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Continuity of care for patients with de novo metastatic cancer during the COVID-19 pandemic: A population-based observational study

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Abstract

During the COVID-19 pandemic recommendations were made to adapt cancer care. This population-based study aimed to investigate possible differences between the treatment of patients with metastatic cancer before and during the pandemic by comparing the initial treatments in five COVID-19 periods (weeks 1–12 2020: pre-COVID-19, weeks 12–20 2020: 1st peak, weeks 21–41 2020: recovery, weeks 42–53 2020: 2nd peak, weeks 1–20 2021: prolonged 2nd peak) with reference data from 2017 to 2019. The proportion of patients receiving different treatment modalities (chemotherapy, hormonal therapy, immunotherapy or targeted therapy, radiotherapy primary tumor, resection primary tumor, resection metastases) within 6 weeks of diagnosis and the time between diagnosis and first treatment were compared by period. In total, 74,208 patients were included. Overall, patients were more likely to receive treatments in the COVID-19 periods than in previous years. This mainly holds for hormone therapy, immunotherapy or targeted therapy and resection of metastases. Lower odds were observed for resection of the primary tumor during the recovery period (OR 0.87; 95% CI 0.77–0.99) and for radiotherapy on the primary tumor during the prolonged 2nd peak (OR 0.84; 95% CI 0.72–0.98). The time from diagnosis to the start of first treatment was shorter, mainly during the 1st peak (average 5 days, $p < .001$). These findings show that during the first 1.5 years of the COVID-19 pandemic, there were only minor changes in the initial treatment of metastatic cancer. Remarkably, time from diagnosis to first treatment was shorter. Overall, the results suggest continuity of care for patients with metastatic cancer during the pandemic.

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COVID-19, metastatic cancer, treatment

What's new?

During the COVID-19 pandemic, about one-fifth of cancer patients in the Netherlands experienced changes in treatment, including delays and discontinuation. In this study, data from the Netherlands Cancer Registry was examined to better understand the impact of the COVID-19 pandemic specifically on the treatment of patients with metastatic cancer. Comparison of data before and during the pandemic revealed no delays and only minor changes in metastatic cancer treatment during the pandemic. Moreover, time between diagnosis and treatment initiation shortened during the pandemic, suggesting that regular and timely cancer care was provided despite increased pressure on the country's healthcare system.

1 | INTRODUCTION

The COVID-19 pandemic affected regular healthcare in multiple ways. Patients were advised to visit general practitioners (GP) or hospitals only with urgent complaints. During the first months of the pandemic in the Netherlands, the number of GP consultations for symptoms that could indicate serious health problems, such as cancer, decreased by 20%.[1] Additionally, the pandemic led to a decrease in the number of new cancer diagnoses worldwide, especially in the lower stages.[2–6] In the Netherlands, the number of cancer diagnoses (excluding skin cancers) was around 25% lower than what would have been expected in the first months of the pandemic.[6]

Changes in cancer treatments also occurred during the COVID-19 pandemic. An online survey of more than 5000 Dutch cancer patients showed that 20% of them experienced treatment changes, including adjustments, delay and/or discontinuation of treatments.[7] Based on data from the Netherlands Cancer Registry, treatment changes were shown to be limited and temporary for patients with colorectal cancer, prostate cancer, bladder cancer and head and neck cancers.[8–11] In patients with breast cancer, changes in treatments mainly included changes in the sequence of treatments.[12,13] No delays in initial treatment were found for any of the above mentioned cancers.

Although the aforementioned studies have provided relevant insights into changes in cancer treatments during the pandemic, these studies focused mainly on lower-stage cancers and therefore on curative treatments. However, the pandemic may have had an equal or even greater impact on treatment decisions for patients with metastatic cancer, as the median survival is low (6.3 months in 2018[14]) and treatment is often palliative rather than curative. Therefore, assessing the risks versus benefits of treatment for these patients is often more complex than in the curative setting. This may have been particularly difficult during the pandemic, with infection risk and limited resources further complicating the treatment decision making process.

Some studies have reported specifically on the treatment of metastatic cancer during the COVID-19 pandemic. The results of a survey study among Italian oncologists showed that they were more likely to prescribe mono-chemotherapy and oral anti-cancer drugs for metastatic breast cancer.[15] A US study found no delays and no difference in treatment selection for patients with de novo metastatic cancer.[16] A Dutch study that focused on the treatment of advanced melanoma showed postponement of systemic therapy and a longer time from diagnosis to start of first treatment during the first months of the pandemic.[17] However, studies conducted on the treatment of metastatic cancer during the pandemic are mainly survey studies or individual clinic-based studies, and population-based insights are lacking. Therefore, the aim of this observational study was to provide insight into the initial treatment of patients with de novo metastatic cancer before and during the COVID-19 pandemic on a nationwide scale.

2 | METHODS

2.1 | Data collection

Data were selected from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and contains data on characteristics and treatment of all histopathologically confirmed, newly diagnosed malignancies. Data on patient and tumor characteristics (age, sex, comorbidities, date of diagnosis and primary tumor type) and date and type of initial treatments were used.

2.2 | Patients and definitions

All patients ≥18 years and diagnosed with de novo metastatic cancer (metastatic cancer at primary cancer diagnosis) between January 2017 and May 2021 were included in this study.

The number of comorbidities was defined as the number of categories according to the Charlson Comorbidity Index[18] and was grouped into 0, 1, >1 or unknown.

Primary tumor location was grouped into respiratory tract, breast, gastrointestinal tract, female reproductive organs, male reproductive organs, urinary tract or other.

Week 1 of 2020 to week 20 of 2021 was considered the total COVID-19 period in this study. This period was divided into five different periods based on the number of COVID-19 hospitalizations and the severity of restrictive measures: Period A, weeks 1–11 of 2020 (pre-COVID-19 period); Period B, weeks 12–20 of 2020 (1st COVID-19 peak and national lockdown); Period C, weeks 21–41 of 2020 (recovery period); Period D, weeks 42–53 of 2020 (2nd COVID-19 peak and national lockdown); and Period E, weeks 1–20 of 2021 (prolonged 2nd COVID-19 peak and extended national lockdown) (Figure 1).[19] The corresponding periods in 2017–2019 were used as a reference. Patients were categorized into a period based on their date of diagnosis.

Initial treatments were defined as the treatments received within 6 weeks of the diagnosis of de novo metastatic cancer. This interval was based on Dutch standards for oncological care, which state that treatment should start within 6 weeks of the first outpatient visit.[20] Treatment modalities were grouped into surgical resection of the primary tumor, surgical resection of a metastasis, radiotherapy of the primary tumor, chemotherapy, hormone therapy and immunotherapy/targeted therapy. Time to first treatment was defined as the average number of days between the diagnosis of de novo metastatic cancer and the start of the first treatment.

2.3 | Statistical analysis

Patient and tumor characteristics, as well as the proportion of patients receiving a treatment modality within 6 weeks of their diagnosis, were compared between patients diagnosed in the COVID-19 periods (period A to E of 2020/2021) and patients diagnosed in the corresponding reference periods (2017–2019) using chi-squared tests. Logistic regression analyses were performed to determine the odds of receiving a treatment modality in the COVID-19 periods compared to the reference periods, adjusted for age, sex and primary tumor location. Additionally, the logistic regression analyses were stratified by tumor type. A treatment modality was included in these stratified analyses when the number of patients receiving it was large enough (at least the tenfold of the number of independent variables included in the regression analysis). This was assessed for each period independently. The average number of days between diagnosis and the start of the first treatment, irrespective of type of treatment and stratified by type of first treatment, was compared between the COVID-19 periods and the corresponding reference periods using Mann–Whitney *U* tests. Statistical analyses were performed using Stata version 17.0 software (StataCorp LLC, College Station, Texas, USA). A two-tailed *p*-value <.05 was considered statistically significant.

3 | RESULTS

In total, 23.391 patients diagnosed in the COVID-19 period and 50.817 patients diagnosed in the reference period were included. Age at diagnosis was comparable between patients diagnosed in the COVID-19 periods and the corresponding reference periods in 2017–2019 (Table 1). During the recovery period (period C), the proportion of female patients was slightly higher compared to previous years (43% in 2020 vs. 41% in 2017–2019, $p = .03$). The distribution of the primary tumor location was slightly different compared to previous years in some COVID-19 periods, especially in the prolonged 2nd peak in 2021 (period E). During this period, fewer patients had a primary tumor located in the gastrointestinal tract (33% in 2021 vs. 37% in 2017–2019, $p = .01$). Additionally, patients diagnosed during the prolonged 2nd peak had significantly fewer comorbidities compared to previous years.

3.1 | Initial treatments

Some differences in initial treatment modalities for patients with de novo metastatic cancer were observed between the COVID-19 periods and the preceding years, most notably a higher proportion of patients receiving hormone therapy and surgical resection of metastases (Figure 2). The proportion of patients receiving immunotherapy or targeted therapy was higher in all COVID-19 periods as well as in the pre-COVID period. In the pre-COVID period, fewer patients received chemotherapy (25.2% vs. 27.0%, $p = .04$).

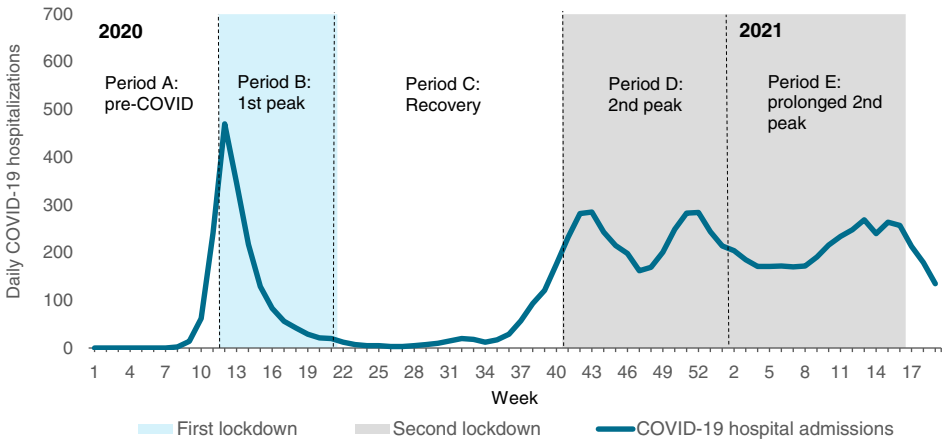

FIGURE 1 COVID-19 periods based on the number of COVID-19 hospitalizations and severity of restrictive measures.

TABLE 1 Patient and tumor characteristics of patients diagnosed with de novo metastatic cancer by period of diagnosis.

	Period A (weeks 1–11) Pre-COVID			Period B (weeks 12–20) 1st peak			Period C (weeks 21–41) Recovery			Period D (weeks 42–53) 2nd peak			Period E (weeks 1–20) Prolonged 2nd peak		
	2017–2019	2020	*p*-value	2017–2019	2020	*p*-value	2017–2019	2020	*p*-value	2017–2019	2020	*p*-value	2017–2019	2021	*p*-value
Number of patients	10,733	3710		8709	2573		20,574	7277		10,761	3920		19,482	5911	
Age (mean, SD)	69	70		70	70		70	71		70	71		70	70	
Gender			.45			.54			.03*			.73			.49
Male	6326 (59)	2152 (58)		5139 (59)	1501 (58)		12,068 (59)	4162 (57)		6274 (58)	2273 (58)		11,465 (59)	3449 (58)	
Female	4447 (41)	1558 (42)		3570 (41)	1072 (42)		8506 (41)	3115 (43)		4487 (42)	1647 (42)		8017 (41)	2462 (42)	
Comorbidities			.48			.19			.04			.75			<.001*
0	1729 (49)	587 (47)		1367 (48)	482 (51)		3081 (48)	1240 (50)		1565 (48)	653 (49)		3096 (48)	1050 (54)	
1	1159 (33)	429 (34)		929 (33)	280 (30)		2083 (33)	735 (30)		1077 (33)	425 (32)		2088 (33)	564 (29)	
>1	662 (19)	240 (19)		543 (19)	183 (19)		1188 (19)	481 (20)		635 (19)	261 (19)		1205 (19)	338 (17)	
Unknown	7223	2454		5870	1628		14,222	4821		7484	2581		13,093	3959	
Original tumor			.85			.01*			.11			.07			.01*
Gastrointestinal tract	3757 (35)	1267 (34)		3053 (35)	929 (36)		7034 (34)	2412 (33)		3603 (34)	1303 (33)		6783 (37)	1962 (33)	
Respiratory tract	3953 (37)	1342 (36)		3221 (37)	906 (35)		7755 (38)	2719 (37)		3938 (37)	1420 (36)		7174 (37)	2133 (36)	
Breast	534 (5)	198 (5)		439 (5)	115 (5)		963 (5)	361 (5)		505 (5)	203 (5)		973 (5)	349 (6)	
Female genital	348 (3)	120 (3)		278 (3)	105 (4)		671 (3)	278 (4)		357 (3)	165 (4)		626 (3)	201 (3)	
Male genital	1348 (13)	489 (13)		1123 (13)	298 (12)		2609 (13)	977 (13)		1486 (14)	549 (14)		2471 (13)	805 (14)	
Urinary tract	560 (5)	194 (5)		429 (5)	153 (6)		1078 (5)	367 (5)		604 (6)	190 (5)		989 (5)	301 (5)	
Other	273 (3)	100 (3)		193 (2)	67 (3)		464 (2)	163 (2)		268 (3)	90 (2)		466 (2)	160 (3)	

*Indicates a significant difference ($p < .05$).

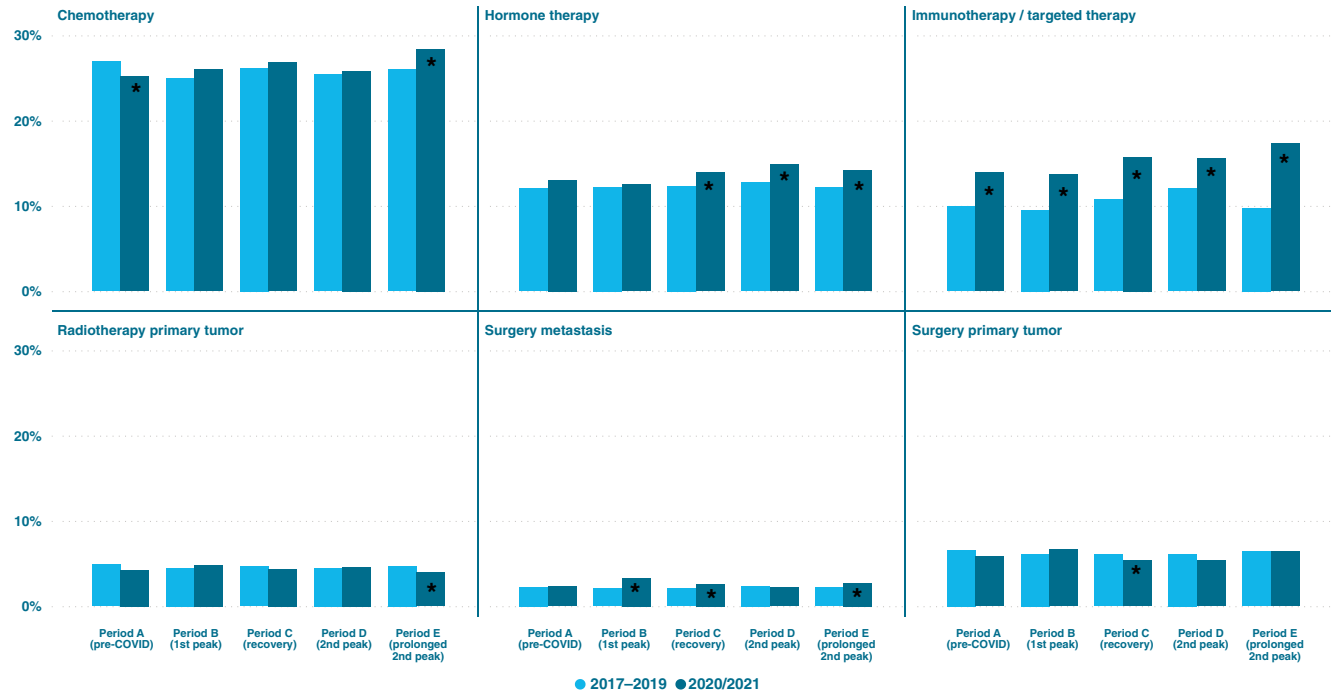

FIGURE 2 Proportion of all patients diagnosed with de novo metastatic cancer that received a certain treatment within 6 weeks of their diagnosis during the COVID-19 pandemic compared to the years 2017–2019. * Indicates a significant difference ($p < .05$).

During the recovery period (period C) fewer patients received a surgical resection of the primary tumor (5.3% vs. 6.1%, $p = .03$) and during the prolonged 2nd peak in 2021 (period E) fewer patients received radiotherapy of the primary tumor (3.9% vs. 4.7%, $p = .01$), but all differences were small.

The average time from diagnosis to the start of the first treatment was significantly shorter during the 1st peak (period B) and the recovery period (period C) compared to the years 2017–2019 (Figure 3). During the 1st peak patients started treatment on average 26 days after diagnosis, compared to 31 days in the previous years (5 days sooner, $p < .001$). The differences in the time from diagnosis to first treatment were similar for the different treatment modalities (Figures S1–S6).

3.2 | Multivariable association between the COVID-19 periods and treatments received

Overall, patients with de novo metastatic cancer were more likely to receive treatments in the COVID-19 periods compared with the reference periods (Table 2). This was particularly true for hormonal therapy, immunotherapy or targeted therapy, and surgical resection of metastases. These higher odds were mainly observed in patients with metastatic cancer of the male reproductive organs (hormonal therapy) and respiratory tract (immunotherapy/targeted therapy and surgical resection of metastases) (Table S1). The odds of receiving chemotherapy as initial treatment were higher during the prolonged 2nd peak (period E) (OR 1.12; 95% CI 1.05–1.20).

However, lower odds of receiving treatments were also observed. Surgery of the primary tumor was less likely during the recovery period (period C) (OR 0.87; 95% CI 0.77–0.99), especially for patients diagnosed with primary tumors in the breast (OR 0.24; 95% CI 0.08–0.68) or gastrointestinal tract (OR 0.82; 95% CI 0.69–0.98) (Table S1). Radiotherapy of the primary tumor as initial treatment was less likely during the prolonged 2nd peak in 2021 (period E) (OR 0.84; 95% CI 0.72–0.98), mainly for patients diagnosed with primary tumors in the respiratory tract (OR 0.59; 95% CI 0.43–0.79).

4 | DISCUSSION

This population-based observational study showed that the initial treatments of patients diagnosed with de novo metastatic cancer during the COVID-19 pandemic did not substantially differ from previous years. Overall, minor shifts toward an increase in treatments were observed. Exceptions are a lower proportion of patients receiving surgical resection or radiotherapy of the primary tumor during the recovery period and in the first months of 2021, respectively. The time from diagnosis to first treatment was significantly shorter during the 1st peak and the recovery period of the pandemic compared with previous years.

The results of this study suggest that the treatment of patients diagnosed with de novo metastatic during the COVID-19 pandemic has not been compromised. Most of the observed changes indicate an increase in treatments. This most likely reflects the overall trend in which the availability of treatment options for metastatic cancer has

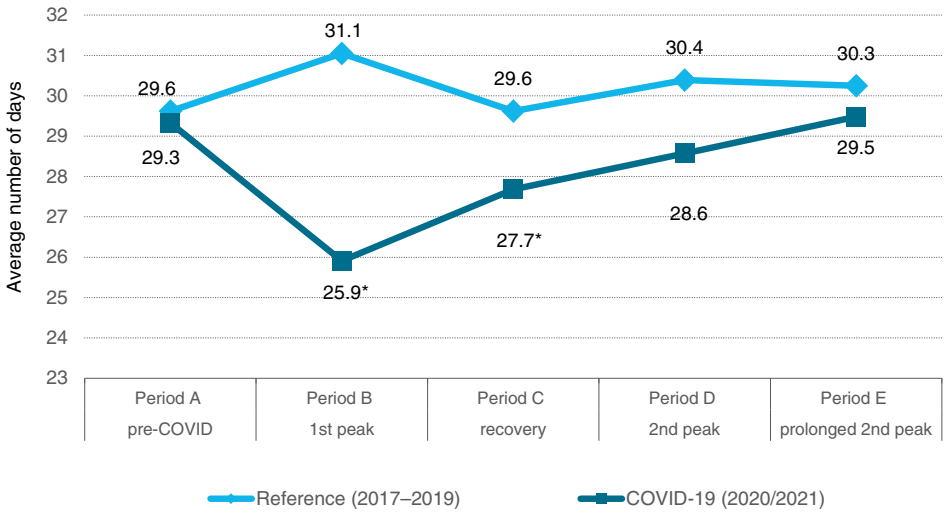

FIGURE 3 Average number of days between diagnosis of de novo metastatic cancer and start of first treatment. * Indicates a significant difference ($p < .05$).

TABLE 2 Adjusted[a] odds ratios of receiving a certain treatment within 6 weeks of diagnosis during the COVID-19 periods (2020/2021) compared to the reference periods in 2017–2019.

Treatment	Period A (pre-COVID)	Period B (1st peak)	Period C (recovery)	Period D (2nd peak)	Period E (prolonged 2nd peak)
Chemotherapy	0.93 (0.85–1.02)	1.04 (0.93–1.16)	1.04 (0.98–1.11)	1.02 (0.93–1.11)	1.12 (1.05–1.20)*
Hormonal therapy	1.07 (0.88–1.31)	1.64 (1.27–2.11)*	1.28 (1.11–1.48)*	1.54 (1.27–1.88)*	1.26 (1.08–1.46)*
Immunotherapy/targeted therapy	1.54 (1.37–1.73)*	1.54 (1.34–1.78)*	1.64 (1.52–1.78)*	1.44 (1.29–1.60)*	2.02 (1.86–2.21)*
Radiotherapy primary tumor	0.88 (0.73–1.06)	1.05 (0.85–1.30)	0.96 (0.84–1.09)	1.03 (0.86–1.23)	0.84 (0.72–0.98)*
Surgery metastasis	1.05 (0.82–1.36)	1.55 (1.19–2.02)*	1.31 (1.10–1.56)*	0.98 (0.76–1.26)	1.25 (1.04–1.51)*
Surgery primary tumor	0.88 (0.75–1.04)	0.98 (0.81–1.19)	0.87 (0.77–0.99)*	0.91 (0.77–1.08)	1.01 (089–1.14)

[a]Odds ratios were adjusted for age, sex and primary tumor location.
*Indicates a significant difference ($p < .05$).

increased over the years, including new hormonal therapies, immunotherapies, and targeted therapies, and new indications for these therapies, as well as improved techniques for surgical resection of metastases.[21–26] Future data should reveal what the post-pandemic trends will be in the proportions of patients receiving the different treatment modalities as initial treatment for metastatic cancer. Furthermore, this study showed no delays in the start of treatment for patients with de novo metastatic cancer. In fact, patients were treated earlier during the COVID-19 pandemic than in the years before the pandemic. This is in line with findings from previous studies in non-metastatic cancers.[8–11,13] A possible explanation may be that, due to downscaling of other elective procedures, more capacity was available for oncology patients. In addition, during the pandemic, more capacity may have been available for more urgent cases, such as metastatic cancers, because treatment of patients with lower-stage cancers may have been postponed and because for some cancer sites the incidence of lower stage tumors declined due to halt of the screening programs.[27,28] Faster treatment initiation during the pandemic may also have been related to a sense of urgency to start treatment before the pandemic situation would worsen. A potential downside of this urgency to start treatment is that there may have been less time to reflect on whether the treatments were in line with patients' wishes, values and needs.

The results of this study indicate that COVID-19 infection and mortality in (elderly) patients with metastatic cancer did not affect treatment, as might have been expected. Since no delay in treatment was observed in our patient group, it is not expected that COVID-19 infections in patients with metastatic cancer significantly affected the time to treatment initiation. Furthermore, analyses stratified by age category (<75 and 75+) showed similar trends in the proportion of patients receiving the different treatment modalities before and during the pandemic, suggesting that excess mortality due to COVID-19 in (elderly) patients did not affect the number of patients eligible to start treatment.

Overall, this study showed limited changes in the initial treatments of patients with de novo metastatic cancer, indicating continuity of care for these patients during the pandemic period. This is likely related to the priority that was given to oncology and to the fact that oncologists have largely been able to continue working within their own specialty, as opposed to other specialties that were scaled down and deployed in COVID-19 departments. However, it is important to note that this study only focused on tumor-directed treatments.

Given that most patients diagnosed with metastatic cancer have an incurable disease, providing palliative and supportive care services that aim to improve or maintain quality of life is an equally important part of the treatment of these patients. Therefore, an understanding of the extent to which palliative and supportive care could be adequately provided to patients with metastatic cancer during the pandemic is necessary to more comprehensively assess the continuity and quality of care for these patients during the COVID-19 pandemic. Findings from interviews with Dutch healthcare providers suggest that the COVID-19 pandemic negatively affected certain aspects of palliative care delivery, mainly in the emotional, spiritual and social domains.[29] However, evidence also suggests that the pandemic may be beneficial to palliative care, by raising awareness of the importance of advance care planning and focusing on individual patient needs and preferences.[29–32]

4.1 | Strengths and limitations

This study is the first to investigate the treatment of patients with de novo metastatic cancer during the COVID-19 pandemic in the Netherlands on a nationwide scale by using high-quality data from the population-based cancer registry, thus reflecting daily practice. Besides this, a long time period was studied, thereby being able to report on treatment during different periods of pandemic intensity. Nevertheless, some limitations need to be addressed. First, data on comorbidities and performance status are not complete in the NCR, while these are important variables to better understand treatment decisions. Therefore, it was not possible to account for these variables in the analyses, thus raising the possibility of residual confounding. Second, in an attempt to minimize overfitting, only those treatments with sufficient observations were included in the stratified regression analyses. However, some treatment numbers were still relatively small when stratified by primary tumor location, thereby limiting the ability to draw strong conclusions.

5 | CONCLUSION

Only minor changes in the initial treatments of patients with de novo metastatic cancer were observed during the COVID-19 pandemic, mainly consisting of increases in treatments compared to the years 2017–2019. Most of the changes appear to reflect adjustments in the treatment of metastatic cancer over the years, showing an increase in the total number of treatments, regardless of the pandemic. No delay in the start of treatment was observed. In fact, the time to first treatment was shorter during the pandemic. Overall, the findings of this study indicate continuity of care for patients with de novo metastatic cancer during the COVID-19 pandemic. Further studies could examine the provision of palliative and supportive care to more comprehensively assess the continuity and quality of care for patients with metastatic cancer during the pandemic.

AUTHOR CONTRIBUTIONS

Ellis Slotman: Conceptualization, data curation, formal analysis, methodology, project administration, visualization, writing—original draft. **Feike Weijzen**: Conceptualization, formal analysis, methodology, visualization, writing—original draft. **Heidi P. Fransen**: Conceptualization, supervision, writing—review & editing. **Jolanda C. van Hoeve**: Conceptualization, supervision. **Auke M. T. Huijben**: Writing—review & editing. **Evelien J. M. Kuip**: Writing—review & editing. **Agnes Jager**: Writing—review & editing. **Peter W. A. Kunst**: Writing—review & editing. **Hanneke W. M. van Laarhoven**: Writing—review & editing. **Jolien Tol**: Writing—review & editing. **Vivianne C. G. Tjan-Heijnen**: Writing—review & editing. **Natasja J. H. Raijmakers**: Supervision, writing—review & editing. **Yvette M. van der Linden**: Writing—review & editing. **Sabine Siesling**: Conceptualization, Funding acquisition, Supervision, writing—review & editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Jolanda C. van Hoeve: Potential financial conflict of interest: ZonMw grant, projectnumber: 10430022010014. **Hanneke W. M. van Laarhoven**: Consultant or advisory role: Amphera, Anocca, Astellas, AstraZeneca, Beigene, Boehringer, Daiichy-Sankyo, Dragonfly, MSD, Myeloid, Servier; Research funding, medication supply, and/or other research support: Auristone, Incyte, Merck, ORCA, Servier; Speaker role: Astellas, Beigene, Benecke, BMS, Daiichy-Sankyo, JAAP, Medtalks, Novartis, Springer, Travel Congress Management B.V. All paid to the institution. **Vivianne C. G. Tjan-Heijnen**: Study grants to the hospital from Novartis, Pfizer, AstraZeneca, Gilead, Daiichi Sankyo, E Lilly, MSD; Advisory board: E Lilly, Novartis.

DATA AVAILABILITY STATEMENT

The data used in this study are available upon reasonable request from the Netherlands Cancer Registry (https://iknl.nl/en/ncr/apply-for-data). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This study was approved by the privacy review board of the Netherlands Cancer Registry (reference number K.22.057).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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