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A single-center retrospective study



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AIM: The impact of COVID-19 pandemic is pronounced in each healthcare process, including the management of breast cancer. The anxiety of COVID-19 changes patient preferences and some delay in routine controls and surgical managements occur. Some disintegration in medical care is to be expected during the pandemic, but the new coping strategies are needed in order to avoid delayed diagnosis of breast cancer.

METHODS: A total number of 140 patients assigned for biopsy and diagnosed with breast cancer in our tertiary clinic between December 1st and August 31st were classified into 3 groups; A (December-February), B (March-May) and C (June-August) in order to compare the stage of breast cancer at the time of diagnosis before, during and after the peak period of pandemic. Clinical stage and age at presentation, family history of breast, ovarian and other types of cancer, BRCA (genetic testing), menopausal status, side of involvement (uni- or bilateral), histopathologic subtype, receptor positivity and molecular subtype were recorded for each patient.

RESULTS: Group A included 20 stage I (27.77 %), 32 stage II (44.44 %), 16 stage III (22.22 %) and 4 stage IV (5.55 %) breast cancer patients. Group B had 5 stage I (22.72 %), 8 stage II (36.36 %), 7 stage III (31.81 %) and 2 stage IV (9.09 %) breast cancer patients. Whereas in group C there were 4 stage I (8.69 %), 21 stage II (45.65 %), 16 stage III (34.78 %) and 5 stage IV (10.86 %) patients with breast cancer. The number of late-stage cancer patients in group C was significantly higher in comparison with the other groups ($p < 0.05$).

CONCLUSION: We speculate that the change in incidence of breast cancer by stage is attributable to a delay in the diagnosis of breast cancer due to COVID-19 related restrictions and presentation of new cases at more advanced stages once the restrictions were eased.

KEY WORDS: Biopsy, Breast cancer, COVID-19, PandemicStage

Introduction

Members of the family Coronaviridae, are large, enveloped, single-stranded RNA viruses, potentially infectious for both humans and animals ¹. As a novel cause

of pneumonia, COVID-19 was first detected in Wuhan city in Hubei province of China in December 2019 and initially spread rapidly to other parts of China and eventually to almost all countries worldwide. The World Health Organization (WHO) declared a pandemic on March 11, 2020 ^{2,3}. The disease is highly contagious and the associated symptoms include fever, dry cough, shortness of breath, fatigue, myalgia, nasal congestion, headache, runny nose, sore throat, vomiting and diarrhea ⁴. The incubation period range between 2-14 days and most of the cases become symptomatic approximately 4-5 days after the first exposure ^{5,6}. Although the

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clinical presentation of COVID-19 is might be a mild flu-like disease and may not require specific treatment at all, the other edge of the clinical spectrum could be critical enough to require intensive care. It is also well-documented that having an infection without any symptoms is quite common despite close contact with COVID-19 patients. Morbidity and mortality increase mostly in association with acute viral pneumonia and acute respiratory distress syndrome (ARDS).

Immune-compromised patients, elderly population and individuals with diabetes mellitus, hypertension, obesity, cancer, cardiac diseases, chronic kidney or lung diseases are more susceptible to coronavirus disease. To date, there are no readily-accessible and medically approved vaccines or an agent-specific medical management⁷. The generally accepted strategy to cope with COVID-19 infection is prevention and deceleration of the spread. Many countries promote social distancing, other precautionary measures, and some local lock-downs when necessary. While promoting the unnecessary admissions to health care facilities, it is also important not to discourage individuals requiring diagnostic and therapeutic interventions to seek for medical help. Patients with chronic and serious conditions need to minimize the risk of transmission but on the other hand, they may require urgent medical help or routine hospital visits. Recently, some regions with less number of cases are re-opening their economies and loosening the restrictions. The chance of survival in breast cancer is remarkably higher with early diagnosis and timely management.

Screening with routine mammography is recommended by the age of 40 and are to be repeated annually. Some changes in the breast before it is clinically noticeable can be revealed by routine mammography⁸. Some patients may feel the change in their breast or the clinical examination may arise a suspicion. In these cases diagnostic mammography are scheduled.

When breast imaging reveals abnormal changes (BIRADS 4 and 5 focal lesions) needle biopsy should be performed in order to establish a pathological diagnosis and to start management accordingly⁹. Screening mammography, ultrasound and MRI were widely postponed during the peak period of the pandemic on the other hand diagnostic studies and biopsies were still being performed. The radiologists or technicians perform biopsy procedures when screening is suspicious of malignancy. The decrease in screening results in a decrease in the number of biopsy procedures in turn. During the pandemic, surgery for benign conditions, risk reducing surgery, autologous flaps were avoided as much as possible. Resources allocated for semi-elective or elective procedures were transferred for the needs of COVID-19 patients requiring hospitalization. Patients were assigned to neoadjuvant chemotherapy and endocrine therapy; surgical procedures and outpatient care were performed when possible¹⁰.

Given the fact that the breast cancer accounts for a quarter of all cancers in women population, the deteriora-

tion of the diagnosis or management might cause a health burden in the future.

Methods

All female breast cancer cases diagnosed by biopsy in a tertiary university hospital in Istanbul, Turkey, between December 1, 2020 and August 31, 2020 were retrospectively reviewed. Between December and February, there were no COVID-19 patients and hospital resources and capacity were as normal. Between March and May, there was an increasing number of COVID-19 patients. The maximum number of cases was reached on 14th April 2020 and the spread decelerated in the following days. By the first week of March 2020 the number of breast imaging, biopsy procedures and breast surgery started to decrease. Between June and August, the number of COVID-19 cases decreased and we observed moderation in the course of the disease.

The patients assigned for biopsy and diagnosed with breast cancer between December 1st and August 31st were classified into 3 groups; A (December-February), B (March-May) and C (June-August) in order to compare the stage of breast cancer at the time of diagnosis before, during and after the peak period of pandemic. In our study, breast cancer was classified as early for stage 0 and 1; advanced for stage 2, 3 and 4 according to the American Joint Committee on Cancer Breast Cancer Staging, 8th edition. Clinical stage and age at presentation, family history of breast, ovarian and other types of cancer, BRCA (genetic testing), menopausal status, side of involvement (uni- or bilateral), histopathologic subtype, receptor positivity, molecular subtype were recorded for each patient.

Breast cancer stage was analyzed in an ordinal logistic regression model. Categorical data were recorded as numbers and percentages. Analysis was performed using the chi-square test. Variables with assigned p-values <0.05 were considered statistically significant. All the statistical analysis was performed in SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

A number of 140 consecutive female patients assigned for biopsy procedure and diagnosed breast cancer were included in the analysis. We compared the average daily number of newly diagnosed breast cancer during the 3 months before the COVID-19 pandemic (December-February) with the 3 months (March-May) of the peak period of the pandemic, and 3 months after the peak period of the pandemic (June-August). The average number of new breast cancer cases daily in December-February decreased from 0.8 to 0.24 in March-May and 0.51 in July-August. The mean age of the patients were

TABLE I - Patient characteristics associated with important clinical features presented as number (%) or mean value.

Patient characteristics	Group A n = (%)	Group B n = (%)	Group C n = (%)	All n = (%)
Number of patients (n=)	72(51.42%)	22(15.71%)	46(32.85%)	140(100%)
Age (mean)	56.37	51.31	53.52	54.64
BRCA(genetic testing)	8(11.11%)	1(4.54%)	2(4.34%)	11(7.85%)
Menopausal status				
Premenopausal	32(44.44%)	12(54.54%)	22(47.82%)	66(47.14%)
Postmenopausal	40(55.55%)	10(45.45%)	24(52.17%)	74(52.85%)
Family history				
Breast cancer	15(20.83%)	5(22.72%)	16(34.78%)	36(25.71%)
Ovarian cancer	8(11.11%)	0(0%)	4(8.69%)	12(8.57%)
Other cancers	34(47.22%)	5(22.72%)	12(26.08%)	51(36.42%)
Side				
Right	34(47.22%)	10(45.45%)	15(32.6%)	59(42.14%)
Left	36(50%)	11(50%)	29(63.04%)	76(54.28%)
Bilateral	2(2.77%)	1(4.54%)	2(4.34%)	5(3.57%)
Histopathologic subtype				
Invasive ductal cancer	59(81.94%)	17(77.27%)	44(95.65%)	120(85.71%)
Invasive lobular cancer	3(4.16%)	3(13.63%)	2(4.34%)	8(5.71%)
Invasive mixed type	8(11.11%)	1(4.54%)	0(0%)	9(6.42%)
Other	2(2.77%)	1(4.54%)	0(0%)	3(2.14%)
Receptor status				
ER	61(84.72%)	17(77.27%)	29(63.04%)	107(76.42%)
PR	53(73.61%)	15(68.18%)	23(50%)	91(65%)
HER-2	8(11.11%)	4(18.18%)	8(17.39%)	20(14.28%)
Ki-67 (>14%)	48(66.66%)	10(45.45%)	38(82.6%)	96(68.57%)
Molecular subtype				
Luminal A	24(33.33%)	6(27.27%)	8(17.39%)	38(27.14%)
Luminal B	38(52.77%)	10(45.45%)	21(45.65%)	69(49.28%)
HER-2 positive	1(1.38%)	2(9.09%)	4(8.69%)	7(5%)
Triple negative	9(12.5%)	4(22.72%)	13(28.26%)	26(18.57%)

TABLE II - Data for clinical stages of the groups.

Clinical Stage	Group A n= (%)	Group B n= (%)	Group C n= (%)	All n= (%)
Stage 1	20(27.77%)	5(22.72%)	4(8.69%)	29(20.71%)
Stage 2	32(44.44%)	8(36.36%)	21(45.65%)	61(43.57%)
Stage 3	16(22.22%)	7(31.81%)	16(34.78%)	39(27.85%)
Stage 4	4(5.55%)	2(9.09%)	5(10.86%)	11(7.85%)

56.37, 51.31, and 53.52 years of the A, B, and C groups, respectively; 44% of the group A, 54% of the group B and 47% of the group C were premenopausal. The number of patients who were asymptomatic and diagnosed with breast cancer by routine screening was 20 for group A (27.77 %), 2 for group B (9.09 %) and 3 for group C (6.52 %). The number of patients who were symptomatic and diagnosed with breast cancer by diagnostic screening is 52 for group A (72.22 %), 20 for group B (90.9 %) and 43 for group C (93.47 %). The most common symptoms were mastalgia (83.57 % of patients) and mass (77.14% of the patients).

Biopsy materials were immunohistopathologically investigated and the expression of ER, PR and KI-67 recep-

tors and HER-2 gene were reported. Breast cancer patients were classified into four subgroups according to the molecular properties: Luminal A, Luminal B, HER2-enriched, and basal like (triple negative) types. The positivity of estrogen, progesterone, HER-2 receptor and Ki-67 value >14% in group A account for 84.72 %, 73.61 %, 11.11 % and 66.66 %, respectively; for 77.27 %, 68.18 %, 18.18 % and 45.45 %, respectively in group B, whereas for 63.04 %, 50 %, 17.39 % and 82.6 % respectively in group C. Among patients with complete histopathology, the majority (85.71%) of the patients in each group had invasive ductal cancer (Table I).

There were 20 of patients with stage I (27.77 %), 32 patients with stage II (44.44 %), 16 patients with stage III (22.22 %) and 4 patients with stage IV (5.55 %) breast cancer in group A. Among patients in the group B, 5 patients had stage I (22.72 %), 8 had stage II (36.36 %), 7 had stage III (31.81 %) and 2 had stage IV (9.09 %) breast cancer. Group C included 4 patients with stage I (8.69 %), 21 patients with stage II (45.65 %), 16 patients with stage III (34.78 %) and 5 patients with stage IV (10.86 %) breast cancer. The number of patients presented with stage I disease (27.77 %) were higher when compared with those in group C (8.69 %), whereas those who presented with stage III disease (34.78

%) in group C was higher in comparison with those in group A (22.22 %) (Table II). The difference between group C and A regarding the incidence of advanced stage breast cancer was statistically significant ($p < 0.05$).

Discussion

Almost all elective interventions were either delayed or postponed in our country due to the pandemic as in many other countries. Breast cancer surgeries might be postponed to some extent but one must keep in mind that timely surgical management is crucial in most of the cases and the adverse outcomes are to be expected if the delay exceeds the tolerable limit.

The prognosis of the breast cancer depends largely on the stage at the presentation and the molecular subtype of the malignancy. Routine screening helps to detect breast cancer at early stages and decreases morbidity and mortality providing a better chance of treatment with less invasive surgical strategies and minimal chemotherapy. Advanced stage at presentation usually necessitates a more aggressive approach and the prognosis is generally worse. Neoadjuvant chemotherapy, radiotherapy to the chest wall, regional lymph node dissection after mastectomy and mastectomy instead of breast-conserving surgery come into question at this point ¹¹. While the 5-year survival rate in early stage breast cancers (stage 0 and 1) is 100%, it decreases to 93% in stage 2, 72% in stage 3, and 22% in stage 4 ¹². When detected by routine screening in asymptomatic women, breast cancers usually present in lower stages in comparison with those, which are diagnosed once being symptomatic. When screening methods used periodically in asymptomatic patients, this is called screening imaging. When imaging is targeted to patients with signs or symptoms of breast cancer, it is referred to as diagnostic breast imaging and usually is a tailored evaluation consisting of some combination of mammography, ultrasound or MRI ¹³. The number of patients who were symptomatic at presentation was 52 (72.22%), 20 (90.9%) and 43 (93.47%) in group A, B and C, respectively; while there were 20 (27.77 %), 2 (9.09%) and 3 (6.52%) patients who were asymptomatic at the initial admission in group A, B and C, respectively. Overall 79.28% of the women who were symptomatic at the presentation in all groups had advanced stage breast cancer (stage 2, 3 and 4). The median stage of those who were symptomatic at presentation was stage 2. Among all three groups, the incidence of advanced stage breast cancer was remarkably higher in group C. We reported an increase in newly diagnosed breast cancer cases once the restrictions regarding the COVID-19 pandemic are eased. The incidence of luminal A subtype is higher in patients who were asymptomatic at presentation and diagnosed through routine screening ^{14,15}. Therefore, the number of patients with luminal A is higher in group A when compared to

group C, while routine imaging was better accessible before the pandemic ($p=0.029$).

Social distancing is not possible while performing breast imaging methods such as mammography and ultrasound or invasive diagnostic methods such as biopsy. Personal protective equipment is always necessary during each breast imaging and biopsy procedures. Social distancing when applicable, sanitization and disinfection of the equipment and common used areas are other measures to be followed. The delay of routine follow-up visits of a breast cancer patient or the routine breast cancer screening should not exceed 3 months and the local health care conditions should also be considered while planning the visits ¹⁶⁻¹⁸. Elective and non-urgent breast imaging was largely postponed until the precautions of COVID-19, especially the social distancing, were eased by the health authorities. These include routine breast imaging, annual follow-up of breast cancer survivors, low-risk lesions and BI-RADS 3 lesions, imaging of gynecomastia, cyst drainage and biopsy of BI-RADS 4A lesions. High priority breast imaging was postponed except for the emergencies of COVID-19 patients or suspected COVID-19 cases. Drainage of breast abscess, hematoma or infected seroma in COVID-19 patients are some examples of these emergent interventions. The conditions of inflammatory breast cancer or locally advanced breast cancer, suspicion of breast cancer in pregnant women were also considered as urgent cases. In case of a newly emerged palpable mass, unilateral or unifocal nipple discharge of bloody or serous characteristic, axillary mass, orange peel skin, retraction of the nipple or the skin breast imaging was not to be delayed and the case was considered as urgent ¹⁹.

Fine Needle Aspiration Biopsy (FNAB), Core Needle Biopsy (CNB) and Vacuum-assisted Biopsy (VAB) are three most common techniques used for preoperative assessment of focal lesions of the breast. High false negative rates, low sensitivity and specificity of FNAB, increased the popularity of CNB as the routine diagnostic method in case of a suspicious breast lesion. On the other hand, FNAB is preferred for cystic lesions, chest wall recurrences and lymph node involvement. Being less invasive, FNAB is useful in patients who are on anticoagulant therapy, given the fact that the technique does not require sedation and is less likely to cause complications. FNAB does not provide information regarding the invasion of malignant cells and the expression of ER, PR and HER-2 is not and the diagnostic accuracy of the technique is operator-dependent. CNB on the other hand reveals the presence of invasion, histological type, the grade of the tumor, the status of the hormone receptors (estrogen receptors (ER) and progesterone receptors (PR)), HER-2 and KI-67 proliferative index in malignant breast lesions and helps to differentiate between in situ and invasive disease. CNB is more invasive procedure and requires local anesthesia and imaging. Although still unlikely, complications such as

hematoma, pain and discomfort may arise following the CNB²⁰. FNAB is affordable and easily applicable, but it may require additional diagnostic measures including CNB in case of suspicious or non-diagnostic results and in turn increase exposure of COVID-19.

During the pandemic, the local health authorities encouraged self-isolation, social distancing and reasonable utilization of the hospital resources. As a result of these precautions routine outpatient visits and in turn breast imaging and biopsy procedures are largely decreased. During these extraordinary conditions, it is crucial to identify the women who need urgent or emergent care²¹.

Especially with the aid of CNB breast cancer cases are classified into molecular subgroups regarding the immunohistochemistry and FNAB was used in order to evaluate the axilla. Alternative treatment approaches are considered in order to postpone surgical interventions as much as possible. Endocrinotherapy was preferred when the case was hormone receptor positive. Premenopausal women with T1cN0 or higher stage triple negative breast cancers, who were ER negative or HER2 positive were assigned to neoadjuvant systemic therapies. T2N0 triple negative breast cancer patients were evaluated individually and were treated either with neoadjuvant systemic therapy or with primary surgical intervention²².

Some guidelines have been published in order to agree upon diagnostic and therapeutic strategies during the COVID-19 pandemic. Some informative manuals are also accessible by the patients. These guidelines and manuals should be followed as much as possible, but each patient must be evaluated individually. Once the COVID-19 cases decrease in number, the patients with breast cancer admitted increasingly. During the peak period of the pandemic, the diagnostic and therapeutic measures were suboptimal and the late admission of breast cancer cases is becoming a huge problem. Unless a medically proven and well-investigated vaccine or medication against COVID-19 becomes readily accessible, it is not likely that the diagnostic and therapeutic measures return back to normal.

Delay in diagnosis is largely due to self-isolation and fear of COVID-19 keeps most of the patients away from hospital. The expectation of a second wave is largely pronounced at this point and in case of a surge in the number of new COVID-19 cases the hospital resources might even be insufficient to provide an optimal care for cancer patients. In order to prevent the delay in diagnosis and treatment, new arrangements and strategies must be considered. Basic measures in outpatient clinics, such as arrangement of the waiting rooms in accordance with social distancing and the disinfection of the rooms between visits, must be followed. Each patient initially should be questioned for the symptoms of COVID-19 and treated accordingly if they are positive. Extra precautions must be considered for the high-risk individuals.

Our study aims to evaluate the delay in the diagnosis of breast cancer but it has some limitations. This study

included a relatively small population and acquired information regarding a short period. In order to provide solid information studies from more than one center with higher number of patients followed for a longer period of time might be necessary. Our study is demonstrative in the way it provides information regarding the impact of COVID-19 pandemic on diagnostic and therapeutic approaches in breast cancer.

Conclusion

The utilization of the healthcare resources, delay in the diagnosis of breast cancer cases and the change of the stage at the presentation before, during and after the peak period of COVID-19 pandemic are investigated in this study. Before the pandemic, the routine imaging, hospital visits and biopsies were higher in number and therefore the number of the newly diagnosed early stage breast cancer cases was higher. Between March and May, the number of COVID-19 cases was high and the routine breast cancer screening was suboptimal. In this period, only the cases with high risk and emergent conditions were prioritized and the number of biopsies performed decreased dramatically. The patients avoided routine admissions since the anxiety of the infection was remarkable. Some patients did not even seek for medical care even if they were symptomatic. By the beginning of June, once the restrictions are eased, the number of patients admitting to outpatient clinics increased. Among patients who were diagnosed in this period, 45% were stage III or IV. The late presentation is largely attributable to the restriction of imaging and pathological investigations. This may cause a significant burden in healthcare systems and will deteriorate the clinical outcomes and quality of life of the patients. Even in early breast cancer cases the delay in management may increase morbidity and mortality. Appropriate triage and timely management is necessary among patients who require surgical interventions or neoadjuvant therapies.

Riassunto

L'impatto della pandemia di COVID-19 è evidente in ogni situazione di patologia, inclusa la gestione del cancro al seno. L'ansia di COVID-19 cambia le preferenze delle pazienti e si verificano alcuni ritardi nei controlli di routine e nelle terapie chirurgiche. Durante la pandemia è prevedibile una certa disorganizzazione dell'assistenza medica, ma sono necessarie nuove strategie per far fronte e per evitare ritardi della diagnosi di cancro al seno.

Abbiamo classificato in tre gruppi un totale di 140 pazienti nella nostra clinica terziaria tra il 1° dicembre e il 31 agosto, destinate a biopsia e con diagnosi di cancro al seno; gruppo A (dicembre-febbraio), gruppo B (mar-

zo-maggio) e gruppo C (giugno-agosto) per confrontare lo stadio del cancro al seno al momento della diagnosi prima, durante e dopo il periodo di picco della pandemia.

Per ogni paziente sono stati registrati stadio clinico ed età alla presentazione, storia familiare di cancro al seno, alle ovaie e altri tipi di cancro, test genetico BRCA, stato della menopausa, lato del coinvolgimento (mono o bilaterale), sottotipo istopatologico, positività del recettore e sottotipo molecolare

RISULTATI: il gruppo A comprendeva 20 pazienti con carcinoma mammario in stadio I (27,77%), 32 in stadio II (44,44%), 16 in stadio III (22,22%) e 4 in stadio IV (5,55%). Il gruppo B aveva 5 pazienti con cancro al seno in stadio I (22,72%), 8 stadio in stadio II (36,36%), 7 stadio in stadio III (31,81%) e 2 in stadio IV (9,09%). Mentre nel gruppo C c'erano 4 pazienti in stadio I (8,69%), 21 in stadio II (45,65%), 16 in stadio III (34,78%) e 5 in stadio IV (10,86%). Il numero delle pazienti affette da cancro in stadio avanzato nel gruppo C è risultato significativamente più alto rispetto agli altri gruppi ($p < 0,05$).

CONCLUSIONE: ipotizziamo che il cambiamento nell'incidenza del cancro al seno per stadio sia attribuibile a un ritardo nella diagnosi di cancro al seno a causa delle restrizioni correlate al COVID-19 e alla presentazione di nuovi casi a stadi più avanzati una volta che le restrizioni sono state allentate.

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