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Bladder Cancer

Conditional Survival After Radical Cystectomy for Bladder Cancer: Evidence for a Patient Changing Risk Profile over Time

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Abstract

Background: Standard survival statistics do not take into consideration the changes in the weight of individual variables at subsequent times after the diagnosis and initial treatment of bladder cancer.
Objective: To assess the changes in 5-yr conditional survival (CS) rates after radical cystectomy for bladder cancer and to determine how well-established prognostic factors evolve over time.
Design, setting, and participants: We analyzed data from 8141 patients treated with radical cystectomy at 15 international academic centers between 1979 and 2012.
Interventions: Radical cystectomy and pelvic lymph node dissection.
Outcome measurements and statistical analysis: Conditional cancer-specific survival (CSS) and overall survival (OS) estimates were calculated using the Kaplan-Meier method. The multivariable Cox regression model was used to calculate proportional hazard ratios for the prediction of mortality after stratification by clinical characteristics (age, perioperative chemotherapy status) and pathologic characteristics (pT stage, grade, lymphovascular invasion, pN stage, number of nodes removed, margin status). The median follow-up was 32 mo.
Results and limitations: The 5-yr CSS and OS rates were 67.7% and 57.5%, respectively. Given a 1-, 2-, 3-, 5- and 10-yr survivorship, the 5-yr conditional OS rates improved by +5.6 (60.7%), +8.4 (65.8%), +7.6 (70.8%), +3.0 (72.9%), and +1.9% (74.3%), respectively. The 5-yr conditional CSS rates improved by +5.6 (71.5%), +9.8 (78.5%), +7.9 (84.7%), +7.2 (90.8%), and 5.6% (95.9%), respectively. The 5- and 10-yr CS improvement was

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primarily noted among surviving patients with advanced stage disease. The impact of pathologic parameters on CS estimates decreased over time for both CSS and OS. Findings were confirmed on multivariable analyses. The main limitation was the retrospective design.

Conclusions: CS analysis demonstrates that the patient risk profile changes over time. The risk of mortality decreases with increasing survivorship. The CS rates improve mainly in the case of advanced stage disease. The impact of prognostic pathologic features decreases over time and can disappear for long-term CS.

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1. Introduction

The management of muscle-invasive bladder cancer is based on radical cystectomy (RC) with pelvic lymph node dissection [1]. Nevertheless, even after RC, 5-yr overall survival rates were estimated at only 60% in recent series [2–4]. Five-year relative survival statistics are often used to measure cancer control and to assess international comparisons. Efforts have been made to better individualize patient prognosis [5,6]. Nevertheless, the probabilities of recurrence and death evolve over time given that these risks are higher in the first years of follow-up.

Cancer prognosis assessed at the time of surgical treatment provides a static view of risk without postoperative follow-up information and does not continue to define individual prognosis accurately and to take into account the changing impact of well-known prognostic factors over time. Conditional survival (CS), in contrast, is derived from the concept of conditional probability [7,8]. CS measures the probability that a cancer patient will survive some additional number of years, given that the patient has already survived for a certain number of years. CS analysis integrates patient survivorship and provides better estimates of survival probability at each follow-up time [9]. That might lead to more informative and individualized prognostic information and might be helpful in patient monitoring.

The usefulness of CS analysis was highlighted in large population-based or tumor-specific cohorts of oncology patients [10–15]. Few studies have investigated the relevance of CS in urologic malignancies, however [9,16–19]. Only one series previously assessed CS in RC patients, highlighting the improvement of cancer-specific survival (CSS) after the first 2 yr [9]. However, this series, which analyzed the Surveillance Epidemiology and End Results (SEER) database, had several noted limitations including the exclusion of patients <66 yr of age, the lack of overall survival (OS) analysis, and the risk of overestimation of CSS. Although it has been suggested that the impact of stage reduces and can disappear for long-term CS, this trend has not been thoroughly assessed in surgically treated bladder cancer [13].

The aim of the present study was to evaluate temporal changes in 5-yr CS in a large multicenter cohort and to determine how the predictive value of well-known prognostic factors at the time of RC evolves over time.

2. Materials and methods

2.1. Patient selection and data collection

This 15-center study was approved by the respective institutional review boards and included 8141 patients who underwent RC with bilateral lymph node dissection for bladder cancer between 1979 and 2012. All patients had pathologic documentation of urothelial carcinoma of the bladder, with no evidence of distant metastasis at the time of surgery. Data included clinical characteristics, pathologic features, perioperative chemotherapy status, oncologic follow-up, and death and its underlying cause. All surgical specimens were processed according to standard pathologic procedures. Tumor grade was assigned according to the 2004 World Health Organization grading system. Pathologic stage was reassigned according to the 2002 American Joint Committee on Cancer TNM staging system. Pelvic lymph node dissection was examined grossly, and all lymphoid tissue was submitted for histologic examination. The extent of dissection was at the surgeon's discretion. Positive soft tissue surgical margins were defined as the presence of tumor at inked areas of soft tissue on the RC specimen. Urethral and ureteral margins were not considered positive margins. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls. Cause of death was determined by treating physicians by chart review corroborated by death certificates or by death certificates alone.

2.2. Statistics

The estimation of survival probabilities was performed using the Kaplan-Meier method. CSS and overall survival (OS) were assessed. The CS was estimated using the multiplicative law of probability [20]. That is, the 5-yr CS represents the probability of surviving an additional 5 yr, given that the person has already survived x years (x = time elapsed since RC). For example, for a patient who is alive after 3-yr follow-up, the 5-yr CS rate is calculated by using the 8-yr survival rate divided by the 3-yr survival rate [9].

Patient survival was computed from the day of surgery until the most recent follow-up visit or until death. Variables significantly related to patient survival at Kaplan-Meier analysis were used for the 5-yr CS calculation. Survival rates were then compared with the log-rank test and used in the calculation of the 5-yr CS.

The multivariable Cox regression model was used to calculate proportional hazard ratios for the prediction of mortality after stratification by clinical (age, perioperative chemotherapy status) and pathologic characteristics (pT stage, grade, lymphovascular invasion, pN stage, number of nodes removed, margin status). All tests were two sided with a statistical significance limit at $p < 0.05$. Statistical analyses were performed using SPSS v.19.0 software (IBM Corp., Armonk, NY, USA).

3. Results

Table 1 shows the patient characteristics. After a median follow-up of 32 mo, 44% of the patients ($n = 3582$) died including 27% ($n = 2198$) of bladder cancer–related causes. Median time to death was 24.6 mo. The 5-yr CSS and OS rates were 67.7% and 57.5%, respectively.

Table 2 shows the conditional 5-yr OS rates as a function of the length of patient survivorship. Specifically, given a

Table 1 – Patient cohort characteristics

	n = 8141
Age, yr	
Median (IQR)	68.0 (60–74)
Male (%)	6472 (79.5)
pT stage (%)	
pT0/Tis/Ta/T1	2638 (32.4)
pT2	1986 (24.4)
pT3	2605 (32.0)
pT4	912 (11.2)
Tumor grade (%)	
Low	236 (2.9)
High	7905 (97.1)
Positive lymph nodes (%)	1929 (23.7)
No. of removed nodes	
Median (IQR)	16.0 (10–26)
No. of positive nodes, if positive	
Median (IQR)	2.0 (1–5)
Lymphovascular invasion (%)	2646 (32.5)
Positive soft tissue surgical margins (%)	431 (5.3)
Perioperative chemotherapy (%)	
Neoadjuvant	236 (2.9)
Adjuvant	1685 (20.7)
Follow-up, mo	
Median (IQR)	32.2 (15–70)
Deaths (%)	3582 (44.0)
Deaths related to bladder cancer (%)	2198 (27.0)

IQR = interquartile range.

1-, 2-, 3-, 5-, and 10-yr survivorship, the 5-yr OS rates were improved by +5.6 (60.7%), +8.4 (65.8%), +7.6 (70.8%), +3.0 (72.9%), and +1.9% (74.3%), respectively.

The impact of various prognostic factors on CSS was likewise assessed. All parameters were significantly associated with 5-yr survival at baseline and after a 1- and 2-yr survivorship. After a 3-yr survivorship, tumor grade and margin status were not statistically predictive for OS. None of the pathologic features maintained a predictive value for OS after a 10-yr survivorship. There was a slightly continuous loss of predictive value of pathologic parameters. The 5-yr CS rate was improved by 100% at baseline when comparing pT3–4 with pT1 tumors (from 38.9% to 78.9%) and only by 10% after a 10-yr survivorship (from 68.4% to 75.7%). Conversely, age was significantly predictive whatever the survivorship. Patients <65 yr had a 5-yr survival rate improved by 23% at baseline compared with their older counterparts, and by 30% after a 10-yr survivorship. Receipt of adjuvant chemotherapy was associated with significantly adverse OS during the first 2-yr postoperative period, and thereafter it was associated with improved outcome after a 5-yr survivorship. The absence of adjuvant chemotherapy improved the 5-yr CS at baseline by 45% and decreased it by 11% after a 10-yr survivorship.

Comparable analyses were run for CSS and are shown in Table 3. Given a 1-, 2-, 3-, 5-, and 10-yr survivorship, the 5-yr CS rates were improved by +5.6 (71.5%), +9.8 (78.5%), +7.9 (84.7%), +7.2 (90.8%), and 5.6% (95.9%), respectively. The impact of pathologic variables decreased with increasing survivorship. The 5-yr CS rate was improved by 80% at baseline when comparing pT3–4 with pT1 tumors (from 48.6% to 87.7%), and it was equivalent whatever the pT stage after a 10-yr survivorship (96.3% and 95.9%). The 5-yr non–cancer-specific CS rates were 84.2%, 83.9%, 83.1%, 82.7%, and 79.5%, respectively.

Because patients with poor adverse pathologic features were more likely to receive adjuvant chemotherapy than those with good prognosis disease, we further assessed the effect of adjuvant chemotherapy on CS after stratification by these pathologic parameters. Table 4 demonstrates the CS at baseline and after a 1-, 2-, 3-, 5-, and 10-yr survivorship. In pT3–4/N0 patients, the use of adjuvant chemotherapy positively influenced the OS. In pN1–3 patients, both CSS and OS were significantly improved by adjuvant chemotherapy even after long-term survivorship.

The changing impact of parameters on conditional OS was assessed upon multivariable Cox regression analysis illustrated in Table 5. A continuous increase in the hazard risk (from 1.5 to 2.3) was achieved in patients >65 yr of age as compared with their younger counterparts. Conversely, the effect of each pathologic parameter decreased over time as illustrated by the decrease in the hazard risks. Interestingly, after taking into account all pathologic parameters, receipt of adjuvant chemotherapy was independently associated with survival. An increase in the hazard risk protective effect (from 0.72 to 0.56) was reported over time for receipt of adjuvant chemotherapy. Similar findings were noted for CSS (data not shown). Findings from multivariable models were not different when using lymph node density instead of pN stage.

To illustrate CS estimates, Kaplan-Meier curves are provided in Figure 1 (OS) and Figure 2 (CSS) and report the conditional probability of surviving a certain number of years from RC according to the number of years elapsed after surgery.

Kaplan-Meier curves were then stratified by pathologic parameters by combining pT and pN stages (Fig. 3). As in Figures 1 and 2, tables included in the figure show the probability of OS 5 yr after surgery according to the number of years elapsed after surgery. The conditional 5- and 10-yr OS improved mainly for disease-free surviving patients with adverse pathologic factors at cystectomy (pT3–4 stage and/or pN1–3 stage). For example, among patients with pT3–4N1–3, the probability of surviving to year 5 increased from 25% at the time of presentation to 73% for patients surviving 3 yr after surgery (+190%). The corresponding improvement in CS was only 30% and +69% in pT2N0 and pT3–4N0 patients, respectively.

4. Discussion

Survival statistics are useful for clinicians in patient surveillance planning and for patients to estimate their prognosis. However, cumulative survival statistics are often just a snapshot estimate of projected survival at the time of diagnosis, whereas the patient-relative probability of survival for another 5 yr changes. CS data published from Canadian cancer sites showed that the prognosis improved over time from cancer diagnosis for all studied cancers except chronic lymphocytic leukemia [8].

Table 2 – Five-year conditional overall survival rates of patients in relation to clinical and tumor characteristics

		Time elapsed since radical cystectomy				
	Baseline	1 yr	2 yr	3 yr	5 yr	10 yr
Cohort, *n*	8141	6583	4841	3760	2422	901
5-yr CS rates, %	57.5 ± 0.6	60.7 ± 0.7	65.8 ± 0.8	70.8 ± 0.9	72.9 ± 1.1	74.3 ± 1.7
Survival gain,‡, %		+5.6	+14.4	+23.1	+26.8	+29.2
Survival gain,‡‡, %		+5.6	+8.4	+7.6	+3.0	+1.9
Age >65 yr						
No	64.5 ± 1.0	68.1 ± 1.0	73.8 ± 1.1	78.7 ± 1.2	82.2 ± 1.3	82.7 ± 1.9
Yes	52.4 ± 0.9	54.9 ± 1.0	59.4 ± 1.1	64.1 ± 1.3	64.4 ± 1.6	63.4 ± 2.9
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Lymph node status						
Negative	66.0 ± 0.7	67.0 ± 0.8	69.3 ± 0.9	72.5 ± 0.9	72.9 ± 1.2	73.8 ± 1.8
Positive	30.2 ± 1.2	36.6 ± 1.6	48.5 ± 0.9	60.3 ± 2.5	73.2 ± 3.0	78.4 ± 4.8
p value	<0.001	<0.001	<0.001	<0.001	0.900	0.684
No. of removed nodes						
1–19	55.6 ± 0.8	58.7 ± 0.9	64.3 ± 1.5	69.0 ± 1.7	70.7 ± 1.5	75.5 ± 2.5
≥20	60.7 ± 1.0	63.8 ± 1.1	68.0 ± 1.3	73.4 ± 1.3	75.7 ± 1.6	73.7 ± 2.3
p value	<0.001	<0.001	0.039	0.024	0.062	0.927
Lymph node density						
0%	66.0 ± 0.7	67.0 ± 0.8	69.3 ± 0.9	72.5 ± 0.9	72.9 ± 1.2	73.8 ± 1.8
<20%	39.0 ± 2.5	41.1 ± 2.1	52.9 ± 2.5	65.7 ± 2.9	78.4 ± 3.6	84.1 ± 7.1
≥20%	16.7 ± 3.2	27.1 ± 2 .6	37.7 ± 3.9	43.2 ± 5.0	56.9 ± 6.2	76.9 ± 5.5
p value	<0.001	<0.001	<0.001	<0.001	0.003	0.836
Tumor grade						
Low	79.9 ± 3.1	78.3 ± 3.4	69.0 ± 4.4	71.0 ± 4.7	66.1 ± 5.7	74.0 ± 8.7
High	55.2 ± 0.7	58.5 ± 0.8	64.4 ± 0.9	69.8 ± 0.9	72.7 ± 1.1	74.2 ± 1.8
p value	<0.001	<0.001	0.044	0.312	0.761	0.477
LVI						
No	66.9 ± 0.7	68.0 ± 0.8	70.5 ± 0.9	74.0 ± 1.0	74.7 ± 1.2	74.4 ± 1.5
Yes	37.7 ± 1.1	42.7 ± 1.3	52.0 ± 1.7	60.2 ± 2.0	66.5 ± 2.4	74.0 ± 4.0
p value	<0.001	<0.001	<0.001	<0.001	0.001	0.962
Surgical margins						
Negative	59.2 ± 0.7	61.7 ± 0.7	66.3 ± 0.8	70.7 ± 0.9	73.1 ± 1.1	74.5 ± 1.7
Positive	26.1 ± 2.6	35.6 ± 3.6	50.7 ± 4.8	73.4 ± 5.6	67.0 ± 7.9	66.0 ± 13.4
p value	<0.001	<0.001	<0.001	0.065	0.196	0.135
pT stage						
pT1	78.9 ± 1.0	76.4 ± 1.1	75.6 ± 1.2	76.6 ± 1.3	74.0 ± 1.7	75.7 ± 2.5
pT2	62.8 ± 1.3	64.0 ± 1.4	66.1 ± 1.6	70.1 ± 1.7	73.8 ± 2.1	77.3 ± 3.0
pT3–4	38.9 ± 1.0	44.6 ± 1.1	54.9 ± 1.4	64.1 ± 1.6	70.6 ± 2.0	68.4 ± 3.6
p value	<0.001	<0.001	<0.001	<0.001	0.035	0.298
Adjuvant chemotherapy						
No	61.6 ± 0.7	64.3 ± 0.8	67.5 ± 0.9	71.2 ± 1.0	71.6 ± 1.2	72.9 ± 1.9
Yes	42.6 ± 1.4	46.8 ± 1.6	58.6 ± 1.9	68.7 ± 2.1	79.5 ± 2.4	81.5 ± 3.7
p value	<0.001	<0.001	<0.001	0.597	<0.001	0.007

CS = conditional survival; LVI = lymphovascular invasion.
Values are plus or minus standard error (SE). For each value, the 95% confidence interval can be calculated as [value] ± 1.96 × SE.
‡ As compared with baseline.
‡‡ As compared with previous time point.

It was previously suggested in other malignancies that the risk of death from the disease decreases with increasing length of survival and that CS analysis might improve patient prognosis and help adjust it over time [10–15]. Authors also highlighted that for individual patients, CS is more useful because it is more optimistic and moves throughout the cancer experience [21].

For bladder cancer patients surviving after RC at a certain point, the probability of mortality at longer follow-up might also significantly change according to the duration of the postoperative period [9]. Sonpavde et al suggested that disease-free survival rates at 2 and 3 yr were a predictor and potential surrogates for 5-yr OS [22]. Only one series has previously assessed CS in radical cystectomy patients [9]. However, this series analyzed the cancer-specific CS rates after RC using files from the SEER database. The SEER database is a useful tool for population-based analysis of survival, but several important limitations of that data set should be noted. Only patients >66 yr of age were included, highlighting an important selection bias and preventing the authors from assessing the impact of age on CS (median patient age: 77 yr). No OS analysis was available, and the authors suggested that CSS might have been overestimated. Thus the generalization of such results can be questioned.

Given these limitations, we aimed to study the impact of CS in the context of bladder cancer in a large multicenter cohort. We also assessed how CS differs according to patient and disease characteristics.

In the present study, the 5-yr CSS and OS rates were 67.7% and 57.5%, respectively, in line with contemporary series. That is, in a 1100-patient cohort from an expert

Table 3 – Five-year conditional cancer-specific survival rates of patients in relationship to clinical and tumor characteristics

		Time elapsed since radical cystectomy				
	Baseline	1 yr	2 yr	3 yr	5 yr	10 yr
Cohort, n	8141	6583	4841	3760	2422	901
5-yr CS rates, %	67.7 ± 0.6	71.5 ± 0.7	78.5 ± 0.7	84.7 ± 0.7	90.8 ± 0.7	95.9 ± 0.8
Survival gain,‡, %		+5.6	+15.9	+25.1	+34.1	+41.7
Survival gain,‡‡, %		+5.6	+9.8	+7.9	+7.2	+5.6
Age >65 yr						
No	70.7 ± 0.9	74.1 ± 1.0	80.2 ± 1.0	86.1 ± 1.0	92.4 ± 0.9	97.4 ± 0.8
Yes	65.4 ± 0.8	69.5 ± 0.9	77.1 ± 1.0	83.4 ± 1.0	89.2 ± 1.1	94.0 ± 1.4
P value	<0.001	<0.001	0.017	0.010	0.002	0.017
Lymph node status						
Negative	77.1 ± 0.6	78.9 ± 0.7	83.2 ± 0.7	87.1 ± 0.7	91.3 ± 0.7	95.8 ± 0.8
Positive	36.5 ± 1.4	42.7 ± 1.6	55.6 ± 2.1	70.5 ± 2.4	87.5 ± 2.2	96.6 ± 2.0
p value	<0.001	<0.001	<0.001	<0.001	0.080	0.736
No. of removed nodes						
1–19	66.0 ± 0.8	69.8 ± 0.9	76.9 ± 1.0	82.9 ± 1.4	88.6 ± 1.0	94.6 ± 1.3
≥20	70.5 ± 1.0	74.3 ± 1.0	80.9 ± 1.1	87.4 ± 1.0	93.7 ± 0.9	97.2 ± 0.9
p value	<0.001	<0.001	0.003	0.001	<0.001	0.085
Lymph node density						
0%	77.1 ± 0.6	78.9 ± 0.7	83.2 ± 0.7	87.1 ± 0.7	91.3 ± 0.7	95.8 ± 0.8
<20%	46.0 ± 2.6	46.8 ± 2.2	58.2 ± 2.5	73.3 ± 2.7	90.8 ± 2.4	96.7 ± 2.4
≥20%	21.4 ± 3.8	34.3 ± 2.8	49.2 ± 4.1	59.3 ± 5.4	74.9 ± 5.8	96.2 ± 3.8
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.886
Tumor grade						
Low	86.0 ± 2.7	86.6 ± 2.8	83.7 ± 3.6	87.5 ± 3.5	83.8 ± 4.8	97.1 ± 2.9
High	65.6 ± 0.7	69.9 ± 0.7	77.2 ± 0.8	83.8 ± 0.8	90.7 ± 0.7	96.2 ± 0.8
p value	<0.001	<0.001	0.058	0.478	0.325	0.946
LVI						
No	77.0 ± 0.7	78.8 ± 0.7	83.4 ± 0.7	87.9 ± 0.7	92.3 ± 0.7	95.6 ± 0.9
Yes	47.1 ± 1.2	53.2 ± 1.4	64.0 ± 1.7	74.2 ± 1.8	85.1 ± 1.8	97.3 ± 1 .4
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.732
Surgical margins						
Negative	69.6 ± 0.6	72.7 ± 0 .7	79.2 ± 0.7	84.9 ± 0.7	90.9 ± 0.7	95.8 ± 0.8
Positive	31.8 ± 2.9	41.0 ± 3.9	56.1 ± 5.0	77.9 ± 5.4	87.6 ± 5.3	–
p value	<0.001	<0.001	<0.001	0.096	0.641	0.418
pT stage						
pT1	87.7 ± 0.8	86.7 ± 0.9	87.3 ± 1.0	90.3 ± 0.9	91.2 ± 1.1	95.9 ± 1.1
pT2	74.0 ± 1.2	75.6 ± 1.3	80.0 ± 1.3	83.3 ± 1.4	92.6 ± 1.2	95.5 ± 1.5
pT3–4	48.6 ± 1.0	55.0 ± 1.2	67.5 ± 1.4	78.8 ± 1.4	88.5 ± 1.4	96.3 ± 1.6
p value	<0.001	<0.001	<0.001	<0.001	0.071	0.542
Adjuvant chemotherapy						
No	73.0 ± 0.7	76.4 ± 0.7	81.5 ± 0.8	86.1 ± 0.8	90.8 ± 0.8	95.2 ± 0.9
Yes	48.8 ± 1 .5	53.5 ± 1.6	66.0 ± 1.8	78.3 ± 1.9	90.7 ± 1.7	99.3 ± 0.7
p value	<0.001	<0.001	<0.001	<0.001	0.455	0.038

CS = conditional survival; LVI = lymphovascular invasion.
Values are plus or minus standard error (SE). For each value, the 95% confidence interval can be calculated as [value] ± 1.96 × SE.
‡ As compared with baseline.
‡‡ As compared with previous time point.

center, Hautmann et al recently reported long-term oncologic outcomes after RC showing 5-yr OS and cancer-free survival rates of 58% and 71%, respectively [2].

Several points need to be highlighted in the present study. Patient prognosis improved with each additional year survived after surgery even after a long-term period. Given that about 50% of patients die in the first 2 yr after RC (median survival: 24.6 mo), surviving patients beyond this period may expect a better prognosis. Thus the risk of dying of bladder cancer after surgery is not constant over time, with most deaths occurring in the first 2 yr. Therefore, the 5-yr survival probability of a patient who survives this critical period improves as compared with that calculated at baseline. This is important because many patients want to know how their chances of long-term survival might improve.

Previous reports have suggested that a stratification of CS estimates by age group and prognostic pathologic factors at diagnosis provides more relevant clinical information for clinicians and cancer patients [8,19]. In bladder cancer, specific mortality after RC depends on various features including pT stage, pN stage, number of nodes removed, lymphovascular invasion, and the status of soft tissue surgical margins. A combination of these variables provides better and more accurate predictions of oncologic outcomes [5,6]. One of the strengths of our study was to present age- and stage-specific CS in addition to the overall CS. In the present study, clinical (age, perioperative chemotherapy

Table 4 – Impact of adjuvant chemotherapy on conditional cancer-specific and overall survival after stratification according to pTNM stage

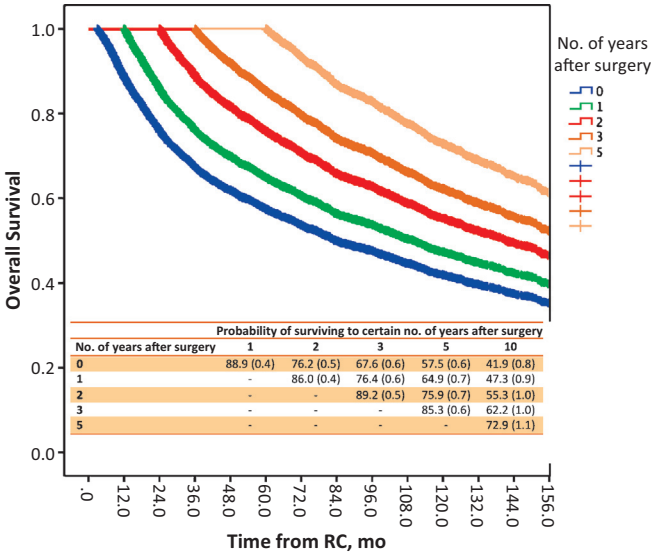
	Baseline	1 yr	2 yr	3 yr	5 yr	10 yr
Cancer-specific survival						
pT3–4/N0 patients*	*n* = 2032	*n* = 1575	*n* = 1083	*n* = 846	*n* = 548	*n* = 190
Adjuvant chemotherapy						
No	60.7 ± 1.5	66.3 ± 1.6	76.2 ± 1.8	82.0 ± 1.9	87.5 ± 2.0	95.0 ± 2.6
Yes	62.7 ± 2.8	65.9 ± 2.9	74.8 ± 3.1	82.8 ± 3.0	93.2 ± 2.4	97.9 ± 2.1
p value	0.084	0.906	0.762	0.643	0.163	0.646
pTxN+ patients*	*n* = 1933	*n* = 1355	*n* = 824	*n* = 531	*n* = 296	*n* = 111
Adjuvant chemotherapy						
No	32.0 ± 2.1	39.4 ± 2.8	50.2 ± 3.7	64.3 ± 4.2	82.7 ± 4.3	89.4 ± 5.9
Yes	39.5 ± 1.8	44.4 ± 2.0	58.4 ± 2.5	73.6 ± 2.8	89.8 ± 2.6	100
p value	<0.001	0.140	0.184	0.008	0.010	0.010
Overall survival						
pT3–4/N0 patients*	*n* = 2032	*n* = 1575	*n* = 1083	*n* = 846	*n* = 548	*n* = 190
Adjuvant chemotherapy						
No	47.4 ± 1.4	51.6 ± 1.7	58.8 ± 2.0	63.9 ± 2.2	66.6 ± 2.8	64.8 ± 4.9
Yes	53.5 ± 2.8	57.0 ± 3.0	65.5 ± 3.3	73.5 ± 3.5	82.1 ± 4.0	77.9 ± 7.1
p value	<0.001	0.014	0.033	0.009	0.001	0.133
pTxN+ patients*	*n* = 1933	*n* = 1355	*n* = 824	*n* = 531	*n* = 296	*n* = 111
Adjuvant chemotherapy						
No	24.0 ± 1.8	31.7 ± 2.5	41.4 ± 3.5	52.6 ± 4.2	64.5 ± 5.6	74.5 ± 8.5
Yes	34.5 ± 1.7	38.9 ± 2.0	52.2 ± 2.5	64.3 ± 3.1	77.7 ± 3.5	79.9 ± 5.8
p value	<0.001	0.002	0.027	<0.001	0.002	0.036

CS = conditional survival.
* No. of patients alive at each time point.

Table 5 – Proportional hazard ratios in multivariable Cox regression analysis for prediction of overall mortality*

	Baseline	1 yr	2 yr	3 yr	5 yr	10 yr
Age >65 yr						
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HR	1.50	1.58	1.72	1.91	2.20	2.29
95% CI	1.40–1.61	1.46–1.71	1.56–1.90	1.70–2.15	1.89–2.55	1.83–2.87
Positive lymph node						
p value	<0.001	<0.001	<0.001	<0.001	0.363	0.268
HR	1.90	1.78	1.70	1.43	1.12	1.26
95% CI	1.74–2.07	1.61–1.98	1.48–1.95	1.19–1.70	0.88–1.44	0.84–1.89
≥20 removed nodes						
p value	0.003	0.010	0.222	0.365	0.738	0.239
HR	0.90	0.90	0.94	0.95	0.98	1.15
95% CI	0.84–0.96	0.83–0.97	0.85–1.04	0.85–1.06	0.84–1.13	0.91–1.44
High tumor grade						
p value	0.484	0.585	0.631	0.822	0.612	0.296
HR	1.09	1.07	1.07	1.03	0.92	1.37
95% CI	0.86–1.39	0.83–1.38	0.82–1.39	0.77–1.39	0.66–1.28	0.76–2.46
LVI						
p value	<0.001	<0.001	<0.001	0.001	0.004	0.783
HR	1.42	1.35	1.28	1.27	1.31	0.96
95% CI	1.31–1.53	1.24–1.48	1.14–1.82	1.11–1.46	1.09–1.57	0.70–1.32
Positive surgical margins						
p value	<0.001	<0.001	0.002	0.732	0.775	0.311
HR	1.62	1.45	1.44	1.06	1.07	1.45
95% CI	1.42–1.83	1.23–1.72	1.14–1.82	0.75–1.50	0.68–1.68	0.71–2.99
pT3–4 stage						
p value	<0.001	<0.001	<0.001	0.001	0.062	0.076
HR	2.10	1.74	1.33	1.25	1.17	1.28
95% CI	1.91–2.32	1.59–1.89	1.20–1.48	1.10–1.42	0.99–1.38	0.98–1.67
Adjuvant chemotherapy						
p value	<0.001	0.002	0.008	0.001	<0.001	0.004
HR	0.72	0.84	0.83	0.74	0.61	0.56
95% CI	0.65–0.78	0.76–0.94	0.72–0.95	0.62–0.88	0.48–0.78	0.37–0.83

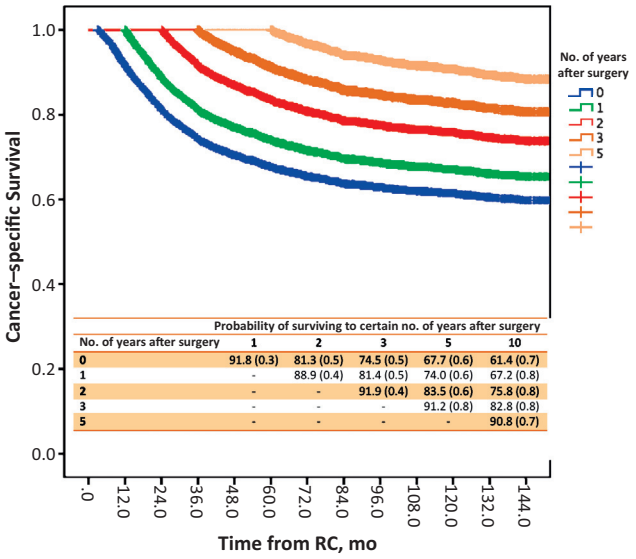
CI = confidence interval; HR = hazard ratio; LVI = lymphovascular invasion.
* Stratification by clinical and tumor characteristics.



Probability of surviving to certain no. of years after surgery

No. of years after surgery	1	2	3	5	10
0	88.9 (0.4)	76.2 (0.5)	67.6 (0.6)	57.5 (0.6)	41.9 (0.8)
1	-	86.0 (0.4)	76.4 (0.6)	64.9 (0.7)	47.3 (0.9)
2	-	-	89.2 (0.5)	75.9 (0.7)	55.3 (1.0)
3	-	-	-	85.3 (0.6)	62.2 (1.0)
5	-	-	-	-	72.9 (1.1)

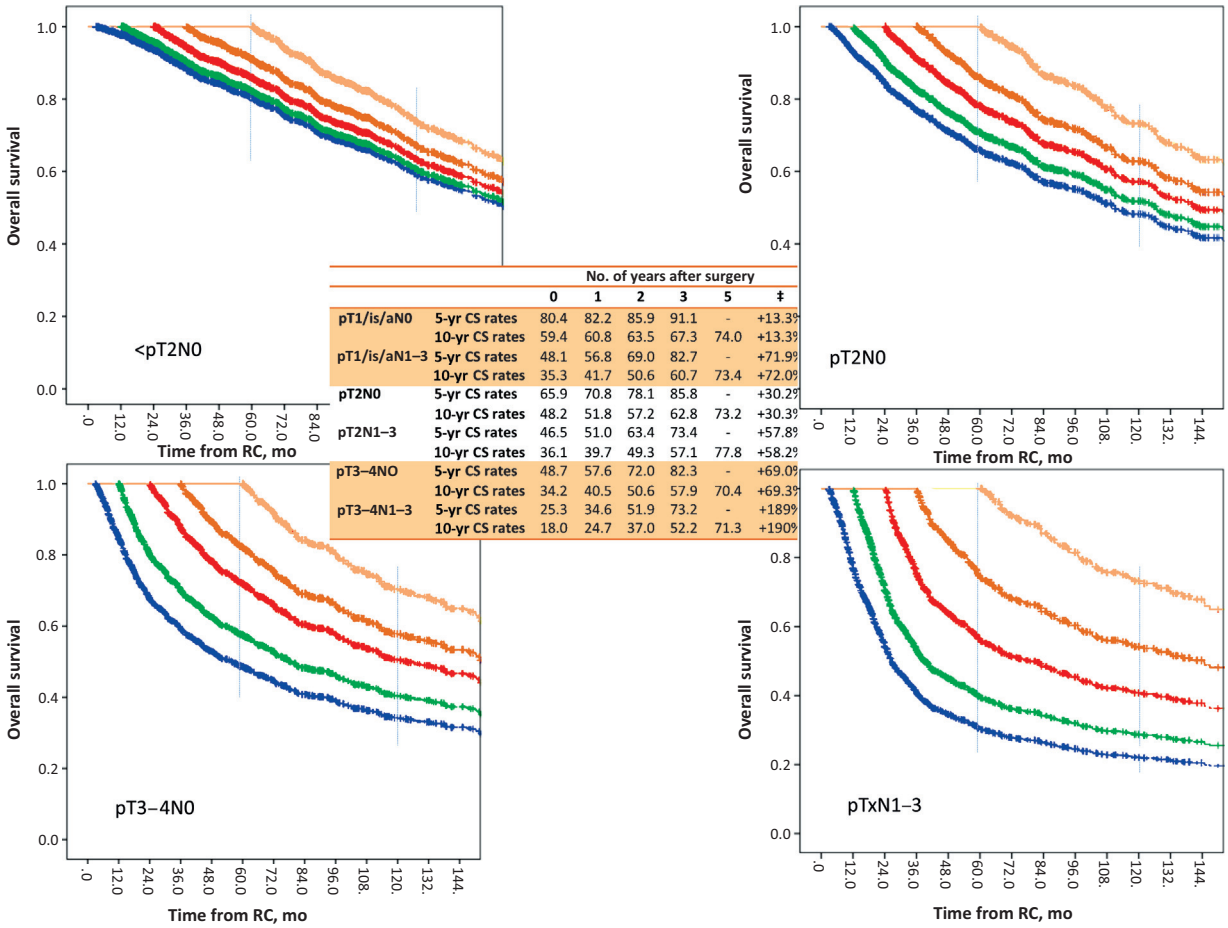
Fig. 1 – Conditional overall survival curves according to the number of years after radical cystectomy (RC). The table shows the conditional probability of surviving a certain number of years after RC according to the number of years elapsed after surgery. Standard errors in parentheses.



Probability of surviving to certain no. of years after surgery

No. of years after surgery	1	2	3	5	10
0	91.8 (0.3)	81.3 (0.5)	74.5 (0.5)	67.7 (0.6)	61.4 (0.7)
1	-	88.9 (0.4)	81.4 (0.5)	74.0 (0.6)	67.2 (0.8)
2	-	-	91.9 (0.4)	83.5 (0.6)	75.8 (0.8)
3	-	-	-	91.2 (0.8)	82.8 (0.8)
5	-	-	-	-	90.8 (0.7)

Fig. 2 – Conditional cancer-specific survival curves according to the number of years after radical cystectomy (RC). The table shows the conditional probability of surviving a certain number of years after RC according to the number of years elapsed after surgery. Standard errors in parentheses.



		No. of years after surgery					
		0	1	2	3	5	‡
pT1/is/aN0	5-yr CS rates	80.4	82.2	85.9	91.1	-	+13.3%
	10-yr CS rates	59.4	60.8	63.5	67.3	74.0	+13.3%
pT1/is/aN1–3	5-yr CS rates	48.1	56.8	69.0	82.7	-	+71.9%
	10-yr CS rates	35.3	41.7	50.6	60.7	73.4	+72.0%
pT2N0	5-yr CS rates	65.9	70.8	78.1	85.8	-	+30.2%
	10-yr CS rates	48.2	51.8	57.2	62.8	73.2	+30.3%
pT2N1–3	5-yr CS rates	46.5	51.0	63.4	73.4	-	+57.8%
	10-yr CS rates	36.1	39.7	49.3	57.1	77.8	+58.2%
pT3–4NO	5-yr CS rates	48.7	57.6	72.0	82.3	-	+69.0%
	10-yr CS rates	34.2	40.5	50.6	57.9	70.4	+69.3%
pT3–4N1–3	5-yr CS rates	25.3	34.6	51.9	73.2	-	+189%
	10-yr CS rates	18.0	24.7	37.0	52.2	71.3	+190%

Fig. 3 – Conditional overall survival (OS) curves according to the number of years after radical cystectomy (RC) stratified by pTN stage. Traditional Kaplan-Meier estimates of OS (blue line) overlaid by conditional survival (CS) estimates at 1 yr (green line), 2 yr (red line), 3 yr (dark orange line), and 5 yr (light orange line) are shown from the time of RC. The vertical dotted lines mark the 5- and 10-yr conditional OS. The table shows the conditional probability of surviving 5 and 10 yr after RC according to the number of years elapsed after surgery.
‡ Survival gain in 5- and 10-yr CS rates between patients at the time of surgery and those who have already survived 3 yr after surgery.
N0 = negative lymph nodes; N1–3 = positive lymph nodes.

status) and pathologic characteristics (pT stage, grade, lymphovascular invasion, pN stage, number of nodes removed, margin status) improved CS prediction during the first 2 yr after RC in univariable analyses. Thereafter, the impact of each parameter evolved over time. Interestingly, contrary to what has been reported in renal cell carcinoma, the effect of CS according to age groups in bladder cancer patients was not negligible when other prognostic variables were taken into account [19]. That is, a continuous increase in the hazard risk was achieved in patients >65 yr of age compared with their younger counterparts when looking at OS. Patients diagnosed at older ages also tended to have lower relative conditional CSS, but this effect was reduced after surviving 5–10 yr.

The effect of each pathologic parameter decreased over time as illustrated by the decrease in the hazard risks. These findings were reported concerning both CSS and OS estimates. Importantly, by presenting age- and stage-specific CS estimates, urologists can assess patterns in CS as a function of clinical and pathologic factors, thus gaining a greater understanding of ongoing survival expectations. The literature demonstrates that the greatest differences in CS are for patients with cancers who initially had poor survival [11,12]. A similar pattern can be extrapolated for cancers diagnosed at an advanced stage. The impact of disease stage on survival expectations at diagnosis is expected to decrease as time elapses since diagnosis for most types of cancer.

That the greatest improvement occurred in the patients with poor risk further draws attention to the fact that these patients have a disease with a biologic high growth rate due to poorly differentiated tumor cells that primarily recur during the first 2 yr after RC. The chance to heal the disease is then strongly increased when no recurrence appears during this initial follow-up. Our findings demonstrated that the impact of bladder cancer stage and aggressiveness reduces and can disappear for long-term CS. Given that, the assessment of new clinicopathologic factors at the time of disease recurrence would have great importance for subsequent survival analysis after disease recurrence.

Notable gains in survival probability were observed among patients with adverse pathologic features. In other words, whereas survival gains are slight for good prognosis bladder cancer patients, the probability of survival markedly increased over time in patients with high-stage disease. For example, the probability of surviving 5 additional years increased from 39% at the time of RC to 71% after 5-yr follow-up in pT3–4 cancer patients (+81%). By comparison, the survival gain was only +17% in pT2 tumors. To compare with the age variable, the survival gain was relatively comparable between patients >65 yr and their younger counterparts (23% and 27%, respectively). These findings confirm those previously reported in other malignancies that 5-yr CS improved mainly for surviving patients with advanced stage disease [19,23]. Similarly, after 2 yr of survivorship, the survival of a patient with soft tissue surgical margins has no more impact [24].

The impact of adjuvant chemotherapy was mainly reported in OS analysis. This might be explained by the fact that patients receiving adjuvant chemotherapy are also selected by their comorbidity status and are healthier that those who do not receive adjuvant therapy, and thus they have a better non–cancer-specific life expectancy.

Other survival analyses have been shown to improve cumulative statistics. In the cumulative Kaplan-Meier method, a patient experiencing a competing-risk event is censored in an informative manner. Hence the Kaplan-Meier estimation procedure may not be directly applicable when estimating disease incidence. The cumulative incidence function for an event of interest must be calculated by appropriately accounting for the presence of competing-risk events. Failure to account for such competing events results in an overestimate of the cumulative incidences [25].

There is a need for competing-risk modeling when studying survival in patients at high risk of dying from other causes. Prostate cancer is a good example. In bladder cancer, the main cause of mortality is the cancer itself. This competing-risks analysis does not take into account the disease-free interval. Because the risk of disease progression improves with an increasing disease-free interval, the absence of adjustment for a disease-free interval presents the clinician with an excessively somber estimate of cancer control over time. The CS analysis allows adjustment for the survivorship interval. In the present study, we chose to assess CS after stratification by risk grouping to build an easy-to-use predictive model. Various studies have documented the superior performance of nomograms compared with risk grouping [26]. Nomograms also allow adjustment for competing risks and for a disease-free interval. Further CS analysis in bladder cancer should assess its predictive value in nomograms.

Our present study had several limitations. The findings are based on retrospective data introducing collection biases. This study pools the contribution of multiple surgeons. Although it allows for more generalizability, the multicenter design led to the lack of standardized data collection, the lack of a central pathology review, and the heterogeneity in patient monitoring and in perioperative chemotherapy use. The low number of patients receiving neoadjuvant chemotherapy did not allow us to reach sufficient statistical power. The number of nodes removed was available, but it depends on various factors. For example, sending the lymph nodes in packets rather than as one specimen improves the quality of the pathologic assessment. The exact anatomic boundaries of lymph node dissection may be a better comparison factor. Unfortunately, this variable was not available [27].

Our database did not allow us to study the impact of other important information such as smoking, performance, and comorbidity statuses. Comorbidity status has been suggested to be predictive of 5-yr all-cause mortality after RC [28]. Other studies found comorbidity and performance indices to be predictors of cancer-independent mortality but not of cancer-specific mortality [29]. We recognize that assessment of association of these variables with CS would be of great value. For example, continued smoking status may modify oncologic outcomes after RC. Nevertheless, a recent systematic review highlighted that the marked

heterogeneity across studies limits strong conclusions in that setting [30].

5. Conclusions

CS analysis in RS patients demonstrates that the patient risk profile changes over time. The period elapsed after surgery represents an important predictor of CSS and OS. The risk of mortality decreases with increasing survivorship. The 5-yr CS improves mainly for surviving patients with advanced-stage disease. Our findings also suggest that the impact of prognostic pathologic features decreases over time and can disappear for long-term CS. Pending validation, our findings highlight that CS provides relevant information for physicians and for cancer survivors and should play a major role in patient counseling and surveillance planning.

Author contributions: Wassim Kassouf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Ploussard, Shariat, Dragomir, Kassouf.
Drafting of the manuscript: Ploussard, Kassouf.
Critical revision of the manuscript for important intellectual content: Shariat, Dragomir, Kluth, Xylinas, Masson-Lecomte, Rieken, Rink, Matsumoto, Kikuchi, Klatte, Boorjian, Lotan, Roghmann, Fairey, Fradet, Black, Rendon, Izawa.
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