Research Article

Surgical Management of Breast Cancer during COVID-19 Pandemic

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Abstract

Background: Breast cancer is the most common cancer in women worldwide, including Pakistan. Pakistan has the highest prevalence of breast cancer in Asia, according to reports.

Objective: To compare the management of breast cancer patients in pre and post COVID-19 timeline, and to observe for any stage progression in both groups.

Methods: In this retrospective cohort study, conducted at West Surgical Ward, Mayo Hospital Lahore, from July 2019 to Dec 2020, adult female patients aged 18 years or older with a history of breast cancer surgery or who visited the breast clinic with the a diagnosis of breast cancer were enrolled. We divided them into pre and post COVID-19 subgroups assessed in nine months each. Variables including ASA grade, BMI, referral, size of tumor, number of lymph nodes removed, surgical procedure performed including axillary surgery, TNM stage, type of cancer. extracted from patient charts retrospectively. Univariate regression analysis performed for the progression of the stage. P-value ≤0.05 considered significant.

Results: Two hundred and sixty-two (n=262) patients presented during the pre-COVID-19 time (Group A) and one hundred seventy-one (n=171) presented in post-COVID-19 times (Group B). All were female patients, with a mean age of 46.6±10.1 year's in-group A and 45.6±11.8 years in-group B. Significantly, referral patients attendance reduced in group B (10.5%) as compared to group A (70.6%). Metastatic disease (stage 4) also seen in higher number in post COVID-19 (26.2% vs. 35%). Stage progression was real in post Covid-19 group (24.6% vs. 6.5%). Results showed waiting time before visiting the breast clinic (p<0.001) and before radiotherapy (p=0.04) were contributing factors to the progression of the disease.

Conclusion: Stage progression is real in the post-COVID-19 subgroup. Waiting time before visiting the breast clinic and before radiotherapy were main factors for the progression of the disease.

Introduction

Breast cancer is the most common cancer in women worldwide, including Pakistan. Pakistan has the highest prevalence of breast cancer in Asia, according

to reports.[1] According to a recent report, most patients with breast cancer in Pakistan are identified at an advanced stage, and the percentage of early stage (stage I, II) patients has remained constant over the previous two decades.[2] According to another Pakistani study, 69.9 percent of breast cancer patients had stage III or IV malignancy at the time of their initial diagnosis.[3] An early breast cancer diagnosis is important because smaller tumor sizes and reducing risk of metastasis,

contribute to better prognosis and survival.[4]

The COVID-19 pandemic, which caused the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) illness, has significantly influenced the management of patients with cancer, especially breast cancer.[5] In June 2020, the Journal of Cancer Research reported that cancer patients are more vulnerable to critical disease like COVID-19 and risk of dying than the infected cases among general population with COVID.[6]

As the COVID-19 pandemic spread through Pakistan in early 2020, health facilities were under pressure to lower down outpatient and elective surgery services.[7] Brown JM et al. showed that the COVID-19 pandemic has escalated the need for prioritization methods to treat breast cancer, where patients with triple-negative breast cancer (TNBC) needs specialized treatment including chemotherapy.[8] A multicentric study specifically showed that the treatment of patients with breast cancer suffered because of a lack of attention regarding diagnostic and surgical procedure.[9] Worldwide, many guidelines published during COVID-19 regarding breast cancer management, including guidelines from the American College of Surgeons to categorize breast cancer patients into priority levels (A, B, C) for the urgency of care across all specialties.[10] In addition, they have submitted therapeutic recommendations for each of these patient situations.[10]

Cancer treatment and research were immensely affected by COVID-19 in Pakistan as well. There was a need to perform a study in our population as our country is lacking in resources and equipment. Our center was already seeing presentation of breast cancer at an advanced age even before and it certainly increased the burden on our healthcare system. There was a definite need to look into the risk of stage progression of breast cancer due to delay in diagnosis and treatment. We should expect a new health emergency for the care of these cancer patients in the immediate future.

Methods

As per the inclusion criteria, in this retrospective single-center cohort study included all surgical patients treated from July 2019 to Dec 2020 (18 months) at Mayo hospital Lahore, Pakistan. Divided into two subgroups 9 months pre- COVID-19 (July 2019-March 2020) and 9 months post COVID-19, i.e. (April-December 2020) when the lockdown was imposed nationwide. Patients' charts were inspected, and if they were over the age of 18 and had undergone breast cancer surgery or visited the hospital's breast clinic, with a diagnosis of breast cancer they were included in the study.

After receiving clearance from the Institutional Review Board and the Ethical Committee, (letter no. 327/RC/KEMU issue date: 01-07-2019), patient-level data retrieved for analysis. We created a proforma to represent all necessary data that needed to be extracted from medical records. We recruited data retrievers among the surgery department's postgraduate residents, who were briefed before data collection.

One of the research interrogators supervised them during their process, but they were unaware of the research's results. Data sampling was done in a convenience mode with an eighteen-month pre-determined period separated into nine-month intervals.

We excluded the patient's data and charts with incomplete data on any of the variables from the analysis and patients tested for COVID-19 before admission to hospital. At our institution, we used reverse transcriptase-polymerase chain reaction testing for SARS-CoV-2, following American and European norms for analysis.

Cancer stage progression refers to the advancement or development of cancer from its initial stage to a more advanced or aggressive stage. The stage of cancer is a critical factor in determining the extent of the disease, prognosis, and treatment options. Stage progression is defined and assessed using TNM staging and pathological staging. The variables included ASA score, comorbidities, tumor size, number of lymph nodes removed positive lymph nodes, mammographic findings, TNM stage, type of surgical procedure in breast and axilla, and initial referral (through primary and secondary healthcare department). Other factors considered were grade of disease, type of cancer, margin status, receptor status, the incidence of postoperative complications, hospital stay in days, median follow-up time. We aimed to determine multiple waiting times patients faced in the pre and post COVID-19 era regarding breast cancer management, e.g. OPD visit time, time to reach a diagnosis, time for surgery, time for chemoradiotherapy. Fear of contracting COVID-19, the usefulness of telemedicine services, and psychological trauma they faced

due to delay of treatment, number of patients lost to follow up considered from the post-COVID-19 subgroup.

Breast-conserving therapy (BCT) with or without onco-plastic approach, mastectomy (with or without imme-diate reconstruction), and other operations designated as surgical operations (i.e., lymph node dissection, lymph node biopsy, repeat excision).

The American Society of Anesthesiologists classifica-tion used to assess the patients' general health before surgery. The TNM classification system used to classify the tumors except Phyllodes tumors. Adjuvant and/or neoadjuvant therapy included hormonal therapy, immu-notherapy, and chemotherapy. A history of cardiovas-cular illness, pulmonary disease, renal disease, and diabetes were among the patient's comorbidities.

The patient and treatment characteristics described using descriptive statistics. Categorical data reported as frequency and percentage, while continuous data as mean and standard deviation. SPSS version 26 (IBM, USA) was used to complete all calculations. P values of $<.05$ on both sides regarded statistically significant.

To investigate the factors that contributed to the disease's progression, univariate regression analysis used. The risk quantified using the odds ratio (OR) and 95% con-fidence intervals (CIs). Age, BMI, referral patient or not, American Society of Anesthesiologists classification, comorbidities, TNM classification, fear of contracting COVID-19, telemedicine, psychological trauma patient suffered, and multiple waiting times patient faced before admission, surgery, and chemoradiotherapy all were possible confounding factors and effect modifiers. Data of the outcome variables was stratified for these effect modifiers and post stratification chi square was applied to see the effect of these on the outcome variable.

Results

Two hundred and sixty-two (n=262) patients presented during pre COVID-19 time (Group A) and one hundred seventy-one (n=171) presented in post-COVID-19 times (Group B). All patients were female in both groups and the total number of lymph nodes removed was n= 16±8 (Group A), n= 15±11 (Group B) and positive lymph nodes were n= 12±7 (Group A) and n= 11±9 (Group B).

Table no. 1 shows that patient demographic details.

Table 1: *Patient demographic data*

	Variables	Pre- COVID 19(n=262)		Post COVID 19(n= 171)	
1	Mean Age(years)	46.6±10.1		45.6±11.8	
2	ASA classification				
•	ASA1	113(43.1%)		90	(52.6%)
•	ASA2	99(37.8%)		63	(36.8%)
•	ASA3	47(17.9%)		9	(5.3%)
•	ASA4	3 (1.1%)		9	(5.3%)
3	BMI	29.5±3.7		27.9±3.5	
4	Referred through screening or not				
	Yes	185	(70.6%)	18	10.5%
	No	77	(29.4%)	153	89.5%
5	Comorbid conditions				
•	Diabetes	54	(20.6%)	48	(28.1%)
•	Cardiovascular	32	(12.2%)	33	(19.3%)
•	Multiple	34	(13.0%)	18	(10.5%)
•	None	142	(54.2%)	72	(42.1%)

Table 2: *Clinical and radiological features of both groups*

Sr. No.	Clinical and radiological factors	Pre COVID-19(n= 262)		Post COVID-19(n= 171)	
1	Tumor Size, T(cm)				
•	T1(<2cm)	34	(13.0%)	0	(0%)
•	T2(2-5cm)	6	(23.3%)	18	(10.5%)
•	T3(<5cm)	61	(23.3%)	36	(21.1%)
•	T4	106	(40.5%)	117	(68.4%)
2	Lymph node(N)				
•	N0	34	13.0%	3	(1.8%)
•	N1	153	58.4%	120	(70.2%)
•	N2	69	26.3%	42	(24.6%)
•	N3	6	2.3%	6	(3.5%)
3	Metastasis(M)				
•	No metastasis(M0)	199	76.0%	111	(64.9%)
•	Pulmonary	27	10.3%	15	(8.8%)
•	Bone	36	13.7%	45	(26.3%)
4	Mammographic Findings				
•	BIRAD 3	10	3.8%	3	(1.8%)
•	BIRAD 4	81	30.9%	71	(41.5%)
•	BIRAD 5	120	45.8%	70	(40.9%)
•	BIRAD 6	51	19.5%	27	(15.8%)

Figure 1 shows the stage presentation in each group according to percentage. Table no 2 shows the clinical and radiological features of patients of COVID -19 in both groups. And Table no. 3 shows that treatment moda-

lities, histopathological status and post-operative complications in both groups.

Table 3: *Treatment modalities, histopathological status and post-operative complications in both groups*

| Sr. No.	Treatment modalities				
1	**Types of Surgery**				
•	Not done in Metastatic Disease	39	14.9%	63	36.8
•	BCT	69	26.3%	9	5.3
•	MRM	125	47.7%	99	57.9
•	Mastectomy +Reconstruction	23	8.8%	0	0%
•	Re-Excisional or Recurrent surgery	6	2.3%	0	0%
2	**Axilla**				
•	No Axillary Surgery in Metastatic Disease	39	14.9%	63	36.8%
•	SLNB	33	12.6%	3	1.8%
•	ALND	190	72.5%	105	61.4%
3	**Histological type of CA**				
•	DCIS	18	6.9%	2	1.2%
•	Invasive Ductal Carcinoma	194	74.0%	154	91.2%
•	InvasiveLobular Carcinoma	15	5.7%	3	1.8%
•	Phyllodes	8	3.1%	3	1.8%
•	Other types of Cancer	27	10.3%	9	5.3%
4	**Grade of Tumor**				
	Grade 1	34	13.0%	36	21.1%
	Grader 2	163	62.2%	51	29.8%
	Grade 3	65	24.8%	84	49.1%
5	**Receptor Status**				
	ER,PR +ve,Her2 neu +ve	108	41.2%	54	31.6%
	ER +ve,PR +ve,Her2 neu-ve	31	11.8%	12	7.0%
	ER +ve,PR-ve,Her 2 neu +ve	9	3.4%	6	3.5%
	ER+ve,PR-ve,Her 2 neu-ve	9	3.4%	12	7.0%
	ER-ve,PR-ve,Her 2 +ve	6	2.3%	12	7.0%
	ER-ve,PR-ve,Her 2 neu -ve	99	37.8%	75	43.9%
6	**Margin Status**				
	Not applicable as surgery not done	39	14.9%	60	35.1%
	Surgery being done:	223	(100%)	111	(100%)
	Free of tumor	200	89.6%	102	91.9%
	Close Margin	17	7.6%%	6	5.4%
	Involved	6	2.6%	3	2.7%
7	**Post-Op Complications**				
	Surgery not done	36	13.7%	66	38.6%
	Surgery done:	224	(100%)	105	(100%)
	No Complication	159	70.9%	63	60%
	Wound Infection	9	4.0%	12	11.4%
	Seroma Formation/ Lympedema	28	12.5%	12	11.4%
	Flap necrosis	4	1.7%	6	5.7%
	Chronic pain and pareshthes	21	9.3%	12	11.4%
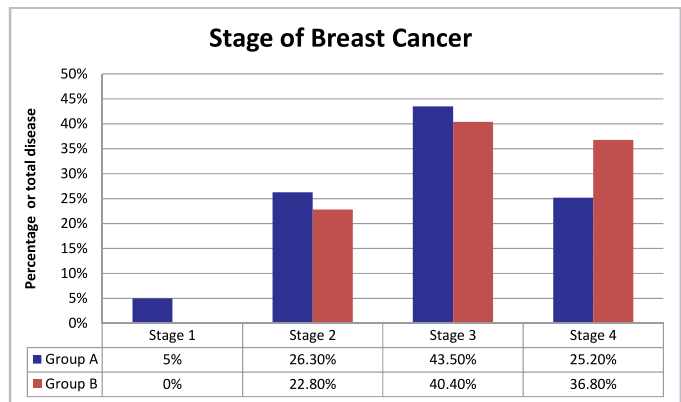
Figure 1: *Breast cancer stage presentation*

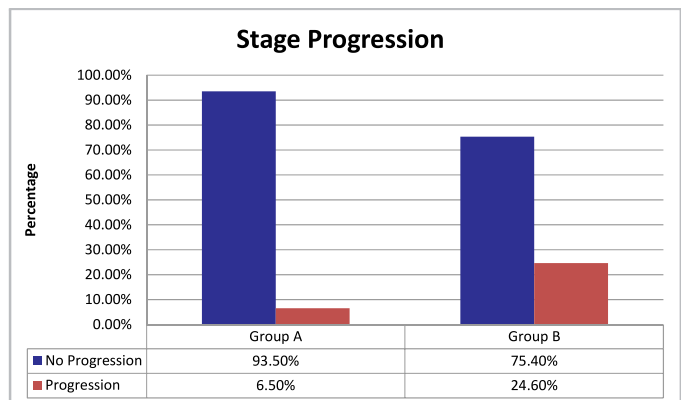(Figure 2) shows the percentage of stage progression in both groups.

Figure 2: *Comparison of Breast cancer stage progression in both groups*

There was no need for chemotherapy in n=13 (5%) in Group A, while there was no patient in Group B for which we omitted chemotherapy. Neoadjuvant chemotherapy given to n=115 (43.9%) in Group A and n=36 (21.1%) in Group B. Adjuvant or palliative chemotherapy given to n= 134 (51.1%) in Group A and n=135 (78.9%) in Group B. Similarly, there was a need for radiotherapy in n=236(90.1%) in Group A and n=162 (94.7%) in Group B respectively.

Regarding hormonal therapy in Group A, n=102 (38.9%) did not require any hormonal therapy while n=160 (61.1%) required. The practice changed during COVID-19 with introducing neoadjuvant hormonal therapy so n=33(19.3%) had neoadjuvant hormonal therapy and n=54 (31.6%) had adjuvant hormonal therapy while we gave no hormonal therapy in n=84 (49.1%). Mean hospital stay for Group A was 4±2 days and for Group B2±2 days. Mean follow-up time was 7±4 days for Group A and 10±4 days for GroupB.

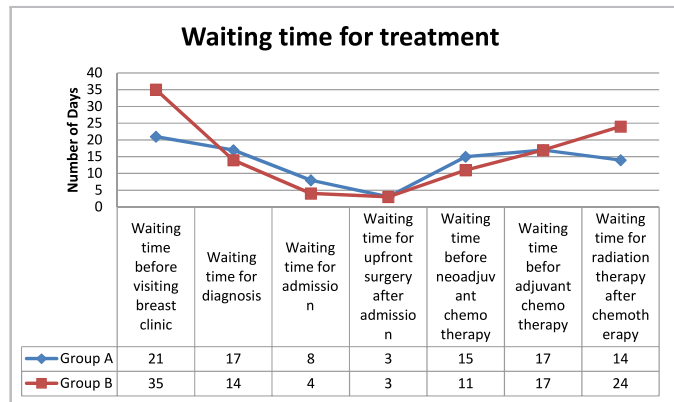(Figure 3) shows different waiting times patient faced for their treatment.

	Waiting time before visiting breast clinic	Waiting time for diagnosis	Waiting time for admission	Waiting time for upfront surgery after admission	Waiting time before neoadjuvant chemo therapy	Waiting time befor adjuvant chemo therapy	Waiting time for radiation therapy after chemotherapy
Group A	21	17	8	3	15	17	14
Group B	35	14	4	3	11	17	24

Figure 3: *Comparison of different waiting times patient faced in both groups*

Further, it revealed every patient had a fear of contracting COVID-19 in Group B while n=09 (5.3%) contracted COVID-19 while being waiting for treatment, n=156 (91%) thought telemedicine services were helpful and finally, n=24 (14%) lost to follow up. Sixty, n=60 (35.1 %) faced psychological trauma due to delay in treatment. Univariate regression analysis showed waiting time before visiting the breast clinic (p<.001) and waiting time before radiotherapy (p=0.04) contributed to the progression of the disease.

Discussion

The COVID-19 pandemic had a negative effect on cancer care, causing delays in diagnosis and treatment, as well as the suspension of clinical trials. As a result, healthcare facilities are increasingly reorganizing cancer programs to ensure that patients continue to access critical care while limiting their susceptibility to the SARS-CoV-2 virus[11]. Asia is home to the world's most heavily populated regions, and its emerging nations face demographic and healthcare problems. COVID-19 is rapidly undermining low- and low-to-middle-income countries' vulnerable and overburdened health systems. Asian subcontinent is facing the dual task of managing the spread of COVID-19 while still supplying and sustaining cancer services because of its aging population of chronic diseases and an increasing burden of cancer.[12]

The COVID-19 pandemic has halted outpatient care in Pakistani hospitals, affecting the number of breast cancer surgical procedures.[13] Surgeries postponed because of the fear of contracting COVID-19, resulting in a decline of patient presenting to hospital.[13] Our study findings revealed a reduction by 53% in the breast cancer surgeries during the COVID-19 pandemic, which was consistent with a Dutch analysis undertaken by Filipe MD et al.[14]

Unfortunately, Pakistan lacks an effective national breast cancer screening program; however, our hospital continues to receive referrals from other primary and secondary level hospitals. The number of referrals from primary and secondary healthcare decreased during the COVID-19 period by 16% according to Gathani T et al.[15], same way our study showed number of patients decreasing by 35% on year to year basis.

The COVID-19 pandemic affected healthcare systems around the world. Many of the actions taken by hospitals in less-affected areas, such as reallocating healthcare services and prioritizing treatment designed after the pandemic's worst-affected countries' experiences.[16] To meet the increased need for COVID-19 services in hospitals, the protocols recommended only offering the most critical (oncologic) treatment and surgical procedures.[17] In Pakistan, as in other nations, authorities advised only conducting critical and utmost required surgery during COVID-19 prompting to postpone all elective surgeries during the third phase of the disease.[18]

Waiting times have soared and stage progression is attributed to a variety of patient issues as well, e.g. travel inconvenience because of lockdown, financial problems, patients traveling from long distance, lodging, and food-related issues.[19] Our study showed no significant change in other waiting times except waiting time before visiting the breast clinic which increased from mean time of 3 week to 5 week interval.

Neoadjuvant therapy is usually needed within 6 weeks of the initial cancer diagnosis in Pakistan; however, patients reported delays in waiting time before attending a breast clinic[20] and our study showed the same pattern. However, other waiting times have remained unchanged.

Many findings have shown that during the COVID-19 pandemic, breast cancer patients present with a more progressive and advanced stage of the disease as compared to the same period in 2019.[21,22] There was also a decline in stage T1-T2, N0 tumors, which could be attributed to the temporary closure of OPDs and an increase in the time spent waiting for medical advice.

Pre-operative endocrine treatment was beneficial for women who had longer wait periods and diagnosed with early stage breast cancer, most of physicians (66%) changed their practice based on a MDT based discussion.[23] Our center has changed its approach too and began pre-operative hormone treatment in 19% hormone positive patients after working with an oncologist. In the last weeks of our study, implementing telemedicine facilities and the launch of a breast cancer clinic using the COVID-19 protocol gradually raised the number of patients.

The American Society of Plastic Surgery (ASPS) advises against immediate autologous reconstruction and instead opts for immediate tissue expander or direct implants accordingly.[24] However, due to budget constraints, all reconstructive breast operations delayed in our hospital or referred to other facilities. Radiotherapy and/or systemic chemotherapy are the treatments of choice for women with breast cancer, and they are part of multi-disciplinary treatment strategies. Systemic Chemotherapy or palliative chemotherapy offered to more patients in the post COVID-19 timeline, as metastatic disease increased by 11% consistent with study done by İlgün AS et al showing 6% rise in de novo breast cancer.[25] Breast conservation therapy (BCT) decreased by 21 % in COVID-19 procedures in our center consistent with results by Vijaykumar DK et al reporting 27% decrease in BCT.[26]

There were some drawbacks to this analysis. For example, the number of patients that were included in the study were low. As a result, the number of stage T1-T2 tumors' were limited, making pattern detection more difficult for this patient population. The low number of stage N0 tumors faced similar pattern recognition problems. Second, since it was a single-center analysis, the data must be contrasted to our Pakistani hospitals. However, the results of our research revealed a strong growing trend in the number of advanced-stage tumors in Group B (Post-COVID) relative to Group A (Pre-COVID) during the study period. The combination of a temporary pause in referral points and a drop in new breast cancer admissions is concerning, as it means that cases were not sent to hospitals, and those who did were diagnosed late.

Conclusion

According to this study, the COVID-19 pandemic has resulted in a significant reduction in the number of breast cancer surgeries performed. In addition, the progression of breast cancer stage is real in third world countries like Pakistan. Progression resulted not only due to lack of referral from other hospitals but mainly because of increase waiting time for patients to come to breast clinics and waiting time for radiotherapy.

Authors' Contribution:

GA: Conception & design, critical revision for important intellectual content, final approval

AS: Conception & design, final approval of the version to be published

US: Drafting the article or revising it critically for important intellectual content

SM: Drafting the article or revising it critically for important intellectual content

KJ: Acquisition of data, analysis & interpretation of data

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