Treatment for breast cancer patients during the special period of novel coronavirus pneumonia outbreak

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Hong Pan
The First Affiliated Hospital with Nanjing Medical University

Hui Xie
The First Affiliated Hospital with Nanjing Medical University

Jiaxin Zhang
Affiliated Hospital of Xuzhou Medical University

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The Affiliated Huai’an No.1 People’s Hospital of Nanjing Medical University

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Affiliated hospital of Nantong University

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Jun Gu
Jinling Hospital

Tongbo Yi
Jiangsu Taizhou People’s Hospital

Xiaoan Liu
The First Affiliated Hospital with Nanjing Medical University

Wenbin Zhou
The First Affiliated Hospital with Nanjing Medical University

zhouwenbin@njmu.edu.cn Corresponding Author

Shui Wang
The First Affiliated Hospital with Nanjing Medical University

ws0801@hotmail.com Corresponding Author

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Abstract
Purpose: The outbreak of novel coronavirus pneumonia occurred worldwide. 2019 novel coronavirus disease (COVID-19) can be transmitted from human to human, cause hospital infection, and seriously threatens surgical staffs and inpatients. The treatment of patients with breast cancer may be affected in this special period.

Methods: From 24th January to 8th March 2020, patients diagnosed with breast cancer were enrolled from 16 hospitals in Jiangsu Province, and patients, who were candidates for surgery after neoadjuvant chemotherapy, were also enrolled. Patients from 24th January to 8th March 2019 were included as control with the same criteria.

Results: In 2019, 520 patients were diagnosed with breast cancer in these 16 hospital; however, only 229 patients (decreased by 56%) were diagnosed with breast cancer in the same period of 2020. The clinical characteristics were similar between the two groups, and core biopsy was performed to more patients in 2020 than that in 2019 (4.1 days ±3.2 vs 3.2 days ±2.6, P < 0.001), and more patients underwent mastectomy and axillary lymph node dissection in 2020. After neoadjuvant chemotherapy, the mean interval between last time of neoadjuvant chemotherapy and surgery in 2020 was significantly longer than that in 2019 (29.2 days ±11.1 vs 17.7 days ±8.2, P < 0.001). After examinations to rule out COVID-19, no COVID-19 was found in any patient.

Conclusions: In the special period of novel coronavirus pneumonia outbreak, the treatment of patients with breast cancer was delayed, but the treatment was safe after strict exclusions of COVID-19.

Introduction
The outbreak of novel coronavirus pneumonia occurred at the end of 2019 in Wuhan China[2], which has been reported in 203 other countries, including Korea, Japan, Italy, Iran, America and so on. The novel coronavirus pneumonia was named 2019 novel coronavirus disease (COVID–19) by the World Health Organization (WHO) on 7th January 2020. By 1st April 2020, the rapid spread of disease has caused 82,631 cases and 3,321 deaths in China, and 796,349 cases and 38,563 deaths in other countries. After the outbreak of this disease, China has launched the “first level response” on 24th January 2020. On 30th January 2020, the WHO declared the Chinese outbreak of COVID-19 to be a
Public Health Emergency of International Concern [13], and now COVID-19 is a pandemic.
The characteristic of COVID-19, including high contagiousness, herd susceptibility and clinical phenotype diversity, made a serious influence on people’s daily life[15]. The epidemic situation brings anxiety and distress to the general population. Many patients are afraid to go to the hospital, because of the possibility of hospital infection, which seriously threatens surgical staffs and inpatients. Therefore, the diagnosis and treatment of patients with other diseases have been greatly affected. Due to the systemic immunosuppressive state caused by cancer and anticancer treatments, cancer patients are more susceptible to infection than individuals without cancer[5, 6, 8]. Compared with patients without cancer, patients with cancer were observed to have a higher risk of COVID–19[7]. The epidemic of COVID-19 poses new challenges to diagnosis and treatment of patients with malignant tumors.
By far, the duration of the epidemic is uncertain worldwide, if patients with malignant tumors won’t get effective treatment for a long time, they may suffer from disease progression. Breast cancer is the most frequent malignancy in women, and delayed surgery and chemotherapy have adverse effects on the prognosis of some patients with breast cancer.
To the best of our knowledge, the details of the treatment of breast cancer patients in this special period is not known. We summarized the experiences of the diagnosis and management of patients with breast cancer in Jiangsu Province with 107,200 square kilometers and more than 80,000,000 persons, where COVID–19 was well controlled. We hope our experiences will be beneficial to other hospitals for the management of breast cancer.
Materials And Methods
Patient enrollment
From 24th January to 8th March 2020, patients diagnosed with breast cancer in this special period were enrolled from 16 hospitals in Jiangsu Province, and patients, who were candidates for surgery after neoadjuvant chemotherapy, were also enrolled. Moreover, patients from 24th January to 8th March 2019 were selected as control with the same criteria. This study was approved by the ethics committee of enrolled hospitals, and all patients provided informed consent for their clinical
information to be reviewed by us. This study was in compliance with the Helsinki Declaration.

Data collection
The demographic variables, including age, sex, and menopause status, were collected. Moreover, the basic clinical characteristics and pathological variables of the enrolled patients were collected by trained interviewers. Additionally, the treatment strategies were also recorded.

Statistical analysis
In the present study, percentiles, medians and ranges were analyzed for continuous variables. Differences between the two groups were examined using the Chi-square test or Fisher’s exact test for unordered categorical variables, and the differences of the averages between the two groups was tested using a T-test. All statistical analyses were performed by using Stata version 11.0 (StataCorp, College Station, Tex). A two-sided level of significance of 0.05 was applied in all tests.

Results
COVID–19 in Jiangsu Province
Up to 8th March 2020, 631 patients were diagnosed with COVID–19 in Jiangsu Province, and all patients recovered till now. From 24th January to 24th February, the “first level response” has been launched by Jiangsu Province, as the highest level in China. After 24th February, the “second level response” was launched.

Patients newly diagnosed with breast cancer
Sixteen hospitals from 12 cities in Jiang Province (13 cities in all) were enrolled in this study. From 24th January to 8th March in 2019, 520 patients were newly diagnosed with breast cancer in these 16 hospitals; however, only 229 patients (decreased by 56% compared to 2019) were diagnosed with breast cancer in the same period of 2020. Of these 16 hospitals, less patients were diagnosed with breast cancer in 2020 than in 2019 in 15 hospitals (Figure 1). Only 1–2 patients with breast cancer were treated in 5 hospitals. In Jiangsu Breast Disease Center, 44 patients were newly diagnosed in 2020, decreased by 72% in comparison to 2019 with 156 cases (Figure 1). However, more patients were treated in 2020 than in 2019 in one hospital.

Of 229 patients diagnosed from 24th January to 8th March in 2020, the clinical characteristics were similar to that in 2019 (Table 1). Furthermore, the treatment selection was still similar to that in 2019. However, core biopsy was performed to more patients in 2020 than that in 2019 ($P = 0.005$). Similar
results were found in Jiangsu Breast Disease Center (Supplementary Table 1). Of these 229 patients, 201 were underwent surgery firstly (Table 2). The mean interval from the day admitted to hospital to surgery in 2020 was significantly longer than that in 2019 (4.1 days ±3.2 vs 3.2 days ±2.6, P < 0.001). Compared to 2019, significantly more patients underwent mastectomy and axillary lymph node dissection in 2020 (Table 2). After pathological examinations, tumor size and node status between the two periods were similar. The significant difference of molecular subtype between the two periods may be due to the unknown status of a large sample size in 2020. In Jiangsu Breast Disease Center, there was no significant difference in surgery types, tumor size, node status, and molecular subtypes between the two periods (Supplementary Table 2).

**Surgery after neoadjuvant chemotherapy**

In 2019, a total of 38 patients were candidates for surgery after neoadjuvant chemotherapy, and the intervals between last time of neoadjuvant chemotherapy and surgery were all available. Of these 38 cases, 31 (81.6%) underwent surgery ≤ 21 days after neoadjuvant chemotherapy, with a range of 3-40 days. In 2020, 19 patients were candidates for surgery in the same period. Of these 19 patients, the intervals were available in 14 patents, with a range of 9-43 days. Up to 8th March, surgery was still not performed to three patients, and only 3 patients (21.4%) underwent surgery ≤ 21 days after neoadjuvant chemotherapy. The mean interval in 2020 was significantly longer than that in 2019 (29.2 days ±11.1 vs 17.7 days ±8.2, P < 0.001, Figure 2).

**Safety of surgery during the epidemic period**

Above all, 217 patients (16 after NAC) underwent surgery successfully from 24th January to 8th March in 2020. Blood examination, chest CT scan and Real-time PCR panel were performed to all patients before surgery in these 16 hospitals to rule out COVID-19. Modified radical mastectomy was performed to most patients, and no any serious adverse effect was observed. Importantly, no COVID-19 was found in any patient.

**Discussion**

In this present study, we have collected and analyzed 229 cases from 24th January 2020 to 8th March 2020, and 520 cases from 24th January 2019 to 8th March 2019, from 16 hospitals in Jiangsu Province, China. We found that the number of patients admitted to hospital and received treatment
decreased to 44 %, which means that the majority of patients might have suffered from delays in breast cancer treatment, especially for surgery.

To suppress the spread of COVID-19, the Chinese government has implemented control measures including travel restriction, reducing crowd gathering and setting up special hospitals. And many medical resources are invested in the war against the epidemic situation. Some hospitals in China reduced surgical operation at a minimal level to prevent cross infection in this special period. On the other hand, the epidemic situation brings anxiety and distress to the general population. Because of the possibility of hospital infection, most patients are afraid to go to the hospital and see a doctor. Daily medical treatments of cancer patients have been affected in varying degrees.

Breast cancer is the most common cancer and leading of cancer death for women[12]. As we know, even small delays in the treatment of breast cancer are a frequently expressed concern of patients and their families. The most anxiety-provoking time for patients is the period from diagnosis to treatment initiation[4]. Moreover, previous studies [1, 3, 10, 16] have suggested the length of the interval between diagnosis and surgery could affect the survival outcomes in early stage breast cancer. Thus, patients with early stage breast cancer should receive surgery as soon as possible. If the patients cannot receive surgery in a short time, neoadjuvant chemotherapy is highly recommended for breast cancer.

In the special period, we have taken out over 200 surgeries for breast cancer patients. More importantly, compared with 2019, the number of surgeries increased in one hospital. As we take measures to protect patients and medical staffs, we can provide high quality medical services under the premise of ensuring safety. The largely decrease in the number of surgeries in Jiangsu Breast Disease Center may partly due to the travel restriction. However, the proportion of core needle biopsy is very high in Jiangsu Breast Disease Center, and the proportion increased during the epidemic period. The longer interval from the day admitted to hospital to surgery in this special period may be attributed to the Real-time PCR panel to exclude COVID-19.

There are also several studies [9, 11, 14] investigating the impact of timing of surgery after NAC on survival, suggesting that the delay of surgery after NAC shows poorer survival. In a word, for patients
who received NAC, the best time of surgery after NAC is < 3 weeks, and not > 8 weeks. In our study, the delay with about 11 days was found for surgery in this special period. Therefore, we propose several strategies for operative management and perioperative management of patients with breast cancer. First, pre-admission screening should be done in order to rule out COVID–19. Epidemiological inquiry is essential for each patient and the escort, including fever > 37.3°C, travel history within 14 days, and contact history within 14 days. Second, blood examination, C-response protein, chest CT and Real-time PCR panel scan should be conducted for patients. Third, the breast cancer patients should be placed in the isolated room with separate medical devices before ruling out the possibility of COVID–19. Forth, prevention measures for both medical staffs and the screen-negative admitted patients should also be enhanced because of the possibly false negative.

The topic of our study is highly clinically relevant. COVID–19 has raised intense attention not only within China but internationally. In the special period of novel coronavirus pneumonia outbreak, the treatment of patients with breast cancer was delayed, but the treatment was safe after strict exclusions of COVID–19. As the spread of COVID–19 continues, we should select appropriate therapeutic measures and optimize treatment process to prevent the propagation and cross infection of COVID–19, as well as to treat breast cancer patients effectively without delay. How to balance the prevention and control of the epidemic situation with the standard treatment of breast cancer deserves further efforts.

Declarations

Compliance with Ethical Standards

Funding

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Conflict of Interest

The authors declare that they have no competing interests.

Ethical approval
This study was approved by the ethics committee of enrolled hospitals, and all patients provided informed consent for their clinical information to be reviewed by us. This study was in compliance with the Helsinki Declaration.

**Informed consent**

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1. All new diagnosed breast cancer patients

| Variables              | 2019 (520) | 2020 (229) | P value |
|------------------------|------------|------------|---------|
| Age, y                 |            |            |         |
| ≤ 50                   | 219        | 99         | 0.776   |
| > 50                   | 301        | 130        |         |
| Menopause status       |            |            |         |
| Premenopause           | 228        | 97         | 0.745   |
| Postmenopause          | 290        | 130        |         |
| Male#                  | 2          | 2          |         |
| Clinical Tumor size    |            |            |         |
| ≤ 2 cm                 | 224        | 105        | 0.740   |
| 2-5 cm                 | 239        | 104        |         |
| > 5 cm                 | 21         | 12         |         |
| Unknown#               | 36         | 8          |         |
| Clinical node status   |            |            |         |
| Negative               | 405        | 177        | 0.858   |
| Positive               | 115        | 52         |         |
| Distant metastasis     |            |            |         |
| Yes                    | 7          | 4          | 0.744   |
| No                     | 513        | 225        |         |
| Core biopsy            |            |            |         |
| Yes                    | 204        | 115        | 0.005   |
| No                     | 316        | 114        |         |
| Treatment              |            |            | 0.600*  |
| Neoadjuvant chemotherapy| 45         | 24         |         |
| Surgery                | 467        | 201        |         |
| Salvage                | 7          | 4          |         |
| Unknown                | 1          | 0          |         |

*Fisher’s exact test

Table 2. Patients who underwent surgery firstly in 2019 and 2020
| Variables                | 2019 (467) | 2020 (201) | P value |
|-------------------------|------------|------------|---------|
| Local surgery           |            |            |         |
| Mastectomy              | 290        | 171        | 0.043   |
| Lumpectomy              | 77         | 28         |         |
| Unknown #               | 0          | 2          |         |
| Regional surgery        |            |            |         |
| SLNB                    | 203        | 68         | 0.026   |
| ALND                    | 256        | 127        |         |
| Unknown #               | 8          | 6          |         |
| Tumor size              |            |            | 0.547   |
| DCIS                    | 59         | 17         |         |
| T1                      | 178        | 76         |         |
| T2                      | 183        | 71         |         |
| T3                      | 7          | 4          |         |
| Unknown #               | 40         | 33         |         |
| Node status             |            |            | 0.282   |
| Positive                | 150        | 66         |         |
| Negative                | 313        | 113        |         |
| Unknown #               | 4          | 22         |         |
| Molecular subtype       |            |            | 0.009   |
| Luminal                 | 279        | 54         |         |
| HER2 positive           | 108        | 38         |         |
| Triple negative         | 77         | 29         |         |
| Unknown #               | 3          | 80         |         |

# not included for analysis

**Figures**

![Figure 1](image)

The numbers of patients diagnosed with breast cancer in 16 hospitals of Jiangsu Province from 24th January to 8th March in 2019 and 2020.
Figure 2

The interval between last time of neoadjuvant chemotherapy and surgery during the epidemic period and in 2019.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
S Tables(1).docx