ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 572.e21−572.e28

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

The impact of pathologic response to neoadjuvant chemotherapy on conditional survival among patients with muscle-invasive bladder cancer

Nikhil Waingankar, M.D., M.S.H.P.*, Rachel Jia, Ph.D., Kathryn E. Marqueen, B.A., Francois Audenet, M.D., John P. Sfakianos, M.D., Reza Mehrazin, M.D., Bart S. Ferket, M.D., Ph.D., Madhu Mazumdar, Ph.D., Matthew D. Galsky, M.D.

Icahn School of Medicine, The Mount Sinai Hospital, New York, NY

Received 3 January 2019; received in revised form 19 April 2019; accepted 22 April 2019

Abstract

Purpose: Achieving a pathologic complete response (pCR) with neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (MIBC) is associated with a favorable prognosis. Patients with pathologic residual disease (pRD) generally have poor outcomes. However, prognosis after radical cystectomy (RC) improves with ongoing survivorship. Our objective was to determine whether the difference in prognosis of patients with pCR and pRD changes over time.

Materials and Methods: We queried the National Cancer Database for patients who received NAC and RC for localized MIBC (cT2-T4aN0M0) between 1998 and 2012. pCR was defined as ≤Tis disease. Kaplan-Meier analysis was used to estimate conditional survival to 5 years given survival to 1, 2, 3, and 4 years post-RC. Cox proportional hazard modeling was used to estimate the effect of pRD vs. pCR on overall survival.

Results: The cohort comprised 1,553 patients (pCR: 314 and pRD: 1,239). With median follow-up 2.65 years (range 0.01−9.97), median survival was 2.5 years (95% confidence interval 2.2−2.9) and not reached for pRD and pCR, respectively. All patients had improved conditional survival with each additional year of survivorship. Patients with pCR had improved overall survival relative to those with pRD. The effect of pRD vs. pCR on conditional survival did not differ over time ($P = 0.7$).

Conclusions: MIBC patients with pCR after NAC have improved conditional survival relative to those with pRD post-RC. This survival advantage does not significantly change over time. These findings may inform patient counseling, surveillance intensity, and novel adjuvant approaches for patients with pRD.

Keywords: Bladder cancer; Complete response; Conditional survival; Cystectomy; Neoadjuvant chemotherapy

1. Introduction

The inverse association between stage and survival among patients with muscle-invasive bladder cancer (MIBC) is well established, with published 5-year survival rates of 63%, 46%, and 15% for patients with Stage II, III, and IV disease, respectively [1]. While the gold standard treatment of MIBC is radical cystectomy (RC), level 1 evidence supports the use of neoadjuvant chemotherapy (NAC) [2], which is associated with a survival benefit [3]. Therefore, optimal management of MIBC requires a multidisciplinary approach [4].

Several studies have demonstrated that patients achieving a pathologic complete response (pCR) after NAC experience improved survival compared with patients with evidence of pathologic residual disease (pRD) in their RC specimen. For example, in the Southwest Oncology Group 8710 trial which compared 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by RC vs. RC alone, median survival was not reached 14 years after randomization among patients with pCR while those

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Corresponding author. Tel.: 718-808-7777/347-924-5351; fax: 718-808-7758.

E-mail address: nikhil.waingankar@mountsinai.org (N. Waingankar).

https://doi.org/10.1016/j.urolonc.2019.04.027

1078-1439/

with pRD had a median survival of 3.8 years [3]. While such findings have provided further support for the utility of NAC, and have led to the use of pCR rate as an intermediate end point in neoadjuvant clinical trials exploring novel regimens, the role of pathologic response information in counseling and management of individual patients remains poorly defined. Patients achieving a pCR currently proceed with post-RC surveillance in a manner identical to patients with pRD. Further, because the prognosis of patients with MIBC improves with longer survival post-RC, whether the survival benefit associated with a pCR diminishes with longer follow-up has not been established.

Conditional survival is an analytic technique that estimates a patient's probability of further survival given that the patient has already survived for a given duration post-diagnosis or treatment. We sought to determine the impact of pathologic response to NAC on conditional survival post-RC for MIBC.

2. Materials and methods

2.1. Analytic cohort

The National Cancer Database (NCDB) is a project of the American College of Surgeons and the American Cancer Society that prospectively collects cancer data from more than 1,500 Commission on Cancer facilities representing an estimated 70% of incident cancer cases in the United States [5]. We queried the NCDB for patients diagnosed with MIBC who underwent treatment with NAC and RC. Our starting dataset included 603,298 patients diagnosed with bladder cancer between 1998 and 2012 in NCDB. We included only patients with urothelial histology (International Classification of Disease-O-3 morphologic codes 8120, 8130; $n = 565{,}548$), and those with clinical T2 to T4 disease ($n = 60{,}299$). We excluded patients without multiagent NAC within 6 months prior to definitive surgery ($n = 2{,}522$), those who underwent surgery more than 1 year after diagnosis ($n = 2{,}431$), and those who had radiation or palliative surgery ($n = 2{,}322$). Finally, we excluded those with missing survival data ($n = 1{,}825$) and those with undefined pathological status ($n = 1{,}553$) (Fig. 1).

2.2. Patient-, tumor-, and system-level variables

Patient-level covariates of interest included age, gender, race (white, black, and other), insurance status (uninsured, private insurance, Medicare, Medicaid, and other government), median income, level of education, Charlson comorbidity score, clinical T stage, distance to treatment center, and year of diagnosis. Hospital-level covariates of interest included facility type (community, comprehensive community, academic, and integrated network), geographic location (New England, Mid-Atlantic, South Atlantic, East and West North Central, East and West South Central, Mountain, and Pacific), rural/urban classification (rural, urban, and metro), and annual RC volume group (<5, 5−14, ≥15). pCR was defined as a pathologic stage of Ta, Tis, or T0 and N0. All patients with ≥ pT1 disease and/or ≥pN1 were defined as harboring residual disease (pRD).

2.3. Statistical analyses

Baseline patient characteristics were compared between pCR and pRD cohorts using chi-square test for categorical variables and Wilcoxon test for continuous variables. Overall survival (OS) was calculated from the time of RC and survival in the pCR and pRD cohorts was estimated using the Kaplan-Meier method. Patients still alive were censored at the date of last follow-up.

Conditional survival was defined as the probability of surviving up to 5 years given survival of 1, 2, 3, and 4 years after RC, and was estimated using landmark analyses in each subcohort who have lived up to the landmark time points, with confidence intervals estimated using the Greenwood formula. A Cox proportional hazard model was used to estimate the average effect of pRD vs. pCR on survival from the time of RC, and the proportional hazard assumption was tested using a Schoenfeld residual test. In addition, a flexible Cox model with time-varying covariate was used to estimate the interval-specific hazard ratio (HR) of pRD vs. pCR at 0-1, 1-2, 2-3, 3-4, and beyond 4 years. Those variables with $P < 0.1$ in univariable testing were included in multivariable analyses. The advantage of the flexible model is to utilize all data to jointly estimate the effects of pRD vs. pCR on conditional survival updated from each landmark time point. Goodness of fit of the flexible model was assessed against the average effect model through the likelihood ratio test [6−9].

3. Results

Our final cohort included 1,553 patients, of whom 314 had pCR and 1,239 had pRD. The median follow-up duration for the entire cohort was 2.65 (0.01−9.97) years, and 2.38 (0.04−9.60) and 2.76 (0.01−9.97) years for pCR and pRD patients, respectively. Relative to patients with pRD, those with pCR more frequently had lower clinical T stage (cT2: 79.0% vs. 71.9%; cT3: 14.3% vs. 18.4%; cT4: 6.7% vs. 9.7%; $P = 0.04$), more recent year of diagnosis (2010: 30.6% vs. 18.8%, $P < 0.001$), and management at an academic (71.6% vs. 59.2%, $P < 0.001$) or high-volume RC facility (>15 cases per year: 61.1% vs. 48.7%, $P < 0.001$). Complete univariable comparisons of patients with pCR vs. those with pRD are shown in Table 1.

Table 2 details the conditional probability of survival to annual time points up to 5 years following NAC and RC given a specified duration of survival time has already passed. For example, if a patient achieves a pCR at RC (time zero), the initial survival estimates are 95%, 91%, 86%, 83%, and 80% at years 1, 2, 3, 4, and 5, respectively. If this patient survives to follow-up at year 1, the

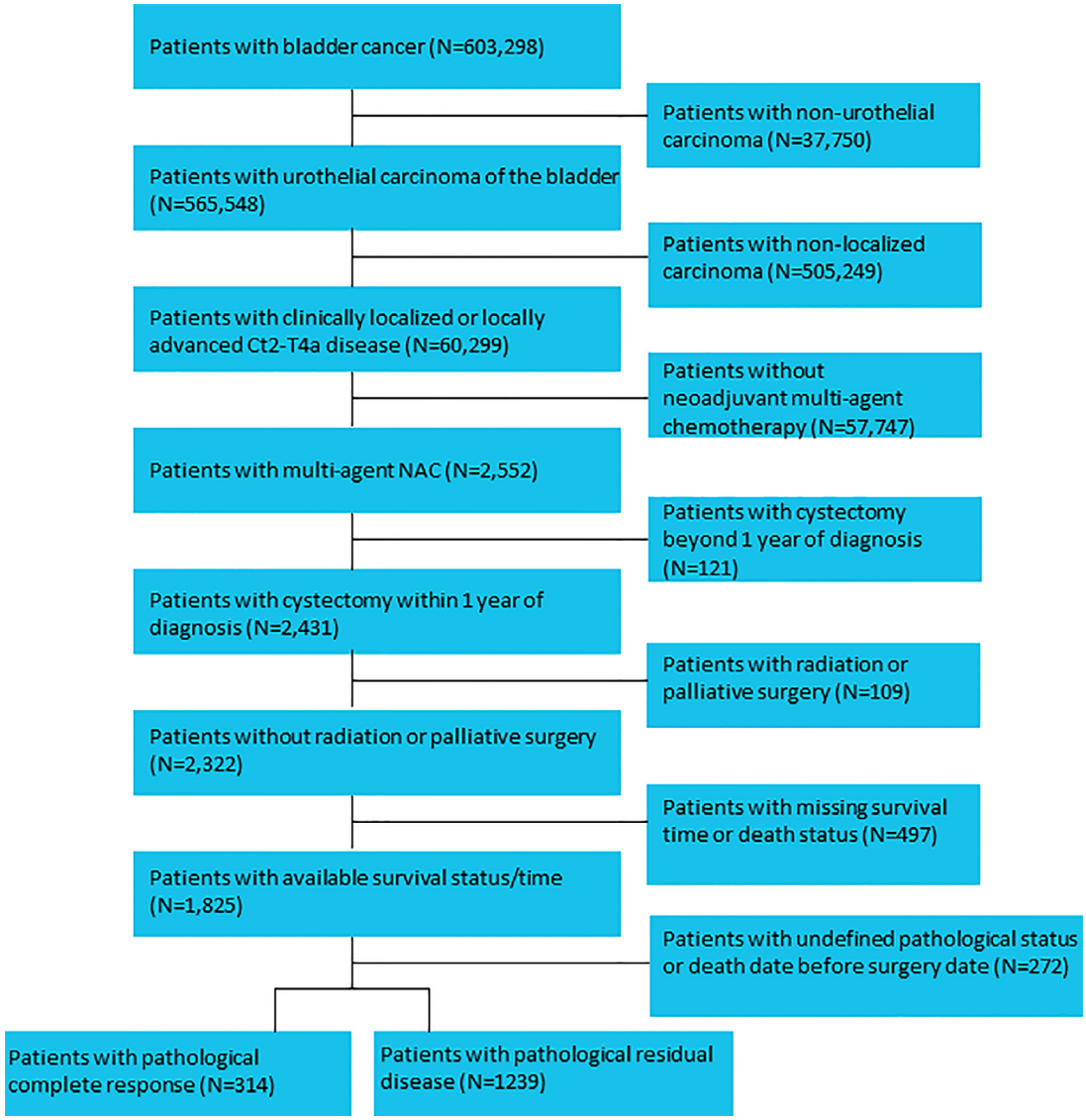

Fig. 1. Number of patients after application of inclusion and exclusion criteria.

conditional survival probabilities improve to 96%, 90%, 88%, and 84% at years 2, 3, 4, and 5, respectively. Continued survival to year 2 after a pCR further improves the conditional survival estimates to 95%, 92%, and 88% at years 3, 4, and 5, respectively, and so on. Conditional survival probabilities similarly improve over duration of given survival for patients with pRD. For example, the initial probability of survival to year 5 following NAC and RC in a patient with pRD is 36%. However, if the same patient survives to year 2, this probability improves to 66%. For patients with pRD, considerable improvements in dynamic survival probabilities are noted for those who survive despite harboring loco-regionally advanced disease (pT3, pT4, and ≥N1; Supplemental Figures 1 and 2).

Figs. 2 through 6 demonstrate the comparison of initial survival estimates and survival probabilities conditional upon annual survival up to 4 years post-RC for patients with pCR and pRD. Patients with pCR have a significantly higher initial probability of survival in year 0 ($P < 0.001$, Fig. 2); this effect of response to NAC is sustained conditional upon survival to year 1 ($P < 0.001$, Fig. 3), year 2 ($P < 0.001$, Fig. 4), and year 3 ($P = 0.02$, Fig. 5). While point estimates for differential survival appear to converge thereafter (Fig. 6), further analysis into the relative impact of response to NAC on conditional survival with a flexible Cox model indicates that the effect of pCR is sustained. The adjusted HRs for pRD relative to pCR at the post-treatment intervals of year 0-1, year 1-2, year 2-3, year 3-4, and year 4+ are 5.31 (95% confidence interval 3.19−8.84), 5.80 (3.10−10.88), 3.33 (1.61−6.86), 3.89 (0.91−16.62), and 2.02 (0.79−5.21), respectively. The average HR over time is 4.56 (3.34−6.26) (Table 3); the likelihood ratio test of the interval-specific HR model against the average HR model yields $P = 0.7$, indicating the effect of pRD vs. pCR on survival and conditional survival does not differ significantly over time.

Table 1
Patient, tumor and facility-level characteristics

Factor	Complete response (n = 314)	Residual disease (n = 1,239)
Age	Median 65 (29–86)	Median 66 (31–90)
Gender		
Male	239 (76.1%)	930 (74.2%)
Female	75 (23.9%)	320 (25.8%)
Race		
White	288 (91.7%)	1129 (91.0%)
Black	15 (4.8%)	74 (6.0%)
Other	5 (1.6%))	27 (2.2%)
Missing	6 (1.9%)	10 (0.8%)
Insurance status		
Not insured	8 (2.5%)	35 (2.8%)
Private insurance	151 (48.1%)	468 (37.7%)
Medicaid	11 (3.5%)	68 (5.5%)
Medicare	141 (44.9%)	630 (50.8%)
Other government	1 (0.3%)	12 (1.0%)
Missing	2 (0.6%)	27 (2.2%)
Median household income		
<$30,000	26 (8.3%)	121 (9.8%)
$30,000–$34,999	37 (11.8%)	212 (17.1%)
$35,000–$45,999	78 (24.8%)	325 (26.2%)
>$46,000	158 (50.3%)	521 (42.0%)
Missing	15 (4.8%)	61 (4.9%)
Education		
29% or more	25 (8.0%)	136 (11.0%)
20–28.9%	51 (16.2%)	271 (21.9%)
14–19.9%	88 (28.0%)	299 (24.1%)
Less than 14%	135 (43.0%)	473 (38.1%)
Missing	15 (4.8%)	61 (4.9%)
Charlson/Deyo score		
0	238 (75.8%)	942 (76.0%)
1	63 (20.1%)	243 (19.6%)
≥2	13 (4.1%)	55 (4.4%)
Clinical T stage		
cT2	248 (79.0%)	892 (71.9%)
cT3	45 (14.3%)	228 (18.4%)
cT4	21 (6.7%)	120 (9.7%)
Year of diagnosis		
2002	5 (1.6%)	36 (2.9%)
2003	3 (1.0%)	53 (4.3%)
2004	12 (3.8%)	45 (3.6%)
2005	6 (1.9%)	67 (5.4%)
2006	23 (7.3%)	107 (8.6%)
2007	43 (13.7%)	191 (15.4%)
2008	59 (18.8%)	271 (21.9%)
2009	67 (21.3%)	237 (19.1%)
2010	96 (30.6%)	233 (18.8%)
Facility type		
Community	10 (3.2%)	81 (6.5%)
Comprehensive community	77 (24.5%)	419 (33.8%)
Academic	225 (71.6%)	734 (59.2%)
Integrated network	2 (0.6%)	6 (0.5%)
Other		
Facility location		
New England	12 (3.8%)	96 (7.7%)
Middle Atlantic	80 (25.4%)	159 (12.8%)
South Atlantic	54 (17.2%)	309 (24.9%)
East North Central	68 (21.7%)	272 (21.9%)
East South Central	13 (4.1%)	69 (5.6%)
West North Central	30 (9.6%)	112 (9.0%)
West South Central	17 (5.4%)	50 (4.0%)
Mountain	10 (3.2%)	56 (4.5%)
Pacific	30 (9.6%)	117 (9.4%)
Rural/urban		
Metro	7 (2.2%)	29 (2.3%)
Urban	52 (16.6%)	213 (17.1%)
Rural	241 (76.8%)	935 (75.4%)
Missing	14 (4.5%)	63 (5.1%)
Distance		
Median (IQR)	21.4 (8.5–49.1)	18.9 (7.3–48.4)
Missing	7 (2%)	36 (3%)
Facility cystectomy volume		
Median (IQR)	23 (8–41.75)	14 (4.75–33)
<5	10 (12.7)	308 (25.5%)
5–14	82 (26.1%)	324 (26.3%)
≥15	192 (61.1%)	600 (48.7%)
Missing	8 (3%)	0 (0%)

(*continued*)

Table 1 (***Continued***)

4. Discussion

Prognosis after cancer treatment is dynamic rather than static. Patients with MIBC post-RC often request updated prognostic information during the course of follow-up, wanting to know if they are "out of the woods." Therefore, the survival of patients conditional on the duration of follow-up post-RC may provide valuable information for patient counseling and follow-up.

Our study describes, to our knowledge, the first analysis of conditional survival in patients with MIBC treated with NAC followed by RC seeking to reconcile the impact of pCR with the "test of time." Strikingly, we did not find a statistically significant change in survival benefit over time among patients achieving a pCR vs. those with pRD despite survival to 1 to 4 years post-RC. Nonetheless, the relative gains in conditional survival were much more dramatic in patients with pRD vs. pCR; for example, patients achieving a pCR had improvements in 5-year survival by 8% and 13% given survival to years 2 and 3, respectively, compared with 5-year survival improvements of 30% and 44% in patients with pRD who survive to years 2 and 3, respectively.

The practical utility of our analysis extends beyond patient counseling and prognostic updating, and has potential benefit of informing a more tailored post-treatment surveillance strategy. Bladder cancer remains one of the costliest diseases to manage, with a lifetime cost per patient up to $187,000 dollars (2001 figures) from diagnosis to death [10]. Surveillance and treatment of recurrence accounts for up to 60% of the total cost [11]. Currently, patients' post-NAC and RC proceed with identical surveillance regimens typically including frequent cross sectional imaging. This is not only associated with a financial burden, but could also be associated with hidden risks in patients at low risk for bladder-cancer associated mortality, including

Table 2
Conditional probability of surviving a certain number of years from the time of cystectomy

		Probability of surviving to certain no. of years from surgery (95% CI)				
		1	2	3	4	5
Complete response ($N = 314$)						
No. of year from surgery	No. at risk (death)					
0	314 (41)	95% (92–97%)	91% (87–94%)	86% (81–90%)	83% (78–89%)	80% (73–87%)
1	261 (25)		96% (93–98%)	90% (86–95%)	88% (83–93%)	84% (77–92%)
2	176 (15)			95% (91–985)	92% (87–97%)	88% (81–95%)
3	114 (7)				97% (94–100%)	93% (87–100%)
4	67 (5)					96% (90–100%)
Residual disease ($n = 1,239$)						
0	1,239 (647)	74% (71–76%)	55% (53–58%)	46% (43–49%)	42% (39–45%)	36% (33–40%)
1	848 (332)		75% (72–78%)	62% (58–66%)	57% (53–61%)	49% (45–54%)
2	534 (136)			82% (79–86%)	76% (71–80%)	66% (60–71%)
3	323 (54)				92% (89–95%)	80% (74–86%)
4	192 (32)					87% (81–92%)

radiation exposure and potential morbidity associated with false positive results [12]. Our findings raise the hypothesis that a risk-adapted approach to post-RC surveillance may be more attractive than the current approach. However, additional studies are required to determine the impact of response to NAC on conditional recurrence-free survival along with cost-effectiveness analyses to further develop a potential risk-adapted surveillance strategy.

Our findings are also important in the context of current and planned trials exploring novel strategies for patients with pRD after NAC. At least 3 international randomized trials are enrolling such patients to treatment with PD-1/PD-L1 blockade vs. placebo/observation and additional trials are planned. Understanding in detail both outcomes and event rates in such patients is critical to generating assumptions and sample size calculations in this setting.

At a superficial level, our study identified similar fundamental concepts to the previous works on conditional survival of patients with MIBC: the risk of death is highest during the initial surveillance period following treatment, and baseline estimates of prognosis can be refined with extended durations of survival post-RC. For example, in a study by Sun et al. utilizing data from 5,000 patients abstracted from SEER-Medicare, estimated 5-year cancer-specific survival (CSS) improvements of 13.6% and 17.8% were observed given survivorship to years 2 and 3 post-RC,

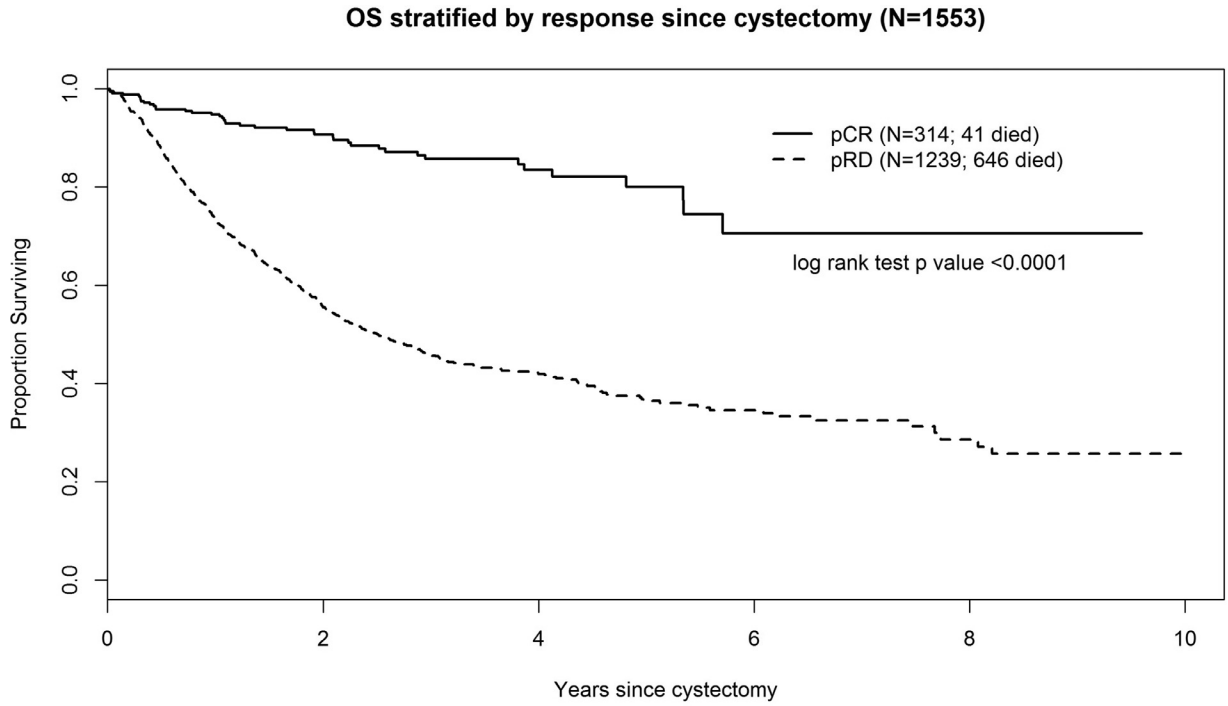

Fig. 2. Overall survival following cystectomy stratified by response to chemotherapy: baseline estimates.

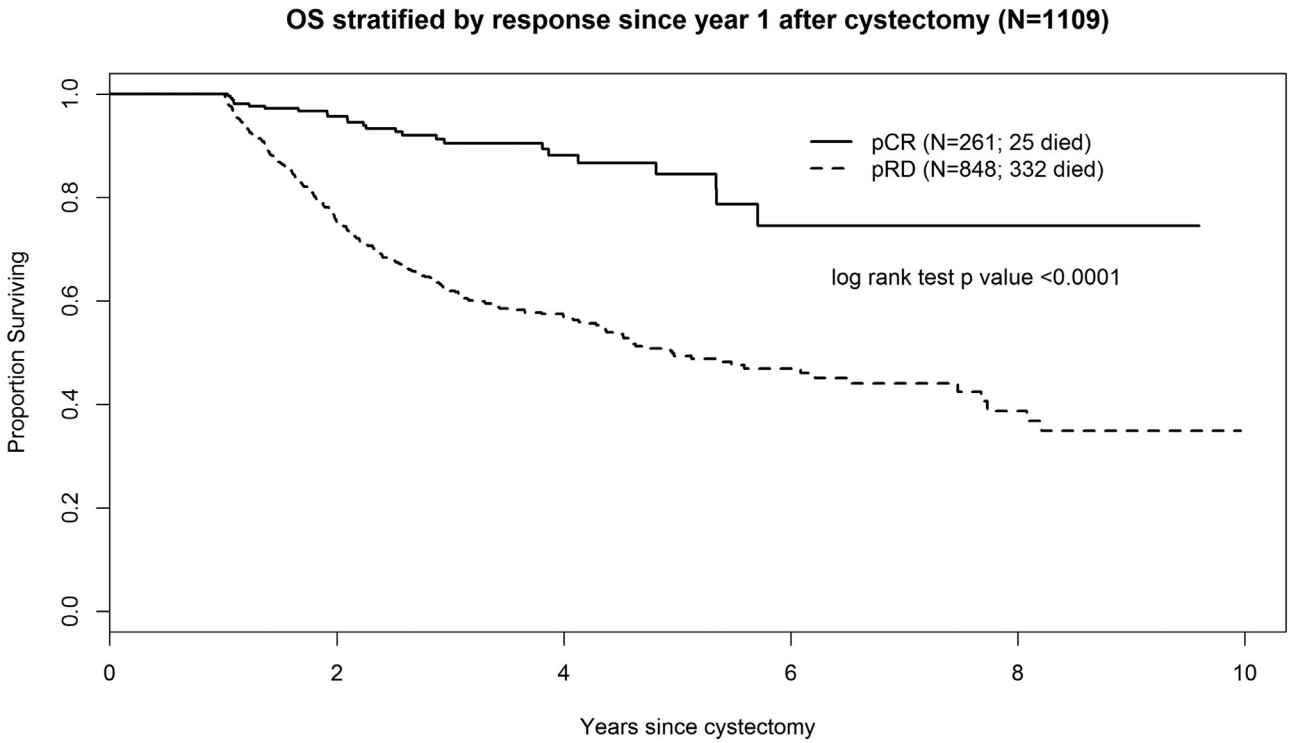

Fig. 3. Overall survival following cystectomy stratified by response to chemotherapy, conditional upon survival to 1 year.

respectively. Survival gains conditional upon survival to 2 years were most notable among those with pT2 to pT4 disease [13]. Ploussard et al. described similar findings for both CSS and OS in their study analyzing data from over 8,000 MIBC patients treated with RC at 15 institutions. With survival to 2 years post-RC, CSS improved by 15.9% from a baseline estimate of 67.7% while OS improved by 14.4% from a baseline estimate of 57.5%. These condi-

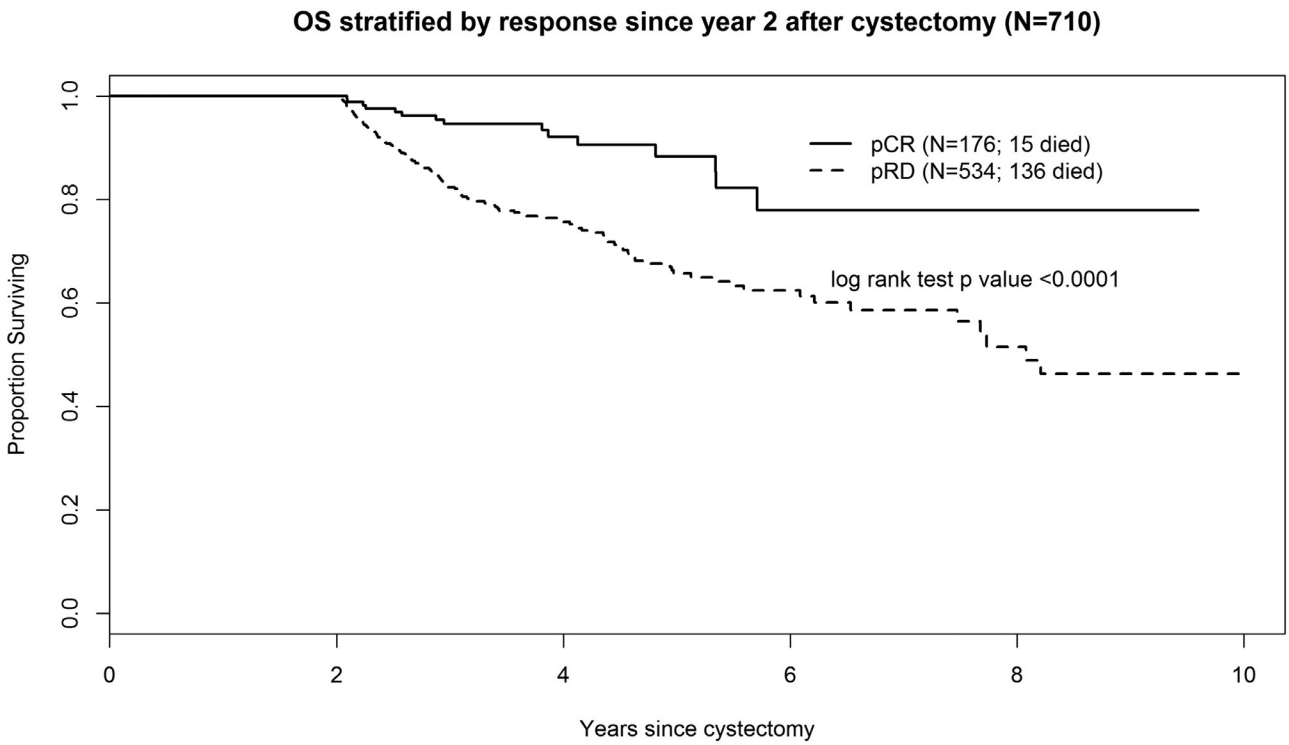

Fig. 4. Overall survival following cystectomy stratified by response to chemotherapy, conditional upon survival to 2 years.

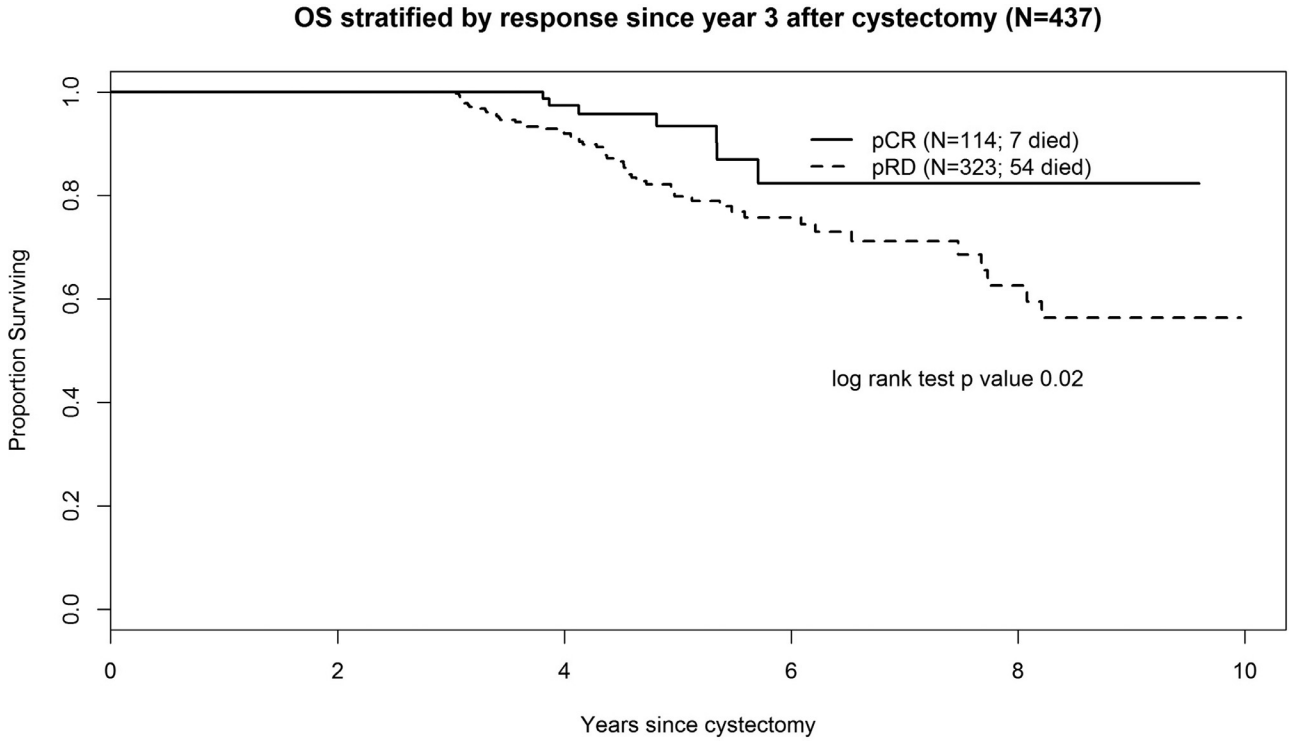

Fig. 5. Overall survival following cystectomy stratified by response to chemotherapy, conditional upon survival to 3 years.

tional survival estimates were most striking for those with positive lymph nodes, higher stage of disease, and positive margins [14,15]. Our study adds to this fund of knowledge by identifying that this similarly holds true for patients with pRD after NAC and RC, regardless of T and N stage, while those with pCR maintain a survival advantage over time.

Limitations of our study are those commonly encountered in large, registry datasets. First, data granularity can

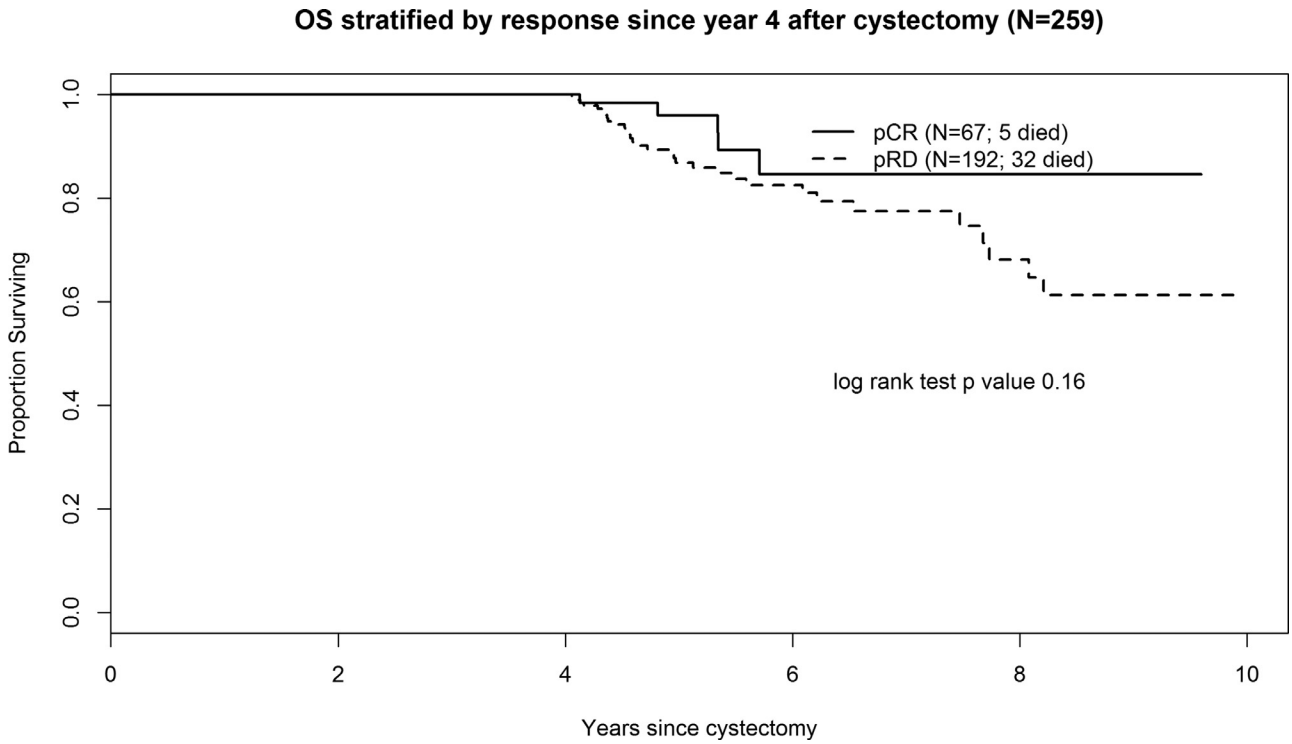

Fig. 6. Overall survival following cystectomy stratified by response to chemotherapy, conditional upon survival to 4 years.

Table 3
Covariate adjusted analysis of pRD vs. pCR on conditional survival since each landmark time point

Interval specific HR	HR*	95% CI
Year 0–1	5.31	(3.19, 8.84)
Year 1–2	5.80	(3.10, 10.88)
Year 2–3	3.33	(1.61, 6.86)
Year 3–4	3.89	(0.91, 16.62)
Beyond year 4	2.02	(0.79, 5.21)
Average HR	4.56	(3.34, 6.26)

* Adjusted for variables with $P < 0.1$ in univariable analysis including: clinical T stage, insurance type, Charlson-Deyo score and facility type. 29 (1.8%) records were removed due to missing values.

be problematic, and includes an inability to risk-adjust models beyond the ternary Charlson scoring system used in NCDB. This, combined with an inability to calculate CSS, makes it impossible to identify any changes in competing risks of death relative to the dynamic conditional OS we identified. Second, some patients may have achieved a pCR with TUR alone – identification of the relative impact of transurethral resection (TUR) and NAC on pCR is not possible in this dataset. Third, we did not adjust for data clustering on the facility level (i.e., patients from the same facility may be more similar than those from a different facility); while this is an increasingly common practice in NCDB analyses, we elected to forego adjustment for clustering in our work as it can decrease the independent sample size and inflate *P* values [16]. Finally, the proportion of MIBC patients receiving NAC is historically under 25% [17]; with the low rate of pCR (20% in our study), this yields a sparse subset of patients to follow over time for particular outcomes of interest, and attrition over follow-up time from this number yields an even smaller analytic cohort. Indeed, converging point estimates for pCR and pRD after year 3 may be a product of a low event rate within a small denominator of patients. This is also reflected in the wide confidence intervals at later time points in our analysis, and conclusions must be tempered accordingly.

5. Conclusions

Prognoses for patients with MIBC improve with ongoing survivorship, both for patients with pCR and pRD following NAC and RC. Patients with pCR have a conditional survival advantage over those with pRD, and we found no statistical evidence that this difference changes over time. This analysis can impact ongoing patient counseling, facilitate the design of trials enrolling patients with pRD after NAC, and may set the stage for a risk-adapted approach to post NAC + RC surveillance.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.027.

References

[1] Howlader N., Noone A.M., Krapcho M., et al. (eds).: SEER cancer statistics review, 1975–2012. National Cancer Institute. Bethesda, MD.
[2] Clark PE, Spiess PE, Agarwal N, et al. NCCN guidelines insights: bladder cancer, version 2.2016. J Natl Compr Canc Netw 2016;14:1213–24.
[3] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
[4] Alva AS, Tallman CT, He C, et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: a multidisciplinary approach. Cancer 2012;118:44–53.
[5] Lerro CC, Robbins AS, Phillips JL, et al. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. Ann Surg Oncol 2013;20:1759–65.
[6] Steyerberg EW. Clinical prediction models. Springer; 2012.
[7] Klein JP, Moeschberger ML. Survival analysis techniques for censored and truncated data. Springer; 2010.
[8] Harrell FE Jr. Regression Modelling Strategies, with applications to linear models, logistic regression, and survival analysis. Springer; 2001.
[9] Putter H, Houwelingen HCV. Understanding landmarking and its relation with time-dependent Cox regression. Stat Biosci 2017;9 (2):489–503.
[10] Botteman MF, Pashos CL, Redaelli A, et al. The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics 2003;21:1315–30.
[11] Avritscher EB, Cooksley CD, Grossman HB, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology 2006;68:549–53.
[12] Spiess PE, Agarwal N, Bangs R, et al. Bladder cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:1240–67.
[13] Sun M, Abdollah F, Bianchi M, et al. Conditional survival of patients with urothelial carcinoma of the urinary bladder treated with radical cystectomy. Eur J Cancer 2012;48:1503–11.
[14] Gandaglia G, Sun M. Bladder cancer: Conditional survival after radical cystectomy. Nat Rev Urol 2014;11:8–9.
[15] Ploussard G, Shariat SF, Dragomir A, et al. Conditional survival after radical cystectomy for bladder cancer: evidence for a patient changing risk profile over time. Eur Urol 2014;66:361–70.
[16] Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Wiley; 2004.
[17] Reardon ZD, Patel SG, Zaid HB, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol 2015;67: 165–70.