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The influence of the COVID-19 pandemic on the use of medical imaging during the breast cancer care pathway

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October 2023

Abstract

The COVID-19 pandemic has had a significant impact on healthcare systems, causing disruptions in various medical services. The aim of this study is to investigate the influence of the COVID-19 pandemic on the use of medical imaging during the breast cancer pathway in the Netherlands.

The data is obtained from the Netherlands Cancer Registry and the Dutch Hospital Data. A total of 73,285 patients were included. To analyse the influence of COVID-19 on medical imaging during breast cancer diagnostics, treatment and follow-up, two periods were compared: the COVID period (week 2, 2020 – week 28, 2021) and the pre-COVID period (week 2, 2018 – week 28, 2019). These periods were both divided into five periods: period A till period E. For diagnostics, a Sankey diagram was computed and a Poisson regression was performed on the number of medical imaging events. For treatment, a comparable Poisson regression was performed and for follow-up logistic regression was performed on a yearly follow-up mammogram.

Within the first five diagnostic medical imaging events, during the COVID-19 period 76.5% of patients is diagnosed, compared to 29.4% in the pre-COVID period. For treatment, the incidence rate ratios for the utilization of medical imaging across the four therapy types were lower during the COVID-19 period compared to the pre-COVID-19 period, especially in period A, B, and C. Regarding follow-up, the Odds Ratio of a yearly control mammogram being performed in the COVID period is 0.27 (0.23-0.32) during period A, 0.07 (0.06-0.08) during period B, 0.22 (0.20-0.24) during period C, 0.43 (0.39-0.47) during period D, and 1.12 (1.02-1.23) during period E.

The study reveals notable changes in medical imaging utilization. During the pandemic, patients were diagnosed after fewer medical imaging events, a decrease was found in the use of medical imaging for monitoring responses to systemic therapies, and a smaller proportion of patients received a follow-up mammogram.

Keywords: COVID-19, breast cancer, care pathway, medical imaging

Background

December 2019, multiple cases of pneumonia with an unknown cause were identified in Wuhan, China. The Chinese authorities shared the existence of a new virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the world on January 12, 2020. The disease caused by this virus has since been named COVID-19 [1]. On February 27, 2020, the first COVID-19 case in the Netherlands was detected in the south of the country [2]. In the following weeks, the virus gradually spread to the other regions of the country. Countermeasures such as social distancing, closing universities and institutions of higher professional education, and cancelling gatherings with more than 100 people were applied by the Dutch government beginning in the second week of March [3]. Another aspect of the new policy was the decision for hospitals to focus on COVID-19 patients, because of the enormous inflow of patients showing COVID symptoms. Furthermore, to prevent spread of the virus and to lower the burden on health care, other health care domains received a lower priority. This, in combination with the advice for elderly and vulnerable patients to stay at home, caused a halt of the national screening programs, and postponement of cancer diagnostics, treatment, and follow-up. Even though less urgent cancer care was postponed, emergency surgeries still had a high priority [4][5].

The suspension of the screening program reduced the incidence of breast cancer. Even though this led to about 2000 delayed screen-detected breast cancers, there was no shift observed towards a higher breast cancer stage at diagnosis up to August 2020 [6]. For patients with Ductal Carcinoma In Situ (DCIS) and grade I-II breast cancer, the number of breast cancer treatments started per week and the treatment strategy overall were adapted during the COVID-19 pandemic. For these patients, surgery was postponed and neo-adjuvant endocrine therapy was started. Also, a decrease in time intervals between diagnosis and surgery was shown for emergency patients, due to a decrease in number of patients, the prioritization of oncological care and the postponement of elective surgeries [4]. Follow-up visits were often either changed to telephone or video consultations or postponed [7]. It is yet to be determined how the COVID-19 pandemic influenced the use of medical imaging during the breast cancer care pathway.

Prior to the COVID-19 pandemic, patients either were referred to the breast cancer care unit from the general practitioner due to self-suspected breast cancer or after a suspect screen mammogram within the national screening program if they fell within the age range of 50 to 75 years. The initial diagnostic step in the hospital for these patients involved a mammogram. In cases where the mammogram reveals abnormal findings, an ultrasound of the breast is often performed. The Breast Imaging Reporting and Data System (BI-RADS) scoring system is utilized to determine if additional diagnostic steps are necessary. A BI-RADS score of 0, 1, or 2 indicates that no oncological workup or treatment is required since there is no suspicion of a malignancy. However, if the BI-RADS score is 3, 4, or 5, histology and/or cytology are necessary. Histological punctures are performed with the assistance of ultrasound, x-ray, or MRI [8].

With the histology results, the tumour stage is defined based on the TNM system [9]. Depending on the tumour stage, additional medical imaging will be indicated if necessary. After determining the preoperative tumour stage, depending on the treatment options such as neoadjuvant therapy, surgery, and/or systemic therapy, imaging is required. A CT scan is performed prior to starting radiotherapy and MRI is used for preoperative planning for either breast conserving surgery or mastectomy. To monitor the response to systemic therapy, either PET-CT or MRI can be used.

After finalizing the primary breast cancer treatment, follow-up is initiated. According to the guideline, for the first five years post-treatment, patients undergo an annual follow-up that includes a yearly mammogram. After this five-year period, the follow-up schedule changes to an annual follow-up for patients aged 60 years and younger, biennial follow-up for patients aged between 60 and 75 years old, and no follow-up for patients older than 75 [10].

Contrary to the new video/telephone consultations which enabled patients to stay at home, to undergo medical imaging, a visit to the hospital is required. Since during the COVID-19 pandemic hospital visits were limited, the use of medical imaging might be influenced. The aim of this study is to make a comparison regarding the use of medical imaging in the breast cancer care pathway between the pre-COVID period (2018-2019) and the COVID period (2020-2021). The influence of different factors on the use of medical imaging during diagnostics, treatment and follow-up in breast cancer will be studied.

Method

The data for this research is obtained from the Netherlands Cancer Registry (NCR) and the Dutch Hospital Data (DHD). The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), who receive notifications from the national pathology archive (PALGA). Specially trained datamanagers gather data on patient (e.g. gender, age at diagnosis), tumour (e.g. morphology, TNM stage, differentiation grade) and treatment characteristics (e.g. type of surgery) directly from patient files in all hospitals in the Netherlands. The *Landelijke Basisregistratie Ziekenhuiszorg* (LBZ) data, provided by the DHD, includes all medical procedures performed regarding the patient’s care pathway (diagnostics, treatment and follow up) and is obtained from the patient files through an automatic datatransfer. These two datasets are merged into one dataset. Men, patients under 18 and patients without data on tumour stage, region and age, were excluded from the study.

Definitions

In order to find the effects of COVID-19 on the use of medical imaging for diagnosis, treatment and follow up, the focus lies on finding the variations between the different defined sub-periods of the pre-COVID period and the COVID period. In this, the 2018/2019 pre-COVID period will function as a reference group for the 2020/2021 period. With the aim of comparing these two periods, the data set is split into five periods for 2020/2021. Period A is the period before the first COVID patient in the Netherlands (week 2-11), group B is the first peak (week 12-20), group C is the first recovery (week 21-39), group D is the second peak (week 40-5) and group E is the second recovery (week 6-28). In 2018/2019, these five periods are also used for reference. To gain insight the number of COVID infections during these periods, more information is needed on the incidence. Therefore, the incidence is plotted against the week of diagnosis.

Patients were divided into one of the following age groups: 18-39, 40-49, 50-64, 65-74 and 75+. Patients were also categorized into the region corresponding with the hospital they first visited regarding their tumour. These regions were: North (Groningen, Drenthe, Friesland), Middle-East (Overijssel, Flevoland), Middle (Utrecht, Gelderland), West (Noord-Holland, Zuid-Holland, Zeeland), and South (Noord-Brabant, Limburg). The hospitals were also divided into one of the following groups: Academic hospital, Top-Clinical hospital and general hospital. In the Netherlands, there were a total of 8 academic hospitals, 27 educational hospitals and 34 general hospitals.

Tumours were grouped according to the TNM staging guidelines: DCIS, and stage I, II, III, IV. If available, the pathological stage was used. When the pathological stage was unknown, the clinical stage was used. Additionally, tumours were grouped by subtype based on the human epidermal growth factor receptor 2 (HER2) and hormone receptor (HR) status: HER2+/HR+, HER2+/HR-, HER2-/HR+. HER2-/HR- and unknown.

Statistical analysis

Diagnostics

For diagnostics, a subset was made for patients diagnosed with breast cancer between week 2 – 2018 till week 29 – 2019 and week 2 – 2020 till week 29 2021. These were the patients that were diagnosed with breast cancer within period A till period E for both the pre-COVID period and the COVID period.

Concerning the diagnostic care pathway analysis, two methods have been used. In order to get an overview of the entire diagnostic care pathway of breast cancer patients, a Sankey diagram was computed. A Sankey diagram shows the flow between different stages in the care pathway in sequential order. Within the LBZ-data for diagnostics, a maximum of 22 care activities was included with 16 possible diagnostic procedures for each care activity. These were divided into different categories, based on the underlying imaging technique: X-ray, Ultrasound, CT, MRI and PET. A sixth category, termed 'No Imaging', was established for diagnostic procedures that did not involve medical imaging, given the focus of this study on medical imaging. Despite its lack of relevance to the imaging aspect of the study, the 'No Imaging' category was deemed essential to retain within the dataset for comprehensive analysis. When the diagnostic pathway of a patient was completed, from that point onwards the care activities indicated 'No Imaging' as well. Once a patient is in the 'No Imaging' group, the patient stays in that group, meaning the 'No Imaging' group is cumulative.

Secondly, the number of events per imaging modality gives insight into the diagnostic care pathway of a patient. To obtain insight in factors influencing the number of medical imaging events, multivariate Poisson regression was used with which the Incidence Rate Ratio's (IRR) were calculated, corrected for age, region, hospital type and mode of detection (screening). The Incidence Rate Ratio is a suitable outcome because it enables the comparison of event rates between different categorical predictors, quantifying the proportional change in rates and revealing the relative impact of these variables on medical imaging events.

Treatment

The subset utilized for treatment analysis comprised all medical imaging events occurring between the date of diagnosis and 18 months thereafter. This time interval was selected as most therapies are completed within 18 months post-diagnosis. According to the guideline, radiotherapy, chemotherapy, and targeted therapy have maximum durations of six weeks [11], six months [12], and one year [13], respectively. Hormonal therapy is the only treatment with a longer duration of five years [14].

The treatment LBZ-data encompasses 27 care activities, within which a total of 78 distinct medical imaging events were identified. All medical imaging events utilizing MRI and PET were selected, as these were the imaging modalities most commonly employed for therapy monitoring [15][16]. For each therapy, the NCR-data included variables indicating whether the patient had received the therapy and whether it was administered pre- or post-surgery, as well as the start and stop dates of the treatment. Hormonal therapy did not have a stop date due to its long term use and the dataset only containing data from January 1st, 2017 to July 31st, 2021. For patients receiving hormonal therapy, July 31st, 2021 was designated as the stop date of the therapy. In cases where the stop date was missing for other therapies, a stop date was generated by adding the therapy durations mentioned above to the start date of the therapy. For radiotherapy, a new stop date was created by adding six months to the start date of the therapy, since medical imaging is rarely performed during radiotherapy. This newly created stop date allowed for analysis of medical imaging used for monitoring the response to radiotherapy after the actual stop date of the therapy, as response monitoring is typically conducted after radiotherapy.

For analysis, the dataset was divided into four separate datasets: a separate dataset for each type of systemic therapy, containing all patients that underwent that therapy. These new datasets contained data on medical imaging specific to each therapy by retaining only medical imaging events occurring between the start and stop dates of the respective therapy (chemotherapy, targeted therapy and hormonal therapy). For radiotherapy, all medical imaging events within the defined time interval were included. This allowed analysis of the medical imaging used during the four therapies, since all four therapies have a different duration. To obtain insight in factors influencing the number of medical imaging events during each therapy, multivariate Poisson regression was used with which the IRRs were calculated, corrected for age, tumour stage, HER2-status, HR-status, region, hospital type and mode of detection (screening).

Follow-Up

For follow-up analysis, a subset was created for patients diagnosed with breast cancer between week 1 – 2017 till week 29– 2020. These were the patients that can have a yearly surveillance mammogram, since the dataset contained data till the 30th of July, 2021, and generally follow-up takes place around 12 months following treatment. Additionally, patients without any follow-up data were excluded.

The follow-up LBZ data contained up to 149 care activities in which the focus lies on a yearly surveillance mammogram. For patients with breast cancer, the guideline is to perform a yearly mammogram for the first five years after diagnosis [10]. Within the 149 care activities, 19 unique follow-up procedures existed, of which mammography, 3D mammography and MR mammography were selected as an option for the yearly follow-up mammogram. For the pre-COVID period, a histogram of the number of days between the date of surgery and the date of the follow-up events was computed. The results of this histogram determined the interval in which a mammogram would count as a yearly follow-up mammogram. Contrary to diagnostics and treatment, logistic regression was used, since the desired outcome is the Odds Ratio on whether a patient received a yearly follow-up mammogram. Logistic regression was performed on a yearly follow-up mammogram, which was defined as having a mammogram within the interval, observed in the histogram. From the logistic regression, the Odds Ratios were calculated, corrected for region, age, tumour stage, HER2-status, HR-status and hospital type. The regression was performed only for the first year after surgery, since for the patients receiving surgery during the COVID period, only one year of follow-up data was available.

R (version 4.2.2) was used for statistical analysis. For the entire statistical analysis, a P value of < 0.05 was deemed as statistically significant.

Results

Based on the inclusion and exclusion criteria, a total of 73,285 patients were included in the study. As indicated in Table 1, the number of patients was lower in 2020 and 2021, with 14,256 and 9,769 patients, respectively. The proportion of patients diagnosed through the national screening program was lowest in 2020 (26.6%). Additionally, in 2020, the proportion of patients with tumour stage I was the lowest (42.0%), while the proportion of patients with tumour stage II (28.8%), III (6.6%) and IV (5.3%) was higher than in all other years.

Table 1

Overview of the patient cohort

Year of Diagnosis	***2017***	***2018***	***2019***	***2020***	***2021****
Total	16656	16145	16459	14256	9769
	n(%)	n(%)	n(%)	n(%)	n(%)
Age					
18-39	719 (4.3)	693 (4.3)	737 (4.5)	739 (5.2)	407 (4.2)
40-49	2337 (14.0)	2252 (13.9)	2267 (13.8)	2009 (14.1)	1230 (12.6)
50-64	6182 (37.1)	5977 (37.0)	5965 (36.2)	4981 (34.9)	3599 (36.8)
65-74	4706 (28.3)	4361 (27.0)	4497 (27.3)	3742 (26.2)	2686 (27.5)
75+	2712 (16.3)	2862 (17.7)	2993 (18.2)	2785 (19.5)	1847 (18.9)
Tumour Stage					
I	7583 (45.5)	7127 (44.1)	7200 (43.7)	5981 (42.0)	4350 (44.5)
II	4598 (27.6)	4517 (28.0)	4579 (27.8)	4105 (28.8)	2641 (27.0)
III	1040 (6.2)	978 (6.1)	969 (5.9)	937 (6.6)	555 (5.7)
IV	673 (4.0)	740 (4.6)	730 (4.4)	761 (5.3)	459 (4.7)
DCIS	2762 (16.6)	2783 (17.2)	2981 (18.1)	2472 (17.3)	1764 (18.1)
HER2 status					
HER2-	12236 (73.5)	11937 (73.9)	12157 (73.9)	10713 (75.1)	7359 (75.3)
HER2+	1866 (11.2)	1817 (11.3)	1844 (11.2)	1601 (11.2)	1086 (11.1)
Unknown	2554 (15.3)	2391 (14.8)	2458 (14.9)	1942 (13.6)	1324 (13.6)
Receptor status					
HR-	2145 (12.9)	2110 (13.1)	2156 (13.1)	1986 (13.9)	1292 (13.2)
HR+	9971 (59.9)	9498 (58.8)	9770 (59.4)	8451 (59.3)	5854 (59.9)
Unknown	4540 (27.3)	4537 (28.1)	4533 (27.5)	3819 (26.8)	2623 (26.9)
Screening Detected					
No	10469 (62.9)	10334 (64.0)	10722 (65.1)	10521 (73.8)	6319 (64.7)
Yes	6187 (37.1)	5811 (36.0)	5737 (34.9)	3735 (26.2)	3450 (35.3)
Region					
Middle	3827 (23.0)	3616 (22.4)	3871 (23.5)	3305 (23.2)	2248 (23.0)
Middle East	1170 (7.0)	1264 (7.8)	1279 (7.8)	1231 (8.6)	804 (8.2)
North	2078 (12.5)	1988 (12.3)	1931 (11.7)	1581 (11.1)	1126 (11.5)
South	3763 (22.6)	3612 (22.4)	3750 (22.8)	3201 (22.5)	2240 (22.9)
West	5818 (34.9)	5665 (35.1)	5628 (34.2)	4938 (34.6)	3351 (34.3)

* It should be noted that the dataset only contains data up until July 31st, 2021.

Diagnostics

As illustrated in the incidence plot (Figure 1), both lines represent the daily number of registered breast cancer patients. The incidence during the pre-COVID period appears relatively stable, with minor fluctuations and an overall decrease in the number of registered breast cancer patients over the course of 80 weeks. During the COVID-19 period, a significant trough is observed in periods B and C. In period D, the number of registered breast cancer patients increases. From period E onwards, the two incidence lines follow a similar trajectory, with the incidence during the COVID-19 period being slightly lower.

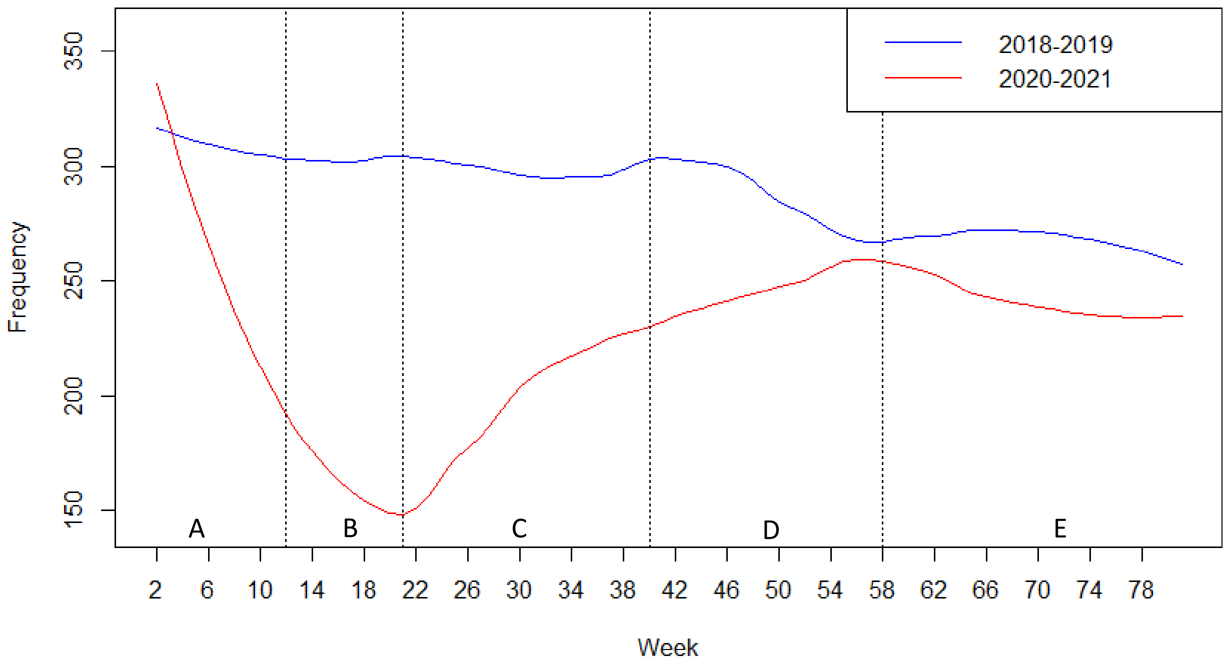

Figure 1 – Breast cancer incidence during different phases of the pre-COVID and the COVID period

Two Sankey Diagrams are presented (Figure 2). Upon initial examination, it is evident that the percentage of patients referred from the national screening program is higher in the pre-COVID period compared to the COVID-19 period (35.6% versus 13.4%). For both the pre-COVID and COVID-19 periods, the 'No Imaging' group increases in size after each imaging procedure. However, after five diagnostic medical imaging events, the proportion of diagnosed patients during the COVID-19 period is 76.5%, compared to 29.4% in the pre-COVID period.

The majority of patients receive either an ultrasound or a mammogram as their first form of medical imaging. However, the percentage of patients receiving a mammogram as their first diagnostic care activity (excluding screening) is nearly ten percent higher during the COVID-19 period compared to the pre-COVID period (29.3% versus 19.9%). This difference decreases during the second diagnostic care activity, with 54.5% of patients receiving a mammogram during the COVID-19 period compared to 48.3% during the pre-COVID period. Additionally, the percentage of patients receiving an MRI scan is lower for all five care activities during the COVID-19 period compared to the pre-COVID period.

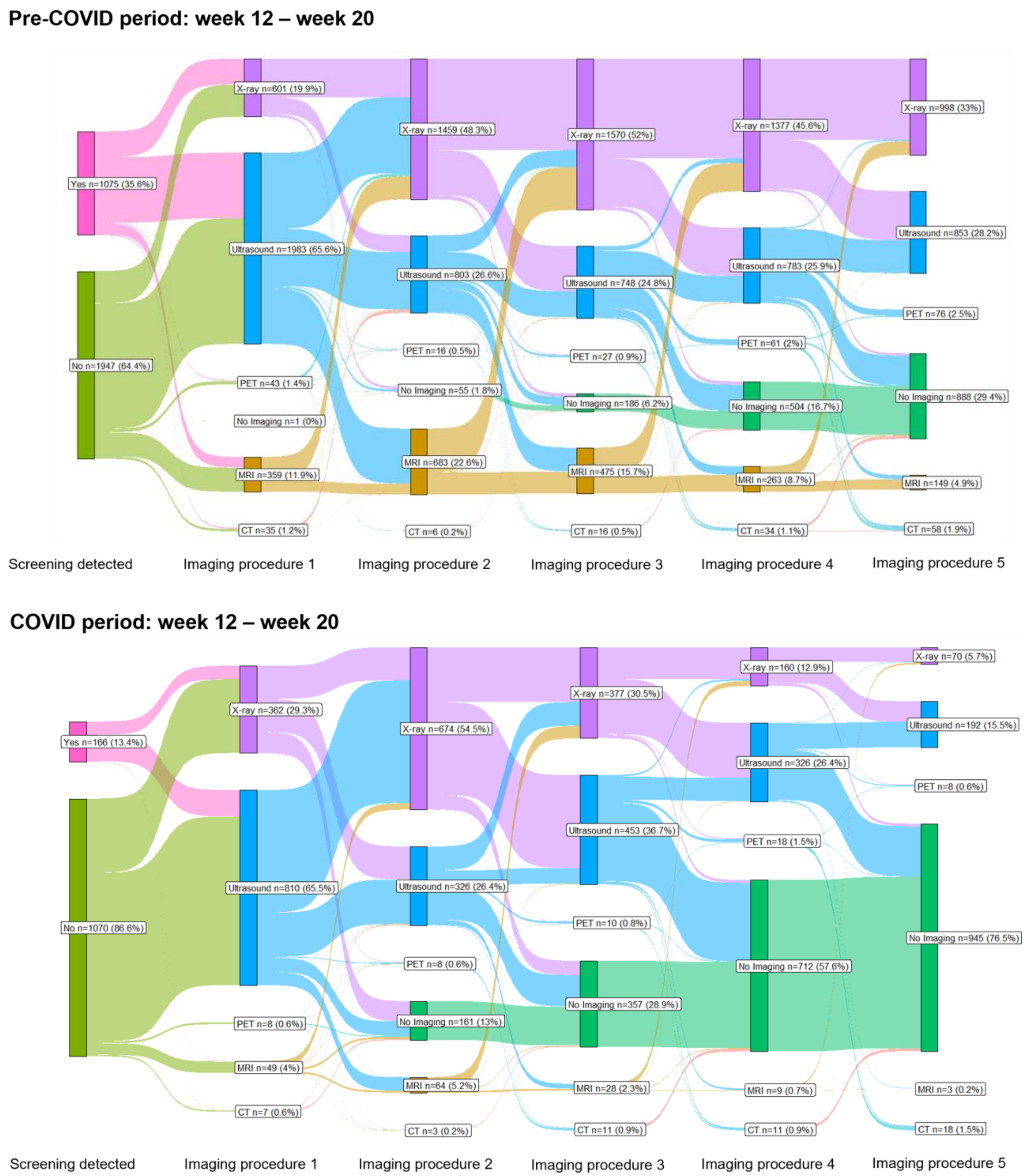

Figure 2 – Two Sankey diagrams of the patient flow during the first five medical imaging procedures of the diagnostic phase.

The incidence rate ratio (IRR) for all medical imaging modalities during the COVID period is at its lowest in period A, with the exception of mammography (Table 2). For ultrasound, CT, MRI, and PET, the IRR increases from period A onwards until it reaches its highest value in period E. Mammography follows a different trajectory, with the lowest IRR observed in period C. In period E of the COVID-19 period, the IRR values for CT, MRI, and PET are not significantly different from those of the pre-COVID period. All other IRR values for the five COVID-19 periods are significantly different from those of the pre-COVID period.

Table 2
Poisson regression model on the IRRs of medical imaging events during diagnostics. The periods indicate the period in which a patient was diagnosed. For each period, the reference is the corresponding period of the pre-COVID period.

	X-Ray (IRR)	Ultrasound (IRR)	CT (IRR)	MRI (IRR)	PET (IRR)
Period					
A	0.56**	0.64**	0.16**	0.12**	0.12**
B	0.57**	0.64**	0.24**	0.15**	0.19**
C	0.52**	0.68**	0.27**	0.17**	0.18**
D	0.54**	0.76**	0.40**	0.27**	0.26**
E	0.71**	0.92**	0.88	0.97	1.10
Age					
50-64	ref	ref	ref	ref	ref
18-39	0.86**	1.18**	1.19**	1.60**	1.46**
40-49	0.94**	1.06**	0.99	1.32**	1.04
60-74	0.99	0.95**	0.95	0.66**	0.81**
75+	0.81**	0.94**	0.64**	0.22**	0.50**
Screening detected					
No	ref	ref	ref	ref	ref
Yes	1.08**	0.89**	0.42**	0.55**	0.29**
Hospital type					
General	ref	ref	ref	ref	ref
Academic	1.03	0.90**	0.11**	1.16**	1.21**
Educational	0.97**	0.85**	0.78**	0.91**	1.19**
Region					
West	ref	ref	ref	ref	ref
Middle	0.95**	1.09**	1.06	0.98	1.10*
Middle East	0.96**	1.08**	0.76**	1.10**	0.91
North	1.13**	0.88**	0.39**	1.03	1.03
South	0.92**	0.83**	0.79**	1.16**	0.87**

* P value < 0.05, ** P value < 0.01

Treatment

In terms of treatment, the same trend is observed (Table 3) as during diagnostics. Overall, the incidence rate ratios (IRR) for the utilization of medical imaging across the four therapies were lower during the COVID-19 period compared to the pre-COVID-19 period. This was particularly pronounced during periods A, B, and C. During periods D and E, fewer significant differences were observed between the COVID-19 and pre-COVID-19 period. Notably, the IRR values for academic and educational hospitals were generally higher than those for general hospitals. The IRR values for PET during chemotherapy and targeted therapy in period B are 0.00, compared to the pre-COVID period. This is the same for the use of MRI during hormonal therapy for HER2+/HR-. However, these differences are not significant.

Table 3

Poisson regression model on the IRRs of PET and MRI during chemotherapy, radiotherapy, hormonal therapy and targeted therapy. The periods indicate the period in which systemic treatment was started.. For each period, the reference is the corresponding period of the pre-COVID period.

Therapy	**Chemotherapy**		***Radiotherapy***		***Hormonal therapy***		***Targeted therapy***	
Imaging modality	MRI (IRR)	PET (IRR)	MRI (IRR)	PET (IRR)	MRI (IRR)	PET (IRR)	MRI (IRR)	PET (IRR)
Period								
A	0.10**	0.29*	0.02**	0.16**	0.06**	0.04**	0.11**	0.13**
B	0.31**	0.00	0.12**	0.18**	0.08**	0.11**	0.24**	0.00
C	0.19**	0.14**	0.10**	0.05**	0.11**	0.08**	0.21**	0.13**
D	0.56**	0.23	0.13	0.4	0.44*	0.60	0.59*	0.53
E	0.42**	1.01	1.22	0.38	0.43	0.40*	0.37**	0.31
HER2/HR status								
HER2-/HR-	ref	ref	ref	ref	ref	ref	ref	ref
HER2-/HR+	0.90	0.33**	1.34	0.39**	0.31**	0.18**	2.07	1.53
HER2+/HR-	3.02**	1.45	0.34	1.03	0.00	0.43	1.89	2.98
HER2+/HR+	3.07**	1.20	0.55	0.46*	0.19**	0.13**	1.86	1.45
Unknown	1.87**	0.95	1.28	0.37**	0.31**	0.20**	2.10	1.88
Tumour stage								
I	ref	ref	ref	ref	ref	ref	ref	ref
II	0.91	2.10*	0.57**	1.6*	0.94	1.18	1.10	1.26
III	1.35*	3.65**	1.74*	4.1**	1.55**	3.08**	1.30	2.99**
IV	0.69	12.00**	1.33	6.5**	1.37	8.00**	0.47**	8.70**
DCIS	1.92**	1.84	1.32	0.84	1.40	1.93**	1.73**	1.02
Age								
50-64	ref	ref	ref	ref	ref	ref	ref	ref
18-39	1.04	0.63	1.69	0.81	1.99**	1.16	1.05	0.65
40-49	1.28*	1.66*	1.1	1.29	0.91	0.76	1.20	1.00
65-74	0.80	0.49	0.77	1.08	0.79*	0.84	0.86	0.38**
75+	1.00	0.70	0.19**	0.49*	0.45**	0.71*	0.61*	0.20**
Screening detected								
No	ref	ref	ref	ref	ref	ref	ref	ref
Yes	0.74*	0.69	0.54**	0.71	0.60**	0.77	0.67**	0.56

Hospital type								
General	ref	ref	ref	ref	ref	ref	ref	ref
Academic	1.24	0.96	2.33**	1.59	1.77**	1.17	0.90	0.73
Educational	1.56**	0.87	1.62**	1.51*	1.20	1.60**	1.34**	1.78**
Region								
West	ref	ref	ref	ref	ref	ref	ref	ref
Middle	0.83	0.75	1.71**	2.18**	1.29*	1.35*	0.83	1.84*
Middle East	1.44**	0.33	0.74	0.75	1.00	0.56*	0.67*	0.44
North	1.20	1.01	3.78**	0.97	1.43**	1.13	0.84	1.23
South	0.87	1.68	0.54*	0.94	0.62**	0.84	0.77*	1.22

* P value < 0.05, ** P value < 0.01

Follow-Up

The interval in which imaging could be linked to a follow-up mammogram was set at 310 till 410 days after surgery, since a peak was found around 360 days after diagnosis in the histogram. There is a significant difference in Odds Ratio's between the pre-COVID and the COVID period (Table 4). Compared to the pre-COVID period, the Odds Ratio of a yearly control mammogram being performed is 0.27 (0.23 – 0.32) during period A, 0.07 (0.06 - 0.08) during the first peak (B), 0.22 (0.20 - 0.24) during the first recovery (C), 0.43 (0.39 - 0.47) during the second peak (D), and 1.12 (1.02 - 1.23) during the second recovery (E).

Table 4
Logistic regression model: the odds of having a yearly follow-up mammogram. The periods indicate the period in which the yearly follow-up mammogram should have taken place. For each period, the reference is the corresponding period of the pre-COVID period.

	Odds Ratio	**95% CI**
Period		
A	0.27	(0.23 - 0.32)
B	0.07	(0.06 - 0.08)
C	0.22	(0.20 - 0.24)
D	0.43	(0.39 - 0.47)
E	1.12	(1.02 - 1.23)
Age		
50-64	ref	ref
18-39	0.64	(0.56 - 0.72)
40-49	0.82	(0.76 - 0.88)
65-74	1.11	(1.05 - 1.18)
75+	0.98	(0.91 - 1.06)
Tumour stage		
I	ref	ref
II	0.86	(0.82 - 0.91)
III	0.60	(0.54 - 0.67)
IV	0.45	(0.31 - 0.63)
DCIS	0.56	(0.50 - 0.62)

Receptor status		
HER2-/HR+	ref	ref
HER2-/HR-	0.74	(0.68 - 0.81)
HER2+/HR-	0.79	(0.69 - 0.90)
HER2+/HR+	0.88	(0.79 - 0.98)
Unknown	0.92	(0.86 - 0.98)
Hospital type		
General	ref	ref
Academic	0.35	(0.30 - 0.40)
Educational	0.93	(0.88 - 0.98)
Region		
West	ref	ref
Middle	1.47	(1.37 - 1.56)
Middle East	1.23	(1.12 - 1.36)
North	2.15	(1.98 - 2.32)
South	1.22	(1.14 - 1.30)

Discussion

During the pandemic, patients were diagnosed after fewer medical imaging procedures, a decrease was found in the use of medical imaging for monitoring responses to systemic therapies, and a smaller proportion of patients received a follow-up mammogram. Overall, these effects were mainly visible during period A and period B of the COVID period. The use of medical imaging started to increase again from period C onwards.

Diagnostics

The trough observed in period B of the COVID-19 pandemic (2018-2019) can be attributed to the cessation of the screening program. An alternative explanation could be that patients were hesitant to visit the hospital due to fear of falling victim to COVID-19, particularly given the high number of infections reported at hospitals.

In reference to the Sankey Diagram for diagnostics, the observed decrease in the number of patients referred from the national screening program during the COVID-19 pandemic can be attributed to the halting of the screening program during the first peak. However, it would be expected that the percentage of patients referred from the screening program would be zero if the program was halted. One possible explanation for this discrepancy is that some patients were screened and referred to the hospital prior to the first peak, but did not visit the hospital until during the first peak. Alternatively, some patients may have been screened and initiated their diagnostic process at the hospital prior to the first peak, but had not yet received a diagnosis.

The impact of the halt in the national screening program is visible in the first diagnostic care activity of the COVID-19 period. The proportion of patients receiving a mammogram as their first diagnostic care activity increased by nearly ten percent. Typically, patients between the ages of 50 and 75 are invited to participate in the national screening program for a screening mammogram. It is important to note that when patients within this age group are referred from the national screening program, at the mamma care unit can be decided to not take an additional mammogram if the screening mammogram is sufficient [17]. However, due to the halt in the screening program, this group of patients did not receive their mammogram. As a result, an additional mammogram was required at the hospital. Since a mammogram is often the first step in the diagnostic process for breast cancer, this additional mammogram occurred during the first diagnostic care activity. Regarding MRI, the decrease in the percentage of patients receiving an MRI scan during the first five care activities could mean that proportionally fewer patients under the age of 50 visited the mamma care unit, since MRI is more commonly used during the diagnostic care pathway of younger breast cancer patients [18].

The higher percentage of breast cancer patients being diagnosed after five diagnostic care activities during the COVID-19 period (76.5% during the first COVID peak versus 29.4% during the pre-COVID period) indicates that fewer medical imaging events were required to diagnose patients during the first peak of the COVID-19 pandemic. The same trend is for instance observed in the incidence rate ratio of mammography during period B of the COVID-19 period which is 0.57 compared to period B of the pre-COVID period. This indicates that the incidence rate of mammography being used for breast cancer diagnosis is 43% lower during the COVID-19 period compared to the pre-COVID period. The IRR is significantly lower for all medical imaging modalities and for the entire COVID period compared to the pre-COVID period, with the exception of period E. In this period, the IRR values for CT, PET, and MRI are not significantly different from those of the pre-COVID period, meaning that the incidence rate of these medical imaging modalities being used for breast cancer diagnosis during the COVID-19 period is not lower than during the pre-COVID period. This suggests that for patients with a higher tumour stage, the diagnostic care pathway started to follow the diagnostic guidelines that were active before the COVID-19 pandemic, since CT, PET, and MRI are often used for higher tumour stages.

Treatment

Overall, the use of medical imaging during systematic treatment has decreased during the COVID period compared to the pre-COVID period. Whilst MRI is generally used for monitoring the response to chemotherapy, the number of MRIs used for monitoring breast cancer patients treated with chemotherapy during the entire COVID-19 pandemic has significantly decreased.

The fact that the IRR value is so small whilst not being significantly smaller for the use of MRI during the response monitoring of hormonal therapy for HER2+/HR- patients, is explained by the fact that hormone therapy does not work for HR- patients [19]. The non-significant 0.00 values for the use of PET for monitoring the response to chemotherapy and targeted therapy during period B, indicate that few patients undergoing chemotherapy and targeted therapy were monitored with PET during period B of both the COVID period and the pre-COVID period.

Follow-up

For follow-up monitoring, the established guideline stipulates that breast cancer patients should undergo mammography one year following treatment [10] A decline is visible in the odds ratio of receiving the follow-up mammogram during the initial peak of the COVID period relative to the pre-COVID period. From period C onward, the odds ratio increases until it reaches a value of 1.12 in period E, indicating a slight increase in the likelihood of receiving a follow-up mammogram during the COVID period compared to the pre-COVID period. This trend is consistent with expectations, as cancer care was partially suspended during the first peak and gradually resumed in accordance with guidelines from the first recovery phase onward.

An interesting observation in the diagnostic and treatment phase, is that the incidence rate ratios for period A were consistently lower during the COVID-19 period relative to the pre-COVID-19 period. The same is shown in the logistic regression model regarding the yearly follow-up mammogram. This is unexpected, as period A spans from week 2 to week 11, prior to the implementation of the first countermeasures by the Dutch government. The first COVID-19 patient in the Netherlands was however diagnosed in week 9 of 2020 (February 27th). There is a gap of 2.5 weeks between the first COVID-19 patient and the first peak. During this time, the number of COVID-19 diagnoses increased, and the government advised individuals to stay at home and exercise caution to avoid infection with COVID-19. This may have influenced people’s decisions to visit hospitals.

Strengths and limitations

The database includes over 73,000 patients, representing a significant strength of this study. The data from the NKR and LBZ provide comprehensive coverage of nearly the entire Netherlands, enhancing the generalizability and reliability of the study’s conclusions. Furthermore, the large sample size increases the statistical power of the analysis. For treatment analysis, data is available until 18 months after date of diagnosis. While the current data is sufficient for chemotherapy, targeted therapy, and radiotherapy, additional data is necessitated for hormonal therapy. This is due to the extended duration of hormonal therapy, which can span up to five years. Additionally, some patients have an overlap in treatments they receive. Whilst it is possible for patients to follow multiple therapies at the same time, this also causes uncertainty about for which of the therapies the medical imaging event is registered. Since all medical imaging events during the duration of the therapies are counted as monitoring for that therapy, some will be counted double if a patient receives two therapies at the same time. This can be seen for example in the IRR values for monitoring of the response to hormonal treatment. The reference group, HER2-/HR-, relatively has the highest IRR values. This indicates that medical imaging is used for monitoring the response of hormonal therapy for patients with tumours without hormonal receptors. This is unexpected, since hormonal therapy is usually not given to hormone-receptor negative breast cancer patients.

In order to compute the Poisson regression model for diagnostics and treatment and the Logistic regression model for follow-up, an extra period was created in the dataset. Originally the same time periods were used, with a small difference: period E ranged from week 6 to week 29 instead of week 6 to week 28. Because all five periods are multicollinear as independent variables, this causes a dummy tap. The consequence of this is that period E is not in the multivariate analysis. To counter this, an extra period was added: period F (Week 29, the last week of period E). By adding an extra period, the dummy trap is avoided. This means that the data from week 29 of the second year of both the pre-COVID and the COVID period is not included in the Poisson regression model for diagnostics and treatment and the Logistic regression model for follow-up.

Conclusion

During the COVID period, there has been a marked decrease in the utilization of medical imaging compared to the pre-COVID period. During the diagnostic phase, patients were diagnosed after fewer medical imaging events. Furthermore, less medical imaging was employed for monitoring responses to various systemic therapies. Additionally, during the COVID-19 pandemic, a smaller proportion of patients received a follow-up mammogram.

The long-term implications of these changes in medical imaging usage during the COVID period as compared to the pre-COVID period are currently difficult to ascertain. The reduction in medical imaging for diagnosis, treatment, and follow-up of breast cancer patients during the COVID-19 period may potentially impact patient survival or quality of life. Therefore, further research is necessary to gain knowledge about these long-term effects.

Additionally, an analysis could be performed on the financial effects of the changes that have been made regarding the use of medical imaging during the COVID-19 pandemic. This, together with the long term effects of the decrease in the use of medical imaging would provide the input for a cost-effectiveness analysis, providing valuable insights about what we can learn from the impact of the COVID-19 pandemic on breast cancer care.

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