Association between time from diagnosis to radical cystectomy and oncologic outcomes in muscle-invasive urothelial carcinoma of the bladder

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ABSTRACT

Introduction: A delay beyond 12 weeks from diagnosis to radical cystectomy (RC) is considered to impart worse oncologic outcomes for patients with muscle-invasive bladder cancer (MIBC); however, no randomized clinical trials have examined this question. We therefore emulated a hypothetical target clinical trial using contemporary data to evaluate the association between time from diagnosis to RC and oncologic outcomes.

KEY MESSAGES

- A delay from diagnosis to RC is thought to impart worse outcomes in patients with MIBC.
- No randomized clinical trial has examined this question.
- Late RC was not associated with an increased risk of pathologic upstaging.
- There was no significant difference in OS for late and early RC across patient groups.
- Traditional guidelines for RC timing need to be re-examined in contemporary patients.

Methods: We conducted observational analyses using the National Cancer Database from 2006−2015 to emulate a hypothetical target trial in adults aged 40−79 years with incident cT2−4

N0 M0 urothelial carcinoma of the bladder, treated with RC from 4−18 weeks after diagnosis. We evaluated the association of late RC with pathologic upstaging at RC and overall survival (OS) and conducted exploratory analyses evaluating the association of time to RC with each outcome modeled flexibly.

Results: A total of 3747 patients were included, of which 2992 underwent early RC. Median followup was 32.2 months. In adjusted analyses, late RC was not associated with an increased risk of pathologic upstaging compared to early RC. In addition, there was no statistically significant difference in adjusted OS for late and early RC, respectively. Similar findings were observed across categories of cT stage, age, Charlson index, and gender.

Conclusions: In observational analyses designed to emulate a hypothetical target trial of early vs. late RC, the timing of RC was not associated with a statistically significant increase in pathologic upstaging or a difference in OS when performed from 4−18 weeks after diagnosis. These results suggest the need to re-examine the traditional recommendations for timing of RC following diagnosis.

INTRODUCTION

Bladder cancer is the 4th most common cancer in the Unites States with an annual estimated incidence of 82,290 new cases per year.[1] Radical cystectomy (RC) is the standard of care surgical treatment for muscle-invasive disease.[2] The prompt timing of RC relative to diagnosis is considered important in optimizing oncologic outcomes. Historically, a delay from diagnosis to RC has been associated with poorer survival in these patients. Several studies suggested that delaying radical cystectomy greater than 12 weeks is associated with higher pathological stage at surgery and poorer clinical outcomes.[3-8] However, these data represent historical cohorts, and notably, the optimal timing of RC has never been investigated in a randomized controlled trial.

We sought to examine the association of time from diagnosis to RC to evaluate whether a delay to RC is associated with worse oncologic outcomes, and to characterize the magnitude of this association relative to the timing of surgery. Since a randomized clinical trial comparing early versus delayed RC is both infeasible and unethical, we emulated a hypothetical target trial using a contemporary, nationwide oncology dataset. Emulating a target clinical trial when randomized evidence is lacking has a number of potential advantages, ultimately leading to improved causal inferences, that have been previously described. [9-12]

Herein, we emulate a hypothetical target trial of early versus late RC using the traditional 12-week threshold to examine the association of timing of RC with pathologic upstaging and overall survival (OS). In addition, we conduct exploratory analyses to flexibly model the timing of RC to evaluate whether an empiric threshold for optimizing oncologic outcomes exists.

METHODS

Target clinical trial

This study met institutional review board (IRB) criteria that it did not constitute human subjects research. We conducted observational analyses designed to emulate a hypothetical target trial of early versus late RC using a framework for conducting observational analyses designed to emulate a real or hypothetical target clinical trial described by Hernan and Robins.[9] The components of the hypothetical target trial are described in Supplementary Table 9.

Patient population

We identified adults age 40-79 years with Charlson score 0-1 who were diagnosed with incident cT2-4 N0 M0 urothelial carcinoma of the bladder from 2006-2015 in the National Cacer Database (NCDB) and were treated with RC without neoadjuvant chemotherapy. We defined two treatment arms of early or late RC as RC performed from ≥4 to 12 weeks or ≥12 to 18 weeks following diagnosis, respectively. We excluded patients who received palliative treatment, had a diagnosis of prior malignancy, or received neoadjuvant chemotherapy or preoperative/intraoperative radiotherapy (Supplementary Figure 1 and 2). We also excluded patients who underwent very early or very late cystectomy, before 4 weeks or >18 after diagnosis, as these may represent outlier cases.

Clinicopathologic features and outcomes

We abstracted the following characteristics from the NCDB: age, sex, race, Hispanic origin status, Charlson comorbidity index, insurance status, geographic location, rurality, facility type, distance to hospital, zip code income and educational level, annual RC volume, clinical and pathologic TNM stage, tumor grade, surgical margin status, number of lymph nodes removed, number of positive lymph nodes, and time from diagnosis to RC

The co-primary outcomes were overall survival (OS) and pathologic upstaging at the time of RC. Pathologic upstaging was defined according to cT stage at diagnosis: pT3-T4 or pN+ disease for cT2; pT4 or pN+ for cT3; and pN+ for cT4.

Statistical methods

Baseline characteristics were summarized using medians and interquartile ranges (IQR) or frequency counts and percentages, and compared across treatment groups using the Wilcoxon rank sum or chi-square tests.

We modeled early versus late RC as a point intervention at zero time, which was defined as the date of diagnosis. We utilized a propensity-score based approach to adjust for difference in baseline characteristics between treatment groups.[13] First, we estimated a propensity score for late RC using a multivariable logistic regression model that included the covariates listed in Table 2, except the post-RC covariates of pT stage, pN stage, surgical margin status, and number of LNs removed. We conducted a complete case analysis, excluding observations with missing data for any of the covariates included in the PS model. Continuous covariates were modeled as continuous linear variables, while categorical variables were modeled as shown in Table 2.

Covariate balance was assessed using standardized differences (SDs) after re-weighing by stabilized inverse probability of treatment weights (sIPWs). The propensity score model was revised until covariate balance was obtained.

We then estimated absolute and relative measures of treatment effects for the co-primary outcomes after reweighing with sIPWs. First, we estimated the association of early versus late RC with pathologic upstaging using a logistic regression model with reweighing by sIPWs. Results are reported using odds ratios (ORs) with 95% CIs. Next, we estimated OS, stratified by early versus late RC, using the Kaplan-Meier method with reweighing by sIPWs. We also estimated the association of early versus late RC with all-cause mortality using a Cox regression model with reweighing by sIPWs. Results are reported using hazard ratios (HRs) with 95% confidence intervals (95% CI). In order to avoid immortal time bias for the survival analyses performed herein, we conducted 18-week landmark-time analyses, excluding patients with less than 18-weeks of follow-up.

We evaluated for heterogeneity of treatment effects in separate regression models for each outcome to examine how treatment effects varied across clinically relevant covariates that were specified a priori. These covariates were cT stage, age, Charlson index, and sex.

Since cancer-specific survival is not available in the NCDB, we also conducted a sensitivity analysis in which we truncated follow-up at 60 months in order for OS to better approximate cancer-specific survival, as the bladder cancer is the dominant cause of death in the 5-years following diagnosis of MIBC. In this sensitivity analysis, we repeated the analyses for the outcomes of OS and all-cause mortality above.

To further evaluate the association of time from diagnosis to RC with oncologic outcomes, we conducted an exploratory analysis in which we modeled time from diagnosis to RC flexibly using two methods. First, we performed univariable and multivariable regression to evaluate the association of time to RC modeled as a linear continuous variable with pathologic upstaging (logistic regression) and all-cause mortality (Cox regression). Second, we repeated the multivariable models with time from diagnosis to RC modeled flexibly using restricted cubic splines with 3 knots.[14] The association of time from diagnosis to RC was visualized graphically using adjusted OR and adjusted HR ratios for pathologic upstaging and all-cause mortality, respectively.

Statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and P-values <0.05 were considered statistically significant.

RESULTS

A total of 3,747 patients were included in the study cohort, including 2,992 (80%) who underwent RC from ≥4 to 12 weeks following diagnosis (early RC) and 755 (20%) who underwent RC from ≥12 to 18 weeks following diagnosis (late RC). Baseline characteristics are summarized in Supplementary Table 1 (available at *cuaj.ca*). Median age was 67 (IQR 60-73)

years, and 24% of the cohort was female. Clinical tumor stage was cT2 in 3,195 (85%), cT3 in 350 (9%), and cT4 in 202 (5%). Compared to patients who underwent early RC, those who underwent late RC had a statistically significantly higher Charlson index (30% vs 26% Charlson 1; p=0.04), and were more likely to be Hispanic (4% vs 2%; p<0.01), insured with Medicaid (7% vs 4%; p<0.01), and treated at an academic/research facility (56% vs 50%; p=0.01). After sIPW-reweighing, pre-operative baseline characteristics were well balanced (Supplementary Table 2; available at *cuaj.ca*).

Pathologic upstaging occurred in 1914 (51%) of the study cohort. Adjusted rates of pathologic upstaging, stratified by treatment group, are summarized in Supplementary Table 3 (available at *cuaj.ca*). There was no statistically significant difference in the rate of pathologic upstaging between patients treated with late versus early RC (48% vs 52%; p=0.07). In adjusted logistic regression models, late RC was not associated with a statistically significant difference in pathologic upstaging in the overall cohort (OR 0.86; 95% CI 0.73-1.01; p=0.07), nor across categories of cT stage, age, Charlson score, or gender, except a lower risk of pathologic upstaging among cT2 patients (OR 0.83; 95% CI 0.69-0.99; p=0.04; Figure 1).

Baseline characteristics for the survival (i.e., landmark time) analysis cohort are summarized in Supplementary Table 4 (available at *cuaj.ca*). After sIPW re-weighing, preoperative baseline characteristics were well-balanced (Supplementary Table 5; available at *cuaj.ca*). Median follow-up was 32.2 (IQR 14.7, 60.1) months. During follow-up, a total of 1636 all-cause deaths occurred. After IPW-reweighing, late RC was not associated with a statistically significant difference in OS compared to early RC, with 5-year OS of 46% vs. 50%, respectively (p=0.17) (Figure 2, Supplementary Table 6; the latter available at *cuaj.ca*). In adjusted Cox regression models, late RC was not associated with a statistically significant difference in OS compared to early RC in the overall cohort (HR 1.09; 95%CI 0.96-1.24; p=0.17), nor across categories of cT stage, age, Charlson index, or sex (Figure 3). Similar results were obtained in a sensitivity analysis that truncated follow-up at 5-years to better approximate cancer-specific survival with OS (HR 1.07; 95% CI 0.94-1.22; p=0.28; Figure 4 and Figure 5).

We conducted two exploratory analyses to flexibly model the association of time from diagnosis to RC. First, when modeled as a continuous linear covariate, increasing time from diagnosis to RC was associated with a modest decrease in the odds of pathologic upstaging (adjusted unit OR 0.98; 95% CI 0.96-1.00 per week; Supplementary Table 7; available at *cuaj.ca*). However, time from diagnosis to RC was not associated with a statistically significant difference in all-cause mortality (adjusted unit HR 1.01; 95% CI 1.00-1.03 per week; Supplementary Table 8; available at *cuaj.ca*). Similar results were obtained when time from diagnosis to RC was modeled flexibly using restricted cubic splines. Specifically, there was a modest reduction in the adjusted risk of pathologic upstaging with a longer time from diagnosis to RC (Figure 6). However, there was no statistically significant difference in the risk of all-cause mortality (Figure 7).

DISCUSSION

In this study, we did not observe a statistically significant association between early versus late RC and pathologic upstaging or OS when using the traditional threshold of 12 weeks from diagnosis. In exploratory analyses that flexibly modeled time from diagnosis to RC, longer time to RC was associated with a modest but statistically significant reduction in the odds of pathologic upstaging, but no difference in all-cause mortality. These observations suggest the need to re-examine traditional recommendations for the optimal timing of RC following a diagnosis of MIBC.

The ideal timing of radical cystectomy after diagnosis of MIBC remains uncertain due to the lack of randomized clinical trials. The association between worse clinical outcome and time to RC greater than 3 months after diagnosis of MIBC was first described by Sanchez-Ortiz et al. in 2003.[8] This was a retrospective, single-institution study, which reported that a greater than 12 week time from diagnosis to upfront RC was associated with advanced pathological stage and decreased survival. When patients were dichotomized to 12 week or less versus greater than 12 week groups, the latter group had worse disease specific survival (HR 2.51, 95% CI 1.30-4.84, p = 0.006). The latter group was also at higher risk of pathologic upstaging (≥pT3a or N+) (84% vs 42.9%, p<0.01). Notably, the study was limited with only 19 patients who had RC beyond 12 weeks after diagnosis, and six of these patients waited more than two years before undergoing RC, which likely introduced bias that could limit the validity of the results. Several other historical studies also reported worse clinical outcome when RC was performed more than 3 months after diagnosis.[3-7] In a 2009 SEER database study, Gore et al examined 441 patients with cT2 bladder cancer diagnosed between 1992 and 2001, and found that compared to immediate RC, those who had RC delayed by 12-24 weeks had worse overall survival (HR 1.6, p<0.01). Other covariates associated with worse outcome were older age (HR 1.04, p<0.01) and Charlson comorbidity ≥3 vs 0-1 (HR 2.0, p<0.01). In another study, Chu et al also examined a SEER cohort of 1509 patients with cT2 bladder cancer diagnosed between 2004 and 2012, and similarly observed that a delay to RC of 12 weeks was associated with worse OS, whether patients received neoadjuvant chemotherapy or not. In the non-neoadjuvant group, delayed RC was associated with worse OS with a HR of 1.34 (95% CI 1.03-1.76). Still, other evidence does not support an association between a 12-week delay to RC and worse clinical outcomes. For example, in one multi-institutional study, Nielsen and colleagues reported no difference in pathologic staging, disease-specific, or overall survival with a delay to RC of greater than 3 months.[15]

This is the first study, to our knowledge, to emulate a hypothetical target trial to evaluate the association of the timing of RC with pathologic upstaging and survival. Conducting such a randomized clinical trial in patients with recent diagnosis of muscle-invasive bladder cancer would pose ethical and logistical problems for both the investigators and the participants alike; therefore, emulation of a clinical trial represents one solution in such a setting where a real-world trial is infeasible. This approach has a number of methodological benefits, such as reducing

intractable confounding, ensuring treatment arms are well defined, and appropriate specification of time zero with consideration of immortal time bias. The advantages of the emulation framework have been described elsewhere in more detail.[9, 16]

This study has a number of limitations. First, the NCDB does not capture all potentially relevant covariates, and therefore unmeasured confounding may affect the results of the study. In support of potential confounding by indication, we observed a modest reduction in risk of pathologic upstaging with longer time to RC in exploratory analyses. In addition, we were only able to evaluate OS, as cancer-specific mortality is not captured in the NCDB; however, given the aggressive nature of urothelial cancer, we hypothesize that the OS within 5 years of RC sis an appropriate surrogate for cancer-specific survival, and results were similar in a sensitivity analysis that examined this. Finally, we addressed for immortal bias related to the definition of the treatment groups through landmark time analyses, but other methodological approaches exist. Still, the present study benefited from a robust methodological framework that required explicit specification of the target trial to be emulated.

CONCLUSIONS

In observational analyses designed to emulate a hypothetical target trial of early versus late RC, timing of RC was not associated with a statistically significant difference in pathologic upstaging or OS when performed from 4 to 18 weeks after diagnosis. These results suggest the need to examine the traditional recommendation for timing of RC following diagnosis.

REFERENCES

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. *CA Cancer J Clin* 2023;73:17-48. https://doi.org/10.3322/caac.21763
2. Ploeg M, Aben KKH, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009;27:289-93. https://doi.org/10.1007/s00345-009-0383-3
3. Chu AT, Holt SK, Wright JL, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. *Cancer* 2019;125:2011-7. https://doi.org/10.1002/cncr.32048
4. Hara I, Miyake H, Hara S, et al. Optimal timing of radical cystectomy for patients with invasive transitional cell carcinoma of the bladder. *Jpn J Clin Oncol* 2002;32:14-8. https://doi.org/10.1093/jjco/hyf002
   Lee CT, Madii R, Daignault S, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease-specific and overall survival. *J Urol* 2006;175:1262-7. https://doi.org/10.1016/S0022-5347(05)00644-0
5. May M, Nitzke T, Helke C, et al. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. *Scand J Urol Nephrol* 2004;38:231-5. https://doi.org/10.1080/00365590410029141
6. Gore JL, Lai J, Setodji CM, et al. Mortality increases when radical cystectomy is delayed more than 12 weeks: Results from a SEER-Medicare analysis. *Cancer* 2009;115:988-96. https://doi.org/10.1002/cncr.24052
7. Sanchez-Ortiz RF, Huang WC, Mick R, et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003;169:110-5. https://doi.org/10.1016/S0022-5347(05)64047-5
8. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;183:758-64. https://doi.org/10.1093/aje/kwv254
9. Bacic J, Thoumas L, Thompson RH, et al. Emulating target clinical trials of radical nephrectomy with or without lymph node dissection for renal cell carcinoma. *J Urol* 2020;204:140-6. https://doi.org/10.1016/j.urology.2020.01.039
10. Reitblat C, Fleishman A, Kaplan IA, et al. Radical prostatectomy versus external beam radiation therapy for high-grade, clinically localized prostate cancer: Emulation of a target clinical trial. *Urol Oncol* 2021;39:785.e1-785.e9. https://doi.org/10.1016/j.urolonc.2021.03.017
11. Bharadwaj M, Kaul S, Fleishman A, et al. Adjuvant chemotherapy versus observation following radical cystectomy for locally advanced urothelial carcinoma of the bladder. *Urol Oncol* 2022;40:274.e15-274.e23. https://doi.org/10.1016/j.urolonc.2022.02.002
12. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81. https://doi.org/10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
13. Harrell FE Jr. Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis. 2nd ed. Springer; 2015. https://doi.org/10.1007/978-3-319-19425-7

14. Nielsen ME, Palapattu GS, Karakiewicz PI, et al. A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome. *BJU Int* 2007;100:1015-20. https://doi.org/10.1111/j.1464-410X.2007.07132.x
15. Gershman B, Guo DP, Dahabreh I. Using observational data for personalized medicine when clinical trial evidence is limited. *Fertil Steril* 2018;109:946-51. https://doi.org/10.1016/j.fertnstert.2018.04.005

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FIGURES AND TABLES

Figure 1. Forest plot of adjusted associations of late RC with pathologic upstaging.
CI: confidence interval; OR: odds ratio.

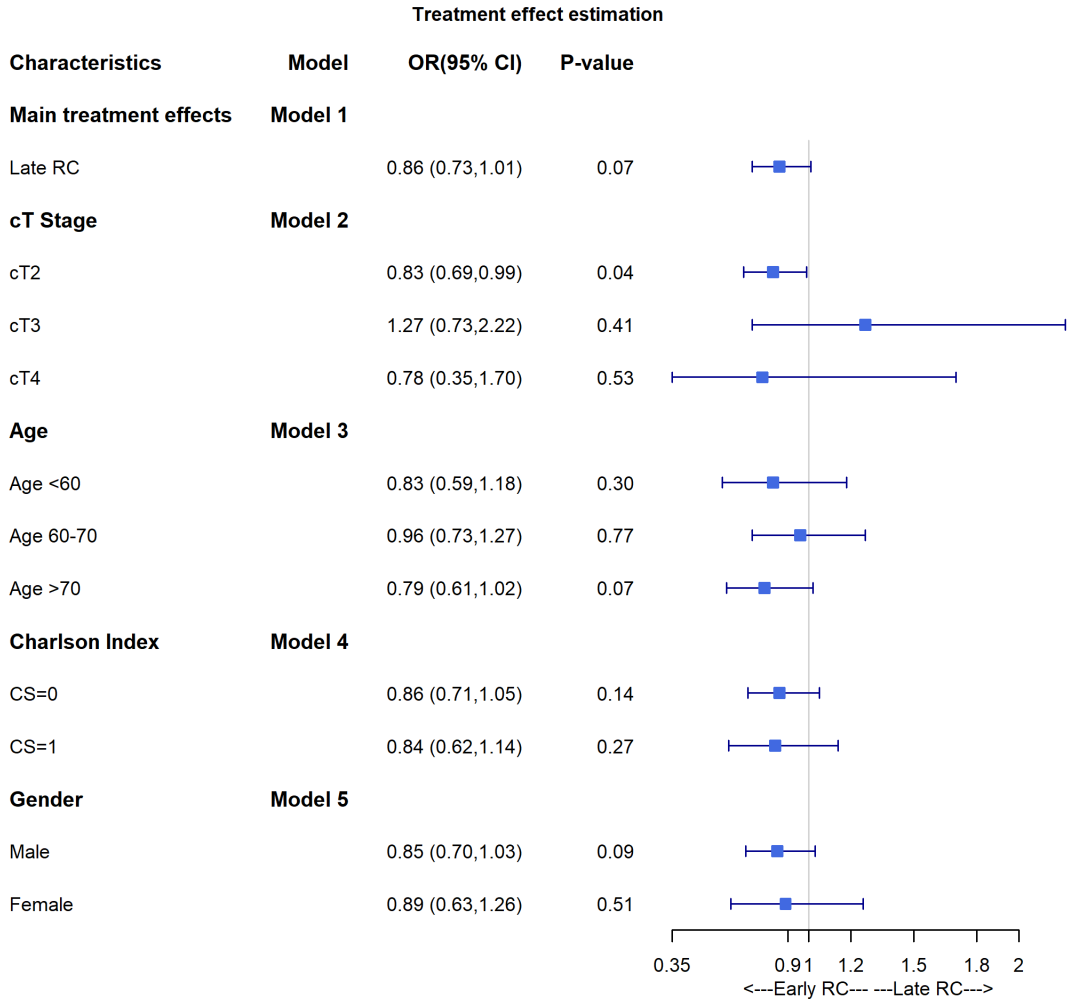

Figure 2. Adjusted overall survival stratified by early vs. late RC in the survival (landmark time) analysis cohort (sIPW-adjusted).

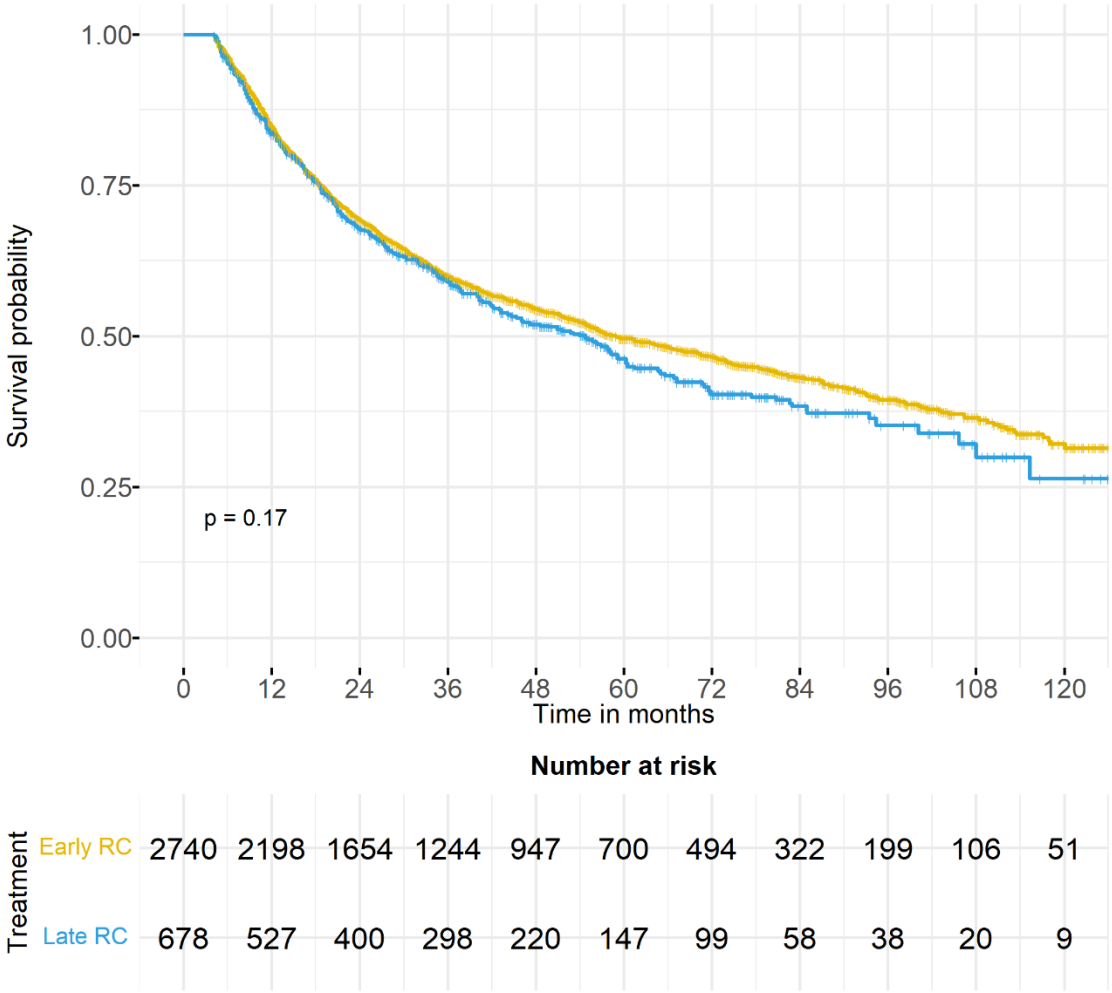

Figure 3. Forest plot of adjusted associations of late RC with overall survival across selected baseline characteristics in the survival (landmark time) analysis cohort. CI: confidence interval; HR: hazard ratio.

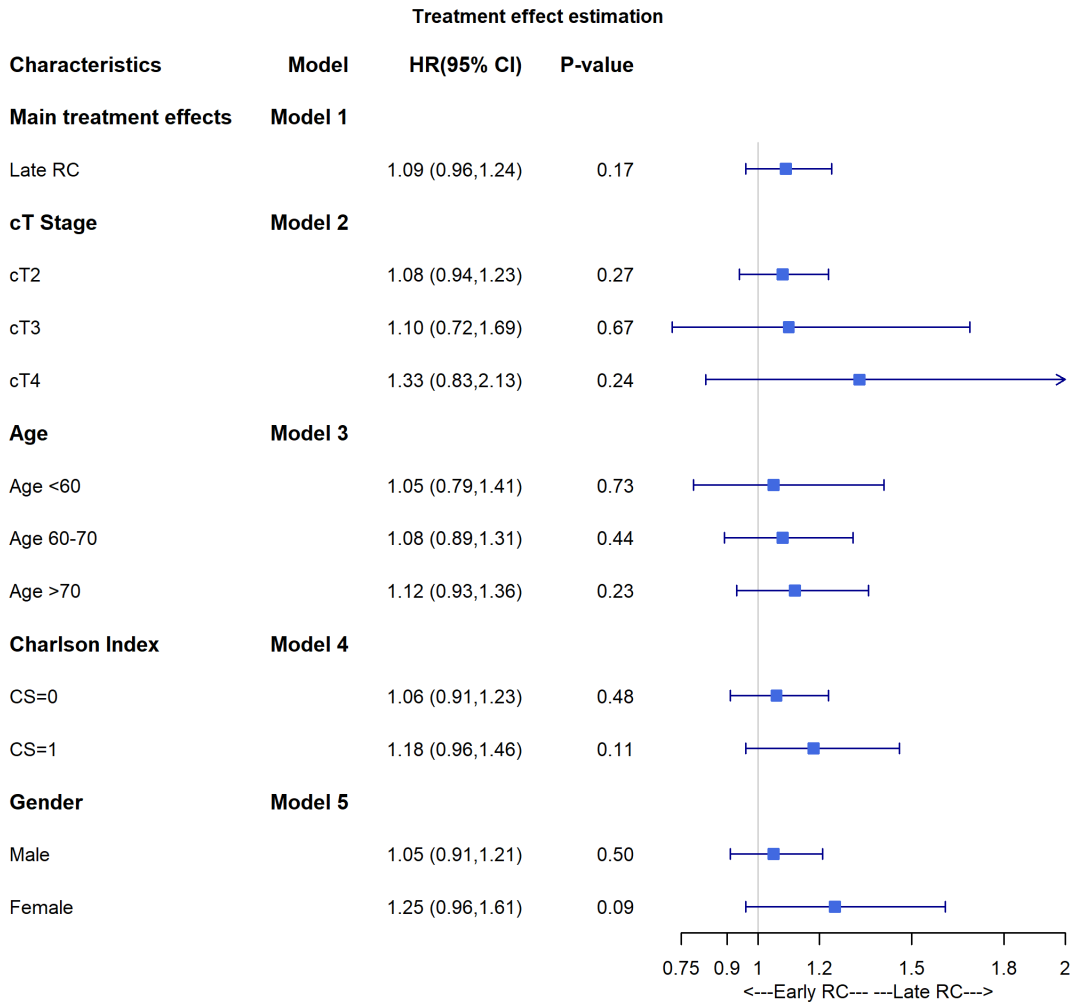

Figure 4. Adjusted overall survival stratified by early vs. late RC in the survival (landmark time) analysis cohort, sensitivity analysis truncating follow-up at 5-years (sIPW-adjusted).

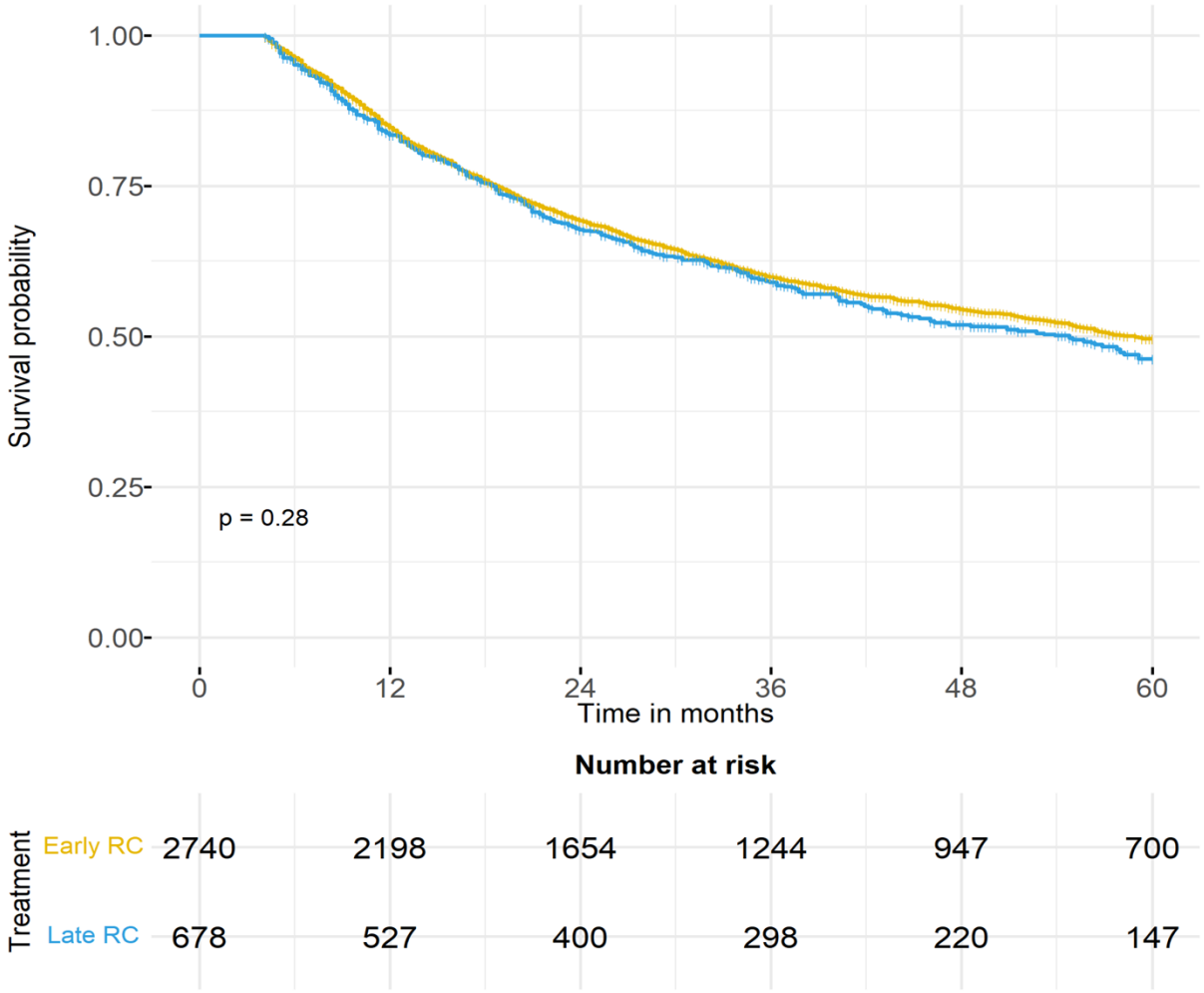

Figure 5. Forest plot of adjusted associations of late RC with overall survival across selected baseline characteristics in the survival (landmark time) analysis cohort, sensitivity analysis truncating followup at 5 years. CI: confidence interval; HR: hazard ratio.

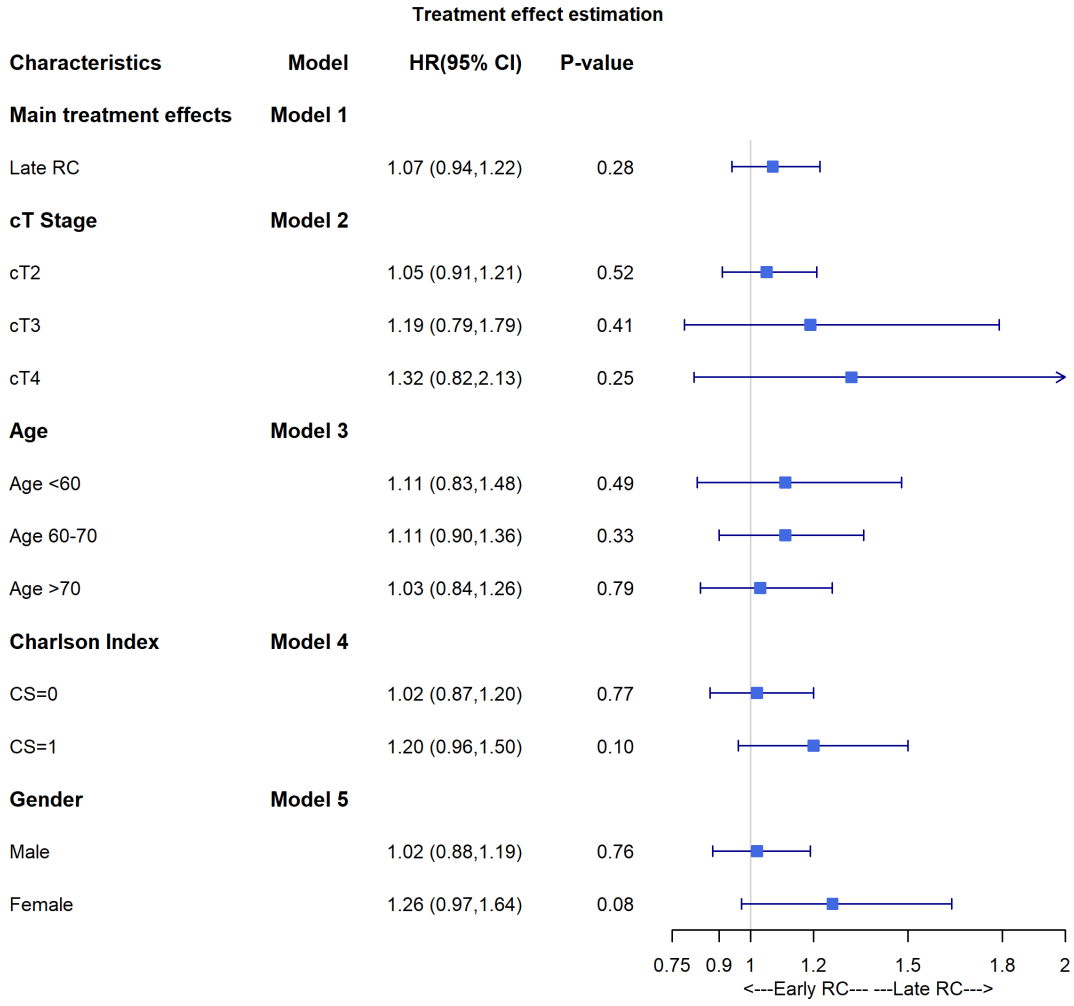

Figure 6. Adjusted association of time from diagnosis to RC, flexibly modeled using restricted cubic splines with 3 knots, and pathologic upstaging at RC.

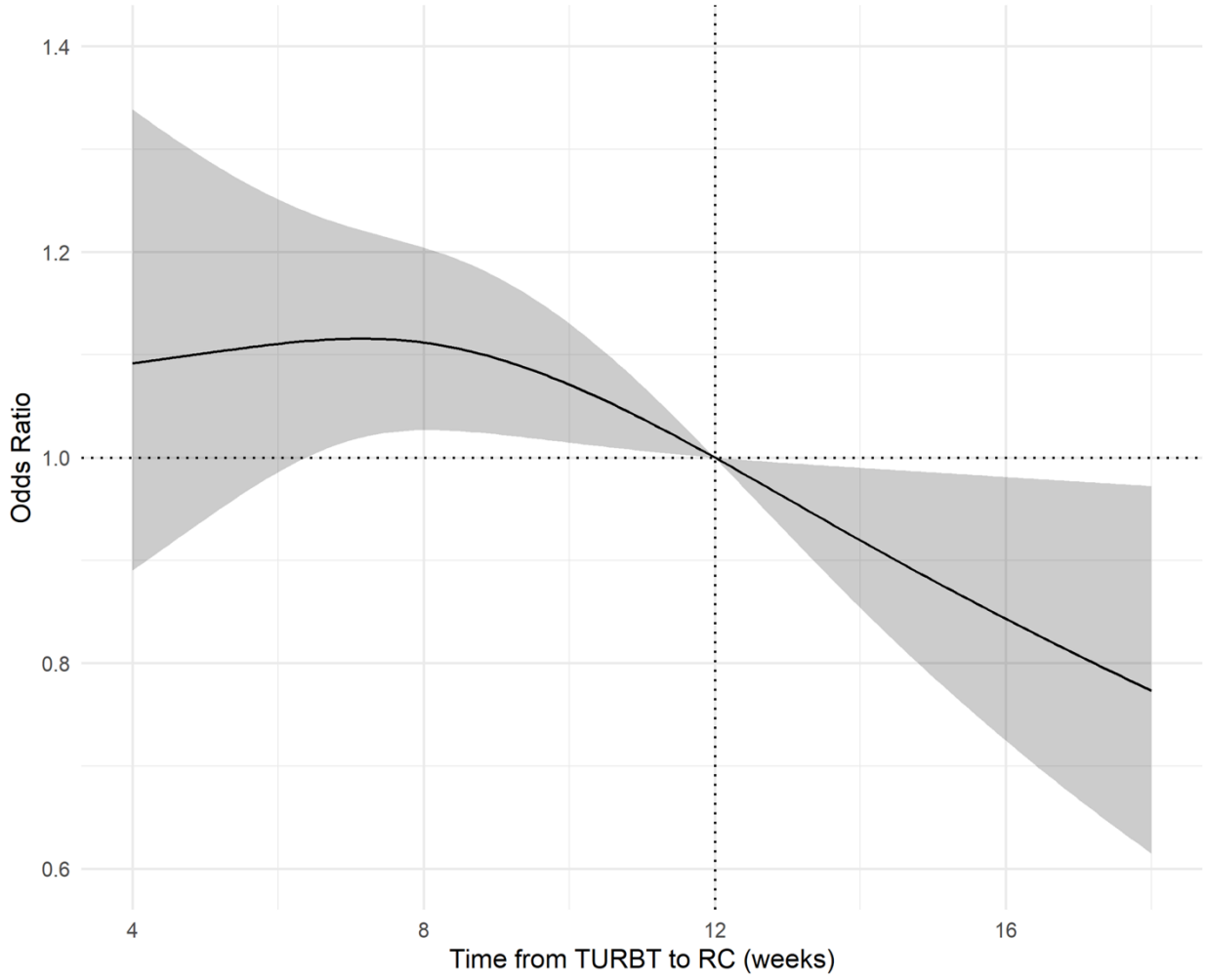

Figure 7. Adjusted association of time from diagnosis to RC, flexibly modeled using restricted cubic splines with 3 knots, and all-cause mortality.