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SYSTEMATIC REVIEW

Delay to elective colorectal cancer surgery and implications for survival: a systematic review and meta-analysis

Thomas M Whittaker[1] | Mohamed E. G. Abdelrazek[1] | Aran J. Fitzpatrick[1] | Joseph L. J. Froud[1] | Jack R. Kelly[1] | Jeremy S. Williamson[2] | Gethin L. Williams[2]

[1]Cardiff University Medical School, Cardiff, UK

[2]Department of Colorectal Surgery, Royal Gwent Hospital, Newport, UK

Correspondence
Gethin L. Williams, Consultant Colorectal Surgeon, Department of Colorectal Surgery, Royal Gwent Hospital, Newport NP20 9UB, UK.
Email: gethin.williams2@wales.nhs.uk

Abstract

Aim: The Covid-19 pandemic has delayed elective colorectal cancer (CRC) surgery. The aim of this study was to see whether or not this may affect overall survival (OS) and disease-free survival (DFS).

Method: A systematic review was carried out according to PRISMA guidelines (PROSPERO ID: CRD42020189158). Medline, EMBASE and Scopus were interrogated. Patients aged over 18 years with a diagnosis of colon or rectal cancer who received elective surgery as their primary treatment were included. Delay to elective surgery was defined as the period between CRC diagnosis and the day of surgery. Meta-analysis of the outcomes OS and DFS were conducted. Forest plots, funnel plots and tests of heterogeneity were produced. An estimated number needed to harm (NNH) was calculated for statistically significant pooled hazard ratios (HRs).

Results: Of 3753 articles identified, seven met the inclusion criteria. Encompassing 314 560 patients, three of the seven studies showed that a delay to elective resection is associated with poorer OS or DFS. OS was assessed at a 1 month delay, the HR for six datasets was 1.13 (95% CI 1.02–1.26, $p = 0.020$) and at 3 months the pooled HR for three datasets was 1.57 (95% CI 1.16–2.12, $p = 0.004$). The estimated NNH for a delay at 1 month and 3 months was 35 and 10 respectively. Delay was nonsignificantly negatively associated with DFS on meta-analysis.

Conclusion: This review recommends that elective surgery for CRC patients is not postponed longer than 4 weeks, as available evidence suggests extended delays from diagnosis are associated with poorer outcomes. Focused research is essential so patient groups can be prioritized based on risk factors in future delays or pandemics.

KEYWORDS
colorectal, delay, surgical oncology

This paper is not based on previous communication to a society or meeting.

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INTRODUCTION

Outcomes after cancer surgery have been negatively affected by the economic recession in 2007 and the recent SARS-CoV-2 (Covid-19) pandemic [1,2]. Both have had a detrimental effect globally. Surgery, the cornerstone of any curative treatment, has inevitably been delayed. Under 'normal' circumstances, any treatment for colorectal cancer (CRC) should start within 2 months of the diagnosis at the latest and ideally within 1 month [3].

Covid-19 will continue to have a devastating effect on healthcare systems as the pandemic enters further waves of global infection. A recent multicentre observational study encompassing 24 countries reported that infection with Covid-19 in the perioperative period was associated with a significant mortality [4]. This, as well as the pressure on high-dependency beds, led to elective CRC surgery being delayed or cancelled. National and international learned societies suggested optimal treatment strategies to surgeons and their multidisciplinary teams. Some guidelines recommended that elective cancer surgery be deferred until such time that the environment was safe [5]. There were projections that nearly 40% of cases would be postponed during the initial 12 weeks of the Covid-19 pandemic [6].

Systematic reviews and a meta-analysis in the literature confirm that a delay in diagnosis is associated with an increased risk of the patient presenting with an advanced stage of CRC [7]. This conclusion may be less relevant in the context of the current healthcare crisis where access to secondary care has been challenging, even with the rapid adoption of the faecal immunochemical screening test (FIT). Indeed, a recent systematic review demonstrated that delayed colonoscopy following a positive FIT was associated with a higher incidence of advanced CRC [8]. One large-scale cohort study recommended that any treatment should be within 30 days of the diagnosis [9]. This may be more relevant to rectal than colonic cancer in terms of long-term survival [10].

Although common sense dictates that delay leads to poorer outcome in CRC, evidence is surprisingly scant, contradictory and difficult for surgeons and their patients to decipher. There is therefore a need for clarification of this risk, especially at a time when it has been reported that during the Covid-19 pandemic just 20% of UK hospitals are providing treatment within 31 days of the decision to treat [11].

The aim of this systematic review was to determine how detrimental delay to treatment of resectable nonmetastatic CRC is in terms of overall survival (OS) and disease-free survival (DFS).

METHOD

Data sources, search strategy and selection criteria

A systematic review was conducted utilizing the Cochrane collaboration-specified protocol and reported as per the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [12,13].

The PICO model was used to identify the criteria for searching for and selecting studies [14]. Studies reporting patients over the age of 18 years diagnosed with colon or rectal cancer receiving elective surgery as their primary treatment and reporting the time elapsed from diagnosis to surgical intervention were included. Studies were not initially excluded based on the year of publication, but this detail was considered during the full article screening process. Publications in languages other than English were excluded. Those studies which included neoadjuvant chemoradiotherapy were excluded, since this strategy is likely to have extended the time between diagnosis and surgery. There were no randomized controlled trials to include in the meta-analysis, presumably due to the ethical implications of delaying necessary treatment. Nonrandomized cohort studies and trial registries were included, as well as grey literature, including conference abstracts.

The authors updated a systematic search of the literature on 14 December 2020 using three databases: Medline (1946 to 14 December 2020), EMBASE (1947 to 14 December 2020) and Scopus (1966 to 14 December 2020). Screening of the references of the chosen studies was also performed to identify relevant literature. The search in all databases was executed using the following terms:

wait OR delay* adj3 surg* OR delay* adj3 colo* OR delay* adj3 survival* AND colorectal surg* OR colo* neoplas* OR rect* neoplas* OR colo* canc* OR rect* canc* OR colo* adj3 canc* OR rect* adj3 canc* OR colo* surg* OR rect* surg* OR colo* adj3 surg* OR rect* adj3 surg* OR resect* AND survival* OR overall survival* OR 5 year survival*

All search terms were modified in accordance with the search system of each database used. Duplicates were removed and then article titles and abstracts were screened by two independent authors using the reference management software EndNote X9.

Data extraction and outcomes measures

Two authors independently evaluated full-text versions of selected studies and performed data extraction and assessment of methodological quality. Any disagreements were discussed between all authors until consensus was established.

Extracted data included: first author, year of study, study type and design, number of participants, patient demographics, disease characteristics, surgical modality and treatment outcomes. Also extracted was the time elapsed between diagnosis and surgical intervention, which was defined on an individual study basis due to lack of homogeneity in methodology, with no minimum or maximum value established. Treatment outcomes measured were OS and DFS, and outcome events were captured when two or more studies presented extractable data. Data were extracted at maximal follow-up. The study protocol was registered with the PROSPERO database (record ID CRD42020189158) before data extraction and analyses.

Assessment of study quality

Quality assessment of the selected studies was conducted using the risk of bias in nonrandomized studies of interventions tool (ROBINS-I) [15].

Statistical analysis

Meta-analyses were produced using Revman v.5.3 [16]. Where hazard ratios (HRs) were available, meta-analysis was performed using a random effects generic inverse variance model to create forest plots for OS and DFS and reported with 95% per cent confidence intervals (CIs). This model was chosen as the outcomes were adjusted for varied confounders in each study (listed in Table 3). The random effects model produced pooled HRs as well as heterogeneity chi-square and I^2 scores [17]. Funnel plots were utilized to assess publication bias.

For statistically significant pooled HRs, an estimated number needed to harm (NNH) was calculated according to the Cochrane Handbook for Systematic Reviews of Interventions [12,18] (Figure 1). As the outcomes are detrimental to patients, the difference in risk is described as NNH as opposed to number needed to treat. The assumed control risk in patients not delayed (interval <30 days) for OS is from Bagaria et al. [19]. This study was selected as it is a large-scale cohort study presenting mortality risk in the control group (<30 days delay to surgery) used in all analyses.

RESULTS

Paper search and selection process

The search conducted across Medline, EMBASE and Scopus yielded 5506 results. After the removal of duplicates using EndNote X9 software, 3753 titles and abstracts were screened, leaving 39 articles which were then reviewed in full. A total of seven articles fulfilled the inclusion criteria. Full details are shown in a PRISMA flow diagram (Figure 2) [13]. Details of the excluded studies are shown in Table 1. Following this, reference lists of the final seven studies were screened; however, no articles fulfilled the inclusion criteria [19–25]. One study was excluded as it did not match the time frames required for statistical analysis [10]. Two of the included studies received funding for their work. Trepanier et al. [24] was supported by

$$\mathrm{NNT} = \frac{1}{\left| \mathrm{ACR} - \frac{\mathrm{OR} \times \mathrm{ACR}}{1 - \mathrm{ACR} + \mathrm{OR} \times \mathrm{ACR}} \right|}$$

FIGURE 1 Formula from the Cochrane Handbook for Systematic Reviews of Interventions [12] for calculation of the number needed to harm (ACR, assumed control rate; NNT, number needed to treat; OR, odds ratio). The formula describes NNT, but as per convention in this study it is described as 'number needed to harm' as the outcome is a detriment to the patient

research scholarships from the Quebec Health Sciences Research Fund and the Canadian Institute for Health Research, and Shin et al. [22] received a grant from the Ministry of Health and Welfare, Korea.

Study design and baseline characteristics

The selected studies had a range of epidemiological characteristics with variation in several categories including the number of patients, country or delay cut-off times. Study publication dates ranged from 2013 to 2020. The sample sizes for the included studies ranged from 408 to 187 319 patients. Six articles selected for this review are retrospective cohort studies [19–24] whilst one is a prospective cohort study [25]. The seven studies varied in geographical location, with three from the USA [19–21], two from Canada [24,25] and one each from the Netherlands [23] and South Korea [22]. Four studies were limited to colon cancer [19–21,25], This was because rectal cancers differ in pathology, epidemiology and treatment [26–28] (Table 2). All the included studies performed confounder adjustments; the variables chosen for each study can be seen in Table 3.

The ROBINS-I tool measured the risk of bias in the studies included in this meta-analysis. Four studies are reported to have a moderate risk of bias while three studies are considered to have a serious risk of bias (Figure 3).

Outcomes

Outcome data for each study are presented in Table 3. There was wide heterogeneity between studies in categorizing delay from diagnosis to surgery. According to the data that could be extracted from each study, two categories of delay were chosen: 1 month and 3 months.

Overall survival

Seven studies containing 314 560 patients reported outcomes of OS. Six studies with comparable delay times of approximately 1 month demonstrated a pooled HR of 1.13 (95% CI 1.02–1.26, p = 0.020) [20–25] associated with delay. HRs for 1 month and over for each study were pooled to create comparable time frames (Figure 4). A single study reported a possible reduction in risk with delay (HR 0.82, 95% CI 0.63–1.08) [25]. One study could not be included in this analysis due to noncomparable categorization of delay [19].

A funnel plot (Figure 5) analysing studies which reported the effects of a 1 month delay to surgery on OS demonstrated slight asymmetry in studies with a high standard error. Further analyses to quantify publication bias were incompatible due to the number of studies being below 10 [29]. There was moderate heterogeneity between studies reporting a 4 week delay (I^2 = 51%). The calculated estimated NNH for a 1 month delay to surgery was 35.

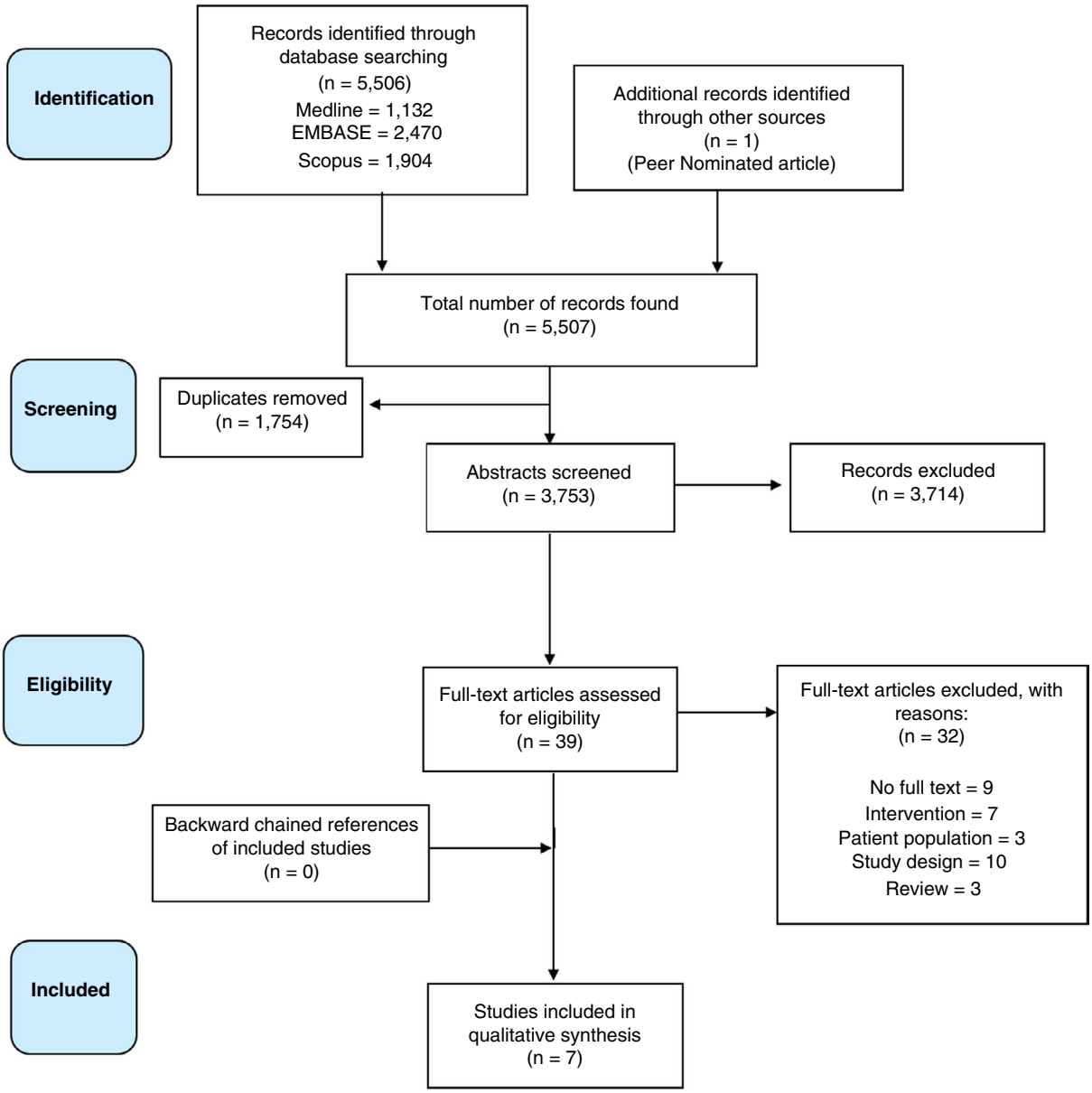

FIGURE 2 PRISMA flow diagram showing how the search was conducted

Three studies containing 193 950 patients reported outcomes following a delay of 12 weeks or longer to surgery and were suitable for comparison [19,21,22], The pooled HR associated with a 12 week delay to surgery was 1.57 (95% CI 1.16–2.12, p = 0.004) (Figure 6). Analysis of a funnel plot and statistical tests for publication bias were not compatible due to the small number of studies [29]. There was a high degree of heterogeneity in studies reporting a 12 week delay (I^2 = 64%).

Four studies could not be included in the 12 week delay forest plot as the delay categories did not correspond appropriately [20,23–25]. A study using data from a US national database used a spline curve to extrapolate collected data and forecast that a delay of 12 weeks was associated with a 1.4 times greater risk of mortality [20]. A study from the Netherlands set the upper limit of delay at over 49 days and found the OS HR to be 1.155 (95% CI 0.776–1.720, p = 0.478) [23]. One study from Canada set the maximum threshold delay at over 8 weeks, and in this study OS HR was 2.15 (95% CI 0.59–7.81). The calculated estimated NNH for a 12 week delay to surgery was 10 [24].

Disease-free survival

Three publications evaluated DFS as an outcome for surgical delay [23–25]. HRs for 1 month and over for each study were pooled to create comparable time frames. A meta-analysis of these three corresponding studies found a nonsignificant association between a 1 month delay to surgery and DFS (HR 0.97, 95% CI 0.74–1.28, p = 0.830) (Figure 7). It was not possible to extract data at 12 weeks due to a lack of reporting at this time point between studies. The I^2

TABLE 1 List of the studies excluded from full text reading and justification for the exclusion

Author	Year	Title	Justification for exclusion
Abdulaal et al.	2018	Diagnostic and treatment delays do not impact survival in colorectal cancer patients	Full study not available, abstract only
Abdulaal et al.	2020	Effect of health care provider delays on short term outcomes in patients with colorectal cancer: multicenter population-based observational study	Not able to use dataset in meta-analysis and therefore incomparable
Allen et al.	2017	Direct access colonoscopy: impact of intervention on time to colorectal cancer diagnosis and treatment in North West Tasmania	Incompatible with our methods, looks at delay from referral to diagnosis
Amri et al.	2014	Treatment delay in surgically treated colon cancer: does it affect outcomes?	This is a review and cannot be used in our meta-analysis
Anderson et al.	2012	Compliance with the 62-day target does not improve long-term survival	Included therapy prior to surgery
Aslam et al.	2014	Delay in treatment from time of diagnosis does not have an adverse effect on patient survival	Full paper unavailable
Carmona-Garcia et al.	2020	Comorbidities, timing of treatments, and chemotherapy use influence outcomes in stage III colon cancer: a population-based European study	Data used for OS and DFS could include preoperative chemotherapy. Not defined that there are no preoperative therapeutics
Comber et al.	2005	Delays in treatment in the cancer services: impact on cancer stage and survival	Full paper unavailable
Currie et al.	2012	The impact of the two-week wait referral pathway on rectal cancer survival.	Incomparable dataset
Di Girolamo et al.	2018	Can we assess cancer waiting time targets with cancer survival? A population-based study of individually linked date from the National Cancer Waiting Times monitoring dataset in England	Used patients under 18 years of age
Flemming et al.	2017	Association between the time to surgery and survival among patients with colon cancer: a population-based study	Used in a systematic review in 2018 and dataset not able to be used in our meta-analysis
Hansen et al.	2018	The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: a systematic review	Systematic review
Helewa et al.	2013	Longer waiting times for patients undergoing colorectal cancer surgery are not associated with decreased survival	Definition of delay was not just diagnosis to surgery
Iversen et al.	2009	Therapeutic delay reduces survival of rectal cancer but not colonic cancer	Radiotherapy done prior to surgery
Jalali et al. 2014	2014	Effect of delay in surgical treatment of colon cancer on survival	Full paper unavailable
Langenbach et al.	2003	Delay in treatment of colorectal cancer: multifactorial problem	Delay defined as symptoms to surgery
Lee et al.	2019	Effect of length of time from diagnosis to treatment on colorectal cancer survival: a population-based study	Chemoradiotherapy included so unable to use in our meta-analysis
Lino-Silva et al.	2019	Impact of time to surgery on oncological outcomes of patients with colon cancer	Full paper unavailable
Millas et al.	2015	Treatment delays of colon cancer in a safety-net hospital system	Chemotherapy done prior to surgery
Minicozzi et al.	2020	Comorbidities, timing of treatments, and chemotherapy use influence outcomes in stage III colon cancer: a population-based European study	Used patients under 18 years of age
Mirkin et al.	2018	When does delay in treatment impact survival in non-metastatic colon cancer?	Full paper unavailable

(Continues)

TABLE 1 (Continued)

Author	Year	Title	Justification for exclusion
Patel et al.	2018	Compliance with the 62-day target does not improve long-term survival	Used in systematic review in 2018 and data time period not applicable to meta-analysis
Pruitt et al.	2013	Do diagnostic and treatment delays for colorectal cancer increase risk of death?	Chemo and radiotherapy used in dataset
Quereshy et al.	2019	Association of time to surgery with post-operative complication and overall and disease-free survival after surgery for sigmoid and rectal cancer	Full paper unavailable
Ramos et al.	2007	Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review	Previous meta-analysis done
Redaniel et al.	2014	The association of time between diagnosis and major resection with poorer colorectal cancer survival: a retrospective cohort study	Patients under 18 years of age
Satish et al.	2018	Time to surgery in colon cancer: predictors and association with survival – an analysis of the National Cancer Database	Full paper unavailable
Simunovic et al.	2009	Influence of delays to nonemergent colon cancer surgery on operative mortality, disease specific survival and overall survival	Used in previous systematic review and incomparable time periods for our meta-analysis
Turaga et al.	2020	Are we harming cancer patients by delaying their cancer surgery during the Covid-19 pandemic?	Dataset incompatible
Wangjam et al.	2017	Delays in treatment for colorectal cancer patients in an NCI-designated cancer center serving a Hispanic majority community	Full paper unavailable
Yun et al.	2012	The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery	Used in previous systematic review and age of patients not compatible
Zafar et al.	2012	The 2-week wait referral system does not improve 5-year colorectal cancer survival	Assesses referral to diagnosis so not relevant to our study

Abbreviations: DFS, disease-free survival; OS, overall survival.

value for these data was 43%, indicating low heterogeneity. A funnel plot and statistical tests for publication bias were not compatible due to the small number of studies.

DISCUSSION

This analysis has identified several international cohort studies which compared OS and DFS for patients undergoing surgery for CRC after a period of delay. Data on over 300 000 patients were evaluated from seven studies. These were of variable quality, with a high degree of heterogeneity. Four studies received a 'moderate' rating and the remaining three a 'serious' rating, according to the ROBINS-I assessment tool. Despite this, all reported the use of confounder adjustment.

This systematic review and the meta-analysis confirmed a significant risk of poorer OS with increasing delays to surgery, and particularly after 3 months. There was a lack of uniformity in categorizing delay, and several studies could not be included in the meta-analysis. These studies consistently reported adverse HRs associated with a variable delay to surgery, ranging from 1.15 to 2.15. The variability of categorizing delay was in part due to studies aligning their outcomes with inconsistent national guidelines. A previous systematic review published in 2018, which assessed five observational studies, did not report a significantly increased risk to survival if there was a delay to surgery. In contrast to our study, the number of patients was small, it used historical data and a meta-analysis could not be performed due to shorter and noncomparable categorization of delays [30].

The heterogeneity scores generated in our analysis demonstrated a high level of discrepancy in the methods of the individual studies. Several studies based their definition of delay on national or local guidelines [22–25]. Other studies based it on the statistical distribution of the sample gathered, or chose parameters which the authors thought were clinically relevant [19–21]. Six studies were performed retrospectively, introducing selection and information bias to the results and creating heterogeneity between the research studies [19–24]. Future prospective studies would provide a more balanced answer to this research question, especially as randomized controlled trials are not applicable. Researchers conducting this work would be advised to conduct large-scale prospective studies with a delay parameter that is universally agreed to allow for descriptive and statistical comparison.

The calculated NNH provides further clinically relevant quantification of the risk encountered in delaying surgery. In line with

TABLE 2 Study design, scope, population characteristics, disease characteristics, and outcome measurements (grouped by outcome measure)

Study	Site	Sample size	Age (years)	Sex (M/F) (%)	Tumour staging	Study design	Follow-up period	Outcome measurement
Overall survival as only outcome:								
Bagaria et al. (2019) [19]	Right 55.0% Left 33.5% Transverse 10.8% Overlapping 0.6%	4685	71 (18–99)	52.4/47.6	I 24.3% II 33.0% III 29.8% IV 13.0%	Retrospective cohort study	1990–2012	OS
Grass et al. (2020) [20]	Right 45.4% Left 37.2% Transverse 17.5%	118504	69 (median (59–78)	48.3/51.7	I 32.8% II 34.2% III 30.6%	Retrospective cohort study	2004–2013	OS
Kucejko et al. (2020) [21]	Right 56.0% Left 31.6% Colon, NOS 10.3%	187319	68.5 (SD 13.5)	46.6/53.4	I 15.0% II 37.1% III 47.9%	Retrospective cohort study	1998–2019	OS
Shin et al. (2013) [22]	N/A	1946	61.8 (SD 11.7)	24.7/75.3	Local 34.7% Regional 65.3%	Retrospective cohort study	2003–2005	OS
Overall survival and disease-free survival as outcomes:								
Strous et al. (2019) [23]	Ileocaecal 15.6% Right hemicolon 13.7% Transverse 4.3% Left hemicolon 5.1% Sigmoid 32.2% Rectal 29.2%	790	70 (SD 10.0)	54.3/45.7	I 28.4% II 39.7% III 31.9%	Retrospective cohort study	2010–2016	OS, cancer-free survival
Trepanier et al. (2020) [24]	Right 53.6% Left 30.7% Rectal 15.7%	408	69.8 (SD 11.2)	54.9/45.1	I 29.9% II 36.5% III 33.6%	Retrospective cohort study	2009–2014	OS, DFS
Wanis et al. (2017) [25]	Right 54% Transverse 13% Left 5% Sigmoid 27%	908	<60–16% 60–79 57% ≥80-27%	50/50	I 21.0% II 44.0% III 35.0%	Prospective cohort study	2006–2015	OS, DFS

Note: Tumour staging was in accordance with the American Joint Committee on Cancer (AJCC) unless otherwise stated. Age is provided as mean and range unless otherwise stated.

Abbreviations: DFS, disease-free survival; NOS, not otherwise specified; OS, overall survival.

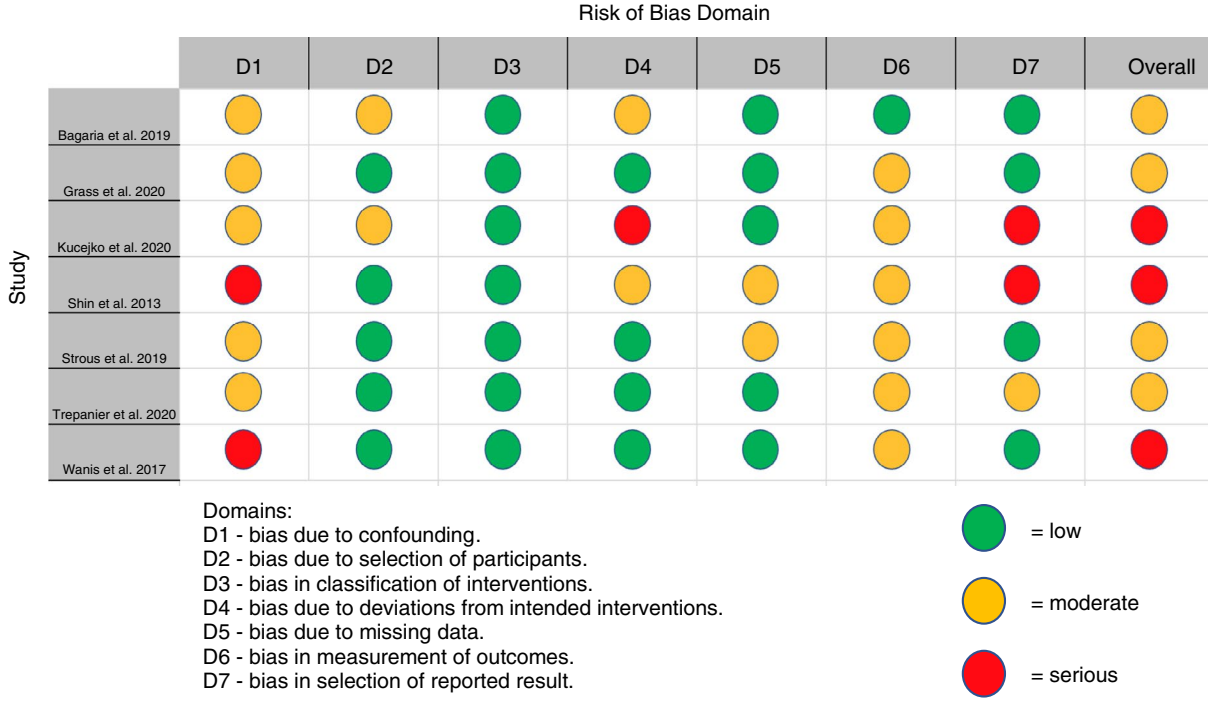

FIGURE 3 The risk of nonrandomized studies of interventions tool (ROBINS-I) assessment of included studies

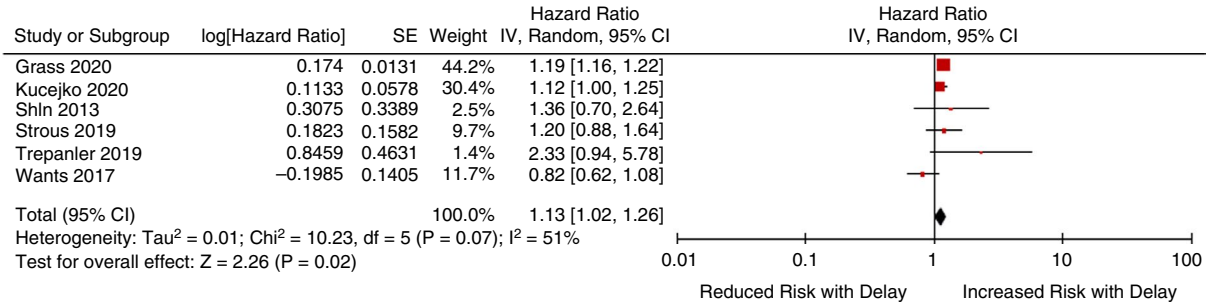

FIGURE 4 A random effects generic inverse variance forest plot and calculated pooled hazard ratio for the effects of 1 month's delay to curative colorectal cancer surgery on overall survival

the literature, this study shows that an increased delay of 12 weeks provides a much lower NNH compared with a delay of 1 month. We estimate that NNH at 1 month's delay was 35 compared with a NNH of 10 for those waiting 3 months for surgery. These figures could be used by the healthcare team to counsel patients on the personalized risks and benefits of waiting or proceeding to the surgery during the pandemic or other exceptional circumstances. CIs could not be calculated for the NNHs from the pooled HRs as both lower figures were approaching 1 [31].

In light of the Covid-19 pandemic, governing bodies have updated their guidance for prioritization of cancer services. The Academy of Royal Medical Colleges states that CRC patients fall into 'level 2 prioritization' and that surgery should be undertaken within 4 weeks [32]. A recent American study assessing over 4 million cancer (all types) patients from the National Cancer Database reported that a 5 week delay was the maximum time for safe postponement of CRC surgery

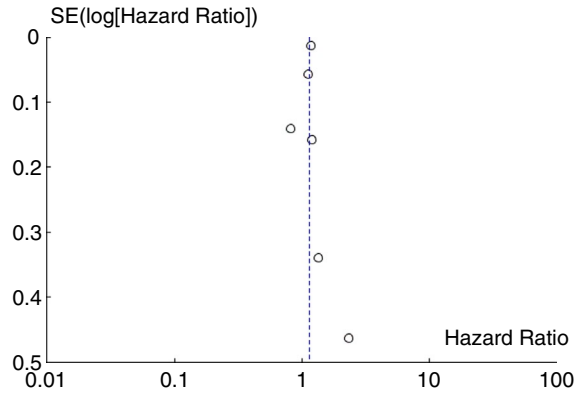

FIGURE 5 A funnel plot with the log of standard error (SE) on the vertical axis and the hazard ratios for the studies assessing effects of 1 month's delay to curative colorectal cancer surgery on overall survival on the horizontal axis

TABLE 3 Definition of exposure, outcomes, and covariates in statistical adjustments. Grouped by outcome measure

Study	Definition of delay	Delay to surgery categories as defined by study	Reason for delay	Outcome	Confounding factors adjusted for
Overall survival as only outcome:					
Bagaria et al. (2019) [19]	Number of days between diagnosis and colectomy. Control group 1–7 days delay	8–21 days 22–42 days 43–84 days ≥84 days	Delay was associated with increased age [OR (10 year increase) 1.31 (95% CI 1.05–1.64, $p = 0.019$)] and distance to hospital [OR (doubling in distance) 1.13 (95% CI 1.01–1.26, $p = 0.039$)]. Delay was inversely associated with histology grades three and four [OR 0.56 (95% CI 0.32–0.98, $p = 0.044$)]	Up to 84 days all results were nonsignificant After 84 days OS HR of 1.47 (95% CI 1.02–2.11, $p = 0.038$).	Age at surgery, gender, Charlson comorbidity index, marital status, hospital, year of surgery, colon cancer site, grade, number of regional nodes examined, pathological stage
Grass et al. (2020) [20]	Number of days from diagnosis to treatment	Short delay <16 days Long delays ≥37 days	Delay was associated with increased number of comorbidities ($p < 0.0001$). Delay was inversely associated with tumour stage ($p < 0.0001$)	Long delay OS HR 1.19 (95% CI 1.18–1.20, $p < 0.0001$) compared with a short delay HR of 1 Per 14 days, up to 140 days, OS HR increased by 1.06 (95% CI 1.05–1.07, $p < 0.001$) Treatment delay of 3 months was associated with 1.4 times greater risk of mortality	Socioeconomic factors (including race and insurance type), facility type, year of diagnosis (2004–2013)
Kucejko et al. (2020) [21]	Number of weeks between diagnosis and surgery. Compared with week 3–4	Increments of 2 weeks	Unable to determine cause. Highest proportion of black patients were having surgery past 6 weeks ($p < 0.05$).	For patients over 65 at 12 weeks: OS HR 1.68 (CI 95% 1.46–1.93) For patients under 65 at 12 weeks: OS HR 1.35 (CI 95% 1.26–1.44).	Age, sex, race, AJCC stage, tumour size, tumour grade, nodes positive, nodes examined
Shin et al. (2013) [22]	Number of weeks from diagnosis to surgery. Compared with >1–4 weeks	≤1 weeks >1–4 weeks >4–8 weeks >8–12 weeks >12 weeks	Large national database. Unable to determine cause. Delay was inversely associated with comorbidity [OR 0.84 (95% CI 0.74–0.95)] and low tertial income [OR 0.88 (95% CI 0.79–0.99)]. Delay was associated with surgery in hospital outside of referral area [OR 1.45 (95% CI 1.25–1.68)]	Surgery done >12 weeks compared with reference of surgery done 1–4 weeks after diagnosis has a HR of 2.65 (95% CI 1.5–4.7, $p < 0.00$) Between 4 and 12 weeks no correlation was found between delay and OS	Age at diagnosis, sex, Surveillance, Epidemiology and End Results stage, and income tercile, stratified by place of residence

(Continues)

TABLE 3 (Continued)

Study	Definition of delay	Delay to surgery categories as defined by study	Reason for delay	Outcome	Confounding factors adjusted for
Overall survival and disease-free survival as outcomes overall survival and disease-free survival as outcomes:					
Strous et al. (2019) [23]	Number of days from diagnostic biopsy to surgery	>35 days >49 days	No patients received prehabilitation. Delay was associated with male gender [OR 1.390 (95% CI 1.042–1.853)], localization in the rectum [OR 2.160 (95% CI 1.581–2.950)] and tumour stage ($p < 0.001$).	Over 35 days: CRC OS: HR 1.202 (95% CI 0.880–1.642, $p = 0.249$) Over 35 days: CRC DFS: HR 1.256 (95% CI 0.878–1.799, $p = 0.212$) Over 49 days: CRC OS: HR 1.155 (95% CI 0.776–1.720, $p = 0.478$) Over 49 days: CRC DFS: HR 0.932 (95% CI 0.574–1.513, $p = 0.776$)	Gender, age, body-mass-index, existence of comorbidities, ASA classification, occurrence of postoperative complications and severity according to the Clavien–Dindo classification and tumour characteristics as location, differentiation grade. tumour stage according to TNM-classification
Trepanier et al. (2020) [24]	Number of weeks between date of initial biopsy and surgery	<4 weeks 4–<8 weeks ≥8 weeks	Delay was inversely associated with right-sided tumours ($p < 0.001$). Delay was associated with rectal tumours in comparison to colonic ($p < 0.001$), low anterior and resections, abdominoperineal resection procedures ($p = 0.04$), stoma creation ($p < 0.001$), increased BMI ($p = 0.003$) and ASA score ($p = 0.009$)	4–8 weeks DFS: HR 0.96 (CI 95% 0.47–1.95) 4–8 weeks OS: HR 2.51 (CI 95% 0.70–9.03) Over 8 weeks DFS: HR 0.86 (CI 95% 0.42–1.78) Over 8 weeks OS: HR 2.15 (CI 95% 0.59–7.81) Overall, no association between delay and worse OS or DFS	Age, gender, ASA ≥3, laparoscopic approach, rectal tumour, TNM stage, severe postoperative complications, receipt of adjuvant systemic therapy
Wanis et al. (2017) [25]	Number of days from primary investigation to surgery	≤30 days >30 days	Large national database. No information on associations to delay	>30 days DFS: HR 0.886, (95% CI 0.611–1.283, $p = 0.522$) >30 days OS: HR 0.823 (0.627–1.081, $p = 0.163$). Remained non-significant up to and over 120-day delay	DFS: pathological stage, margin status, lymphovascular invasion, grade, adjuvant chemotherapy OS: age, pathological stage, grade, lymphovascular invasion, adjuvant chemotherapy

Note: Delay to surgery categories were heterogeneous and are described as reported in each study.

Abbreviations: ASA, American Society of Anesthesiologists score; BMI, body mass index; CRC, colorectal cancer; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; TNM, Tumour Node Metastasis score.

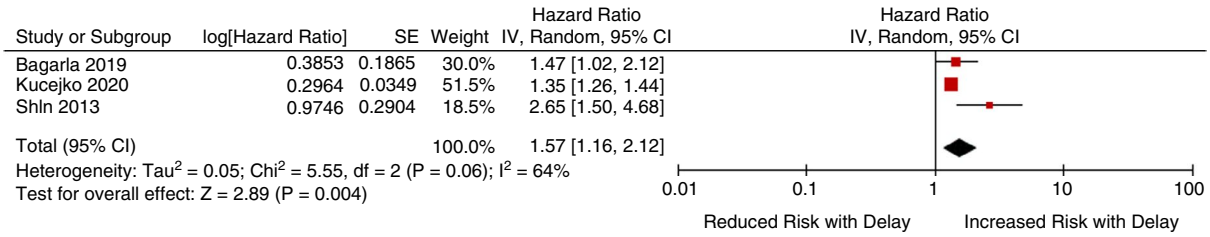

FIGURE 6 A random effects generic inverse variance forest plot and calculated pooled hazard ratio for the effects of a 12-week delay to curative colorectal cancer surgery on overall survival

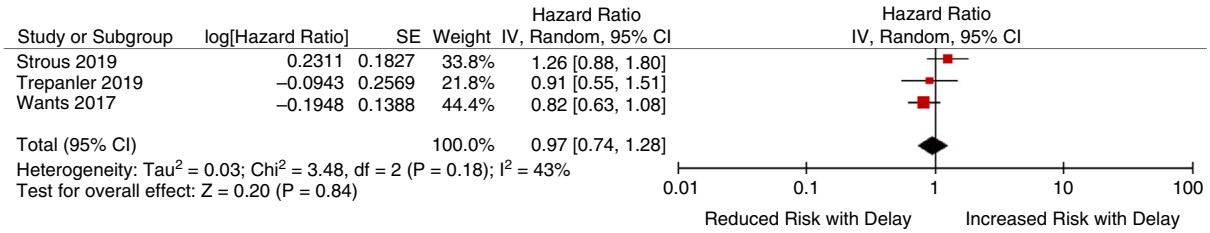

FIGURE 7 A random effects generic inverse variance forest plot and calculated pooled hazard ratio for the effects of a month's delay to curative colorectal cancer surgery on disease-free survival

[33]. Another recent study modelling the potential damage of delaying all resectional cancer surgery in England during the Covid-19 pandemic suggested that a 3 month delay would lead to 1000 excess CRC deaths at 1 year, and after a 6 month delay this would rise to 2980. This modelling also assessed the length of life lost due to this delay, and found that for all cancers a 6 month delay would result in a loss of 2.19 years per patient [34]. These findings are consistent with the results reported in our analysis.

The risk of delaying surgery also needs to be balanced against the considerable risks associated with developing Covid-19. The international CovidSurg project demonstrated that for patients undergoing elective surgery who contracted Covid-19 in the perioperative period, mortality was 18.9% and even greater for patients undergoing cancer surgery [1].

Our findings, although pertinent to the current Covid-19 pandemic, also have a broader application to other worldwide crises. Economic recession may also have had an adverse effect on cancer treatment with the time from 'decision to treat' to surgery dropping 5.9% in England in the period from October 2009 to October 2019 [35,36]. Our study, therefore, has relevance to treatment decisions when the Covid-19 pandemic has receded and in the event of a national or global economic recession.

Ironically, there may be an upside to treatment delay as it has given the opportunity to implement and study prehabilitation which can decrease pulmonary and other morbidity after major abdominal surgery [37]. Prehabilitation programmes of 2–6 weeks' duration can safely counterbalance the detrimental effects of delay to surgery of 1 month [37]. Extending this any longer would need to be justified by focused research and would not currently be supported by our study.

Our review suggests that increased comorbidity and anaesthetic risk were commonly quoted as the reason for surgical delay (Table 2). This period allows time for optimization of patients' comorbidities and prehabilitation which are strategies which improve postoperative outcomes across surgical disciplines [38,39]. However, none of the studies that were included in the analysis documented the use of a prehabilitation programme.

The psychological impact of delay to surgery must not be underestimated. Longer waiting times for elective general surgery are associated with a prolonged period of decreased health and has considerable impact on the psychological well-being and social life of patients [40]. Preoperative psychological distress may affect wound healing, length of stay and lung function [41].

There are several limitations to this study. Whilst confounder adjustment was reported in all studies, it is difficult to control for some confounding factors. These include disease-specific factors such as tumour stage, lymphovascular invasion and differentiation. In one study, no record of comorbidity was available [25]. In another, the use of adjuvant chemotherapy was not reported or described [21]. The reasons for surgical delay were not explicitly stated for each patient and it is likely that some would affect survival. Advanced comorbidity and frailty are major potential confounders since they may prompt further medical or anaesthetic assessment, further delay to surgery and perhaps lead to spurious associations with poorer outcome. No randomized studies were available for analysis for obvious reasons, and only a single study was conducted prospectively.

CONCLUSION

This systematic review and meta-analysis evaluated the current accessible data on the risk of delay to elective surgery for CRC. The quality of available data is weak but there is some evidence that a delay of 3 months or more has a deleterious effect on OS of CRC

patients. The enforced delays to treatment of CRC during the Covid-19 pandemic should provide prospective data to answer this question and hopefully improve patient care in the future [42].

ETHICAL APPROVAL

No ethical approval was required for this paper.

CONFLICT OF INTEREST

None.

FUNDING INFORMATION

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AUTHOR CONTRIBUTION

TW contributed to the data collection, analysis of the data, interpretation and drafting of the manuscript. MA contributed to data collection, statistical analysis and drafting of the manuscript. AF, JF and JK contributed to data collection, manuscript revision and study analysis. JW contributed to data interpretation, study design and manuscript drafting. GW contributed to study design, data collection and interpretation and drafting of the manuscript. All authors read and approved the final version.

DATA AVAILABILITY STATEMENT

The data used in these studies to generate our meta-analysis can be found in the Medline, Scopus and EMBASE databases.

ORCID

Thomas M Whittaker https://orcid.org/0000-0002-0594-9691
Mohamed E. G. Abdelrazek https://orcid.org/0000-0002-3469-6494

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