Rising incidence of late stage breast cancer after COVID-19 outbreak. Real-world data from the Italian COVID-DELAY Study

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Abstract

Purpose

Breast cancer (BC) patients’ (pts) management was affected by a global reorganization after Coronavirus disease 2019 (COVID-19). Our multicenter study aimed to assess the impact of COVID-19 on access to diagnosis, staging and treatment for BC pts compared to pre-pandemic.

Methods

Medical records of all consecutive newly diagnosed BC pts referred to 6 Italian Institutions between March and December 2020 were assessed. Monthly access rate and temporal intervals between date of symptoms onset, radiological, cytohistological diagnosis and treatment start were analyzed and compared with those of 2019.

Results

A reduction (25%) in newly diagnosed BC pts was observed compared to 2019 (666 vs 890). New BC pts in 2020 were less likely to be diagnosed with early stage (stage 0-I-II) BC (77% vs 83%, p<0.01), had a worse ECOG PS (19.8% had PS>0 in 2020 vs 16.5% in 2019, p<0.01) and fewer patients were asymptomatic at diagnosis in 2020 (54% vs 71%, p<0.01). COVID-19 did not negatively impact in terms of access to diagnosis, staging and treatment. Time intervals between symptom onset and radiological diagnosis, symptom onset and cytohistological diagnosis, cytohistological diagnosis and treatment start were maintained or even improved. However, less BC cases were discussed in multidisciplinary tumor meetings during 2020 (60% vs 73%, p<0.01).

Conclusions

Our data proved an alarming reduction of BC early stage diagnoses in 2020. Despite the upheaval generated by COVID-19, our study shed light on the effective performance delivered by Italian Oncology Departments to guarantee diagnostic-therapeutic pathways.

1. Introduction

In March 2020, the Coronavirus Disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization, reporting 175 million infections and over 3 million deaths to date. Italy was the first European country and one of the most affected, especially during the first pandemic wave [1]. Consequently, there was a complete reorganization of the National Health System, including reallocation of crucial human and economic health resources. This inevitably impacted on hospital’s admissions for non-communicable diseases hampering both inpatients and outpatients care. In particular, all elective
activities were paused or postponed in order to preserve the Health Care System capacity for COVID-19 patients [2]. The Italian Government introduced emergency social restrictions to reduce the human-to-human viral transmission and protect the most vulnerable, such as cancer patients at risk of deferring, suspending or never starting anticancer treatment due to COVID-19 infection [3, 4]. In this setting, Oncology Departments have made many efforts in order to guarantee access to care and high-quality standards for diagnostic-therapeutic pathways [5–7] according to international guidelines [8]. However, screening programs have been temporarily halted or delayed between March and May 2020, with a potential unfavorable impact on cancer patients’ prognosis [9, 10]. Female breast cancer (BC) represents the most commonly diagnosed tumor worldwide with 2.26 million cases in 2020 [11]. In Italy, approximately 55,000 women receive a BC diagnosis every year [12]. The majority of these diagnoses, especially in the early stage, results from screening programs, with an estimated prognosis improvement of 45% in Western countries during the past 10-20 years [13]. Recent studies suggest that pausing BC screening programs during lockdown produced delayed cancer diagnoses associated with significant repercussions on cancer mortality and health economic losses [14, 15]. Gathering data from 6 Italian Institutions, the aim of our multicenter study was to investigate COVID-19 impact on new BC diagnoses in terms of access to diagnosis, staging and treatment after March 2020 compared to pre-pandemic period.

2. Materials And Methods

2.1. Study design and population

Patient data were retrieved from the COVID-DELAY study (“Evaluation of COVID-19 impact on DELAYing diagnostic-therapeutic pathways of cancer patients in Italy”). The study included patients with lung, colorectal and breast cancer diagnosis. Hereby we report data on the BC cohort. Primary objective was to assess whether the COVID-19 outbreak impacted the BC patients’ likelihood of receiving timely diagnosis and access to treatment in 2020. To investigate this objective, we assessed the total number of new diagnoses, access rate (number of patients/month) and temporal intervals between date of symptoms onset, diagnosis, first oncological appointment, treatment start and first radiological reassessment. We compared the obtained data with those of the same months of 2019 (“pre-pandemic” period). As a secondary objective, we also assessed the impact of COVID outbreak on the stage of disease at diagnosis in 2020 compared to 2019.

In total, 6 Italian Institutions provided data about BC patients. Clinical records of all consecutive newly diagnosed BC patients referred to those Institutions between March and December 2020 or 2019, who received at least one type of oncological treatment (either surgery, radiotherapy, or systemic therapy) after diagnosis and had available data about their diagnostic-therapeutic pathways (date of symptom onset, radiological diagnosis, cytohistological diagnosis, first oncological appointment, treatment start, and first radiological reassessment), were reviewed (Supplementary Table 1). Patients with relapsed BC or breast metastases from cancer of a different organ were excluded. Baseline (at diagnosis) data about patient, tumor and treatment characteristics were also retrieved and differences between the two years were computed. To avoid negative values, patients who had a BC diagnosis following the first oncological
appointment (as per standard practice of some referral Hospitals) were not included in the calculation of these specific temporal intervals (Fig. 1).

Approval to conduct this study was granted by the respective local ethical committees on human experimentation of each participating center, after previous approval by the coordinating center ("Comitato Etico Regionale delle Marche - C.E.R.M.", Reference Number 2021 139). As subgroup analyses, we also investigated whether the COVID-19 outbreak impacted differently BC patients according to the lockdown period, the infection rate of the provinces where BC patients were diagnosed (high- vs medium/low-infected provinces), and the hospital volume (high volume: ≥200 new BC diagnoses in the 2-year timeframe vs low/medium volume: <200 diagnoses). As a conventional time interval of about 1 month between diagnosis and first oncological appointment was expected, April 1, 2020-June 30, 2020 was considered as reference time period for the lockdown, instead of March 8, 2020-May 4, 2020 actually imposed by the Italian Government.

2.2. Statistical analysis

A 20% reduction of newly diagnosed BC cases in the pandemic year (2020) compared to 2019 was postulated. Therefore, assuming a 95% confidence interval (95%CI) range of 10% (±5%), a sample size of at least 250 newly diagnosed BC patients in 2019, corresponding to 200 new diagnoses in 2020 was required to test the null hypothesis. Baseline patient, disease and treatment characteristics were presented using count and percentage for categorical variables, median, and range for continuous variables. Pearson chi-square or Fisher’s exact tests (for categorical variables) and paired Student t test, or the Mann-Whitney U test (for continuous variables) were used for analysis of differences between 2020 and 2019. All statistical analyses were performed using R 3.6.0 (R Foundation for Statistical Computing) with a two-tailed level of significance of p < 0.05.

3. Results

3.1 Population

A total of 1,556 patients were included in the study (Fig. 1). A notable reduction (-25%) in newly diagnosed BC was seen in 2020 (n = 666) when compared with 2019 (n= 890). The mean monthly access rate was significantly reduced in 2020 compared to pre-pandemic year (66.6 vs 89.0, p < 0.01) (Fig. 2).

Remarkably, the clinical stage at diagnosis was different between the two cohorts. Specifically, in 2020 new BC patients were less likely to be diagnosed with early stage disease (stage 0-I-II) compared to previous year (77% vs 83%, p < 0.01) (Fig. 3a).

Median age was similar in the two groups (61 years in 2020 vs 62 years in 2019, p = 0.62). Male patients represented a slighter portion in both cohorts with no significant difference between years (0.3% in 2020 vs 0.7% in 2019, p = 0.50) and only 3% of patients had a bilateral disease in both cohorts (p = 1.00). Histotype and “molecular subtype” were similar regardless of the year (p= 0.51 and p= 0.79, respectively)
with ductal histotype accounting for 78% and "luminal A" subtype for 42% of the cases in both years. Regarding the treatment setting, a lower percentage of BC patients received adjuvant therapy in 2020 compared to 2019 (66% vs 70%, \( p = 0.01 \)). However, no significant difference emerged between the two years looking at the number of patients treated with radiotherapy (64% in 2020 vs 66% in 2019, \( p = 0.32 \)). The proportion of patients treated in clinical trials were similar in both cohorts (0.3% in 2020 vs 0.5% in 2019, \( p = 0.70 \)). Looking at symptom onset, a significantly lower number of asymptomatic patients was diagnosed in 2020 compared to 2019 (54% vs 71%, \( p < 0.01 \)) (Fig. 3b).

The ECOG Performance Status (PS) at the start of treatment was significantly different between the two years, with 19.8% of patients with PS > 0 in 2020 vs 16.5% in 2019 (\( p < 0.01 \)). This made the pair with the more advanced stage at diagnosis, as stage III-IV patients were more likely to be symptomatic (\( p < 0.01 \)) and have higher ECOG PS (\( p < 0.01 \)). The multidisciplinary management of patients was significantly impacted by the pandemic: 60% of new BC cases were reviewed in 2020 in multidisciplinary team meetings compared to 73% in 2019 (\( p < 0.01 \)) (Fig. 3c).

Table 1. Patients’ characteristics by year of diagnosis
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2019 (%)</th>
<th>2020 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>890</td>
<td>666</td>
<td></td>
</tr>
<tr>
<td>Monthly access rate</td>
<td>89.0</td>
<td>66.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>62 (29-96)</td>
<td>61 (27-94)</td>
<td>0.62</td>
</tr>
<tr>
<td>Male gender</td>
<td>6 (0.7)</td>
<td>2 (0.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Asymptomatic disease onset *</td>
<td>371 (71)</td>
<td>219 (54)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilateral Disease</td>
<td>27 (3)</td>
<td>20 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Histological subtype *</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>695 (78)</td>
<td>523 (78)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>96 (11)</td>
<td>62 (9)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>59 (7)</td>
<td>55 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>37 (4)</td>
<td>26 (5)</td>
<td></td>
</tr>
<tr>
<td>Molecular subtype *</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal A</td>
<td>351 (42)</td>
<td>260 (42)</td>
<td></td>
</tr>
<tr>
<td>Luminal B HER2-</td>
<td>276 (33)</td>
<td>221 (35)</td>
<td></td>
</tr>
<tr>
<td>Luminal B HER2+</td>
<td>44 (5)</td>
<td>32 (5)</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>83 (10)</td>
<td>63 (10)</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>85 (10)</td>
<td>53 (8)</td>
<td></td>
</tr>
<tr>
<td>Stage at diagnosis *</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0-I-II</td>
<td>735 (83)</td>
<td>510 (77)</td>
<td></td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>146 (17)</td>
<td>150 (23)</td>
<td></td>
</tr>
<tr>
<td>Grading *</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>136 (16)</td>
<td>82 (13)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>440 (52)</td>
<td>345 (53)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>273 (32)</td>
<td>222 (34)</td>
<td></td>
</tr>
<tr>
<td>Treatment *</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>618 (70)</td>
<td>440 (66)</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>96 (10)</td>
<td>104 (16)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Year 2020</th>
<th>Year 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic</td>
<td>41 (5)</td>
<td>40 (6)</td>
</tr>
<tr>
<td>Follow up</td>
<td>132 (15)</td>
<td>81 (12)</td>
</tr>
<tr>
<td><strong>Multidisciplinary discussion</strong> *</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>653 (73)</td>
<td>399 (60)</td>
</tr>
<tr>
<td>No</td>
<td>236 (27)</td>
<td>266 (40)</td>
</tr>
<tr>
<td><strong>Treatment within clinical trials</strong> *</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (0.5)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>No</td>
<td>751 (99.5)</td>
<td>580 (99.7)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong> *</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>565 (66)</td>
<td>388 (64)</td>
</tr>
<tr>
<td>No</td>
<td>288 (34)</td>
<td>222 (36)</td>
</tr>
<tr>
<td><strong>ECOG PS at start of treatment</strong> *</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>592 (83.5)</td>
<td>446 (80.2)</td>
</tr>
<tr>
<td>1</td>
<td>107 (15.1)</td>
<td>85 (15.3)</td>
</tr>
<tr>
<td>2</td>
<td>10 (1.4)</td>
<td>24 (4.3)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status.

* % has been calculated excluding NA (not available) values.

### 3.2. Time intervals

Looking at BC patients’ management, COVID-19 did not seem to negatively impact 2020 in terms of access to diagnosis, staging and treatment (*Table 2 and Supplementary Figure S1*).

**Table 2.** Temporal intervals between date of symptoms onset, radiological diagnosis, cytohistological diagnosis, first oncological appointment, treatment start, and first radiological reassessment by year of diagnosis.
<table>
<thead>
<tr>
<th>Time interval</th>
<th>2019 Median, days (IQR)</th>
<th>2020 Median, days (IQR)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset/radiological diagnosis</td>
<td>24.5 (30)</td>
<td>20 (35)</td>
<td>0.08</td>
</tr>
<tr>
<td>Symptom onset/cytohistological diagnosis</td>
<td>38 (55.5)</td>
<td>32 (42)</td>
<td>0.08</td>
</tr>
<tr>
<td>Symptom onset/first oncological appointment</td>
<td>96 (73)</td>
<td>81 (51.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cytohistological diagnosis/first oncological appointment</td>
<td>63 (49.5)</td>
<td>49 (51)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptom onset/treatment start</td>
<td>113 (74)</td>
<td>94.5 (56.5)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytohistological diagnosis/treatment start</td>
<td>75 (48.5)</td>
<td>61 (53)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>First oncological appointment/treatment start</td>
<td>9.5 (22)</td>
<td>8 (20)</td>
<td>0.12</td>
</tr>
<tr>
<td>Treatment start/first radiological evaluation</td>
<td>104 (149)</td>
<td>71.5 (82.8)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range.

<sup>a</sup> Mann-Whitney U test comparing time intervals between 2019 and 2020. P values were calculated excluding patients with unknown values. Data of patients who had their breast cancer diagnosis after first oncological appointment (as per standard practice of referral Hospitals) were also excluded in the calculation of these specific temporal intervals.

<sup>b</sup> Statistically significant (P < .05).

In particular, time intervals between symptoms onset and radiological diagnosis (median 20 days in 2020 vs 24.5 in 2019, p = 0.08) and symptoms onset and cytohistological diagnosis (median 32 vs 38 days, p = 0.08) were similar between the two years. Strikingly, the intervals between symptoms onset and first oncological visit (median 81 vs 96 days, p = 0.03) and cytohistological diagnosis and first oncological visit (median 49 vs 63 days, p < 0.01) appeared even shorter in 2020. Moreover, focusing on access to treatment, time intervals between symptoms onset and treatment start (median 94.5 vs 113 days, p < 0.01) and cytohistological diagnosis and treatment start (median 61 vs 75 days, p < 0.01) were also improved in 2020 compared to 2019. Temporal intervals between first oncological appointment and treatment start were similar in 2020 compared to 2019 (median 8 vs 9.5 days, p = 0.12); conversely, time interval between treatment start and first radiological re-evaluation was significantly reduced in 2020 (median 71.5 vs 104 days, p < 0.01). Temporal intervals by year are shown in Table 2.

3.3. Subgroup analysis

Considering that COVID-19 might have impacted differently on BC diagnoses according to time of the year, hospital volume and provincial infection rate, sensitivity analyses were performed in some subgroups of patients. Unexpectedly, no significant difference appeared in terms of new BC diagnoses between the lockdown period and the rest of 2020 (-21% vs -26%, p = 0.64). June was the month with the
greatest percentage drop in terms of new BC diagnoses (-37%) (Fig. 2). Regarding the percentage of patients referring to high-volume hospitals vs low/medium-volume hospitals, no significant difference emerged during the pandemic compared to 2019. The percentage was 87% in both years (p = 0.83). Moreover, no difference was described in terms of BC patients referred to hospitals in high-infected vs low/medium-infected provinces during the pandemic (58% in 2020 vs 61% in 2019, p = 0.23).

4. Discussion

Following the direct consequences of COVID-19 on a close to collapse global health care system, the 2020 leaves the cancer care setting in complete awe of future prospects. With our country in the eye of the pandemic storm, Italian Medical Oncologists strived to navigate the uncharted waters of COVID-19 [5, 17]. When desperate times called for drastic measures, diagnostic procedures and screening programs were deprioritized, routine clinical practices (such as follow up visits and multidisciplinary tumor meetings) reoriented to virtual care to reduce risk exposure and ease the pressure on hospital facilities [6, 18]. Cancer patients, as a highly vulnerable population to better manage at a safe distance [19, 20], remotely experienced this improvised disaster response coping with the fear of being left orphan of specialist care [21, 22]. Considering the downside of this forced historic transition to telemedicine, the post-pandemic Oncological scenario will hardly look the same in the forthcoming years [23]. Held hostage by such a global health crisis, alarming predictions have shortly warned the scientific community against neglecting the enduring cancer pandemic by diverting the attention on COVID-19 outbreak [24]. With a great research interest now growing on the repercussions of COVID-19 on cancer incidence and mortality rates, we aimed to shed light on the effectiveness of the measures adopted to deliver new tailored standards of Oncology care for BC patients in Italy after March 2020. Our data indicate a steep reduction (-25%) in BC new diagnoses in 2020 (n=666) compared to pre-pandemic time (n=890), reflecting previous concerning findings worldwide [25-28]. Such drop shows consistency with former observations demonstrating the greater diagnostic backlog after the shutdown of screening programs [26].

Specifically, according to Kaufmann et al. breast cancer diagnosis experienced the sharpest decrease among several malignancies in their first pandemic wave's report of United States (US) weekly cancer incidence [25]. Firstly however, our expanded analysis throughout 2020 revealed that this decline hit its highest point (26%) after the flattening of the first epidemic curve and the resumption of cancer screenings (June 2020). Supporting this finding as a bounce-back after COVID-19 explosion, Dinmohamed et al. also suggest that the composite outcome of diagnostic delays might gain more consideration as the follow up period extends [26]. As the most common diagnosed tumor globally, mainly benefitting in the early stage disease from screening detection [29], it is of utmost importance to consider the potential effect of BC delayed diagnoses on patients’ outcome, ultimately resulting in divergent therapeutic intents (curative vs palliative) [30]. In this regard, our study has strikingly proved that new incidence BC in 2020 were detected at a more advanced stage (23% vs 17%, p < 0.01) and more frequently with a symptomatic onset compared to pre-pandemic time. This notable setback in early stage (stage 0-I-II) diagnoses (77% vs 83%, p < 0.01) after March 2020 parallels the dramatic decline in cancer
screenings reported by the Italian National Screening Network (-34.5% of mammography invitations in the first 9 months of 2020) [31] and by London et al. in their extensive US networks assessment (mammography dropping by 89.2% during lockdown) [32]. Although it is too soon to accurately predict how this much-feared upstaging effect might bear upon cancer survival, early findings from a large United Kingdom (UK) modelling study have suggested for BC mortality rate an increase of 9.6% in the 5 years following diagnosis [33, 34]. In addition, we cannot afford to overlook the economic impact on a pandemic-exhausted health system of the projected excess in cancer deaths resulting from delayed diagnosis. It might outdo a per capita basis, as estimated by Gheorghe et al., the productivity loss accountable to COVID-19 [14]. Differing from former US and European investigations regarding continuum of care [35, 36] our results proves that Italian Oncology Departments were up to the challenge of unwaveringly keeping the cancer care ship afloat despite the unparalleled times. In particular, no gap between years occurred from our analysis in the management system of BC patients in terms of temporal intervals at any step of the Oncology care pathway. This unexpectedly improved performance given during 2020 in the context of diagnostic - therapeutic pathway might be partly explained with the decline in the number of early-stage BC cases more likely amenable to surgery, thus hastening the referral of late stage BC to Medical Oncologists. Contrarily, our study observed a 13% drop in post-pandemic multidisciplinary BC cases discussions (60% vs 73%, p < 0.01). In this regard, Schroeder et al. have formerly investigated the challenges posed by COVID-19 on tumor board members’ interactions, hampered by social distancing along with technical and organizational issues after specialists’ reallocation to COVID-19 units [37]. With the multidisciplinary decision-making process firmly laying the ground for best oncology practice, it may not be a stretch to speculate the magnitude of this result on cancer outcome [38]. We acknowledge that our work has potential limitations as a retrospective investigation. With the start of COVID-19 vaccination campaign at the end of December 2020 in Italy, the effect of the plan for the prevention of SARS COV-2 infections on cancer care was not an object of the present analysis. Nevertheless, as a multicenter study carried out from a broad national collaboration, it also reflects the heterogeneous response to COVID-19 across different levels, including pandemic geographic distribution and local governments’ crisis management. More significantly, while previous investigations were largely conducted through network comparisons, by reviewing 1,556 medical records our real-world study owns the value of avoiding potential informatic reporting biases in such turbulent times.

5. Conclusion

Ultimately from our analysis we can conclude that, while COVID-19 has left its trail on cancer care, the impact of the fewer but later-stage BC diagnoses might clearly unfold in the years to come. Pandemic's challenges considered, our study offers a valuable picture of Italian Oncology Departments’ performance to ensure timely diagnosis, staging and treatment for BC patients during the first pandemic year. Setting the bar of Oncology to revised standards of care, Italian Oncologists stepped in to prevent cancer patients from paying the highest price of disaster unpreparedness. Moreover, as the pandemic continues to rage, the path already covered should indicate the next steps towards the end of the COVID-19 tunnel. Further
studies with a forward-looking perspective, including comparisons between countries differently affected by the pandemic, are warranted to address how COVID-19 crisis will globally resonate in tomorrow’s Oncology.

Declarations

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Conflict of Interest: Rita Chiari received fees for speaker’s bureau and advisory boards participation in BMS, MSD, Roche, Pfizer, AZD, Takeda, Amgen, Boheringer, Novartis. Rossana Berardi is a consultant/advisory board member for Astra Zeneca, Boehringer Ingelheim, Novartis, MSD, Otsuka, Eli-Lilly, Roche. Nicla La Verde declare the following financial interests/personal relationships which may be considered as potential competing interests: grants from EISAI; speaker bureau, travel expenses for conference from ROCHE, GENTILI; advisory role from NOVARTIS and CELGENE; advisor role, travel expenses for conference from PFIZER; advisory board from MSD. All other authors declare that there is no conflict of interest.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics approval: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Comitato Etico Regionale delle Marche - C.E.R.M., (protocol code 2021 139 approved on
References


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Figures
Figure 1

STROBE diagram. Identification and selection of study population according to inclusion and exclusion criteria

Newly diagnosed BC patients referred to 6 Italian Oncology Departments (n=1620)

Patients excluded (n=64) for:

- First oncological appointment between January and February 2020 or 2019
- Any treatment received for breast cancer
- No availability of first oncological appointment date
- No availability of histological diagnosis of breast cancer
- Recurrent breast cancer
- Breast metastases from cancer of different primary origin

Patients included in the study (n=1556)

Availability of data about temporal intervals between:

- date of symptoms onset and date of radiological diagnosis: n=904
- date of symptoms onset and date of histological diagnosis: n=306
- date of symptoms onset and date of first oncological appointment: n=335
- date of histological diagnosis and date of first oncological appointment: n=1234
- date of symptoms onset and date of treatment start: n=963
- date of histological diagnosis and date of treatment start: n=912
- date of first oncological appointment and date of treatment start: n=1158
- date of treatment start and date of first radiological reassessment: n=574

2019: 890
2020: 666
Figure 2

Monthly differences of new breast cancer diagnoses between 2019 and 2020. April, May, and June 2020 (in bold type) were considered as the lockdown timeframe.

<table>
<thead>
<tr>
<th>Month</th>
<th>2019</th>
<th>2020</th>
<th>Absolute difference</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>March</td>
<td>76</td>
<td>75</td>
<td>-1</td>
<td>-1.3%</td>
</tr>
<tr>
<td>April</td>
<td>78</td>
<td>79</td>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>May</td>
<td>93</td>
<td>69</td>
<td>-24</td>
<td>-25.8%</td>
</tr>
<tr>
<td>June</td>
<td>86</td>
<td>54</td>
<td>-32</td>
<td>-37.2%</td>
</tr>
<tr>
<td>July</td>
<td>91</td>
<td>70</td>
<td>-21</td>
<td>-23.1%</td>
</tr>
<tr>
<td>August</td>
<td>88</td>
<td>58</td>
<td>-30</td>
<td>-34.1%</td>
</tr>
<tr>
<td>September</td>
<td>105</td>
<td>68</td>
<td>-37</td>
<td>-35.2%</td>
</tr>
<tr>
<td>October</td>
<td>102</td>
<td>65</td>
<td>-37</td>
<td>-36.3%</td>
</tr>
<tr>
<td>November</td>
<td>85</td>
<td>58</td>
<td>-27</td>
<td>-31.7%</td>
</tr>
<tr>
<td>December</td>
<td>82</td>
<td>74</td>
<td>-8</td>
<td>-9.8%</td>
</tr>
</tbody>
</table>
Figure 3

a Difference in breast cancer stages at diagnosis between 2019 and 2020

b Percentage of asymptomatic new breast cancer patients between 2019 and 2020

c Difference in the percentage of breast cancer cases reviewed during multidisciplinary team meetings between 2019 and 2020

Supplementary Files

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- Supplementarymaterial.doc