Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study

Amit Sud, Bethany Torr*, Michael E Jones, John Broggio, Stephen Scott, Chey Loveday, Alice Garrett, Firza Gronthoud, David L Nicol, Shaman Jhanji, Stephen A Boyce, Matthew Williams, Elio Riboli, David C Muller, Emma Kipps, James Larkin, Neal Navani, Charles Swanton, Georgios Lyratzopoulos, Ethna McFerran, Mark Lawler, Richard Houlston, Clare Turnbull*

Summary

Background During the COVID-19 lockdown, referrals via the 2-week-wait urgent pathway for suspected cancer in England, UK, are reported to have decreased by up to 84%. We aimed to examine the impact of different scenarios of lockdown-accumulated backlog in cancer referrals on cancer survival, and the impact on survival per referred patient due to delayed referral versus risk of death from nosocomial infection with severe acute respiratory syndrome coronavirus 2.

Methods In this modelling study, we used age-stratified and stage-stratified 10-year cancer survival estimates for patients in England, UK, for 20 common tumour types diagnosed in 2008–17 at age 30 years and older from Public Health England. We also used data for cancer diagnoses made via the 2-week-wait referral pathway in 2013–16 from the Cancer Waiting Times system from NHS Digital. We applied per-day hazard ratios (HRs) for cancer progression that we generated from observational studies of delay to treatment. We quantified the annual numbers of cancers at stage I–III diagnosed via the 2-week-wait pathway using 2-week-wait age-specific and stage-specific breakdowns. From these numbers, we estimated the aggregate number of lives and life-years lost in England for per-patient delays of 1–6 months in presentation, diagnosis, or cancer treatment, or a combination of these. We assessed three scenarios of a 3-month period of lockdown during which 25%, 50%, and 75% of the normal monthly volumes of symptomatic patients delayed their presentation until after lockdown. Using referral-to-diagnosis conversion rates and COVID-19 case-fatality rates, we also estimated the survival increment per patient referred.

Findings Across England in 2013–16, an average of 6281 patients with stage I–III cancer were diagnosed via the 2-week-wait pathway per month, of whom 1691 (27%) would be predicted to die within 10 years from their disease. Delays in presentation via the 2-week-wait pathway over a 3-month lockdown period (with an average presentational delay of 2 months per patient) would result in 181 additional lives and 3316 life-years lost as a result of a backlog of referrals of 25%, 361 additional lives and 6632 life-years lost for a 50% backlog of referrals, and 542 additional lives and 9948 life-years lost for a 75% backlog in referrals. Compared with all diagnostics for the backlog being done in month 1 after lockdown, additional capacity across months 1–3 would result in 90 additional lives and 1662 live-years lost due to diagnostic delays for the 25% backlog scenario, 183 additional lives and 3362 life-years lost under the 50% backlog scenario, and 276 additional lives and 5075 life-years lost under the 75% backlog scenario. However, a delay in additional diagnostic capacity with provision spread across months 3–8 after lockdown would result in 401 additional lives and 7332 life-years lost due to diagnostic delays under the 25% backlog scenario, 811 additional lives and 14 873 life-years lost under the 50% backlog scenario, and 1231 additional lives and 22 635 life-years lost under the 75% backlog scenario. A 2-month delay in 2-week-wait investigatory referrals results in an estimated loss of between 0·0 and 0·7 life-years per referred patient, depending on age and tumour type.

Interpretation Prompt provision of additional capacity to address the backlog of diagnostics will minimise deaths as a result of diagnostic delays that could add to those predicted due to expected presentational delays. Prioritisation of patient groups for whom delay would result in most life-years lost warrants consideration as an option for mitigating the aggregate burden of mortality in patients with cancer.

Funding None.

Introduction

After the announcement by the UK Government on March 23, 2020, of implementation of a nationwide lockdown to combat the COVID-19 pandemic, hospital referrals for non-COVID-19-related illnesses have decreased substantially.[1] As the lockdown is lifted, a surge in presentations for non-COVID-19-related medical issues is anticipated.

Lancet Oncol 2020; 21: 1035–44

Published Online July 20, 2020 https://doi.org/10.1016/S1470-2045(20)30392-2

See Comment page 1000

*Contributed equally

Division of Genetics and Epidemiology (A Sud PhD, B Torr MSc, M E Jones PhD, C Loveday PhD, A Garrett MSc, Prof R Houlston DSc, Prof C Turnbull PhD), **Division of Clinical Studies** (D L Nicol FRACS, Prof J Larkin PhD), **and Division of Cancer Biology** (S Jhanji PhD), **Institute of Cancer Research, London, UK; National Cancer Registration and Analysis Service, Public Health England, London, UK** (J Broggio MSci, Prof G Lyratzopoulos PhD, Prof C Turnbull); **RM Partners, West London Cancer Alliance, London, UK** (S Scott BSc, E Kipps PhD); **Microbiology** (F Gronthoud MD), **Urology Unit** (D L Nicol), **Department of Anaesthesia, Perioperative Medicine and Critical Care** (S Jhanji), **The Breast Unit** (E Kipps), **Skin and Renal Unit** (Prof J Larkin), **and Department of Clinical Genetics** (Prof R Houlston, Prof C Turnbull), **Royal Marsden NHS Foundation Trust, London, UK; Department of Colorectal Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (S A Boyce PhD); **Department of Clinical Oncology, Imperial College Healthcare NHS Trust, London, UK** (M Williams PhD); **Computational Oncology Group** (M Williams), **School of Public Health** (Prof E Riboli MD, D C Muller PhD), **Imperial College London, London, UK; Department of Thoracic Medicine, University College London Hospital, London, UK** (N Navani PhD); **Lungs for Living Research Centre, UCL Respiratory** (N Navani PhD)

and Epidemiology of Cancer Healthcare and Outcomes (ECHO) Group (Prof G Lyratzopoulos), University College London, London, UK; Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK (Prof C Swanton FRS); Cancer Evolution and Genome Instability Laboratory, University College London Cancer Institute, London, UK (Prof C Swanton); Patrick G Johnston Centre for Cancer Research, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK (E McFerran PhD, Prof M Lawler PhD); and DATA-CAN, The UK Health Data Research Hub for Cancer, London, UK (Prof M Lawler)

Correspondence to: Prof Clare Turnbull, Division of Genetics and Epidemiology, Institute of Cancer Research, London, SM2 5NG, UK
clare.turnbull@icr.ac.uk

Research in context

Evidence before this study

We searched PubMed, with no language or date restrictions, on March 10, 2020, for observational studies of cancer pathway delays in English using the terms (["cancer" OR "neoplasm"] AND ["delay" OR "interval" OR "wait"] AND ["diagnosis" OR "treatment]). Studies typically reported data extracted from institutional, regional, or national databases. Overall, studies are highly heterogeneous in design and findings, including the durations of delay studied, the duration of survival follow-up, the method by which impact is captured (percentages, odds ratios, hazard ratios), and how and when staging is done. Each study typically focused on a single tumour type and most did not stratify impact by stage of cancer. To our knowledge, no study had modelled the impact in lives and life-years lost of systematic delays in referral pathways in a standardised fashion across tumour types until we recently reported a health-care resource analysis focused on systemic delays at point of surgery.

Added value of this study

Across multiple tumour types, we used a standardised approach using per-day fatality hazard ratios to quantify the effect of different durations of delay on survival, examining both the referred patient and the diagnosed patient, and examining delays for individual tumour types and subtypes and aggregated across major tumour types. This study focuses specifically on cancers diagnosed via the 2-week wait pathway because this pathway is most amenable to interventions. Although pertinent to ongoing forecasting of the impact of COVID-19-related delays, these models could apply to any systemic delays to cancer pathways.

Implications of all the available evidence

Incorporating previous observational studies of delay and examining crudely estimated, non-naturalistic per-patient delays, our models predict that COVID-19-related delays in presentation, diagnosis, and subsequent treatment, will result in loss of life and life-years that varies widely according to patient age and tumour type. Data regarding the true duration and extent of service disruption and per-patient cancer pathway delay across the UK as a result of the COVID-19 lockdown are currently immature. Direct predictions regarding attributable cancer deaths will be possible once more accurate patient-level data become available.

Any delay in cancer treatment has the real risk of patients' tumours progressing from being curable (with near-normal life expectancy) to becoming non-curable (with very reduced life expectancy). Specific pathways have been established in the UK for referral from primary care for urgent specialist evaluation and investigation of individuals with so-called red flag symptoms suggestive of a specific cancer type, termed the 2-week-wait pathway. Reductions of up to 84% have been reported in 2-week-wait referrals in March–May, 2020 (Lawler M, unpublished).[2–4] Large backlogs of patients accrued as a consequence of the lockdown are predicted to first place pressure on diagnostic services in secondary care, and affect other areas of the pathway thereafter.[5]

For more on the **National Cancer Registration and Analysis Service website** see https://www.gov.uk/guidance/national-cancer-registration-and-analysis-service-ncras

We aimed to address two key questions relating to this potential surge in presentations of symptomatic patients. First, we explored the effect of a range of scenarios of provision of additional diagnostic capacity to address patient backlogs, assuming no prioritisation of patient groups. For each scenario, we assessed the degree of so-called diagnostic delay incurred on top of the so-called presentation delay accrued during lockdown. Second, accounting for the risk of death associated with nosocomial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, we examined the gain in survival and life-years through prompt investigation per patients referred via 2-week-wait investigatory referral by age group and tumour referral group (the high-level grouping of tumour types via which referrals are made [appendix 1 pp 4–5]). To do these analyses, we developed a model using data on 10-year cancer survival for 2008–17 (stratified by age and cancer stage) combined with a per-day hazard ratio (HR) for delay and applied it to age-specific and stage-specific case and referral volumes based on the 2-week-wait pathway.[6]

See Online for appendix 1

Methods

Data sources

In this modelling study, we obtained patient numbers, age-stratified and cancer stage-stratified 5-year (2013–17) and age-stratified 10-year (2008–17) cancer survival data for all diagnoses, and those cancers associated with surgical resection for non-haematological malignancies, from Public Health England's National Cancer Registration and Analysis Service (NCRAS), including by subtype of breast cancer (appendix 1 pp 1–3). We obtained data on route to diagnosis by age and cancer stage from National Health Services (NHS) England Clinical Commissioning Groups collections.[7] We used data on proportion of referrals for suspected cancer that translated into cancer diagnoses (the diagnostic-conversion rate) from Cancer Waits-Faster Diagnosis Standard data for west London, UK, for 2019–20.[8] We used data from across England for cancer cases diagnosed when the patient was aged 30 years or older. We concentrated our analysis on the 20 most common cancers referred via 2-week-wait pathways, for which we analysed NCRAS survival data from 2 314 822 cancer cases (2008–17) and 2-week-wait diagnoses for 385 156 cancer cases (2013–16) (appendix 1 pp 4–5). We calculated life expectancy on the basis of UK Office of National Statistics life tables for 2016–18.[9] We estimated nosocomial infection rates and median duration of hospital stay for treatment of each cancer type on the basis of aggregated and anonymised information from

three large UK surgical oncology centres (Gronthoud F, unpublished). For the calculation of the case-fatality rate associated with unselected COVID-19 infection, we used published data from China because UK COVID-19 case-fatality rate estimates were only available for patients who had been admitted to hospital.[10,11]

Model development

We used net survival estimates in which crude survival has been adjusted for background age-specific death rates in the general population to reflect cancer-specific mortality. Since long-term survival rates for most cancers are only known 5–10 years after diagnosis, we used 10-year cancer stage-specific survival data in our calculations. Because 10-year stage-specific survival data are not directly available for recent cancer cohorts in England, we estimated these data using established methods, by taking the ratio of stage-specific to all-stage 5-year survival data and applying it to 10-year all-stage survival data.[12] We used the midpoint per 10-year age group for life expectancy to estimate life-years gained, averaged per patient.[9]

To calculate COVID-19-related mortality in patients with cancer, we first estimated peri-surgical mortality from nosocomial infection as the product of operation-specific duration of surgical admission, age-specific case-fatality rates, and the rate of nosocomial infection per day (1%, 2%, 5%, or 10%). Then we estimated COVID-19-related mortality in the community ascribing the patient a year of active cancer management status; this estimate was the product of the likelihood of community-acquired COVID-19 during the year (1%, 10%, 20%, or 50%), age-specific case-fatality rates, and the increase in COVID-19 case-fatality rate as a consequence of cancer as a comorbidity (two times or five times).[10,11]

For the calculation of the HR for per-day delay in management, we used published data on the impact of delay in cancer surgery on overall survival for stage I–III disease to estimate per-day HRs associated with delay to definitive treatment.[13–21] Since sufficient observational data were only available to generate summary delay HRs for breast, colorectal, and bladder cancers, we assigned delay HRs to other tumours on the basis of similarity of 5-year survival, categorising tumour progressiveness as being low (with a 5-year survival for stage II disease being >90%), moderate (50–90%), or high (<50%). Because of the scarcity of published observational data on tumours of high progressiveness (eg, oesophageal and gastric cancers), we conservatively considered this group as having a similar delay HR as moderately progressive tumours (appendix 1 pp 1–3). Finally, we assumed that delay to treatment for stage IV cancer would not affect 10-year survival.

Because patients younger than 60 years with stage I–III cancers typically have treatment with curative intent, we generated the stage-specific ratio from this group of those having major resection to those having other definitive treatment (eg, endoscopic resection or curative radiotherapy). We applied this ratio to age-specific and cancer stage-specific strata for those aged 60 years and older having major resection to estimate the proportion of patients who have been diagnosed who are having other types of definitive treatment.

To estimate 10-year survival for individuals diagnosed with stage I–III cancer who have no delay in treatment, we used NCRAS 10-year survival data and adjusted for COVID-19-related peri-surgical and community mortality. To estimate 10-year survival associated with delay, we applied the delay HR relating to the specified number of days of delay, along with the COVID-19-related peri-surgical and community mortality, to the NCRAS 10-year survival (formulas are in appendix 1 [pp 1–3]). We conservatively assumed that no additional downstream delays would occur after the diagnostic delay.

We quantified the annual numbers of cancers diagnosed via the 2-week-wait pathway using the 2-week-wait age-specific and stage-specific breakdowns. From these, our outcome measures were estimated aggregate number of lives lost and life-years lost in England for per-patient delays of 1–6 months.

Scenarios analysed using the model

We assessed the scenario of a 3-month period of lockdown during which a proportion of symptomatic patients delayed their presentation until after lockdown (ie, backlog patients), set at 25%, 50%, and 75% of normal monthly volumes. We assumed normal volumes of incident symptomatic patients presenting after lockdown. We considered different scenarios of extra capacity for catching up on this backlog applied across months 1–8 after lockdown. The backlog patients were assigned an average presentational delay of 2 months. Backlog and incident patients then accrued diagnostic delay in rounded whole months. We estimated the attributable lives and life-years lost, compared with the default position in which all backlog patients would complete investigatory referral within month 1 after lockdown. We modelled all backlog patients presenting in month 1 after lockdown or with variable presentation across months 1–3 (appendix 2).

See Online for appendix 2

We then did a per-patient risk–benefit analysis for 2-week-wait investigatory referral. A 2-week-wait investigatory referral was assigned as being 0·5 days of exposure to nosocomial infection. We combined per-day rates of nosocomial infection with the age-specific COVID-19 case-fatality rates to quantify the COVID-19-related fatality associated with investigatory referral. We combined this estimate with a so-called technical fatality risk for invasive investigations (eg, a one in 10 000 risk of death from perforation from colonoscopy)[22] to produce a combined per-referral mortality.

Using the diagnostic-conversion rates, we estimated the survival benefit per patient from an investigatory referral for each age group and tumour group. We considered the potential to delay referral by 2, 4, and 6 months against varying rates of nosocomial infection per investigatory

	Age group (years)					
	30–39	40–49	50–59	60–69	70–79	≥80
Bladder	15·79%	14·95%	14·29%	15·48%	**17·15%**	**17·03%**
Brain	11·75%	14·15%	**17·82%**	**18·24%**	16·64%	16·70%
Breast	4·88%	3·27%	2·49%	2·14%	3·71%	7·70%
Cervix	5·59%	9·03%	12·20%	15·73%	**17·98%**	15·52%
Colorectal	10·22%	11·38%	10·82%	10·59%	13·10%	16·36%
Kidney	5·01%	6·50%	8·53%	10·53%	13·10%	**17·41%**
Larynx	11·07%	14·29%	13·45%	14·94%	15·86%	16·79%
Liver	16·68%	**17·29%**	16·17%	14·67%	11·89%	14·78%
Lung	16·87%	**18·26%**	16·80%	15·37%	11·78%	6·70%
Melanoma of skin	3·13%	3·96%	4·89%	5·66%	7·32%	12·56%
Oesophagus	16·85%	16·21%	16·12%	15·18%	12·28%	4·59%
Oral cavity	12·83%	16·98%	**18·27%**	**18·28%**	**17·88%**	16·62%
Oropharynx	11·79%	14·48%	16·77%	**18·31%**	**17·08%**	13·73%
Ovary	7·24%	13·87%	**17·38%**	**18·28%**	**17·08%**	15·86%
Pancreas	12·86%	11·76%	12·11%	9·00%	7·18%	10·74%
Prostate	0·68%	0·67%	0·32%	0%	0%	3·69%
Stomach	**18·58%**	**18·54%**	**18·03%**	**17·34%**	16·11%	8·85%
Testis	0·58%	0·36%	0·76%	0·35%	0·63%	1·62%
Thyroid	0·11%	0·63%	1·33%	0·22%	2·57%	0%
Uterus	2·43%	5·27%	6·04%	8·68%	11·83%	14·43%

Figure 1: **Reduction in 10-year net survival incurred from a 3-month delay for the 20 most common tumour types, by age group**
Red indicates the highest decile of survival decrement, scaling down through orange and yellow to pale green, which indicates the lowest decile of survival decrement.

referral (5% being very high, 2·5% being high, 1% being moderate, and 0·5% being low). By age group and tumour type, we compared the benefit of prompt investigatory referral versus different periods of delay or no referral (absolute survival benefit). We estimated benefit in proportional survival and life-years gained from gain in cancer survival versus the combined fatality risk (COVID-19 and technical).

Statistical analysis

We combined individual log(HR)s, by stage and days of delay, using weighted linear regression to calculate the summary per-day delay-log(HR) (ie, delay HR) and SD of this estimate (ie, SE), expressing it as a percentage of the estimate. We did multivariate sensitivity analyses across ranges of parameter estimates, including 2 SD of delay HR and per day nosocomial infection rates of 1%, 2%, 5%, and 10%. Unless otherwise specified, we applied the default values for likelihood of community-acquired COVID-19, which was 20%, and per-day rate of nosocomial infection, which was 2%, which were selected to be conservatively high. For cancer-related increase in mortality due to community-acquired COVID-19, we used a default value of two times, which is at the low-to-intermediate end of the published estimates (reflecting a non-metastatic cancer population; appendix 1 p 1). Assumptions and parameter estimates are justified in detail in appendix 1 (pp 1–3). We did all analyses using STATA (version 15).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For several cancers, including those of the colorectum, oesophagus, lung, liver, bladder, pancreas, stomach, larynx, and oropharynx, a 3-month delay to diagnosis is predicted to result in a reduction in long-term (10-year) survival of more than 10% in most age groups (figure 1). Delays of 6 months are predicted to reduce 10-year mortality by more than 30% in many of these tumour types (appendix 1 p 6). Differences in the effects of a 3-month diagnostic delay were observed for different cancer stages across all tumour types and for different subtypes and stages of breast cancer (appendix 1 p 7).

The aggregated impact of universal delays in the 2-week-wait pathway on lives lost and life-years lost varies widely by tumour type (figure 2). These predicted outcomes are driven by aspects of the model including age-specific incidence, the proportion of cancers diagnosed via the 2-week-wait pathway, the proportion of cancers diagnosed as stage I–III via the 2-week-wait pathway, and the aggressiveness of the tumour (appendix 1 pp 4–5). Attributable lives lost are highest for colorectal cancer and attributable life-years lost are highest for breast cancer. The aggregate effect from delays in prostate cancer pathways is predicted to be low, predominantly due to the high proportion of indolent cases inherent to the model. Similarly, pancreatic, gastric, and liver cancers only contribute moderately to the estimated total lives and life-years lost because fewer patients present via the 2-week-wait pathway and high proportions have stage IV disease at presentation (appendix 1 pp 4–5).

Across the 20 cancer types, on average an estimated 243 098 cancers are diagnosed annually. Of these, an estimated 96 289 are diagnosed via the 2-week-wait pathway, of which 75 369 (78·3%) are diagnosed at stage I–III (table). 20 293 (26·9%) of 75 369 patients would be predicted to die due to cancer within 10 years of diagnosis, representing a loss of 304 129 life-years. A uniform per-patient delay of 1 month would be predicted to result in attributable additional lives lost of 1412 and

	Number of cases diagnosed per year	Number of cases diagnosed per year via pathway	Attributable lives lost by length of delay						Attributable life-years lost by length of delay					
			1 month	2 months	3 months	4 months	5 months	6 months	1 month	2 months	3 months	4 months	5 months	6 months
Bladder	8524	3654	81	168	260	355	450	544	1430	2979	4633	6365	8139	9910
Brain	8102	140	8	16	23	31	37	43	159	324	490	654	813	962
Breast	41845	22678	228	472	734	1014	1312	1629	4733	9839	15339	21255	27608	34418
Cervix	2128	471	10	22	34	47	61	75	264	559	887	1246	1636	2054
Colorectal	32979	10620	296	624	981	1366	1773	2196	4308	9126	14460	20296	26591	33275
Kidney	8764	2459	50	106	168	236	309	388	923	1968	3143	4452	5897	7471
Larynx	1850	887	29	60	93	128	165	201	514	1079	1692	2344	3027	3725
Liver	4712	683	8	15	21	25	29	31	143	270	379	467	532	578
Lung	36668	10343	189	356	497	610	695	753	3605	6873	9704	12030	13829	15128
Melanoma of skin	12110	7642	138	296	476	682	913	1171	2501	5403	8756	12614	17028	22051
Oesophagus	7427	3339	72	137	192	236	268	291	1498	2850	4011	4952	5665	6163
Oral cavity	2629	1161	33	67	100	133	163	190	695	1415	2145	2864	3551	4183
Oropharynx	2905	1710	18	37	57	76	95	112	437	900	1379	1866	2347	2810
Ovary	6398	2142	81	163	244	323	397	464	1688	3445	5239	7027	8765	10406
Pancreas	8260	1594	12	21	27	32	34	36	224	402	533	623	678	709
Prostate	40834	19272	3	6	9	12	16	20	56	116	183	255	334	420
Stomach	5332	1654	38	74	107	135	159	177	719	1411	2051	2619	3096	3475
Testis	1355	829	1	3	4	6	8	10	55	116	182	254	333	419
Thyroid	2673	620	1	2	3	5	6	8	24	50	79	110	144	181
Uterus	7604	4390	117	249	397	562	743	939	1837	3932	6305	8970	11936	15201
Total	243098	96289	1412	2892	4429	6013	7633	9280	25812	53057	81589	111263	141950	173540

Figure 2: **Annual lives and life-years lost attributable to delay, aggregated for all patients diagnosed via the 2-week-wait pathway for the 20 most common tumour types**
Based on 10-year net survival data for England, UK, 2008–17. Greatest decrements in lives and life-years lost are shown in darker shades of orange.

life-years lost of 25 812 and a per-patient delay of 6 months would be attributed to an additional 9280 lives and 173 540 life-years lost over the subsequent 10 years for an annual cohort of cancer cases diagnosed via 2-week wait at stage I–III (figure 2).

On the basis of preliminary estimates of 2-week-wait referral decreases, we estimated the predicted effects of 25%, 50%, and 75% reductions in presentations over a 3-month lockdown period (appendix 2).[2–4] Based on data for 2013–16, for these 20 cancer types on average an estimated 149 000 2-week-wait referrals are made each month, resulting in 8024 diagnoses of cancer, of which 6281 are diagnosed at stage I–III (appendix 1 pp 4–5). 1691 (27%) of these 6281 patients will typically die from their cancer within 10 years.[7] We estimated the national toll of presentational delay accrued over a 3-month lockdown period to be 181 attributable additional lives and 3316 life-years lost for a backlog rate of 25%, 361 additional lives and 6632 life-years lost for a backlog rate of 50%, and 542 additional lives and 9948 life-years lost assuming a backlog rate of 75%, with an average presentational delay of 2 months per patient. Assuming the patients all present in month 1 after lockdown, normal diagnostic capacity would need to work at least 175% under the 25% backlog scenario, 250% under the 50% backlog scenario, and 325% under the 75% backlog scenario to clear the backlog (appendix 2). However, it is unlikely that all extra diagnostic capacity required can be provided in a single month; therefore, we estimated the additional lives and life-years that might be lost due to subsequent diagnostic delays. Rapid provision of additional capacity over months 1–3 would result in 90 additional lives and 1662 live-years lost due to diagnostic delays for the 25% backlog scenario, 183 additional lives and 3362 life-years

	Proportion of annual cancer diagnoses that are 2-week-wait diagnoses	Proportion by age group (years)						Proportion by cancer stage					Diagnostic conversion rate		Estimated annual 2-week-wait referrals
		30–39	40–49	50–59	60–69	70–79	≥80	Stage I	Stage II	Stage III	Stage IV	Stage I–III	Proportion of any cancer	Proportion of cancers in tumour referral group	
Bladder	3654/8524 (42·9%)	0·3%	2·1%	7·4%	23·4%	36·2%	30·6%	51·9%	29·1%	6·7%	12·3%	87·7%	16·9%	98·2%	21 624
Brain	140/8102 (1·7%)	8·7%	8·4%	16·4%	31·2%	25·2%	10·1%	N/A	N/A	N/A	N/A	N/A	1·0%	100·0%	13 982
Breast	22 678/41 845 (54·2%)	6·1%	19·1%	16·2%	16·3%	20·5%	21·8%	31·2%	50·9%	13·0%	4·9%	95·1%	4·9%	99·3%	462 822
Cervix	471/2128 (22·1%)	16·6%	15·8%	18·1%	19·7%	17·3%	12·4%	29·3%	40·1%	15·0%	15·6%	84·4%	3·1%	97·4%	15 183
Colorectal	10 620/32 979 (32·2%)	0·8%	3·1%	13·0%	21·5%	33·0%	28·5%	15·4%	28·2%	32·5%	23·9%	76·1%	2·8%	78·4%	379 272
Kidney	2459/8764 (28·1%)	2·3%	8·1%	17·7%	27·8%	27·5%	16·7%	45·3%	11·4%	21·8%	21·6%	78·4%	16·9%	98·2%	14 551
Larynx	887/1850 (48·0%)	0·5%	5·2%	19·4%	33·3%	28·2%	13·4%	36·6%	19·3%	17·8%	26·3%	73·7%	2·9%	74·0%	30 599
Liver	683/4712 (14·5%)	0·7%	1·9%	10·1%	25·2%	34·3%	27·7%	7·6%	10·6%	15·6%	66·1%	33·9%	5·7%	85·9%	11 989
Lung	10 343/36 668 (28·2%)	0·3%	2·2%	10·2%	30·2%	35·8%	21·3%	15·4%	9·9%	27·9%	46·8%	53·2%	10·9%	93·7%	94 893
Melanoma*	7642/12 110 (63·1%)	10·4%	14·2%	17·8%	23·0%	20·3%	14·3%	71·5%	20·4%	6·5%	1·6%	98·4%	4·4%	98·1%	173 673
Oesophagus	3339/7427 (45·0%)	0·4%	3·0%	12·9%	29·0%	31·0%	23·8%	7·4%	16·1%	41·2%	35·3%	64·7%	5·7%	85·9%	58 571
Oral cavity	1161/2629 (44·1%)	2·9%	9·7%	22·4%	29·4%	20·9%	14·8%	27·3%	15·8%	10·4%	46·5%	53·5%	2·9%	74·0%	40 022
Oropharynx	1710/2905 (58·9%)	1·4%	12·1%	34·7%	33·8%	14·2%	3·8%	2·8%	6·1%	13·4%	77·6%	22·4%	2·9%	74·0%	58 960
Ovary	2142/6398 (33·5%)	4·2%	8·4%	21·0%	28·9%	25·4%	12·0%	31·9%	7·8%	41·7%	18·6%	81·4%	3·1%	97·4%	69 112
Pancreas	1594/8260 (19·3%)	0·2%	2·1%	9·4%	26·0%	36·1%	26·1%	5·8%	14·7%	13·7%	65·8%	34·2%	5·7%	85·9%	27 962
Prostate	19 272/40 834 (47·2%)	0·0%	0·9%	9·6%	32·9%	38·2%	18·2%	27·9%	21·6%	26·0%	24·5%	75·5%	16·9%	98·2%	114 037
Stomach	1654/5332 (31·0%)	0·4%	3·0%	12·9%	29·0%	31·0%	23·8%	8·3%	18·5%	27·2%	46·1%	53·9%	5·7%	85·9%	29 024
Testis	829/1355 (61·2%)	61·7%	22·4%	10·9%	3·4%	1·2%	0·4%	86·6%	7·8%	3·1%	2·5%	97·5%	9·0%	75·0%	9213
Thyroid	620/2673 (23·2%)	28·3%	19·0%	18·1%	15·1%	12·2%	7·3%	44·4%	10·0%	19·0%	26·7%	73·3%	2·9%	74·0%	21 388
Uterus	4390/7604 (57·7%)	0·2%	2·3%	19·1%	35·8%	29·2%	13·4%	75·7%	7·5%	11·0%	5·9%	94·1%	3·1%	97·4%	141 614

Data shown are proportion of all diagnoses made via 2-week-wait pathway, with a breakdown by cancers diagnosed via this pathway by age and cancer stage, diagnostic conversion rate, and average annual referrals. Diagnostic conversion rates reflect all diagnoses of invasive cancers (exceptions are that breast includes carcinoma in situ, skin excludes basal cell carcinomas, urology excludes pTa bladder tumours). N/A=not applicable. *Of the skin.

Table: **Cancer diagnoses made through the 2-week-wait pathway for 2013–16**

lost under the 50% backlog scenario, and 276 additional lives and 5075 life-years lost under the 75% backlog scenario (appendix 2). Conversely, delayed additional capacity provided across months 3–8 after lockdown would result in 401 additional lives and 7332 life-years lost due to diagnostic delays under the 25% backlog scenario, 811 additional lives and 14 873 life-years lost under the 50% backlog scenario, and 1231 additional lives and 22 635 life-years lost under the 75% backlog scenario (appendix 2).

We assessed the risk–benefit balance per individual for investigatory referral, considering different rates of nosocomial infection. First, we considered absolute survival benefit, comparing prompt referral, diagnosis, and management with no referral or subsequent medical intervention (appendix 1 p 9). There was a per-patient survival benefit from referral for nearly all tumour types and age groups at a nosocomial infection risk of 1% or less. If the risk of infection is high (≥2·5% per referral), for patients older than 70 years, the risk associated with investigatory referral might exceed the absolute survival benefit for tumour-referral groups with poorer outcomes, such as upper gastrointestinal (pancreas, oesophagus, liver, and stomach) and brain tumours (appendix 1 p 9).

Second, we sought to address a common dilemma for primary care physicians—namely, to establish in which patients referral could be delayed by a few months, either to await reduction in nosocomial infection rates or to reduce pressure on diagnostic services. A 2-month delay in 2-week-wait investigatory referrals results in an average loss of between 0·0 and 0·7 life-years per referred patient, depending on age and tumour type (appendix 1 p 12). We compared risk of death from investigatory referral with delay-associated increase in risk of cancer death per patient referred (figure 3; appendix 1 pp 10–11). Factors associated with benefit of immediate referral over delay included younger patient age (<70 years), high tumour progressiveness, high diagnostic-conversion rates, and higher proportion of cases diagnosed with stage I–III disease (appendix 1 pp 1, 4, 10, 12). For those younger than 60 years, provided daily nosocomial infection rates are 2·5% or lower, even for short delays (2 months) the delay-related cancer-fatality rate largely exceeds investigation-related fatality. However, for patients older than 70 years,

	Nosocomial SARS-CoV-2 infection rate (per investigatory referral)																							
	0·5%						1·0%						2·5%						5·0%					
Age group, years	30–39	40–49	50–59	60–69	70–79	≥80	30–39	40–49	50–59	60–69	70–79	≥80	30–39	40–49	50–59	60–69	70–79	≥80	30–39	40–49	50–59	60–69	70–79	≥80
Bladder	1·47%	1·38%	1·31%	1·12%	0·82%	0·09%	1·46%	1·38%	1·30%	1·10%	0·78%	0·02%	1·46%	1·37%	1·28%	1·05%	0·65%	–0·21%	1·46%	1·36%	1·25%	0·95%	0·45%	–0·58%
Brain	0·07%	0·09%	0·11%	0·10%	0·08%	0·04%	0·07%	0·09%	0·10%	0·09%	0·04%	–0·03%	0·07%	0·08%	0·08%	0·03%	–0·09%	–0·26%	0·06%	0·07%	0·05%	–0·06%	–0·29%	–0·63%
Breast	0·14%	0·09%	0·07%	0·05%	0·07%	0·06%	0·14%	0·09%	0·06%	0·03%	0·03%	–0·01%	0·14%	0·09%	0·04%	–0·03%	–0·09%	–0·23%	0·14%	0·08%	0·01%	–0·12%	–0·29%	–0·60%
Cervix	0·09%	0·14%	0·19%	0·17%	0·09%	–0·02%	0·09%	0·14%	0·18%	0·15%	0·05%	–0·09%	0·08%	0·13%	0·16%	0·10%	–0·07%	–0·31%	0·08%	0·12%	0·13%	0·01%	–0·27%	–0·68%
Colorectal	0·10%	0·11%	0·10%	0·08%	0·09%	0·06%	0·09%	0·11%	0·09%	0·06%	0·05%	–0·02%	0·09%	0·10%	0·07%	0·01%	–0·07%	–0·24%	0·09%	0·09%	0·04%	–0·08%	–0·28%	–0·62%
Kidney	0·40%	0·52%	0·68%	0·78%	0·81%	0·45%	0·40%	0·52%	0·68%	0·76%	0·77%	0·38%	0·40%	0·51%	0·66%	0·71%	0·64%	0·15%	0·39%	0·50%	0·62%	0·61%	0·43%	–0·22%
Larynx	0·11%	0·14%	0·13%	0·12%	0·11%	0·09%	0·11%	0·14%	0·12%	0·10%	0·07%	0·01%	0·10%	0·13%	0·10%	0·05%	–0·05%	–0·21%	0·10%	0·12%	0·07%	–0·04%	–0·25%	–0·59%
Liver	0·19%	0·20%	0·18%	0·12%	0·06%	–0·02%	0·19%	0·19%	0·18%	0·10%	0·02%	–0·10%	0·19%	0·19%	0·16%	0·05%	–0·11%	–0·32%	0·18%	0·18%	0·12%	–0·04%	–0·31%	–0·69%
Lung	0·59%	0·67%	0·63%	0·46%	0·27%	–0·01%	0·59%	0·67%	0·62%	0·44%	0·22%	–0·08%	0·58%	0·66%	0·60%	0·38%	0·10%	–0·30%	0·58%	0·65%	0·56%	0·29%	–0·10%	–0·68%
Melanoma of skin	0·08%	0·10%	0·12%	0·13%	0·15%	0·26%	0·08%	0·10%	0·11%	0·11%	0·11%	0·19%	0·08%	0·09%	0·10%	0·06%	–0·01%	–0·03%	0·07%	0·08%	0·06%	–0·03%	–0·21%	–0·41%
Oesophagus	0·37%	0·36%	0·35%	0·29%	0·13%	–0·06%	0·37%	0·36%	0·35%	0·27%	0·09%	–0·14%	0·37%	0·35%	0·33%	0·21%	–0·04%	–0·36%	0·36%	0·34%	0·29%	0·12%	–0·24%	–0·73%
Oral cavity	0·09%	0·12%	0·13%	0·11%	0·08%	0·02%	0·09%	0·12%	0·13%	0·09%	0·04%	–0·05%	0·09%	0·12%	0·11%	0·04%	–0·08%	–0·28%	0·08%	0·11%	0·07%	–0·05%	–0·28%	–0·65%
Oropharynx	0·03%	0·04%	0·05%	0·03%	0%	–0·05%	0·03%	0·04%	0·04%	0·01%	–0·04%	–0·12%	0·03%	0·03%	0·02%	–0·04%	–0·16%	–0·34%	0·03%	0·02%	–0·01%	–0·13%	–0·36%	–0·71%
Ovary	0·11%	0·21%	0·27%	0·25%	0·18%	0·06%	0·11%	0·21%	0·26%	0·23%	0·13%	–0·01%	0·11%	0·21%	0·24%	0·18%	0·01%	–0·24%	0·10%	0·20%	0·21%	0·09%	–0·19%	–0·61%
Pancreas	0·16%	0·14%	0·14%	0·07%	0·01%	–0·05%	0·16%	0·14%	0·14%	0·05%	–0·03%	–0·13%	0·15%	0·14%	0·12%	–0·01%	–0·15%	–0·35%	0·15%	0·13%	0·08%	–0·10%	–0·35%	–0·72%
Prostate	0·05%	0·05%	0·02%	–0·02%	–0·04%	–0·06%	0·05%	0·05%	0·01%	–0·04%	–0·08%	–0·14%	0·05%	0·04%	–0·01%	–0·09%	–0·20%	–0·36%	0·04%	0·03%	–0·04%	–0·18%	–0·40%	–0·73%
Stomach	0·33%	0·33%	0·32%	0·26%	0·19%	–0·02%	0·33%	0·32%	0·31%	0·24%	0·15%	–0·09%	0·32%	0·32%	0·29%	0·19%	0·03%	–0·31%	0·32%	0·31%	0·26%	0·10%	–0·18%	–0·68%
Testis	0·02%	0·01%	0·03%	0%	–0·01%	–0·01%	0·02%	0·01%	0·02%	–0·02%	–0·05%	–0·09%	0·02%	0%	0%	–0·08%	–0·17%	–0·31%	0·01%	–0·01%	–0·03%	–0·17%	–0·37%	–0·68%
Thyroid	0%	0%	0·01%	–0·02%	–0·01%	–0·07%	0%	0%	0%	–0·03%	–0·05%	–0·15%	0%	0%	–0·02%	–0·09%	–0·17%	–0·37%	–0·01%	–0·01%	–0·05%	–0·18%	–0·37%	–0·74%
Uterus	0·04%	0·09%	0·10%	0·14%	0·17%	0·17%	0·04%	0·09%	0·09%	0·12%	0·13%	0·09%	0·04%	0·08%	0·07%	0·06%	0·01%	–0·13%	0·03%	0·07%	0·04%	–0·03%	–0·19%	–0·51%

***Figure 3:* Per-patient net survival gain from urgent investigatory referral compared with 2-month delay for the 20 most common tumour types, with varying rates of nosocomial SARS-CoV-2 infection, by age group**
Red indicates benefit of urgent investigatory referral and green indicates no benefit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

when the nosocomial infection rate is higher than 1%, investigation-related fatality for several tumour types of good prognosis (eg, prostate, testicular, and thyroid) or very poor prognosis (eg, pancreas, liver, oropharynx) is predicted to be greater than delay-related cancer fatality for as long as 6 months (appendix 1 pp 10–11). Bladder and kidney cancers exemplify tumour types for which prompt referral is most impactful, since these groups have a high diagnostic-conversion rate, the tumours are moderately progressive, but are predominantly stage I–III at diagnosis. In the event of stable, low nosocomial infection rate (≤0·5% per referral), we determined life-years lost for delayed referrals (appendix 1 p 12). For those referred with symptoms of bladder cancer, for a 2-month delay the average decrement per referred patient is 0·69 life-years for those aged 30–39 years and 0·10 life-years for those aged 70–79 years; for those referred with symptoms of brain tumour, the average decrement is 0·03 life-years for those aged 30–39 years and 0·01 for those aged 70–79 years.

In multivariate sensitivity analyses, outcomes from the model were mostly sensitive to changes in the estimated per-day delay HR. Varying the delay HR by 2 SDs (eg, 16%) in the scenario of a 2% nosocomial infection rate, the total lives lost annually for the 2-week-wait population attributable to a 2-month delay ranged from 2412 to 3378, and attributable life-years lost ranged from 44 192 to 62 055 (appendix 1 p 13). Using a proportionately higher per-day delay HR for tumours of high progressiveness (delay HR=0·0105 *vs* default delay HR=0·0056) increased the impact of a 2-month delay to 3772 lives lost and 72 053 life-years lost. Varying the rate of nosocomial infection, the community infection rate, and the cancer mortality multiplier had a small effect on the impact of delay on survival.

Discussion

For most solid cancers, 10-year survival is generally considered to equate to cure, reflecting the proportion of stage I–III tumours for which their surgery (or radical radiotherapy) has enabled the restoration to normal or near-normal life expectancy. Our estimates suggest that, for many cancers, delays to treatment of 2–6 months will lead to a substantial proportion of patients with early-stage tumours progressing from having curable to incurable disease. However, this varies widely between tumour types, reflecting variation in the proportion of patients diagnosed through the 2-week-wait pathway, the proportion diagnosed with stage I–III tumours, the age profile of patients diagnosed with those cancers, and the diagnostic-conversion rate, which inevitably means that the overall impact of delays in referral via the 2-week-wait pathway is far from uniform between cancers.

During the lockdown in the UK in March–June, 2020, substantial temporal and geographical variation has been seen in rates of patient deferment in accessing urgent referral for cancer symptoms, with estimates as high as 84% (Lawler M, unpublished).[2,3] Substantial additional mortality from diagnostic delay on top of the presentational delay accrued during patient deferment is possible, especially if additional diagnostic capacity for catching up with the backlog is delayed. The additional capacity must include not only expanded technical provision for endoscopy, imaging, interventional radiology, and nuclear medicine, but also increased staffing for specialist assessment and pathology. Delivery will be further challenged by new requirements for personal protective equipment, physical distancing, and infection control. Innovative solutions will be required to deliver this extra capacity in a timely fashion, which might include procurement of private sector provision, expanded roles for health-care professionals such as endoscopy nurses, and pathway adaptation—eg, use of faecal immunochemical testing (FIT) for triage of colorectal cancer referrals.

Investment in expansion of capacity for NHS diagnostics and treatment is a priority if cancer services are to become more resilient to future extrinsic disruption, which could include additional waves of COVID-19. Additionally, more responsive informatic connections between primary care, diagnostic, and treatment services would enable improved agility in adaption of pathways and prioritisation of referrals. Furthermore, pre-emptive public education is required to discourage patients from deferring presentation of cancer symptoms along with modification of pathways to and through primary care.

Diagnostic delays will affect patient groups differently. For younger patients (<70 years), all delays should be avoided. Our data show that survival decrement for even small delays (ie, 2 months) is substantial for most tumours. Conversely, for older groups (≥70 years), per-referral risk of death from nosocomial infection is much higher and might exceed the average decrement of a moderate delay, in particular for more indolent cancer types (eg, prostate cancer) or cancers with a poor overall prognosis (eg, upper gastrointestinal tract cancers). Even in the absence of concerns about nosocomial infection, if there are pressures on diagnostic capacity, prioritisation and deprioritisation of patients according to tumour referral group and age warrants consideration as a strategy to mitigate the population-level cost of diagnostic delays in terms of lives and life-years lost.

Whether or not deaths due to SARS-CoV-2 infection, both direct and indirect (eg, compromise in collateral health-care delivery) will be outweighed by the positive impacts on mortality (eg, reduced air pollution, fewer road-traffic accidents, and handwashing) as a result of the COVID-19 and lockdown period is a matter of debate. Although our analyses examine cancer-specific survival only, the estimations of life-years gained would be altered by any sizeable shifts in life expectancy.

Here we used data for England, but cancer survival is similar across most economically developed countries, so we believe our estimates of the impact of delay for each tumour type are broadly applicable. Overall, in areas where cancer incidence, population structure, and

background rates of population mortality are broadly similar to those in England, our model would provide insights relevant to other health systems, although pathways to diagnosis for different cancers, eligibility criteria, and proportions of different cancers ascertained differ between countries. Issues of capacity and delays in diagnosis are of global interest as part of moving towards benchmarked metrics (eg, International Cancer Benchmarking Partnership).[3,23]

Our analysis focused only on invasive disease in common adult tumour types. Additional analyses might extend across rarer cancers, tumours of childhood, and non-invasive lesions such as dysplastic colonic adenomas. We only considered the impact of delay on patients with stage I–III disease having treatment with curative intent. Additional analyses will be required to assess the impact of delays for those having non-curative treatments.

As with all modelling, the accuracy of our predictions is contingent on the validity of assumptions and parameter estimates. Although we identified suitable observational data for delays in treatment for stages I–III for three tumour types, uniform application of these delay HRs across tumour types and over time will invariably oversimplify the complex, dynamic, tumour type-specific, age-specific, and stage-specific nature of cancer progression. To enable systematic insights across tumour types, routine capture of delays in referral pathways should be incorporated into all national cancer data collections.

Our analyses at the level of referral are subject to the limitations of data collection for diagnostic-conversion rates, which were only available at the level of tumour-referral group, precluding analyses specific to age stratum or tumour type-specific symptomatology. Furthermore, our analysis does not capture the impact of delay on survival when a 2-week-wait referral resulted in diagnosis of a different cancer outside of the index tumour-referral group (appendix 1 pp 4–5).

The current model presents a what-if prediction, in which we have included what we believe to be plausible estimates of delay applied in a simplistic non-naturalistic manner. Delay patterns will likely be complex and vary between individuals, by tumour type, over time, and by geographical location. The severity of local COVID-19 patterns, method-specific diagnostic capacity, and organisation of cancer services will all have an effect, as will local variation in pathway innovations in both diagnostics (FIT triage, colonography) and treatment (a priori use of radiotherapy and hormonal treatments). Initiatives such as DATA-CAN, the UK Health Data Research Hub for Cancer, are assembling accurate real-world data quantifying in detail true delays and patient volumes and distributions; these data could be applied to our models to refine our predictions. Over the coming months, we will also be able to quantify whether the post-lockdown surge in presentations directly mirrors the deficit during lockdown in standard 2-week-wait presentations, or whether a proportion of these patients genuinely self-resolve (ie, do not need medical attention).[24]

The availability of models such as those we have used will also enable more agile prospective resource planning in the face of future instances of systematic disruption of cancer services, which could include future major waves of COVID-19, other pandemics, or economic contractions.

Although the linear elements vary for the different routes to diagnosis (urgent, routine, emergency, and screening), at each step convergence exists in the resources used for diagnostics and treatment. For diagnostics, cross-competition will exist between tumour-referral groups for routine radiology, interventional radiology, and endoscopy resources. For each tumour type, a hierarchy of investigation exists. For example, patients referred for suspected lung cancer typically receive a CT scan, but only a subset of patients have an endobronchial ultrasound or bronchoscopy; nevertheless, subsequent PET-CT for staging might be the narrowest of bottlenecks in the lung pathway. To optimise recovery, integrated time-course health system analyses across different routes to diagnosis will be required, accounting for all the linear steps up to and including surgical and adjuvant treatment and considering local variation in bottlenecks to capacity.[6]

The impact of COVID-19-related disruption on cancer care is likely to be an ongoing issue until a vaccine or effective treatment is identified. Our modelling suggests a clinically significant impact in lives and life-years lost if delays to the 2-week-wait pathway are extensive and prolonged. Unlike acute pathologies, such as stroke and myocardial infarction, the true excess mortality due to COVID-19-related disruption to cancer pathways will not be fully evident for 10 years or longer.

Contributors

AS, CT, and RH designed the model. JB generated and did appropriate check to assert completeness and accuracy of data in the NCRAS datasets. SS generated and did appropriate checks to assert completeness and accuracy of data from the Clinical Commissioning Group-Cancer Waiting Times datasets. MEJ provided cancer progression models. BT provided mitigation models. AS and CT wrote the code for the model. MEJ, JB, ML, EM, CT, RH, AS, GL, ER, DCM, and MW provided epidemiological expertise in the parameterisation of the model and relevant literature. FG provided microbiology expertise in the estimation of nosocomial infection rates. SAB, SJ, DLN, JL, EK, CS, and NN provided details of clinical pathways. BT, AS, AG, and CL assembled the figures. CT drafted the manuscript, with substantial contribution from AS, RH, GL, ML, and EM. All authors contributed to the final manuscript.

Declaration of interests

ML reports personal fees and grants from Pfizer and personal fees from Roche outside of the submitted work. CS reports grants from Pfizer and Boehringer Ingelheim; grants and personal fees from Bristol Myers Squibb, AstraZeneca, Ono Pharmaceutical, and Roche-Ventana; personal fees from Novartis, MSD, Illumina, Celgene, GlaxoSmithKline, Genentech, Medicxi, and Sarah Canon Research Institute; personal fees and stock options from GRAIL; stock options from EPIC Biosciences and Apogen Biotech; and personal fees and being a co-founder of Achilles Therapeutics during the conduct of the study. CS has patents issued for an immune checkpoint intervention in cancer (PCT/EP2016/071471), for a method for treating cancer based on identification of clonal neo-antigens (PCT/EP2016/059401), for methods for lung cancer detection

For more on **DATA-CAN** see https://uclpartners.com/work/data-can-health-data-research-hub-cancer/

(PCT/US2017/028013), for a method of detecting tumour recurrence (PCT/GB2017/053289), for a method for treating cancer (PCT/EP2016/059401), for a method of treating cancer by targeting insertion/deletion mutations (PCT/GB2018/051893), for a method of identifying insertion/deletion mutation targets (PCT/GB2018/051892), for a method for determining whether an HLA allele is lost in a tumour (PCT/GB2018/052004), for a method for identifying responders to cancer treatment (PCT/GB2018/051912), and for a method of predicting survival rates for cancer patients (PCT/GB2020/050221). JL reports grants and personal fees from Achilles Therapeutics, Bristol-Myers Squibb, MSD, Nektar, Novartis, Pfizer, Roche, and Immunocore; personal fees from AstraZeneca, Boston Biomedical, Eisai, EUSA Pharma, GlaxoSmithKline, Ipsen, Imugene, Incyte, iOnctura, Kymab, Merck Sorono, Pierre Fabre, Secarna, Vitaccess, and Covance; and grants from Aveo and Pharmacyclics outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

AS, CT, RH, and MEJ are supported by the Institute of Cancer Research. MEJ also received funding from Breast Cancer Now. BT and AG are supported by Cancer Research UK (C61296/A27223). CL and CT receive support from the Movember foundation. RH is supported by Cancer Research UK (C1298/A8362) and Bobby Moore Fund for Cancer. GL is supported by a Cancer Research UK Advanced Clinician Scientist Fellowship Award (C18081/A18180) and is Associate Director of the multi-institutional CanTest Collaborative funded by Cancer Research UK (C8640/A23385). DCM is supported by Cancer Research UK (C57955/A24390). AS is in receipt of an Academic Clinical Lectureship from National Institute for Health Research and Biomedical Research Centre post-doctoral support. EM receives post-doctoral support from Health Data Research UK and Cancer Focus Northern Ireland grants. ML is funded by Health Data Research UK and UK Research and Innovation Industrial Strategy Challenge Fund. CS is a Royal Society Napier Research Professor. This work was supported by the Francis Crick Institute that receives its core funding from Cancer Research UK (FC001169), the UK Medical Research Council (FC001169), and the Wellcome Trust (FC001169).

References

1 Philpotts E. GPs made 30% fewer referrals to secondary care during March. Pulse, May 14, 2020. http://www.pulsetoday.co.uk/clinical/gps-made-30-fewer-referrals-to-secondary-care-during-march/20040818.article (accessed June 29, 2020).

2 Daily updates: Thursday 14 May. Providers NHS, 2020. https://nhsproviders.org/topics/covid-19/coronavirus-member-support/national-guidance/government-updates/daily-updates (accessed May 15, 2020).

3 Lai AG, Pasea L, Banerjee A, et al. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. *medRxiv* 2020; published online June 1. https://doi.org/10.1101/2020.05.27.20083287 (preprint).

4 Bower E. Urgent referrals rejected for one in three GPs during COVID-19 outbreak. GPonline, May 5, 2020. https://www.gponline.com/urgent-referrals-rejected-one-three-gps-during-covid-19-outbreak/article/1682282 (accessed June 29, 2020).

5 Bostock N. Patients waiting more than a month for urgent cancer checks amid COVID-19 crisis. GPonline, May 20, 2020. https://www.gponline.com/patients-waiting-month-urgent-cancer-checks-amid-covid-19-crisis/article/1681673 (accessed June 29, 2020).

6 Sud A, Jones M, Broggio J, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. *Ann Oncol* 2020; published online May 19. https://doi.org/10.1016/j.annonc.2020.05.009

7 CCG Cancer Assessment 2017/18. NHS England; Aug 16, 2018. https://www.england.nhs.uk/publication/ccg-cancer-assessment-2017-18/ (accessed June 29, 2020).

8 The Cancer Waiting Times Data Collection (CWT). NHS Digital. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/cancerwaitingtimescwt (accessed July 14, 2020).

9 National life tables: UK. Office for National Statistics, Sept 25, 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables (accessed June 29, 2020).

10 The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Wkly* 2020: **2:** 113–22. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51 (accessed July 14, 2020).

11 Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369:** m1985.

12 Andersson TM, Dickman PW, Eloranta S, Lambert PC. Estimating and modelling cure in population-based cancer studies within the framework of flexible parametric survival models. *BMC Med Res Methodol* 2011; **11:** 96.

13 Lee YH, Kung PT, Wang YH, Kuo WY, Kao SL, Tsai WC. Effect of length of time from diagnosis to treatment on colorectal cancer survival: a population-based study. *PLoS One* 2019; **14:** e0210465.

14 Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999; **353:** 1119–26.

15 Mano R, Vertosick EA, Hakimi AA, et al. The effect of delaying nephrectomy on oncologic outcomes in patients with renal tumors greater than 4cm. *Urol Oncol* 2016; **34:** 239.

16 Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. *JAMA Surg* 2013; **148:** 516–23.

17 Chu AT, Holt SK, Wright JL, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. *Cancer* 2019; **125:** 2011–17.

18 Sánchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003; **169:** 110–15.

19 May M, Nitzke T, Helke C, Vogler H, Hoschke B. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. *Scand J Urol Nephrol* 2004; **38:** 231–35.

20 Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. *JAMA Oncol* 2016; **2:** 330–39.

21 Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. *Br J Cancer* 1999; **79:** 858–64.

22 Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. *J Natl Cancer Inst* 2003; **95:** 230–36.

23 International Cancer Benchmarking Partnership (ICBP). Cancer Research UK, 2020. https://www.cancerresearchuk.org/health-professional/data-and-statistics/international-cancer-benchmarking-partnership-icbp (accessed June 29, 2020).

24 Dinmohamed AG, Visser O, Verhoeven RHA, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. *Lancet Oncol* 2020; **21:** 750–51.