Newly diagnosed cancer and the COVID-19 pandemic: tumour stage migration and higher early mortality

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ABSTRACT

Background We compared the new outpatient clinic referrals during the first 10 months of the COVID-19 pandemic with the year before.

Methods We compared baseline characteristics of the 2208 new referrals in 2020 (n=922) and 2019 (n=1286) with X^2 and Mann-Whitney U tests and calculated ORs with binary logistic regression. To evaluate the expected changes in the cancer survival secondary to stage migration, we used the 5-year survival data of Survival, Epidemiology and End Results (SEER) Program 2010–2016.

Results The percentage of patients with inoperable or metastatic disease was significantly increased during the pandemic (49.8% vs 39%, OR: 1.553, 95% CI: 1.309 to 1.843, p<0.001). We observed a significant decrease in the percentage of patients diagnosed via the screening methods (18.8% vs 28.7%, OR: 1.698, 95% CI: 1.240 to 2.325, p=0.001). The 90-day mortality after the cancer diagnosis was significantly higher during the pandemic (10.5% vs 6.6%, OR: 1.661, 95% CI: 1.225 to 2.252, p=0.001). Due to the increased advanced-stage disease rate at first referral, significant decreases in 5-year survival rates were expected for breast cancer (–8.9%), colorectal cancer (–11.1%), cervix cancer (–10.3%) and melanoma (–7%).

Conclusion We think that collaborative efforts are paramount to prevent the pandemic of late cancer diagnoses and ensure patient safety during the pandemic.

Key messages

What was already known?

⇒ The COVID-19 pandemic could significantly disrupt the cancer care.

⇒ Screening is among the most affected cancer care domain during the pandemic.

What are the new findings?

⇒ We observed a cancer stage migration during the pandemic.

⇒ The percentage of screen-detected cancers decreased while the early mortality increased during the pandemic.

What is their significance?

a. Clinical

⇒ Efforts to reimplement cancer screening is vital to prevent cancer stage migration.

b. Research

⇒ The long-term effects of cancer stage migration on 5-year cancer survival should be prospectively evaluated.

INTRODUCTION

SARS-CoV-2 created the most significant pandemic of the last century and affected all domains of our lives.[1] The people with chronic comorbidities had increased hospitalisation, mechanical ventilation and mortality risks with COVID-19.[1 2] Patients with cancer are especially vulnerable to these adverse outcomes.[3 4]

In addition to the increased risk of COVID-19 mortality and morbidity,[3] the magnitude of collateral damage to cancer care could be as huge.[5] Many institutions halted the cancer screening procedures, postponed elective surgeries and allocated hospital resources to COVID-19 care.[6 7] Additionally, the referral cascade from the primary care for the preliminary cancer diagnosis was impaired.[8] These reasons could cause a wave of late cancer diagnoses, cancer stage migration and decreased cancer survival. Two recent models from the UK reported more than 5% increased cancer mortality risk with

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the late diagnosis and the delayed referrals during the pandemic.[8 9] However, the exact magnitude of stage migration and the early detrimental effects of this collateral damage on patients with cancer are yet to be defined. From this point, we evaluated the disease stages of the newly referred patients to our clinic in the first 10 months of pandemic in comparison with the year before. Additionally, we evaluated several other outcomes reflecting the cancer care disruptions.

PATIENTS AND METHODS

We reviewed the data of new outpatient medical oncology clinic referrals during the first 10 months of the COVID-19 pandemic (March–December 2020) and compared these data with the same time frame of the previous year (March–December 2019). We recorded the patient age and sex, tumour types, disease stages (localised vs metastatic), dates of first referral, and death dates from the hospital electronic registry system and patient files. We recorded COVID-19 infections and the deaths due to COVID-19 to prevent confounding due to COVID-19-related deaths in mortality rates. For the five screen-detectable cancers (breast, colorectal, non-small cell lung cancer (NSCLC), cervix cancer and melanoma), Eastern Cooperative Oncology Group (ECOG) statuses, TNM stages (I–IV), diagnosis route (screening or symptoms), hospitalisation and palliative radiotherapy needs at the first referral, and clinical trial enrolment rates were recorded.

We presented baseline characteristics with medians and IQRs for continuous variables and frequencies and percentages for categorical variables. We compared baseline characteristics of the patients in 2020 and 2019 with X^2 and Mann-Whitney U tests and evaluated the changes in disease stages between 2 years with X^2 and Fisher's exact tests and calculated ORs with binary logistic regression. To evaluate the expected changes in the cancer survival secondary to stage migration in the screen-detected cancers, we used the 5-year survival data of Survival, Epidemiology and End Results (SEER) Program 2010–2016.[10] We multiplied the percentage of localised, intermediate and advanced stages in the tumour group with the 5-year survival for each stage and added these three figures to determine the expected 5-year survival in this individual tumour type. All statistical analyses were performed in SPSS V.25 (IBM) software, and a type-I error level of 5% ($p<0.05$) was considered as the threshold limit for statistical significance.

RESULTS

We evaluated the data of 2208 new patient referrals. The median ages of the patients were 61 (IQR 50–69) and 60 (IQR 49–68) years in 2020 and 2019, respectively ($p=0.211$). The sex distributions were similar in 2 years and showed a slight male predominance (54.4% vs 50.5% male in 2020 and 2019, $p=0.070$). The distribution of the tumour types was similar in 2 years ($p=0.136$) and showed the predominance of breast, NSCLC and colorectal cancer cases in both years (42.2% vs 43.6% of all cases in 2020 and 2019, respectively) (table 1).

Table 1 Baseline characteristics of the first referrals in 2020 and 2019

Year		2019 n (%)	2020 n (%)	P value
Median age (IQR)		60 (49–68)	61 (50–69)	0.211
Sex	Female	636 (49.5)	420 (45.6)	0.070
	Male	650 (50.5)	502 (54.4)	
Primary tumour	Breast	236 (18.4)	136 (14.8)	0.136
	NSCLC	161 (12.5)	121 (13.1)	
	Colorectal	163 (12.7)	132 (14.3)	
	Other	726 (56.4)	533 (57.8)	
Disease stage	Localised	785 (61)	463 (50.2)	**<0.001**
	Advanced/ metastatic	501 (39)	459 (49.8)	
Diagnosis via screening methods	Present	165 (27)	70 (17.9)	**0.001**
	Absent	447 (73)	322 (82.1)	
Symptoms at diagnosis	Present	520 (85.8)	345 (89.6)	0.080
	Absent	86 (14.2)	40 (10.4)	
Palliative radiotherapy need at first referral	Present	129 (20.6)	75 (18.6)	0.422
	Absent	497 (79.4)	329 (81.4)	
Hospitalisation need at first referral	Present	67 (10.6)	43 (10.6)	0.987
	Absent	566 (89.4)	362 (89.4)	

*bold values denote statistical significance ($p<0.05$)
NSCLC, non-small cell lung cancer.

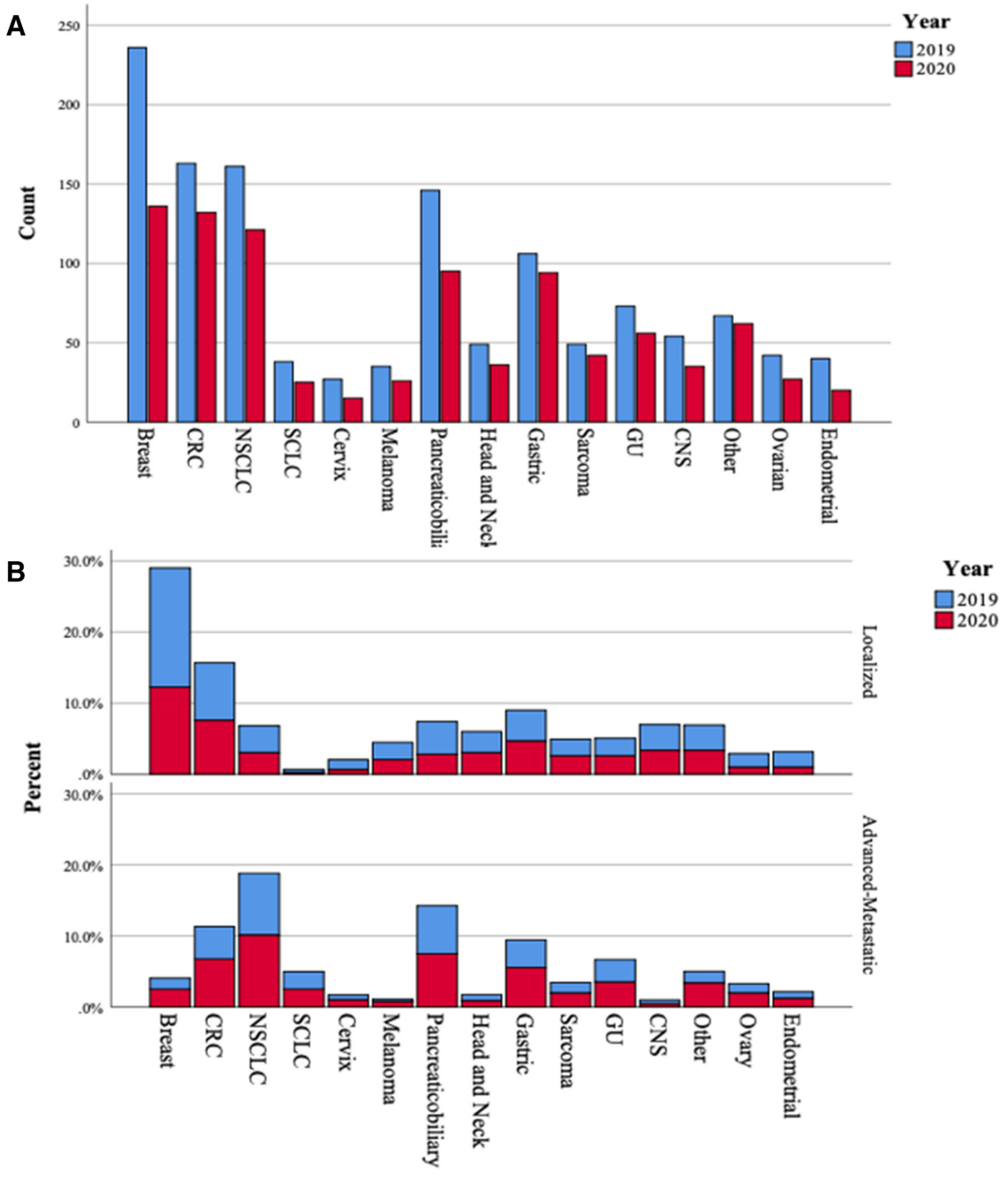

Figure 1 (A–B) Changes in the new patient referrals according to tumour types and stages in 2020 and 2019. CNS, central nervous system; CRC, colorectal cancer; GU, genitourinary; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

The number of new patient referrals was significantly reduced in 2020 compared with 2019 (922 vs 1286, −28.3%). The reductions were consistent in all tumour types (figure 1A). Compared with the year before the pandemic, the percentage of patients with inoperable or metastatic disease was significantly increased during the first 10 months of the COVID-19 pandemic (49.8% vs 39%, OR: 1.553, 95% CI: 1.309 to 1.843, p<0.001) with a trend towards increased risk of advanced-stage disease in most tumour types (figure 1B).

Additional analyses were conducted in 1052 patients with screen-detectable cancers (breast, NSCLC, colorectal, cervix and melanoma). The percentage of patients with metastatic disease at referral was significantly increased in 2020 (45.1% vs 32.8%, OR: 1.684, 95% CI: 1.308 to 2.170, p<0.001), while the percentage of patients diagnosed with the screening methods was significantly decreased (18.8 vs 28.7%, OR: 1.698, 95% CI: 1.240 to 2.325, p=0.001). The increased risk of metastatic disease at first referral was especially prominent in breast cancer and colorectal cancer (CRC) during the pandemic (table 2). The patients with the hospitalisation (p=0.936) and palliative radiotherapy needs at the first referral (p=0.524) were similar between 2020 and 2019. The clinical

Table 2 Percentage of symptomatic disease, diagnosis via screening and the disease stage at first referral in screen-detectable cancer

			Breast n (%)	CRC n (%)	NSCLC n (%)	Cervix n (%)	Melanoma n (%)
Symptoms at first presentation	2019	Absent	44 (20.1)	13 (9.2)	19 (12.7)	1 (4.5)	5 (18.5)
		Present	175 (79.9)	128 (90.8)	131 (87.3)	21 (95.5)	22 (81.5)
	2020	Absent	22 (19)	8 (7.3)	8 (7.3)	0 (0)	0 (0)
		Present	94 (81)	101 (92.7)	102 (92.7)	11 (100)	15 (100)
Diagnosis via screening	2019	Absent	106 (47.7)	115 (81.6)	138 (91.4)	19 (82.6)	24 (88.9)
		Present	116 (52.3)	26 (18.4)	13 (8.6)	4 (17.4)	3 (11.1)
	2020	Absent	72 (61)	100 (91.7)	103 (91.2)	11 (91.7)	13 (81.3)
		Present	46 (39)	9 (8.3)	10 (8.8)	1 (8.3)	3 (18.7)
Stage at first referral	2019	I	45 (20.7)	8 (5.2)	11 (6.9)	2 (8)	1 (6.7)
		II	110 (50.5)	42 (27.1)	12 (7.6)	10 (40)	4 (26.7)
		III	42 (19.2)	43 (27.7)	21 (13.2)	8 (32)	5 (33.3)
		IV	21 (9.6)	62 (40)	115 (72.3)	5 (20)	5 (33.3)
	2020	I	17 (14.3)	7 (5.8)	3 (2.5)	2 (15.4)	1 (10)
		II	47 (39.5)	17 (14)	12 (10)	2 (15.4)	1 (10)
		III	30 (25.2)	30 (24.8)	17 (14.2)	5 (38.4)	4 (40)
		IV	25 (21)	67 (55.4)	88 (73.3)	4 (30.8)	4 (40)

CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

trial enrolment was not significantly affected during the pandemic and even increased during the first 10 months of the pandemic (9.2% vs 5.1%, p=0.014). The 90-day mortality rate was significantly higher during the COVID-19 pandemic (10.5% vs 6.6%, OR: 1.661, 95% CI: 1.225 to 2.252, p=0.001). A total of 31 patients had COVID-19 infection and 2 patients died secondary to COVID-19 infection. The increase in 90-day mortality rates remained significant after excluding the deaths secondary to COVID-19 infection (p=0.002).

In order to evaluate the possible expected changes in the 5-year survival secondary to late diagnoses during the pandemic, the SEER 2010–2016 data were used.[10] For this calculation, patients with stages 1 and 2 tumours were included to localised, stage 3 tumours to regional, and stage 4 tumours to metastatic groups of SEER classification. Due to increased rates of advanced-stage disease at first referral, decreased estimated 5-year survival was expected for breast cancer (−8.9%), colorectal cancer (−11.1%), cervix cancer (−10.3%) and melanoma (−7%). The expected decrease in the estimated 5-year survival for NSCLC was significantly lower (−0.8%), possibly due to more than 70% metastatic cases in both years (online supplemental file).

DISCUSSION

The COVID-19 pandemic could affect all patients with cancer and even the patients in remission,[11] and cancer care disruption is among the most researched problem from the start of the pandemic. However, the exact magnitude of these disruptions and their expected consequences are yet to be defined. In this study, we focused on cancer stage migration as an area of concern. A recent international survey among oncologists reported a significant decrease of new patient referrals with a rebound increase in the advanced stage cases as the pandemic progresses.[12] Similarly, we observed significant decreases in new patient referrals, and the percentage of patients diagnosed via screening methods with an increased percentage of advanced-stage cancers in the first 10 months of the COVID-19 pandemic. Clinical trial enrolment remained unaffected, possibly due to the increased frequency of advanced disease at first referral and flexible approaches like telehealth visits and extended interval dosing to maintain clinical trial enrolment during the pandemic. However, the possibility of confounding stemmed from the changes in clinical trial availability between 2 years could not be excluded.

Cancer screening is one of the most affected cancer care domains during the resource allocations in pandemic peaks due to the elective nature.[13] Unfortunately, this obligatory allocation could be costly in the long term, as evidenced by the more than 10% increase in the stage III breast cancers with only 2 months of interruption of screening mammographies.[14] Ricciardiello *et al* constructed a procedural model for changes in CRC outcomes due to delays in screening colonoscopies and projected a more than 10% increase in CRC mortality with over 12-month delays in screening similar to our projections.[15] Furthermore, Ward *et al* projected over 3000 excess cancer deaths in Chile until 2025 due to stage migration during the pandemic[16] . In a pioneer report from the Netherlands, the new cancer diagnoses were decreased up to 30% in the first 2 months of the pandemic.[6] The COVID-19 fear of the patients, late referrals for non-specific symptoms and halting the screening procedures were all proposed

to cause this decrease, although the changes in the cancer stages were not reported at that time.[6] A recent preprint paper from Korea specifically evaluated the cancer stage migration in the data of 873 patients encompassing 2 months before and 2 months after the pandemic. The authors reported a significant stage migration in breast cancer with a 15% increase in stage III cases and a 13.5% increase in the use of chemotherapy as the first treatment. Similar trends were observed for the gastric and colorectal cancer cases.[17] Both the Korean study and our study were conducted in the countries that did not implement a nationwide lockdown during the study periods. We think that the stage migration could be more pronounced in countries needing strict nationwide lockdowns during the pandemic peaks.

In our study, 30-day and 90-day mortality rates after the first referral were increased in 2020. Although the exact mechanisms of this risk increase are unknown, increased frequency of advanced cases and symptomatic disease at presentation could lead to increased early mortality rates in our study. Additionally, shortages in intensive care resources due to allocation of services to COVID-19 care could be among the reasons for increased early unexpected mortality risk during the pandemic. Morais *et al* reported a similar decrease in short-term survival during the pandemic, although the mortality seemed to be affected by the treatment-related factors (radiotherapy, surgery, no active treatment), and the negative effect lost statistical significance after adjustments for age and stage.[18] We think that more research is needed to delineate the collateral damage of COVID-19 pandemic on early cancer mortality.

Our study has several limitations. We included a relatively small patient cohort treated in a single institution which precluded us from detecting subtle stage changes in individual tumour types and reaching firm conclusions in the less frequent tumour types. Our study was conducted in a tertiary medical oncology centre, which mostly involves in the care of advanced-stage disease, while the patients with early stage disease are generally followed by the surgical oncology and radiation oncology. This issue limits our study power on reflecting the magnitude of stage migration and makes our results hypothesis generating rather than definite, especially in the earlier stage disease. Nationwide studies encompassing surgical and medical oncology clinics are needed to delineate the stage migration's magnitude better. However, despite these limitations, we think that a consistent stage migration across different tumour types in the referrals of the same institution should still ring the alarms.

In conclusion, we observed an increased frequency of advanced cancers at first referral and increased early mortality after cancer diagnosis in the first year of pandemic. We think that the collateral damage of COVID-19 on cancer care could create a setback to the continuous improvements in cancer care. Collaborative efforts are paramount to prevent the pandemic of late cancer diagnoses and ensure patient safety during and after the pandemic.

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Contributors DCG and NK have planned the work. DCG, TKS, HCY, EC, FGGI, YT, EU, MSA, SCG, OHA, ZA, OD, SY, SA, SK and NK participated in patient care and data collection. All authors, namely DCG, TKS, HCY, EC, FGGI, YT, EU, MSA, SCG, OHA, ZA, OD, SY, SA, SK and NK have made significant and substantive contributions to the reporting of the work. All authors have participated in the review of relevant literature, drafting of the manuscript, review and revisions of the final draft. DCG, TKS, HCY and NK have analysed the data and determined the main conclusions. DCG has prepared the first draft of the manuscript. All authors reviewed and participated in the preparation of the revised and final version of the manuscript. DCG and NK are responsible for the overall content as guarantors. All coauthors qualify the criteria for authorship according to Vancouver protocol.

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Supplement. Projected five-year survival changes in screen-detectable cancers due to COVID-19 related stage migration.

		SEER 5-year survival (%)	**2019 (%)**	**5-year survival 2019 (%)**	**2020 (%)**	**5-year survival 2020 (%)**	**Survival Change (%)**
Breast Cancer	Localized	98.9	71.1	89.6	53.8	80.7	**-8.9**
	Regional	85.6	19.3		25.2		
	Distant	28	9.6		21		
Colorectal Cancer	Localized	90.2	32.3	54.7	19.8	43.6	**-11.1**
	Regional	71.8	27.7		24.8		
	Distant	14.3	40		55.4		
NSCLC	Localized	59	14.5	16.9	12.5	16.1	**-0.8**
	Regional	31.7	13.2		14.2		
	Distant	5.8	72.3		73.3		
Cervix Cancer	Localized	91.8	48	65.9	30.8	55.6	**-10.3**
	Regional	57.6	32		38.4		
	Distant	16.8	20		30.8		
Melanoma	Localized	99	33.3	64.2	20	57.2	**-7**

	Regional	66.2	33.3		40		
	Distant	27.3	33.4		40		