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

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Abstract:	Background: During the COVID-19 lockdown, referrals via the 2 Week Wait (2WW) urgent pathway for suspected cancer in England are reported to have dropped by up to 84%. We aimed to examine the impact on cancer survival of different scenarios of lockdown-accumulated-backlog. We also aimed to examine by tumour-referral-group and age, survival benefit per referred patient considering survival decrement from delayed referral versus risk of death from nosocomial SARS-CoV-2 infection. Methods: To construct the underlying models, we used age- and stage-stratified 10 year-cancer survival estimates for England 2007-2017 for 20 common tumour-types.

	We applied per-day hazard ratios for cancer progression generated from observational studies of delay-to-treatment. We quantified the annual numbers of cancers diagnosed via the 2WW-pathway using the 2WW age- and stage-specific breakdowns. From these, for per-patient delays of 1-6 months, we estimated aggregate number of lives lost and life-years lost in England. Using referral-to-diagnosis conversion rates and COVID-19 case fatality rates, we also estimated the survival increment per patient referred. Findings: Per month across England in 2013-2016, on average 6,281 patients with Stage 1-3 cancer were diagnosed via the 2WW pathway of whom 1,691 would be predicted to die within 10 years from their disease. We estimated 2WW-pathway presentational-delay from three months of lockdown will result in total in 181/361/542 attributable additional deaths (if % reduction in referrals was 25/50/75% respectively). Limited diagnostic capacity to address the backlog may result in additional delays: 401/811/1,231 attributable additional deaths are estimated if additional diagnostic capacity is delayed until months 3-8 post-lockdown. 2-month delay in 2WW investigatory referral results in average loss of life-years per-referred-patient of between 0 and 0.7, depending on age and tumour-type. Interpretation: Prompt provision of additional capacity for 'catch-up' in diagnostics will minimise deaths consequent from 'diagnostic-delay' accumulated on top of the 'presentational-delay'. 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. Funding: None

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

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ABSTRACT

Background: During the COVID-19 lockdown, referrals via the 2 Week Wait (2WW) urgent pathway for suspected cancer in England are reported to have dropped by up to 84%. We aimed to examine the impact on cancer survival of different scenarios of lockdown-accumulated-backlog. We also aimed to examine by tumour-referral-group and age, survival benefit per referred patient considering survival decrement from delayed referral versus risk of death from nosocomial SARS-CoV-2 infection.

Methods: To construct the underlying models, we used age- and stage-stratified 10 year-cancer survival estimates for England 2007-2017 for 20 common tumour-types. We applied per-day hazard ratios for cancer progression generated from observational studies of delay-to-treatment. We quantified the annual numbers of cancers diagnosed via the 2WW-pathway using the 2WW age- and stage-specific breakdowns. From these, for per-patient delays of 1-6 months, we estimated aggregate number of lives lost and life-years lost in England. Using referral-to-diagnosis conversion rates and COVID-19 case fatality rates, we also estimated the survival increment per patient referred.

Findings: Per month across England in 2013-2016, on average 6,281 patients with Stage 1-3 cancer were diagnosed via the 2WW pathway of whom 1,691 would be predicted to die within 10 years from their disease. We estimated 2WW-pathway presentational-delay from three months of lockdown will result in total in 181/361/542 attributable additional deaths (if % reduction in referrals was 25/50/75% respectively). Limited diagnostic capacity to address the backlog may result in additional delays: 401/811/1,231 attributable additional deaths are estimated if additional diagnostic capacity is delayed until months 3-8 post-lockdown. 2-month delay in 2WW investigatory referral results in average loss of life-years per-referred-patient of between 0 and 0.7, depending on age and tumour-type.

Interpretation: Prompt provision of additional capacity for 'catch-up' in diagnostics will minimise deaths consequent from 'diagnostic-delay' accumulated on top of the 'presentational-delay'. 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.

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(323 words)

INTRODUCTION

Following announcement by the United Kingdom (UK) government on 23rd March 2020 of nationwide lockdown to combat the COVID-19 pandemic, hospital referrals for non-COVID-related healthcare problems have plummeted (1). As the lockdown is lifted, it is anticipated there will be a surge in presentations for non-COVID-19 medical issues.

Any delay in cancer treatment carries the real risk of patients' tumours progressing from being curable (with near-normal life expectancy) to becoming non-curable (with limited life expectancy). Specific pathways have been established in the UK for referral from primary care for urgent specialist evaluation and investigation of individuals with 'red-flag' symptoms suggestive of a specific cancer type, termed "the 2 Week Wait (2WW) pathway". Reductions of up to 84% have been reported in 2WW referrals in March-May 2020 (2-4) (personal communication M.Lawler). It is predicted that sizeable backlogs accrued as a consequence of the lockdown will likely first place pressure on diagnostic services in secondary care (5).

We addressed two key questions relating to this potential surge in presentations of symptomatic patients. Firstly, we explored the impact of a range of scenarios of provision of additional diagnostic capacity to address patient backlogs, assuming no prioritisation of patient groups. For each, we evaluated the degree of 'diagnostic-delay' incurred on top of the 'presentation delay' accrued during lockdown. Secondly, accounting for the risk of death associated with nosocomial COVID-19 infection, we examined by tumour-referral-group and age the gain in survival and life-years per-referred-patient from 2WW investigatory referral. To perform these analyses, we have developed a model using 10-year age- and stage-stratified cancer survival (2007-2017) combined with a per-day hazard ratio for delay (delay-HR) and applied it to 2WW-pathway age- and stage-specific case and referral volumes (6). For this model, assumptions and parameter estimates were required; whilst we made use of well-evidenced published data where available, as with any modelled analysis, the accuracy of the predictions will be directly dependent on the validity of assumptions and parameter estimates.

METHODS

Data sources

We obtained patient numbers, age-stage-stratified 5-year (2013-2017) and age-stratified 10-year (2008-2017) cancer survival for all diagnoses and those associated with surgical resection for non-haematological malignancies from Public Health England's National Cancer Registration Service (NCRAS) (7) (**Appendix p 1**). We obtained data on route to diagnosis by age and stage from NHS England Clinical Commissioning Groups collections (8). Conversion rates from referrals for suspected cancer to cancer diagnoses ('diagnostic-conversion-rate') were based on Cancer Waits/Faster Diagnosis Standard data for West London 2019/20 (9). We concentrated our analysis on the 20 most common cancers with 2WW-pathways (Table 1), for which we analysed NCRAS survival data from 2,314,822 cancer cases (2008-2017) and 2WW diagnoses for 385,156 cancer cases (2013-2016) (**Table 1, Appendix p 4**). Life expectancy was based on UK Office of National Statistics (ONS) life tables for 2016-2018 (10). Estimates for nosocomial infection rates and median duration of hospital stay for each cancer type were based on information from three large UK surgical oncology centres (personal communication F. Gronthoud). For case-fatality rate (CFR) associated with unselected COVID-19 infection, we used published data from China (as UK COVID-19 CFR estimates are only currently available for hospitalised cases) (11, 12).

Model development

10-year net survival

We used net survival estimates, in which crude survival has been adjusted for background age-specific death rates to reflect cancer-specific mortality. Since cure rates for most cancers are only known 5-10 years post-diagnosis, we employed 10-year stage-specific survival data in our calculations. Because these data are not available for recently diagnosed patients, using established methods, this was estimated by applying the ratio of stage-specific/all-stage 5-year survival data to 10-year all-stage data (7, 13). We used the midpoint per 10-year age-group for life expectancy to estimate life-years gained, averaged per patient (10).

COVID-19-related mortality for cancer patients

We considered two elements of COVID-associated mortality. Firstly, peri-surgical mortality from nosocomial infection was estimated as the product of operation-specific duration of surgical admission, age-specific case fatality rates and per-day rate of nosocomial infection (1%, 2%, 5% or 10%). Secondly, we estimated COVID-related mortality in the community ascribing the patient a year of 'active cancer management' status; this was the product of the likelihood of community-acquired COVID-19 during the year (1%, 10%, 20%, 50%), age-

specific case fatality rates and increase in COVID CFR as a consequence of cancer as a co-morbidity (2-times, 5-times) (11, 12).

Per day hazard ratio for delay in management

We employed published data on the impact on overall survival from delay in cancer surgery for Stage 1-3 disease to estimate per-day hazard ratios (HRs) associated with delay to definitive treatment (delay-HR) (14-22). Since there was only sufficient data to generate summary delay-HRs for breast, colorectal and bladder cancers, we assigned delay-HRs to other tumours based on comparability of 5-year survival, categorising tumours as being of low, moderate or high progressiveness (5-year survival for Stage 2 disease being >90%, 50-90%, <50% respectively) (7). Due to lack of published observational data on tumours of high progressiveness (*e.g.* oesophageal, gastric), we conservatively considered this group as having a comparable delay-HR to moderately progressive tumours (**Appendix p 5**). Finally, we assumed that delay to treatment for Stage 4 cancer would not impact on 10-year survival.

Proportion of diagnosed patients having treatment with curative intent

Because patients <60 years-old with Stage 1-3 cancers typically have treatment with curative intent, we generated from this group, stage-specific ratios for definitive treatment [major resection: 'other definitive treatment']. We applied these ratios to age- and stage-specific strata >60 years-old undergoing major resection to estimate the proportion of diagnosed patients having 'other' types of definitive treatment.

Estimation of adjusted 10-year survival

To estimate 10-year survival for those diagnosed currently with cancer stage 1-3 who experience no delay in treatment, we used NCRAS 10-year survival and adjusted for COVID-related peri-surgical and COVID-related community mortality. To estimate 10-year survival associated with delay, we applied to the NCRAS 10-year survival the delay-HR relating to the specified number of days of delay, along with the COVID-related peri-surgical and COVID-related community mortality (see **Appendix p 1** for formulae). We conservatively assumed that there would be no additional downstream delays following diagnostic-delay.

Outcome Measures

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

Provision of 'supra-normal' diagnostic capacity to manage lockdown backlog

We evaluated the scenario of a 3-month period of lockdown during which a proportion of symptomatic patients delayed their presentation until post-lock-down ('backlog patients',

25%,50%,75% of normal monthly volumes). We assumed normal volumes of incident symptomatic patients presenting after lockdown. We considered different scenarios of extra capacity for 'catch-up' applied across months 1-8 post-lockdown. The 'backlog patients' are assigned an averaged 'presentational-delay' of 2 months. Backlog and incident patients then accrue 'diagnostic-delay' in rounded whole months. We estimated the attributable lives and life-years lost, comparing to the default position (in which there would be a full catch up of all backlog patients in month 1 post-lockdown). We modelled all backlog patients presenting in month 1 post-lockdown (**Supplementary Table 5a**) or with variable presentation across months 1-3 (**Supplementary Table 5b**).

Per-patient risk-benefit analysis for 2WW investigatory referral

A 2WW investigatory referral was assigned as being a half-day 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-related fatality associated with investigatory referral. We combined this with a "technical" fatality risk for invasive investigations (*e.g.* 1 in 10,000 risk of death from perforation from colonoscopy) (23) to produce a combined per-referral mortality.

Using the diagnostic-conversion-rates, we estimated for each age-stratum the survival benefit per-patient from an investigatory referral. We considered potential to delay referral by 2, 4, and 6 months against varying rates of nosocomial infection per investigatory referral (5% - very high, 2·5% - high), 1% - moderate and 0·5% - low). To assess by age-group and tumour-type the risk-benefit of investigatory referral, we compared the benefit in cancer survival against the combined fatality risk (COVID-19 and technical), estimating benefit in % survival and life-years gained.

Statistical Analyses

Analyses were performed using STATA (version 15). 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) and SD of this estimate (*i.e.* standard error), expressing this as a percentage of the estimate. We performed multivariate sensitivity analyses across ranges of parameter estimates, including +/- 2SD of delay-HR. Unless otherwise specified, we applied as default values for community infection rate (20%) and per-day rate of nosocomial infection (2%), selected to be conservatively high. For cancer-related elevation in mortality from community-acquired COVID-19 infection, we used a default value of 2-times, which is at the low-intermediate end of the published estimates (reflecting a non-metastatic cancer population). Assumptions and parameter estimates are justified in detail in **Appendix p 1**.

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 the final decision to submit the manuscript.

RESULTS

For many 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 over 10% reduction in long-term (10-year) survival (**Figure 1, Appendix p 6**). Influence of constituent underlying disease stage and subtype is well illustrated by comparison between Stage 1 ER+ disease and Stage 3 ER- breast cancer (*e.g.* 0·8% vs 10·3% estimated survival reduction from 3-month delay for those aged 40-49, **Appendix p 7**).

The representation of a tumour-type in the aggregated impact of universal delays in the 2WW-pathway varies widely, driven by (i) the age-specific incidence, (ii) % cancers diagnosed by 2WW-pathway, (iii) % cancers diagnosed as Stage 1-3 in the 2WW-pathway and (iv) tumour aggressiveness (**Figure 2**). Breast and colorectal cancers make the most sizeable contribution to lives and life-years lost. Aggregate impact from delays in prostate cancer pathways is predicted as low, predominantly on account of the high proportion of indolent cases. Pancreatic, gastric and liver cancers likewise only contribute modestly to the estimated totality of lives and life years lost as (i) fewer cases present via the 2WW route and (ii) the majority have Stage 4 disease at presentation.

Across these 20 cancer types, on average ~243,098 cancers are diagnosed annually; of these ~96,289 are diagnosed via the 2WW pathway of which 75,369 are diagnosed at stage 1-3. 20,293/75,369 would be predicted to suffer cancer-related mortality within 10 years of diagnosis, representing loss of 304,129 life years. A uniform per-patient delay of 1 month/6 months would be predicted to result in attributable additional lives lost of 1,412/ 9,280 and life-years lost of 25,812/ 173,540 over the following ten years for an annual cohort of cancer cases diagnosed via 2WW at stage 1-3.

On the basis of preliminary estimates of 2WW referral drop, we considered 25%, 50% and 75% reduction in presentations over the 3-month lockdown period (**Supplementary Table 5a,5b**) (2-4).

Each month on average in England, for these 20 cancer types, ~149,000 2WW referrals are made, resulting in 8,024 diagnoses of cancer of which 6,281 are diagnosed at Stage 1-3. Of these 1,691/6,281 will typically die from their cancer within 10 years (8). The toll nationally of 'presentational-delay' accrued over a 3-month lockdown period was estimated to be 181/3316, 361/6632 or 542/9948 attributable additional lives/life-years assuming backlog rates of 25%/50%/75% with an average presentational delay of 2 months per patient. Assuming the patients all present in month 1 post-lockdown and that the requisite 175%/250%/325% of normal diagnostic capacity is unlikely to be immediately "on tap", we estimated the additional

lives/life-years that might be lost due to subsequent 'diagnostic-delay'. Rapid provision of additional capacity over months 1-3 results in 90/1662, 183/3362 276/5075 additional lives/life-years lost due to 'diagnostic-delay' (for 25%/50%/75% backlog rates). Conversely, delayed additional capacity provided across months 3-8 post-lockdown, would result in 401/7332, 811/14,873, 1,231/22,635 additional lives/life-years lost due to 'diagnostic-delay' (for 25%/50%/75% backlog rates).

We assessed the risk-benefit balance per individual for investigatory referral, considering different rates of nosocomial infection. Firstly, we considered absolute survival benefit, comparing prompt referral/diagnosis/management to no referral/diagnosis/management (**Appendix p 9**). There was per-patient survival benefit from referral for nearly all tumour-type/age-groups at nosocomial risk ≤1%. If the risk of infection is high (>2·5%/referral), for patients over >70 years the risk associated with investigatory referral may exceed the absolute survival benefit for tumour-referral-groups of poorer outcome such as upper GI (pancreas, oesophagus, liver, stomach) and brain tumours.

Secondly, we sought to address a common dilemma for primary care physicians, namely for which groups of patients might referral be delayed a few months, either to await reduction in nosocomial infection rates or to reduce pressure on diagnostics? We compared per-patient-referred, risk of death from investigatory referral versus delay-associated increase in risk of cancer death (**Figure 3, Appendix p 10**). This balance is strongly predicated on (i) patients age (due to high COVID CFR for patients >70), (ii) tumour 'progressiveness' (iii) diagnostic-conversion-rate (iv) proportion of cases diagnosed with Stage 1-3 disease. For those age <60, provided daily nosocomial infection rates are ≤2·5%, even for short delays (2 months) the delay-related-cancer-fatality largely exceeds investigation-related fatality. However, for patients aged >70 when nosocomial infection rate is higher than 1%, for several tumour groups investigation-related fatality may be greater than cancer-fatality related to delays as long as 6 months. 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 1-3 at diagnosis. In the event of stable, low nosocomial infection rate (≤0·5% per procedure), we determined life-years lost for delayed referrals (**Appendix p 12**). For those with symptoms of bladder cancer, for a 2-month delay the average decrement in life years per referred patient is 0.69 for those aged 30-39 year-old and 0.1 for those aged 70-79; for those referred with symptoms of brain tumour the average decrement are 0.03 and 0.00 respectively.

In multivariate sensitivity analysis, outcomes from the model were mostly sensitive to changes in the estimated per-day delay-HR. Varying the delay-HR by ±2SD (±16%), the total lives lost

annually for the 2WW population attributable to 2-months delay ranged from 2,412 to 3,378, and attributable life-years lost ranged from 44,192 to 62,055 **(Appendix p 13).** Using a proportionately higher per-day delay-HR for tumours of high progressiveness (delay-HR=0.0105), increased the impact of 2-month delay to 3,772 lives lost and 72,053 life-years lost. Varying individually the rate of nosocomial infection, the community infection rate or the 'cancer mortality multiplier' had a modest effect on the impact of delay on survival.

DISCUSSION

The impact of COVID-related disruption on cancer care is likely to be an ongoing issue until a vaccine or effective treatment is identified. Unlike acute pathologies such as stroke and myocardial infarction, the excess mortality consequent from COVID-related disruption to cancer pathways may not be fully evident for 10 years (or longer).

For most solid cancers, 10-year survival is generally considered to equate to cure, reflecting the proportion of Stage1-3 tumours for which their surgery (or radical radiotherapy) has enabled the restoration to (near) normal life expectancy. Our estimates suggest that for many cancers, delays to treatment of 2-6 months will lead in a sizeable proportion of patients with early-stage tumours, to progression from having curable to non-curable disease. However, this varies widely between tumour-types reflecting variation (i) proportion diagnosed through the 2WW-pathway, (ii) proportion diagnosed with Stage 1-3, (iii) age profile of cancers diagnosed and (iv) the diagnostic-conversion-rate, which inevitably means that the overall impact of 2WW-pathway-delay is far from uniform between cancers.

During the lockdown, there have been significant temporal and geographic variation in rates of patient deferment in accessing urgent referral for cancer symptoms, with estimates ranging up to 84% (2, 3) (personal communication M.Lawler). There is potential for significant additional mortality from ‘diagnostic-delay’ on top of the ‘presentational-delay’ accrued during patient deferment, especially if additional diagnostic capacity for ‘catch-up’ is delayed. The additional capacity must include not only expanded technical provision for endoscopy, imaging, interventional radiology and nuclear medicine but also increased manpower for specialist assessment and pathology. Delivery will be further challenged by new requirements for personal protective equipment (PPE), social distancing and infection control. Innovative solutions will be required to deliver this extra capacity in a timely fashion, which may include procurement of private sector provision, expanded roles for healthcare professionals such as endoscopy nurses, and pathway adaptation, for example, use of faecal immunochemical testing (FIT) for triage of colorectal cancer referrals.

Investment in expansion of capacity for NHS diagnostics and treatment is first and foremost if cancer services are to become more resilient to future extrinsic disruption, which could include additional ‘waves’ of COVID-19 infection. Secondly, more responsive informatic connections between primary care, diagnostic and treatment services would enable greater nimbleness in adaption of pathways and prioritisation of referrals. Thirdly, pre-emptive public education is required to discourage deferment of patients with cancer symptoms along with modification of pathways to and through primary care.

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

Many have speculated as to final net balance of mortality from the COVID pandemic and lockdown period, and whether direct deaths from the virus, compromise in collateral healthcare delivery and negative behaviour changes such as increased alcohol consumption will be outweighed by the positive impact on mortality of reduced air pollution, fewer road-traffic accidents and hand-washing. Although our analyses examine cancer-specific survival only, the estimations of 'life years gained' would be altered by any sizeable shifts in life expectancy.

While we have used data for England, cancer survival is comparable across most economically-developed countries, so the per tumour-type estimations of the impact of delay are broadly applicable. Overall, where cancer incidence, population structure, background rates of population mortality are broadly similar to those of England, our model would provide insights relevant to other health systems, although, there will be international variation in pathways to diagnosis for different cancers, eligibility criteria and proportions of different cancers ascertained therein. Issues of capacity and delays in diagnosis are of global interest as part of moving towards benchmarked metrics (*e.g.* International Cancer Benchmarking Partnership (ICBP)) (3, 24).

Our analysis focuses 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 1-3 disease having treatment with curative intent. Additional analyses will be required to evaluate 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 (**Appendix p 1**, **p 13**). Whilst we identified suitable observational data for delay-to-treatment for Stages 1-3 for three tumour-types, uniform application of these delay-HRs across tumour-types and over time invariably will oversimplify

the complex, dynamic, tumour-type-specific, age-specific, stage-specific nature of cancer progression. To enable systematic insights across tumour-types, routine capture of pathway-delays 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 survival impact of delay when a 2WW referral resulted in diagnosis of a different cancer outside of the index tumour-referral-group (**Appendix p 4**).

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 fashion. Delay patterns will likely be complex and vary between individuals, by tumour-type, over time and by geography. The severity of local COVID-19 patterns, modality-specific diagnostic-capacity and organisation of cancer services will all have an impact, 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 DATACAN, the UK Health Data Research Hub for Cancer, are assembling accurate real-world data quantifying in detail the true delays and patient volumes/distributions thereof; this can be applied ***retrospectively*** to these models to refine our predictions. Over the coming months, we shall also be able to quantify whether the post-lockdown 'bulge' directly mirrors the deficit during lockdown in standard 2WW presentations, or whether a proportion of these genuinely 'self-resolve' (25).

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

Although the linear elements differ for the different routes to diagnosis (urgent, routine, emergency, screening), there is convergence at each step in the resources utilised for diagnostics and treatment. For diagnostics, there will be 'cross-competition' between tumour-referral-groups for resources within routine radiology, interventional radiology and endoscopy. For each tumour-type, a hierarchy of investigation exists. Referrals for suspected lung cancer typically receive CT, but only a subset of patients undergo Endobronchial Ultrasound or bronchoscopy; nevertheless, it is anticipated that subsequent Positron Emission Tomography - Computed Tomography for staging may be the narrowest of bottlenecks in the lung pathway (personal communication N.Navani). To optimise recovery, integrated time-course health systems analyses across the different routes to diagnosis will be required, accounting for all

391 the linear steps up to and including surgical and adjuvant treatment and considering local
392 variation in capacity bottlenecks (6).

393 AUTHOR CONTRIBUTIONS

394 A.S., C.T. and R.S.H. designed the model. J.B. generated and quality-assured the NCRAS
395 datasets. S.S generated and quality-assured the CGG/CWT datasets. M.E.J. provided cancer
396 progression models. B.T provided mitigation models. A.S. and C.T wrote the code for the
397 model. M.E.J., J.B. M.L., E.McF., C.T., R.S.H., A.S., G.L., E.R., D.C.M and M.W. provided
398 epidemiological expertise in the parameterisation of the model and relevant literature. F.G
399 provided microbiology expertise in the estimation of nosocomial infection rates. S.A.B, S.J.,
400 D.L.N, J.L., E.K., C.S and N.N. provided details of clinical pathways. B.T., A.S. A.G. and C.L.
401 assembled figures for presentation. C.T drafted the manuscript, with substantial contribution
402 from A.S., R.S.H., G.L., M.L and E.McF. All authors contributed to the final manuscript.

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417 DECLARATION OF INTEREST

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RESEARCH IN CONTEXT

Evidence before this study

Observational studies of cancer pathway delays were identified on bibliographic database searching for English Language articles using terms [[cancer OR neoplasm], [delay OR interval OR wait], [diagnosis OR treatment]]. Studies typically report data extracted from institutional, regional or national databases. Patient experiencing pathway delay may be biased in regard of socio-economic status. Studies of shorter delay periods in particular are recognised to suffer confounding by indication (*i.e.* those with shortest delays often have the worst outcomes as rapidity of management can be a reflection of a sicker patient). Overall studies are highly heterogeneous in design and findings, including the durations of delay studied, the duration of survival follow-up, the metric by which impact is captured (percentages, odds ratios, hazard ratios) and how/when staging is performed. Each study typically focuses on a single tumour type +/- stage thereof. There had been no studies modelling in a standardised fashion across tumour-types the impact in lives and life-years-lost of systematic pathways delays until the current authors recently reported a healthcare resource analysis focused on systemic delays at point of surgery.

Added value of this study

Across multiple tumour-types, we present application of a standardised approach (i) using per-day fatality hazard ratios enabling quantitation of the impact of different durations of delay on survival (ii) examining both the referred patient and the diagnosed patient (iii) examining individual tumour-type and in aggregate across major tumour-types. This study focuses specifically on cancers diagnosed via the 2-week-wait (2WW) pathway as this pathway is most amenable to interventions. Whilst highly pertinent to current forecasting of COVID-related impact of delays, these models are applicable 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 COVID19-related delays in presentation, diagnosis and/or treatment will result in loss of life and life years that vary widely according to patient age and tumour type. Summed at national level, the impact in attributable deaths of COVID-19-related delays in presentation and diagnosis of cancer patients ascertained through the 2WW-pathway would currently be estimated from these models to be in the hundreds to low thousands. Data are currently immature regarding the true duration and extent of service disruption and per-patient cancer pathway delay across the UK. Direct

predictions regarding attributable cancer deaths will be possible once more accurate patient-level data become available.

LEGENDS FOR FIGUES/TABLES

Table 1: Cancer diagnoses made through the '2-Week Wait' pathway.

Proportion of all diagnoses made through 2WW, breakdown of 2WW cancers diagnosed by age and stage, diagnostic-conversion-rates (any cancer; cancer within TRG (tumour referral group), average annual cancer diagnoses total and via 2WW-pathway. Diagnostic-conversion-rates reflect all diagnoses of invasive cancers (exception: breast includes CIS, skin excludes basal cell carcinomas, urology excludes pTa bladder tumours)

Figure 1: Reduction in 10-year net survival incurred from a 3-month delay.

20 common tumour-types included. Red indicates the highest tertile of survival decrement; green indicates the lowest tertile of survival decrement.

Figure 2: Annual attributable lives and life-years lost from delay, aggregated for all patients diagnosed via 2WW-pathway.

Based on 10-year net survival data for England 2008-2017. Greatest decrements in lives and life-years lost are represented in darker shades of orange.

Figure 3: Per-patient risk-benefit from urgent investigatory referral compared to 2 month delay with varying rates of nosocomial COVID-19

Comparing impact on net survival of urgent investigatory referral compared to 2-month delay; red indicates benefit and green indicates disbenefit.

REFERENCES

1. GPs made 30% fewer referrals to secondary care during March. Pulse. 2020 14/05/20.
2. Cancer referrals fell from 40,000 to 10,000 per week in April: NHS Providers; 2020 [updated 15/05/2020. Available from: https://nhsproviders.org/topics/covid-19/coronavirus-member-support/national-guidance/government-updates/daily-updates.
3. Lai AG, Pasea L, Banerjee A, Denaxas S, Katsoulis M, Chang WH, et al. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. medRxiv. 2020.
4. Bower E. Urgent referrals rejected for one in three GPs during COVID-19 outbreak. GPOnline. 2020.

5. Bostock N. Patients waiting more than a month for urgent cancer checks amid COVID-19 crisis. GPonline. 2020 29/4/20.
6. Sud A, Jones M, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol. 2020.
7. National Cancer Registration and Analysis Service (NCRAS). Public Health England; 2018.
8. Clinical Commissioning Groups Cancer Assessment 2017/18. NHS England; 2018.
9. The Cancer Waiting Times dataset. National Cancer Waiting Times system2019.
10. National Life Tables (2016-2018). Office for National Statistics (ONS), U.K. .
11. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). China CCDC; 2020 17/2/2020.
12. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, 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 (Clinical research ed). 2020;369:m1985.
13. 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 medical research methodology. 2011;11:96.
14. 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(1):e0210465.
15. 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(9159):1119-26.
16. Mano R, Vertosick EA, Hakimi AA, Sternberg IA, Sjoberg DD, Bernstein M, et al. The effect of delaying nephrectomy on oncologic outcomes in patients with renal tumors greater than 4cm. Urologic Oncology: Seminars and Original Investigations. 2016;34(5):239.e1-.e8.
17. Smith EC, Ziogas A, Anton-Culver H. Delay in Surgical Treatment and Survival After Breast Cancer Diagnosis in Young Women by Race/Ethnicity. JAMA Surgery. 2013;148(6):516-23.
18. Chu AT, Holt SK, Wright JL, Ramos JD, Grivas P, Yu EY, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. Cancer. 2019;125(12):2011-7.
19. 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. The Journal of urology. 2003;169(1):110-5; discussion 5.
20. 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. Scandinavian Journal of Urology and Nephrology. 2004;38(3):231-5.
21. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong Y-N, et al. Time to Surgery and Breast Cancer Survival in the United States. JAMA oncology. 2016;2(3):330-9.
22. 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. British journal of cancer. 1999;79(5-6):858-64.
23. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. Journal of the National Cancer Institute. 2003;95(3):230-6.
24. International Cancer Benchmarking Partnership (ICBP). Cancer Research UK (CRUK); 2020.
25. Dinmohamed AG, Visser O, Verhoeven RHA, Louwman MWJ, van Nederveen FH, Willems SM, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. The Lancet Oncology. 2020;21(6):750-1.

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

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ABSTRACT

Background: During the COVID-19 lockdown, referrals via the 2 Week Wait (2WW) urgent pathway for suspected cancer in England are reported to have dropped by up to 84%. We aimed to examine the impact on cancer survival of different scenarios of ~~scenarios of~~ lockdown-accumulated-backlog ~~and additional diagnostic capacity for 'catch-up', measuring attributable lives and life-years lost~~. We also aimed to examine by tumour-referral-group and age, survival benefit per referred patient considering survival decrement from delayed referral versus risk of death from nosocomial SARS-CoV-2 ~~COVID-19 nosocomial~~ infection.

Methods: To construct the underlying models, we used age- and stage-stratified 10 year-cancer survival estimates for England 2007-2017 for 20 common tumour-types. We applied per-day hazard ratios for cancer progression generated from observational studies of delay-to-treatment. We quantified the annual numbers of cancers diagnosed via the 2WW-pathway using the 2WW age- and stage-specific breakdowns~~We integrated these with age- and stage-specific distributions of cancers detected via the 2WW-pathway~~. From these, for per-patient delays of 1-6 months, we estimated aggregate number of lives lost and life-years lost in England. Using referral-to-diagnosis conversion rates and COVID-19 case fatality rates, we also estimated the survival increment per patient referred.

Findings: Per month across England~~,~~ in 2013-2016, on average 6,281 patients with Stage 1-3 cancer we~~a~~re diagnosed via the 2WW pathway of whom 1,691 would be predicted to die within 10 years from their disease. We estimated 2WW-pathway presentational-delay ~~during~~ from three months of lockdown will result in total in 181/361/542 attributable additional deaths (if % reduction in referrals was 25/50/75% respectively). ~~We estimated that diagnostic-delay from delivery of additional~~ Limited diagnostic capacity to address the backlog may result in additional delays~~-~~: ~~spread across months 1-3 post-lockdown will incur 90/183/276 attributable additional deaths. If additional capacity is delayed until months 3-8 post-lockdown, we estimate this will incur~~ 401/811/1,231 attributable additional deaths are estimated if additional diagnostic capacity is delayed until months 3-8 post-lockdown. ~~Contribution to this burden of mortality is not uniform by age-group nor proportionate to tumour-type incidence.~~ 2-month delay in 2WW investigatory referral results in average loss of life-years per-referred-patient of between 0 and 0.7, depending on age and tumour-type.

Interpretation: Prompt provision of additional capacity for 'catch-up' in diagnostics will minimise deaths consequent from 'diagnostic-delay' accumulated on top of the 'presentational-delay'. 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.

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INTRODUCTION

Following announcement by the United Kingdom (UK) government on 23rd March 2020 of nationwide lockdown to combat the COVID-19 pandemic, hospital referrals for non-COVID-related healthcare problems have plummeted (1). As the lockdown is lifted, it is anticipated there will be a surge in presentations for non-COVID-19 medical issues.

Any delay in cancer treatment carries the real risk of patients' tumours progressing from being curable (with near-normal life expectancy) to becoming non-curable (with limited life expectancy). Specific pathways have been established in the UK for referral from primary care for urgent specialist evaluation and investigation of individuals with 'red-flag' symptoms suggestive of a specific cancer type, termed "the 2 Week Wait (2WW) pathway". Reductions of up to 84% have been reported in 2WW referrals in March-May 2020 (2-4) (personal communication M.Lawler). It is predicted that sizeable backlogs accrued as a consequence of the lockdown will likely first place pressure on diagnostic services in secondary care (5).

We addressed two key questions relating to this potential surge in presentations of symptomatic patients. Firstly, we explored the impact of a range of scenarios of provision of additional diagnostic capacity to address patient backlogs, assuming no prioritisation of patient groups. For each, we evaluated the degree of 'diagnostic-delay' incurred on top of the 'presentation delay' accrued during lockdown. Secondly, accounting for the risk of death associated with nosocomial COVID-19 infection, we examined by tumour-referral-group and age the gain in survival and life-years per-referred-patient from 2WW investigatory referral. To perform these analyses, we have developed a model using 10-year age- and stage-stratified cancer survival (2007-2017) combined with a per-day hazard ratio for delay (delay-HR) and applied it to 2WW-pathway age- and stage-specific case and referral volumes (6). For this model, assumptions and parameter estimates were required; whilst we made use of well-evidenced published data where available, as with any modelled analysis, the accuracy of the predictions will be directly dependent on the validity of assumptions and parameter estimates.

METHODS

Data sources

We obtained patient numbers, age-stage-stratified 5-year (2013-2017) and age-stratified 10-year (2008-2017) cancer survival for all diagnoses and those associated with surgical resection for non-haematological malignancies from Public Health England's National Cancer Registration Service (NCRAS) (7) (**Appendix p 1~~/ Supplementary Table 1~~**). We obtained data on route to diagnosis by age and stage from NHS England Clinical Commissioning Groups collections (8). Conversion rates from referrals for suspected cancer to cancer diagnoses ('diagnostic-conversion-rate') were based on Cancer Waits/Faster Diagnosis Standard data for West London 2019/20 (9). We concentrated our analysis on the 20 most common cancers with 2WW-pathways (Table 1), for which we analysed NCRAS survival data from 2,314,822 cancer cases (2008-2017) and 2WW diagnoses for 385,156 cancer cases (2013-2016) (**Table 1, Appendix p 4~~5/ Supplementary Table 2~~**). Life expectancy was based on UK Office of National Statistics (ONS) life tables for 2016-2018 (10). Estimates for nosocomial infection rates and median duration of hospital stay for each cancer type were based on information from three large UK surgical oncology centres (personal communication F. Gronthoud). For case-fatality rate (CFR) associated with unselected COVID-19 infection, we used published data from China (as UK COVID-19 CFR estimates are only currently available for hospitalised cases) (11, 12).

Model development

10-year net survival

We used net survival estimates, in which crude survival has been adjusted for background age-specific death rates to reflect cancer-specific mortality. Since cure rates for most cancers are only known 5-10 years post-diagnosis, we employed 10-year stage-specific survival data in our calculations. Because these data are not available for recently diagnosed patients, using established methods, this was estimated by applying the ratio of stage-specific/all-stage 5-year survival data to 10-year all-stage data (7, 13). We used the midpoint per 10-year age-group for life expectancy to estimate life-years gained, averaged per patient (10).

COVID-19-related mortality for cancer patients

We considered two elements of COVID-associated mortality. Firstly, peri-surgical mortality from nosocomial infection was estimated as the product of operation-specific duration of surgical admission, age-specific case fatality rates and per-day rate of nosocomial infection (1%, 2%, 5% or 10%). Secondly, we estimated COVID-related mortality in the community ascribing the patient a year of 'active cancer management' status; this was the product of the

likelihood of community-acquired COVID-19 during the year (1%, 10%, 20%, 50%), age-specific case fatality rates and increase in COVID CFR as a consequence of cancer as a co-morbidity (2-times, 5-times) (11, 12).

Per day hazard ratio for delay in management

We employed published data on the impact on overall survival from delay in cancer surgery for Stage 1-3 disease to estimate per-day hazard ratios (HRs) associated with delay to definitive treatment (delay-HR) (14-22). ~~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) and SD of this estimate (*i.e.* standard error), expressing this as a percentage of the estimate.~~ Since there was only sufficient data to generate summary delay-HRs for breast, colorectal and bladder cancers, we assigned delay-HRs to other tumours based on comparability of 5-year survival, categorising tumours as being of low, moderate or high progressiveness (5-year survival for Stage 2 disease being >90%, 50-90%, <50% respectively) (7). Due to lack of published observational data on tumours of high progressiveness (*e.g.* oesophageal, gastric), we conservatively considered this group as having a comparable delay-HR to moderately progressive tumours (**Appendix p 5**~~/ **Supplementary Table 2**~~). Finally, we assumed that delay to treatment for Stage 4 cancer would not impact on 10-year survival.

Proportion of diagnosed patients having treatment with curative intent

Because patients <60 years-old with Stage 1-3 cancers typically have treatment with curative intent, we generated from this group, stage-specific ratios for definitive treatment [major resection: 'other definitive treatment']. We applied these ratios to age- and stage-specific strata >60 years-old undergoing major resection to estimate the proportion of diagnosed patients having 'other' types of definitive treatment.

Estimation of adjusted 10-year survival

To estimate 10-year survival for those diagnosed currently with cancer stage 1-3 who experience no delay in treatment, we used NCRAS 10-year survival and adjusted for COVID-related peri-surgical and COVID-related community mortality. To estimate 10-year survival associated with delay, we applied to the NCRAS 10-year survival the delay-HR relating to the specified number of days of delay, along with the COVID-related peri-surgical and COVID-related community mortality (see **Appendix p 1**~~/ **Supplementary Table 1**~~ for formulae). We conservatively assumed that there would be no additional downstream delays following diagnostic-delay.

Outcome Measures

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

Provision of 'supra-normal' diagnostic capacity to manage lockdown backlog

We evaluated the scenario of a 3-month period of lockdown during which a proportion of symptomatic patients delayed their presentation until post-lock-down ('backlog patients', 25%,50%,75% of normal monthly volumes). We assumed normal volumes of incident symptomatic patients presenting after lockdown. We considered different scenarios of extra capacity for 'catch-up' applied across months 1-8 post-lockdown. The 'backlog patients' are assigned an averaged 'presentational-delay' of 2 months. Backlog and incident patients then accrue 'diagnostic-delay' in rounded whole months. We estimated the attributable lives and life-years lost, comparing to the default position (in which there would be a full catch up of all backlog patients in month 1 post-lockdown). We modelled all backlog patients presenting in month 1 post-lockdown (~~Appendix p 10/~~ **Supplementary Table 5a**) or with variable presentation across months 1-3 (~~Appendix p 14/~~ **Supplementary Table 5b**).

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Per-patient risk-benefit analysis for 2WW investigatory referral

A 2WW investigatory referral was assigned as being a half-day 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-related fatality associated with investigatory referral. We combined this with a "technical" fatality risk for invasive investigations (*e.g.* 1 in 10,000 risk of death from perforation from colonoscopy) (23) to produce a combined per-referral mortality.

Using the diagnostic-conversion-rates, we estimated for each age-stratum the survival benefit per-patient from an investigatory referral. We considered potential to delay referral by 2, 4, and 6 months against varying rates of nosocomial infection per investigatory referral (5% - very high, 2·5% - high), 1% - moderate and 0·5% - low). To assess by age-group and tumour-type the risk-benefit of investigatory referral, we compared the benefit in cancer survival against the combined fatality risk (COVID-19 and technical), estimating benefit in % survival and life-years gained.

Statistical Analyses

Analyses were performed using STATA (version 15). 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) and SD of this estimate (*i.e.* standard error), expressing this as a percentage of

the estimate. We performed multivariate sensitivity analyses across ranges of parameter estimates, including +/- 2SD of delay-HR. Unless otherwise specified, we applied as default values for community infection rate (20%) and per-day rate of nosocomial infection (2%), selected to be conservatively high. For cancer-related elevation in mortality from community-acquired COVID-19 infection, we used a default value of 2-times, which is at the low-intermediate end of the published estimates (reflecting a non-metastatic cancer population). Assumptions and parameter estimates are justified in detail in **Appendix p 1**~~/ Supplementary Table 1~~.

Role of the Funding Source

There was no funding source for this study ~~The funding sources had no part in the study design, in the collection of data, in the analysis and interpretation of the data, in the writing of the report, or the decision to submit the manuscript~~. The corresponding author had full access to all the data in the study and had the final decision to submit the manuscript.

RESULTS

For many 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 over 10% reduction in long-term (10-year) survival (**Figure 1, Appendix p 67/Supplementary Table 3**). Influence of constituent underlying disease stage and subtype is well illustrated by comparison between Stage 1 ER+ disease and Stage 3 ER- breast cancer (*e.g.* 0·8% vs 10·3% estimated survival reduction from 3-month delay for those aged 40-49, **Appendix p 78/ Supplementary Table 4**).

The representation of a tumour-type in the aggregated impact of universal delays in the 2WW-pathway varies widely, driven by (i) the age-specific incidence, (ii) % cancers diagnosed by 2WW-pathway, (iii) % cancers diagnosed as Stage 1-3 in the 2WW-pathway and (iv) tumour aggressiveness (**Figure 2**). Breast and colorectal cancers make the most sizeable contribution to lives and life-years lost. Aggregate impact from delays in prostate cancer pathways is predicted as low, predominantly on account of the high proportion of indolent cases. Pancreatic, gastric and liver cancers likewise only contribute modestly to the estimated totality of lives and life years lost as (i) fewer cases present via the 2WW route and (ii) the majority have Stage 4 disease at presentation.

Across these 20 cancer types, on average ~243,098 cancers are diagnosed annually; of these ~96,289 are diagnosed via the 2WW pathway of which 75,369 are diagnosed at stage 1-3. 20,293/75,369 would be predicted to suffer cancer-related mortality within 10 years of diagnosis, representing loss of 304,129 life years. A uniform per-patient delay of 1 month/6 months would be predicted to result in attributable additional lives lost of 1,412/ 9,280 and life-years lost of 25,812/ 173,540 over the following ten years for an annual cohort of cancer cases diagnosed via 2WW at stage 1-3.

On the basis of preliminary estimates of 2WW referral drop, we considered 25%, 50% and 75% reduction in presentations over the 3-month lockdown period (**Appendix p 10, p 14/ Supplementary Table 5a,5b**) (2-4).

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Each month on average in England, for these 20 cancer types, ~149,000 2WW referrals are made, resulting in 8,024 diagnoses of cancer of which 6,281 are diagnosed at Stage 1-3. Of these 1,691/6,281 will typically die from their cancer within 10 years (8). The toll nationally of 'presentational-delay' accrued over a 3-month lockdown period was estimated to be 181/3316, 361/6632 or 542/9948 attributable additional lives/life-years assuming backlog rates of 25%/50%/75% with an average presentational delay of 2 months per patient. Assuming the patients all present in month 1 post-lockdown and that the requisite 175%/250%/325% of

normal diagnostic capacity is unlikely to be immediately "on tap", we estimated the additional lives/life-years that might be lost due to subsequent 'diagnostic-delay'. Rapid provision of additional capacity over months 1-3 results in 90/1662, 183/3362 276/5075 additional lives/life-years lost due to 'diagnostic-delay' (for 25%/50%/75% backlog rates). Conversely, delayed additional capacity provided across months 3-8 post-lockdown, would result in 401/7332, 811/14,873, 1,231/22,635 additional lives/life-years lost due to 'diagnostic-delay' (for 25%/50%/75% backlog rates).

We assessed the risk-benefit balance per individual for investigatory referral, considering different rates of nosocomial infection. Firstly, we considered absolute survival benefit, comparing prompt referral/diagnosis/management to no referral/diagnosis/management (**Appendix p 9~~15/ Supplementary Table 6~~**). There was per-patient survival benefit from referral for nearly all tumour-type/age-groups at nosocomial risk ≤1%. If the risk of infection is high (>2·5%/referral), for patients over >70 years the risk associated with investigatory referral may exceed the absolute survival benefit for tumour-referral-groups of poorer outcome such as upper GI (pancreas, oesophagus, liver, stomach) and brain tumours.

Secondly, we sought to address a common dilemma for primary care physicians, namely for which groups of patients might referral be delayed a few months, either to await reduction in nosocomial infection rates or to reduce pressure on diagnostics? We compared per-patient-referred, risk of death from investigatory referral versus delay-associated increase in risk of cancer death (**Figure 3, Appendix p 10~~6/ Supplementary Table 7~~**). This balance is strongly predicated on (i) patients age (due to high COVID CFR for patients >70), (ii) tumour 'progressiveness' (iii) diagnostic-conversion-rate (iv) proportion of cases diagnosed with Stage 1-3 disease. For those age <60, provided daily nosocomial infection rates are ≤2·5%, even for short delays (2 months) the delay-related-cancer-fatality largely exceeds investigation-related fatality. However, for patients aged >70 when nosocomial infection rate is higher than 1%, for several tumour groups investigation-related fatality may be greater than cancer-fatality related to delays as long as 6 months. 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 1-3 at diagnosis. In the event of stable, low nosocomial infection rate (≤0·5% per procedure), we determined life-years lost for delayed referrals (**Appendix p 12~~8/ Supplementary Table 8~~**). For those with symptoms of bladder cancer, for a 2-month delay the average decrement in life years per referred patient is 0.69 for those aged 30-39 year-old and 0.1 for those aged 70-79; for those referred with symptoms of brain tumour the average decrement are 0.03 and 0.00 respectively.

In multivariate sensitivity analysis, outcomes from the model were mostly sensitive to changes in the estimated per-day delay-HR. Varying the delay-HR by ±2SD (±16%), the total lives lost annually for the 2WW population attributable to 2-months delay ranged from 2,412 to 3,378, and attributable life-years lost ranged from 44,192 to 62,055 **(Appendix p 139).** Using a proportionately higher per-day delay-HR for tumours of high progressiveness (delay-HR=0.0105), increased the impact of 2-month delay to 3,772 lives lost and 72,053 life-years lost. Varying individually the rate of nosocomial infection, the community infection rate or the 'cancer mortality multiplier' had a modest effect on the impact of delay on survival.

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DISCUSSION

The impact of COVID-related disruption on cancer care is likely to be an ongoing issue until a vaccine or effective treatment is identified. Unlike acute pathologies such as stroke and myocardial infarction, the excess mortality consequent from COVID-related disruption to cancer pathways may not be fully evident for 10 years (or longer).

For most solid cancers, 10-year survival is generally considered to equate to cure, reflecting the proportion of Stage1-3 tumours for which their surgery (or radical radiotherapy) has enabled the restoration to (near) normal life expectancy. Our estimates suggest that for many cancers, delays to treatment of 2-6 months will lead in a sizeable proportion of patients with early-stage tumours, to progression from having curable to non-curable disease. However, this varies widely between tumour-types reflecting variation (i) proportion diagnosed through the 2WW-pathway, (ii) proportion diagnosed with Stage 1-3, (iii) age profile of cancers diagnosed and (iv) the diagnostic-conversion-rate, which inevitably means that the overall impact of 2WW-pathway-delay is far from uniform between cancers.

During the lockdown, there have been significant temporal and geographic variation in rates of patient deferment in accessing urgent referral for cancer symptoms, with estimates ranging up to 84% (2, 3) (personal communication M.Lawler). There is potential for significant additional mortality from 'diagnostic-delay' on top of the 'presentational-delay' accrued during patient deferment, especially if additional diagnostic capacity for 'catch-up' is delayed. The additional capacity must include not only expanded technical provision for endoscopy, imaging, interventional radiology and nuclear medicine but also increased manpower for specialist assessment and pathology. Delivery will be further challenged by new requirements for personal protective equipment (PPE), social distancing and infection control. Innovative solutions will be required to deliver this extra capacity in a timely fashion, which may include procurement of private sector provision, expanded roles for healthcare professionals such as endoscopy nurses, and pathway adaptation, for example, use of faecal immunochemical testing (FIT) for triage of colorectal cancer referrals.

Investment in expansion of capacity for NHS diagnostics and treatment is first and foremost if cancer services are to become more resilient to future extrinsic disruption, which could include additional 'waves' of COVID-19 infection. Secondly, more responsive informatic connections between primary care, diagnostic and treatment services would enable greater nimbleness in adaption of pathways and prioritisation of referrals. Thirdly, pre-emptive public education is required to discourage deferment of patients with cancer symptoms along with modification of pathways to and through primary care.

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

Many have speculated as to final net balance of mortality from the COVID pandemic and lockdown period, and whether direct deaths from the virus, compromise in collateral healthcare delivery and negative behaviour changes such as increased alcohol consumption will be outweighed by the positive impact on mortality of reduced air pollution, fewer road-traffic accidents and hand-washing. Although our analyses examine cancer-specific survival only, the estimations of 'life years gained' would be altered by any sizeable shifts in life expectancy.

While we have used data for England, cancer survival is comparable across most economically-developed countries, so the per tumour-type estimations of the impact of delay are broadly applicable. Overall, where cancer incidence, population structure, background rates of population mortality are broadly similar to those of England, our model would provide insights relevant to other health systems, although, there will be international variation in pathways to diagnosis for different cancers, eligibility criteria and proportions of different cancers ascertained therein. Issues of capacity and delays in diagnosis are of global interest as part of moving towards benchmarked metrics (*e.g.* International Cancer Benchmarking Partnership (ICBP)) (3, 24).

Our analysis focuses 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 1-3 disease having treatment with curative intent. Additional analyses will be required to evaluate 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 (**Appendix p 1**, **p 1**~~**39/ Supplementary Tables 1, 9**~~). Whilst we identified suitable observational data for delay-to-treatment for Stages 1-3 for three tumour-types, uniform application of these delay-HRs across tumour-types and over time

invariably will oversimplify the complex, dynamic, tumour-type-specific, age-specific, stage-specific nature of cancer progression. To enable systematic insights across tumour-types, routine capture of pathway-delays 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 survival impact of delay when a 2WW referral resulted in diagnosis of a different cancer outside of the index tumour-referral-group (**Appendix p 45~~/ Supplementary Table 2~~**).

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 fashion. Delay patterns will likely be complex and vary between individuals, by tumour-type, over time and by geography. The severity of local COVID-19 patterns, modality-specific diagnostic-capacity and organisation of cancer services will all have an impact, 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 DATACAN, the UK Health Data Research Hub for Cancer, are assembling accurate real-world data quantifying in detail the true delays and patient volumes/distributions thereof; this can be applied ***retrospectively*** to these models to refine our predictions. Over the coming months, we shall also be able to quantify whether the post-lockdown 'bulge' directly mirrors the deficit during lockdown in standard 2WW presentations, or whether a proportion of these genuinely 'self-resolve' (25).

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

Although the linear elements differ for the different routes to diagnosis (urgent, routine, emergency, screening), there is convergence at each step in the resources utilised for diagnostics and treatment. For diagnostics, there will be 'cross-competition' between tumour-referral-groups for resources within routine radiology, interventional radiology and endoscopy. For each tumour-type, a hierarchy of investigation exists. Referrals for suspected lung cancer typically receive CT, but only a subset of patients undergo Endobronchial Ultrasound or bronchoscopy; nevertheless, it is anticipated that subsequent Positron Emission Tomography - Computed Tomography for staging may be the narrowest of bottlenecks in the lung pathway (personal communication N.Navani). To optimise recovery, integrated time-course health

systems analyses across the 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 capacity bottlenecks (6).

AUTHOR CONTRIBUTIONS

A.S., C.T. and R.S.H. designed the model. J.B. generated and quality-assured the NCRAS datasets. S.S generated and quality-assured the CGG/CWT datasets. M.E.J. provided cancer progression models. B.T provided mitigation models. A.S. and C.T wrote the code for the model. M.E.J., J.B. M.L., E.McF., C.T., R.S.H., A.S., G.L., E.R., D.C.M and M.W. provided epidemiological expertise in the parameterisation of the model and relevant literature. F.G provided microbiology expertise in the estimation of nosocomial infection rates. S.A.B, S.J., D.L.N, J.L., E.K., C.S and N.N. provided details of clinical pathways. B.T., A.S. A.G. and C.L. assembled figures for presentation. C.T drafted the manuscript, with substantial contribution from A.S., R.S.H., G.L., M.L and E.McF. All authors contributed to the final manuscript.

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DECLARATION OF INTEREST

M.L reports personal fees from Pfizer, grants from Pfizer, personal fees from Roche, outside the submitted work. C.S reports grants from Pfizer, grants from Boehringer Ingelheim, grants and personal fees from Bristol Myers Squibb, grants and personal fees from AstraZeneca, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Roche-

Ventana, personal fees from Novartis, personal fees from MSD, personal fees from illumina, personal fees from Celgene, personal fees from GSK, personal fees from Genentech, personal fees from Medixci, personal fees and stock options from GRAIL, stock options from EPIC Biosciences, stock options from Apogen Biotech, personal fees and is co-founder of Achilles Therapeutics, personal fees from Sarah Canon Research Institute, during the conduct of the study. In addition, C.S has a patent Immune checkpoint intervention in cancer (PCT/EP2016/071471), issued, a patent Method for treating cancer based on identification of clonal neo-antigens (PCT/EP2016/059401) issued, a patent Methods for lung cancer detection (PCT/US2017/028013 issued, a patent ethod of detecting tumour recurrence (PCT/GB2017/053289), issued, a patent Method for treating cancer (PCT/EP2016/059401). issued, a patent Method of treating cancer by targeting insertion/deletion mutations (PCT/GB2018/051893) issued, a patent Method of identifying insertion/deletion mutation targets (PCT/GB2018/051892) issued, a patent Method for determining whether an HLA allele is lost in a tumour (PCT/GB2018/052004) issued, a patent Method for identifying responders to cancer treatment (PCT/GB2018/)051912) issued, and a patent Method of predicting survival rates for cancer patients (PCT/GB2020/050221) issued. A.S, B.T, M.E.J, J.B, S.S, C.L, A.G, F.G, D.L.N, S.J, S.A.B, M.W, E.R, D.C.M, E.K, J.L, N.N, G.L, E.M.F, R.S.H, C.T declare no competing interests.

RESEARCH IN CONTEXT

Evidence before this study

Observational studies of cancer pathway delays were identified on bibliographic database searching for English Language articles using terms [[cancer OR neoplasm], [delay OR interval OR wait], [diagnosis OR treatment]]. Studies typically report data extracted from institutional, regional or national databases. Patient experiencing pathway delay may be biased in regard of socio-economic status. Studies of shorter delay periods in particular are recognised to suffer confounding by indication (*i.e.* those with shortest delays often have the worst outcomes as rapidity of management can be a reflection of a sicker patient). Overall studies are highly heterogeneous in design and findings, including the durations of delay studied, the duration of survival follow-up, the metric by which impact is captured (percentages, odds ratios, hazard ratios) and how/when staging is performed. Each study typically focuses on a single tumour type +/- stage thereof. There had been no studies modelling in a standardised fashion across tumour-types the impact in lives and life-years-lost of systematic pathways delays until the current authors recently reported a healthcare resource analysis focused on systemic delays at point of surgery.

Added value of this study

Across multiple tumour-types, we present application of a standardised approach (i) using per-day fatality hazard ratios enabling quantitation of the impact of different durations of delay on survival (ii) examining both the referred patient and the diagnosed patient (iii) examining individual tumour-type and in aggregate across major tumour-types. This study focuses specifically on cancers diagnosed via the 2-week-wait (2WW) pathway as this pathway is most amenable to interventions. Whilst highly pertinent to current forecasting of COVID-related impact of delays, these models are applicable 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 COVID19-related delays in presentation, diagnosis and/or treatment will result in loss of life and life years that vary widely according to patient age and tumour type. Summed at national level, the impact in attributable deaths of COVID-19-related delays in presentation and diagnosis of cancer patients ascertained through the 2WW-pathway would currently be estimated from these models to be in the hundreds to low thousands. Data are currently immature regarding the true duration and extent of service disruption and per-patient cancer pathway delay across the UK. Direct

predictions regarding attributable cancer deaths will be possible once more accurate patient-level data become available.

LEGENDS FOR FIGUES/TABLES

Table 1: Cancer diagnoses made through the '2-Week Wait' pathway.

Proportion of all diagnoses made through 2WW, breakdown of 2WW cancers diagnosed by age and stage, diagnostic-conversion-rates (any cancer; cancer within TRG (tumour referral group), average annual cancer diagnoses total and via 2WW-pathway. Diagnostic-conversion-rates reflect all diagnoses of invasive cancers (exception: breast includes CIS, skin excludes basal cell carcinomas, urology excludes pTa bladder tumours)

~~**Table 1: Cancer diagnoses made through the '2-Week Wait' pathway.**~~

~~Proportion of all diagnoses made through 2WW, breakdown of 2WW cancers diagnosed by age and stage, diagnostic-conversion-rates: cancers (any cancer; cancer within tumour referral group), average annual cancer diagnoses total and via 2WW pathway. For diagnostic-conversion rates: breast cancer includes in situ cancers (all others are invasive only); skin only includes melanomas and SCCs (so excludes BCCs); urology excludes pTa bladder tumours.~~

Figure 1: Reduction in 10-year net survival incurred from a 3-month delay.

20 common tumour-types included. Red indicates the highest tertile of survival decrement; green indicates the lowest tertile of survival decrement.

Figure 2: Annual attributable lives and life-years lost from delay, aggregated for all patients diagnosed via 2WW-pathway.

Based on 10-year net survival data for England 2008-2017. Greatest decrements in lives and life-years lost are represented in darker shades of orange.

Figure 3: Per-patient risk-benefit from urgent investigatory referral compared to 2 month delay with varying rates of nosocomial COVID-19

Comparing impact on net survival of urgent investigatory referral compared to 2-month delay; red indicates benefit and green indicates disbenefit.

REFERENCES

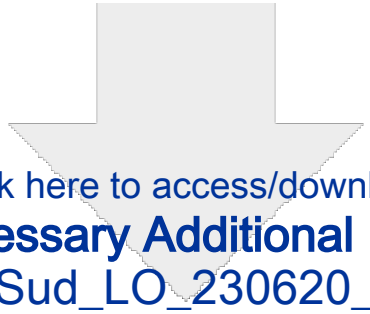
1. GPs made 30% fewer referrals to secondary care during March. Pulse. 2020 14/05/20.
2. Cancer referrals fell from 40,000 to 10,000 per week in April: NHS Providers; 2020 [updated 15/05/2020. Available from: https://nhsproviders.org/topics/covid-19/coronavirus-member-support/national-guidance/government-updates/daily-updates.
3. Lai AG, Pasea L, Banerjee A, Denaxas S, Katsoulis M, Chang WH, et al. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. medRxiv. 2020.
4. Bower E. Urgent referrals rejected for one in three GPs during COVID-19 outbreak. GPOnline. 2020.
5. Bostock N. Patients waiting more than a month for urgent cancer checks amid COVID-19 crisis. GPonline. 2020 29/4/20.
6. Sud A, Jones M, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol. 2020.
7. National Cancer Registration and Analysis Service (NCRAS). Public Health England; 2018.
8. Clinical Commissioning Groups Cancer Assessment 2017/18. NHS England; 2018.
9. The Cancer Waiting Times dataset. National Cancer Waiting Times system2019.
10. National Life Tables (2016-2018). Office for National Statistics (ONS), U.K. .
11. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). China CCDC; 2020 17/2/2020.
12. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, 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 (Clinical research ed). 2020;369:m1985.
13. 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 medical research methodology. 2011;11:96.
14. 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(1):e0210465.
15. 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(9159):1119-26.
16. Mano R, Vertosick EA, Hakimi AA, Sternberg IA, Sjoberg DD, Bernstein M, et al. The effect of delaying nephrectomy on oncologic outcomes in patients with renal tumors greater than 4cm. Urologic Oncology: Seminars and Original Investigations. 2016;34(5):239.e1-.e8.
17. Smith EC, Ziogas A, Anton-Culver H. Delay in Surgical Treatment and Survival After Breast Cancer Diagnosis in Young Women by Race/Ethnicity. JAMA Surgery. 2013;148(6):516-23.
18. Chu AT, Holt SK, Wright JL, Ramos JD, Grivas P, Yu EY, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. Cancer. 2019;125(12):2011-7.
19. 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. The Journal of urology. 2003;169(1):110-5; discussion 5.
20. 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. Scandinavian Journal of Urology and Nephrology. 2004;38(3):231-5.
21. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong Y-N, et al. Time to Surgery and Breast Cancer Survival in the United States. JAMA oncology. 2016;2(3):330-9.

22. 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. British journal of cancer. 1999;79(5-6):858-64.
23. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. Journal of the National Cancer Institute. 2003;95(3):230-6.
24. International Cancer Benchmarking Partnership (ICBP). Cancer Research UK (CRUK); 2020.
25. Dinmohamed AG, Visser O, Verhoeven RHA, Louwman MWJ, van Nederveen FH, Willems SM, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. The Lancet Oncology. 2020;21(6):750-1.

Table 1

	Proportion 2WW	Proportion by age group (2WW)						Proportion by stage (2WW)					Conversion to cancer		Cancer diagnoses (year)		
		30-39	40-49	50-59	60-69	70-79	80+	1	2	3	4	st1-3	% any cancer	% of cancers in TRG	All	2WW	Referrals (2WW) (year)
Bladder	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%	**8,524**	**3,654**	**21,624**
Brain	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%	**8,102**	**140**	**13,982**
Breast	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%	**41,845**	**22,678**	**462,822**
Cervix	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%	**2,128**	**471**	**15,183**
Colorectal	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%	**32,979**	**10,620**	**379,272**
Kidney	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%	**8,764**	**2,459**	**14,551**
Larynx	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%	**1,850**	**887**	**30,599**
Liver	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%	**4,712**	**683**	**11,989**
Lung	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%	**36,668**	**10,343**	**94,893**
Melanoma of skin	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%	**12,110**	**7,642**	**173,673**
Oesophagus	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%	**7,427**	**3,339**	**58,571**
Oral cavity	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%	**2,629**	**1,161**	**40,022**
Oropharynx	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%	**2,905**	**1,710**	**58,960**
Ovary	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%	**6,398**	**2,142**	**69,112**
Pancreas	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%	**8,260**	**1,594**	**27,962**
Prostate	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%	**40,834**	**19,272**	**114,037**
Stomach	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%	**5,332**	**1,654**	**29,024**
Testis	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%	**1,355**	**829**	**9,213**
Thyroid	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%	**2,673**	**620**	**21,388**
Uterus	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%	**7,604**	**4,390**	**141,614**
20 cancer types															**243,098**	**96,289**	**1,788,491**

Appendix_Sup_Tables_1-12(ex5)



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Necessary Additional Data

D-20-01167_Sud_LO_230620_Appendix.pdf

Figure1,2,3

	30-39 y	40-49 y	50-59 y	60-69 y	70-79 y	80+ y
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%	0.00%	0.00%	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%	0.00%
Uterus	2.43%	5.27%	6.04%	8.68%	11.83%	14.43%

	Cases		Attributable Lives Lost						Attributable Life Years Lost					
	All	2WW	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	**8,524**	**3,654**	81	168	260	355	450	544	1,430	2,979	4,633	6,365	8,139	9,910
Brain	**8,102**	**140**	8	16	23	31	37	43	159	324	490	654	813	962
Breast	**41,845**	**22,678**	228	472	734	1,014	1,312	1,629	4,733	9,839	15,339	21,255	27,608	34,418
Cervix	**2,128**	**471**	10	22	34	47	61	75	264	559	887	1,246	1,636	2,054
Colorectal	**32,979**	**10,620**	296	624	981	1,366	1,773	2,196	4,308	9,126	14,460	20,296	26,591	33,275
Kidney	**8,764**	**2,459**	50	106	168	236	309	388	923	1,968	3,143	4,452	5,897	7,471
Larynx	**1,850**	**887**	29	60	93	128	165	201	514	1,079	1,692	2,344	3,027	3,725
Liver	**4,712**	**683**	8	15	21	25	29	31	143	270	379	467	532	578
Lung	**36,668**	**10,343**	189	356	497	610	695	753	3,605	6,873	9,704	12,030	13,829	15,128
Melanoma of skin	**12,110**	**7,642**	138	296	476	682	913	1,171	2,501	5,403	8,756	12,614	17,028	22,051
Oesophagus	**7,427**	**3,339**	72	137	192	236	268	291	1,498	2,850	4,011	4,952	5,665	6,163
Oral cavity	**2,629**	**1,161**	33	67	100	133	163	190	695	1,415	2,145	2,864	3,551	4,183
Oropharynx	**2,905**	**1,710**	18	37	57	76	95	112	437	900	1,379	1,866	2,347	2,810
Ovary	**6,398**	**2,142**	81	163	244	323	397	464	1,688	3,445	5,239	7,027	8,765	10,406
Pancreas	**8,260**	**1,594**	12	21	27	32	34	36	224	402	533	623	678	709
Prostate	**40,834**	**19,272**	3	6	9	12	16	20	56	116	183	255	334	420
Stomach	**5,332**	**1,654**	38	74	107	135	159	177	719	1,411	2,051	2,619	3,096	3,475
Testis	**1,355**	**829**	1	3	4	6	8	10	55	116	182	254	333	419
Thyroid	**2,673**	**620**	1	2	3	5	6	8	24	50	79	110	144	181
Uterus	**7,604**	**4,390**	117	249	397	562	743	939	1,837	3,932	6,305	8,970	11,936	15,201
Total	**243,098**	**96,289**	**1,412**	**2,892**	**4,429**	**6,013**	**7,633**	**9,280**	**25,812**	**53,057**	**81,589**	**111,263**	**141,950**	**173,540**

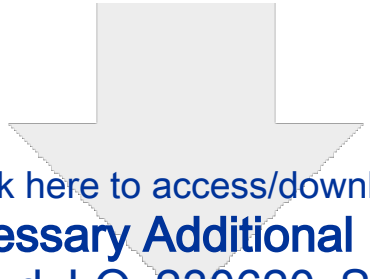
Nosocomial COVID-19 infection rate (per investigatory referral)	0.5%						1%						2.5%						5%					
Age (years)	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80+**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80+**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80+**	**30-39**	**40-49**	**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%	0.00%	-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%	0.00%	-0.01%	-0.01%	0.02%	0.01%	0.02%	-0.02%	-0.05%	-0.09%	0.02%	0.00%	0.00%	-0.08%	-0.17%	-0.31%	0.01%	-0.01%	-0.03%	-0.17%	-0.37%	-0.68%
Thyroid	0.00%	0.00%	0.01%	-0.02%	-0.01%	-0.07%	0.00%	0.00%	0.00%	-0.03%	-0.05%	-0.15%	0.00%	0.00%	-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%

Editorial comment	Response	Line number (clean)
1. Editorial comment 6: As no specific funding supported this study, I'm afraid your paper is not eligible for open access.	Normally our library will support OA fees. We contacted them and their response was: *"If ICR staff are the corresponding author(s) then we can pay the open access fee. Can you cite the grant acknowledgements in the paper. If there is none, we can still pay the fee; however, if the publisher refuses the OA option then we can't progress further with it."*. If there is a formulation by which we can make OA, that would be great, but I appreciate that this may not be possible. The rules governing this remain a mystery to me. The second author (starred) is fully supported by CRUK award C61296/A27223; arguably, we could ascribe the work to that award, albeit that the project was not explicitly articulated within the program plan.	
2. Editorial comment 8: thank you, please consider this title with a slight amendment: Effect of delays in the UK two-week wait cancer referral pathway during the COVID-19 pandemic on cancer survival: a modelling study	We are very happy with your proposed title and have amended: Effect of delays in the UK two-week wait cancer referral pathway during the COVID-19 pandemic on cancer survival: a modelling study	1
3. Editorial comment 12: Research in context panel: a. Please include any language or date restrictions used in your literature search.	We did not use a date restriction on our search, but did restrict to English language. We have amended: Observational studies of cancer pathway delays were identified on bibliographic database searching **for English Language articles** using terms [[cancer OR neoplasm], [delay OR interval OR wait], [diagnosis OR treatment]].	443
4. Editorial comment 13b: the main outcomes are not clearly stated in the Summary Methods. Please explicitly state what outcomes were assessed—eg, considering adding the following sentences from the main manuscript Methods to the Summary Methods: "We quantified the annual numbers of cancers	We have amended the methods, adding the additional text as you advise. We also added the 'per-referral survival increment' here: **Methods:** To construct the underlying models, we used age- and stage-stratified 10 year-cancer survival estimates for England 2007-2017 for 20 common tumour-types. We applied per-day hazard ratios for cancer progression generated from observational studies of delay-to-treatment. We quantified the annual numbers of cancers diagnosed via the 2WW-pathway using the 2WW age- and stage-specific breakdowns. From these, for per-patient	56

diagnosed via the 2WW-pathway using the 2WW age- and stage-specific breakdowns. From these, for per-patient delays of 1-6 months, we estimated aggregate number of lives lost and life-years lost in England."	delays of 1-6 months, we estimated aggregate number of lives lost and life-years lost in England. Using referral-to-diagnosis conversion rates and COVID-19 case fatality rates, we also estimated the survival increment per patient referred.	
5. Editorial comment 13d: please state the exact dates of recruitment and median follow-up (IQR) for the analyses presented in the Summary Findings.	There is not 'recruitment' as such to the Cancer Waiting Times and PHE NCRAS datasets as they reflect routine mandatory reporting with linkage to ONS mortality. Thus, there is full 100% follow-up for the 10 year follow-up for the NCRAS data. I think this is covered in the Methods in: To construct the underlying models, we used age- and stage-stratified 10 year-cancer survival estimates for England 2007-2017 We have added the reference period to which the 2WW (CWT) data pertain to contextualise this monthly figure. Per month across England, in 2013-2016 on average 6,281 patients with Stage 1-3 cancer were diagnosed via the 2WW pathway of whom 1,691 are predicted to die within 10 years from their disease. We estimated 2WW-pathway presentational-delay during lockdown will result in total in 181/361/542 attributable additional deaths (if % reduction in referrals was 25/50/75% respectively).	56 64
	We shortened the Findings section to reduce words in the Summary (which had got to >350) as below. It now reads: **Findings:** Per month across England, in 2013-2016 on average 6,281 patients with Stage 1-3 cancer were diagnosed via the 2WW pathway of whom 1,691 would be predicted to die within 10 years from their disease. We estimated 2WW-pathway presentational-delay from three months of lockdown will result in total in 181/361/542 attributable additional deaths (if % reduction in referrals was 25/50/75% respectively). Limited diagnostic capacity to address the backlog may result in additional delays: 401/811/1,231 attributable additional deaths are estimated if additional diagnostic capacity is delayed until months 3-8 post-	64

	lockdown. 2-month delay in 2WW investigatory referral results in average loss of life-years per-referred-patient of between 0 and 0.7, depending on age and tumour-type. Essentially, we shortened to one clause; We estimated that diagnostic-delay from delivery of additional diagnostic capacity spread across months 1-3 post-lockdown will incur 90/183/276 attributable additional deaths. If additional capacity is delayed until months 3-8 post-lockdown, we estimate this will incur 401/811/1,231 attributable additional deaths. And removed Contribution to this burden of mortality is not uniform by age-group nor proportionate to tumour-type incidence. We are happy if you want to reinstate either bit…The abstract currently stands at 320 words.	66 70
6. Editorial comment 13h: thank you for confirming that no direct funding supported this study. Please could you add the following to the end of the Summary: Funding: None.	We have added this statement to the summary Funding: None	77
7. Editorial comment 15: please reorder the paragraphs in the Methods section so that all relevant statistical analyses are included under the Statistical analysis section (eg hazard ratio calculation).	We have moved the section on SD to the statistical analysis section 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) and SD of this estimate (*i.e.* standard error), expressing this as a percentage of the estimate. We performed multivariate sensitivity analyses across ranges of parameter estimates, including +/- 2SD of delay-HR.	199
8. Editorial comment 16: Role of the Funding Source: As there was no direct funder of the study, please change the first sentence to '"There was no funding source for this study". The line about access to data should remain.	We have amended the funding statement as recommended. **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 the final decision to submit the manuscript.	209

9. Editorial comment 31: thank you for providing your appendix as a PDF. Given that supplementary table 5 is interactive, please feel free to remove it from the appendix and supply it as a single XLSX file. A placeholder for suppl table 5 can be inserted in the PDF in its place—eg, after suppl table 4, add "Supplementary table 5 is provided as a separate XLSX file.	We have extracted Sup Table 5 as a standalone xlsx. We have supplied the remainder of the supplementary tables as a PDF appendix. We have updated the references in the manuscript to reflect this configuration.	
10. Editorial comment 39: Completed, signed, author contribution forms from all authors were not included with your revised manuscript. Please supply with your next revised manuscript. The form can be downloaded at download.thelancet.com/flatcontentassets/authors/tlo-author-signatures.pdf.	Apologies. We realised we were short one reply. These have been emailed on 23/6/20 at09:51	
11. Editorial comment 41: Completed ICMJE COI forms for each author were not included with your revised manuscript. Please supply with your next revised manuscript. he form can be found at http://www.icmje.org/conflicts-of-interest/.	Apologies. We realised we were short one reply. These have been emailed on 23/6/20 at 09:51.	
12. Editorial comment 51: Please provide table 1 as a Word doc.	Apologies. This is now supplied as a Word Doc. The Legends are included in the manuscript.	



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Necessary Additional Data

D-20-01167_Sud_LO_230620_Sup_Table_5.xls