The impact of COVID-19 on treatment, use of expensive medications and treatment delays of patients with de novo metastatic cancer

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Abstract

Introduction: The COVID-19 pandemic had an impact on cancer care around the world. The first confirmed COVID-19 infection in the Netherlands was on February 27, 2020. Recommendations were made on how to manage cancer care during the pandemic. This study aims to investigate the impact of the pandemic on patients with de novo metastatic cancer.

Methods: Patients who were diagnosed with de novo metastatic cancer between January 2017 and May 2021 were included and divided into different periods depending on the severity of the pandemic. The percentage of patients that received a certain treatment or expensive medication within the same period they were diagnosed in, was compared between the years 2020/2021 and the years 2017-2019 with a Chi-squared test and a logistic regression. For the expensive medication the moving average over the last four weeks during 2020 was plotted. Average time between the diagnosis and the initial treatment was analyzed with a Mann Whitney test.

Results: In total, 63,731 patients were included from the Dutch Cancer registry and the Dutch Hospital Data. Slight changes were found regarding the percentage of patients that received a certain treatment. Less surgeries were given in the periods after the initial peak in hospital admissions. A rise of 4.34% was found in the percentage of patients that received chemotherapy in the first weeks of 2021. The odds ratio of receiving surgery for patients with metastatic breast cancer after the initial first peak in hospital admissions was 0.31 (0.12-0.79). A small peak could be seen in the moving average plot in the amount of expensive cytotoxic medication given in period C. Average time between diagnosis and initial treatment decreased with nearly 4.5 days during the initial peak in hospital admissions.

Conclusion: Despite the disruptive impact, the COVID-19 pandemic had on cancer care worldwide, the impact on treatments for patients with de novo metastatic cancer care in the Netherlands was limited and not only negative, for example the time to treatment decreased.

Keywords: Metastatic cancer, COVID-19, treatments, time to treatment, medication

Introduction

On the 31st of December 2019, the WHO was notified that there were several cases of viral pneumonia occurring in Wuhan. This quickly became known as the COVID-19 virus and it spread all over the world [1]. In February of 2020 the virus spread to the Netherlands and the first hospitalization of a COVID-19 patient was on the 27th of February. At the peak of the first COVID-19 period in March more than 3000 regular hospital beds were occupied by COVID-19 patients, which was approximately 6% of all beds [2] [3]. National breast and colorectal cancer screening programs were discontinued from March 16 and gradually resumed at the beginning of June [4].

Patients were advised to only go to the general practitioner (GP) or the hospital with urgent complaints. During the start of the pandemic, GP's noticed a reduced demand for appointments [5]. In the Netherlands, this resulted in a decline of consultations to 75% of the usual number of consultations [6-8]. The pandemic and associated measures impacted the number of new cancer diagnoses, mainly in the lower stages [9–18]. In the Netherlands, during the first few months of the pandemic around 25% fewer cancer patients were diagnosed compared to what would be expected [19].

Because the hospitals in the Netherlands needed so much capacity for COVID-19 patients and protective measures had to be taken, regular care was affected. Recommendations by the European Society for Medical Oncology (ESMO) and the Dutch Association of Medical Oncology (NVMO) have been made on how to manage cancer treatment during the COVID-19 pandemic [20] [21]. Part of these recommendations was to adapt the cancer care to the severity of the pandemic. This was done to prevent COVID-19 infections in vulnerable cancer patients and to decrease the burden on health care. In line with a decrease in the number of diagnoses, a decrease of up to 50% in the number of surgical treatments was observed during the outbreak of the pandemic [22]. In other countries changes in treatments were observed as well. Of the clinics that were included in the study of Riera et al. 97.4% reported changes in radiation therapy schemes [23]. In the Netherlands, an online survey that was held among 5302 cancer patients found that 30% of patients experienced consequences in their treatments. The treatment types that were adjusted the most, according to the survey, were chemotherapy (30%) and immunotherapy (32%) [24]. No delays were found in either breast, colorectal or head and neck cancers initial treatments in early-stage cancers [25 -27].

In the aforementioned studies treatment often is curative, whereas in patients with de novo metastatic cancer the median survival was only 6.3 months in 2018 [28]. Therefore, treatment for these patients is also often palliative. In advanced cancer care, the impact of the pandemic was limited. It was shown that the initial treatment of advanced melanoma had not changed during the pandemic [29]. The study of Fedele et al. made use of a survey of oncologists to determine changes in treatment for metastatic breast cancer [30]. The results of this survey showed that Italian oncologists preferred to not suspend or delay chemo- or immunotherapy. However a high proportion of the oncologists were prescribing more oral cytotoxic medication to reduce the hospital access. There

were limited studies on the influence of the pandemic on patients with de novo metastatic cancers. A study from the United States also found no delays and no difference in treatment selection for patients with de novo metastatic cancer [31]. The studies conducted for advanced cancer care were mainly surveys or individual clinic-based studies.

Therefore, the aim of this study is to deliver insight on a nationwide scale in how treatments for patients with de novo metastatic cancers were affected by COVID-19.

Methods

Patient population

Patients aged over 18 years and diagnosed with de novo metastatic cancer between January 2017 and May 2021 were selected from the Netherlands Cancer Registry (NCR). The NCR is hosted by the Netherlands Comprehensive cancer organization (IKNL) and has records of all histopathologically confirmed, newly diagnosed malignancies since 1989. Detailed information on expensive medication was added through linkage with a dataset from Dutch Hospital Data (DHD). This resulted in a database that contained the following data for every patient: patient characteristics (age, gender, comorbidities, and original tumor type), treatment type within 3 months of diagnosis (chemotherapy, surgery, local surgery, hormonal therapy, radiation therapy, targeted therapy), medication (type of medication and date of use), the date of diagnosis and date of treatment.

Definitions

In this study the COVID-19 period was divided into five different periods expressing the severity of the pandemic. These were based on the hospital bed occupancy by COVID-19 patients in the Netherlands (Figure 1) [2]. Period A was the period in 2020 before the COVID-19 pandemic started. Period B was the first peak and has the highest amount of hospital admissions. In period C the hospital admissions were relatively low. During period D the hospital admissions were rising again. This could be considered the second wave of hospital admissions. This second wave continued into the next year. Period E was the period with high hospital admissions in 2021. Patients were divided into groups based on their date of diagnosis. If a patient was diagnosed in a certain period, only the treatment and expensive medication in that period was included in the study.
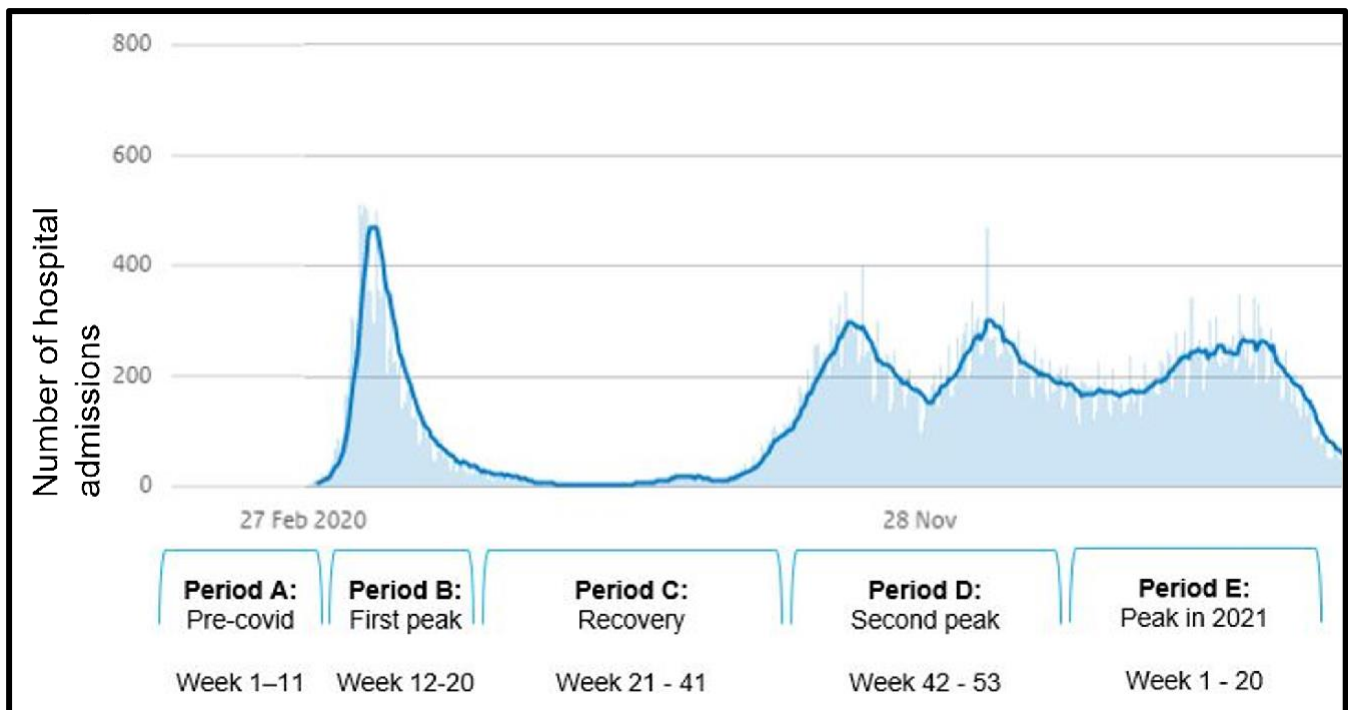
Figure 1: Different periods based on hospital admissions

The NCR dataset was larger and contained more general information about medications, whereas the DHD dataset contained more detailed information about medications. An overview was made for the newly approved expensive medications since 1989 from the DHD set, which were approved for patients with metastatic cancer (Appendix A). These were clustered in different types of expensive medication (e.g. cytotoxic, immunotherapies).

The original tumor types of the patients with de novo metastatic cancer were clustered into different groups: respiratory tract, breast, gastrointestinal tract, female genital, male genital, urinary tract and other cancers (bone, endocrine glands, eye, head, neck and skin).

Statistical analysis

The characteristics of included patients were compared between patients diagnosed in period A-E of 2020/2021 and patients diagnosed in these same periods in 2017-2019 using Chi-squared tests.

The proportions of patients receiving a particular treatment or expensive medication in the period of their diagnosis was calculated per period in 2020/2021 and compared to the same period in 2017-2019 with a Chi-squared test.

A logistic regression analysis was performed to determine the odds ratio per period of getting a certain treatment/medicine in the years 2020/2021 compared with 2017-2019 corrected for potential confounders. A logistic regression was also done per tumor type to determine whether some specific tumor types showed differences.

To take trends in use of expensive medication into account, a moving average over the last four weeks of the weekly incidence of the use of expensive medication was calculated and plotted.

The average number of days between the date of diagnosis and the first treatment, irrespective of type of treatment was compared between the periods in 2020/2021 and the periods in the years 2017-2019 using a Mann-Whitney U test.

For the analysis of the data STATA 17 was used. A p-value of <0.05 was considered statistically significant.

Results

Patient population

A total of 62,745 patients were included of which 19,247 were included in the years 2020 and 2021.

Table 1: Baseline patient characteristics

Period		A(17-19)	A(2020)	P-value	B(17-19)	B(2020)	P-value	C(17-19)	C(2020)	P-value
Number of patients	N	9222	3146		7455	2247		17598	6199	
Age	Median	69	71		70	70		70	71	
Gender	Men	5419 (58,8%)	1845 (58,7%)	0,909	4419 (59,3%)	1306 (58,1%)	0,33	10351 (58,8%)	3573 (57,6%)	0,105
	Women	3803 (41,2%)	1301 (41,4%)		3036 (40,7%)	941 (41,9%)		7247 (41,2%)	2626 (42,4%)	
Number of comorbidities	0	1622 (17,6%)	561 (17,8%)	0,106	1283 (17,2%)	465 (20,7%)	0	2964 (16,8%)	1176 (19,0%)	0
	1	1024 (11,1%)	381 (12,1%)		826 (11,1%)	258 (11,5%)		1856 (10,6%)	669 (10,8%)	
	>1	705 (7,7%)	268 (8,5%)		562 (7,5%)	191 (8,5%)		1277 (7,3%)	525 (8,5%)	
	Unknown	5871 (63,7%)	1936 (61,5%)		4784 (64,2%)	1333 (59,3%)		11501 (65,4%)	3829 (61,8%)	
Tumor type	Respiratory tract	2550 (27,7%)	858 (27,2%)	0,904	2090 (28,0%)	609 (27,1%)	0,045	5091 (28,9%)	1758 (28,4%)	0,016
	Breast	530 (5,8%)	194 (6,2%)		431 (5,8%)	114 (5,1%)		950 (5,4%)	367 (5,9%)	
	Gastrointestinal tract	3723 (40,4%)	1242 (39,5%)		3002 (40,3%)	926 (41,2%)		6974 (39,6%)	2352 (37,9%)	
	Female genital	342 (3,7%)	118 (3,8%)		278 (3,7%)	107 (4,8%)		671 (3,8%)	282 (4,6%)	
	Male genital	1328 (14,4%)	465 (14,8%)		1088 (14,6%)	294 (13,1%)		2535 (14,4%)	954 (15,4%)	
	Urinary tract	487 (5,3%)	172 (5,5%)		377 (5,1%)	131 (5,8%)		941 (5,4%)	326 (5,3%)	
	Other*	262 (2,8%)	97 (3,1%)		189 (2,5%)	66 (2,9%)		436 (2,5%)	160 (2,6%)	

Period		D(17-19)	D(2020)	P-value	E(17-19)	E(2021)	P-value	total(17-19)	total(20-21)	P-value
Number of patients	N	9223	3307		16677	4384		43498	19247	
Age	Median	70	71		70	70		70	70	
Gender	Men	5418 (58,7%)	1931 (58,4%)	0,723	9838 (59,0%)	2495 (56,9%)	0,013	25607 (58,9%)	11553 (57,1%)	0
	Women	3805 (41,3%)	1376 (41,6%)		6839 (41,0%)	1889 (43,1%)		17891 (41,1%)	8680 (42,9%)	
Number of comorbidities	0	1519 (16,5%)	614 (18,6%)	0	2905 (17,4%)	892 (20,4%)	0	7388 (17,0%)	3909 (19,3%)	0
	1	951 (10,3%)	367 (11,1%)		1850 (11,1%)	428 (9,8%)		4657 (10,7%)	2197 (10,9%)	
	>1	695 (7,5%)	294 (8,9%)		1267 (7,6%)	343 (7,8%)		3239 (7,5%)	1792 (8,4%)	
	Unknown	6058 (65,7%)	2032 (61,5%)		10655 (63,9%)	2721 (62,1%)		28214 (64,9%)	12425 (61,4%)	
Tumor type	Respiratory tract	2593 (28,1%)	923 (27,9%)	0,044	4640 (27,8%)	1203 (27,4%)	0	12324 (28,3%)	5619 (27,8%)	0
	Breast	488 (5,3%)	195 (6,0%)		961 (5,8%)	334 (7,6%)		2399 (5,5%)	1358 (6,7%)	
	Gastrointestinal tract	3556 (38,6%)	1260 (38,1%)		6725 (40,3%)	1713 (39,1%)		17255 (39,7%)	7793 (38,5%)	
	Female genital	355 (3,9%)	161 (4,9%)		620 (3,7%)	192 (4,4%)		1646 (3,8%)	957 (4,7%)	
	Male genital	1455 (15,8%)	528 (16,0%)		2416 (14,5%)	557 (12,7%)		6406 (14,7%)	2824 (14,0%)	
	Urinary tract	525 (5,7%)	154 (4,7%)		864 (5,2%)	246 (5,6%)		2330 (5,4%)	1089 (5,4%)	
	Other*	251 (2,7%)	86 (2,6%)		451 (2,7%)	139 (3,2%)		1138 (2,6%)	593 (2,9%)	

* Other cancers: bone, endocrine glands, eye, head and neck and skin

The age characteristics were all very similar between the groups (Table 1). In period E (2021), the percentage of women diagnosed with de novo metastatic cancer was 43.1%, compared to the same period in the years 2017-2019 (41.0%) this was higher (P<0.05).

In period B, C, D and E the percentage of patients without comorbidities was higher in the years 2020 and 2021 compared to the years 2017 to 2019 (P<0.05). When omitting the unknown comorbidities, only period E was significantly different with more patients without comorbidities in 2021.

In period B and E fewer patients were diagnosed with male genital cancers and more patients with female genital cancers as tumor type in the years 2020 and 2021 compared to the years 2017 to 2019 (P<0.05). Additionally more patients were diagnosed with breast cancer as tumor type in 2021.

Treatments

A significant decrease in the percentage of patients that received surgery was observed in Period A, C and D (Figure 2). Period D also showed a decrease in the percentage of patients that received targeted therapy. In contrast, period D showed a significant increase in the percentage of patients that received hormonal therapy. Finally, period E showed a significant increase in the percentage of patients receiving chemotherapy, targeted therapy or local surgery, with the percentage of chemotherapy showing the largest increase at 4,34%.
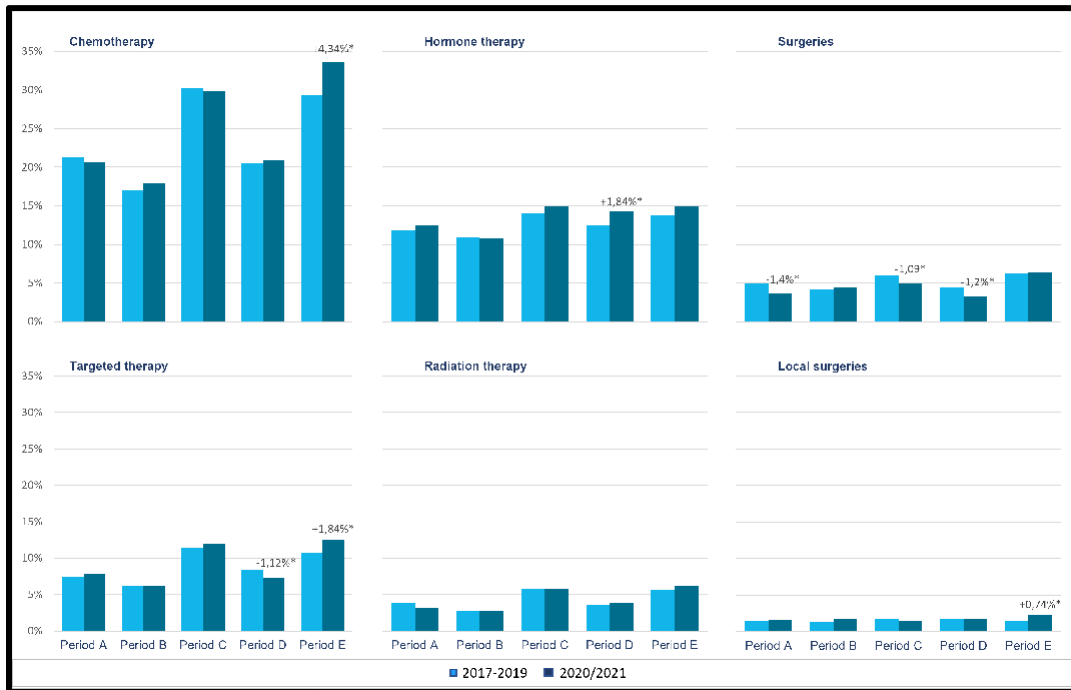
Figure 2: Percentage of all de novo metastatic patients that received a certain treatment within the period that they were diagnosed (NKR dataset)

Medication

The percentage of patients receiving immunotherapy was higher in the years 2020 and 2021 when compared to the years 2017 to 2019 (Figure 3). The percentage of patients that received newly approved cytotoxic medication was higher in the periods C and E. Additionally, the percentage for targeted therapy was higher in period E in 2021.
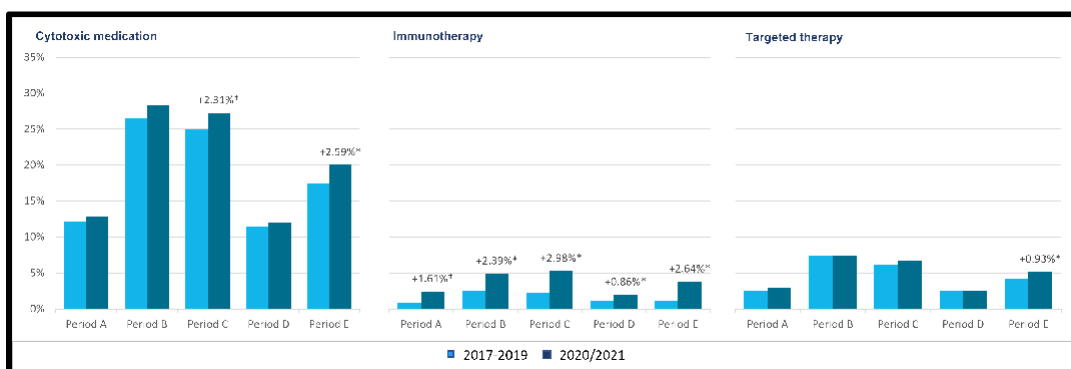
Figure 3: Percentage of patients that received newly approved medication within the period of their diagnosis (DHD dataset)

Table 2 presents the odds ratios of receiving a certain treatment\expensive medication depending on which year a patient was diagnosed, corrected for potential confounders. The odds ratios of receiving a certain treatment for the confounding variables can be found in Appendix B.

*Table 2: Odds ratio (CI) of receiving a type of therapy in 2020/2021 compared to 2017-2019 corrected for potential confounders** per period on which patients were diagnosed with de novo metastasized cancer*

| Tumor type	Treatment	Period A	Period B	Period C	Period D	Period E
All tumor types	Chemotherapy	1(0.9-1.11)	1.06(0.94-1.21)	1(0.94-1.07)	1.03(0.93-1.15)	**1.24(1.15-1.33)***
	Surgery	**0.77(0.62-0.95)***	1.05(0.83-1.34)	**0.84(0.74-0.96)***	**0.79(0.64-0.99)***	1.01(0.88-1.16)
	Hormonal therapy	1.04(0.87-1.26)	1.25(1.00-1.56)	0.99(0.86-1.14)	**1.32(1.1-1.58)***	**1.46(1.24-1.73)***
	Radiation therapy	0.82(0.65-1.03)	1(0.75-1.33)	1.03(0.91-1.17)	1.06(0.86-1.31)	1.13(0.99-1.31)
	Targeted therapy	1.1(0.94-1.28)	1(0.82-1.22)	**1.12(1.02-1.23)***	0.92(0.78-1.07)	**1.16(1.04-1.29)***
	Local surgery	0.9(0.63-1.3)	1.06(0.7-1.62)	0.77(0.59-1.00)	1.18(0.83-1.67)	**1.89(1.42-2.51)***
	Cytotoxic medication#	1.12(0.99-1.27)	1.1(0.99-1.23)	**1.17(1.1-1.26)***	1.08(0.95-1.22)	**1.19(1.09-1.3)***
	Immunotherapy#	**3.48(2.5-4.86)***	**2.16(1.67-2.8)***	**2.63(2.25-3.08)***	**1.96(1.42-2.71)***	**3.61(2.9-4.48)***
Gastrointestinal tract	Chemotherapy	1.05(0.89-1.24)	1.11(0.91-1.36)	0.99(0.88-1.1)	1.09(0.93-1.28)	**1.3(1.15-1.46)***
	Surgery	**0.72(0.55-0.95)***	1.13(0.85-1.51)	**0.79(0.67-0.95)***	0.9(0.69-1.18)	1.14(0.95-1.35)
	Hormonal therapy	1.41(0.5-3.99)	2.34(0.83-6.62)	1.19(0.66-2.16)	1.02(0.37-2.8)	**1.84(1.02-3.32)***
	Radiation therapy	**0.71(0.53-0.95)***	1.01(0.71-1.43)	0.98(0.83-1.17)	1.04(0.8-1.36)	1.1(0.91-1.31)
	Targeted therapy	1.06(0.8-1.4)	1.2(0.86-1.68)	1.11(0.95-1.31)	1.24(0.95-1.62)	**1.4(1.18-1.66)***
Respiratory tract	Chemotherapy	1.01(0.85-1.21)	1.11(0.9-1.38)	1(0.89-1.12)	0.91(0.76-1.08)	**1.16(1.01-1.33)***
	Surgery	0.77(0.25-2.32)	1.77(0.66-4.77)	0.78(0.39-1.58)	0.29(0.07-1.26)	1.06(0.54-2.09)
	Radiation therapy	0.79(0.48-1.29)	0.88(0.45-1.71)	0.82(0.63-1.08)	0.94(0.59-1.49)	0.78(0.55-1.11)
	Targeted therapy	**1.52(1.2-1.94)***	0.97(0.7-1.35)	**1.22(1.05-1.41)***	0.91(0.72-1.15)	**1.23(1.03-1.46)***
Breast	Chemotherapy	0.83(0.54-1.27)	1.34(0.77-2.35)	1.19(0.9-1.57)	0.75(0.49-1.13)	0.95(0.7-1.27)
	Surgery	0.4(0.14-1.19)	0.47(0.06-3.85)	**0.31(0.12-0.79)***	1.03(0.31-3.41)	**0.4(0.17-0.96)***
	Hormonal therapy	0.91(0.63-1.3)	1.06(0.67-1.66)	0.98(0.76-1.26)	1.11(0.78-1.59)	1.03(0.79-1.34)
	Targeted therapy	0.94(0.59-1.5)	1.23(0.66-2.31)	1.19(0.88-1.6)	0.73(0.46-1.18)	1.24(0.9-1.7)
Female genital	Chemotherapy	1.29(0.83-2.00)	0.96(0.59-1.56)	0.96(0.72-1.28)	**1.51(1.02-2.21)***	1.32(0.94-1.85)
	Surgery	0.75(0.35-1.62)	0.43(0.15-1.29)	1.18(0.84-1.65)	0.82(0.4-1.69)	1.04(0.69-1.56)
Male genital	Chemotherapy	**0.64(0.45-0.91)***	**0.48(0.26-0.86)***	1.09(0.9-1.31)	0.95(0.67-1.33)	**1.45(1.17-1.8)***
	Surgery	1.11(0.35-3.47)	1.31(0.32-5.47)	1.64(0.76-3.55)	1.56(0.51-4.78)	**2.31(1.04-5.11)***
	Hormonal therapy	1.07(0.85-1.35)	1.29(0.98-1.7)	0.99(0.82-1.18)	**1.43(1.14-1.79)***	**2.11(1.62-2.75)***
Urinary tract	Chemotherapy	0.95(0.43-2.07)	1.24(0.52-2.94)	0.96(0.63-1.46)	1.69(0.88-3.25)	1.57(1.00-2.45)
	Surgery	1.11(0.6-2.05)	0.86(0.41-1.81)	1.04(0.67-1.61)	0.45(0.2-1.03)	**0.56(0.33-0.94)***
Other	Chemotherapy	2.49(0.88-7.07)	1.24(0.26-5.82)	0.73(0.33-1.61)	**3.28(1.08-9.98)***	0.91(0.36-2.32)
	Surgery	0.91(0.18-4.61)	1.78(0.55-5.79)	0.98(0.4-2.39)	0.21(0.03-1.7)	1.52(0.62-3.77)
	Radiation therapy	**2.84(1.12-7.2)***	0.41(0.05-3.41)	1.15(0.62-2.14)	0.61(0.2-1.86)	0.86(0.41-1.8)
	Local surgery	1.12(0.55-2.29)	1.69(0.68-4.17)	1.3(0.79-2.16)	**3.33(1.72-6.45)***	0.91(0.52-1.6)

∗ significant difference between 2020/2021 and 2017-2019 P <0.05, ∗∗ Gender, age, tumor type and comorbidities more details in Appendix B, # Data from DHD

Patients diagnosed in period C and D during the pandemic were less likely to receive surgery in the same period during the covid pandemic than the years before, (odds=0.84(0.74-0.96) and (odds=0.79(0.64-0.99) respectively. With the least chance for patients with breast cancer in period C, odds of 0.31 (0.12-0.79). The chances of receiving chemotherapy in period E was higher for all tumor types combined (1.24 (1.15-1.33), with a positive odds ratio for all cancer, except for breast cancer and other cancers. Patients also had higher chance (odds =1.46(1.24-1.73)) of receiving hormonal therapy in period E during the pandemic when compared to Period E before the pandemic. The chances of receiving hormonal therapy during the pandemic were the highest for the gastrointestinal tract cancers (1.84(1.02-3.32)) and for the male genital cancers (2.11(1.62-2.75)).

Patients were more likely to receive immunotherapy medication when diagnosed in the years 2020/2021 compared to the years 2017-2019 for all periods. A significant increase in use of cytotoxic medication was found in period E, odds ratio of 1.19 (1.09-1.3), in the year 2021 when compared with the years 2017-2019, the other periods showed no significant difference.

(a) Chemotherapy

(b) Immunotherapy
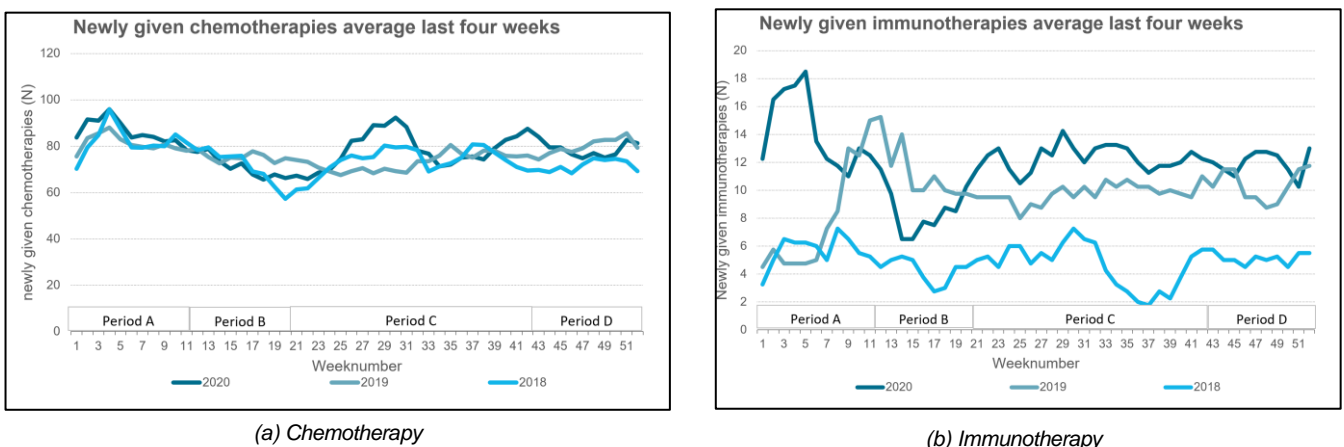
Figure 4: Moving average of the amount of expensive medication given over the last four weeks during the pandemic

A peak in the year 2020 can be seen during period C for the newly given chemotherapies (Figure 4a). Contrary, during the first peak of the pandemic (period B) a decline can be seen in the amount of newly given immunotherapies in 2020 (Figure 4b).

Time between diagnosis and initial treatment

The average time to treatment was significantly shorter in period B,C and D in years 2020/2021 comparing to the years 2017-2019. In period B of 2020 patients were treated 4.34 days sooner on average than in the same period of the years before the pandemic (Figure 5). The time until initial treatment per treatment type can be seen in Appendix C.
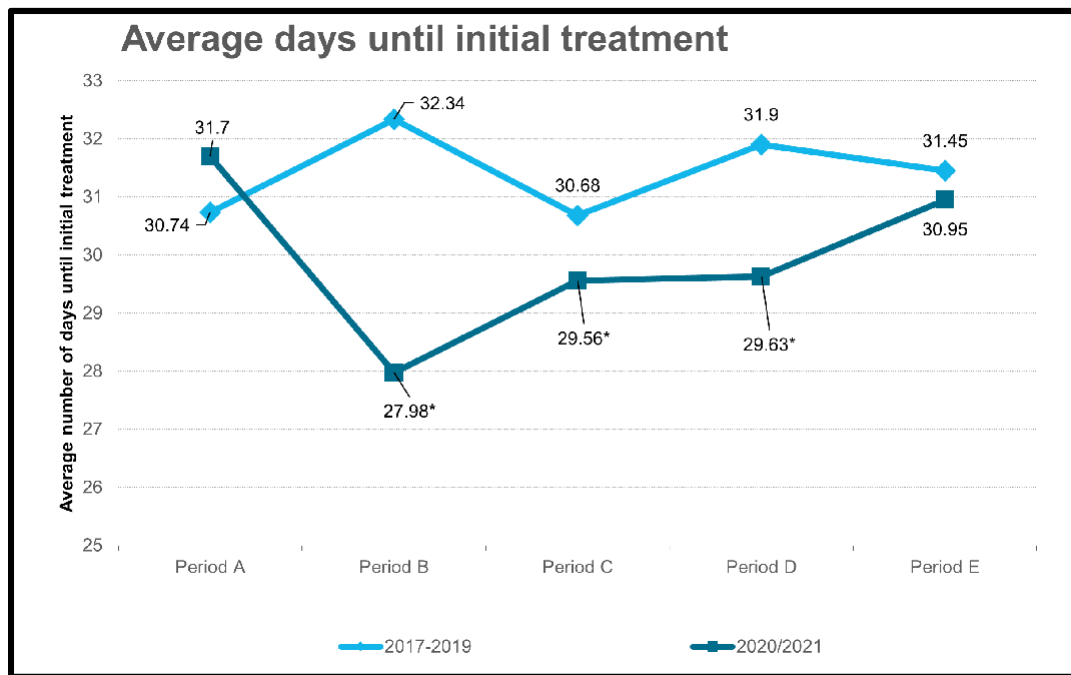
Figure 5: Average number of days from day of diagnosis until day of treatment

Discussion

This population-based study showed that the COVID-19 pandemic had a limited impact on the treatment of patients with de novo metastatic cancer. Recommendations about the management of cancer care were followed. Based on NCR and DHD data, it was revealed that the percentage of patients who underwent surgery within the period that they were diagnosed in decreased during the pandemic. In the first weeks of 2021 (period E) the percentage of patients that received chemotherapy, targeted therapy and local surgery increased compared to the same period in the years 2017 to 2019. Based on the results on expensive medication, the percentage of patients that received expensive cytotoxic medication increased during the pandemic in the period after the initial peak & in the first weeks of 2021. For expensive immunotherapies the percentage rose in every period during the pandemic. Differences were seen between different primary tumor types. Breast cancer and gastrointestinal tract cancer patients had a reduced chance of receiving surgery in period C, while other tumor types had no reduced chance. Gastrointestinal tract cancer patients and male genital cancer patients had a higher chance of receiving hormonal therapy in period E than other tumor types. Patients with respiratory tract cancer were more likely to receive targeted therapy in period C and period E. Patients with de novo metastatic cancer were treated earlier on average than before the pandemic.

It is shown that the percentage of patients who had surgery, during the same period they were diagnosed in, dropped during the pandemic. This mainly applied to breast cancer patients. This may be due to the postponement and cancellation of planned cancer surgeries [32]. Intensive care capacity also had to be available for COVID-19 patients. Differences in treatments between tumor types can be caused by different treatment capacities.

Period E showed an increase in the percentage of patients that received chemotherapy, targeted therapy and locale surgeries. Part of the reason for this may be the number of comorbidities patients presented. The number of patients with more than one comorbidity was lower in period E of 2021 when compared to the years 2017-2019. Which means patients were most likely healthier and therefore could be more suitable to receive treatment. Also, more women and more patients with breast cancer as their original tumor type were included in period E.

In accordance with what was found for lower stage cancer treatments, the treatments of patients with de novo metastatic cancer experienced no delays [25] [27] [31]. In fact patients were treated earlier in the COVID-19 pandemic comparing to the years before. A possible explanation for this could be that other treatments were halted and more capacity was available for patients with de novo metastatic cancer.

This study is the first to look at the effect of COVID-19 on patients with de novo metastatic cancer on a nationwide scale by using data from the NCR and DHD databases, thereby reflecting daily practice. However, the study has some limitations. Firstly, the DHD database has some overlap with the NCR database, therefore the cytotoxic medication results from DHD are quite similar to the chemotherapy results of the NCR. Also, in this study only patients with de novo metastatic cancers were taken into account, more complete insight in treatment for all patients with metastatic cancer would have been possible if patients with recurrent metastatic cancer would also be included. The use of expensive medication per tumor type has not yet been investigated, but should be added in this study to provide insight into the impact on expensive medication per tumor type. Furthermore, the periods in which the pandemic was divided were not of equal length, therefore a simple comparison between the periods was not possible, however a fair comparison with the same periods from earlier years was possible.

Because the NKR data set only includes treatments up to approximately 9 months after diagnosis, it was not possible to include all patient treatments. It is also important to clearly define the period and thus the severity of the pandemic in order to see its influence on the treatments taking place at that time. The data set only contained patients diagnosed from 2017 and later, therefore it is not possible to take all treatments in a period as a reference, because the patients from, for example, 2016 who receive a treatment in 2017 would not be included. This way you get unequally distributed groups between the years and you cannot make a fair comparison. To allow for a fair comparison between the years, it was decided to only include the treatments in the period in which a patient was diagnosed. A limitation of this is that patients who are diagnosed late in a certain period do not have much time to be treated within that period and in that case they are not included in this study.

The logistic regression corrected for some potential confounding variables, however there may be more confounding variables that were not included, e.g. the region where the patient lives. Trends in treatments should also be considered, for example immunotherapies for cancer patients is still a growing field [33]. That could be a reason for an increase in immunotherapies given. This also affects other treatments, because if a patient receives immunotherapy they will not receive, e.g. chemotherapy. As such these results should be interpreted with care. In this study a lot of tests are conducted, no correction has been made to correct for multiple testing errors.

Information about treatments from the NCR in this study was limited to only approximately 9 months after diagnosis, therefore changes in treatment or changes in treatment schedule were not studied. In breast cancer patients it was shown that changes in chemotherapy scheduling had an influence on survival [34]. There is reason to believe that this also applies to patients with de novo metastatic cancer, due to the similar origin of the disease. Further research will require a longer period of treatments that is included, to investigate the effect the pandemic had on treatment schedules.

In a few years time this study could be used to examine how differences in treatments, use of expensive medication and earlier treatment affected outcomes such as survival and quality of life for patients with de novo metastatic cancer during the pandemic.

Conclusion

The COVID-19 pandemic affected the treatment for patients with de novo metastatic cancer. This differed per tumor type. COVID-19 mainly impacted the percentage of patients who underwent surgery. The other treatment types were impacted less. However there was an increase in the number of chemotherapy treatments and use of expensive cytotoxic medication in the first weeks of 2021.
Efforts to maintain the best care for cancer patients seemed to result in a small impact of the pandemic on de novo metastatic cancer. During the peak of the pandemic initial treatments were even given sooner than before the pandemic.
Future studies will need to investigate what these changes in treatments, medication and time to treatment mean for the long-term effects on outcomes such as survival.

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Appendix A

Targeted therapy	Cytotoxic	Hormonal therapy	Immunotherapy	Other
Abemaciclib	Cabazitaxel	Abiraterone	Atezolizumab	lutetium (177Lu) oxodotreotide
Afatinib	Capecitabine	Anastrozol	Avelumab	
Alectinib	Carboplatin	Bicalutamide	Interferon alfa 2b	
Alpelisib	Cisplatin	Degarelix	Interleukin-2 (IL-2)	
Apalutamide	Dacarbazine	Enzalutamide	Ipilimumab	
Axitinib	Docetaxel	Exemestane	Nivolumab	
Bevacizumab	Doxorubicin (liposomaal)	Flutamide	Pembrolizumab	
Bevacizumab	Epirubicin	Fulvestrant	Pembrolizumab	
Binimetinib	Eribulin	Gosereline	Sacituzumab Govitecan	
Brigatinib	Etoposide	Letrozol		
Cabozantinib	FLOT	Nilutamide (Anandron)		
Ceritinib	FOLFOXIRIr	Tamoxifen		
Cetuximab	Gemcitabine			
Cobimetinib	Irinotecan			
Crizotinib	Irinotecan liposomaal			
Dabrafenib	mFOLFOX6			
Dacomitinib	Nab-Paclitaxel			
Darolutamide	Nab-Paclitaxel (Abraxane)			
Denosumab	Oxaliplatin			
Durvalumab	Paclitaxel			
Encorafenib	Pemetrexed			
Entrectinib	S-1 (Teysuno)			
Erlotinib	Temozolomide			
Everolimus	Teniposide			
Gefitinib	Topotecan			
Imatinib	Trabectedine			
Lapatinib	Trifluridine/tipiracil TAS 102(Lonsurf)			
Larotrectinib	Vinflunin			
Lenvatinib	Vinorelbine			
Lorlantinib				
Nintedanib				
Niraparib				
Olaparib				
Olaratumab				
Osimertinib				
Palbociclib				
Panitumumab				
Pazopanib				
Pertuzumab				
Ramucirumab				
Regorafenib				
Ribociclib				
Ripretinib				
Rucaparib				
Selpercatinib				
Sorafenib				
Sunitinib				
Talazoparib				
Temsirolimus				
Tivozanib				
Trametinib				
Trastuzumab				
Trastuzumab-Emtansine				
Tucatinib				
Vandetanib				
Vemurafenib				

Appendix B

All tumor types

Period A		Chemotherapy	Surgery	Hormonal therapy	Radiation therapy	Targeted therapy	Local surgery
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.86(0.78-0.96)*	1.13(0.93-1.37)	1.73(0.85-3.51)	0.76(0.62-0.93)*	1.02(0.88-1.18)	0.95(0.67-1.35)
Age		0.96(0.95-0.96)*	0.97(0.96-0.98)*	1.03(1.03-1.04)*	0.99(0.99-1)	0.97(0.96-0.97)*	1(0.99-1.02)
Tumor type	Gastrointestinal tract	Reference	Reference	Reference	Reference	Reference	Reference
	Respiratory tract	1.38(1.22-1.56)*	0.05(0.03-0.07)*	0.14(0.03-0.61)*	0.53(0.41-0.69)*	1.61(1.34-1.93)*	0.27(0.04-2.14)
	Breast	0.81(0.65-1)	0.25(0.16-0.38)*	111.09(61.17-201.74)*	0.25(0.13-0.51)*	2(1.53-2.6)*	
	Female genital	2.32(1.86-2.89)*	1.27(0.89-1.8)	5(2.16-11.58)*	0.25(0.11-0.56)*	0.06(0.02-0.25)*	0.87(0.11-6.79)
	Male genital	0.62(0.52-0.74)*	0.21(0.15-0.31)*	598.05(312.85-1143.25)*	0.16(0.09-0.26)*		
	Urinary tract	0.24(0.17-0.33)*	1.46(1.1-1.95)*		0.17(0.08-0.35)*	2.51(1.94-3.25)*	92.6(50.74-169.01)*
	Other	0.15(0.09-0.24)*	0.21(0.11-0.41)*	2.41(0.7-8.27)	1.01(0.64-1.61)	1.79(1.28-2.5)*	98.52(50.51-192.17)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.82(0.69-0.98)*	0.89(0.65-1.21)	1.04(0.52-2.05)	1.24(0.91-1.69)	0.86(0.65-1.14)	0.94(0.59-1.5)
	>1	0.57(0.46-0.72)*	0.82(0.56-1.19)	0.74(0.34-1.6)	1.11(0.78-1.59)	0.64(0.44-0.92)*	2(1.28-3.11)*
	Unknown	1(0.87-1.14)	1.99(1.59-2.49)*	1.37(0.84-2.22)	0.92(0.7-1.2)	1.16(0.94-1.42)	0.28(0.17-0.45)*

Period B		Chemotherapy	Surgery	Hormonal therapy	Radiation therapy	Targeted therapy	Local surgery
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.87(0.76-0.98)*	1.34(1.07-1.67)*	1.02(0.42-2.47)	0.49(0.37-0.65)*	0.83(0.69-1)	0.96(0.64-1.45)
Age		0.95(0.95-0.96)*	0.97(0.96-0.98)*	1.03(1.03-1.04)*	1(0.99-1.01)	0.97(0.96-0.97)*	1(0.99-1.02)
Tumor type	Digestive	Reference	Reference	Reference	Reference	Reference	Reference
	Airway	1.56(1.34-1.8)*	0.06(0.04-0.1)*	0.09(0.01-0.67)	0.48(0.34-0.67)*	1.55(1.24-1.94)*	
	Breast	0.66(0.5-0.87)*	0.1(0.05-0.19)*	149.38(69.72-320.07)*	0.13(0.03-0.55)*	1.76(1.24-2.48)*	
	Female genitalie	3.06(2.38-3.93)*	0.94(0.61-1.45)	2.15(0.56-8.25)	0.41(0.16-1.04)	0.16(0.05-0.51)*	
	Male genitalia	0.48(0.38-0.61)*	0.21(0.13-0.32)*	358.61(181.99-706.66)*	0.19(0.1-0.34)*		5.11(0.81-32.21)
	Urinary tract	0.34(0.23-0.49)*	1.49(1.06-2.09)*		0.19(0.08-0.48)*	3.18(2.37-4.27)*	326.8(103.03-1036.54)*
	Other	0.14(0.07-0.28)*	0.51(0.28-0.9)*	1.03(0.13-7.83)	0.68(0.33-1.4)	2.75(1.87-4.03)*	270.43(80.96-903.35)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.77(0.62-0.96)*	0.56(0.37-0.84)*	1.01(0.44-2.31)	1.03(0.7-1.5)	0.92(0.65-1.3)	0.98(0.58-1.66)
	>1	0.64(0.48-0.85)*	0.65(0.41-1.04)	1.1(0.45-2.66)	0.54(0.32-0.92)*	0.74(0.49-1.14)	1.33(0.8-2.21)
	Unknown	1.02(0.87-1.2)	1.9(1.48-2.44)*	1.32(0.77-2.28)	0.77(0.55-1.07)	1.22(0.95-1.57)	0.24(0.14-0.42)*

Period C		Chemotherapy	Surgery	Hormonal therapy	Radiation therapy	Targeted therapy	Local surgery
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.88(0.82-0.94)*	1.17(1.03-1.33)*	0.36(0.21-0.62)*	0.64(0.57-0.73)*	1.01(0.92-1.1)	1.06(0.83-1.34)
Age		0.95(0.95-0.95)*	0.98(0.97-0.98)*	1.03(1.02-1.03)*	0.99(0.98-0.99)*	0.96(0.96-0.97)*	1(0.99-1)
Tumor type	Digestive	Reference	Reference	Reference	Reference	Reference	Reference
	Airway	1.15(1.06-1.24)*	0.05(0.03-0.06)*	0.04(0.01-0.16)*	0.56(0.48-0.65)*	1.29(1.16-1.44)*	0.4(0.09-1.75)
	Breast	0.67(0.58-0.78)*	0.19(0.14-0.26)*	237.58(142.39-396.38)*	0.26(0.17-0.39)*	1.37(1.16-1.62)*	1.02(0.13-7.81)
	Female genitalie	2.45(2.11-2.84)*	2.67(2.21-3.23)*	13.41(7.4-24.32)*	0.5(0.35-0.71)*	0.18(0.12-0.29)*	
	Male genitalia	0.71(0.64-0.79)*	0.12(0.09-0.16)*	325.01(235.58-448.38)*	0.37(0.29-0.46)*	0(0-0.02)*	1.82(0.59-5.59)
	Urinary tract	0.27(0.22-0.32)*	1.19(0.97-1.46)	0.24(0.06-0.98)*	0.16(0.1-0.25)*	1.86(1.57-2.2)*	159.33(95.7-265.25)*
	Other	0.14(0.1-0.19)*	0.38(0.26-0.56)*	0.76(0.24-2.43)	1.18(0.89-1.56)	2.16(1.75-2.66)*	152.91(88.59-263.93)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.87(0.77-0.97)*	0.86(0.7-1.05)	1(0.64-1.57)	1(0.82-1.2)	0.92(0.77-1.1)	1.27(0.94-1.72)
	>1	0.57(0.49-0.66)*	0.84(0.66-1.07)	0.89(0.54-1.49)	0.96(0.77-1.19)	0.71(0.57-0.89)*	1.26(0.91-1.75)
	Unknown	1.05(0.96-1.15)	2.11(1.82-2.43)*	1.42(1.03-1.95)*	0.84(0.72-0.98)*	1.56(1.37-1.78)*	0.28(0.2-0.39)*

Period D		Chemotherapy	Surgery	Hormonal therapy	Radiation therapy	Targeted therapy	Local surgery
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.94(0.84-1.04)	1.44(1.18-1.76)*	1.07(0.5-2.27)	0.69(0.56-0.85)*	1.15(1-1.33)	1.05(0.76-1.46)
Age		0.96(0.95-0.96)*	0.97(0.96-0.98)*	1.03(1.02-1.03)*	0.99(0.98-1)	0.97(0.96-0.97)*	1(0.98-1.01)
Tumor type	Digestive	Reference	Reference	Reference	Reference	Reference	Reference
	Airway	1.35(1.19-1.54)*	0.05(0.03-0.08)*	0.06(0.01-0.42)*	0.55(0.42-0.72)*	1.63(1.36-1.96)*	
	Breast	1.04(0.84-1.29)	0.12(0.07-0.21)*	112.95(59.69-213.71)*	0.39(0.21-0.73)*	1.8(1.38-2.34)*	
	Female genitalie	2.61(2.12-3.21)*	1.12(0.79-1.6)	6.43(2.93-14.13)*	0.33(0.17-0.65)*	0.08(0.03-0.26)*	
	Male genitalia	0.56(0.47-0.67)*	0.21(0.14-0.3)*	422.11(233.75-762.23)*	0.1(0.06-0.19)*		2.78(0.67-11.53)
	Urinary tract	0.28(0.21-0.38)*	1.5(1.12-2.01)*		0.13(0.06-0.29)*	2.8(2.17-3.59)*	234.16(102.92-532.73)*
	Other	0.15(0.09-0.25)*	0.45(0.26-0.79)*		1.12(0.72-1.74)	2.41(1.75-3.32)*	175.99(74.3-416.85)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.94(0.79-1.12)	0.97(0.7-1.34)	0.61(0.31-1.2)	1.07(0.79-1.45)	0.82(0.61-1.1)	0.84(0.55-1.3)
	>1	0.69(0.55-0.86)*	0.77(0.51-1.16)	0.44(0.21-0.92)*	1.15(0.82-1.61)	0.42(0.27-0.64)*	1.18(0.76-1.82)
	Unknown	0.89(0.77-1.02)	2.18(1.72-2.75)*	0.99(0.63-1.57)	0.76(0.58-1)	1.41(1.14-1.74)*	0.31(0.2-0.47)*

Period E		Chemotherapy	Surgery	Hormonal therapy	Radiation therapy	Targeted therapy	Local surgery
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.89(0.83-0.96)*	1.22(1.07-1.39)*	1.1(0.7-1.72)	0.69(0.6-0.79)*	1(0.91-1.1)	0.8(0.62-1.05)
Age		0.95(0.95-0.95)*	0.98(0.97-0.98)*	1.04(1.03-1.04)*	0.99(0.99-1)	0.96(0.96-0.97)*	0.99(0.98-1)
Tumor type	Digestive	Reference	Reference	Reference	Reference	Reference	Reference
	Airway	1.17(1.08-1.28)*	0.05(0.04-0.07)*	0.07(0.02-0.21)	0.44(0.38-0.52)*	1.24(1.11-1.39)*	0.66(0.19-2.26)
	Breast	0.66(0.57-0.76)*	0.17(0.13-0.24)*	115.73(77.84-172.06)*	0.25(0.16-0.38)*	1.49(1.25-1.77)*	
	Female genitalie	2.46(2.1-2.88)*	2.08(1.69-2.56)*	4.53(2.6-7.89)*	0.32(0.2-0.51)*	0.16(0.1-0.26)*	0.58(0.08-4.42)
	Male genitalia	0.85(0.76-0.95)*	0.17(0.13-0.22)*	446.86(309.67-644.83)*	0.33(0.26-0.41)*	0(0-0.02)*	0.52(0.07-3.95)
	Urinary tract	0.28(0.23-0.34)*	1.09(0.89-1.34)		0.17(0.11-0.27)*	1.98(1.66-2.35)*	151.24(92.71-246.7)*
	Other	0.11(0.08-0.16)*	0.38(0.27-0.56)*	1.55(0.66-3.63)	1.08(0.82-1.44)	2.27(1.84-2.8)*	112.99(66.5-191.97)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.86(0.76-0.97)*	0.69(0.56-0.85)*	1.21(0.75-1.93)	1.22(1-1.49)	0.8(0.67-0.96)*	1.1(0.78-1.55)
	>1	0.7(0.6-0.81)*	0.75(0.58-0.96)*	0.74(0.42-1.3)	1.13(0.9-1.42)	0.76(0.62-0.94)*	1.71(1.22-2.4)*
	Unknown	0.99(0.9-1.08)	1.76(1.52-2.03)*	1.53(1.1-2.12)*	1.04(0.88-1.23)	1.15(1.01-1.3)*	0.2(0.14-0.28)*

∗ significant difference P <0.05

Chemotherapy

		Gastrointestinal tract	Respiratory tract	Breast	Female genital	Male genital	Urinary tract	Other
Period A		Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	1.05(0.89-1.24)	1.01(0.85-1.21)	0.83(0.54-1.27)	1.29(0.83-2)	0.64(0.45-0.91)*	0.95(0.43-2.07)	2.49(0.88-7.07)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.75(0.65-0.87)*	1.04(0.89-1.22)				0.55(0.24-1.23)	0.44(0.14-1.39)
Age		0.96(0.95-0.96)*	0.96(0.95-0.97)*	0.95(0.94-0.96)*	0.98(0.97-1)	0.93(0.92-0.94)*	0.99(0.96-1.02)	0.95(0.92-0.98)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.82(0.67-1.01)	0.69(0.38-1.24)	0.46(0.05-4.68)	0.85(0.51-1.43)	0.13(0.01-1.24)	0.4(0.11-1.46)	
	>1	0.56(0.43-0.74)*	0.38(0.19-0.79)*		0.63(0.31-1.25)	0.18(0.02-1.76)	0.69(0.23-2.06)	
	Unknown	0.96(0.81-1.14)	0.95(0.66-1.36)	0.93(0.32-2.68)	0.73(0.45-1.19)	0.49(0.18-1.33)	1.7(0.78-3.68)	
Period B								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	1.11(0.91-1.36)	1.11(0.9-1.38)	1.34(0.77-2.35)	0.96(0.59-1.56)	0.48(0.26-0.86)*	1.24(0.52-2.94)	1.24(0.26-5.82)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.7(0.58-0.83)*	1.1(0.92-1.32)				0.57(0.22-1.43)	1.68(0.39-7.3)
Age		0.96(0.95-0.97)*	0.96(0.95-0.97)*	0.95(0.93-0.96)*	0.98(0.96-1)	0.92(0.9-0.94)*	0.97(0.94-1.01)	0.92(0.87-0.96)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.78(0.6-1)	1.1(0.52-2.34)	0.92(0.08-10.18)	0.42(0.23-0.78)*	1.82(0.38-8.83)	0.67(0.17-2.54)	
	>1	0.49(0.35-0.7)*	1.41(0.63-3.14)		1.04(0.5-2.15)		0.39(0.08-1.84)	
	Unknown	0.94(0.77-1.15)	1.61(1.01-2.55)*	0.94(0.3-2.93)	0.53(0.29-0.94)*		2.12(0.9-4.95)	
Period C								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	0.99(0.88-1.1)	1(0.89-1.12)	1.19(0.9-1.57)	0.96(0.72-1.28)	1.09(0.9-1.31)	0.96(0.63-1.46)	0.73(0.33-1.61)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.83(0.76-0.92)*	0.94(0.85-1.04)				1.13(0.77-1.64)	1.01(0.52-1.99)
Age		0.95(0.94-0.95)*	0.95(0.95-0.96)*	0.94(0.93-0.95)*	0.96(0.95-0.97)*	0.92(0.92-0.93)*	0.97(0.95-0.98)*	0.94(0.92-0.96)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.82(0.72-0.94)*	1.1(0.7-1.72)	0.74(0.2-2.75)	0.91(0.65-1.29)	0.19(0.04-0.94)*	0.98(0.56-1.69)	
	>1	0.5(0.42-0.59)*	0.77(0.47-1.27)	0.92(0.16-5.17)	0.73(0.44-1.2)	0.24(0.06-0.98)*	0.95(0.54-1.68)	4.61(0.39-54.73)
	Unknown	1(0.9-1.12)	1.13(0.83-1.53)	1.13(0.55-2.29)	0.77(0.55-1.08)	0.81(0.39-1.71)	1.44(0.93-2.23)	13.19(3.08-56.54)*
Period D								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	1.09(0.93-1.28)	0.91(0.76-1.08)	0.75(0.49-1.13)	1.51(1.02-2.21)*	0.95(0.67-1.33)	1.69(0.88-3.25)	3.28(1.08-9.98)*
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.94(0.82-1.09)	0.93(0.79-1.08)				0.9(0.47-1.73)	0.6(0.18-2)
Age		0.96(0.95-0.97)*	0.96(0.95-0.97)*	0.95(0.94-0.96)*	0.98(0.97-1)	0.92(0.91-0.93)*	0.97(0.94-1)	0.94(0.91-0.97)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	1.01(0.82-1.23)	0.37(0.17-0.82)*		0.79(0.47-1.3)	0.11(0.01-1)	1.03(0.41-2.55)	2.17(0.17-27.18)
	>1	0.59(0.45-0.76)*	0.65(0.31-1.37)		0.82(0.45-1.5)		1.38(0.58-3.33)	4.33(0.33-56.82)
	Unknown	0.94(0.79-1.11)	0.53(0.34-0.84)*	0.65(0.24-1.73)	0.59(0.37-0.93)*	0.31(0.13-0.76)*	1.5(0.7-3.21)	5.25(1.07-25.88)*
Period E								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2021	1.3(1.15-1.46)*	1.16(1.01-1.33)*	0.95(0.7-1.27)	1.32(0.94-1.85)	1.45(1.17-1.8)*	1.57(1-2.45)	0.91(0.36-2.32)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	0.82(0.74-0.91)*	1.01(0.9-1.13)				0.71(0.46-1.09)	0.75(0.36-1.55)
Age		0.95(0.95-0.96)*	0.95(0.95-0.96)*	0.95(0.94-0.95)*	0.96(0.95-0.97)*	0.92(0.91-0.93)*	0.97(0.95-0.99)*	0.96(0.93-0.98)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.84(0.73-0.97)*	1.05(0.71-1.55)	1(0.23-4.27)	0.69(0.47-1)	0.61(0.18-2.13)	0.68(0.37-1.24)	
	>1	0.6(0.5-0.72)*	0.74(0.46-1.18)	1(0.18-5.64)	0.89(0.54-1.49)	1.12(0.34-3.69)	0.89(0.51-1.56)	0.3(0.04-2.28)
	Unknown	0.97(0.86-1.08)	1.1(0.87-1.41)	1.4(0.7-2.8)	0.7(0.49-1.01)	1.32(0.6-2.88)	0.52(0.32-0.83)*	

Surgery

		Gastrointestinal tract surgery	Respiratory tract surgery	Breast surgery	Female genital surgery	Male genital surgery	Urinary tract surgery	Other surgery
Period A								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	0.72(0.55-0.95)*	0.77(0.25-2.32)	0.4(0.14-1.19)	0.75(0.35-1.62)	1.11(0.35-3.47)	1.11(0.6-2.05)	0.91(0.18-4.61)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	1.16(0.94-1.44)	0.42(0.15-1.17)				0.98(0.55-1.76)	2.4(0.62-9.23)
Age		0.99(0.98-0.99)*	0.97(0.93-1.02)	1.05(1.02-1.08)*	0.98(0.95-1)	0.84(0.82-0.87)*	0.95(0.93-0.98)*	0.99(0.95-1.04)
Comorbidities	0	Reference		Reference	Reference	Reference	Reference	
	1	0.84(0.58-1.22)		1.57(0.19-12.9)	0.51(0.2-1.29)		1.6(0.74-3.47)	
	>1	0.73(0.46-1.16)	2.03(0.26-15.67)		0.7(0.23-2.16)	1.46(0.07-28.66)	0.83(0.31-2.22)	1.48(0.17-12.71)
	Unknown	2.3(1.77-2.99)*			0.5(0.22-1.16)	0.08(0.01-0.68)*	2.07(1.06-4.05)*	
Period B								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	1.13(0.85-1.51)	1.77(0.66-4.77)	0.47(0.06-3.85)	0.43(0.15-1.29)	1.31(0.32-5.47)	0.86(0.41-1.81)	1.78(0.55-5.79)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	1.29(1.01-1.66)*	1.49(0.58-3.85)				1.04(0.53-2.07)	2.87(0.89-9.23)
Age		0.98(0.97-0.99)*	0.98(0.94-1.03)	1.04(0.99-1.09)	0.97(0.94-1)	0.82(0.78-0.86)*	0.97(0.94-1)	0.99(0.95-1.03)
Comorbidities	0	Reference	Reference	Reference	Reference		Reference	Reference
	1	0.47(0.29-0.77)*	2.12(0.13-34.91)		0.81(0.28-2.34)		0.55(0.18-1.75)	
	>1	0.45(0.24-0.82)*	2.68(0.16-44.7)		0.78(0.17-3.7)		1.04(0.41-2.61)	
	Unknown	2.04(1.53-2.72)*	0.86(0.11-6.64)	0.55(0.06-4.66)	0.84(0.29-2.41)		1.42(0.68-2.96)	3.31(0.41-26.47)
Period C								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	0.79(0.67-0.95)*	0.78(0.39-1.58)	0.31(0.12-0.79)*	1.18(0.84-1.65)	1.64(0.76-3.55)	1.04(0.67-1.61)	0.98(0.4-2.39)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	1.14(0.98-1.31)	1.2(0.68-2.14)				1.12(0.75-1.67)	1.3(0.6-2.84)
Age		0.99(0.98-1)	0.95(0.93-0.98)*	1.01(0.99-1.03)	0.97(0.96-0.98)*	0.86(0.84-0.88)*	0.97(0.95-0.98)*	0.98(0.96-1.01)
Comorbidities	0	Reference	Reference	Reference	Reference		Reference	Reference
	1	0.92(0.71-1.18)	0.46(0.05-4.52)		0.9(0.59-1.37)		0.47(0.23-0.96)*	2.3(0.14-37.64)
	>1	0.73(0.53-1)	1.36(0.22-8.44)	5.82(0.96-35.29)	0.74(0.39-1.41)		1.06(0.6-1.89)	
	Unknown	2.7(2.26-3.23)*	0.44(0.13-1.43)	0.57(0.17-1.93)	0.58(0.38-0.89)*		1.69(1.08-2.63)*	12.27(1.65-91.45)
Period D								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2020	0.9(0.69-1.18)	0.29(0.07-1.26)	1.03(0.31-3.41)	0.82(0.4-1.69)	1.56(0.51-4.78)	0.45(0.2-1.03)	0.21(0.03-1.7)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	1.45(1.16-1.82)*	1.22(0.51-2.91)				0.99(0.56-1.76)	2.3(0.75-7.07)
Age		0.99(0.98-1)	0.98(0.94-1.02)	1.02(0.98-1.06)	0.97(0.95-1)	0.84(0.82-0.87)*	0.97(0.95-1)	0.98(0.95-1.02)
Comorbidities	0	Reference		Reference	Reference	Reference	Reference	Reference
	1	0.69(0.45-1.05)		10.88(1.08-109.44)*	1.51(0.68-3.33)	16.31(1.77-150.05)*	1.35(0.62-2.9)	0.34(0.04-2.84)
	>1	0.62(0.37-1.03)			0.64(0.18-2.28)		0.92(0.38-2.26)	0.84(0.1-7.21)
	Unknown	2.46(1.87-3.24)*	0.43(0.06-3.29)		0.53(0.21-1.36)		1.39(0.71-2.73)	
Period E								
Year	2017-2019	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	2021	1.14(0.95-1.35)	1.06(0.54-2.09)	0.4(0.17-0.96)*	1.04(0.69-1.56)	2.31(1.04-5.11)*	0.56(0.33-0.94)*	1.52(0.62-3.77)
Gender	Men	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Women	1.24(1.07-1.43)*	0.93(0.53-1.63)				0.95(0.62-1.47)	2.04(0.98-4.26)
Age		0.99(0.99-1)	0.95(0.93-0.98)*	1.04(1.02-1.06)*	0.98(0.97-0.99)*	0.83(0.81-0.86)*	0.95(0.94-0.97)*	0.97(0.95-0.99)*
Comorbidities	0	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	1	0.65(0.51-0.84)*			0.64(0.39-1.04)		1(0.5-2.01)	3.02(0.18-50.49)
	>1	0.67(0.5-0.9)*	1.57(0.14-17.7)	4.7(0.27-82.45)	0.61(0.31-1.22)	2.09(0.11-39.75)	0.96(0.47-1.99)	4.65(0.28-78.18)
	Unknown	1.95(1.64-2.31)*	1.55(0.37-6.42)	2.86(0.38-21.34)	0.65(0.41-1.02)	0.21(0.03-1.67)	2.02(1.24-3.3)*	13.35(1.75-101.67)

Hormonal therapies

		Gastrointestinal tract	Breast	Male genital
Period A		**Hormonal therapy**	**Hormonal therapy**	**Hormonal therapy**
Year	2017-2019	Reference	Reference	Reference
	2020	1.41(0.5-3.99)	0.91(0.63-1.3)	1.07(0.85-1.35)
Gender	Men	Reference	Reference	Reference
	Women	1.97(0.76-5.1)		
Age		0.99(0.95-1.03)	1.03(1.02-1.05)*	1.04(1.03-1.05)*
Comorbidities	0	Reference	Reference	Reference
	1	0.82(0.07-9.13)	1.44(0.34-6.09)	0.95(0.27-3.32)
	>1		1.04(0.16-6.7)	0.45(0.13-1.52)
	Unknown	6.39(1.45-28.11)*	1.34(0.56-3.23)	0.8(0.33-1.95)
Period B				
Year	2017-2019	Reference	Reference	Reference
	2020	2.34(0.83-6.62)	1.06(0.67-1.66)	1.29(0.98-1.7)
Gender	Men	Reference	Reference	Reference
	Women	1.25(0.45-3.48)		
Age		0.97(0.93-1.01)	1.03(1.02-1.05)*	1.04(1.02-1.05)*
Comorbidities	0	Reference	Reference	Reference
	1	2.67(0.44-16.29)	0.14(0.01-1.3)	4.13(0.97-17.68)
	>1		0.84(0.12-5.92)	4.66(1.02-21.22)*
	Unknown	4.51(0.98-20.74)	0.54(0.25-1.18)	3.17(1.18-8.51)*
Period C				
Year	2017-2019	Reference	Reference	Reference
	2020	1.19(0.66-2.16)	0.98(0.76-1.26)	0.99(0.82-1.18)
Gender	Men	Reference	Reference	Reference
	Women	0.34(0.18-0.64)		
Age		0.97(0.95-0.99)*	1.03(1.02-1.04)*	1.03(1.02-1.04)*
Comorbidities	0	Reference	Reference	Reference
	1	0.98(0.29-3.38)	3.59(1.2-10.72)*	0.25(0.08-0.76)*
	>1	2.25(0.74-6.83)	0.79(0.19-3.2)	0.35(0.12-1.02)
	Unknown	5.33(2.38-11.93)*	1.01(0.56-1.82)	0.6(0.26-1.43)
Period D				
Year	2017-2019	Reference	Reference	Reference
	2020	1.02(0.37-2.8)	1.11(0.78-1.59)	1.43(1.14-1.79)*
Gender	Men	Reference	Reference	Reference
	Women	0.9(0.38-2.14)		
Age		1.01(0.97-1.04)	1.04(1.02-1.05)*	1.02(1.01-1.03)*
Comorbidities	0	Reference	Reference	Reference
	1	0.3(0.03-2.56)	0.51(0.05-5.71)	0.28(0.08-1.04)
	>1			0.19(0.05-0.7)*
	Unknown	2.52(0.91-6.98)	1.36(0.51-3.64)	0.35(0.12-1.02)
Period E				
Year	2017-2019	Reference	Reference	Reference
	2021	1.84(1.02-3.32)*	1.03(0.79-1.34)	2.11(1.62-2.75)*
Gender	Men	Reference	Reference	Reference
	Women	1.14(0.67-1.95)		
Age		0.98(0.96-1)	1.04(1.03-1.05)*	1.04(1.03-1.05)*
Comorbidities	0	Reference	Reference	Reference
	1	3.25(0.94-11.2)	1.08(0.36-3.26)	1.48(0.52-4.19)
	>1	1.41(0.26-7.82)	0.86(0.24-3.09)	0.72(0.27-1.95)
	Unknown	9.47(3.38-26.5)*	0.9(0.53-1.55)	1.46(0.74-2.89)

Radiation therapies

		Gastrointestinal tract	Respiratory tract	Other
Period A		**Radiation therapy**	**Radiation therapy**	**Radiation therapy**
Year	2017-2019	Reference	Reference	Reference
	2020	0.71(0.53-0.95)*	0.79(0.48-1.29)	2.84(1.12-7.2)*
Gender	Men	Reference	Reference	Reference
	Women	0.73(0.56-0.93)*	0.78(0.52-1.19)	0.76(0.28-2.01)
Age		0.99(0.98-1)	0.99(0.97-1.01)	1.04(1-1.08)
Comorbidities	0	Reference	Reference	Reference
	1	1.29(0.94-1.79)	2.99(0.54-16.67)	
	>1	1.11(0.76-1.64)	2.66(0.43-16.31)	
	Unknown	0.78(0.57-1.05)	2.34(0.57-9.63)	6.53(0.83-51.1)
Period B				
Year	2017-2019	Reference	Reference	Reference
	2020	1.01(0.71-1.43)	0.88(0.45-1.71)	0.41(0.05-3.41)
Gender	Men	Reference	Reference	Reference
	Women	0.37(0.25-0.53)*	0.93(0.53-1.62)	1.67(0.41-6.92)
Age		1(0.98-1.01)	1.01(0.98-1.04)	0.99(0.94-1.05)
Comorbidities	0	Reference	Reference	Reference
	1	1.02(0.68-1.53)	0.4(0.04-3.68)	1.47(0.09-25.33)
	>1	0.56(0.32-0.98)*		
	Unknown	0.72(0.49-1.04)	0.65(0.23-1.84)	1.57(0.18-13.44)
Period C				
Year	2017-2019	Reference	Reference	Reference
	2020	0.98(0.83-1.17)	0.82(0.63-1.08)	1.15(0.62-2.14)
Gender	Men	Reference	Reference	Reference
	Women	0.54(0.46-0.63)*	1.02(0.81-1.29)	0.47(0.25-0.89)*
Age		0.99(0.99-1)	0.97(0.96-0.98)*	1.01(0.99-1.03)
Comorbidities	0	Reference	Reference	Reference
	1	0.94(0.77-1.15)	1.17(0.44-3.1)	1.29(0.21-7.97)
	>1	0.94(0.74-1.19)	1.31(0.47-3.61)	
	Unknown	0.71(0.59-0.85)*	1(0.5-1.97)	8.15(2.5-26.6)*
Period D				
Year	2017-2019	Reference	Reference	Reference
	2020	1.04(0.8-1.36)	0.94(0.59-1.49)	0.61(0.2-1.86)
Gender	Men	Reference	Reference	Reference
	Women	0.56(0.44-0.73)*	1.13(0.75-1.68)	0.67(0.25-1.78)
Age		0.99(0.98-1)	0.97(0.95-0.98)*	1(0.97-1.03)
Comorbidities	0	Reference	Reference	Reference
	1	0.99(0.72-1.38)	1.09(0.28-4.25)	2.62(0.35-19.81)
	>1	1.01(0.7-1.46)	0.59(0.11-3.17)	3.73(0.48-29.29)
	Unknown	0.69(0.51-0.94)*	0.39(0.15-1)	4.58(1.03-20.42)*
Period E				
Year	2017-2019	Reference	Reference	Reference
	2021	1.1(0.91-1.31)	0.78(0.55-1.11)	0.86(0.41-1.8)
Gender	Men	Reference	Reference	Reference
	Women	0.57(0.48-0.67)*	1.03(0.79-1.34)	1.07(0.6-1.9)
Age		0.99(0.99-1)	0.98(0.97-1)	1.01(0.99-1.03)
Comorbidities	0	Reference	Reference	Reference
	1	1.22(0.99-1.51)	1.56(0.56-4.4)	0.42(0.05-3.85)
	>1	1.05(0.82-1.35)	1.95(0.66-5.74)	1.3(0.23-7.45)
	Unknown	0.9(0.74-1.08)	1.73(0.84-3.53)	4.61(1.61-13.24)

Targeted therapies

		Gastrointestinal tract	Respiratory tract	Breast
Period A		**Targeted therapy**	**Targeted therapy**	**Targeted therapy**
Year	2017-2019	Reference	Reference	Reference
	2020	1.06(0.8-1.4)	1.52(1.2-1.94)*	0.94(0.59-1.5)
Gender	Men	Reference	Reference	Reference
	Women	0.7(0.54-0.89)*	1.35(1.08-1.69)*	
Age		0.96(0.95-0.97)*	0.97(0.96-0.98)*	0.96(0.95-0.97)*
Comorbidities	0	Reference	Reference	Reference
	1	0.95(0.63-1.43)	0.97(0.51-1.87)	1.3(0.2-8.62)
	>1	0.74(0.44-1.27)	0.75(0.36-1.56)	
	Unknown	2.52(1.88-3.36)*	0.45(0.3-0.69)*	0.81(0.26-2.52)
Period B				
Year	2017-2019	Reference	Reference	Reference
	2020	1.2(0.86-1.68)	0.97(0.7-1.35)	1.23(0.66-2.31)
Gender	Men	Reference	Reference	Reference
	Women	0.76(0.56-1.03)	1.01(0.76-1.33)	
Age		0.96(0.95-0.97)*	0.96(0.95-0.98)*	0.98(0.97-1)
Comorbidities	0	Reference	Reference	Reference
	1	0.68(0.39-1.16)	1.38(0.6-3.19)	1.9(0.15-24.15)
	>1	0.47(0.22-1.01)	1.69(0.69-4.14)	
	Unknown	2.23(1.59-3.14)	0.65(0.38-1.13)	1.64(0.38-7.12)
Period C				
Year	2017-2019	Reference	Reference	Reference
	2020	1.11(0.95-1.31)	1.22(1.05-1.41)*	1.19(0.88-1.6)
Gender	Men	Reference	Reference	Reference
	Women	0.78(0.68-0.9)*	1.28(1.12-1.46)*	
Age		0.96(0.95-0.96)*	0.97(0.96-0.98)*	0.97(0.96-0.98)*
Comorbidities	0	Reference	Reference	Reference
	1	0.86(0.67-1.1)	1.32(0.82-2.15)	0.54(0.13-2.19)
	>1	0.74(0.54-1.02)	0.76(0.43-1.34)	0.42(0.05-3.75)
	Unknown	2.99(2.52-3.54)*	0.64(0.46-0.9)*	0.79(0.39-1.6)
Period D				
Year	2017-2019	Reference	Reference	Reference
	2020	1.24(0.95-1.62)	0.91(0.72-1.15)	0.73(0.46-1.18)
Gender	Men	Reference	Reference	Reference
	Women	1.01(0.8-1.29)	1.33(1.09-1.63)*	
Age		0.96(0.95-0.97)*	0.97(0.97-0.98)*	0.97(0.96-0.98)*
Comorbidities	0	Reference	Reference	Reference
	1	0.81(0.54-1.22)	0.75(0.28-2.04)	
	>1	0.42(0.23-0.78)*	0.34(0.09-1.26)	
	Unknown	2.13(1.61-2.82)*	0.8(0.43-1.5)	0.65(0.23-1.86)
Period E				
Year	2017-2019	Reference	Reference	Reference
	2021	1.4(1.18-1.66)*	1.23(1.03-1.46)*	1.24(0.9-1.7)
Gender	Men	Reference	Reference	Reference
	Women	0.89(0.76-1.02)	1.12(0.97-1.31)	
Age		0.96(0.95-0.96)*	0.97(0.96-0.98)*	0.96(0.95-0.97)*
Comorbidities	0	Reference	Reference	Reference
	1	0.67(0.51-0.87)*	0.87(0.57-1.34)	2.43(0.61-9.61)
	>1	0.84(0.62-1.13)	0.95(0.59-1.53)	0.71(0.08-6.56)
	Unknown	2.37(2-2.8)*	0.43(0.33-0.56)*	1.47(0.67-3.21)

Local surgeries

		Other
Period A		**Local surgery**
Year	2017-2019	Reference
	2020	1.12(0.55-2.29)
Gender	Men	Reference
	Women	0.99(0.51-1.95)
Age		1.01(0.99-1.04)
Comorbidities	0	Reference
	1	0.35(0.1-1.19)
	>1	1.45(0.5-4.18)
	Unknown	0.19(0.09-0.41)*
Period B		
Year	2017-2019	Reference
	2020	1.69(0.68-4.17)
Gender	Men	Reference
	Women	0.79(0.33-1.91)
Age		1.01(0.98-1.04)
Comorbidities	0	Reference
	1	0.84(0.26-2.68)
	>1	1.42(0.38-5.32)
	Unknown	0.13(0.05-0.36)*
Period C		
Year	2017-2019	Reference
	2020	1.3(0.79-2.16)
Gender	Men	Reference
	Women	1.01(0.63-1.63)
Age		1.01(0.99-1.02)
Comorbidities	0	Reference
	1	1.12(0.59-2.11)
	>1	0.9(0.39-2.08)
	Unknown	0.17(0.1-0.3)*
Period D		
Year	2017-2019	Reference
	2020	3.33(1.72-6.45)*
Gender	Men	Reference
	Women	0.88(0.44-1.74)
Age		1.01(0.99-1.04)
Comorbidities	0	Reference
	1	1.18(0.48-2.89)
	>1	0.66(0.2-2.14)
	Unknown	0.19(0.08-0.42)*
Period E		
Year	2017-2019	Reference
	2021	0.91(0.52-1.6)
Gender	Men	Reference
	Women	0.67(0.39-1.13)
Age		1(0.98-1.02)
Comorbidities	0	Reference
	1	1.03(0.49-2.16)
	>1	1.36(0.6-3.09)
	Unknown	0.25(0.14-0.45)*

Appendix C

Average days until treatment for chemotherapy

Average days until initial treatment (Chemotherapy)

Y-axis: Average number of days until initial treatment (27 to 35)

X-axis: Period A, Period B, Period C, Period D, Period E

2017-2019 series: 32.37174, 34.00092, 32.22552, 33.83217, 33.08412

2020/2021 series: 31.7017, 29.3893, 30.92784, 33.19841, 31.38625

Legend: 2017-2019, 2020/2021
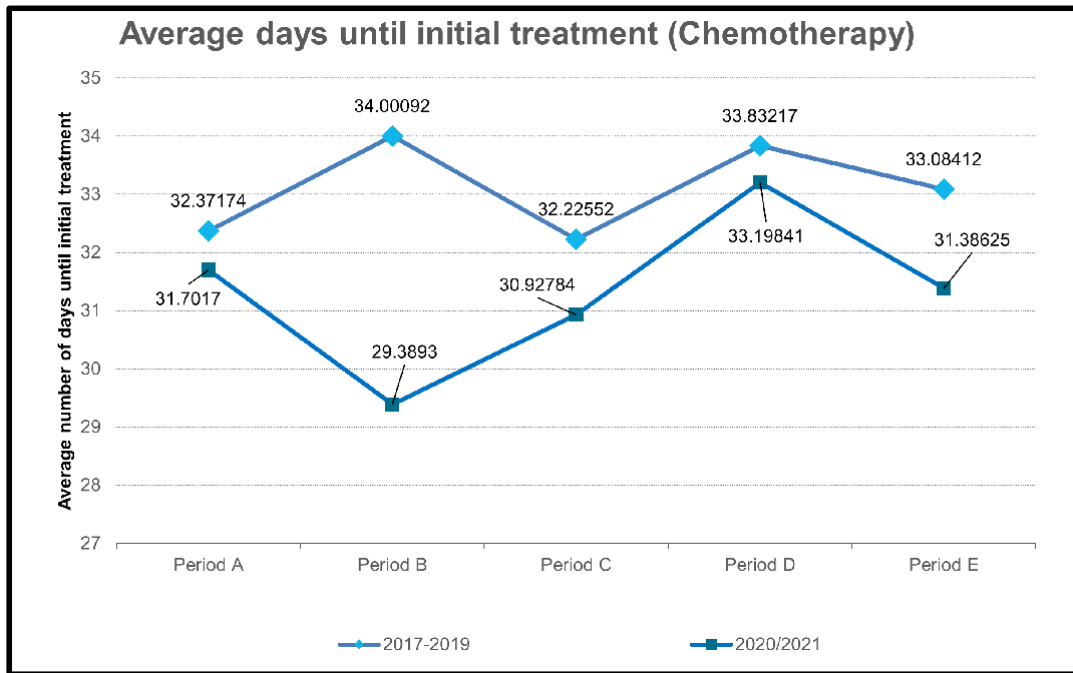
Average days until treatment for surgery

Average days until initial treatment (Surgery)

Y-axis: Average number of days until initial treatment (23 to 37)

X-axis: Period A, Period B, Period C, Period D, Period E

2017-2019 series: 30.6919, 29.98829, 32.17588, 29.93269, 30.38995

2020/2021 series: 30.36095, 26.27692, 31.84967, 31.26573, 35.16041

Legend: 2017-2019, 2020/2021
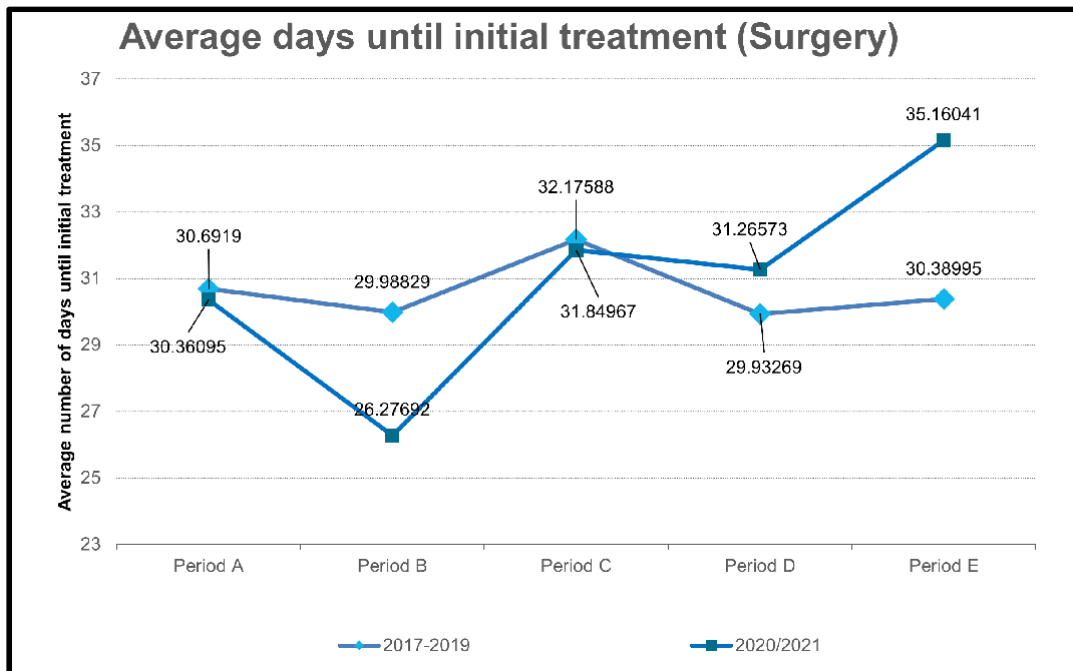
Average days until treatment for hormonal therapy

Average days until initial treatment (Hormonal therapy)
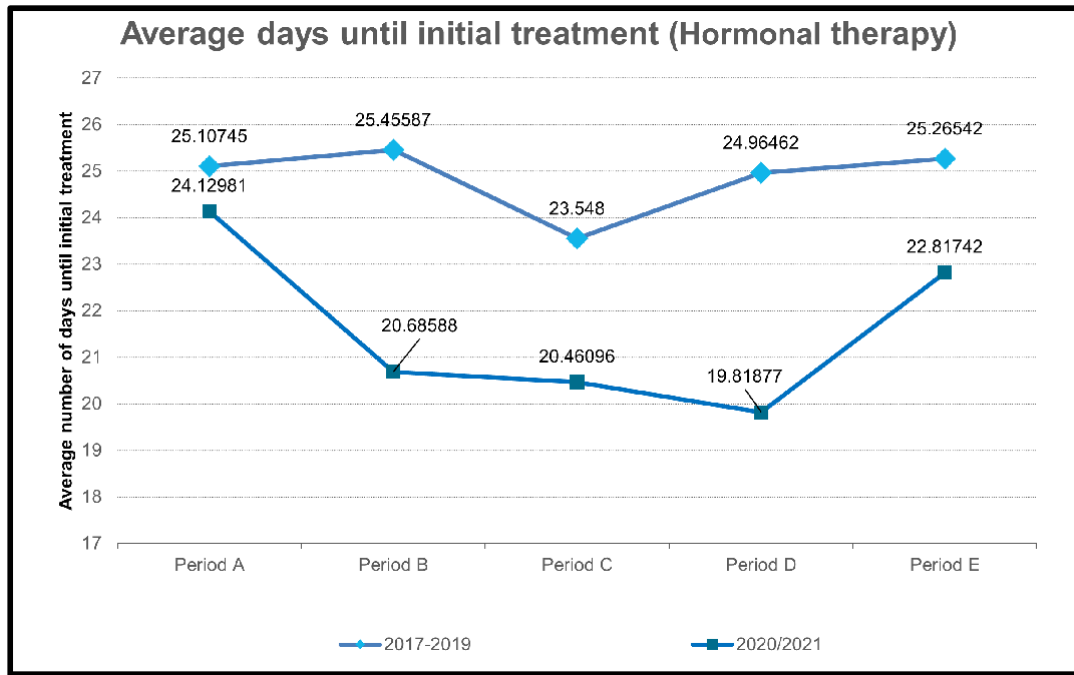
Average days until treatment for radio therapy

Average days until initial treatment (Radio therapy)
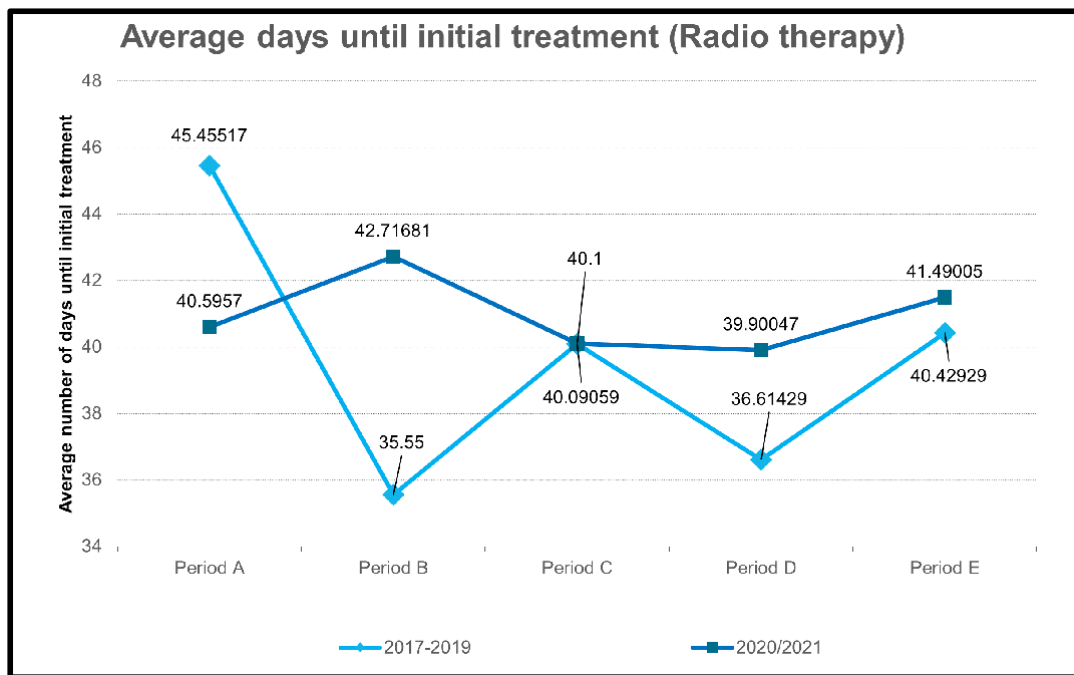
Average days until treatment for targeted therapy

Average days until initial treatment (Targeted therapy)