

Impact of the COVID-19 epidemic on cancer burden and cancer care in Slovenia: a follow-up study

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Background. In Slovenia, cancer care services were exempt from government decrees for COVID-19 containment. Nevertheless, cancer control can be impacted also by access to other health services and changes in health-seeking behaviour. In this follow up study, we explored changes in cancer burden and cancer care beyond the first months after the onset of the COVID-19 epidemic.

Materials and methods. We analysed routinely collected data for the period January 2019 through July 2022 from three sources: (1) pathohistological and clinical practice cancer notifications from two major cancer centres in Ljubljana and Maribor (source: Slovenian Cancer Registry); (2) referrals issued for oncological services (source: e-referral system); and (3) outpatient appointments and diagnostic imaging performed (source: administrative data of the Institute of Oncology Ljubljana – IOL). Additionally, changes in certain clinical and demographic characteristics in patients diagnosed and treated during the epidemic were analysed using the Hospital-Based Cancer Registry of the IOL (period 2015–2021).

Results. After a drop in referrals to follow-up cancer appointments in April 2020, in June-August 2020, there was an increase in referrals, but it did not make-up for the drop in the first wave; the numbers in 2021 and 2022 were even lower than 2020. Referrals to first cancer care appointments and genetic testing and counselling increased in 2021 compared to 2019 and in 2022 increased further by more than a quarter. First and follow-up outpatient appointments and cancer diagnostic imaging at the IOL dropped after the onset of the epidemic in March 2020 but were as high as expected according to 2019 baseline already in 2021. Some deficits remain for follow-up outpatients' appointments in surgical and radiotherapy departments. There were more CT, MRI and PET scans performed during the COVID-19 period than before. New cancer diagnoses dropped in all observed years 2020, 2021 and until July 2022 by 6%, 3% and 8%, respectively, varying substantially by cancer type. The largest drop was seen in the 50–64 age group (almost 14% in 2020 and 16% in 2021), while for patients older than 80 years, the numbers were above expected according to the 2015–2019 average (4% in 2020, 8% in 2021).

Conclusions. Our results show a varying effect of COVID-19 epidemic in Slovenia for different types of cancers and at different stages on the patient care pathway – it is probably a mixture of changes in health-seeking behaviour and systemic changes due to modifications in healthcare organisation on account of COVID-19. A general drop in new cancer cases reflects disruptions in the pre-diagnostic phase and could have profound long-term consequences on cancer burden indicators.

Key words: cancer; COVID-19; delay in diagnosis; referral

Introduction

The COVID-19 pandemic and the non-pharmacological measures adopted by governments for containment of its spread have substantially influenced the provision and use of health care system services for health problems unrelated to COVID-19 in different countries.¹⁻⁵ Although healthcare services for serious conditions, such as cancer, were mostly exempt from restriction measures, nevertheless, they were affected by the COVID-19 pandemic.⁶⁻¹⁶

As previously reported for Slovenia¹⁷, a middle European country with a universal health care system, in the first wave of COVID-19 containment measures (from March 2020 until May 2020) there was a decrease of over 30% in the number of new cancer diagnoses, 30% in referrals to cancer care (33% for first appointments, 46% for follow-up appointments and 85% for genetic testing and counselling), 20% in the number of outpatients appointments at the Institute of Oncology Ljubljana (IOL) and 40% in the number of diagnostic imaging performed, despite the fact that provision of oncology services was included among exemptions to healthcare-related restriction measures and was thus not directly scaled-down.

An overview of the COVID-19 epidemic in Slovenia

The first wave of the COVID-19 epidemic in Slovenia, starting in March 2020, has been previously described in detail.¹⁷ After the declaration of the epidemic on 12th March 2020, strict control measures were implemented. All non-essential ambulatory visits, elective surgery appointments and even preventive care activities, including all three national screening programmes (for cervical, breast and colorectal cancer), were temporarily stopped. On 9th May, all restrictions concerning the provision of healthcare services were lifted and on 31st May 2020, the end of the epidemic was declared. Throughout the whole period, oncological healthcare was exempt from these mandates. The cancer screening programmes began operating normally in June 2020. They provided extra services during the summer months of 2020 and by the end of 2020 eliminated the deficits in services caused by their mandatory suspension.¹⁸ In the following epidemic waves, the cancer screening programmes were not stopped again.

Following a rise in cases, on 19th October 2020 the epidemic was declared for a second time and

restriction measures were re-introduced. In addition to various measures concerning movement of people and public gatherings, all non-emergency health services with the exception of oncology services were once again suspended, strict triage measures were introduced at the primary health care level, COVID-19 hospitals/departments were set-up and staff were temporarily reallocated. The highest number of COVID-19 cases needing hospital treatment was between November 2020 and February 2021. By the end of year 2020, Slovenia introduced rapid antigen testing and commenced vaccinations in December 2020. Vaccination uptake was at first limited to priority groups such as the elderly and healthcare workers and was thus relatively slow. After April 2021, it started improving and has reached around 60% by the end of 2021 but has plateaued since.¹⁹ Cases among healthcare staff were highest during observed peaks^{20,21}, increasing the COVID-19 strain on healthcare through staff shortages^{22,23} and limiting provision of services. Furthermore, by the end of 2020 pandemic fatigue had already started to appear among Slovenian residents.^{24,25} In January and April 2021, new surges of COVID-19 cases appeared, while afterwards cases started to decrease. The 15th June 2021 was the last day of the epidemic being officially declared, though most of the restrictive measures and process adaptations concerning the health care system remained.^{20,21}

On 15th September 2021, due to the growing number of infections with the Delta variant of the novel coronavirus 2 (SARS-CoV-2), the recovered/vaccinated/tested (RVT) rule was implemented for most services. Emergency visits were exceptions. Alongside the RVT implementation, demand for vaccination among the general population grew. The Delta wave caused a new surge in COVID-19 hospitalizations and admissions to intensive care units (most notably during November and December 2021 and between September and November 2021, Slovenia had one of the highest rates among EU countries with a large number of excess deaths²⁶). Healthcare shortages were also very pronounced. During the Omicron wave in January and February 2022 the largest number of COVID-19 confirmed cases were recorded. However, proportionally less infected people needed hospital or intensive care treatment. Since 18th February 2022, COVID-19 in Slovenia is no longer considered a quarantine disease, meaning close contacts are no longer required by law to self-isolate. From this point on, COVID-19 cases decreased until the beginning of June 2022.

From February 2022, restrictions imposed due to COVID-19 began to be lifted, with the final regulation annulling all COVID-19 restrictions, including limitations imposed on access and provision of health care services, implemented on 30th May 2022.^{21,27,28}

Monitoring of cancer burden and cancer care in Slovenia

Cancer is a non-communicable chronic disease and rapid changes in incidence are not expected in normal circumstances. On rare occasions we have an opportunity to observe rapid changes in cancer burden indicators during crisis situations, for example due to catastrophes resulting in an increased exposure to certain cancer risk factors or major and/or prolonged disruptions of a country's health system, such as occur during wars or widespread epidemics.²⁹

Population-based cancer registries, such as the Slovenian Cancer Registry (SCR), are public health entities that are established on a national or regional level for continuous systematic collection of data on the occurrence, characteristics, and outcome of reportable cancers, and are thus able to record such events.³⁰ Even though many registries across the world reported disruptions in cancer registration during COVID-19^{4,5}, in Slovenia active registration was uninterrupted and allowed for up-to date national trend estimates.³¹ The Hospital-Based Cancer Registry of the IOL collects data on all new first-time patients seen at the IOL for cancer diagnostics and treatment. These data are the source of valuable information for medical work and research at the IOL; at the same time, the data are promptly forwarded also to the population-based SCR, thus upgrading the central database. Cancer treatment in Slovenia is highly centralised. The IOL provides more than 80% of all systemic treatments, over 60% of all cancer surgeries and almost all radiotherapy treatments in Slovenia. The University Medical Centre (UMC) Maribor is Slovenia's second oncological centre. Both provide up-to-date information to the SCR on newly diagnosed cancer patients through an online-based registration process.³¹ The IOL provided care almost exclusively for cancer patients, establishing its first department for COVID-19 patients as late as the first half of 2022, whereas UMC Maribor had been a COVID-19 hospital during the whole time, but its oncology department was running normally, if we disregard disruptions caused by staff shortages at both centres.

Slovenia has a gate-keeping system in place, where specialised health care is only possible with referrals from general practitioners. Thus, the number of referrals is an accurate reflection of demand for specialist cancer care. The e-referral system was introduced in 2017 and is maintained by the National Institute of Public Health (NIPH).³²

Shortly after the start of the COVID-19 pandemic, we carried out a preliminary analysis of its impact on cancer diagnosis and care in Slovenia¹⁷ using the preliminary data from the SCR and other available health databases. After receiving widespread interest following publication of the preliminary results, to provide healthcare experts, policy-makers and the general public with up-to date continuous monitoring of the effect of COVID-19 epidemic on oncology services and cancer burden, in 2021 we set up a web page named onKOvid (available at <http://www.slora.si/en/onkovid>) where up-to-date indicators on cancer burden and management are available to the professional and lay public.³³

Aim of the study

In order to provide an update on the situation and expand the scope of the preliminary study of the COVID-19 epidemic impact on cancer burden in Slovenia during the first 2020 wave, we aimed to analyse the impact of the COVID-19 epidemic on cancer diagnosis and management in Slovenia in over two years since the onset of the epidemic in more detail. Primarily, we focused on fluctuations in cancer diagnoses from the two main cancer centres during this period, while also examining whether there were declines in demand for specialized oncological care at the national level. Furthermore, we provide an overview of certain diagnostic and treatment procedures carried out at the IOL during the epidemic.

Materials and methods

Our study was based on routinely collected data for the period March 2020 – July 2022. For the analysis of the impact of COVID-19 epidemic on cancer burden and care indicators in Slovenia, four routine data sources were used:

The SCR data on new cancer diagnoses collected via active registration (direct access to electronic patient files) from the two major cancer centres in Ljubljana and Maribor for the evaluation of possible delays in cancer diagnoses.

The Hospital-Based Cancer Registry of the IOL for the evaluation of changes in the distribution of prognostic factors in patients diagnosed and treated during the epidemic.

The national e-referral system for the evaluation of changes in demand for specialized cancer care.

The administrative hospital data of the IOL for analysing the level of realization of services during the epidemic.

From the SCR, we extracted the most up-to-date data on online cancer notifications for the two major oncological centres in Slovenia, the IOL and the UMC Maribor. Active notifications from other hospitals were not available yet in 2019, the start of the study period, therefore we were unable to include them. Notifications were extensively computer processed to extract only one (most relevant) cancer diagnosis per person and as such serve as a good approximation to cancer incidence, i.e. the number of new cases diagnosed in these two hospitals. The analyses were carried out for all new cancer diagnoses and for selected cancer types: colorectal cancer (ICD-10 codes C18–C20), breast (C50), lung (C33–C34), prostate (C61), skin, non-melanoma (C44), skin melanoma (C43) and lymphoma (C81–C85).

For patients seen for the first time at the IOL for diagnostics and/or treatment of a particular disease up to the end of 2021, in addition to the location of cancer, data was available also on the stage at diagnosis and the reason for the first outpatient appointment or hospitalisation (hereafter first visit) at the IOL. Thus, for the cohort of patients first seen at the IOL in 2020 and 2021, stratification was possible by gender (males; females), age groups according to the age at first visit to the IOL (20–49; 50–64; 65–79; 80+), stage at diagnosis (local; regional; distant; unknown; not applicable – for haematological cancers) and the reason for the first visit to the IOL (primary cancer diagnostics; primary cancer treatment; diagnostics or treatment for disease relapse; other or unknown).

The data source for the analysis of referrals to cancer care services was the national e-referral system, operated by NIPH. From the NIPH, we retrieved the absolute number of all monthly referrals issued in Slovenia for selected types of cancer care services as coded in the Codebook of Healthcare Services, namely the first cancer appointment, control cancer appointment and oncological genetic testing and counselling.

We also examined the administrative data of the IOL on monthly outpatient visits, stratified according to first and follow-up visits by divisions (medi-

cal oncology, surgery, radiotherapy), and data on cancer diagnostic imaging, namely the monthly number of X-rays, mammograms, ultrasounds, CT, MRI and PET scans performed.

In all the analyses the monthly (or yearly) absolute numbers of new diagnoses, referrals, appointments and imaging tests performed for the epidemic years 2020, 2021 and up-to July 2022 were compared with the expected absolute numbers, where the baseline was the monthly (or yearly) numbers observed in 2019. The exception was the analysis performed for the cohort of patients first seen at the IOL in 2020 and 2021, where the baseline represents the average for the period 2015–2019 and where the data for 2022 were not yet available for the analysis.

We calculated the relative difference, expressed in percent change, between epidemic and pre-epidemic numbers. To evaluate statistically significant differences, we calculated confidence intervals (CI) using Fisher's exact test where observed cases in years 2020 to 2022 were compared to expected cases (2019 data). An alpha level of 0.05 was set for statistical significance. Data management and analysis was performed in R software version 4.1.2 and some additional calculations and graphical presentations in Microsoft Excel 2019.

Results

Cancer incidence

Based on cancer notifications received by the SCR from the two major oncological centres in Slovenia, we can observe a drop in newly diagnosed cancers in all three epidemic years (2020–2022) for most cancer types except lung cancer (Figure 1).

The overall number of notifications for new cancer diagnoses in the years 2020, 2021 and until July 2022 was lower than in 2019, that is 6%, 3% and 8%, respectively, largely varying by cancer type. The most prominent drops in cancer notifications were for prostate (around 20% in all years) and breast cancer (up to 25%), while notifications for lung cancer increased by over 10%.

In general, drops in the monthly number of new cancer diagnoses were more coincidental with imposed restrictions, which were more pronounced at the beginning of the observed period, than with observed surges in COVID-19 cases (Figure 2). The largest drop in new diagnoses was observed in April 2020 (around 30%). The results show, that the second and third wave of COVID-19 (autumn 2020, winter and spring 2021) had a smaller nega-

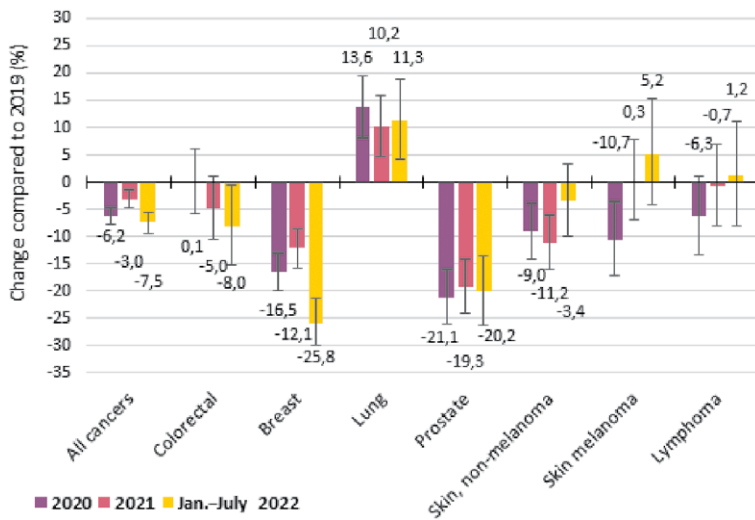


FIGURE 1. Change in the number of newly diagnosed cases of different types of cancers in years 2020, 2021, 2022 compared to the pre-COVID-19 year 2019. Data were collected from the two major cancer centres (Institute of Oncology Ljubljana and University Medical Centre Maribor). For 2022, only data from January to July are included and compared to corresponding months in 2019.



FIGURE 2. Monthly change in the number of newly diagnosed cancer cases (%) in years 2020, 2021 and up-to July 2022 compared to corresponding months in 2019. Data were collected from the two major cancer centres (Institute of Oncology Ljubljana and University Medical Centre Maribor).

tive effect on the number of new cancer diagnoses, around 10%. In the second half of 2021, the number of new cancer diagnoses was roughly the same as in 2019. Looking at the whole period, no compensatory surges in new cancer diagnoses are visible that would make up for the significant drops in the first, second or third wave. At the beginning of 2022 (the Omicron wave), there was another drop in the number of new cancer cases (around 15%) compared to 2019.

Monthly fluctuations in new cancer diagnoses for specific cancer types are available in the supplementary material (Supplementary Figure 1). In the first wave of the epidemic, the largest drop was for prostate cancer (54% in April 2020), non-melanoma skin cancer (45% in March and April 2020), skin melanoma (41% in March 2020), breast cancer (between 37% and 41% in March–June 2020) and lymphoma (33% in May 2020). Most peaks above expected numbers were during summer months.

Characteristics of patients and their disease

There was a 6% decrease in the number of patients first seen at the IOL in 2020 and over 8% in 2021 compared to the average in the 2015–2019 pre-COVID-19 period (Table 1). The decrease was similar in males and females. The largest decrease was seen in the 50–64 age group (almost 14% in 2020 and 16% in 2021), while for patients older than 80 years, the numbers were above expected (4% in 2020, 8% in 2021 (Figure 3).

Compared to the 2015–2019 average, in 2020 we observed 11% less first visits due to diagnostics and treatment of progression and relapse of cancer, while drops in first visits for primary cancer diagnostics (not significant) and primary cancer treatment (6%) were smaller. Regarding drops in first visits by stage of cancer at diagnosis, of those who were first seen at the IOL for primary diagnostic work-up or primary cancer treatment, fewer than expected were diagnosed in regional (9%) and distant (8%) stage (Table 1), whereas the decrease for localized stage was not statistically significant. The situation was somewhat reversed in 2021, when drops were more pronounced for primary cancer diagnostics (14%) and primary cancer treatment (9%) than for diagnostics and treatment of progression or relapse (not significant) and the drops were larger for localized (9%) and regional (16%) stage, while the drop for distant stage (8%) was similar as in 2020.

Demand for and realization of specialist oncological care

In 2020 there was a drop in referrals in Slovenia to first and follow-up cancer appointments as well as to oncological genetic testing and counselling (Table 2). Monthly fluctuations in investigated measures are presented in the supplementary material (Supplementary Figures 2–5). Decreases were first observed during the first wave (March

TABLE 1. Number of cancer patients, who first visited the Institute of Oncology Ljubljana (outpatient appointments and hospitalisations together) for a particular disease in years 2021 and 2022 with percentage change compared to the 2015–2019 average by year of first visit, gender, age group at first visit, reason for the first visit and stage at diagnosis (only for those admitted for primary cancer diagnostics or primary cancer treatment). The 2015–2019 average is accompanied with 95% confidence interval, which the numbers for years 2020 and 2021 are compared to (statistically significant lower/higher number are coloured)

	Average 2015–2019 (95% CI)		N for 2020	Change (%) in 2020 against average (95% CI)	N for 2021	Change (%) in 2021 against average (95% CI)
Total	6635.4	(6458.9 ; 6811.9)	6217	-6.3 (-8.6 ; -3.9)	6064	-8.6 (-10.9 ; -6.3)
Gender						
Males	3334.0	(3219.4 ; 3448.6)	3157	-5.3 (-8.6 ; -1.9)	2978	-10.7 (-13.9 ; -7.4)
Females	3301.4	(3218.9 ; 3383.9)	3060	-7.3 (-10.6 ; -4.0)	3086	-6.5 (-9.8 ; -3.2)
Age group						
20-49	939.6	(911.9 ; 967.3)	935	-0.5 (-6.8 ; 6.1)	901	-4.1 (-10.3 ; 2.4)
50-64	2287.6	(2189.2 ; 2386.0)	1958	-14.4 (-18.2 ; -10.5)	1912	-16.4 (-20.1 ; -12.6)
65-79	2651.6	(2534.0 ; 2769.2)	2546	-4.0 (-7.7 ; -0.2)	2493	-6.0 (-9.6 ; -2.2)
80+	695.4	(676.2 ; 714.6)	721	3.7 (-3.7 ; 11.5)	750	7.9 (0.3 ; 15.9)
Reason for the first visit to Institute of Oncology Ljubljana						
Primary diagnostics	904.4	(858.9 ; 949.9)	884	-2.3 (-8.6 ; 4.4)	777	-14.1 (-20 ; -7.8)
Primary treatment	4791.2	(4664.9 ; 4917.5)	4493	-6.2 (-8.9 ; -3.4)	4358	-9.0 (-11.7 ; -6.3)
Diagnostics or treatment for relapse	874.8	(824.9 ; 924.7)	779	-11.0 (-17.1 ; -4.5)	838	-4.2 (-10.6 ; 2.5)
Other or unknown	65.0	(43.5 ; 86.5)	61	-6.2 (-28.2 ; 20.5)	91	40.0 (12.7 ; 71.9)
Stage at diagnosis (for primary diagnosis and primary treatment only)						
Localized	2029.2	(1956.8 ; 2101.6)	1943	-4.2 (-8.5 ; 0.1)	1843	-9.2 (-13.3 ; -4.9)
Regional	2061.0	(2026.1 ; 2095.9)	1879	-8.8 (-12.9 ; -4.6)	1723	-16.4 (-20.3 ; -12.4)
Distant	1093.4	(1018.3 ; 1168.5)	1010	-7.6 (-13.2 ; -1.8)	1009	-7.7 (-13.3 ; -1.8)
Unknown	41.6	(36.4 ; 46.8)	56	34.6 (1.7 ; 74.8)	92	121.2 (78.3 ; 171.2)
Not applicable	470.4	(430.7 ; 510.1)	489	4.0 (-5.1 ; 13.6)	468	-0.5 (-9.3 ; 8.9)

CI = confidence interval

Red numbers are below and green above the 95% confidence interval for the 2015–2019 average.

and April 2020). In months from June to August 2020, there was an increase in the number of referrals to follow-up cancer appointments, but the increase did not make-up for the drop in the previous months. In 2021, there was a 5.4% increase in the number of referrals to first appointments, while the number of referrals to follow-up appointments was still significantly lower than in 2019 (-14.3%). Demands for first cancer appointments and genetic testing and counselling increased by more than a quarter in 2022 compared to 2019 (27.0%), while referrals to follow-up cancer appointments were even fewer than in 2021 (-28.5%; Table 2).

In general, first and follow-up outpatient appointments and cancer diagnostic imaging per-

formed at the IOL dropped after the onset of the COVID-19 epidemic in March 2020 but had returned to expected levels by 2021, according to the 2019 baseline. Some deficits remain for follow-up outpatients visits in surgical (-2.1%) and radiotherapy departments (-8.1%) (Table 2). There were more CT, MRI and PET scans performed during the COVID-19 period than before (Table 2, Supplementary Figures 2–5).

Discussion

Significant decreases, especially at the beginning of the epidemic, in referrals to first cancer appoint-

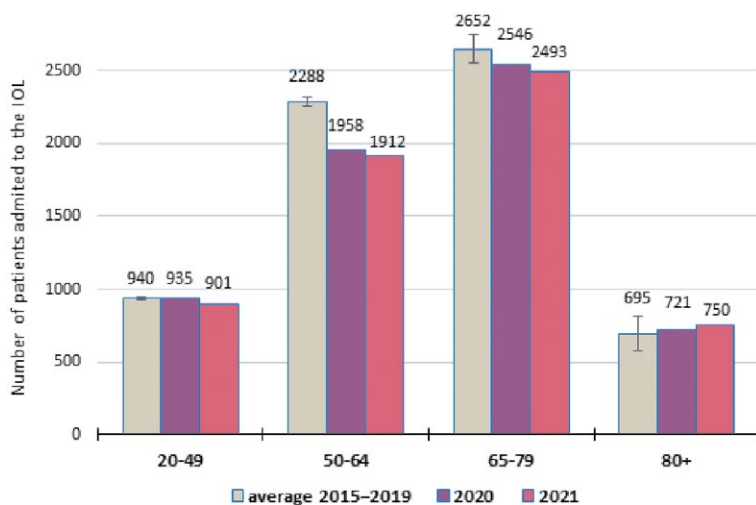


FIGURE 3. Number of cancer patients who first visited the Institute of Oncology Ljubljana (IOL) (outpatient appointments and hospitalisations together) for a particular disease in years 2015–2021 by year of first visit and by age group at first visit with percentage change against 2015–2021 average (an asterisk indicates statistically significant change). For average values for the years 2015–2019, 95% confidence intervals are also presented.

ments, as well as drops in first cancer appointments, X-rays, mammograms and ultrasounds performed at the IOL along with drops in new cancer diagnoses from the two major cancer centres point to a delay in diagnosis and treatment for some cancer patients during the COVID-19 epidemic in Slovenia. Similar findings were reported in many other countries worldwide.^{8,9,12,14} The reasons that led to this decline cannot be assessed in our study but are presumed to be a combination of changes in health-seeking behaviour of patients, day-to-day work of doctors as well as the organization of the health care system and its management during the COVID-19 peaks. Pandemic fatigue also likely played a role in service provision and uptake in 2021 and 2022, especially during summer months when both healthcare staff as well as patients were eager for a return to normal holidaying after a period of travel restrictions. Cancer registries themselves experienced disruptions with their regular operations due to changes in the work modalities for the personnel, as well as difficulties in accessing sources and/or receiving the notifications on cancer registration and cancer care.^{4,5}

We did not incorporate the number of COVID-19 cases into the analyses, since governmental control measures did not always follow changes in the number of COVID-19 cases and, furthermore,

the severity of restrictions was not proportional to the number of cases (for example, in spring 2020 the restrictions were much more severe compared to autumn 2021 despite the fact that the number of cases was 120-times higher).²¹ Monthly fluctuations of analysed data were more in line with the severity of restrictions than the absolute number of COVID-19 cases, the former being the mildest during summer months.²¹

Overall, fewer new cancer cases were reported from the two major centres during COVID-19. It is important to emphasize that the average growth of new cancer cases (crude incidence rate on the population level) was 2% per year before the epidemic in 2010–2019.³¹ Regarding specific cancer types, there was a drop in the number of newly diagnosed cancers in all of the observed epidemic years for breast, prostate and non-melanoma skin cancer. For these cancers, it is also important to note that from the pre-epidemic trends an increase in incidence would have been otherwise expected, since the annual percentage change in incidence during 10 years before the epidemic was 2.6% for female breast, 0.7% for prostate and 5.4% for non-melanoma skin cancers.³¹ The drop in new diagnoses of non-melanoma skin cancer during the epidemic in Slovenia could be explained by changes in health-seeking behaviour on the part of patients, since most non-melanoma skin changes occur over a longer period and would thus not be considered urgent by many people³⁴. Results from a national survey among adults regarding the impact of the COVID-19 pandemic on people's lives (SI-PANDA) have shown that in 2020 and beginning of 2021, more than 35% of respondents avoided seeing a doctor for reasons other than COVID-19; by the end of 2021, over 26% of respondents still reported they avoided seeing a doctor.^{24,25} Another contributing factor is that probably, access to doctor appointments was limited due to epidemic adaptations in healthcare services organization. The access was likely limited both at primary as well as secondary levels, most notably when strict mandates on provision of non-urgent care were in place which limited investigations for non-specific, early cancer symptoms. The primary level was reorganized in such a way, that a dual-track approach was implemented, meaning primary health care providers had to perform COVID-19 response services and at the same time maintain essential health services.³⁵ This put an unprecedented strain on the primary level, especially during COVID-19 peaks. Throughout most of the period, people had to contact their doctor

TABLE 2. Change (%) with 95% confidence interval in the referrals to cancer care services, and patient care provided at the Institute of Oncology Ljubljana in years 2020, 2021, 2022 compared to pre-COVID-19 year 2019. For 2022, only data from January to July are included and compared to corresponding months in 2019

	2020	2021	Jan.□July 2022
Referrals			
First cancer appointment	-1.8 (-4.4; 0.9)	5.4 (2.6; 8.2)	29.0 (25.0; 33.1)
Follow-up cancer appointment	-2.8 (-3.8; -1.9)	-14.3 (-15.2; -13.3)	-28.5 (-29.6; -27.4)
Oncological genetic testing and counselling	-11.9 (-16.3; -7.3)	15.3 (10.2; 20.5)	27.0 (20.1; 34.3)
First outpatient appointments at the Institute of Oncology Ljubljana			
Radiotherapy	5.7 (2.7; 8.8)	12.6 (9.4; 15.8)	13.8 (9.7; 18.1)
Surgery	-10.9 (-13.5; -8.3)	5.8 (3.0; 8.7)	15.7 (11.8; 19.6)
Medical oncology	-2.0 (-5.7; 1.8)	2.4 (-1.4; 6.3)	10.9 (5.7; 16.4)
All	-3.1 (-4.8; -1.3)	8.7 (6.9; 10.6)	15.3 (12.8; 17.8)
Follow-up outpatient appointments at the Institute of Oncology Ljubljana			
Radiotherapy	-13.6 (-14.6; -12.6)	-2.6 (-3.7; -1.6)	-2.1 (-3.5; -0.8)
Surgery	-13.2 (-14.3; -12.1)	-4.7 (-5.9; -3.5)	-8.1 (-9.6; -6.6)
Medical oncology	2.3 (1.3; 3.3)	12.8 (11.8; 13.9)	18.4 (17.0; 19.9)
All	-6.9 (-7.5; -6.3)	7.0 (6.3; 7.6)	8.1 (7.3; 9.0)
Cancer diagnostic imaging at the Institute of Oncology Ljubljana			
X-ray	-8.4 (-10.3; -6.4)	-0.5 (-2.5; 1.5)	-2.2 (-4.8; 0.5)
Mammography	2.8 (0.8; 4.8)	7.7 (5.7; 9.7)	8.2 (5.5; 10.8)
Ultrasound scans	-4.5 (-6.2; -2.8)	9.6 (7.8; 11.4)	19.6 (17.1; 22.1)
CT imaging	22.8 (20.8; 24.9)	45.7 (43.6; 47.9)	70.1 (67.0; 73.3)
MRI	14.8 (11.5; 18.1)	35.9 (32.4; 39.6)	38.5 (33.8; 43.3)
PET	4.6 (0.5; 8.8)	8.9 (4.8; 13.2)	11.7 (6.2; 17.4)

Change (in %) are coloured red when their 95% confidence interval is below zero; they are coloured green when their 95% confidence interval is above zero.

over the telephone or via e-mail to get an appointment, and they were also triaged over the telephone to determine whether an in-person visit was deemed necessary or not as well as then having to undergo a triage at entry points before seeing their doctor. Getting through on the telephone was relatively hard, since demand was great on account of COVID-19-related calls, while doctors at the primary level had also been reallocated to COVID-19 primary ambulatory clinics and to vaccination centres, which further limited their availability. Since most of the population with non-melanoma skin cancer are elderly (more than 69% of cases occur in people older than 65 years)³¹, contact by e-mail was not a suitable alternative for a major part of this population. Access to dermatological appointments was lower during the epidemic, since there were periods when non-urgent appointments were banned by a governmental

decree and all health care workers were asked to participate in the management of COVID-19.²⁸ Even in pre-pandemic times, getting a dermatological appointment was relatively hard, since waiting times for dermatological appointments within the public health care network in Slovenia are lengthy – in February 2020, the average waiting time for a first dermatological visit via a regular referral was almost 190 days and over 70 days for a very fast referral.³² Thus, already in the pre-epidemic period a significant number of patients likely paid out of pocket for services at privately owned dermatological practices.³⁶

Annual percentage growth of new skin melanoma diagnoses in Slovenia before the epidemic was among the highest, 2.6%.³¹ Because they share similar risk factors as well as pathways through the health care system, a similar trend in incidence as for non-melanoma is expected for skin

melanoma. Our results show that shortly after the epidemic started, the number of new skin melanoma diagnoses decreased significantly, however in 2021 the incidence was at the 2019 level and rose by 5% in 2022 compared to 2019 – as expected if we consider pre-epidemic trends. The increase in melanoma cases could also result from a public health campaign that was launched in Slovenia to raise awareness about cancer and featured widely in Slovenian media³⁷. The campaign aimed to raise public awareness on the pandemic's staggering disruption of cancer care by an overarching message: "Don't let COVID-19 stop you from tackling cancer".

Further, the up-to-date reports at onKOvid internet web page on delays in cancer diagnosis, which were also presented to the media, informed patients and decision-makers on the detrimental influence of COVID-19 epidemic restriction measures on oncology care, regardless of the fact that oncology services were exempt from measures and should have in theory remained undisturbed. We hypothesise that the intense public health interventions to raise general public awareness on the need to seek care when experiencing cancer related symptoms reflected also in the reversal of trends in new lymphoma cases during the epidemic – the number of diagnoses dropped in the beginning of the epidemic, but returned to expected numbers shortly afterwards, but we will only be able to evaluate this claim properly once standard registration procedures for the pandemic incidence years have been completed with more precise data on stage distribution and other characteristics. Furthermore, the heightened awareness perhaps also influenced doctors to be more alert to non-specific symptoms in patients that might be due to cancer.

If women in Slovenia are experiencing breast cancer symptoms, the first step in the care pathway is either their family doctor or primary level gynaecologist. During most pronounced restrictions, only urgent gynaecological services were performed, which limited their availability, while changes in health-seeking behaviour also likely played a role. The national screening programme for breast cancer, DORA programme, was stopped for two and a half months in total (since the middle of March until the beginning of June 2020). The programme managed to provide additional services during the summer months in 2020 and ended the year with only slightly lower numbers of performed mammographies (close to 8%), and discovering only 4% less breast cancers than in

2019.³⁸ In 2021, the programme performed 5% more mammographies and discovered 1% more cancers than in 2019.³⁹

Likewise, the cervical and colorectal cancer screening programmes also resolved backlogs by the end of 2020 and did not report any backlogs in 2021, therefore, a negative outcome on population health in terms of a surge in cancers that would otherwise have been detected through screening programmes is not expected.^{18,40,41} For colorectal cancer, there was no difference in the number of newly diagnosed cases in 2020 (after the initial drop in March through May, the numbers increased and were comparable to 2019 at the end of 2020), while yearly numbers decreased in 2021 (by 5%) and 2022 (by 8%), which is in line with the pre-epidemic downward incidence trend observed since 2010.³¹

There is no organised screening programme for prostate cancer in place in Slovenia, however many cases are diagnosed by opportunistic PSA testing. PSA testing is usually performed by a physician at the primary level or at higher levels following a referral issued by primary physicians. As already described, their accessibility was limited and thus fewer men had an opportunity to be offered PSA testing during a doctor visit, resulting in the observed drop of newly diagnosed prostate cancer cases.

Lung cancer was the only cancer with persistently higher diagnostic rates in the three epidemic years 2020, 2021 and 2022 compared to 2019. We theorize that this could be due to changed hospitalization patterns due to establishment of COVID-19 hospitals. In normal conditions, approximately one quarter of all lung cancer cases are treated at the University Clinical Hospital Golnik^{31,42}, which is a specialized hospital for lung diseases. During the epidemic, this hospital was converted into one of three referral hospitals for COVID-19 patients in Slovenia, which would mean that patients who under normal circumstances would be treated at University Clinical Hospital Golnik would have instead been referred to other hospitals. Since IOL is in relative proximity to the University Clinical Hospital Golnik and usually provides radiation therapy for all lung cancer cases, a significant number of lung cancer patients that would otherwise have been referred to the University Clinical Hospital Golnik were instead referred to the IOL due to changes in patient pathways. Since data from the University Clinical Hospital Golnik were not included in this analysis, the rise in lung cancer cases observed might not reflect the true pop-

ulation trend. However, the rise in detected lung cancer cases could also be the result of more intense imaging diagnostics for COVID-19 patients, the disease that affects the same organ, the lung. More reliable and detailed analyses are needed once standard incidence procedures for this period are completed.

The overall decline in the number of new cancer cases may be a real decline in incidence (eg. due to competing causes such as death from COVID-19) or it may simply reflect delays in diagnosis that the health system in Slovenia has not yet caught up with. Delays in diagnosis can lead to a higher proportion of cancers being detected at higher stages, which could result in worse outcomes (worse prognosis, poorer quality of life and, in some cases, earlier death) as shown in an Italian study of lung cancer patients⁴³ or the Swiss study on malignant melanoma.⁶ Our results show, that at least at the IOL, the stage distribution of patients first seen for diagnostics or treatment has not significantly changed in comparison to the pre-epidemic period 2015–2019. However, there were significantly fewer patients first seen at the IOL in 2020 and 2021 at almost all ages except the oldest group (80+), but most pronounced for ages 50–64 years, and in 2020 fewer were seen for cancer progression or relapse. This age group might stand out because they were under a lot of stress with respect to employment during COVID-19 as well as perhaps having school-aged children who they had to take care of, with high levels of pandemic fatigue contributing to changed health-seeking behaviors. The impact of COVID-19 epidemic on the long-term indicators of cancer burden, such as survival, will only be possible to evaluate correctly in the longer term.

In general, outpatient appointments and cancer diagnostic imaging at the IOL dropped after the onset of COVID-19 epidemic. The exception was the CT imaging where the numbers were higher also immediately after the onset of COVID-19 epidemic. CT imaging was preferred to ultrasounds and x-rays as distance preventive measures were easier to implement and furthermore the relocation of personnel from other imaging diagnostic procedures was needed to make up for the CT scan delays from before the epidemic, which was considered urgent. This is also reflected in the significant drop of other cancer diagnostic imaging in March and April 2020, followed by a rise by the end of 2020 compared to 2019 to make up for the back-logs. In total, there were more cancer diagnostic imaging tests performed in 2020 compared to 2019 (with the exception of ultrasound scans)

with numbers rising even more in 2021 and 2022. This rise was probably caused by cancer patients from other hospitals who were referred to IOL for imaging since other hospitals were overburdened with COVID-19 patients.

After a drop in 2020, the number of referrals to first cancer appointments and oncological genetic testing and counselling increased by more than a quarter in 2022 compared to 2019 figures. In particular, the staggering 77% drop in April 2020 (compared to April 2019) in oncological genetic testing and counselling was followed by intensive catch up in the following months (figures are available in the supplementary material). The Department of Oncological Clinical Genetics at the IOL reorganized its daily practice in line with official requirements, shifting appointments to additional hours in months with a lower COVID-19-burden, introducing telegenetic consultations that can also be performed when working from home, and introducing other new clinical pathways for genetic counselling and treatment. They carried out more first consultations, which helped them catch up on cancelled genetic consultations. With a good reorganization of the work, personnel reinforcement and the acquisition of premises for outpatient activities, they managed to catch up on the backlog of the first wave.⁴⁴

In contrast to the first appointments, non-urgent care was largely postponed at the IOL. First outpatient appointments were not affected but the number of follow-up outpatient appointments dropped by more than 13% for both radiotherapy and surgery in 2020 compared to 2019, which persisted in 2021 and 2022. These could be due to changed clinical practice pathways.⁴⁵

Cancer registries have a legal background for accessing many different data sources and they can and should convey their point of view on the COVID-19 epidemic. The SCR has a rich history of data collection, operating uninterrupted since 1950, and is considered one of the highest quality cancer registries that is leading the way in modern registration practices. Traditionally, hospitals report cases to the cancer registry via a customized paper-based Cancer Notification Form. In 2018, the gradual transition from passive (paper) to active (web) registration allowed for up-to-date online access to cancer records in health institutions. Active registration is an important advantage of the SCR and has enabled carrying out a real-time analysis of the impact of COVID-19 epidemic on delays in cancer diagnosis, based on the fact that delays in cancer diagnosis can be detected as tem-

porary drops in incidence over time. Under regular cancer registration procedures, delays in registration would have meant changes in trends could have been evaluated only after two to three years and would not have been as informative for decision makers who need up-to-date knowledge during crisis responses. Additionally, unlike the national cancer registry, the Hospital-Based Cancer Registry of the IOL has shorter delays in cancer registration, which allowed for more detailed real-time analyses including more patient characteristics. However, coverage in active registration and the IOL Hospital Registry is not national and including only the two major cancer centres is a disadvantage of our study as unknown biases might prevent extrapolations to the whole of Slovenia. We think the coverage is sufficient to minimise the potential for this type of bias in normal circumstances, but we cannot assess the scale of redirecting patients across health institutions due to measures for controlling the COVID-19 epidemic, which could have influenced observed trends. The IOL and the UMC Maribor are two out of three largest oncological centres in Slovenia and as such good representatives of all diagnosed cancer cases. For additional clarification we should emphasize that data on cancer cases cannot be interpreted as true incidence (number of all newly diagnosed cases of a disease that develop in a defined population in defined time period) but are simply comparisons of received cancer notification forms. At the time of conducting the present analysis, the SCR completed registration procedures up to the incidence year 2019. Additional reasoning not to conduct analyses on (estimated) incidence for years from 2020 on was that procedures on death certificates and notifications from Slovenian screening programmes were not yet processed. Based on CRS's previous analyses, this data sources could contribute to incidence up to 10%.⁴⁶

Furthermore, to determine changes in cancer burden and cancer care we used a variety of sources, some with national coverage (referrals) and all pointing to a possibility of delay in cancer diagnosis, which makes our results more reliable. One of the disadvantages is that we were not able to evaluate and identify the causes behind results and were only able to hypothesise on causes. Of course, routinely collected data on a population level, which were used in our study, cannot convey the problems experienced on a patient's level – we recommend further studies based on individual-level retrospective investigation of cancer patients and how measures for controlling epidemic or

having COVID-19 influenced their cancer diagnostics and treatment.

Conclusions

Our results show that the effects of the COVID-19 epidemic on cancer management in Slovenia vary for different cancers as well as by the level of the patient-care pathway – it is probably a mixture of changes in health-seeking behaviour and systemic changes due to modifications in healthcare organisation on account of COVID-19.

During the COVID-19 pandemic, management of cancer, which often starts with non-specific symptoms not deemed urgent but which need to be addressed quickly, was significantly affected. In Slovenia, the delay in cancer services from the first wave of the epidemic from March through May 2020 has been eliminated by 2022, but we still see fewer than expected new cancer cases in 2022, which reflects disruptions in the pre-diagnostic phase and could have profound long-term consequences on cancer burden indicators. To make incidence figures fully comparable with previous years on the population level, it is necessary to review all the notifications obtained by the SCR for the study period. Due to different disease trajectories of different cancer types we expect different medium- and long-term effects, such as the population-based survival of cancer patients, which serves as a complex indicator reflecting the characteristics of patients as well as the organization, accessibility, quality and efficiency of healthcare system, and which could be examined in a few years' time.

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