The relation of follow-up recommendations after breast cancer during the COVID-19 pandemic to the individual risk of breast cancer recurrence

Master Thesis

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Preface

Before you is the master thesis: “The relation of follow-up recommendations after breast cancer during the COVID-19 pandemic with the risk of breast cancer recurrence”. First, I would like to thank my supervisors Prof. Dr. Sabine Siesling, Dr. Jolanda C. van Hoeve, and Jet W. Ankersmid (MSc) for the time and effort invested in supervising me with the creation of this thesis. Also, I would like to thank my supervisors for guiding me through the process. I have learned a lot from it. Furthermore, initially a data request for the Dutch Hospital Data (DHD) was also planned, unfortunately this was not possible, but I hope that even without this request a nice thesis has been delivered. I wish you a pleasant reading.

Marvin Hasper

Abstract

Introduction
Breast cancer is a common disease. With the increasing incidence and survival, the pressure on follow-up after breast cancer is rising. Follow-up consists of aftercare and post-treatment surveillance. Although the treatment of breast cancer is highly personalized, post-treatment surveillance is still one-size-fits-all. When the COVID-19 pandemic began, an advisory report was introduced by the Dutch Society for Surgical Oncology (NVCO), which implied that post-treatment surveillance in breast cancer patients could be postponed. The degree of postponement in the advisory report depends on several variables. It is not clear whether the risk of recurrence is considered. The research question of this study is: "What is the relation of the advisory report for follow-up after breast cancer during the COVID-19 pandemic from the NVCO to the individual risk of breast cancer recurrence?"

Method
A quantitative retrospective study was conducted using a dataset from the Netherlands Cancer Registry (NCR) with female breast cancer patients diagnosed in the Santeon hospitals from 2016 to 2020. With the INFLUENCE-nomogram, a prediction model developed by the University of Twente and the Netherlands Comprehensive Cancer Organisation (IKNL) to determine the locoregional risk of recurrence of breast cancer, the risk of recurrence for the individual patient was estimated. The risks of recurrence of the different groups based on the advisory report were analyzed and compared with the actual risks of the patient groups based on the INFLUENCE-nomogram in which personalized risk is estimated on patient, tumor, and treatment characteristics. The risks between the different groups were tested statistically with a Kruskal-Wallis test.

Results
A total of 6691 patients were selected from the NCR. The low-risk group, as mentioned in the NVCO advisory report had on average the lowest 5-year risk of recurrence (3.7%), the intermediate-risk group a higher risk (4.2%) and the high-risk group the highest risk (8.7%, p=0.004). In the low-risk group, there were no patients with a 5-year risk of recurrence above 10%. In the intermediate-risk group, 184 patients had a 5-year risk of recurrence above 10% (5.2%), including 15 patients above 15%. The high-risk group contained 206 patients with a 5-year risk of recurrence of 5% and below (29.8%).

Conclusion
The conclusion of this study is that (temporary) policy changes were mostly related to the risk of breast cancer recurrence. If a new pandemic or any other situation where priority needs to be made for the post-treatment surveillance of breast cancer, it is wise, to let the individual risk of recurrence estimated using the INFLUENCE-nomogram form the basis for policy changes and prioritizing patient groups.

Introduction

Breast cancer is a common disease; it is the most common type of cancer among women. (1) Breast cancer can arise from many places in the breast. The disease is most common in women between the ages of 50 and 70. Treatment often consists of surgery; this can be a breast conserving surgery or a radical mastectomy. Additional treatments include radiotherapy, chemotherapy, hormonal therapy, and targeted therapy. (2) The incidence and survival of breast cancer is increasing. The 10-year survival rate for patients with nonmetastatic breast cancer increased from 10 to 20 percent in 1987 to 2007. (3) As a result, there is increasing pressure on the follow-up of breast cancer. The follow-up of breast cancer consists of aftercare and post-treatment surveillance. (4) The terms aftercare and post-treatment surveillance are defined below.

Follow-up is a component of individual patient care during and after breast cancer treatment, this includes 3 elements: (4)
- Detection of new manifestations of the treated breast cancer or new malignancies associated with it (surveillance).
- Education, counseling, responding to complaints and symptoms, identifying immediate or late effects of disease and treatment, and attention to social consequences. (aftercare)
- Evaluation of medical action and its consequences. For this, the initiative for a contact can come from either the physician or the patient.

Post-treatment surveillance aims to detect recurrences. (5) It is the programmatic approach to aftercare that consists of recurrent contacts between the patient and the health care professionals, for example in the form of monitoring schedules. The frequency and duration of the post-treatment surveillance depend on the individual situation of the patient and are related to the type of cancer treated. (4) Although the treatment of breast cancer is highly personalized, post-treatment surveillance is still one-size-fits-all, and the recommendations are uniform and based on consensus. The advice of post-treatment surveillance in breast cancer is shown in Table 1.

Table 1: Recommendations post-treatment surveillance (6)

Post-treatment surveillance in the first 5 years after diagnosis/last mammography before surgery at a patient without BRCA1/2 mutation	
Location	Hospital
Physical examination	1 year
Mammography	Annually
Post-treatment surveillance (at least) 5 years after diagnosis/last mammography before surgery at a patient without BRCA1/2<60 years at the time of post-treatment surveillance	
After breast conserving surgery	
Location	Hospital
Physical examination	Annually
Mammography	Annually
After radical mastectomy	
Location	Hospital
Physical examination	-
Mammography	Annually
Post-treatment surveillance (at least) 5 years after diagnosis/last mammography before surgery without BRCA1/2 60-75 years at the time of post-treatment surveillance	

After breast conserving surgery	
Coordinated by	General practitioner
Physical examination	Annually
Mammography	Every 2 years
After radical mastectomy	
Coordinated by	National breast cancer screening program
Physical examination	-
Mammography	Every 2 years
Post-treatment surveillance (at least) 5 years after diagnosis/last mammography before surgery without BRCA1/2 >75 years at the time of post-treatment surveillance	
Consider ceasing post-treatment surveillance	

To personalize post-treatment surveillance, the risk of a locoregional recurrence of breast cancer can be used. (5). This can be estimated using the INFLUENCE-nomogram, which was developed by the University of Twente and the Netherlands Comprehensive Cancer Organisation (IKNL) based on data from the Netherlands Cancer Registry (NCR). This nomogram estimates the risk of a locoregional recurrence using several variables such as age, tumor size, involved lymph nodes, degree of differentiation, positive or negative hormone receptors, multifocality and type of treatment which the patient received. This model can provide insight in guidelines, daily practice, and the patient's actual risk of recurrence. (5)

The COVID-19 pandemic put pressure on healthcare systems worldwide. This is also the case for oncology care. (7) In March 2020, the COVID-19 pandemic began in the Netherlands. Several studies have described how breast cancer care was affected. Figure 1 shows a strong decline in the number of new breast cancer diagnoses in 2020 compared to 2019. This decrease is over 10 percent and is the largest of any cancer. (8) Figure 2 shows the percentage of new breast cancer patients in 2020 compared to 2017-2019 in different age groups. (8)

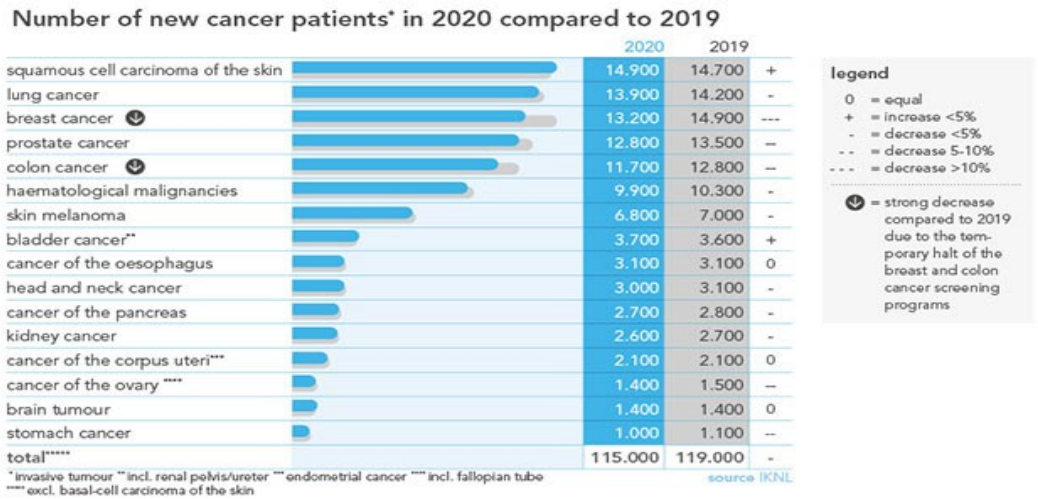

Figure 1: Number of new cancer patients in 2020 compared to 2019 (source: IKNL (8))

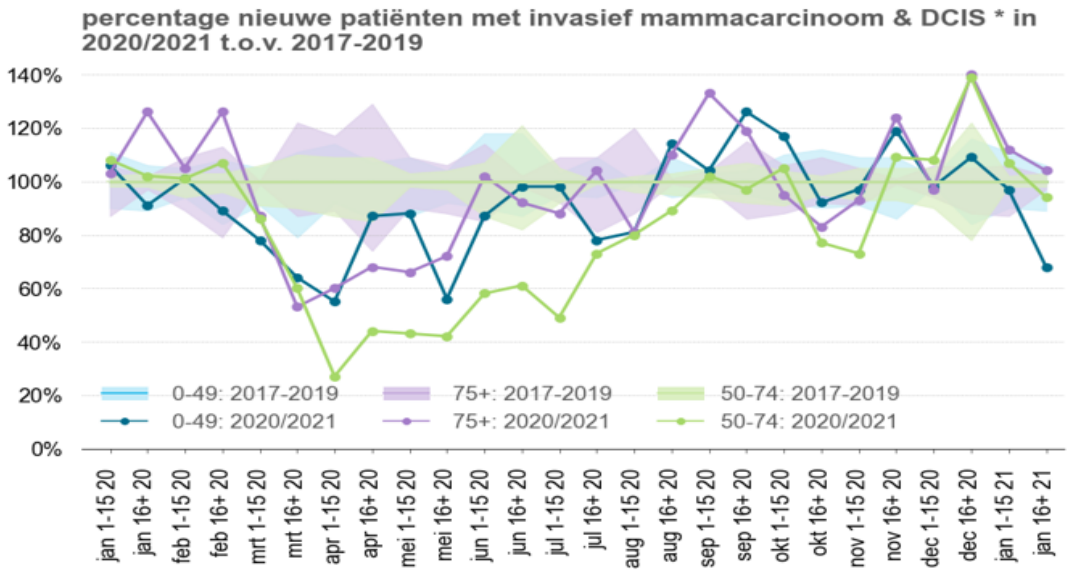

Figure 2: percentage of new breast cancer patients 2020/2021 compared to 2017-2019 in different age categories (source: IKNL (8))

Figure 2 shows that when in March 2020, the "intelligent lockdown" was introduced in the Netherlands, fewer patients were seen (8). One of the reasons was that the breast cancer screening program was temporarily halted. (9) Furthermore, GPs saw a quarter fewer patient in the period from March 9, 2020, to May 24, 2020. (10) There were several reasons for this. First, patients did not go to the GP because they were worried to get COVID-19. Second, they were advised to stay at home as much as possible. In the beginning, GPs also discouraged people from coming for non-urgent complaints. However, people were later urged to see their GP if necessary. Finally, the referral of patients was also not optimal; within oncology fewer patients were referred to the hospital. (11)

The risk of recurrence can be an indicator to prioritize patients for post-treatment surveillance in certain situations, such as the COVID-19 pandemic. (12) In April 2020, the Dutch Society for Surgical Oncology (NVCO) issued an advisory report for post-treatment surveillance of breast cancer during COVID-19. (13) This advice is shown in Table 2.

Table 2: advice post-treatment surveillance during COVID-19 NVCO

General advice
• Accurate performance of follow up will depend in each hospital on the available capacity in that hospital. If there is a reason for follow-up but no capacity, then consult with a colleague in another hospital. • If there are reasons (psychological, complaints etc.) for the X-MG to go ahead, of course, this is possible! • In patients with complaints that could be a COVID-19 infection postpone the X-MG until the patient is symptom free. • In patients > 70 years of age, also consider the risk of covid-19 infection for the patient himself • If an MRI-mamma (screening) is already done, then the MRI is sufficient. • At follow-up X-MG, the result can be discussed by telephone or video consult.

Monitoring in the context of increased risk (gene mutation carriers/familial load)

- Continue screening; if MRI is performed then X-MG can be postponed for a year

Monitoring in the context of postoperative follow-up

Postpone surveillance X-mg one year if:

- Treatment primary tumor was > 5 years ago and age > 50 years **or**
- Age > 50 years and primary tumor involved T1-2, a grade I/II and N0/N1 **or**
- If it involved a DCIS grade I/II

Postpone surveillance X-MG depending on capacity max 6 months in the other patient groups.

Low risk	**After radical mastectomy**	**After breast conserving surgery**
DCIS gr 1 and 2	1 year postponement	1 year postponement
pT1aN0, pT1bN0	1 year postponement	1 year postponement
DCIS gr 3	1 year postponement	Maximum 6 months postponement
Intermediate risk		
pT1c-2N0, > 50 years	1 year postponement	1 year postponement
N + gr 1-2, > 50 years	1 year postponement	Maximum 6 months postponement
High risk		
N + gr 3	Maximum 6 months postponement	
T3-4	Maximum 6 months postponement	

The advisory report is based on a consensus of general practitioners and clinicians based on experience and general knowledge. It is unclear to what extent the advice given is based on the risk of recurrence of individual breast cancer patients.

The research question of this study is:
"What is the relation of the advisory report for follow-up after breast cancer during the COVID-19 pandemic from the NVCO to the individual risk of breast cancer recurrence?"

Method

Study design and setting.
To answer the research question, a quantitative retrospective study was performed. Data from the NCR were used. The NCR was founded in 1989. It is the registration organisation of cancer patients. With this data answers can be given to the questions: How often does the cancer occur? What is the treatment and prognosis? The data leads to better insights, effective interventions, and better outcomes for the patient with cancer. The data is used for scientific research and statistics for cancer and cancer treatment. The data is collected by specially trained data managers from IKNL in hospitals based on the information in the medical record. Various patient data are collected from the electronic patient records (EPD). The notification is achieved through the national automated archive for cytology and histopathology (PALGA), Dutch Hospital Data (DHD) and hematology laboratories. (14)

Study population and procedures
The study population consisted of female patients diagnosed with invasive breast cancer at the seven Santeon hospitals between 2016 and 2020. Santeon is a collaborative organisation founded in 2007 between seven top clinical hospitals: Catharina Hospital in Eindhoven, Canisius Wilhelmina Hospital (CWZ) in Nijmegen, Maasstad Hospital in Rotterdam, Martini Hospital in Groningen, Medical Spectrum Twente (MST) in Enschede, OLVG in Amsterdam and St. Antonius Hospital in Utrecht. Within the Santeon collaboration, hospitals work together to provide better care in the Netherlands. This is achieved by learning from each other and continuously innovating and improving. Santeon has 33,800 employees, which is 11% of the national volume of hospital care. Furthermore, it has a turnover of 3 billion euros. Figure 3 shows the locations of the Santeon hospitals (15,16)

Figure 3: Locations Santeon hospitals

Outcome measures
The outcome measures in this study were the risks of recurrence among the patients being part of the low-risk, intermediate risk or the high-risk group as described in the advisory report from the NVCO. Therefore, variables were required to calculate the risk of recurrence and the variables of the groups that appeared in the NVCO advisory report.

Individual risk of recurrence (INFLUENCE-nomogram)
The risk of recurrence of breast cancer calculated with the INFLUENCE-nomogram with the variables:
- Age
- Tumor size
- Involved lymph nodes
- Degree of differentiation
- Positive or negative hormone receptors
- Multifocality
- Type of treatment of the patient

Risk based on the NVCO advisory report
The variables that appear in the NVCO advisory report are:
- Age above and below 50 years
- Primary tumor T1-T2/T3-T4
- Degree of differentiation I-II/III-IV
- Lymph nodes N0-N1/N2-N3
- Type of surgery (radical mastectomy/breast conserving surgery)

All variables requested and the explanation of the variables appearing in the NVCO advisory report are attached in Appendix 1.

Data analysis
First, the risks of recurrence were estimated using the INFLUENCE-nomogram. Therefore, these above variables needed to calculate the risk of recurrence were processed into categories, allowing the calculation of the risks of recurrence at once for each patient. Due to 'missing data', 3965 patients were omitted.

The frequency of the patients in the different years of diagnosis were determined. To describe the dataset, the mean risk of recurrence of different incidence years was analyzed. To analyze whether the mean 5-year risk of recurrence differed between the different incidence years, a Kruskal-Wallis test was used.

To determine the risk in relation to the groups from the NVCO advisory report, a variable was created to divide patients into groups of patients younger and older than 50 years. Furthermore, the 5-year locoregional risk of recurrence, which was calculated with the INFLUENCE-nomogram, was also divided into categories. These categories are 0% to 5%, 5% to 10%, 10% to 15% and higher than 15%.

Following this, the risks of recurrence of the different groups in the NVCO advisory report: low-risk, intermediate-risk and high-risk were calculated. To analyze whether the locoregional 5-year risk of recurrence differed among these groups, the risks of recurrence among these groups were statistically tested with a Kruskal-Wallis test.

Data analyses were performed using the statistical program STATA. A 95% confidence interval was maintained.

Ethical considerations

Since a large amount of data was collected from patients and privacy is of great importance, an ethical request was made to the Ethics Review Committee of the Faculty of BMS of the University of Twente. This application was approved. The dataset obtained from the NCR was anonymous at the patient level.

Results

A total of 6691 patients were included in the study. In table 3 a description of the cohort is presented.

Table 3: Description data of 6691 patients included in the analysis

Year of diagnosis	Mean locoregional 5-years risk of recurrence	Surgery	Radiotherapy	Chemotherapy	Hormone therapy	Targeted therapy
2016 (n=1430)	4,8%	Radical mastectomy: 413 BCS: 1017	1138 (80%)	520 (36%)	858 (60%)	114 (8%)
2017 (n=1505)	4,9%	Radical mastectomy: 434 BCS: 1071	1177 (78%)	448 (30%)	846 (56%)	103 (7%)
2018 (n=1404)	5,0%	Radical mastectomy: 422 BCS: 982	1077 (77%)	416 (30%)	787 (56%)	96 (7%)
2019 (n=1498)	5,0%	Radical mastectomy: 404 BCS: 1094	1147 (77%)	481 (32%)	836 (56%)	102 (7%)
2020 (n=854)	5,3%	Radical mastectomy: 233 BCS: 621	605 (71%)	162 (19%)	495 (58%)	45 (5%)
Total (n=6691)	5,0%	Radical mastectomy: 1906 BCS: 4785	5144 (77%)	2027 (30%)	3822 (57%)	460 (7%)

*BCS = breast conserving surgery

This table showed that fewer patients were diagnosed in 2020 compared to the other years. Further, patients diagnosed in 2020 had a higher average 5-year risk of recurrence than patients diagnosed in the other years, at an average of 5.3%. For the other years, the average 5-year risk of recurrence for patients was within a range of 4.8% and 5.0%. Based on the Kruskal-Wallis test, it appears that the risks were statistically significantly different between the incidence years. (See Appendix 2)

In table 4 the 5-year risk of recurrence, among the low-risk, intermediate-risk and high-risk groups as indicated in the NVCO advisory report is presented. Based on the Kruskal-Wallis test it appears that the risks between the different risk groups differed statistically significantly. (See Appendix 2). Patients in the high-risk group generally had a higher risk of recurrence than the low-risk and intermediate-risk groups.

Table 4: Risk low, intermediate and high-risk patients NVCO compared to INFLUENCE

Risk group	Type of surgery (n)	0 until 5%	5 until 10%	10 until 15%	>15%
LOW risk (n=1449)					
pT1aN0	Radical mastectomy (66)	42 (64%)	24 (36%)	0 (0%)	0 (0%)
	BCS (282)	248 (88%)	34 (12%)	0 (0%)	0 (0%)
pT1bN0	Radical mastectomy (161)	84 (52%)	77 (48%)	0 (0%)	0 (0%)
	BCS (940)	781 (83%)	159 (17%)	0 (0%)	0 (0%)
INTERMEDIATE risk (n=3518)					

pT1c-2 N0 >50 years	Radical mastectomy (471)	162 (34%)	290 (62%)	19 (4%)	0 (0%)
	BCS (1889)	1473 (78%)	409 (22%)	7 (0%)	0 (0%)
N + gr I-II >50 years	Radical mastectomy (447)	101 (23%)	210 (47%)	122 (27%)	14 (3%)
	BCS (711)	393 (55%)	296 (42%)	21 (3%)	1 (0%)
HIGH risk (n=692)					
N + gr III	Radical mastectomy (224)	67 (30%)	66 (29%)	55 (25%)	36 (16%)
	BCS (218)	126 (58%)	65 (30%)	18 (8%)	9 (4%)
T3-4	Radical mastectomy (212)	10 (5%)	81 (38%)	92 (43%)	29 (14%)
	BCS (38)	3 (8%)	18 (47%)	14 (37%)	3 (8%)

Figures 4, 5 and 6 showed the graphs of the low, intermediate, and high-risk patients, respectively.

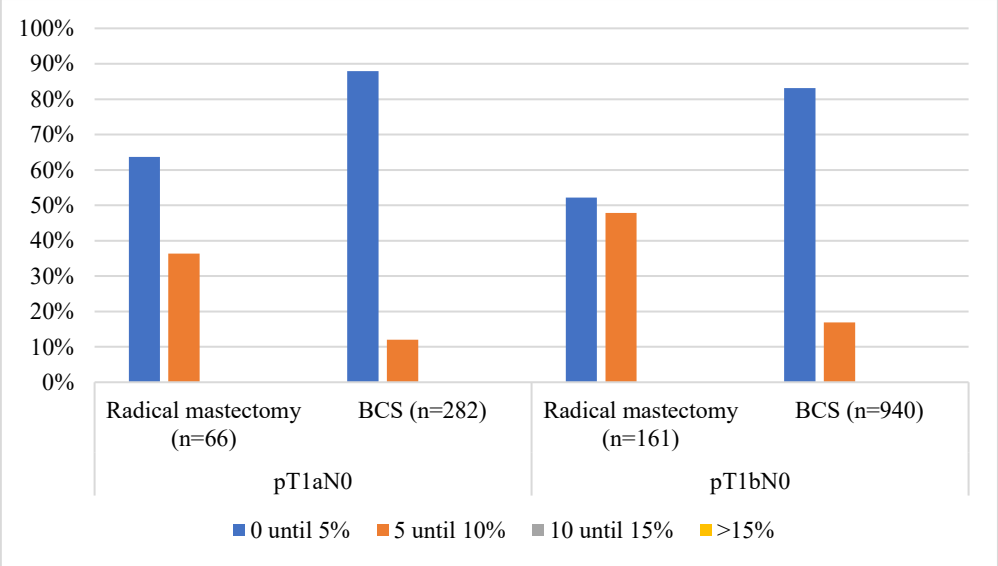

Figure 4: Low-risk group according to NVCO advisory report compared to individual risk INFLUENCE (n=1449)

Figure 4 presented that there were no patients in the low-risk group with an individual 5-year risk of recurrence higher than 10% based on the INFLUENCE-nomogram. The highest percentage of patients which had a 5 to 10% risk were patients with a tumorsize between 5 millimeter and 1 centimeter and no positive lymph nodes who underwent a radical mastectomy.

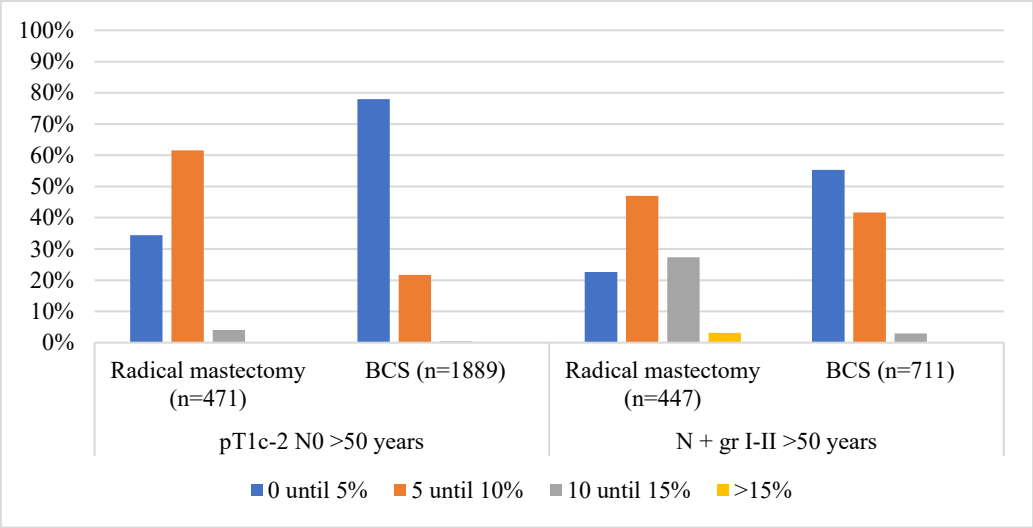

Figure 5: Intermediate-risk group according to NVCO advisory report compared to individual risk INFLUENCE (n=3518)

Figure 5 presented that most patients included in the intermediate-risk group had a 5-year risk of recurrence up to 10%. The highest risks in this group were for the patients who had positive lymph nodes, grade I or II, older than 50 years of age and have had a radical mastectomy. A total of 33% of patients in this group had a risk above 10%.

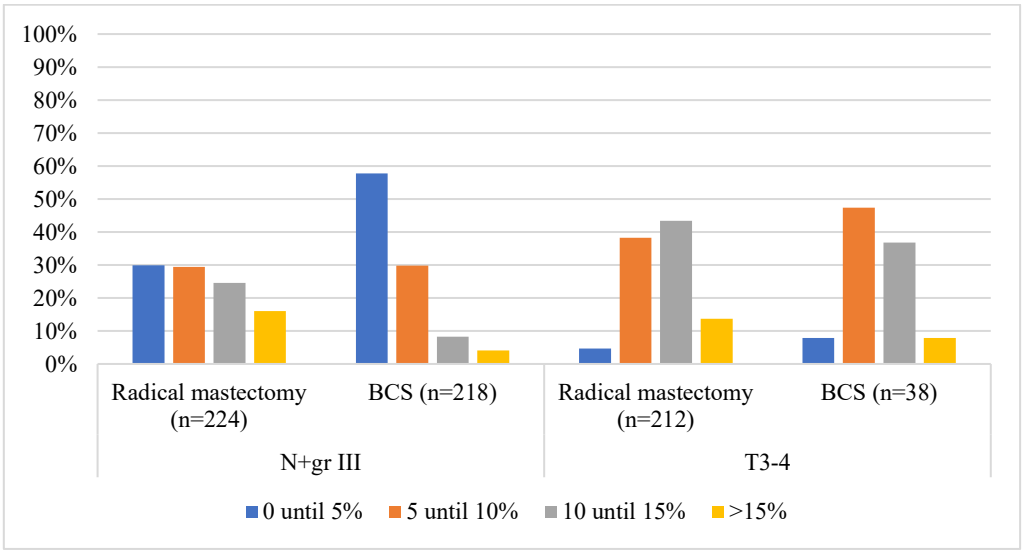

Figure 6: High-risk group according to NVCO advisory report compared to individual risk INFLUENCE (n=692)

Figure 6 presented that the 5-year risks of recurrence of patients included in the high-risk group was higher than the 5-year risks of recurrence of the other groups. There were fewer patients with a risk up to 10% and more patients with a risk above 10% in the high-risk group than in the low- and intermediate-risk group. The highest risks here were for the patients with a tumorsize above 5 centimeters. It should be noted that in this group there were still a large number of patients with a 5-year risk of recurrence of less than 10%.

Discussion

The purpose of this study was to investigate whether the (temporary) policy changes for post-treatment surveillance of breast cancer patients during the COVID-19 pandemic were related to the individual risk of recurrence of breast cancer. To analyze whether this is the case, the numerical prediction model INFLUENCE was used.

The results show that, according to the NVCO advisory report, low-risk patients generally have a lower risk than the intermediate-risk patients. Furthermore, the intermediate-risk patients generally have a lower risk than the high-risk patients. This means that these policy changes are mostly related to the risk of recurrence.

However, the advisory report is not completely related to the individual risk of recurrence. In the low-risk group, all patients have an individual locoregional 5-year risk of recurrence below 10%. . In other words, in the low-risk group, all patients received the recommendation for postponement, which they also would have received if it were based on individual 5-year risk of recurrence. In the intermediate-risk patients, there were 184 (5%) patients who had a 5-year risk of recurrence above 10%, with 15 (0.4%) above 15%. These patients could be classified among the high-risk patients. In the high-risk patient group, 63% have a 5-year risk of recurrence below 10% and could also placed in another group. 206 (30%) patients had a 5-year risk of recurrence of up to 5%. These patients were not at very high risk and would not need to be classified among the high-risk patients and could possibly have had a deferral in accordance with low-risk group.

Recommendations for breast cancer care during the COVID-19 pandemic were introduced by the NVCO. The European Society for Medical Oncology (ESMO) also made recommendations. Here the recommendations were about the same as from the NVCO, where low priority patients (patient condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of the benefit) were recommended to postpone post-treatment surveillance. Only the NVCO went into more detail. (17)

Other countries also made recommendations for breast cancer care during the COVID-19 pandemic. In the Magee Breast Cancer Program, one of the busiest breast care centers in the United States, the recommendation for post-treatment surveillance after breast cancer is to contact the patient to have a virtual visit, postponement, or an appointment to a later date. (18) This advice does also not differ much from the Dutch advice where the post-treatment surveillance after breast cancer is postponed. Only in the Magee Breast Cancer Program no distinction was made between different patient groups.

In a Latin-American study where breast cancer specialists were asked how to manage breast cancer during post-treatment surveillance, it is necessary to dedicate adequate attention to the patients, despite the pandemic. Regarding imaging, this could all be postponed, in exception for patients who need them due to a suspicious lesion found during self-examination and a biopsy or those with a high genetic risk. Regarding treatment the majority of the care givers disagreed in delaying surgeries, chemotherapy, and radiotherapy. (19) This study does not deviate much from the advice in the Netherlands as discussed earlier, where imaging, what is a part of the post-treatment surveillance also is postponed. Only in the previous study all could be postponed, unless absolutely necessary, where the NVCO has a greater distinction in patient groups.

Risks of recurrence were calculated using the INFLUENCE-nomogram. This nomogram has been validated internally and externally. Hereby, the INFLUENCE-nomogram can be used on the Dutch population, but also on non-Dutch populations. The nomogram can effectively assist health professionals to determine the individual locoregional risk of recurrence in primarily cured patients. (20)

The advice in other countries looked about the same as the advisory report for the Netherlands. But it is not known, or the recommendations were based on the risks of recurrence. If that is not the case, then the INFLUENCE-nomogram could also be used for the other institutes in other countries to base their advisory reports for post-treatment surveillance of breast cancer on the risk of recurrence.

Furthermore, in the United States, the advice is to contact the patient to have a virtual visit. (18) This is not the advice in the Netherlands, but a study in Brazil showed that telemedicine can be safely used to maintain the post-treatment surveillance of patients treated of breast cancer. It may be a feasible alternative to reduce in-person medical appointments for post-treatment surveillance of breast cancer. (21)

Another study shows that routinely scheduled in-person post-treatment surveillance is common, but reduced frequency of post-treatment surveillance had no adverse effects. Furthermore, on-demand post-treatment surveillance is associated with a lower cost-per-recurrence detected than scheduled post-treatment surveillance. Most evidence suggest that moving towards a model based on patient-demand is the most effective (22)

A study in England in 2008, where telephone post-treatment surveillance is compared with hospital post-treatment surveillance for women treated with breast cancer with a low to moderate risk of recurrence showed that telephone post-treatment surveillance is suitable for women at low to moderate risks of recurrence. (23) This is something what could be adopted for this study. For the patients with a 5-year risk of recurrence until 10%, telephone post-treatment surveillance could also be an option.

Limitations

After omitting patients from the dataset who had "missing data" for the INFLUENCE-nomogram, which prevented the risk from being calculated, there were 6691 patients left of the 10656 patients. The reason for these missing data is mainly due to the number of unknown lymph nodes and the uncertainty whether the hormone receptors were positive or negative. It should be noted that there was a considerable group of patients not included in the analysis, which could give a bias to the results presented in the study. An unexpected selection of the patients may have taken place. However 6691 patients seems a reasonable group that is left.

Furthermore, this study only included patients diagnosed in Santeon hospitals. Because Santeon consists of a collaboration of only seven top clinical hospitals in the Netherlands, it is uncertain whether the analyses and results can be generalized to all hospitals in the Netherlands. This is because the Santeon hospitals consists of only seven hospitals of the almost 80 hospitals in the Netherlands. To investigate whether the results can be generalized to all hospitals in The Netherlands, additional studies would have to be done with data from other hospitals. This would possibly yield different results, because for example academic or specialized hospitals have different patient groups, with possibly different risks of recurrence.

The mean 5-year risk of recurrence was significantly higher in 2020 than in the other diagnosis years. This is due to the fact that low stage tumors (stage I and stage II) are less detected during the COVID-19 pandemic which is related to the halt of the screening program and reluctance to go to the general practitioner (24) Because of this, there could be a bias for the year 2020. So, this also could be a reason why the risk of recurrence in 2020 is higher on average. Furthermore the patients in 2020 did not had post-treatment surveillance, because this starts a year after the end of treatment.

The majority of local recurrences (65%) were detected by the patient. Some postponement of post-treatment surveillance therefore has little to no effect on survival. (25) However, if post-treatment surveillance is delayed in higher-risk patients they would probably experience more adverse effects as for example a recurrence.

Implications for practice
The (temporary) policy changes are mostly related to the risk of breast cancer recurrence. Because within a part of the patients, the policy changes do not correspond with the risk of recurrence. The INFLUENCE-nomogram can be useful as a basis for the advisory report in case of a new pandemic or other situation in which policy changes are necessary. The advisory report could then be made based on the risk of recurrence. The (temporary) policy changes are then made based on these results.

Future research
In the future it would be interesting to request data on the care activities that took place during the follow-up. With this data it will be possible to analyze the postponed consultations. The frequency of the postponed consultations, the method of consultation, by telephone or face-to-face and the time of postponement can be analyzed. It can be assessed whether the NVCO advice was actually carried out, for example in high-risk patients whether these patients had shorter postponements than low-risk patients. Furthermore, the frequency of consultations in 2020 can also be compared to other incidence years to analyze whether there were actually fewer consultations in 2020 than in the other incidence years. This can be used to estimate how much health damage this has cost, where the loss of consultations in relation to the mortality could be calculated. In addition, the imaging techniques performed at the consultation could also be observed and determined to see if there was a difference in incidence years and to estimate the missed diagnosis of recurrences.

Recommendations
It is recommended that post-treatment surveillance in patients in the intermediate-risk group with breast-conserving surgery, positive lymph nodes, grade I-II and above 50 years should not be postponed more than 6 months. In this group, 22 of the 711 patients have a 5-year risk of recurrence above 10%. The advice in this group in patients with a radical mastectomy is not to postpone the post-treatment surveillance for more than 1 year. The patients who hereby have a 5-year risk of recurrence above 10% are 136 out of 447. Thus, the expectation would be that the advice would have been reversed in this group.

The majority of the patients have been placed in the same group and the policy would have been the same. In 6.9% of patients, the patients could have been categorized in a different group and in 6.5% of patients the measures did not fit the personal risk to such an extent that the policy would have been different. This is mainly because the high-risk group, with a 5-year risk of recurrence until 10% that could be categorized in a lower group.

The main recommendation of this study is that if a new pandemic or other situation in which priority with respect to the implementation of post-treatment surveillance must be done occurs then let the individual locoregional risk of recurrence, which can be determined with the INFLUENCE-nomogram be the basis for prioritizing post-treatment surveillance for breast cancer patients.

Conclusion

In conclusion, the advice is mostly related to the risk of recurrence. Mainly, high-risk patients according to the NVCO advisory report also have a high 5-year risk of recurrence and low-risk patients according to the NVCO advisory report also have a low 5-year risk of recurrence.

In 6.9% of patients, the patients could have been placed in a different group and in 6.5% of patients the measures did not fit the personal risk to such an extent that the policy would have been different if the INFLUENCE-nomogram was used.

If a new pandemic occurs, it would be preferable to base the advice entirely on the risks of recurrence. With this, patients can be categorized tightly by creating groups based on risk of recurrence. Furthermore, the INFLUENCE-nomogram can be used for the implementation of personalized post-treatment surveillance by calculating the risk of recurrence individually for the patient.

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Appendix-1 variables NCR

The variables requested from the NCR are:
- Age at the time of diagnosis
- Gender
- Institution of diagnosis
- Institution of treatment
- Patient number
- Incidence Year
- Morphology
- Lateralization of the tumor
- Topography sub-localization
- Tumor behavior
- Degree of differentiation
- Multifocality
- TNM stage (clinically and pathologically in T, N, and M)
- Lymph nodes examined/positive
- Estrogen receptor
- Progesterone receptor
- Her2neu
- Tumor size
- DNA test done (yes/no)
- Surgery (yes/no)
- Neo-adjuvant systemic therapy
- Type of surgery
- Date of surgery
- Radicality (invasive + possible DCIS component)
- Direct reconstruction (type)
- Chemotherapy (yes/no), IND variable
- Hormone therapy (yes/no), IND variable
- Targeted therapy (yes/no), IND variable
- Radiotherapy (yes/no), IND variable

Explanation of the variables that appear in the NVCO advisory report
The T stands for tumor size, this is divided into 4 stages. In stage T1, the tumor is smaller than 2 centimeters. In stage T2, the tumor is between 2 and 5 centimeters. If the tumor is larger than 5 centimeters then the patient is categorized in stage T3. Stage T4 is when the tumor has grown into surrounding tissues. Here the size of the tumor does not matter. (1)

The degree of differentiation is also divided into four stages. Grade I means that the tumor is low-grade, this means that the cancer cells largely resemble healthy cells, and the cancer cells usually grow slowly. Grade II means intermediate, this is when the cancer cells look less and less like healthy cells and the cancer cells usually grow faster than normal cells and stick together quickly. Grade III is high grade, this means that the cancer cells are poorly differentiated, they look almost nothing like healthy tissue, and they almost always grow much faster than normal cells. There is also a grade IV, this is when the cells no longer resemble healthy cells at all. (1)

The N stands for node, here it is analyzed whether there are metastases in the lymph nodes and if so, how many. Here N0 is no metastases in the lymph nodes, N1 is metastases in 1 to 3 lymph nodes. N2 is metastases in 4 to 9 lymph nodes and N3 is metastases in 10 lymph nodes or more. (1)

There is also a distinction in the type of surgery, which can be radical mastectomy or breast-conserving surgery. In breast-conserving surgery, only part of the breast needs to be removed. In a radical mastectomy, the entire breast is removed, which means that all the glandular tissue of the breast is removed. The muscle of the breast is left in place. (1)

Appendix-2 Kruskal-Wallis tests

Table 5: Kruskal-Wallis 5-years risk of recurrence on year of diagnosis

Kruskal-Wallis equality-of-populations rank test		
Year of diagnosis	**Observations**	**Rank sum**
2016	1430	4.52e+06
2017	1505	4.96e+06
2018	1404	4.72e+06
2019	1498	5.04e+06
2020	854	3.14e+06
chi-squared = 39.853 with 4 d.f. probability = 0.0001 chi-squared with ties = 39.868 with 2 d.f. probability = 0.0001		

Table 6: Kruskal-Wallis 5-years risk of recurrence on risk group

Kruskal-Wallis equality-of-populations rank test		
Risk group	**Observations**	**Rank sum**
High risk	692	2.09e+06
Intermediate risk	3518	9.92e+06
Low risk	1449	4.01e+06
chi-squared = 10.936 with 2 d.f. probability = 0.0042 chi-squared with ties = 10.940 with 2 d.f. probability = 0.0042		