FAST TRACK

Mortality due to cancer treatment delay: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE
To quantify the association of cancer treatment delay and mortality for each four week increase in delay to inform cancer treatment pathways.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
Published studies in Medline from 1 January 2000 to 10 April 2020.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Curative, neoadjuvant, and adjuvant indications for surgery, systemic treatment, or radiotherapy for cancers of the bladder, breast, colon, rectum, lung, cervix, and head and neck were included. The main outcome measure was the hazard ratio for overall survival for each four week delay for each indication. Delay was measured from diagnosis to first treatment, or from the completion of one treatment to the start of the next. The primary analysis only included high validity studies controlling for major prognostic factors. Hazard ratios were assumed to be log linear in relation to overall survival and were converted to an effect for each four week delay. Pooled effects were estimated using DerSimonian and Laird random effect models.

RESULTS
The review included 34 studies for 17 indications (n=1 272 681 patients). No high validity data were found for five of the radiotherapy indications or for cervical cancer surgery. The association between delay and increased mortality was significant (P<0.05) for 13 of 17 indications. Surgery findings were consistent, with a mortality risk for each four week delay of 1.06-1.08 (eg, colectomy 1.06, 95% confidence interval 1.01 to 1.12; breast surgery 1.08, 1.03 to 1.13). Estimates for systemic treatment varied (hazard ratio range 1.01-1.28). Radiotherapy estimates were for radical radiotherapy for head and neck cancer (hazard ratio 1.09, 95% confidence interval 1.05 to 1.14), adjuvant radiotherapy after breast conserving surgery (0.98, 0.88 to 1.09), and cervix cancer adjuvant radiotherapy (1.23, 1.00 to 1.50). A sensitivity analysis of studies that had been excluded because of lack of information on comorbidities or functional status did not change the findings.

CONCLUSIONS
Cancer treatment delay is a problem in health systems worldwide. The impact of delay on mortality can now be quantified for prioritisation and modelling. Even a four week delay of cancer treatment is associated with increased mortality across surgical, systemic treatment, and radiotherapy indications for seven cancers. Policies focused on minimising system level delays to cancer treatment initiation could improve population level survival outcomes.

Introduction

Delay in the treatment of cancer can have adverse consequences on outcome. However, despite its foundational importance, we lack standardised estimates of the effect of treatment delay on survival for most treatment indications. Previous meta-analyses have found evidence supporting a continuous association between delay and mortality[1][2] or local control.[3] A wide variation in reporting of delay estimates has limited meta-analysis.[4] Understanding the impact of delay on mortality and other outcomes such as recurrence or financial impact on patients is essential to designing cancer care systems, pathways, and models of care that deliver affordable and equitable outcomes.[5]

The need for an in-depth understanding of the impact of treatment delay on outcomes has come sharply into focus during the coronavirus 2019 (covid-19) pandemic. Many countries have experienced deferral of elective cancer surgery and radiotherapy, and reductions in the use of systemic treatments[6][7] because systems have reassigned healthcare resources to pandemic preparedness.[8] The lack of high quality data on the impact of deferred and delayed cancer treatment has meant that the impact of covid-19 lockdown measures on patterns of care and subsequent outcomes has not been robustly quantified. More broadly, in non-pandemic times, health systems have developed pathways and targets for intervals from

WHAT IS ALREADY KNOWN ON THIS TOPIC

Delay in the treatment of cancer can have adverse consequences on outcome

Previous meta-analyses of high validity studies have found evidence supporting a continuous relation between delay and mortality or local control

Despite its foundational importance, we lack standardised estimates of the effect of treatment delay for most treatment indications

WHAT THIS STUDY ADDS

This systematic review considered seven major cancer types (bladder, breast, colon, rectum, lung, cervix, and head and neck) and three treatment modalities (surgery, systemic treatment, and radiotherapy)

The data consistently show that a four week treatment delay is associated with increased mortality; further mortality was reported with longer delays

Policies focused on minimising system level delays in cancer treatment initiation could improve population level survival outcomes

the time of diagnosis to receipt of treatment within National Cancer Control Plan frameworks that do not have a strong empirical basis.[9]

Our analysis aims to provide robust evidence to guide national policy making, specifically the prioritisation and organisation of cancer services, by investigating the association between delays in receipt of cancer treatment and mortality. We considered seven common cancers and provide estimates on the impact of delay across all three curative modalities: surgery, systemic treatment, and radiotherapy delivered in the radical, neoadjuvant, and adjuvant setting.

Methods
Population
We investigated seven cancers that together represent 44% of all incident cancers globally[10]: five common cancers (bladder, breast, colon, rectum, lung); cervical cancer, given its global importance as the fourth most common cancer diagnosis among women; and head and neck cancer (a major burden in middle income settings), for which there is an established association between delay and mortality.[10] We selected these cancers by balancing representativeness with comprehensiveness. We also considered rectal and colon cancer separately given that radiotherapy is an integral part of treatment for rectal cancer but not colon cancer. Because of the generally indolent nature of prostate cancer (particularly for low and intermediate risk disease) compared with other cancers, and a preliminary review of the delay literature, this cancer was excluded because delays of the magnitude considered in our analysis were probably not associated with increased mortality.

Exposure
Treatment delay was defined as time from diagnosis to treatment for the first treatment (definitive surgery or radiation), and from time of surgery to treatment for adjuvant indications (chemotherapy or radiation after surgery). For neoadjuvant treatments (those delivered before primary curative therapy, eg, surgery), delay was defined as the time from diagnosis to the start of neoadjuvant treatment, or from the end of neoadjuvant treatment to time of surgery. Delay of curative treatments was investigated (surgery, systemic treatment, and radiotherapy).
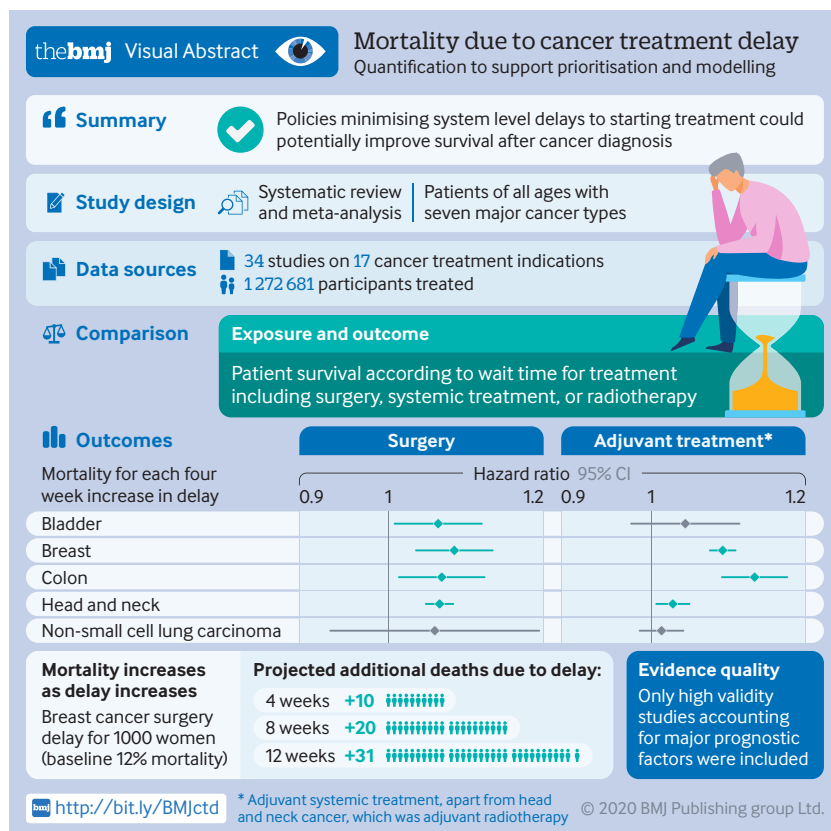
Outcome
A hazard ratio for overall survival was estimated for each four week increase in delay. The hazard ratio represents the risk of death from any cause for patients experiencing the observed treatment delay compared with those treated without the delay.

Systematic review
We undertook a systematic review to identify high validity studies quantifying the impact of treatment delay on mortality. The PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines were followed.[11] We used Ovid Medline to carry out the search (appendix 1). To fully assess the validity of included studies, we did not search the literature for studies in abstract form only. Studies were limited to English language publications, from 2000 to present, and those reporting specifically on treatment delay and survival for the seven cancers being analysed. The year 2000 was selected to be comprehensive, while limiting reports to those reflective of contemporary practice as much as possible. We included studies if they specifically reported on the impact of delay for a well defined cancer indication. Studies that reported predominantly on patients receiving neoadjuvant treatments were excluded when evaluating the impact of treatment delay from diagnosis to definitive surgery. Studies that investigated the therapeutic benefit of intentional moderate delay between completion of neoadjuvant therapy for rectal cancer and surgery were excluded given potential confounding by indication. We did not exclude any studies based on design, except that the study needed to quantify the hazard ratio for overall survival because of treatment delay. The search was run on 10 April 2020, except for the bladder cancer search which was performed on 22 April 2020. Two reviewers screened abstracts by using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Searches of reference lists and Google were also performed.

We reviewed studies for evidence of control for major prognostic factors to assess risk of bias. The criteria used were consistent with those used by our group in other systematic reviews of delay and outcomes.[1-3]

the bmj Visual Abstract — Mortality due to cancer treatment delay
Quantification to support prioritisation and modelling

Summary — Policies minimising system level delays to starting treatment could potentially improve survival after cancer diagnosis

Study design — Systematic review and meta-analysis | Patients of all ages with seven major cancer types

Data sources — 34 studies on 17 cancer treatment indications | 1 272 681 participants treated

Comparison — Exposure and outcome — Patient survival according to wait time for treatment including surgery, systemic treatment, or radiotherapy

Outcomes — Mortality for each four week increase in delay — Hazard ratio 95% CI

	Surgery	Adjuvant treatment*
Bladder		
Breast		
Colon		
Head and neck		
Non-small cell lung carcinoma		

Mortality increases as delay increases — Breast cancer surgery delay for 1000 women (baseline 12% mortality)

Projected additional deaths due to delay:
- 4 weeks +10
- 8 weeks +20
- 12 weeks +31

Evidence quality — Only high validity studies accounting for major prognostic factors were included

http://bit.ly/BMJctd

* Adjuvant systemic treatment, apart from head and neck cancer, which was adjuvant radiotherapy

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Firstly we asked "was the distribution of the relevant prognostic factors adequately described in the groups of patients which were compared?" Relevant prognostic factors for all studies were considered to be age, stage, treatment description, and comorbidity or functional status. If no, the study was classified as not of high validity. If yes, we proceeded to the next question "Were the comparison groups balanced with respect to the relevant prognostic factors?" If yes, the study was classified as high validity. We qualitatively assessed the magnitude of observed differences, and the P value was considered when interpreting these differences. If no, we asked "Were the reported results appropriately adjusted for any differences in the relevant prognostic factors?" If yes, the study was classified as high validity; if no, the study was classified as not high validity. Only studies meeting these criteria were included for subsequent meta-analysis.

For some definitive indications (colon cancer, lung cancer, cervical cancer), it was possible that observed associations between treatment delay and risk of death were attenuated because patients with poorer outcomes might present more quickly with symptomatic disease through emergency or urgent referral pathways (often referred to as the waiting time paradox).[12] To qualify as high validity, such studies were required to have also performed an analysis or subanalysis to investigate the impact of this factor in the observed associations. Similar to Neal and colleagues, this was defined as an analysis or subanalysis of patients clearly including or excluding patients with short diagnosis to treatment interval (eg, less than four weeks) or poor outcomes (eg, death within four to eight weeks of diagnosis).[12]

Converting hazard ratios to four week delay estimates

There was heterogeneous reporting of results, with time intervals reported as dichotomous, ordinal categories or as continuous variables. Results were converted to a common unit—hazard ratio for each four week delay with the assumption of a log linear relation across waiting times based on the findings of other meta-analyses.[1-3] A log linear relation predicts, for example, that patients waiting eight weeks rather than four weeks have a doubling in their risk of death. A unit of four weeks was chosen based on the magnitude of waiting times reported in the literature. We emphasise that the hazard ratio calculated in this study might be converted to shorter (eg, each week or each day) or longer units. Appendix 2 provides further information on the conversion of hazard ratios to each four week delay estimates or other units, and compares the log linear model to the linear model.

Meta-analysis

We obtained the summary hazard ratio estimate by pooling hazard ratios for each four week delay with inverse variance weighting in DerSimonian and Laird random effect models. Heterogeneity between studies was evaluated using the I^2 test. We performed the statistical analysis using the R package metafor (R Foundation for Statistical Computing, Vienna, Austria). We considered a two tailed P value less than 0.05 to be statistically significant. Publication bias was not tested given the small number of studies identified for each indication.

Sensitivity analysis

We undertook a post hoc sensitivity analysis to evaluate the impact of the stringent validity criteria on findings. Studies that had been excluded in the main analysis because of a lack of information on comorbidities or functional status were included in this analysis because other factors such as increasing age could be proxies for these.

Patient and public involvement

The research was informed by patient groups and cancer charities that were concerned about the impact of cancer treatment deferral and delays during the covid-19 pandemic.

Results

Our search identified 2543 articles for review (fig 1).[11] After we added records identified through additional sources, and removed duplicates, 2843 records were screened. The primary reason for exclusion at the screening stage was lack of relevance to the study question. We obtained 275 articles to assess for eligibility. Of these, 241 were excluded, most commonly because they were not high validity studies (n=100), they included the wrong patient population (n=36), or the wrong study design (n=26). This left 34 studies with unique populations for inclusion (fig 1, table 1, table 2).[13-46] These studies included 1 272 681 patients, with a sample size ranging from 174 to 420 792 (appendix 3). Twenty eight studies were population or registry based, and six were institutional reports. All studies were retrospective observational comparisons. Abstracted data on delay were dichotomous in eight, continuous in nine, and categorical in 17 studies. Waiting time data generally covered from three to four weeks, to 16 weeks (appendix 3). Appendix 3 presents the association between treatment delay and survival for individual studies. In addition to adjustments for age, stage, and comorbidity or functional status, 91% of studies accounted for one or more socioeconomic variables in their analysis, 82% accounted for insurance status, 65% for year of treatment or year of diagnosis, and 88% for institutional or geographical factors (appendix 4). We did not find any high validity data for five radiotherapy indications or cervical cancer surgery (table 1, table 2).

Figure 2, figure 3, figure 4 show summary results for all indications, with pooled estimates displayed for treatment site combinations where more than one high validity study exists. The random effects models showed a consistent association of surgical delay with increased mortality, with all indications showing a hazard ratio for each four week delay of between 1.06 and 1.08 (6-8% increased chance of death for each four week delay in treatment). For example,
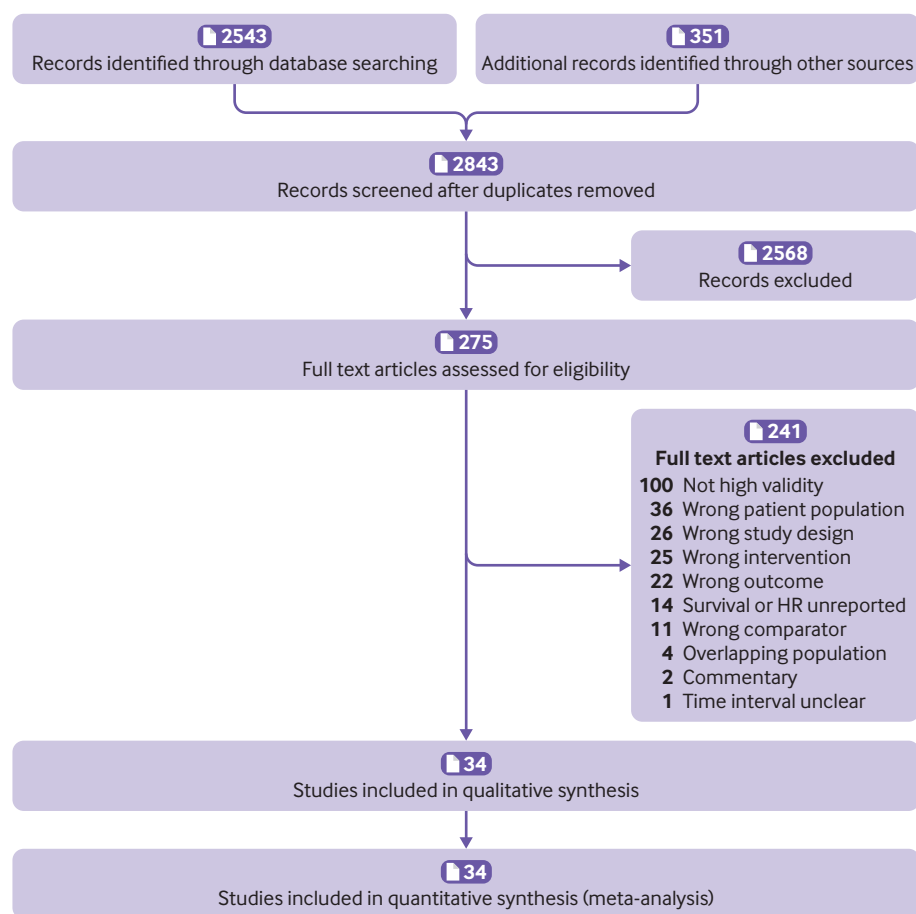
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Fig 1 | PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2009 flow diagram for systematic review of treatment delay and survival for curative surgery, systemic treatment, and radiotherapy for bladder, breast, colon, rectum, lung, cervix, and head and neck cancer. HR=hazard ratio

for head and neck surgery the hazard ratio was 1.06 (95% confidence interval 1.04 to 1.08) and for breast partial or complete mastectomy the hazard ratio was 1.08 (1.03 to 1.13). The results for lung surgery were consistent with other sites, though not statistically significant (1.06, 0.93 to 1.19).

Adjuvant and neoadjuvant systemic treatment indications varied more widely in effect (hazard ratio range 1.01-1.28). We observed significant associations for bladder neoadjuvant systemic treatment (hazard ratio 1.24, 95% confidence interval 1.03 to 1.50), breast adjuvant (1.09, 1.07 to 1.11) and neoadjuvant systemic treatment (1.28, 1.05 to 1.56), and colon and rectal adjuvant chemotherapy (1.13, 1.09 to 1.17). Associations were non-significant for non-small cell lung cancer adjuvant chemotherapy (1.01, 0.99 to 1.04) and bladder adjuvant chemotherapy (1.04, 0.98 to 1.11).

High validity data on curative radiotherapy were limited, but supported a mortality impact of delay for head and neck cancer (eg, radical radiotherapy: 1.09, 1.05 to 1.14) and for cervical cancer adjuvant radiotherapy (1.23, 1.00 to 1.50; P=0.045). We found no significant effect for the single high validity study of adjuvant radiotherapy after breast conserving surgery (0.98, 0.88 to 1.09). No high validity studies were found for delay between diagnosis and start of neoadjuvant therapy for rectal cancer or for four other curative radiotherapy indications (table 2).

Sensitivity analysis

To evaluate the impact of our validity criteria on study findings, we undertook a sensitivity analysis and included studies that could be considered of borderline validity. For this analysis, we included 12 studies that were excluded in the primary analysis solely because of the lack of reporting or adjustment for comorbidity or functional status. We found little change in our estimates, except for breast cancer neoadjuvant systemic treatment (appendix 5).

Discussion

Principal findings

This analysis reports the impact of delay in curative treatment on the risk of death across the seven major tumour types: bladder, breast, colon, rectum, lung, cervix, and head and neck, and across all three major treatment modalities (surgery, systemic treatment, and radiotherapy). Across all three modalities, we found that a treatment delay of four weeks is associated

Table 1 | Summary of characteristics for studies investigating surgical treatment

Indication: surgery	Source	Study design	Dataset (dates)	Median age (years)	Stage	Other study details
Bladder	Chu 2019[13]	Retrospective observational comparison	SEER Medicare database (2004-2012)	75.2 (mean)	II	—
	Gore 2009[14]	Retrospective observational comparison	SEER Medicare database (1992-2001)	≤12 weeks=73.8, ›12 weeks=73.6 (mean)	II	—
	Kulkarni 2009[15]	Retrospective observational comparison	Ontario Cancer Registry (1992-2004)	≤90 days 67.4, ›90 days 69.2 (mean)	Tx, T0, Ta, Tis, T1-T4	—
Breast	Bleicher 2016[16]	Retrospective observational comparison	SEER Medicare database (1992-2009), NCDB (2003-2005) databases	75.2 (mean), 60.3 (mean)	I-III, I-III	Both cohorts were included in meta-analysis as overlap was limited owing to years considered in two cohorts, wider geographical population coverage of NCDB with ≥18 years represented (SEER was ≥66 years)
	Eaglehouse 2019[17]	Retrospective observational comparison	CCR, MDR databases (1998-2010)	54.5 (mean)	I-III	—
	Polverini 2016[18]	Retrospective observational comparison	NCDB (2004-2012)	59.4 (mean)	I-III	—
	Shin 2013[19]	Retrospective observational comparison	KCCR database (2006)	49.3 (mean)	Local and regional (SEER)	—
	Mateo 2020[20]	Retrospective observational comparison	NCDB (2010-2014)	NR	I-III	—
Colon	Bagaria 2019[21]	Retrospective observational comparison	Multicentre, US (1990-2012)	71 (range 18-99)	I-IV (pathological)	—
	Flemming 2017[22]	Retrospective observational comparison	OCR, CIHI DAD, OHIP databases (2002-2008)	71 (IQR 62-78)	I-IV (pathological)	—
NSCLC	Kanarek 2014[23]	Retrospective observational comparison	Institutional US (2003-2009)	61% ≥65	1A, 1B/2A, 2B	—
	Samson 2015[24]	Retrospective observational comparison	NCDB (1998-2010)	‹8 weeks: 67.63 (±10.1), ≥8 weeks: 68.73 (±9.8) (mean (±SD))	I (clinical)	—
Cervix	No high validity data found					
Head and neck	Murphy 2016[25]	Retrospective observational comparison	NCDB (2003-2005)	NR	I-IVB	Oral tongue, oropharynx, larynx, hypopharynx
	Liao 2017[26]	Retrospective observational comparison	Taiwanese Cancer Registry database (2004-2010)	52.8 (mean)	I-IVB (clinical)	Oral cavity

CCR=Department of Defence Central Cancer Registry; CIHI DAD=Canadian Institute for Health Information Discharge Abstract Database; IQR=interquartile range; KCCR=Korean Central Cancer Registry; MDR=Military Health System Data Repository; NCDB=National Cancer Database (US); NR=not reported; NSCLC=non-small cell lung cancer; OCR=Ontario Cancer Registry; OHIP=Ontario Health Insurance Plan; SEER=Surveillance, Epidemiology, and End Results.

with an increase in the risk of death. For surgery, this is a 6-8% increase in the risk of death for every four week delay. This impact is even more marked for some radiotherapy and systemic indications, with a 9% and 13% increased risk of death for definitive head and neck radiotherapy and adjuvant systemic treatment for colorectal cancer, respectively. The one high validity study for breast cancer adjuvant radiotherapy did not show an effect, although a clear effect of delay on local control has been described (hazard ratio for each month of delay 1.08, 95% confidence interval 1.02 to 1.14); longer delays (eg, >20 weeks) have been associated with worse breast cancer specific survival.[47 48]

Policy implications and comparison to other studies
Our analysis builds on the foundations of Mackillop and colleagues, who investigated the mortality impact per one month delay for radiotherapy indications (eg, head and neck, breast) and similarly for systemic treatment (adjuvant colon, breast).[1-3 47] Our study provides a strong empirical basis for estimating the mortality impact of system level delays for different treatment modalities and cancers.

Delays of up to eight weeks and 12 weeks further increase the risk of death. For example, an eight week delay in breast cancer surgery would increase the risk of death by 17% (=$1.08^{8 weeks/4 weeks}$) and a 12 week delay would increase the risk by 26% (=$1.08^{12 weeks/4 weeks}$). Such figures translate into significant population level excess mortality. A surgical delay of 12 weeks for all patients with breast cancer for a year (eg, during covid-19 lockdown and recovery) would lead to 1400 excess deaths in the United Kingdom, 6100 in the United States, 700 in Canada, and 500 in Australia, assuming surgery is the first treatment in 83%, and mortality without delay is 12%.[10 16 49] These results are sobering and suggest that the survival gained by minimising the time to initiation of treatment is of similar (and perhaps greater) magnitude of benefit as that seen with some novel therapeutic agents.[50] Furthermore, our results do not consider the impact of treatment delay on local control rates, functional outcomes (eg, continence, swallowing), complications from more extensive treatments because of progression during delays, quality of life,[51] or the greater economic burden because of higher direct care costs and productivity losses because of premature mortality and morbidity.[52] Therefore, the impact of treatment delay is probably far greater for patients and society than that reflected in our results.

Table 2 | Summary of characteristics for studies investigating systemic treatment and radiotherapy

Indication	Source	Study design	Dataset (dates)	Median age (years)	Stage	Other study details
Systemic treatment						
Neoadjuvant chemotherapy, bladder	Chu 2019[13]	Retrospective observational comparison	SEER Medicare database (2004-2012)	72.9 (mean)	II	Same study as Chu 2019[13] bladder surgery
Adjuvant chemotherapy, bladder	Corbett 2019[27]	Retrospective observational comparison	NCDB (2006-2013)	NR	pT3-T4 or pN+	—
	Booth 2014[28]	Retrospective observational comparison	OCR	38% were ≥70	18% ‹T3, 82% T3-T4, 68% node positive	—
Neoadjuvant chemotherapy, breast	Sanford 2016[29]	Retrospective observational comparison	Research database at University of Texas (1995-2007)	50 (range 24-83)	I-III (clinical)	Time from end of neoadjuvant chemotherapy to surgery
Adjuvant chemotherapy, breast	Gagliato 2014[30]	Retrospective observational comparison	MD Anderson Cancer Center institutional database. (1997-2011)	50 (range 19-85)	I-III	—
	Mateo 2020[20]	Retrospective observational comparison	NCDB (2010-2014)	NR	I-III	—
	Hershman 2006[31]	Retrospective observational comparison	SEER Medicare database (1992-1999)	NR	I-II	—
Adjuvant chemotherapy, colon, rectum	Hershman 2006[32]	Retrospective observational comparison	SEER Medicare database (1992-1999)	NR	III Colon	—
	Cheung 2009[33]	Retrospective observational comparison	SEER Medicare database (1991-2002)	73.3 (IQR 69.8-77.4)	II- III Rectal	—
	Bayraktar 2011[34]	Retrospective observational comparison	Jackson Memorial Hospital and University of Miami Sylvester Comprehensive Cancer Center (2000-2008)	55.7±1.1 for ≤60 days and 56.9±1.8 for ›60 days (mean±SE)	II-III Colon	—
	Lima 2011[35]	Retrospective observational comparison	Alberta Cancer Registry, ambulatory care classification system, discharge abstract database (2000-2005)	NR	III Colon	—
	Becerra 2017[36]	Retrospective observational comparison	New York State Registry, SPARCS (2004-2009)	NR	III Colon	—
	Turner 2018[37]	Retrospective observational comparison	NCDB (2006-2014)	NR	III Colon	—
	Xu 2014[38]	Retrospective observational comparison	SEER Medicare database (1992-2005)	73.6 (IQR 69.8-77.6)	II Colon	—
	Massarweh 2015[39]	Retrospective observational comparison	NCDB (2003-2010)	60.8 (±11.6) (mean (±SD))	III Colon	—
Adjuvant chemotherapy, NSCLC	Booth 2013[40]	Retrospective observational comparison	OCR (2004-2006)	62 (28-85) (mean (range))	I-IV (pathological)	—
	Salazar 2017[41]	Retrospective observational comparison	NCDB (2004-2012)	64 (IQR 57-70)	I-III (pathological)	—
Radiotherapy						
Definitive radiotherapy/ neoadjuvant, bladder	No high validity data found					
Adjuvant radiotherapy, post breast conserving surgery	Hébert-Croteau 2004[42]	Retrospective observational comparison	Random population based sample of five regions of Quebec, Canada for periods covering 1988-1994	NR	I-II	—
Neoadjuvant (chemo)radiation, rectum*	No high validity data found					
NSCLC, stage III chemoradiation	No high validity data found					
SCLC, limited stage chemoradiation	No high validity data found					
Adjuvant chemoradiation, cervix	Jhawar 2017[43]	Retrospective observational comparison	NCDB (2004-2013)	46 (IQR 38-56)	IB1-IIIB	No stratified wait group table but adjusted analysis
Definitive chemoradiation, cervix	No high validity data found					
Radical chemoradiation, head and neck	Sharma 2016[44]	Retrospective observational comparison	NCDB (2003-2006)	57.6 (9.9) (mean (SD))	III-IV (clinical, non-metastatic)	Oropharynx chemoradiation
Adjuvant (chemo)radiation, head and neck	Harris 2018[45]	Retrospective observational comparison	NCDB (2004-2013)	59 (10.9) (mean (SD))	III-IV (non-metastatic)	Interaction between subsite and outcome observed
Radical (chemo)radiation, nasopharyngeal carcinoma	Chen 2016[46]	Retrospective observational comparison	Sun Yat-Sen University Cancer Center, institutional series (2009-2012)	NR, 45% ≤45 (primary cohort)	I-IV (non-metastatic)	99.6% World Health Organization histology type II/III, treated with IMRT

IMRT=intensity modulated radiation therapy; IQR=interquartile range; NCDB=National Cancer Database (US); NR=not reported; NSCLC=non-small cell lung cancer; OCR=Ontario Cancer Registry; SCLC=small cell lung cancer; SD=standard deviation; SE=standard error; SEER=Surveillance, Epidemiology, and End Results; SPARCS=Statewide Planning and Research Cooperative System.
*Delay studies primarily investigating therapeutic benefit of usually short delay between completion of neoadjuvant treatment and surgery for rectal cancer are excepted. No high validity studies investigating time from diagnosis to start of neoadjuvant therapy were found for rectal cancer.
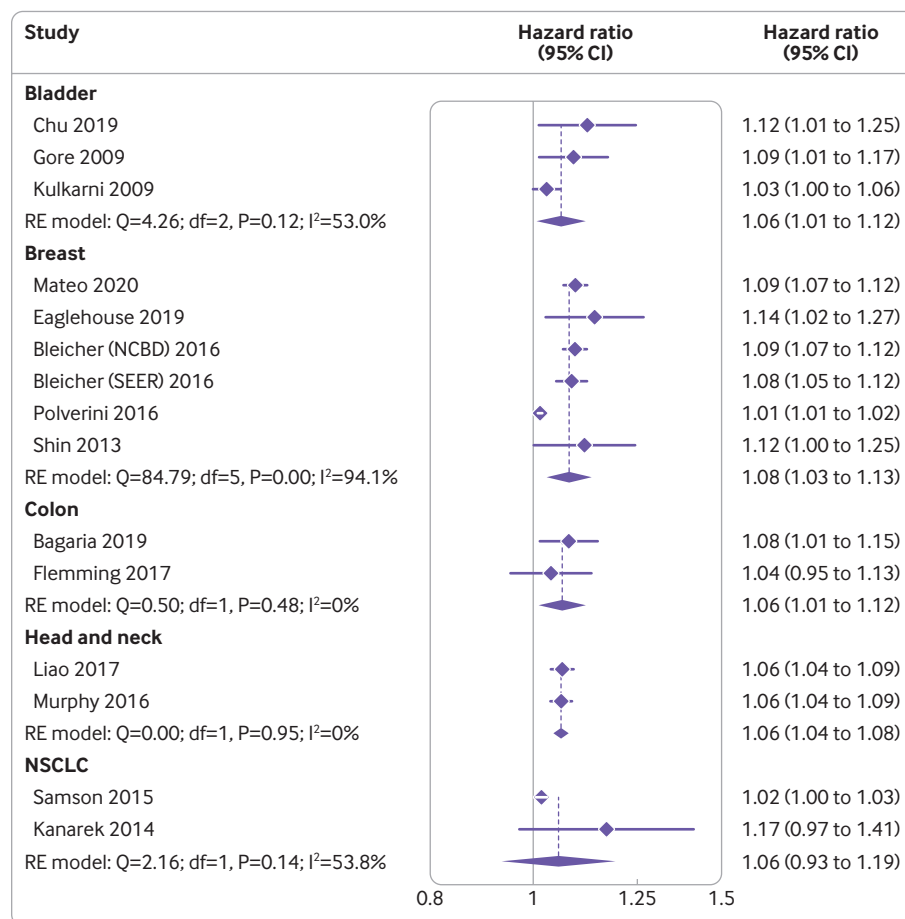
Fig 2 | Forest plot and pooled hazard ratios for association of each four week delay in surgery and overall survival by cancer site. Small purple diamonds represent the hazard ratio for each study and whiskers represent 95% confidence interval. Large purple diamonds represent summary effect estimates with the centre being the estimate and the ends representing 95% confidence intervals. NSCLC=non-small cell lung cancer

Treatment delays could be due to patient factors (eg, need for cardiac workup, postoperative wound infection), disease factors (eg, need for additional imaging investigations), or system factors (eg, waiting for an operating room date, a central line insertion, or a specialist consultation). The main purpose of this discussion is to highlight the need to minimise system level delays. We strongly emphasise that patients should not start surgery, systemic treatment, or radiotherapy until they are medically fit to do so, and have completed appropriate investigations. We also acknowledge that for rectal cancer, for instance, an increasing body of evidence shows that deferral of surgery after radiotherapy might not confer a survival disadvantage for those having a complete response.[53]

A major finding from our study is the paucity of high quality data for several tumour specific indications for radiotherapy, including chemoradiation for non-small cell lung cancer and definitive cervical cancer treatment. Two high validity studies providing delay estimates across multiple treatment modalities for these tumour types suggest an impact of delay in treatment initiation in these settings (cervical cancer mortality for each four week delay: hazard ratio 1.04,

95% confidence interval 1.02 to 1.07[54]; stage III non-small cell cancer: 1.03, 1.01 to 1.06).[55] While the negative impact of treatment interruptions on survival outcomes is well documented for these tumours,[56-58] evidence is insufficient about the exact impact of a delay in starting treatment, which given its importance, should be an urgent research priority.

The study results are timely in light of the current covid-19 pandemic. Internationally, some countries have released national guidance on prioritisation of surgical treatments for cancer, which do not appear to be supported by the results of this study. For example, at the beginning of the pandemic the UK NHS[59] created a short term surgical prioritisation algorithm. Several indications were considered safe to be delayed by 10-12 weeks with no predicted impact on outcome, including all colorectal surgery. Therefore, our results can help to directly inform policy—we found that increasing the wait to surgery from six weeks to 12 weeks would increase the risk of death in this setting by 9%.

We note that a delay of less than four weeks should not be justified as safe based on our findings. For example, our results suggest a 4% increased risk of death for a two week delay for breast cancer surgery ($1.08^{2weeks/4weeks}$;
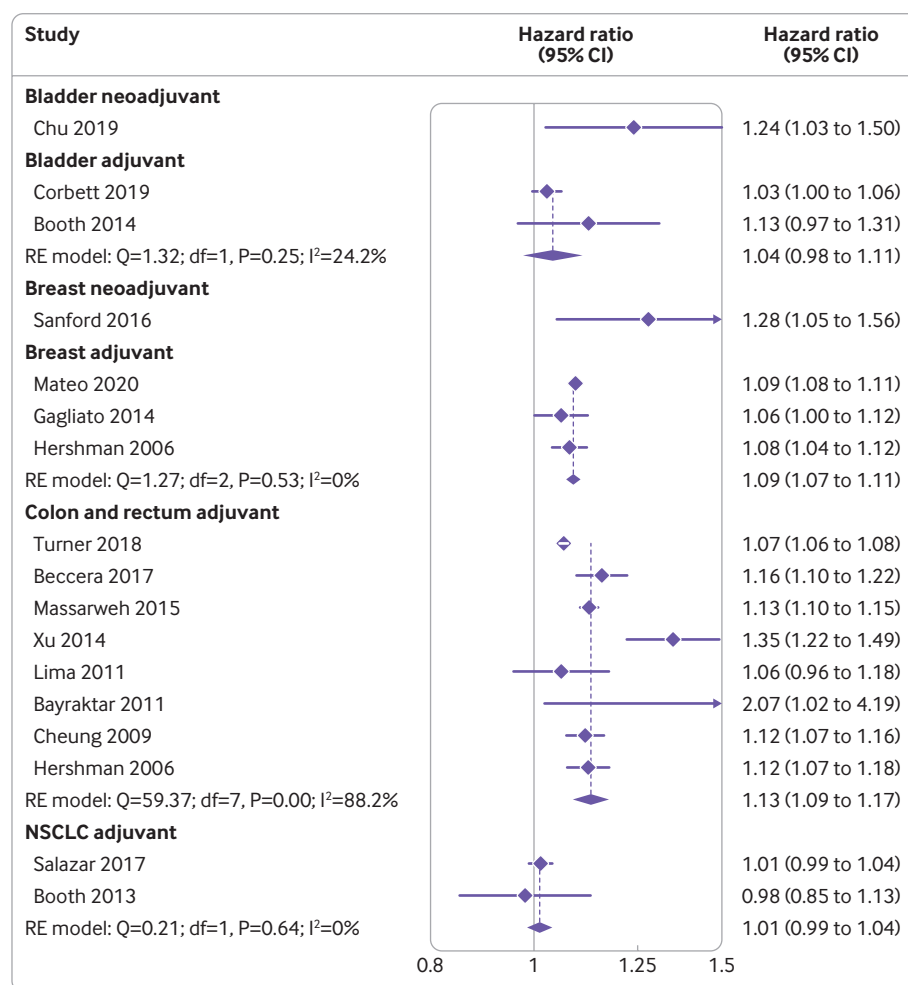
Fig 3 | Forest plot and pooled hazard ratios for association of each four week delay in adjuvant and neoadjuvant systemic treatment and overall survival by cancer site. Small purple diamonds represent the hazard ratio for each study and whiskers represent 95% confidence interval. Large purple diamonds represent summary effect estimate with the centre being the estimate and the ends representing 95% confidence intervals. NSCLC=non-small cell lung cancer

appendix 2). Taken as a whole, these results suggest there is an urgent need to reconsider how we organise our cancer services. The prevailing paradigm has been around access to new treatments to improve outcomes, but from a system level, gains in survival might be achieved by prioritising efforts to minimise the time from cancer diagnosis to initiation of treatment from weeks to days. We acknowledge that treatment delays are multifactorial in cause and that patients should not start treatment before they are medically fit to do so, and have had completed all appropriate evaluations, however these data strongly support efforts to minimise system level delays. For example, national quality indicators around cancer waiting times from diagnosis to treatment are widely used across different health systems. In the UK NHS, current targets for the initiation of primary definitive treatment have been set at 31 days from the decision to treat date; this does not include the lag between receiving a diagnosis and having a surgical or radiation oncology consultation for treatment.[9 60] At a population level, differences in lead times to

treatment of even two or three weeks could be a factor in why survival outcomes differ across health systems and needs further investigation. However, these delays need to be balanced with the necessity to be medically fit for treatment. Additionally, potential opportunities for second opinions could result in more effective or appropriate care, especially where variation in practice or outcomes exist across providers.

Options for decreasing delay after diagnosis include increasing specialist workforce capacity through training initiatives or overcoming these challenges through technological developments. For example, automated treatment contouring and planning is increasingly standardised and reduces the radiotherapy preparation time to hours rather than days.[61] Satellite centres might improve capacity for treating patients, as can reconfiguration of existing infrastructure to high volume super specialised services, or single entry models and team based care.[62] Innovations in surgical technique could also minimise morbidity and reduce time to adjuvant therapy.[63 64]
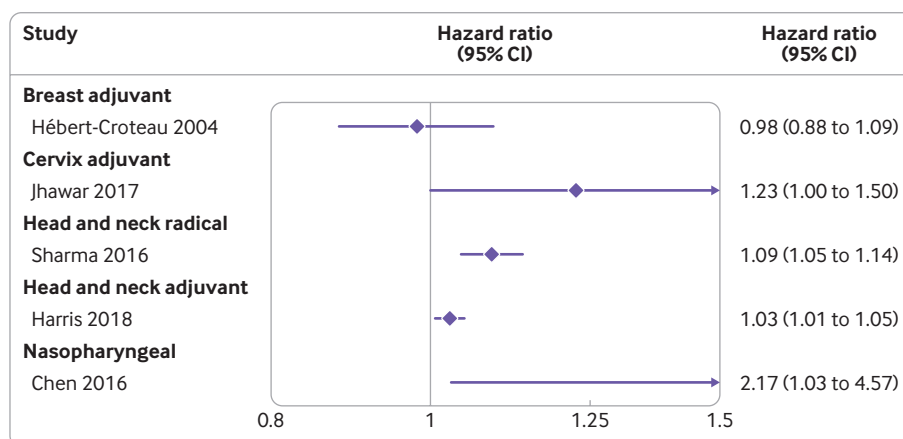
Fig 4 | Forest plot of hazard ratios for association of each four week delay in radical and adjuvant radiotherapy and overall survival by cancer site. Purple diamonds represent the hazard ratio for each study and whiskers represent 95% confidence interval

Strengths and limitations of this study

Our study provides evidence on the association of treatment delay and mortality, covering seven cancer types and three treatment modalities. Our study was based on observational data, and we therefore restricted our sample to high validity studies given the biases inherent to this study design. Our approach provides high level evidence on system delay because randomised trials in this context are not appropriate or feasible.

The most fundamental limitation of our study is the risk of residual confounding. Patients with longer treatment delays could be destined to have inferior outcomes for reasons of comorbidity, treatment morbidity, or performance status. In evaluating the validity of our findings, we note the coherence of overall mortality and cancer specific endpoints (local control, cancer specific survival, disease-free survival) for all past meta-analyses of high validity studies.[1-3 47] We also note major detrimental effects of prolonged waiting times on cancer specific survival outcomes in 13 of 15 studies included in our meta-analysis that reported cancer survival outcomes alongside overall survival.[14 16 22 28 29-36 38 39 46] These studies span seven treatment indications. Factors associated with medical status such as elements of socioeconomic status or insurance status might also be confounding factors; we found that 91% and 82% of identified studies accounted for these, respectively, though this does not completely rule out the possibility of residual confounding. Twenty five of 34 identified studies were from the USA, though no significant heterogeneity was detected compared with other countries.

Our findings cannot be directly applied to other cancer specific treatment indications, or to subgroups or single patients with treatment indications considered here. For example, limited evidence suggests that the impact of delay can vary according to stage, often with consistently greater mortality impact with earlier stage disease.[16-18 25 55] Additionally, our results can only be applied to the range of delay considered in the studies we evaluated. Given evidence derived from cancers representing almost half of all patients, the precautionary principle (acting to avoid or diminish harm in the face of scientific uncertainty) should be used when determining acceptable waiting times for treatment where data are limited.[8] Too few studies were found for most indications to perform a risk of publication bias assessment with funnel plots. For previous meta-analyses where enough studies existed to do so, findings were not explained by publication bias.[1 2]

We acknowledge that the assumption of a log linear relation between waiting time and mortality could be an oversimplification. This assumption was required to estimate per unit time mortality impact of delay from studies that use a variety of wait time representations. However, there is support for this assumption in the primary studies we used. A continuous exposure from nine primary studies assumed (log) linearity. Six studies undertook cubic spline analysis and the results are compatible with log linear effects with the range of wait times considered here (four weeks to 16 weeks).[15 19 21 26 41 45] Moreover, the previous meta-analyses by Biagi and colleagues and Raphael and colleagues suggest a reasonable fit of a log linear relation to delay.[1 2] If a linear relation with delay exists (rather than log linear), the degree of difference in the two models is expected to be sufficiently small to allow use of a log linear model for the specific purposes of modelling the impact of delay on mortality between four and 16 weeks (appendix 2). We emphasise that assuming log linearity outside of the range of wait times used in this analysis is inappropriate. Our findings should also not be used to evaluate whether there is a minimal safe delay, or to estimate the impact of delay beyond 16 weeks.

Our results reflect the impact of delay on large and expectedly heterogeneous populations with varying risks of recurrence. Therefore, these estimates are best used at a policy and planning level for modelling, rather than for individual risk prediction. We also

emphasise that few studies considered the impact of immortal time bias on delay; this could be done through a landmark analysis for survival. Patients that survived a longer wait might have less aggressive tumours, biasing the delay effect towards the null. Our findings could therefore underestimate the impact of delay on mortality.

Conclusions

A four week delay in treatment is associated with an increase in mortality across all common forms of cancer treatment, with longer delays being increasingly detrimental. In light of these results, policies focused on minimising system level delays in cancer treatment initiation could improve population level survival outcomes.

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Web appendix: Appendices