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A systematic review and meta-analysis of delay to radical cystectomy and the effect on survival in bladder cancer patients

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Abstract

Context

The complexity of bladder cancer diagnosis and staging results in delays to definitive treatment of muscle-invasive bladder cancer by radical cystectomy.

Objective

This systematic review and meta-analyses aim to assess the impact of delays to radical cystectomy.

Evidence Aquisition

A systematic review was conducted by searching Medline and Ovid Gateway using protocol-driven search terms in August 2019 with no time limit on the studies included. The identified studies were assessed according to strict criteria and were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool. Meta-analyses were conducted based on type of delay. Random-effects models were used whereby the presence of a delay was the exposure variable and overall survival was the outcome of interest, for which pooled hazard ratios were calculated.

Evidence Synthesis

Nineteen studies were eligible for inclusion (17,532 patients), of which ten were included in the meta-analyses. A longer delay between bladder cancer diagnosis and radical cystectomy resulted in a pooled hazard ratio of 1.34 (95% CI: 1.18-1.53) for overall death. For delay between transurethral resection and cystectomy, we found a pooled hazard ratio of 1.18 (95% CI: 0.99-1.41) for overall death. A pooled hazard ratio of 1.04 (95%CI: 0.93-1.16) was calculated for a longer delay between neoadjuvant chemotherapy and radical cystectomy.

Conclusions

A delay in radical cystectomy after diagnosis was found to have a significantly detrimental effect on overall survival for bladder cancer patients. However, there was huge heterogeneity in how a delay was defined.

Patient Summary

In this review we investigated the effect of a delay in radical treatment on survival. This review highlights the importance of scheduling radical cystectomies in a timely manner whilst monitoring factors such as comorbidities and scheduling in order treat those patients requiring radical cystectomy without delay.

1.0 Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide with around 550,000 new cases in 2018 (1). Five-year disease specific survival rates are 77% in United States of America and around 68% in Europe (2,3). As many as 50% of MIBC patients die from metastatic disease within 3 years of diagnosis despite radical cystectomy (RC) (4). Delaying radical treatment is thought to contribute to risk of metastases and therefore decreased survival (5). Thus, for selected patients with high-risk non-muscle-invasive BC (NMIBC) or muscle-invasive BC (MIBC) who require RC as primary treatment, the European Association of Urology (EAU) recommends RC within 3 months of diagnosis (6,7). However, previous studies have demonstrated both increased and decreased survival associated with delay to RC. The impact of this delay on survival outcomes has recently been identified as one of the top ten unanswered research questions by BC patients and health care professionals thus highlighting the importance of studying this topic (8).

In addition to a delay between the first symptoms and a BC diagnosis, there are several mechanisms by which radical definitive treatment may be delayed for BC patients (9). Patients may not be fit enough for immediate surgery and so require treatment of comorbidities, or may be referred from primary care physicians or urology units to different hospitals for surgery (10). Furthermore, seeking a second opinion and the need for additional investigations, particularly up to date imaging, may also delay RC.

The most recent systematic review of the effects of delays to RC was conducted by Fahmy et al (5) in 2006 and included 13 studies published between 1965 and 2006. Whilst they concluded that delay to radical treatment was associated with a worse outcome, they did not quantify this effect. Given that the last ten years has seen a number of changes to the treatment of MIBC patients by RC (e.g. centralization of RC to larger hospitals, neoadjuvant chemotherapy (NAC), robotic cystectomy, pre-habilitation), we aimed to re-assess this question by reviewing more recent studies, quantifying the effect of a delay on survival using meta-analyses and establishing a standardised definition of a delay in radical treatment.

2.0 Evidence Acquisition

2.1 Search strategy and inclusion criteria

The research question, search strategy, and inclusion and exclusion criteria were defined by a protocol (see Appendix). Studies were identified by conducting searches of Medline (PubMed) and Ovid Gateway (Embase and Ovid) using the search terms: “bladder” and/or “tumours” and/or “cancer”, “survival” or “death” and “delay” or “referral”. Initially, the titles of the studies were screened to identify the relevant studies. The abstracts and subsequently full texts were then carefully read to identify those which met the inclusion criteria. We used the following inclusion criteria: an RCT or observational study, an original article (no commentaries, author’s replies, reviews, supplements, editorials or systematic reviews), written in English, included patients who have undergone RC for bladder cancer, reported outcomes in the form of overall survival and/or BC specific survival and/or 5-year survival estimates, must not be looking at an alternative treatment regime to surgery and must include at least one category of delay between diagnosis of BC to definitive treatment with RC. There were no criteria of selection based on the date of publication as to include all results possible into the meta-analysis. Clinical characteristics, number of study participants, country of study and delay definitions were extracted from each study. The search was carried out in August 2019. Screening of titles, abstracts and full texts was carried out by BR and MVH. There were no disagreements between authors. BR extracted the data from the chosen articles.

2.2 Meta-analyses

Studies were deemed suitable for inclusion in the meta-analysis if they reported both HRs and 95% CIs for overall survival as an outcome.The studies were categorised based on the type of delay investigated (total delay from diagnosis of BC to RC,delay between TURBT and RC and delay between termination of NAC and RC) and each category was meta-analysed separately. Random-effects models were used whereby the presence of a delay was the exposure variable and overall survival was the outcome of interest (measured using the adjusted HRs from each study), for which pooled HRs were calculated. For each meta-analysis, sensitivity analyses were performed by removing each individual study, one at a time, to detect any changes in the overall result. I^2 scores were also reported to define the severity of heterogeneity.

2.3 Quality assessment of studies

All included studies were classified as observational therefore the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 22-item checklist was used asses the quality of the

articles (11). A risk of bias assessment was also carried out using the Risk Of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool (12). The review was also conducted in accordance with the PRISMA guidelines to enhance the quality of the results and was registered on PROSPERO (registration number: CRD42018118936).

3.0 Evidence Synthesis

Our search strategy identified 399 articles (Figure 1). From these, 38 duplicates were excluded and a further 324 texts were excluded based on the inclusion criteria outlined above following title and abstract review. The full texts of 37 articles were then read, of which 19 were deemed suitable for inclusion.

All of the remaining 19 texts were observational studies published between 1991 and 2019. The sample sizes ranged from 10 to 2738, with a total of 17,532 patients who underwent RC in the studies. Eight of the studies were conducted in the USA, four in Canada, two in the UK, two in Germany and one in each of the Netherlands, Sweden and New Zealand.

3.1 Quality of studies

Assessment of each study using the STROBE checklist highlighted those studies of particularly high or poor quality (Supplementary Table 1). Most studies were of good quality according to the checklist; however, the studies by Munro et al (2010) and Kahokehr, Glasson and Studd (2016) appeared to satisfy the fewest checklist items and therefore were deemed to have a lower quality when compared to the other studies. The studies by Gulliford et al (1991), Williams et al (2017), Santos et al (2015), Mahmud et al (2006), Kulkarni et al (2009),Audenet et al (2019) and Boeri et al (2019) were considered to be of high quality. A risk of bias assessment revealed that all of the studies were considered to have either a low or moderate risk of bias (Supplementary Table 2) (12). The impact of this variation was assessed through our leave one out sensitivity analyses (see below). Furthermore, only 6 of the studies stated whether ethical approval or approval to use the respective databases was obtained.

3.2 Delay and survival

The results from the 19 studies varied greatly, as did the methodology and therefore interpretation of the results. There was a variation in the type of delay investigated within the pathway from diagnosis of BC to RC (as shown in Tables 2 and 3). Ten of the studies evaluated the total delay between diagnosis of BC and RC of which one included patients who received NAC (13–22). Seven of the studies assessed the effect of the delay between TURBT and RC; all but one of these looked specifically at the most recent TURBT, whilst Jäger et al (2010) analysed a delay in RC in the context of NMIBC and used the first TURBT as the start date for analysis (23–29). Two of these studies carried out additional analyses for patients who received NAC. There were two studies which only investigated the delay between NAC and RC (30,31).

3.3 Delay between diagnosis of BC and RC

There was disparity in the number of days/months at which a significant association between delay and survival was identified (Tables 2 and 3). Several studies incorporated tumour stage into their analysis, and many concluded that this factor had a significant impact on the results. Overall, four of the studies found a significant association between delay from diagnosis to RC and survival (Tables 2 and 3) (13,16,19,21).

3.4 Delay between TURBT and RC

Kulkarni et al (2009) used cubic spline regression analysis to recommend an ideal wait time of 40 days. Audenet et al (2019) first looked at the time from TURBT and RC as a continuous variable and found no significant association with overall survival. They then looked at this time interval in deciles and concluded no significant cut-off point in predicting worse overall survival up to the ninth decile (222 days) (18). Overall, four of the studies found an association between the delay to RC after TURBT and survival (Tables 2 and 3) (25–28).

3.5 Use of neoadjuvant chemotherapy

Five studies included separate analyses for patients who received NAC to determine whether a delay in time after NAC to RC is associated with survival (18,28–31). Neither studies by Alva et al (2012) or Bruins et al (2016) found a significant association between a delay to RC after NAC and survival (29,30). Other studies included NAC patients in the overall analyses but in the case of Kahokehr, Glasson and Studd (2016), they looked at the time period between the last cycle of treatment and

surgery and its effect on survival. This study concluded a paucity of significance between survival and delay when also including patients who received NAC (24). Chu et al (2019) and Boeri et al (2019 both investigated the time from the last documented infusion with NAC and RC. Both studies found that a longer delay between NAC and RC significantly increased risk of overall death (28,31). Audenet et al (2019) looked at the time from diagnosis to initiation of NAC and concluded that patients with a delay of 6 months or more had a significantly worse overall survival (18).

3.6 Reasons for delays

Several studies included reasons as to why treatment with RC was delayed. The studies by Lee et al (2006) and Alva et al (2012) suggested that scheduling was one of the main causes for delay in surgical treatment, with as many as 46% of the cohort in the study by Lee et al being affected by this. Other causes included seeking multiple medical opinions, social issues and misdiagnosis. Both Lee et al and Gore et al (2009) suggested that a reluctance to treat and patients' comorbidities also contributed to delays, with two other studies also reaching the same conclusion. According to Gore et al, comorbidities affected the delay since patients had to wait to be transferred to centres better-equipped to deal with the burden of care, as well as requiring more time for medical optimisation.

Chu et al (2019) ran a separate logistic regression analysis to identify factors affecting whether the patients experienced a delay or not. They concluded that living in a high-poverty neighbourhood or rural area, and being transferred to another care provider between TURBT and RC were associated with increased RC delays. Conversely, no patient, provider or health system factors were found to be independently associated with RC delays in the NAC cohort (28). Boeri et al also looked into factors associated with a delay and found that patients with a higher CCI (≥1) were associated with a longer median time to cystectomy (31).

3.7 Gender Disparities

Most of the studies investigated gender in terms of the varying delays experienced by patients and/or how survival was affected by delay between genders. Fahmy et al (2008) additionally found a significant association between an increased median delay (defined as the period between visiting a family practitioner to seeing a urologist) in women when compared to men (21). They also concluded that men were more likely to experience a delay of less than 20 days than women for the

same time period. In contrast, Chu et al (2019) identified male gender as an independent characteristic associated with RC delays (28).

3.8 Meta-analyses

The delay definitions for each study are outlined in Figure 2 and these were considered as the exposure variables in the meta-analyses. When studying the delay between diagnosis of BC and RC, the meta-analysis revealed a pooled HR of 1.34 (95% CI: 1.18-1.53) for overall survival (Figure 3). Sensitivity analyses by the removal of individual studies did not identify any significant changes in the results. The I^2 test was 0.0% suggesting a very low level of heterogeneity between the studies. For delay between TURBT and RC, the meta-analysis calculated a pooled HR of 1.18 (95% CI: 0.99-1.41) for overall survival (Figure 3). The removal of individual studies in the sensitivity analyses did not significantly change the overall result for all studies except Kulkarni et al (2009). Removal of this study resulted in a pooled HR of 1.26 (95% CI: 1.06-1.51). The I^2 test was 72.9%, indicating a relatively high level of heterogeneity between the studies. The funnel plots for both meta-analyses appear to suggest a slight publication bias in the direction of worse survival associated with delay (Supplementary Figure 1).

3.9 Discussion

This is the first study to estimate the pooled effect on survival from a delay in RC using results from multiple studies. Our findings suggest that a longer period of time between diagnosing BC and undergoing RC negatively impacts the overall survival of patients and is influenced by many factors. This review also highlights that despite the 12-week EAU guideline, many centres do not adhere to this and/or choose to analyse their data using different cut-offs. We therefore need to work out a safe cut-off, and ensure there is consensus in how delay is defined.

Whilst the pooled meta-analysis for a delay between TURBT and RC was not significant, removal of the study by Kulkarni et al (2009) resulted in a significant result. Interestingly Kulkarni et al treated delay as a continuous variable which may be a contributing factor as to why this result varied from the others.

The previous systematic review conducted by Fahmy and colleagues concluded that the majority of studies confirmed that delays were associated with worse outcomes (5). Similar to the current study, Fahmy and colleagues found that there was a variation in the type of delay investigated and the period of time used to define delay. A major advantage of the current study compared to the previous review is the inclusion of meta-analyses to quantify the impact that delays to RC may have on overall survival. Furthermore, most of the studies included were published after 2006, therefore incorporating data that were not available at the time of the previous review (5).

Comorbidities, scheduling delays and reluctance to be treated were all suggested as substantial contributors to treatment delay (13,16,19,24). Of these three factors, scheduling delays should be both manageable and avoidable. However, the so called “distance bias effect”, suggesting improved survival for patients referred to a distant higher-volume hospital for RC (32), also generates prolonged treatment delay - “a volume delay paradox” that needs to be handled in clinical practice (33). Nevertheless, an awareness of this phenomenon could still motivate hospitals to have patients treated in a timely manner and subsequently improve outcomes. Comorbidities and reluctance to treat are much harder variables to manage; it is crucial that clinicians are aware of their impact on treatment delay and, hence, survival. Accessible patient information and signposting to peer support groups can help patients address their reluctance to be treated, by allowing them to receive encouragement and information directly from other people who have had an RC.

Administering NAC to improve survival after RC also adds complexity to the scheduling process before RC, and delays to the start of such preoperative chemotherapy by more than 8 weeks has been associated with pathological upstaging (18). The studies included in this review found mixed results between a delay in RC and survival in patients who received NAC with the meta-analysis finding no significant association. It is known that NAC prior to RC significantly reduces patient mortality (34,35), however from the current data it is not possible to identify whether the lack of an effect of delay on mortality in those who received NAC is due to the potential beneficial effects of NAC. Furthermore, patients who receive NAC tend to be younger with fewer comorbidities and are therefore already at a survival advantage (36).

Most of the studies investigating disparities in delay time and/or survival amongst men and women did not find any significant association. This suggests that both males and females are equally as

likely to experience delay and are both similarly affected by delays to RC: although delays in the referral of symptomatic female patients from primary care to secondary care may contribute to a stage migration at eventual diagnosis, there is no such disparity in secondary care (37).

Some studies (e.g. Gulliford et al (1991), Munro et al (2010) (14,15)) did not limit their exposure to only include RC and additionally included radical radiotherapy and systemic chemotherapy as treatment options. Therefore, we could not be certain that the delays associated with the risk of survival were accurate for delay to RC and these studies were subsequently excluded from the meta-analysis.

Despite the 3-month guideline set by the EAU, it is clear from this review that not all centres are adhering to this guideline and many of the studies available use varied cut-off points for their analysis. There is also uncertainty as to the definition of the starting point for delay, e.g. at onset of symptoms, at diagnosis, at initial TURBT, or after termination of NAC. For example, the 40 days suggested by Kulkarni et al refers to the delay between TURBT and cystectomy in an era before NAC was widespread (27). However, the development of rapid access diagnostic pathways for patients with macroscopic haematuria strongly suggest the haematuria referral date as the starting point for delay, and facilitate national guideline recommendations on treatment delay (38). Across all malignancies, BC patients experience the longest delays from symptom onset to diagnosis (39) and it is therefore advisable to strive toward a short delay between haematuria clinic assessment and RC (especially when one considers the psychological effects of delaying RC) (40). Equally, one may also argue that the first TURBT date is a clear, measureable time point to start timing a delay from. However, the results from this study suggests that a longer delay from this time point may not impact delay significantly. Possible reasons for this may be the de-bulking of the tumour during the procedure or the variation in the cut-offs used to define delay.

3.10 Strengths and Limitations

Many of the studies included were large cohort studies could generally be considered to have high external validity. However, the data used for the study by Alva and colleagues were obtained from a single-centre and consequently, as stated by the authors, is limited in terms of generalisability.

Tumour stage was found to be a major influential factor for prognosis and was included in most study analyses. However, the study by Santos et al (2015) did not adjust for stage which is a major limitation of this study (19). Alternatively, patients with more advanced tumour stages might be prioritised in scheduling ahead of patients with less advanced asymptomatic tumours (37,41); thus, tumour stage might affect the exposure variable in cohort studies investigating treatment delays. Chu et al (2019) additionally identified positive lymph node status as a strong predictor of an increased mortality among patients who received NAC (28). Therefore, those studies which failed to report pathological N stage are limited.

There were not enough studies acquired in this review to be able to perform subgroup analyses by N or T stage. As mentioned, these variables can have an impact on survival therefore this is a limitation to the current meta-analyses. Another limitation is the paucity of data for fundamental variables in some studies; for example, Nielsen et al (2007) did not collect information on pre-existing co-morbidities, potentially major contributory factors to prolonged delays. The most prominent limitation in this review was the heterogeneity between the studies due to the variation in the definition of delay, as well as the demographic composition of the cohorts and the endpoints of interest. This made comparing these different studies challenging (as noted by Mahmud et al (25)). The heterogeneity of the studies is highlighted in the relatively large I^2 scores reported for the meta-analyses.

3.11 Future research

Results from these studies have shed light on the complexity of the relationship between RC delays and survival. We therefore recommend that future studies consider this complexity when planning data capture. In the setting of the guideline recommended treatment of NAC and RC, we recommend these definitions for periods of delay to be used by future studies:

- Symptom onset to primary care referral for urologic assessment;
- Referral for urologic assessment to actual urologic assessment;
- Initial urologic assessment to TURBT;
- TURBT to commencement of NAC;
- Commencement of NAC to completion of NAC;
- Completion of NAC to RC.

Not all studies will be established to capture all time points, but the relevant components thereof are to be recommended. Furthermore, awareness of all of the components of total delay may highlight individual elements where pathways can be improved and/or optimised.

4.0 Conclusions

This systematic review has updated the data and knowledge regarding delays to RC and patient survival whilst the addition of the meta-analysis is the first time this pooled effect has been quantified. The BC diagnostic and treatment pathway is complex, involving generally elderly patients with multiple comorbidities; hence, some delays may be unavoidable. However, there still remains a lack of consensus as to what period of delay is acceptable before negatively impacting survival hence more work is needed to answer what has recently been identified as one of the top ten unanswered questions in BC. Notwithstanding, we have demonstrated that a longer delay from BC diagnosis to RC is associated with significantly worse survival. This current review has also highlighted the lack of standardisation as to how delays are defined and therefore using more fixed, measurable time points is of interest to future studies. In conclusion, bladder cancer patients who require RC should be treated without delay so as to maximise survival. Several factors impact delay, such as other medical conditions and scheduling, and these must be monitored by medical practitioners in order to minimise unnecessary delays and to maximise survival.

5.0 Acknowledgments

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We can confirm there are no conflicts of interest to declare for this manuscript.

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Tables and Figures

Figure 1. PRISMA Flow diagram for selection of studies in systematic review and meta-analysis

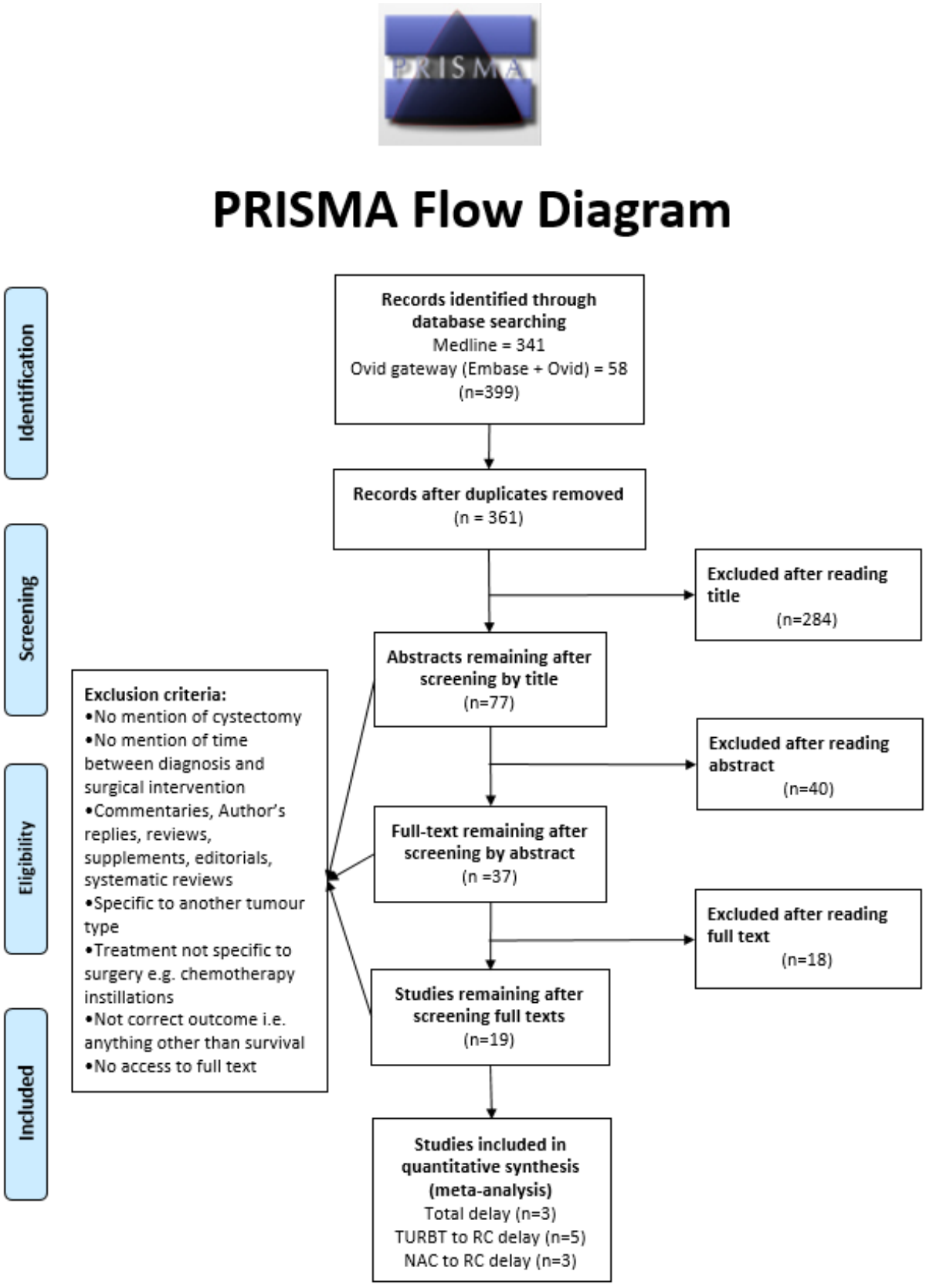


Table 2.

Study ID	Reference	Authors and year of publication	Delay definition	Delay cut-off	Results	
					Median delay	Conclusions
Delay between diagnosis of BC and RC						
1	(13)	Lee et al, 2006	Diagnosis of BC to RC	93 days	61 days	Those delayed longer than 93 days were at a 96% increased risk of death from any cause and 112% increased risk of death from BC compared to those with a cystectomy delay of 93 days or less.
2	(14)	Gulliford et al, 1991	Referral to 1st treatment	84 days	N/A	No change in survival when first treatment was delayed.
3	(22)	Williams et al, 2017	Diagnosis of BC to RC	84 days	N/A	No change in overall or cancer-specific survivals when RC was delayed.
4	(15)	Munro et al, 2010	1st clinic to radiotherapy or RC	84 days	N/A	No change in survival when radiotherapy or RC was delayed.
5	(16)	Gore et al, 2009	Diagnosis of BC to RC	28-56, 56-84, 84-168 & ≥168 days	N/A	A delay of more than 12 weeks between diagnosis and RC was associated with a 201% increased risk of all cause and disease-specific mortality (p=0.003).
8	(17)	Liedberg, Anderson and Månsson, 2005	Diagnosis of BC to RC	60 days	49 days	No change in disease specific survival when there was a delay between diagnosis and RC.
Delay between TURBT and RC						
6	(23)	Nielsen et al, 2007	TURBT to RC	90 days	55 days	No change in survival when there was a delay between the most recent TURBT and RC.
Studies which were also inclusive of NAC patients						

7	(24)	Kahokehr, Glasson and Studd, 2016	TURBT to RC	31 days	Mean = 62 days	No change in survival when there was a delay between TURBT and RC.
9	(18)	Audenet et al, 2019	Diagnosis of BC to RC	From diagnosis to initiation of NAC: 56 days From diagnosis to RC: 183 days	From diagnosis to initiation of NAC: 39 days From initiation of NAC to RC: 112 days	No significant change in overall survival when there was an increase in time from diagnosis to surgery with or without the use of NAC. An increase in time from diagnosis to chemotherapy (≥56 days) was associated with an increased risk of pathological upstaging (OR=1.27, 95% CI: 1.02-1.59).

Table 2. *Delay definitions and summary of results for studies included in systematic review only. TURBT – transurethral resection of the bladder tumour, BC – bladder cancer, RC – radical cystectomy, NAC – neoadjuvant chemotherapy*

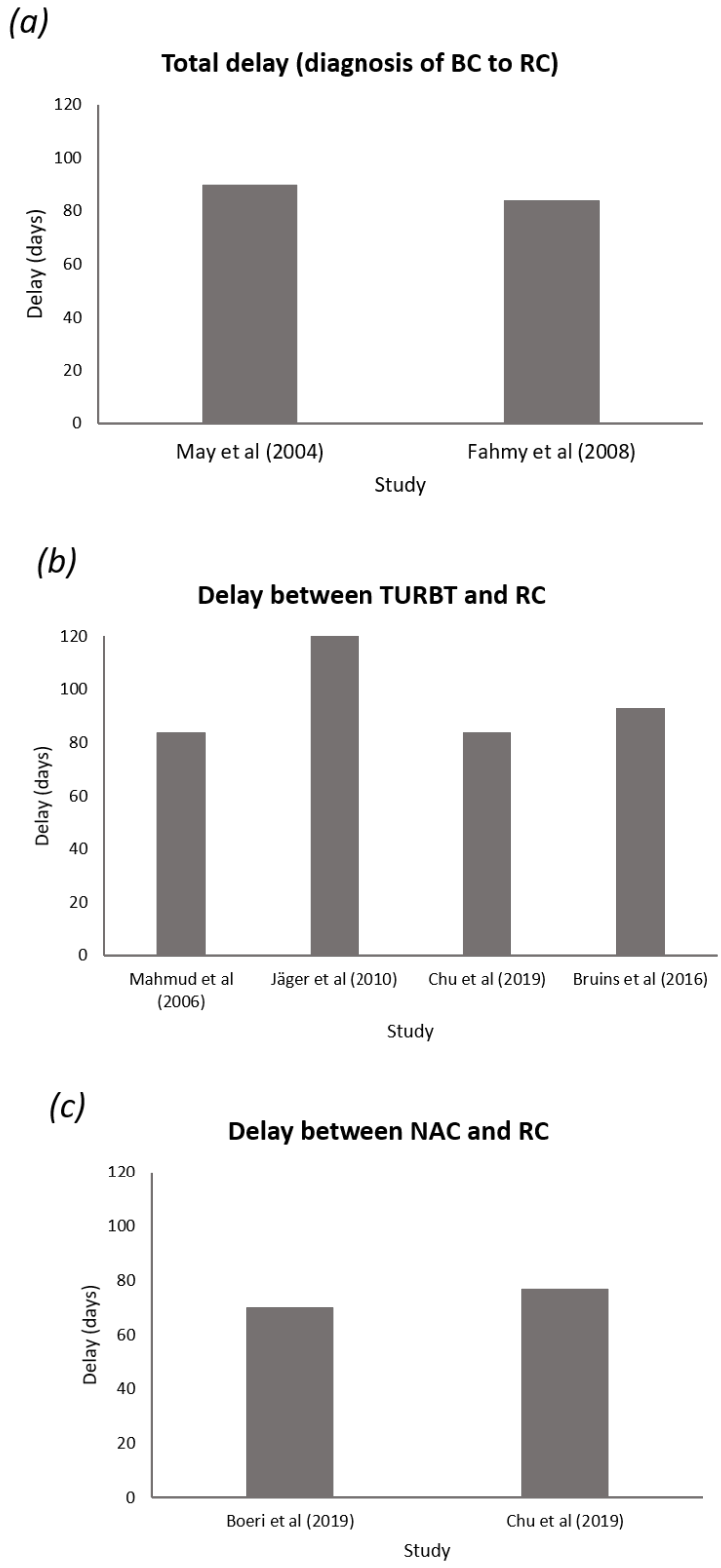
Table 3.

Study ID	Reference	Authors and year of publication	Delay definition	Delay cut-off	Results	
					Median delay	Conclusions
Delay between diagnosis of BC and RC						
12	(19)	Santos et al, 2015	Diagnosis of BC to RC (including referral delay)	Direct/indirect referral	30 days	Patients indirectly referred to a urologist after a first GP visit experienced a 29% increased risk of mortality compared to those directly referred (95% CI: 1.10-1.52).
13	(20)	May et al, 2004	Diagnosis of BC to RC	90 days	55 days	No change in overall survival when RC was delayed, though this relationship was borderline significant (HR=1.62, 95% CI: 0.99-2.66).
14	(21)	Fahmy et al, 2008	Diagnosis of BC to RC	≤24, 24-84, ≥85 days	93 days	A delay of less than 25 or more than 84 days between visiting the family physician and RC was associated with a 230% and 40% increased risk of death from any cause respectively (95% CI: 1.4-3.9 and 1.1-1.8 respectively).
Delay between TURBT and RC						
15	(25)	Mahmud et al, 2006	TURBT to RC	84 days	33 days	A delay of more than 12 weeks between the most recent TURBT and RC is associated with a 20% increased risk of dying from any cause (95% CI: 1.00-1.50).
16	(26)	Jäger et al, 2010	TURBT to RC	120 days	122 days	A delay of more than 120 days between the first TURBT and RC was associated with a significantly worse 5-year cancer-specific survival compared to those with a delay of less than 120 days (77% vs 86% respectively).
17	(27)	Kulkarni et al, 2009	TURBT to RC	90 days	50 days	A delay of more than 90 days between TURBT and RC was associated with an increased risk of death from all causes compared to those with a delay of 90 days or less (HR=1.001, 95% CI:1.000-1.002). This represents

						an increased risk of death for each day a patient waits for an RC.
18	(28)	Chu et al, 2019	TURBT to RC,	From TURBT to RC: 84 days	N/A	Overall survival was significantly reduced in patients who did not receive NAC and were aged less than 80 years old (HR: 1.39, $p<0.05$).
11	(29)	Bruins et al, 2016	TURBT to RC	60 days	No NAC: 50 days NAC: 133 days	No change in survival when there was a delay between diagnosis of BC and RC.
Delay between NAC and RC						
10	(30)	Alva et al, 2012	NAC to RC	28-84 days	From initiation of NAC: 117 days From termination of NAC: 49 days	No change in survival when there was a delay between the termination of NAC treatment and RC or between initiation of NAC to RC.
19	(31)	Boeri et al, 2019	NAC to RC	70 days	53 days	A time to cystectomy (TTC) of more than 10 weeks was associated with an adverse overall and bladder cancer-specific survival
18	(28)	Chu et al, 2019	TURBT to RC and NAC to RC	From completion of NAC to RC: 77 days	N/A	Patients who received NAC and whose RC was delayed suffered significantly higher mortality over time.

Table 3. *Delay definitions and summary of results for studies included in the meta-analyses. The cut-off points for each study is the one from which the HRs and 95% CIs were taken from for the meta-analyses. TURBT – transurethral resection of the bladder tumour, BC – bladder cancer, RC – radical cystectomy, NAC – neoadjuvant chemotherapy*

Figure 2. Delay definitions for total delay (diagnosis of BC to RC) and delay between TURBT and RC

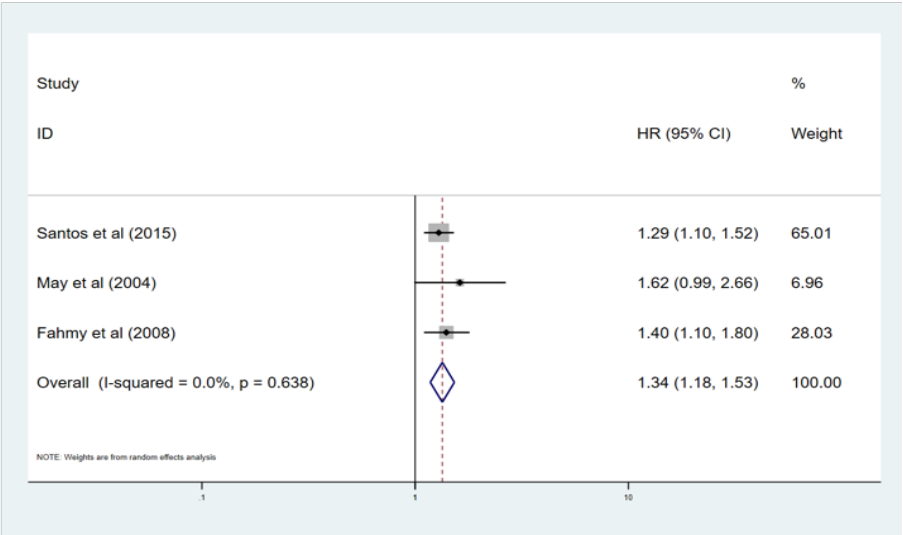


(a) Number of days used by each study to define a total delay in patients receiving treatment by radical cystectomy. Santos et al (2008) is not included as the delay was defined as 'direct' or 'indirect' referral and was therefore not able to be depicted on the diagram. (b) Number of days used by each

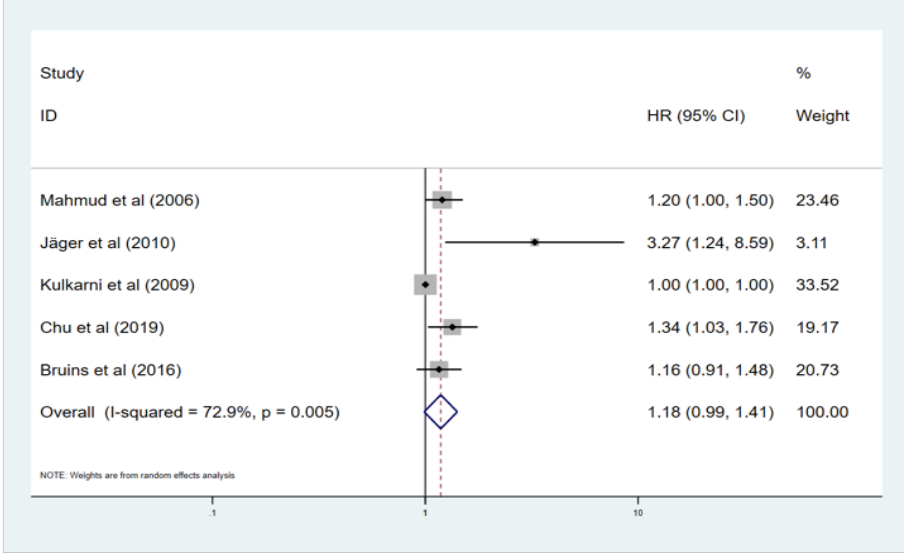
study to define a delay between TURBT and RC. Kulkarni et al (2009) is not included in the diagram as delay was treated as a continuous variable. BC – bladder cancer, RC – radical cystectomy, TURBT – transurethral resection of bladder tumour

Figure 3.
Forest Plots

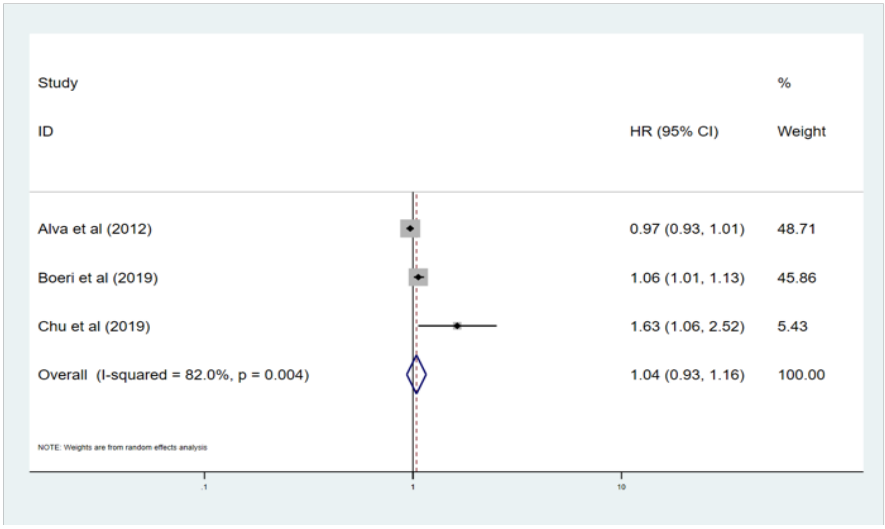
(A)



(B)



(C)

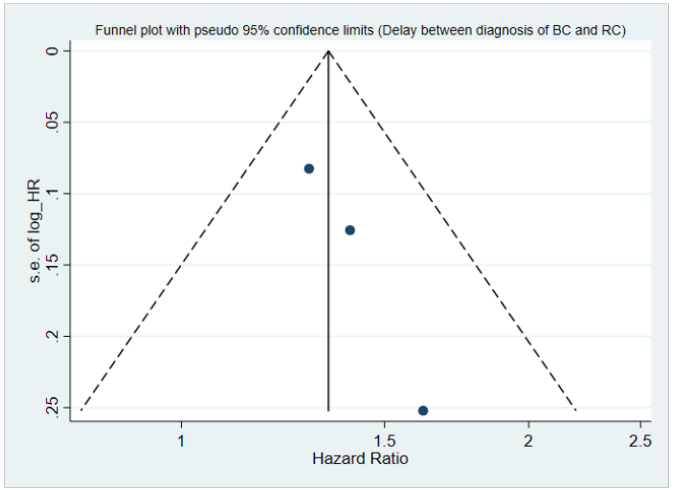


(a) Forest plot for total delay between diagnosis of bladder cancer and radical cystectomy. (b) Forest plot for delay from TURBT to RC. TURBT – transurethral resection of the bladder tumour. (c) Forest plot for delay between termination of NAC and radical cystectomy. RC – radical cystectomy.

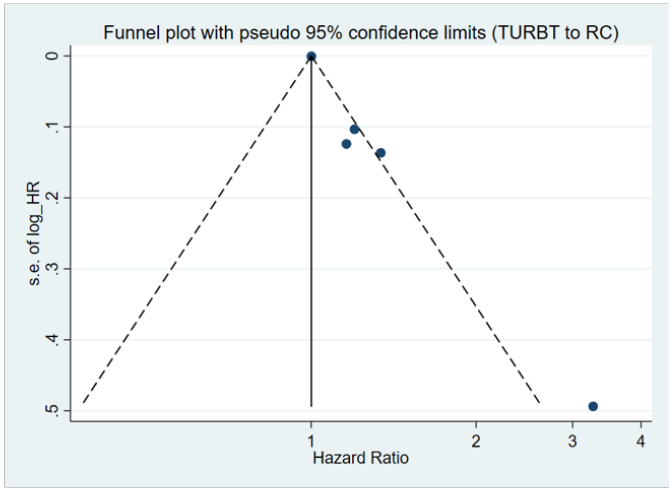
Supplementary Tables and Figures

Supplementary Figure 1. Funnel plots for studies included in meta-analyses

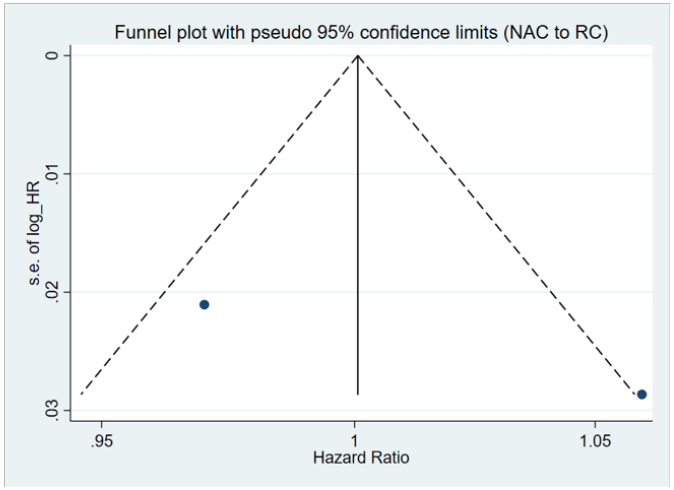
(a)


Funnel plot with pseudo 95% confidence limits (Delay between diagnosis of BC and RC)
s.e. of log_HR
0
.05
.1
.15
.2
.25
1
1.5
2
2.5
Hazard Ratio

(b)


Funnel plot with pseudo 95% confidence limits (TURBT to RC)
s.e. of log_HR
0
.1
.2
.3
.4
.5
1
2
3
4
Hazard Ratio

(c)


Funnel plot with pseudo 95% confidence limits (NAC to RC)
s.e. of log_HR
0
.01
.02
.03
.95
1
1.05
Hazard Ratio

Funnel plot for studies included in meta-analyses. (a) From diagnosis of BC to RC, (b) TURBT to RC, (c) NAC to RC.
RC – radical cystectomy, BC – bladder cancer, TURBT – transurethral resection of the bladder tumour, NAC – neoadjuvant chemotherapy

Supplementary Table 1.

Item	Item No.	Recommendation	Study ID																	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Introduction																					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods																					
Study design	4	Present key elements of study design early in the paper	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up,	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

		and data collection																			
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y
Bias	9	Describe any efforts to address potential sources of bias	N	Y	N	N	Y	N	N	Y	Y	N	N	N/A	N	Y	Y	N	Y	Y	N

Study size	10	Explain how the study size was arrived at	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Y	Y	N	Y	N	N	N	Y	N	N	Y	N/A	N/A	Y	N	N/A	Y	Y
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		(*c*) Explain how missing data were addressed	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N
		(*d*) If applicable, explain how loss to follow-up was addressed	N	N	N	N	N	N	N	N	Y	Y	N	N	N	Y	N/A	N	Y	N	Y
		(*e*) Describe any sensitivity analyses	N	N	N	Y	Y	N	N	Y	N	Y	Y	Y	N	N	Y	N	Y	Y	N
Results																					
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y

		follow-up, and analysed																			
		(b) Give reasons for non-participation at each stage	N	N	N	N	N	N	Y	Y	Y	N	Y	Y	N	Y	N	N	N	Y	N
		(c) Consider use of a flow diagram	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
		(b) Indicate number of participants with missing data for each variable of interest	N	Y	Y	N	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	Y
		(c) Summarise follow-up time (e.g., average and total amount)	N	N	N	N	N	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y
Outcome data	15*	Report numbers of outcome events or summary measures over time	Y	Y	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	Y	N	Y

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		(*b*) Report category boundaries when continuous variables were categorized	Y	Y	Y	N/A	Y	N	N	N/A	Y	Y	N/A	Y	Y	N	Y	Y	N	Y	Y
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion																					
Key results	18	Summarise key results with reference to study objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

		both direction and magnitude of any potential bias																			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	Y
Other information																					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N	N	Y	N	N	Y	Y
Total Score			24	26	26	19	25	20	19	24	26	25	24	29	20	23	26	20	25	24	27

Assessment of studies according to STROBE checklist. *Y=Yes, N=No. Each yes was given a score of 1 and was totalled in the final row.*

Supplementary Table 2.

Signalling questions	Study ID																		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	PN	N	N	N	N	N	PN	PN	PN	N	PN	PN	N	N	PN	PN	PN	N	N
If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, proceed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

to question 1.3.																			
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Questions relating to baseline confounding only		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	Y	Y	PN	PN	PN	PN	Y	PN	PN	PN	N	N	PN	N	PN	Y	Y	Y
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	Y	Y	Y	-	Y	-	-	-	-	PY	-	-	-	PY	-	-	Y	Y	Y

measured validly and reliably by the variables available in this study?																			
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	PN	N	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Questions relating to baseline and time-varying confounding	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risk of bias judgement	Low	Low	Low	Mod	Mod	Mod	Mod	Low	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Low	Low	Low

2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
If N/PN to 2.1: go to 2.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.4. Do start of follow-up and start of intervention coincide for most participants?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
3.1 Were intervention groups clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
If your aim for this study is to assess the effect of assignment to intervention,	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

answer questions 4.1 and 4.2																			
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN	N	N
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4.3. Were important co-interventions balanced across intervention groups?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4.4. Was the intervention implemented successfully for most	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

participants?																			
4.5. Did study participants adhere to the assigned intervention regimen?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
5.1 Were outcome data available for all, or nearly all, participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5.2 Were participants excluded due to missing data on intervention status?	N	NI	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	N	Y	PN	PN	N	N	N	N	Y	N	N	Y	N	N	PN	N	Y	N	N

5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	-	Y	-	Y	-	-	-	-	PY	-	-	PY	-	-	-	-	PY	N/A	N/A
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	-	Y	-	Y	-	-	-	-	PY	-	-	PY	-	-	-	-	Y	Y	N/A
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
6.2 Were outcome assessors aware of the intervention received by study participants?	N/A	N/A	N/A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
6.3 Were the methods of outcome assessment comparable across intervention groups?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	N/A	N/A
Is the reported effect estimate likely to be selected, on the basis of the results, from...	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7.1. ... multiple outcome measurements within the outcome domain?	N	N	PN	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
7.2 ... multiple analyses of the intervention-outcome relationship?	N	N	PN	N	N	N	N	N	N	N	N	PN	N	N	N	N	N	N	N
7.3 ... different subgroups?	N	N	PN	N	N	N	N	N	N	N	N	PY	N	N	N	N	N	N	N
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod	Low	Low	Low	Low	Low	Low	Low
Overall Risk of bias judgement	Low	Low	Low	Mod	Mod	Mod	Mod	Low	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Low	Low	Low

Risk of bias for all studies using the Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. *N= no; PN= probably no; Y = yes; PY= probably yes ; N/A= not applicable. Mod= Moderate risk of bias*

Appendix

Protocol for systematic review

1) Formulate review question

PICOS Question formulation

Population – Bladder cancer patients

Intervention/Exposure – Delayed cystectomy

Comparison – Non-delayed cystectomy

Outcomes – survival

Study designs – RCTs and observational studies, written in English only

In patients with bladder cancer, does having a longer delay between diagnosis and cystectomy have an effect on survival when compared to those who have a shorter time between diagnosis and cystectomy.

2) Define inclusion and exclusion criteria

Search criteria

("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) AND (("tumours"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumors"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND (("mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]) OR ("death"[MeSH Terms] OR "death"[All Fields])) AND (delay[All Fields] OR ("referral and consultation"[MeSH Terms] OR ("referral"[All Fields] AND "consultation"[All Fields]) OR "referral and consultation"[All Fields] OR "referral"[All Fields]))

Inclusion criteria

- RCT or observational study, original article
- Must include patients who have undergone RC
- All patients are bladder cancer patients
- Must include at least one category of delay between diagnosis of BC to definitive treatment with RC
- Report of any overall survival and/or bladder-cancer specific survival and/or 5-year survival estimates

Exclusion criteria

- No mention of cystectomy
- No mention of time between diagnosis and surgical intervention
- Commentaries, Author's replies, reviews, supplements, editorials, systematic reviews
- Specific to another tumour type
- Treatment not specific to surgery e.g. chemotherapy instillations
- No outcome of survival

Databases to be searched:

1. Medline (PubMed)
2. Ovid Gateway (Embase and Ovid)

References:

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Legends:

Figure 1. PRISMA Flow diagram for selection of studies in systematic review and meta-analysis

Table 1.

*Descriptives of the studies included in the systematic review *Included in meta-analysis for total delay between diagnosis of bladder cancer to RC. **Included in meta-analysis for delay between TURBT to RC. ***Included in meta-analysis for delay between NAC and RC. cT/cN = clinical T/N stage*

Table 2.

Delay definitions and summary of results. The cut-off points for each study is the one from which the HRs and 95% CIs were taken from for the meta-analyses. TURBT – transurethral resection of the bladder tumour, BC – bladder cancer, RC – radical cystectomy, NAC – neoadjuvant chemotherapy

Table 3.

Delay definitions and summary of results for studies included in the meta-analyses. The cut-off points for each study is the one from which the HRs and 95% CIs were taken from for the meta-analyses. TURBT – transurethral resection of the bladder tumour, BC – bladder cancer, RC – radical cystectomy, NAC – neoadjuvant chemotherapy

Figure 2. Delay definitions for total delay (diagnosis of BC to RC) and delay between TURBT and RC

(a) Number of days used by each study to define a total delay in patients receiving treatment by radical cystectomy. Santos et al (2008) is not included as the delay was defined as 'direct' or 'indirect' referral and was therefore not able to be depicted on the diagram. (b) Number of days used by each study to define a delay between TURBT and RC. Kulkarni et al (2009) is not included in the diagram as delay was treated as a continuous variable. BC – bladder cancer, RC – radical cystectomy, TURBT – transurethral resection of bladder tumour

Figure 3. Forest Plots

(a) Forest plot for total delay between diagnosis of bladder cancer and radical cystectomy. (b) Forest plot for delay from TURBT to RC. TURBT – transurethral resection of the bladder tumour. RC – radical cystectomy

Supplementary Tables and Figures

Supplementary Figure 1. Funnel plots for studies included in meta-analyses

Funnel plot for studies included in meta-analyses. (a) From diagnosis of BC to RC, (b) TURBT to RC, (c) NAC to RC.
RC – radical cystectomy, BC – bladder cancer, TURBT – transurethral resection of the bladder tumour, NAC – neoadjuvant chemotherapy

Supplementary Table 1.

Assessment of studies according to STROBE checklist. *Y=Yes, N=No. Each yes was given a score of 1 and was totalled in the final row.*

Supplementary Table 2.

Risk of bias for all studies using the Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. *N= no; PN= probably no; Y = yes; PY= probably yes ; N/A= not applicable. Mod= Moderate risk of bias*