram every two years.[4] Since approximately 1 in 8 women will be diagnosed with breast cancer in their lifetime, early detection with screening modalities has an important impact on morbidity and mortality.[3]

At the onset of the COVID-19 pandemic in March of 2020, elective imaging and procedures, including cancer screening modalities, were put on hold in order to conserve personal protective equipment, create hospital capacity and to protect patients and medical personnel from exposure to the virus. On March 26, 2020, the American Society of Breast Surgeons (ASBrS) and the American College of Radiology (ACR) issued a joint statement recommending medical facilities to postpone all breast screening including mammography, ultrasound and MRI.[5] As a result of guidelines and patients' fear of exposure to the virus, there was a significant decrease in the number of breast cancer screening appointments during the initial months of the pandemic. In a study conducted by Grimm and colleagues[6] that utilized the National Mammography Database, screening mammograms were down 63.7% in the time period of March 1- May 31, 2020. Another study looking at the National Breast and Cervical Cancer Early Detection program, a program designed to provide treatment and screening modalities to low income or underserved populations, demonstrated a sharp decline of 87% in the number of screening mammograms in April of 2020 compared to the previous five years.[7]

Consequently, there was a decrease in the number of new breast cancers diagnosed during the moratorium of breast screening modalities.[6] Concerns arose regarding possible worsening of cancer outcomes due to delay in diagnosis. Studies conducted during the early phases of the pandemic predicted that patients would present with more advanced disease resulting in possibly worse cancer outcomes.[8] A recent study published in December 2022 evaluating the National Cancer Database reported a 12.4% deficit in the number of expected cancer diagnoses in 2020. Breast cancer was amongst the largest absolute decrease in the number of cases with approximately 34,000 fewer cases in 2020 than expected.[9]

In May 2020 the Society of Breast Imaging released guidelines on how to proceed with a safe return to imaging, followed by recommendations from the ACR in July 2020.[6] Guidelines provided strategies for health care systems and for patients to safely return to screening practices including expanding hours, spacing out appointments and sanitization strategies. Upon the cessation of elective procedure moratoriums, screening mammography rates began to rebound. According to the study by Grimm and colleagues,[6] the volume of screening mammograms, diagnostic mammograms, and breast biopsies rebounded to 85.3%, 97.8%, and 91.5%, respectively, during March-May of 2021 when compared to the pre-COVID-19 volume from March-May of 2019.

Although early studies predicted patients would present with more advanced disease, more recent retrospective studies looking at the effects of screening delays due to the COVID-19 pandemic on breast cancer stage at the time of diagnosis have shown mixed results. In a single-institution, retrospective review published in April 2021 by a university referral center in Italy, no significant difference in tumor biology was demonstrated but a significant increase in clinical stage III disease and node positive disease at diagnosis was found after a two-month interruption in breast cancer screening.[10] Another retrospective, single-site study, from the first year of the pandemic found no difference in breast cancer stage at diagnosis, method of cancer detection, or tumor biology comparing March-August 2020 (early COVID) to March-August 2019 (pre-COVID).[11] In a more recent retrospective, multi-institutional study published January 2022, there was a slight increase in presenting tumor size and positive nodal status in the newly diagnosed breast cancers during the early phase of the pandemic due to the tumors being self-detected.[12] As soon as regular screening was resumed, the significance was no longer demonstrated.[12]

The overall impact of the breast cancer screening moratorium from COVID-19 is still unknown and ongoing and given the latency in breast cancer diagnosis and mortality, it may take years to be realized.

IMPACT ON BREAST CANCER TREATMENT

In order to mitigate the viral spread and preserve medical equipment, especially PPE and ventilators, cessation of nonessential appointments and elective procedures was imposed in mid-March of 2020.[13] This resulted in the closure of many operating rooms and limitation on all procedures including operations for cancer. These unprecedented times prompted health care systems to implement creative measures and triage strategies with guidance from several medical societies in order to weigh the challenging situation of protecting patients and workers safety by decreasing exposure to the novel virus while continuing to provide medical care.

The COVID-19 Pandemic Breast Cancer Consortium, created by representatives from ACR, ACS, ASBrS, American Society for Clinical Oncology, National Comprehensive Cancer Network and the Society of Surgical Oncology, released an article in April 2020 to provide expert opinion on how to safely provide multidisciplinary breast cancer care during the COVID-19 pandemic.[14] As an effort to evaluate the impact of these expert guidelines and overall impact of the pandemic on breast cancer management in the United States, the ASBrS created a COVID-19 supplemental module to their established registry database.[15]

Conduction of outpatient visits was also changed due to the COVID-19 pandemic. Guidelines recommended implementing a triage strategy to only conduct in person visits with patients who were prioritized as high risk such as patients with a new diagnosis of breast cancer or established patients with new problems such as infections, palpable findings or suffering from severe side effects from their treatment regimens.[14]

During the early phases of the pandemic, it was widely encouraged by institutions across the United States to limit the number of treatment team members during in person visits along with strict visitor restrictions for in person patient encounters.[16]

IMPACT ON SURGERY

In response to the Centers for Disease Control recommending that all elective surgeries and non-essential medical, surgical, and dental procedures be delayed during the novel COVID-19 outbreak, several medical societies published guidelines for providers and health care administrators on how to categorize non-emergent surgery.[17] The COVID-19 Pandemic Breast Cancer Consortium recommendations implemented a triage strategy based on breast cancer tumor biology and disease stage. Surgical intervention was recommended in patients who were completing neoadjuvant chemotherapy for triple-negative disease. Whereas for patients with early stage, hormone positive disease neoadjuvant endocrine therapy was recommended in order to safely delay surgery and avoid undergoing surgery during the height of the pandemic.[14,15]

Along with the implementation of prioritization strategies to determine which patients with breast cancer should undergo surgery, which surgery to offer was also influenced. To minimize the length of hospital stay and potential COVID-19 exposure along with conserving resources, outpatient, same day procedures were encouraged.[15] Patients eligible for breast conservation therapy (BCT) were discouraged from undergoing mastectomy to minimize operative time. In patients who were to undergo mastectomy, contralateral prophylactic mastectomy, and immediate reconstruction were discouraged in order to reduce surgical time and risk of complications.[15,18,19] Increased health care cost due to multiple surgical interventions along with long-term patient psychological effects were acknowledged as possible consequences.[15] All prophylactic surgery as well as breast surgery for benign or high-risk lesions, such as fibroadenoma or atypia were also postponed.

Given the focus on minimizing exposure of patients and health care workers to the virus and shortage of PPE many centers shifted from routine 23-hour observation or admission of patients after mastectomy to same day discharge.[20] This was not only for patients undergoing total mastectomy but also those that underwent mastectomy with immediate reconstruction. Although the COVID-19 pandemic placed unprecedented emphasis on outpatient breast cancer surgery, the initial shift to home recovery after mastectomy began in the early 2000s with literature supporting that home recovery is a safe option for appropriately selected patients without increased risk of complications.[21] A recent study published in January 2023 looked at outcomes of same-day discharge mastectomy pre- and post-COVID19 pandemic and showed no difference in complication rates including hematomas, readmissions or surgical site infections.[20] These studies support the continued effort of enhanced recovery after surgery practices which will likely continue to grow in both the number and types of procedures that will be performed as an outpatient.

IMPACT ON CHEMOTHERAPY

Treatment of breast cancer requires a multidisciplinary approach with medical oncologists providing expertise in hormonal, chemotherapy, and/or targeted therapy regimens. In response to the delays or cancellations of non-emergency surgery in March 2020, the medical management of breast cancer changed, especially the utilization of neoadjuvant endocrine therapy.

The standard of care for early stage, estrogen positive (ER+) breast cancer was generally upfront surgery with partial or total mastectomy with or without axillary

staging, followed by adjuvant endocrine therapy with or without adjuvant radiation or chemotherapy. Prior to the COVID-19 pandemic, the use of neoadjuvant endocrine therapy in ER + breast cancer was recommended to downstage disease in patients with large or locally advanced tumors in order to potentially allow patients to become breast conservation surgery candidates and was used for elderly patients or patients with significant comorbidities contraindicating operative intervention.[22] In response to mandated surgical delays during the early phase of the COVID-19 pandemic, guidelines recommended that patients with ER+/HER2-disease can safely defer surgery and receive neoadjuvant endocrine therapy for 6-12 months without any clinical compromise.[14]

Although the widespread use of neoadjuvant endocrine therapy in early-stage ER + breast cancers has only been widely adopted in the US due to the unprecedented nature of the COVID-19 pandemic and implemented guidelines, this strategy has been used commonly in the UK even prior to the pandemic. Pre-pandemic neoadjuvant endocrine treatment in ER+/HER2-breast cancer use in the US was increasing in patients where the clinical team wanted to decrease tumor size and enable breast-conserving surgery. The pandemic resulted in a significant boost in the use of neoadjuvant endocrine therapy as a bridge until surgery could be safely performed.[15] As we move forward it can also be used post-pandemic when treatment teams anticipate delays in surgery for patients (such as those with comorbidities, or those needing to stop smoking prior to mastectomy with reconstruction) and to assess responsiveness to endocrine therapy.

Medical oncologists were also faced with considering alternative treatment schedules and regimens to minimize the risk of virus exposure in their immunocompromised patient population. Chemotherapy schedules were encouraged to be modified in order to reduce clinic visits by changing dosing intervals.[14] In addition, an increased use of genomic testing on core needle biopsies at diagnosis occurred to aid in medical decision making regarding neoadjuvant chemotherapy versus neoadjuvant endocrine therapy or upfront surgery.[15] While the data on genomic assays were developed using surgical specimens from upfront surgery, genomic assays are now frequently performed on percutaneous core needle biopsy.

IMPACT ON RADIATION THERAPY

As with the medical and surgical treatment of breast cancer, a triaged and personalized approach was recommended for the utilization of radiotherapy in patients with breast cancer. Patients with symptomatic disease who would benefit from palliative regimens and patients progressing on neoadjuvant therapy were considered high priority.[14] Current literature supports that adjuvant radiotherapy initiation can be delayed safely up to 3-6 months in select patients,[18] so the priority of radiotherapy was for high-risk patients, palliative treatment or patients already initiated on a treatment regimen.

In a similar manner to systemic treatment, changes to radiotherapy schedules in order to minimize exposure to the virus were also recommended. Guidelines recommended the use of moderate hypofractionation and ultra-hypofractionation for appropriate patients. In patients with breast cancer without positive regional lymph node disease, moderate hypofractionation was already widely used but the pandemic accelerated the use of ultra-hypofractionation in patients with early-stage breast cancer.[23] As a result of the COVID-19 pandemic, utilization of telemedicine and hypofractionation modalities are likely to remain part of the radiotherapy treatment of breast cancer.

IMPACT ON CLINICAL TRIALS

The COVID-19 pandemic had a significant impact on the recruitment and conduct of clinical trials due to multiple factors. A survey conducted at the beginning of the pandemic suggested that at least 60% of investigators halted or delayed enrollment of patients into clinical trials with 50% reporting prioritizing enrollment to higher priority trials.[24] At the beginning of the pandemic, health care systems were overwhelmed which required the reprioritization of health care resources across the nation. Research efforts including institutional review boards prioritized efforts in the investigation and creation of therapies and vaccinations against the novel virus. The US Food and Drug Administration also issued specific guidelines in order to address situations in which to consider withdrawal of participation in trials in regard to their safety as the pandemic evolved.[25] Although appropriate, this led to a significant backlog in study startups and delay in the opening of new cancer-related clinical trials. Funding for cancer research, including grant funds from large organizations such as the American Cancer Society, were also considerably decreased due to the economic unrest from the pandemic.[3]

In addition to the reallocation of research resources, transmission mitigation strategies including stay at home mandates and transition to working in a remote setting had significant impacts on the conduction of clinical trials. In order to protect health care workers from unnecessary COVID-19 exposure, many "non-essential" personnel were transitioned to working remotely which created challenges in the conduction of trial operations. Even during the initial pandemic recovery phase, on-site research staff continued to be limited causing a decrease in clinical trial enrollment and slowing trial conduction.[26] The cessation of elective procedures also interrupted many aspects of clinical trials such as screening, diagnostic imaging, and research biopsies as these were placed on hold.

Patients enrolled in clinical trials also faced challenges both with the worry of exposure risk, especially amongst immunocompromised patients with cancer, and also with long distance travel to tertiary centers during times of mandated quarantine. Due to this, many patients opted for treatment options that required fewer visits to medical centers which prevented the consideration of some clinical trials.[26] The National Cancer Institute provided interim guidance for enrolled patients which included allowing patients to transfer care to local health care providers and use of local laboratories for blood tests etc. when they could not travel to the enrolling study site.[27]

Despite the initial shutdown and challenges of conducting clinical trials, restarting resumed in a stepwise approach beginning with patients in phase 1 trials, moving on to other treatment trials and observation cohort studies, tissue collection studies, and quality of life studies as the last to resume.[26] The COVID-19 pandemic was an incredibly challenging time for the recruitment and conduction of cancer clinical trials that required the adaptation of a hybrid system of virtual and in person visits. As an unintended consequence, the pandemic may have provided meaningful improvement in the utilization of telehealth and virtual communication platforms in many aspects of the trial process including informed consent.

IMPACT ON MENTAL HEALTH

The COVID-19 pandemic resulted in a significant impact on both breast cancer patient and health care provider mental health. In addition to stay-at home mandates creating social isolation, strict hospital visitor restrictions for hospital stays and appointments incurred additional anxiety for patients during the pandemic. According to the COVID-19 Mental Disorder Collaborator, there was a 27.6% increase in the cases of major

depressive disorder and 25.6% increase in the cases of anxiety disorders globally throughout 2020.[28]

Impacts of the pandemic on physician well-being were studied via the CROWN study which surveyed over 800 breast specialists in the United States. The study aimed to evaluate the effect of delayed patients' treatment on physician emotional wellness. Nearly 80% of breast physicians reported some sort of delay in either screening, surgical interventions, or systemic treatment for their patients. The survey also found that mean anxiety and COVID-19 burnout scores were higher in physicians whose patients experienced delays in their cancer treatments.[29]

DISCUSSION

The COVID-19 pandemic was an unprecedented time with lasting impacts on the diagnosis, treatment, and research of breast cancer in the United States. As a result of the pandemic there have been advancements in the utilization of telehealth methods in patient care and clinical trials, increase in the use of genomic testing on core needle biopsy to guide upfront surgery versus neoadjuvant therapy, increase in the use of neoadjuvant endocrine therapy in patients with early-stage ER + and increase in outpatient surgery for breast disease. Further research is ongoing and necessary to determine the long-term outcomes and psychological impact of the COVID-19 pandemic on patients with breast cancer.

CLINICS CARE POINTS

- Outpatient surgery for patients undergoing mastectomy without and with reconstruction will continue to grow as evidence supports home recovery after mastectomy has no difference in adverse outcomes
- Increased use of neoadjuvant endocrine therapy treatment in ER+/HER2-breast cancer during the pandemic as a bridge to surgery may also be more commonly used post-pandemic to assess responsiveness to endocrine therapy and as a bridge to surgery while awaiting genetic testing or smoking cessation
- The pandemic resulted in an improvement in the infrastructure and increase in the utilization of telehealth and virtual communication with patients.
- The pandemic resulted in the acceptance of telehealth for informed consent and accepting more laboratory testing to be performed locally which will improve access for patients to clinical trials
- Hypofractionation modalities are likely to remain part of the radiotherapy treatment of appropriately selected patients with breast cancer post-pandemic

DISCLOSURES

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