Title

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Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: an international, prospective, cohort study

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Summary

Background Surgery is the main modality of cure for solid cancers and was prioritised to continue during COVID-19 outbreaks. This study aimed to identify immediate areas for system strengthening by comparing the delivery of elective cancer surgery during the COVID-19 pandemic in periods of lockdown versus light restrictions.

Methods This international, prospective, cohort study enrolled 20 006 adult (≥18 years) patients from 466 hospitals in 61 countries with 15 cancer types, who had a decision for curative surgery during the COVID-19 pandemic and were followed up until the point of surgery or cessation of follow-up (Aug 31, 2020). Average national Oxford COVID-19 Stringency Index scores were calculated to define the government response to COVID-19 for each patient for the period they awaited surgery, and classified into light restrictions (index <20), moderate lockdowns (20–60), and full lockdowns (>60). The primary outcome was the non-operation rate (defined as the proportion of patients who did not undergo planned surgery). Cox proportional-hazards regression models were used to explore the associations between lockdowns and non-operation. Intervals from diagnosis to surgery were compared across COVID-19 government response index groups. This study was registered at ClinicalTrials.gov, NCT04384926.

Findings Of eligible patients awaiting surgery, 2003 (10·0%) of 20 006 did not receive surgery after a median follow-up of 23 weeks (IQR 16–30), all of whom had a COVID-19-related reason given for non-operation. Light restrictions were associated with a 0·6% non-operation rate (26 of 4521), moderate lockdowns with a 5·5% rate (201 of 3646; adjusted hazard ratio [HR] 0·81, 95% CI 0·77–0·84; p<0·0001), and full lockdowns with a 15·0% rate (1775 of 11 827; HR 0·51, 0·50–0·53; p<0·0001). In sensitivity analyses, including adjustment for SARS-CoV-2 case notification rates, moderate lockdowns (HR 0·84, 95% CI 0·80–0·88; p<0·001), and full lockdowns (0·57, 0·54–0·60; p<0·001), remained independently associated with non-operation. Surgery beyond 12 weeks from diagnosis in patients without neoadjuvant therapy increased during lockdowns (374 [9·1%] of 4521 in light restrictions, 317 [10·4%] of 3646 in moderate lockdowns, 2001 [23·8%] of 11 827 in full lockdowns), although there were no differences in resectability rates observed with longer delays.

Interpretation Cancer surgery systems worldwide were fragile to lockdowns, with one in seven patients who were in regions with full lockdowns not undergoing planned surgery and experiencing longer preoperative delays. Although short-term oncological outcomes were not compromised in those selected for surgery, delays and non-operations might lead to long-term reductions in survival. During current and future periods of societal restriction, the resilience of elective surgery systems requires strengthening, which might include protected elective surgical pathways and long-term investment in surge capacity for acute care during public health emergencies to protect elective staff and services.

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See **Online** for appendix

Introduction

During the COVID-19 pandemic, government restrictions have aimed to control community SARS-CoV-2 transmission and included reducing population movement, closing public facilities, and restricting gatherings.[1] Restrictions have varied worldwide in stringency, with the most severe leading to so-called lockdowns.[2] Although public and media attention has largely focussed on the economic impact of lockdowns, the broader effects on general health are poorly understood.[3] Lockdowns might have had collateral effects beyond controlling community SARS-CoV-2 rates alone, due to changes in both public behaviour and health system performance.[4] These might have disproportionate effects on vulnerable and

Research in context

Evidence before this study

Guidance from health ministries and national surgical associations prioritised time-dependent cancer surgery to continue during societal restrictions related to COVID-19. We searched PubMed and Embase on Feb 12, 2021, without date limits, for prospective, multicountry studies describing non-operation rates for patients planned to undergo elective surgery during national or regional COVID-19 lockdowns using primary data. We used the search terms "COVID-19", "SARS-CoV-2", "coronavirus", "lockdown" and "pandemic", in combination with "surgery" and "non-operation", "cancellation", "postponement" or "delays", and applied no language restrictions. Several modelling studies estimated total elective surgeries cancelled due to COVID-19, but no primary studies described the impact of lockdowns on non-operation rates for patients due to undergo curative cancer surgery.

Added value of this study

There is limited evidence of the collateral effects of COVID-19 pandemic lockdowns outside of modelling studies. Uniquely, this international study prospectively enrolled patients with a decision for curative surgery awaiting surgery during the SARS-CoV-2 pandemic and tracked their care pathways prospectively. It included data from the 15 most common solid cancer types across all country-income settings, providing wide generalisability to global policy. The analysis allowed a direct comparison of full and moderate lockdowns to light restrictions, accounting for their dynamic nature, where different patients from the same country were exposed to different lockdown states.

Implications of all the available evidence

This study has direct policy, organisational, and clinical implications. It has revealed the fragility of elective cancer surgery systems to lockdowns, particularly health systems in lower-middle-income countries. This study demonstrates the need for system strengthening in elective surgery across all settings to mitigate against impending COVID-19 lockdowns and future pandemics. This should include both global reorganisation to provide protected COVID-19-free elective surgical pathways (and staffing) that sustainably allow safe surgery to continue, and improved surge capacity for acute care during public health emergencies. The potential long-term effects for patients who underwent delayed surgery may require closer follow-up for metastatic disease. This study could inform policy makers' planning regarding the collateral effects of societal restrictions.

marginalised communities.[5,6] Understanding these effects will justify expenditure on targeted system strengthening, as further societal restrictions are predicted at a global level.

In the first COVID-19 waves (ie, the 12 weeks of peak disruption), at least 21 million elective operations were cancelled globally, partly due to concerns over post-operative SARS-CoV-2 infection and partly due to capacity issues within hospitals.[7,8] There was, however, general guidance from health ministries and national surgical associations that time-dependent surgery should continue.[9] This included curative cancer surgery, which is a priority among the oncology community and a high-value topic for society.[10,11] Surgery remains the primary method of cure for most solid cancers.

For the **protocol** see https://globalsurg.org/cancercovidsurg/

Since surgical databases and cancer registries do not capture prospective decision making, they lack fidelity to detect patients who did not undergo planned surgery. In the case of curative surgery, these are the patients who might have suffered the most harm.[12,13] Resection margins alone are an inadequate marker of success, as selection bias in patients who are able to undergo surgery risks underestimating harm from treatment delays, and neglects whole-system effects. We planned the prospective COVIDSurg Cancer study to address these areas and provide an accurate, whole-system analysis of the impact of COVID-19 on planned cancer surgery. Understanding any harms could allow for immediate local and national policy changes, in preparation for future societal restrictions.

Methods

Study design and participants

This international, multicentre, prospective cohort study included adult patients (≥18 years) with a diagnosis of a surgically curable cancer during the COVID-19 pandemic. The study was conducted in accordance with a preregistered protocol (NCT04384926). Local principal investigators were responsible for obtaining clinical audit, institutional review board, or ethical approval in line with local and national regulations. In most settings, a waiver of individual patient consent was obtained. In other countries, formal written or verbal consent was required based on recommendations of local ethics and governance committees. Data were collected online and stored on a secure server running the Research Electronic Data Capture (REDCap) web application.[14]

Any hospital worldwide that performed elective cancer surgery in an area affected by the COVID-19 pandemic was eligible to participate. Patients listed for surgery to cure a solid cancer were included in each centre for 3 months from local emergence of COVID-19, defined on a centre-by-centre basis as the date where first notification of SARS-CoV-2 cases occurred in the local area (between Jan 21 and April 14, 2020). Participating centres identified all patients with a decision for surgery (or would have had a decision for surgery under normal, prepandemic circumstances) from multidisciplinary team meetings, tumour board, outpatient clinics, or local equivalents. Previous international outcomes studies from our group have shown that this method achieves greater than

95% case ascertainment and greater than 98% data accuracy during external validation.[15] If a specialty within a hospital was unable to confirm consecutive enrolment, their data were excluded from analysis. Patients' care pathways were followed up until the point of surgery or until cessation of follow-up at Aug 31, 2020. This date was selected to ensure all patients had a minimum of 12-weeks follow-up. Where a patient underwent surgery, outcome data was collected up to 30 days after surgery. Where patients remained non-operated, their last known status was recorded.

The 15 most common solid cancer types were included in this study, including colorectal, oesophageal, gastric, head and neck (oral, oropharyngeal, laryngeal, hypopharyngeal, salivary, thyroid, paranasal sinus, skin), thoracic (lung, pleural, mediastinal, chest wall), liver, pancreatic, prostate, bladder, renal and upper urinary tract urothelial, gynaecological (uterine, ovarian, cervical, vulval, vaginal), breast, soft-tissue sarcoma, bony sarcoma, and intracranial malignancies. Participating centres could contribute data for either single or multiple cancers. Early cancers that were planned to be managed with endoscopic surgery alone (eg, transurethral resection of bladder tumour, transanal endoscopic microsurgery) were excluded. Patients who were suspected to have an operable cancer, but were later identified to have a non-cancerous condition (eg, on postoperative histopathology), or were treated as benign and unexpectedly identified to be malignant on postoperative histopathology were also excluded.

Definition of lockdowns

We used the Oxford COVID-19 Stringency Index to define each country's national government response to COVID-19. This index is a composite of 19 indicators including measures and behavioural interventions related to containment and closure, economic response, and health systems. Each indicator is scored using an ordinal scale (0 to 2, 3, 4, or 5), with an overall score calculated by adding together individual indicator scores (appendix p 56). Total scores can range from 0 (no restrictions) to 100 (most stringent restrictions). The index has been previously validated by demonstrating associations with population SARS-CoV-2 infection rates and mobile phone mobility data.[1]

The average national Oxford COVID-19 Stringency Index scores were calculated for each patient for the period they waited for surgery. To define cutoffs that were reflective of real-world policy, we sampled reported lockdown dates from a sample of high-income countries, upper-middle-income countries (UMICs), and lower-middle-income countries (LMICs; appendix p 55). Dates were taken from national policy, media, and press sources. On the date of transition into lockdown, the point estimate for the COVID-19 Stringency Index score was extracted (appendix p 55). This point estimate was used to classify patients into three stringency groups: light restrictions (index <20), moderate lockdowns (20–60), and full lockdowns (>60). These groups allowed a direct comparison of full and moderate lockdowns to light restrictions, accounting for their dynamic nature, whereby different patients from the same country were exposed to different lockdown states. For each patient, a median average score while waiting for surgery and the number of weeks in full lockdown were calculated and used in analyses. Full details are given in the appendix (pp 2, 57–58).

Definition of SARS-CoV-2 rates

The case notification rate was calculated at an individual patient level as a median average between the date of local emergence of COVID-19 and the date of surgery or cessation of follow-up via the Our World in Data portal.[16] A high COVID-19 burden area was classified as a median of at least 25 cases per 100 000 per 14 days, representing WHO recommendations at the time of the study (ie, in keeping with first pandemic wave levels). Case rates were used for exploratory analyses only, and stratified by World Bank income tertile (appendix p 58).[17,18]

Other definitions

The World Bank index (2019/20 update) was used to classify countries and patients into three groups based on Gross National Income per capita (US$) calculated using the Atlas method: high-income countries, UMICs, and LMICs (including patients from both low-income countries and LMICs). Data on baseline patient status was collected for the purpose of adjustment for case-mix in exploring associations between lockdowns and surgical capacity (appendix p 59).

Patients were classified into three groups according to their neoadjuvant treatment group: (1) no neoadjuvant therapy (ie, straight to surgery); (2) neoadjuvant therapy, standard care (where the treating clinician administered neoadjuvant treatment in accordance with their usual care); (3) neoadjuvant therapy, COVID-19 decision (where the treating clinician administered a neoadjuvant treatment where this would not typically be indicated). To estimate the impact of lockdown on treatment delays, the relationship between lockdowns and the interval from diagnosis to decision for surgery to surgery was measured. The interval from date of diagnosis to the date of surgery was calculated in whole weeks to identify points of system friction (appendix p 60).

Outcomes

A resilient elective surgical care system is defined as a hospital or network of hospitals that is able to maintain both its capacity and safety during public health crises.[19] As a measure of the ability of surgical systems to maintain their capacity, the primary outcome measure was the non-operation rate. This non-operation rate was defined as an eligible patient (ie, with a plan to undergo surgery) not undergoing their planned operation during

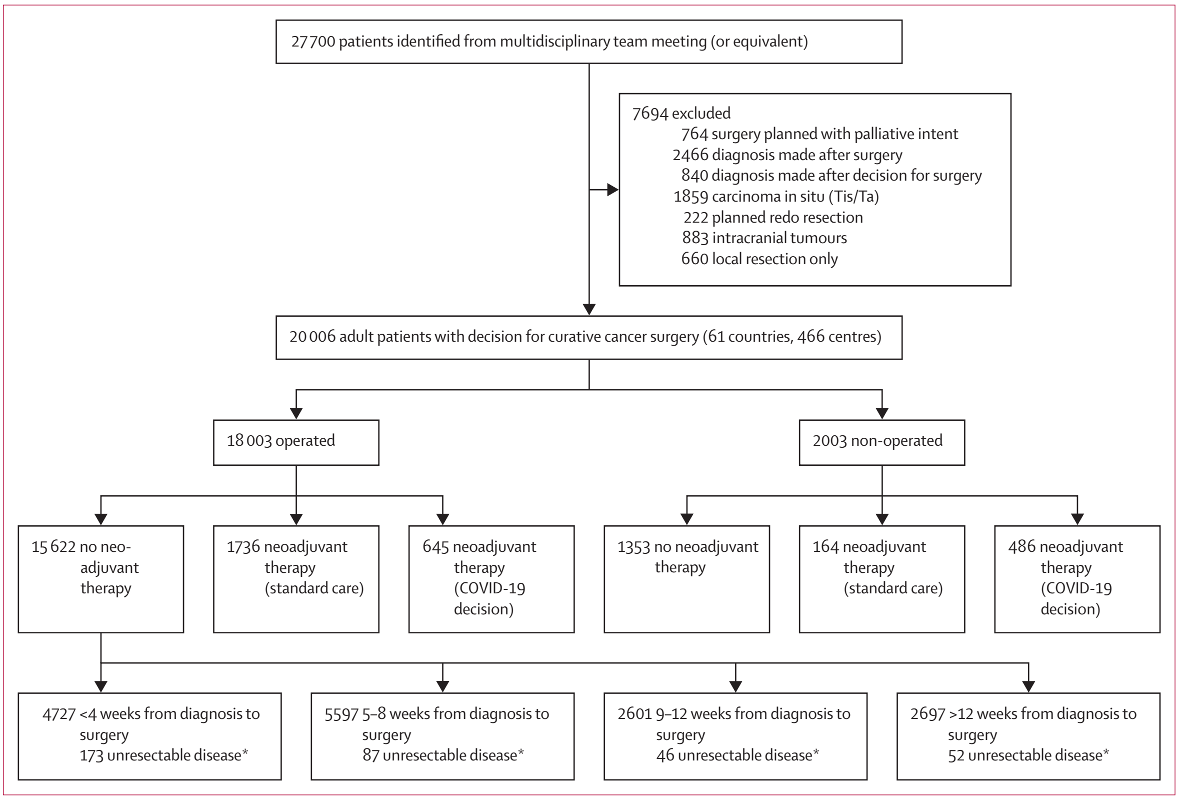

Figure 1: **Flowchart of included patients**
*Found clinically, radiologically, or during surgery.

the study window. Patients were classified as being operated if they underwent surgery, regardless of whether there was a change to the planned urgency (eg, from elective to emergency) or intent (eg, from curative to palliative). Patients who died or progressed to unresectable disease before surgery were classified as non-operated, so these did not act as competing risks.

For patients who did not receive their surgery as planned during the follow-up window, the treating clinical team selected one or more reasons that the patient had not had surgery. These reasons included those explicitly COVID-19 related (eg, decision to delay surgery due to patient risk during COVID-19), and those non-COVID-19 related (eg, delay due to other unrelated medical or surgical condition). More than one reason for non-operation could be selected for each patient, representing the complexity of decision making (full details are given in the appendix p 61).

Secondary outcome measures related to safety of surgery were presented for patients who underwent surgery during the follow-up period: (1) resection margin status for those selected for surgery; (2) resectable disease at the time of surgery; (3) preoperative cancer complication requiring emergency surgery; (3) 30-day postoperative SARS-CoV-2 infection rate; (4) 30-day postoperative mortality rate; (5) new detection of metastatic disease up to a maximum of 30 days after surgery. As neoadjuvant therapy has a complex interplay with treatment interval, an a-priori decision was made to only include patients who went straight to surgery (no neoadjuvant therapy) in exploration of the effects of treatment delay on secondary outcomes (appendix p 62).

Statistical analysis

The full statistical method is presented in the appendix (p 63). Cox proportional hazards regression modelling was used to explore associations between lockdowns and the primary outcome, presented as adjusted hazard ratios (HRs) and 95% CIs. Operation was included as the outcome event, and no censoring was performed for death or progression to unresectable disease to deal with competing risks, given individuals had the same follow-up time (ie, describing sub-distribution rather than cause-specific hazards). An α level was set at 0·05 (5%) for interpretation of significance. Several preplanned sensitivity analyses were conducted for the primary analysis to examine robustness of findings; namely, (1) including elective operations only in the definition of the primary outcome; (2) accounting for an interaction effect between World Bank income group and COVID-19 stringency index group; and (3) accounting for local SARS-CoV-2 case notification rates, stratified by World Bank income group. Two further sensitivity analyses were performed to ensure that differences in cancer case-mix across income settings were not responsible for residual confounding; these included, (1) cancer location removed from the model; and (2) patients older than 50 years only. A secondary analysis was used to explore the incremental effect of weeks in lockdown on a patient's likelihood of non-operation. Intervals from diagnosis to surgery were compared across COVID-19 government response index groups. We only analysed the interval between diagnosis and surgery for patients who did not receive neo-adjuvant therapy to avoid confounding due to legitimate delays to surgery in patients who receive neo-adjuvant therapy. All analyses were carried out using R, version 3.1.1 (packages finalfit, tidyverse, ggsurvplot).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

20 006 patients were eligible for inclusion in 466 hospitals in 61 countries (figure 1). Of these patients, 1891 (9·5%) were from 17 UMICs and 2249 (11·2%) were from 12 LMICs. A wide range of patients, tumours, and operations were included. The most common tumour types included were breast (n=3896; 19·5%), head and neck (n=3517; 17·6%), colon (n=3428; 17·1%), and gynaecological (n=2169; 10·8%). Distribution of patients and cancers across income groups and countries is shown in the appendix (pp 8–9).

Of patients planned for cancer surgery during the COVID-19 pandemic, 4521 (22·6%) of 20 006 were awaiting surgery during a period of light restrictions, 3646 (18·2%) during moderate lockdowns, and 11 827 (59·1%) during full lockdowns (n=12 missing data; appendix p 4). The proportion of patients awaiting surgery in full lockdowns was higher in areas with high than low community SARS-CoV-2 case notification rates and in UMICs and LMICs than in high-income countries (appendix p 10). Patients awaiting surgery during light restrictions had a lower mean number of weeks in full lockdown (2·4 weeks [SD 1·7]) compared with patients awaiting surgery during moderate (5·5 weeks [2·9]) or full lockdowns (12·7 weeks [5·4]; p<0·0001, from one-way ANOVA).

Most patients (16 975 [84·8%] of 20 006) had a plan to progress straight to surgery (no neoadjuvant therapy), with 1900 (9·5%) receiving standard care neoadjuvant therapy, and 1131 (5·7%) receiving a COVID-19 decision for neoadjuvant therapy. During full lockdowns, patients were more likely to have a COVID-19 decision for neoadjuvant therapy than during moderate lockdowns or light restrictions (appendix p 3).

During the COVID-19 pandemic, 2003 (10·0%) of 20 006 patients did not undergo their planned surgery by the end of follow-up (figure 2; appendix p 12). Patients awaiting surgery during periods of light restrictions had a lower rate of non-operation (26 [0·6%] of 4521) than those in moderate lockdowns (201 [5·5%] of 3646) or full lockdowns (1775 [15·0%] of 11 827; appendix p 5).

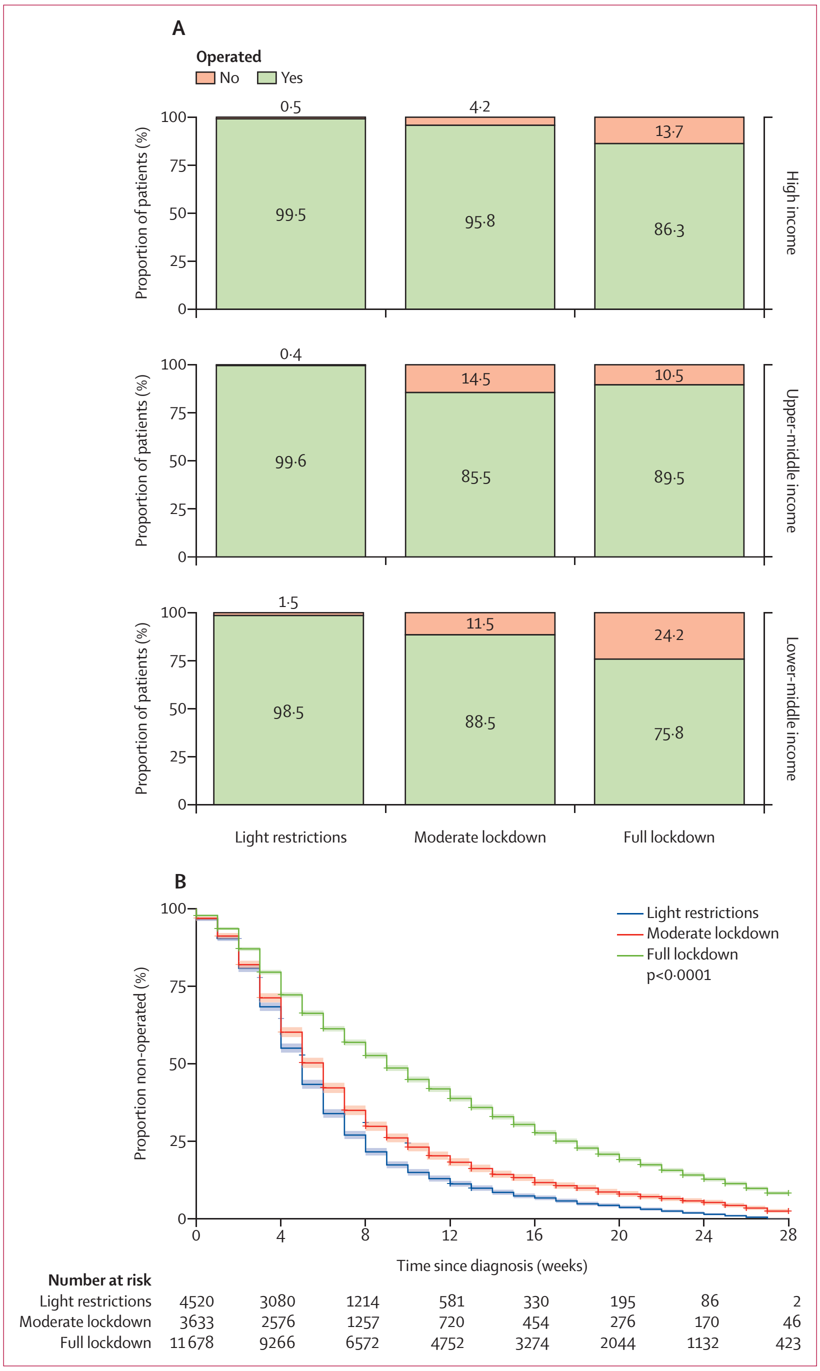

Figure 2: **Effects of lockdowns on surgical capacity**
(A) Differences in resilience of surgical systems across income settings by COVID-19 stringency index group. Percentages represent proportion operated by group. (B) Kaplan-Meier plot demonstrating proportion of patients remaining non-operated over time from cancer diagnosis grouped by COVID-19 stringency index group. Plot censored at 28 weeks maximum follow-up from cancer diagnosis. Shading represents this represents the 95% CI, using the statistical package ggsurvplot.

	n/N	HR (95% CI)	p value
COVID-19 stringency index		Ref	
Light restrictions	4371/4391		
Moderate lockdown	3364/3509	0·81 (0·77–0·84)	p<0·0001
Full lockdown	9862/11 166	0·51 (0·50–0·53)	p<0·0001
World bank index			
High income	14 138/15 115	Ref	
Upper-middle income	1687/1801	0·97 (0·92–1·02)	p=0·2202
Lower-middle income	1772/2150	0·83 (0·78–0·87)	p<0·0001
Age, years			
<50	3228/3527	Ref	
50–59	3636/3916	1·10 (1·05–1·15)	p=0·0002
60–69	4742/5166	1·01 (1·04–1·14)	p=0·0005
70–79	4333/4639	1·17 (1·11–1·23)	p<0·0001
≥80	1658/1818	1·06 (0·99–1·14)	p=0·0772
Sex			
Female	10 175/10 776	Ref	
Male	7422/8290	0·99 (0·95–1·02)	p=0·4569
ASA grade			
1–2	12 549/13 565	Ref	
3–5	5048/5501	0·99 (0·95–1·03)	p=0·5327
ECOG performance status score			
0	10 469/11 201	Ref	
1	5195/5672	0·96 (0·92–0·99)	p=0·0198
≥2	1933/2193	0·89 (0·84–0·94)	p<0·0001
Current smoker			
No	15 555/16 802	Ref	
Yes	2042/2264	1·03 (0·99–1·08)	p=0·1712
Pre-existing respiratory condition			
No	15 598/16 911	Ref	
Yes	1999/2155	0·98 (0·94–1·03)	p=0·4716
RCRI			
0	5413/5682	Ref	
1	8992/9839	1·01 (0·95–1·08)	p=0·7788
2	2531/2810	0·96 (0·89–1·03)	p=0·2449
≥3	661/735	0·90 (0·81–0·10)	p=0·0438
Disease stage			
Early disease	9670/10 453	Ref	
Advanced or nodal disease	7927/8613	0·96 (0·93–0·10)	p=0·0181
Cancer location			
Head or neck	3142/3469	Ref	
Colon	3208/3359	1·16 (1·08–1·24)	p<0·0001
Rectal	1309/1462	0·59 (0·54–0·64)	p<0·0001
Gastric	644/712	0·67 (0·61–0·74)	p<0·0001
Oesophageal	324/435	0·32 (0·28–0·36)	p<0·0001
Lung	1047/1159	0·82 (0·76–0·90)	p<0·0001
Liver	696/759	0·63 (0·57–0·69)	p<0·0001
Pancreatic	628/741	0·73 (0·66–0·81)	p<0·0001
Sarcoma	377/413	0·67 (0·59–0·75)	p<0·0001
Prostate	427/504	0·44 (0·40–0·50)	p<0·0001
Kidney or upper tract urothelial	363/422	0·65 (0·57–0·73)	p<0·0001
Bladder	104/139	0·51 (0·42–0·62)	p<0·0001
Gynaecological	1884/2048	0·86 (0·79–0·93)	p=0·0001
Breast	3135/3444	1·00 (0·94–1·05)	p=0·8835

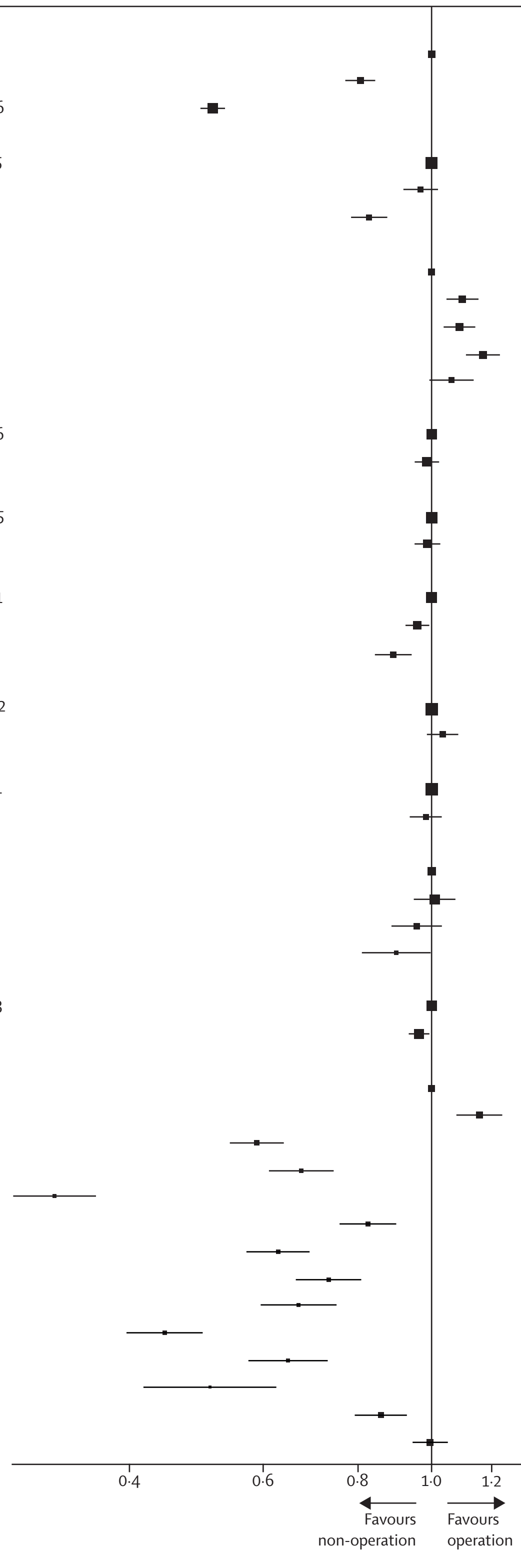

Figure 3: **Multivariable Cox proportional hazards model of factors associated with non-operation during COVID-19**
19 832 in dataframe, 19 066 in model, 766 missing. 17 597 (91·8%) of 19 066 patients included in this model were operated by the end of follow-up. Missing data are described in the appendix (p 10), as well as the full model (p 12). ASA=American Society of Anesthesiologists Physical Status Classification System. ECOG=Eastern Cooperative Oncology Group. RCRI=Revised Cardiac Risk Index.

1775 (88·7%) of 2003 patients who remained non-operated were in regions with full lockdowns (appendix p 11). The baseline rate of non-operation was low across all income settings during periods of light restrictions (22 [0·5%] of 4089 in high-income countries; one [0·4%] of 228 in UMICs; three [1·5%] of 204 in LMICs), and high during periods of full lockdown (1188 [13·7%] of 8644 in high-income countries; 139 [10·5%] of 1329 in UMICs; 448 [24·2%] of 1854 in LMICs). At 12 weeks after diagnosis, 581 [12·8%] of 4520 patients under light restrictions remained non-operated, 720 (19·9%) of 3622 patients during moderate lockdowns, and 4752 (40·7%) of 11678 patients during full lockdowns (figure 2). After multivariable adjustment, both moderate (HR 0·81, 95% CI 0·77–0·84; p<0·0001) and full lockdowns (HR 0·51, 0·50–0·53; p<0·0001) were associated with a lower likelihood of a patient receiving their planned cancer surgery (figure 3; appendix p 10). This was consistent across planned sensitivity analyses (appendix pp 13–16). The overall level of missingness was low (<1%) for all variables included in the models.

Being in an LMIC, increasing frailty (Eastern Cooperative Oncology Group 1 or ≥2), comorbidity (Revised Cardiac Risk Index ≥3), and having locally advanced or nodal disease, or both, were all independently associated with increased likelihood of non-operation. There was significant variability in the likelihood of non-operation by cancer site. Where the primary outcome definition was revised to include elective surgery only, both UMICs and LMICs were observed to have a higher adjusted non-operation rates than high-income countries (appendix p 13). The effect of lockdown on non-operation differed by income group, with LMICs broadly less likely to operate at a given level of lockdown compared with the high-income group (appendix p 15). Patients waiting for surgery in LMICs during full lockdowns were most likely to remain non-operated compared with patients in LMICs during light restrictions (HR 0·41, 95% CI 0·38–0·44; p<0·0001; appendix p 16). In the secondary analysis, waiting for surgery for 5–6 weeks or more in full lockdown was associated with a reduced likelihood of a patient undergoing their cancer operation compared with 0 weeks in full lockdown (5–6 weeks in full lockdown HR 0·86, 95% CI 0·80–0·93, p<0·0001; appendix p 6).

Patients younger than 50 years were less likely than patients 50 years and older to receive their planned surgery across several sensitivity analyses. Patients planned to have surgery aged younger than 50 years were more commonly from LMICs than UMICs or high-income countries commonly from LMICs (appendix pp 18–19). In a sensitivity analysis including only patients older than 50 years, the effect of lockdowns on surgical capacity remained consistent with the primary result (ie, moderate and full lockdowns were associated with a significant increase in the odds of non-operation compared with light restrictions; appendix p 20).

	All patients
COVID-19 related	
Multidisciplinary team decision to delay surgery due to patient risk during COVID-19	1456 (72·8%)
Change to alternative treatment modality because of COVID-19	533 (26·6%)
Patient choice to avoid surgery during COVID-19 pandemic	460 (23·0%)
Ongoing neoadjuvant therapy (COVID decision)	378 (18·9%)
No bed, critical care bed, or operating room space available due to COVID-19	299 (14·9%)
Change of recommendations in society guidelines related to COVID-19	220 (11·0%)
Patient unable to travel to hospital related to COVID-19	140 (7·0%)
Collateral impact on supporting services causing delay	24 (1·2%)
Patient delayed due to SARS-CoV-2 infection	23 (1·1%)
Died of COVID-19 while waiting for surgery	14 (0·6%)
Total	2001 (100·0%)
Non-COVID-19 related	
Progression to unresectable disease	179 (8·9%)
Delay due to other unrelated medical or surgical condition	59 (2·9%)
Died unrelated to COVID-19 while waiting for surgery	34 (1·7%)
Patient unable to afford surgery	24 (1·2%)
Patient choice to avoid surgery unrelated to COVID-19	35 (1·7%)
Total	306 (15·3%)

We anticipated that decisions to delay or cancel surgery during COVID-19 would be complex. Therefore, selecting more than one reason for non-operation during the follow-up window for each patient was permitted. One patient could have both one or more COVID-19-related and non-COVID-19-related reasons selected. Where it was unclear whether a reason was directly COVID-related (eg, disease progression) this was classified as not COVID-19-related. Two patients (0·1%) had no reasons given for non-operation during the follow-up window selected (missing data). Proportions are therefore expressed as a percentage of 2001 non-operated patients and with data available.

Table 1: **Reasons that patients did not received planned surgery**

Increasing SARS-CoV-2 case notification rates were associated with increasing non-operation rates (appendix p 21). Both moderate and full lockdowns were consistently associated with an increased likelihood of non-operation, even after adjustment for local SARS-CoV-2 rates (appendix p 22). The largest magnitude of effect was seen when transitioning from light restrictions or moderate lockdowns to full lockdowns across all income and SARS-CoV-2 case notification rate groups. LMICs were particularly fragile to increasing SARS-CoV-2 rates and full lockdowns, with a non-operation rate of 381 (58·7%) of 649 (appendix p 21).

By the end of the follow-up (median 23 weeks, IQR 16–30), 2003 patients had not undergone planned surgery. 453 (22·6%) of 2003 patients had been formally re-staged. Detection of new metastatic disease is shown in the appendix (p 26).

Of non-operated patients for whom data were available (n=2001; two missing data), all had at least one COVID-19-related reason provided for non-operation (table 1); most commonly this involved a team decision to delay surgery during COVID-19 due to individual patient risk (1456 [72·8%] of 2001). 533 (26·6%) of 2001 patients were provided an alternative treatment modality as a result of COVID-19. 306 (15·3%) patients had at least one non-COVID-19-related reason provided for non-operation.

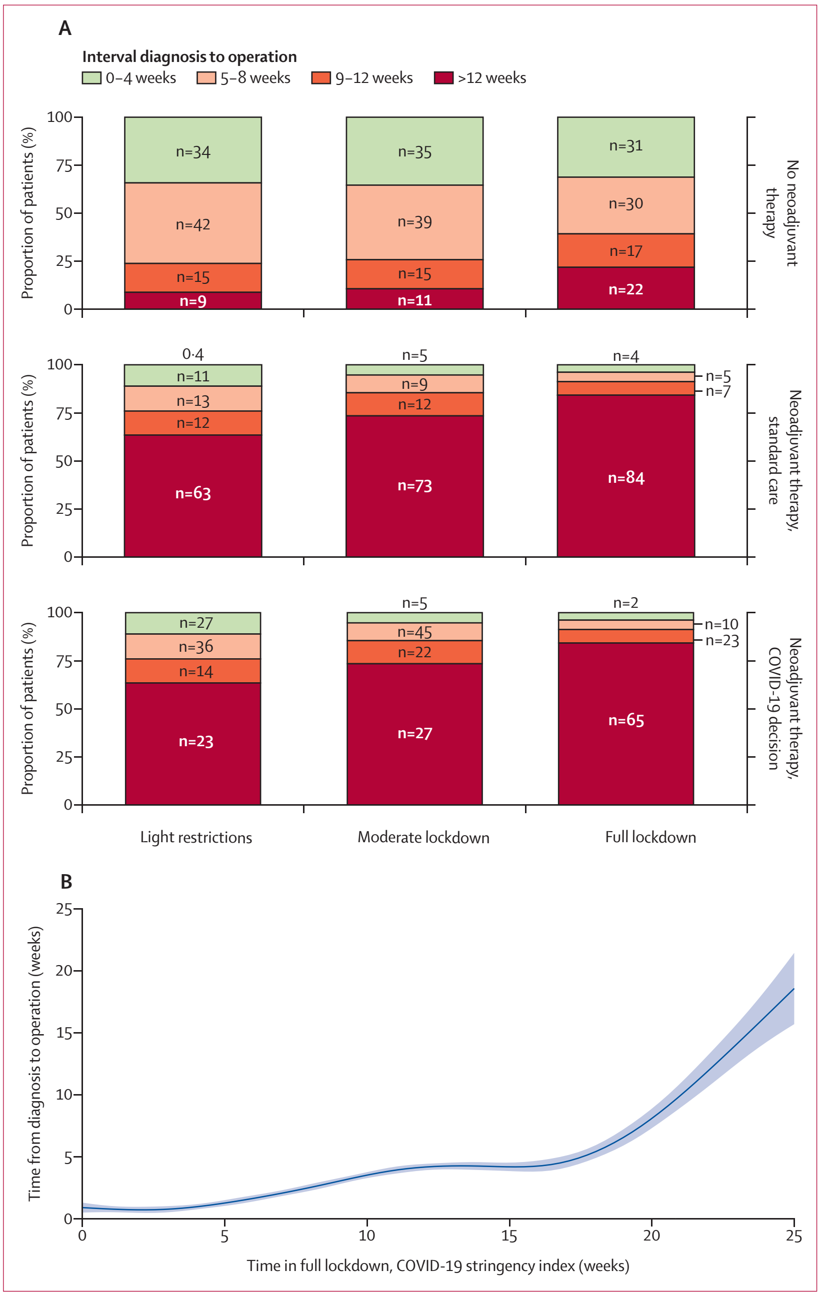

Figure 4: **Lockdown and delay to surgery**

(A) Delay from diagnosis to surgery during lockdowns (according to COVID-19 stringency index group) by neoadjuvant therapy group. Percentages represent proportion of operated patients who were in each interval from diagnosis to operation group. (B) Weeks in full lockdown and interval from cancer diagnosis to operation. Plot displays patients who went straight to surgery (no neoadjuvant therapy only). Full lockdown defined as a COVID-19 stringency index score of more than 60. Plotted line represents a smoothed conditional mean from a fitted generalised additive model. The shaded area denotes bounds of the 95% CI.

179 (8·9%) patients progressed to unresectable disease. 48 (2·4%) patients died before their planned surgery (14 due to COVID-19-related complications, and 34 due to non-COVID-19-related causes).

Delays from diagnosis to operation were observed during full lockdowns for operated patients (n=18 003) across all neoadjuvant treatment groups (figure 4). In patients who went straight to surgery (no neoadjuvant therapy; 15 622 [86·3%] of 18 003), full lockdown was associated with 2001 [23·8%] of 11 827 patients not receiving surgery within 12 weeks of diagnosis compared with 317 (10·4%) of 3646 patients during moderate lockdowns, and 374 (9·1%) of 4521 patients under light restrictions (appendix p 25). For these patients, each additional week in lockdown was associated with treatment delay (p<0·0001; figure 4). Increasing SARS-CoV-2 case notification rates were also associated with increased delays beyond 12 weeks across income groups, with the longest delays observed in UMICs and LMICs during periods with high SARS-CoV-2 rates (appendix p 23). The point of system friction was different across different income groups (appendix p 7). Full lockdown was associated with an increased interval from decision to surgery across all settings compared with both light restrictions and moderate lockdown (figure 4; appendix p 24).

In patients who went straight to surgery (n=15 622), postoperative histopathological and clinical outcomes during light restrictions, moderate lockdowns, and full lockdowns were similar (table 2). Characteristics and outcomes of patients by interval from diagnosis to operation are in the appendix (pp 25–26). Variation in outcomes by income group are shown in the appendix (p 27).

Discussion

The design of this study allowed a holistic overview of different health systems' surgical capacity and outcomes during lockdowns. The analysis allowed a direct comparison during full and moderate lockdowns to periods with light restrictions, taking account of the dynamic nature of government policies, where different patients from the same country were exposed to different lockdown states. During full lockdowns, one in seven patients did not receive their planned operation, all of whom had a pandemic-related reason for non-operation. This finding was robust, and consistent in sensitivity analyses. In a secondary analysis, awaiting surgery in a full lockdown for greater than 6 weeks was associated with an increased likelihood of non-operation. These data reveal the fragility of elective cancer surgery to lockdowns, which was independent of both local SARS-CoV-2 rates and case-mix. Patients with cancer in LMICs, of increasing frailty, or with advanced disease were most vulnerable to lockdown effects. Capacity for major elective cancer should be part of every country's strategy to address whole-population health needs and prevent further collateral harm.

Identifying at-risk groups allows targeted system strengthening during both COVID-19 lockdowns and future pandemics. Firstly, vulnerable patient groups (eg, those with a poorer performance score, more cardiac comorbidities, or advanced cancers) were all less likely to receive surgery. Secondly, certain operation types that require more intensive perioperative care, including those for oesophageal and pancreatic cancer, were at increased risk of cancellation. Thirdly, patients in LMICs were less likely to undergo surgery during lockdowns and SARS-CoV-2 surges, which included a high proportion of young patients (<50 years). Protected elective surgical capacity might include protected COVID-19-free pathways (including dedicated surgical, anaesthetic, and theatre staff) within larger hospitals, or smaller bespoke elective surgery units that function as part of cancer treatment networks.[20] This also requires long-term investment in surge capacity for the acute care workforce and formal operational planning to manage public health emergencies without major disruption to elective care (further details are in the appendix p 64). Together, protected elective surgical capacity might allow essential elective surgery to continue despite external system shocks.[20]

The least resilient systems were in LMIC settings, exacerbating resource scarcity and capacity issues that were present prepandemic in the management of non-communicable diseases.[11,21] Elective cancer surgery systems in LMICs are typically under pressure from a high burden of expedited and emergency presentations.[11,15,21] This pressure was seen in our study, where the likelihood of non-operation was higher in both UMICs and LMICs, despite patients being younger and having fewer comorbidities. These young patients were more frequently affected by financial and geographical causes for non-operation, revealing a particularly vulnerable group. Measures to strengthen the security of global elective cancer surgery must be implemented across all settings, and as a priority in LMICs.[6] Despite data demonstrating the safety of neoadjuvant treatment during COVID-19, the overall rate of neoadjuvant therapy as standard care or a COVID-19 decision was low (15·2%). This low rate might represent safety concerns or highlight capacity issues elsewhere in the cancer care pathway.[22] Developing robust pathways from diagnosis through to definitive surgical treatment, supported by public health teams and financial protection mechanisms, will help to create both pandemic-proof and more equitable systems.

Although we did not find an increase in the positive resection margin rate or new metastatic disease associated with increasing delays, these were highly selected patients and with short-term follow-up only. The high proportion of patients who did not receive planned surgery reveals the true extent of potential harm. This part of our analysis focussed on patients who were treated without neoadjuvant therapy, who are likely to represent the group at highest risk from unplanned delays. Evidence from modelling studies and meta-analyses suggest that 4-week incremental delays before surgery are associated with increased rates of recurrence and excess mortality.[13] Taken together, patients who experienced a delay to surgery during the COVID-19 pandemic might warrant strategies that support closer follow-up for metastatic disease. It is possible that there will be a reverse trend towards worsening cancer survival rates over the next 5 years as a consequence of these capacity issues, although the present study was not designed to directly capture these long-term effects. We acknowledge that for some cancer types, neoadjuvant therapy has equivalent outcomes to the adjuvant application of the same treatment and might be a reasonable strategy to safely delay treatment where this is required (eg, endocrine therapy for oestrogen-receptor-positive breast cancers).[23] The impact of changes to neoadjuvant treatment pathways and both short-term and long-term oncological outcomes requires further exploration.

This study had several further limitations. First, effects seen during lockdowns could be interpreted as normal practice, which would have occurred outside of the pandemic era. We dealt with this by including an internal comparison (light restrictions), which is akin to normal conditions and carried a non-operation rate of 0·5%. We also collected clinicians' reasons for non-operation, which

	Light restrictions (n=4152)	Moderate lockdown (n=3057)	Full lockdown (n=8402)	Total* (N=15 622)	p value†
Margin status					
R0	3471 (83·7%)	2619 (85·8%)	7238 (86·3%)	13 328 (85·5%)	0·0011
R1	381 (9·3%)	223 (7·4%)	581 (6·9%)	1185 (7·7%)	..
R2	79 (1·9%)	61 (2·0%)	157 (1·9%)	297 (1·9%)	..
Pathology unavailable	214 (5·2%)	147 (4·8%)	407 (4·8%)	768 (4·9%)	..
Missing	7	7	19	33	..
Resectable disease at time of surgery					
Resectable	4069 (98·0%)	2967 (97·1%)	8213 (97·8%)	15 249 (97·7%)	0·045
Unresectable	81 (2·0%)	90 (2·9%)	187 (2·2%)	358 (2·3%)	..
Unknown	2	0	2	4	..
Pre-operative cancer-related complication requiring emergency surgery‡					
Elective	4071 (98·2%)	2989 (97·8%)	8199 (97·8%)	15 259 (97·9%)	0·27
Emergency	74 (1·8%)	67 (2·2%)	185 (2·2%)	326 (2·1%)	..
30-day SARS-CoV-2 infection rate‡					
No	4083 (98·3%)	3039 (99·4%)	8362 (99·5%)	15 484 (99·2%)	<0·0001
Yes	69 (1·7%)	18 (0·6%)	40 (0·5%)	127 (0·8%)	..
30-day postoperative mortality rate‡					
No	4080 (98·3%)	3016 (98·7%)	8307 (99·0%)	15 403 (98·8%)	0·0045
Yes	70 (1·7%)	41 (1·3%)	84 (1·0%)	195 (1·2%)	..
Missing	2	0	11	13	..
New detection of metastatic disease§					
No	2191 (98·3%)	1625 (98·3%)	4946 (98·2%)	8762 (98·2%)	0·87
Yes	38 (1·7%)	28 (1·7%)	93 (1·8%)	159 (1·8%)	..
Missing	7	5	15	27	..

Data are n (%) or n. Patients with metastatic disease at baseline removed from denominator (N=8957). Percentages presented by column total; missing data are excluded. R0=no microscopic or macroscopic disease. R1=microscopic disease at the margin. R2=macroscopic disease at the margin. *11 missing this data point. †χ^2 comparing light versus moderate versus full lockdowns for each outcome. ‡Subgroups defined in the appendix (p 62). §Detailed data on detection of new metastatic disease not collected for liver, pancreatic, breast, and gynaecological cancers.

Table 2: **Outcomes across COVID-19 stringency index groups for patients going straight to surgery (no neoadjuvant therapy)**

were overwhelmingly COVID-19 related. Second, we used the Oxford COVID-19 Stringency Index to define lockdowns,[1] calculated for each patient as the median average during their wait for surgery. Although this index has been validated, it is not yet widely used, and the COVIDSurg Collaborative is an early adopter of this metric for research purposes. This health policy measure demonstrated association with patient level outcomes in our dataset. However, we used an aggregate summary statistic that did not reflect all changes in policy during the study period. More work is required to understand the best method to apply this measure in future epidemiological studies. Third, as part of the exposure period to lockdowns occurred after study entry (ie, decision for surgery), this might have been subject to future information bias, where patients remaining non-operated for a longer time might have been more likely to await surgery during different lockdown states, therefore have a central tendency in their median average score.[24] Fourth, this study required prospective capture of team decision making, which might have been subject to biases, although the scale and diversity of the study mitigated against this. Fifth, definition of SARS-CoV-2 rates is dependent on testing performed and reported, so might vary at global scale.[17,18] We present exploratory analyses around SARS-CoV-2 rates stratified by income setting and provide sensitivity analyses to demonstrate that findings were robust. Sixth, we did not present more detailed analyses of between-country or within-country variation. Despite the large numbers in this study, individual numbers per country were low enough to risk type 1 error through multiple hypothesis testing. Seventh, in this analysis we did not explore different hospital types or delay in care for different cancers. There might have been hospitals that shutdown completely and did not take part in this study, meaning outcomes might have been worse. There might be specialty specific findings that allow future strategies to become stratified—eg, patients with rectal and prostate cancer might benefit from scaling up alternative neoadjuvant treatments; breast and gynaecological cancer surgery might be amenable to day case pathways; kidney, bladder, thoracic, and oesophagogastric surgery might require the advanced support of surgical units with critical care facilities; colon cancer could be performed in standalone surgical units. Eighth, we did not capture data on delays to diagnosis. Lockdowns are a system-level issue and high friction in diagnostic pathways was likely to have led to an increasing number of tumours left undetected in the community.[25] When considering resilience of a complete elective surgery system, there is a vital role of timely diagnostics in preventing harm, which might be just as important as delays between diagnosis and surgery. Finally, cancer care is just one component of a functioning health system. When making policy decisions about resourcing to improve resilience, cancer must be balanced with other high-burden conditions (eg, cardiovascular and cerebrovascular disease).[26]

At the time of publication, lockdowns of varying magnitude remain in place across many countries around the world, and further measures might be imposed related to novel variants of concern and variability in vaccine availability around the world (appendix p 64); however, threats to stable elective surgical systems are not limited to COVID-19; other viral pandemics, seasonal pressures, and natural disasters all affect surgical patients on an annual and recurring basis. The lessons from this study might be used to inform surgical system strengthening both during the COVID-19 pandemic and beyond.

Contributors

The writing group (JCG, AAde, AAdi, EA, APA, FA, JA, AMB, AC-C, JE, ME, MF, CF, GG, DG, EAG, EH, PH, IL, SW, HL, SL, EL, GMAG, HM, EJM, JM, DM, KM, MM, RM, DM, FN, FP, MP, PP, AR-DM, KR, ACR, RKS, RS, JFFS, NS, GDS, RS, SS, ST, EHT, RV, DN, AAB) and the statistical analysis group (JCG, KAM, DN, EH, AAB) contributed to writing, data interpretation, and critical revision of the manuscript. The writing group, operations committee, and dissemination committee contributed to study conception, protocol development, study delivery, and management. The collaborators contributed to data collection and study governance across included sites. All members of the writing group had full access to the data in the study, and JCG, KAM, DN, EH, and AAB verified the underlying data in the study. AAB or JCG and the writing committee had final responsibility for the decision to submit for publication. Detailed role descriptions of all contributing collaborating authors are shown in the appendix (pp 28–54).

Declaration of interests

All authors declare no competing interests.

Data sharing

Anonymised individual participant data will be made available upon request to the corresponding authors after the date of publication, with approval of the operations and dissemination committees, and completion of a data sharing agreement.

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