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RESEARCH LETTER

The difficulty of studying the association between pathway delays and survival in cancer – an example from bladder cancer

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Introduction

It is postulated that delaying surgery negatively impacts survival in bladder cancer (BCa) [1]. European Urology (EAU) guidelines recommend that radical cystectomy (RC) should be performed within 3 months after diagnosis in patients not given neoadjuvant chemotherapy (NAC).

We investigated the effect of the total time from referral to treatment on survival whilst also considering time from referral to diagnosis and from diagnosis to treatment to explore possible differences in impact of selection bias in patients with BCa treated with RC.

Methods

We used the Bladder Cancer Database Sweden 2.0 (BladderBaSe 2.0) which links data from The Swedish National Register for Urinary Bladder Cancer (SNRUBC) to several national healthcare and demographic registers [2]. We included BCa patients diagnosed between 2000 and 2019, who underwent RC with curative intent as primary treatment (cT1-cT4a, N0, M0) without or with NAC (Supplemental Figure 1). Patients who underwent NAC but had no date for NAC, those whose referral date was after their diagnosis date or transurethral resection of bladder tumour (TURBT) date was after their RC date were excluded as were patients with missing vital status or who had received intravesical therapy. The study population was split into those who went straight to RC (cystectomy only cohort) and those who had NAC before RC (NAC cohort). To ensure our population only consisted of patients who underwent a primary RC without previous treatments, we also excluded patients with extreme values for total wait time from referral to treatment (over 35 weeks in the cystectomy only cohort, and above 24 weeks in the NAC cohort) (Supplemental Figure 2).

To assess whether any results were influenced by prioritising patients with a worse clinical status and most at need of a RC, we created a restricted cohort defined as: patients aged 50–70, no Charlson comorbidity index (CCI) (CCI = 0), cT2/N0/M0 selected from the cystectomy only cohort.

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As a post-hoc analysis we calculated associations between patient and tumour characteristics and a treatment delay of >12 weeks.

Information on patient demographics included age, civil status (unmarried, married, divorced, widowed), education (low, medium, high) and CCI (0, 1, 2, 3+). Clinical variables included clinical T stage, tumour grade, whether patients underwent NAC, date of NAC, date of TURBT, date of RC, hospital type based on period specific mean annual volume (PSMAV) [3].

Date of referral, diagnosis and start date of NAC were all extracted from BladderBaSe. The date of referral and diagnosis were from the patient report form, while start date of NAC was pulled from the treatment form. Three time periods were assessed as exposures: total time from referral (from GP or similar) to start of treatment, whether this be RC or NAC; time from referral to diagnosis (earliest date for either cystoscopy, radiology or cytology/histology) and time from diagnosis to initiation of treatment. All time periods were analysed in tertiles. Time from diagnosis to treatment was additionally analysed as a binary variable (≤12 weeks vs. >12 weeks), in alignment with the current EAU guideline recommendation [4].

Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for association between delay and overall survival (OS) or disease specific survival (DSS). Survival was calculated from date of

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treatment (RC or NAC) to date of death (any cause or BCa). We used logistic regression models to assess if case severity was associated with treatment delay. Models were adjusted for age, sex, cT stage, tumour grade, civil status, education level, CCI score, and hospital volume (PSMAV).

All data management and statistical analyses were carried out on STATA MP/2 version 16.1 (StataCorp LP, College Station, TX) and R.

Results

Total time from referral to treatment

The total time from referral to RC ranged from 0 to 21 weeks with a median of 13 weeks (Interquartile range: 10–17 weeks) for the 1,967 patients in the cystectomy only cohort (Supplementary Table 1 and 2). A total delay of ≥19 weeks was associated with a decreased risk of death for both overall (HR = 0.82, 95% CI: 0.70–0.96) and BCa-specific death (HR = 0.69, 95% CI: 0.56–0.85) when compared to a total time of ≤12 weeks (Table 1).

In the 308 patients in the NAC cohort, the total time from referral to NAC ranged from 4 to 15 weeks with a median of 11 weeks (IQR: 8–13 weeks) (Supplementary Table 2). A longer time from referral to NAC was not associated with either overall or BCa-specific death (Table 2).

Time from referral to diagnosis

The time from referral to diagnosis was not statistically significantly associated with survival in either cohort (Tables 1 and 2).

Time from diagnosis to treatment

An association was observed for ≥14 weeks for BCa-specific death only (HR = 0.78, 95% CI: 0.63–0.95) in the cystectomy only cohort (Table 1) when compared to ≤9 weeks. This association was, however, not observed when the period was dichotomised (>12 weeks vs. ≤12 weeks). Despite not being statistically significant, the direction of the association was the same for all results in the cystectomy only cohort. Time from diagnosis to treatment was also not associated with survival in the NAC cohort.

Sensitivity analyses

There were no statistically significant associations observed between delay and survival in the restricted cohort (Supplementary Table 3).

Several factors were associated with an increase in the odds of having a delay of over 12 weeks in the cystectomy only cohort

Table 1. Cystectomy only cohort (T1-T4a, N0, M0, diagnosed between 2000 and 2019): Cox regression analysis to assess the association between delay and overall survival and disease specific survival.

Total time	Numbers	Overall survival (OS)				Disease specific survival (DSS)			
		HR	95% CI	HR[a]	95% CI	HR	95% CI	HR[a]	95% CI
Tertiles (weeks)									
≤12	697	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
13–18	698	0.90	0.78–1.04	0.89	0.77–1.03	0.80	0.67–0.96	0.84	0.70-1.00
≥19	572	0.81	0.69–0.94	0.82	0.70–0.96	0.65	0.53–0.79	0.69	0.56-0.85
Time from referral to diagnosis									
Tertiles (weeks)									
≤2	892	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
3–4	441	0.95	0.81–1.11	0.95	0.80–1.11	0.98	0.80–1.19	0.95	0.77-1.16
≥5	634	0.94	0.82–1.08	0.95	0.82–1.09	0.91	0.76–1.09	0.90	0.75-1.08
Time from diagnosis to treatment									
Tertiles (weeks)									
≤9	751	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
10–13	579	0.98	0.84–1.13	0.98	0.84–1.13	0.90	0.75–1.09	0.94	0.78-1.13
≥14	637	0.86	0.74–1.00	0.86	0.74–1.01	0.72	0.59–0.87	0.78	0.63-0.95
Delay > 12 weeks (T1–T4a)									
No	1193	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	774	0.89	0.78–1.02	0.92	0.80–1.05	0.79	0.67–0.94	0.85	0.72-1.02
Delay > 12 weeks (T1)									
No	178	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	220	0.95	0.67–1.34	0.95	0.66–1.39	0.59	0.36–0.96	0.65	0.39-1.09
Delay > 12 weeks (T2)									
No	819	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	481	0.91	0.78–1.06	0.89	0.76–1.04	0.83	0.68–1.01	0.83	0.68-1.02
Delay > 12 weeks (T3–T4a)									
No	196	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	73	0.98	0.71–1.36	0.87	0.62–1.23	1.04	0.70–1.54	0.91	0.60-1.39

HR: Hazard ratio; HR[a]: adjusted hazard ratio; 95% CI: 95% confidence interval; T1-T4a: clinical T stage.

Adjusted models were adjusted for: age, sex, cT stage, tumour grade, civil status, education level, Charlson Comorbidity Index (CCI), and hospital volume (PSMAV).

Table 2. Neoadjuvant Chemotherapy (NAC) Cohort (T2-T4a, N0, M0, diagnosed between 2000 and 2019): Cox regression analysis Cystectomy only cohort (T1-T4a, N0, M0, diagnosed between 2000 and 2019): Cox regression analysis to assess the association between delay and overall survival and disease specific survival.

Total time	Numbers	Overall survival (OS)				Disease specific survival (DSS)			
		HR	95% CI	HR[a]	95% CI	HR	95% CI	HR[a]	95% CI
Tertiles (weeks)									
≤10	120	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
11–14	108	1.11	0.72–1.71	1.05	0.67–1.63	1.04	0.64–1.68	1.03	0.62-1.69
≥15	80	1.26	0.81–1.98	1.17	0.72–1.90	1.30	0.79–2.12	1.29	0.76-2.19
Time from referral to diagnosis									
Tertiles (weeks)									
≤1	109	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
2–4	172	0.79	0.52–1.21	0.79	0.51–1.22	0.78	0.49–1.24	0.79	0.49-1.27
≥5	26	0.95	0.60–1.51	0.89	0.55–1.43	0.98	0.59–1.62	0.98	0.58-1.67
Time from diagnosis to treatment									
Tertiles (weeks)									
≤7	122	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
8–10	94	1.01	0.65–1.58	0.92	0.58–1.45	0.99	0.60–1.62	0.94	0.56-1.57
≥11	92	1.22	0.80–1.87	1.16	0.75–1.79	1.21	0.75–1.94	1.18	0.72-1.91
Delay > 12 weeks (T2–T4a)									
No	263	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	45	1.4	0.88–2.23	1.36	0.85–2.19	1.42	0.85–2.36	1.32	0.78-2.23
Delay > 12 weeks (T2)									
No	223	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	45	1.48	0.91–2.40	1.40	0.84–2.33	1.31	0.75–2.30	1.25	0.69-2.25
Delay > 12 weeks (T3–T4a)									
No	32	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	8	1.69	0.66–4.35	1.63	0.47–5.65	1.88	0.72–4.91	1.75	0.48-6.40

HR: Hazard ratio; HR[a]: adjusted hazard ratio; 95% CI: 95% confidence interval; T1-T4a: clinical T stage.

Adjusted models were adjusted for: age, sex, cT stage, tumour grade, civil status, education level, Charlson Comorbidity Index (CCI), and hospital volume (PSMAV).

(Supplementary Table 4). These included being over the age of 65 , CCI ≥ 3 and a PSMAV of ≥ 7. T stage T2 and T3 was negatively associated with treatment delay of ≥12 weeks. The association with T stage was also reflected when the tumour and patient characteristics were stratified by total delay time whereby those with a higher T stage appeared to have a shorter delay time ($p < 0.001$) (Supplementary Table 4).

Discussion

Patients who went straight to RC with a total wait time between referral and cystectomy of ≥19 weeks had a reduced risk of death from both all-cause and BCa-specific death. In addition, those who waited 14 weeks or more between diagnosis and cystectomy, were also at a decreased risk of BCa-specific death. Our results, did not however, show any significant associations when a delay cut-off of >12 weeks (from diagnosis to cystectomy) was utilised. Though not all results were statistically significant, there did appear to be an overall trend in the direction of the association for the cystectomy only cohort for total and treatment delay, that is, a longer delay was associated with a better survival. There was no significant association between a delay and survival outcomes in those who received NAC before their RC.

The contrast to previous results [1] and the absence of a biological theory as to why a delay could be irrelevant or even beneficial lead us to postulate that the association found is a result of selection bias whereby the sickest of patients are selected for RC first. In the current study, this interpretation is supported by the lack of an association between delay and survival in the restricted cohort and by the association between patient and tumour characteristics and delay time. The results of the sensitivity analyses indicate that the adjusted Cox models are hampered by residual confounding, that is, there are several variables which affect the prioritisation of patients within the stage categorization which our granular categorization was unable to adjust for.

The difference between our results and previous studies may partly be explained by the healthcare setting, where in the current study, RC exclusively is performed within public health care with mainly uniform diagnostic pathways and few different caretakers for BCa. The system facilitates that urologists prioritize patients primarily based on BCa severity and comorbidity. An increasing use of multidisciplinary team consultations likely serve the same purpose, where 69% of all invasive BCa patients in Sweden are discussed at such meetings [5].

For patients who undergo NAC prior to their RC, there was no statistically significant association between a longer time to treatment and survival. This observation resonates with the results from the systematic review and meta-analysis from 2020 [1]. The EAU guidelines state that delays caused by NAC are not the issue when it comes to any association between RC delays and survival [4].

This real-world evidence illustrates the strong selection bias in studies of intended effects introduced by clinicians' choice of clinical action to serve patients' well-being. As for studies of most treatments, studies of effects of patient waiting times require randomization to be un-biased, in this case an unethical study design. The restricted cohort in our study was an attempt to minimize selection bias and confounding, but this cohort is still composed of individuals with a broad set of possible outcomes, which experienced clinicians could anticipate with some accuracy. Furthermore, we lack information on one important confounder, smoking.

To conclude, this study shows how difficult it is to study the possible association between treatment delay and survival in BCa. The problems encountered are probably generalisable to several other cancer types. Given the methodological constraints, our results cannot be taken to dismiss a potential risk with delay and do not in any way contradict the current EAU recommendations.

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Conflicts of interest

There are no conflicts of interest to declare.

Data availability statement

The BladderBaSe data is held on a secure server and is therefore not publicly available. However, applications to access the data can be made by contacting support.rc-norr@vll.se.

References

[1] Russell B, Liedberg F, Khan MS, et al. A systematic review and meta-analysis of delay to radical cystectomy and the effect on survival in bladder cancer patients. Eur Urol Oncol. 2020;3(2):239–249. https://doi.org/10.1016/j.euo.2019.09.008

[2] Häggström C, Hagberg O, Gårdmark T, et al. Cohort profile: Bladder Cancer Data Base Sweden (BladderBaSe) 2.0. BMJ Open. 2022;12(12):e064898. https://doi.org/10.1136/bmjopen-2022-064898

[3] Liedberg F, Hagberg O, Aljabery F, et al. Period-specific mean annual hospital volume of radical cystectomy is associated with outcome and perioperative quality of care: a nationwide population-based study. BJU Int. 2019;124(3):449–456. https://doi.org/10.1111/bju.14767

[4] Alfred Witjes J, Max Bruins H, Carrión A, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2023 guidelines. Eur Urol. 2024;85(1):17–31. https://doi.org/10.1016/j.eururo.2023.08.016

[5] Swedish National Quality Register for Bladder and Urinary Tract Cancer (SNRUBC). 2019. Available from: https://statistik.incanet.se/Urinblasecancer/ [cited 30th May 2024]