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How cancer-specific mortality changes over time after radical cystectomy: Conditional survival of patients with nonmetastatic urothelial carcinoma of the urinary bladder

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Abstract

Objectives: We studied the effect of conditional survival on 5-year cancer-specific mortality (CSM) probability in a contemporary North-American population-based nonmetastatic urothelial carcinoma of urinary bladder cohort treated with radical cystectomy.

Methods and materials: Within the SEER database (2004–2015), we identified pTa/pTis/pT1N0 high grade, pT2 to pT4N0 and pTanyN1-3 patients treated with radical cystectomy for nonmetastatic urothelial carcinoma of urinary bladder. Conditional 5-year CSM-free estimates were assessed after event-free follow-up duration. Multivariable Cox regression models predicted CSM according to event-free follow-up duration.

Results: According to T and N stages, 1,079 (7.9%) pTa/pTis/pT1N0, 5,058 (37.2%) pT2N0, 2,865 (21.1%) pT3N0, 1,211 pT4N0 (8.9%) and 3,382 (24.9%) pTanyN1-3 patients were included. Conditional CSM-free estimates increased from 90.1 to 91.8%, 80.6 to 92.5%, 62.5 to 90.7%, 53.1 to 84.5%, and 37.5 to 84.0% after 5 years of event-free follow-up, in respectively pTa/pTis/pT1N0, pT2N0, pT3N0, pT4N0, and pTanyN1-3 patients. Attrition due to mortality was highest in pTanyN1-3 cohort and lowest in pTa/pTis/pT1N0. In Multivariable Cox regression analyses, pT2N0 (hazard ratio [HR] 1.9 $P< 0.001$), pT3N0 (HR 4.3 $P< 0.001$), pT4N0 (HR 5.8 $P< 0.001$) and pTanyN1-3 (HR 9.1 $P< 0.001$) were independent predictors of higher CSM at baseline, relative to pTa/pTis/pT1N0. A decrease in all conditional HRs to nonsignificant levels was recorded at 60 months for pT4N0 and pTanyN1-3 and at 48 months for pT2N0 and pT3N0.

Conclusions Conditional survival: showed a direct relationship between event-free follow-up duration and survival probability. Conditional CSM-free estimates increased in proportion with event-free follow-up but also resulted in equally proportional increase in attrition rates.

Key words: Nonmetastatic bladder cancer; Conditional survival; Cancer-specific mortality; Radical cystectomy

1. Introduction

Conditional survival (CS) [1] is a clinically important entity that dynamically accounts for changes in the risk of

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death over time. Specifically, it represents the adjustment in probability of survival that is defined according to the duration of event-free follow-up. Therefore, CS is more specific than unadjusted survival, especially in patients with event-free follow-up of several years. The effect of CS may be particularly important to incorporate into patient counselling in individuals with more aggressive disease phenotype.

Three previous studies [2–4] assessed CS in the setting of nonmetastatic urothelial cancer of urinary bladder (nmUCUB) after radical cystectomy (RC) and validated the notion of better survival with increasing event-free follow-up. The first one [2] relied on Surveillance, Epidemiology, and End Results (SEER)-linked Medicare database, thus including 4,991 patients older than 65 years from 1992 to 2005. The second one [3] assessed CS in a large multi-institutional cohort of 8,141 patients treated from 1979 to 2012. Finally, a third one [4] investigated a small single-institution Korean cohort of 487 patients from 1991 to 2012. Unfortunately, both large scale studies are limited with regard to their contemporary patient numbers. Moreover, neither study allowed to assess conditional cancer-specific mortality (CSM)-free estimates in a stratified fashion that accounts for the combined effect of T and N stages.

To address these unmet needs, we tested conditional CSM-free estimates in nmUCUB patients treated with RC, identified within the most recent version of the SEER database (2004–2015). We hypothesized that important reductions in the risk of 5-year conditional CSM-free estimates may be identified with increasing duration of event-free follow-up in this more contemporary cohort according to T and N stage groupings.

2. Materials and Methods

2.1. Data source and study population

Within the SEER database (2004 to 2015) [5], we focused on patients 18 years or older treated with RC for pTa/pTis/pT1 high grade, pT2 to pT4 and/or pN1 nmUCUB (International Classification of Disease for Oncology [ICD-O] site codes C67.0–67.9). CSM (death from UCUB) was the primary endpoint and it was defined according to the SEER mortality code. Exclusion criteria consisted of metastatic UCUB, pTa/pTis/pT1 low grade, unavailable information on T stage, N stage, histology, grade, as well as all autopsy, death certificate and missing follow-up data. These selection criteria yielded a population of 13,595 nmUCUB patients treated with RC.

2.2. Statistical analyses

Our analyses relied on 3 analytical steps. First, conditional 5-year CSM-free estimates was calculated in patients with nmUCUB treated with RC according to T and N stage groupings (pTa/pTis/pT1N0 vs. pT2N0 vs. pT3N0 vs. pT4N0 vs. pTanyN1-3), by applying CS methodology, as previously reported [1,6]. Specifically, CS was calculated as the probability of survival for x additional years, given y years of accumulated survival. The event-free follow-up time points used in CS models consisted of 1, 2, 3, and 5 years after RC. Second, separate multivariable Cox regression (MCR) models predicting CSM were fitted to examine the possible variation for risk of CSM over time. Specifically, MCR models were fitted in the overall population at baseline (time zero) and subsequently 5 separate additional MCR models were fitted in patients who respectively survived 1, 2, 3, 4, and 5 years after surgery. The variables of interest were T and N stages. For all the models, adjustment variables consisted of age, gender, ethnicity, stage, grade (low vs. high), histology, and chemotherapy status (received vs. not received). Finally, we developed a conditional nomogram predicting 5-year CSM, according to duration of event-free interval. The objective of the nomogram was to provide a graphical depiction of the conditional survival, according to risk factors included in the MCR model underlying the nomogram. Since this nomogram was constructed as purely visualization of our MCR models, no data-driven models selection nor formal validation of the nomogram were performed. The discrimination of the nomogram was tested using the concordance index (c-index).

All statistical tests were 2-sided with a level of significance set at $P< 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project. org/).

3. Results

3.1. General characteristics of the study population

From 2004 to 2015, 13,595 patients with nmUCUB were identified. Baseline characteristics of the study population are summarized in Table 1. Overall, stage distribution was as follows: 1,079 (7.9%) pTa/pTis/pT1N0, 5,058 (37.2%) pT2N0, 2,865 (21.1%) pT3N0, 1,211 (8.9%) pT4N0, and 3,382 (24.9%) pTanyN1-3. The median follow-up of the entire cohort was 25.0 months (interquartile range 11.0–58.0 months).

3.2. Conditional 5-year CSM analyses

After RC, the baseline (time zero) 5-year CSM-free rate in pTa/pTis/pT1N0 cohort was 90.1% (Table 2, Fig. 1). Given 12, 24, 36, or 60-months of event-free follow-up, conditional 5-year CSM-free estimates were respectively 91.7%, 89.1%, 89.9%, and 91.8%. Survival gains relative to baseline ranged from the lowest value of −1.0% at 2 years to the highest of +1.7% at 5 years of event-free follow-up.

After RC, the baseline 5-year CSM-free rate in pT2N0 cohort was 80.6% (Table 2, Fig. 1). Given 12, 24, 36, or 60-months of event-free follow-up, conditional 5-year CSM-free estimates were respectively 84.1%, 87.7%, 89.8%, and 92.5%. Survival gains relative to baseline ranged from +4.5% at 1 year to +11.9% at 5 years of event-free follow-up.

Table 1
Descriptive characteristics of 13,595 patients with nonmetastatic urothelial carcinoma of urinary bladder, treated with radical cystectomy, identified within the Surveillance, Epidemiology, and End Results database from 2004 to 2015.

Variable		Number (%)
Age at diagnosis	Median (IQR)	69 (61–76)
Ethnicity	Caucasian	12121 (89.2)
	African American	788 (5.8)
	Others	686 (5)
Gender	Female	3230 (23.8)
	Male	10365 (76.2)
T and N stage groupings	pTa/pTis/pT1N0	1079 (7.9)
	pT2N0	5058 (37.2)
	pT3N0	2865 (21.1)
	pT4N0	1211 (8.9)
	pTanyN1–3	3382 (24.9)
N substage	N0	10213 (75.1)
	N1	1719 (12.6)
	N2	1455 (10.7)
	N3	208 (1.5)
Grade	High grade	13257 (97.5)
	Low grade	338 (2.5)
Chemotherapy	Not received	7974 (58.7)
	Received	5621 (41.3)

After RC, the baseline 5-year CSM-free rate in pT3N0 cohort was 62.5% (Table 2, Fig. 1). Given 12, 24, 36, or 60-months of event-free follow-up, conditional 5-year CSM-free estimates were respectively 70.5%, 79.6%, 84.7%, and 90.7%. Survival gains relative to baseline ranged from +8.0% at 1 year to +28.9% at 5 years of event-free follow-up.

After RC, the baseline 5-year CSM-free rate in pT4N0 cohort was 53.1% (Table 2, Fig. 1). Given 12, 24, 36, or 60-months of event-free follow-up, conditional 5-year CSM-free estimates were respectively 62.4%, 69.9%, 78.4%, and 84.5%. Survival gains relative to baseline ranged from +9.3% at 1 year to +31.4% at 5 years of event-free follow-up.

After RC, the baseline 5-year CSM-free rate in pTanyN1-3 cohort was 37.5% (Table 2, Fig. 1). Given 12, 24, 36, or 60-months of event-free follow-up, conditional 5-year CSM-free estimates were respectively 46.7%, 61.3%, 73.9%, and 84.0%. Survival gains relative to baseline ranged from +9.0% 1 year to +23.6% at 5 years of event-free follow-up.

Attrition due to mortality was the lowest in pTa/pTis/pT1N0 patients (Table 2), as evidenced by conditional CSM-free estimates that ranged from 90.1% to 91.8% at respectively baseline and 5 years of event-free follow-up.

Table 2
Conditional 5-year cancer-specific mortality-free rates and survival gains after radical cystectomy of 13,595 non-metastatic urothelial carcinoma of urinary bladder patients. The analyses were subsequently repeated according to according to T and N stage groupings.

Months survived	0	12	24	36	48	60
pTa/pTis/pT1N0 high grade cohort						
No. at risk[a]	1079	830	638	478	339	199
No. of events[b]	1	26	20	15	4	3
Conditional 5-year CSM-free survival[a]	90.1%	91.7%	89.1%	89.9%	90.8%	91.8%
Survival gain[c]	–	+1.6%	−1.0%	−0.2%	+0.7%	+1.7%
pT2N0 cohort						
No. at risk[a]	5058	4115	3306	2638	2182	1776
No. of events[b]	4	250	241	116	72	49
Conditional 5-year CSM-free survival[a]	80.6%	84.1%	87.7%	89.8%	91.5%	92.5%
Survival gain[c]	–	+4.5%	+8.1%	+9.2%	+10.9%	+11.9%
pT3N0 cohort						
No. at risk[a]	2865	2049	1429	1093	860	700
No. of events[b]	2	353	253	99	55	29
Conditional 5-year CSM-free survival[a]	62.5%	70.5%	79.6%	84.7%	89.0%	90.7%
Survival gain[c]	–	+8.0%	+17.1%	+22.2%	+26.5%	+28.2%
pT4N0 cohort						
No. at risk[a]	1211	780	507	365	267	216
No. of events[b]	3	179	109	54	31	10
Conditional 5-year CSM-free survival[a]	53.1%	62.4%	69.9%	78.4%	81.6%	84.5%
Survival gain[c]		+9.3%	+16.8%	+25.3%	+28.5%	+31.4%
pTanyN1-3 cohort						
No. at risk[a]	3382	2150	1194	782	565	438
No. of events[b]	3	692	475	211	73	38
Conditional 5-year CSM-free survival[a]	37.5%	46.7%	61.3%	73.9%	78.8%	84.0%
Survival gain[c]	–	+9.0%	+15.9%	+18.5%	+21.7%	+23.6%

CSM = cancer specific mortality.
[a] At the beginning of the interval.
[b] At the end of the interval.
[c] Relative to baseline.

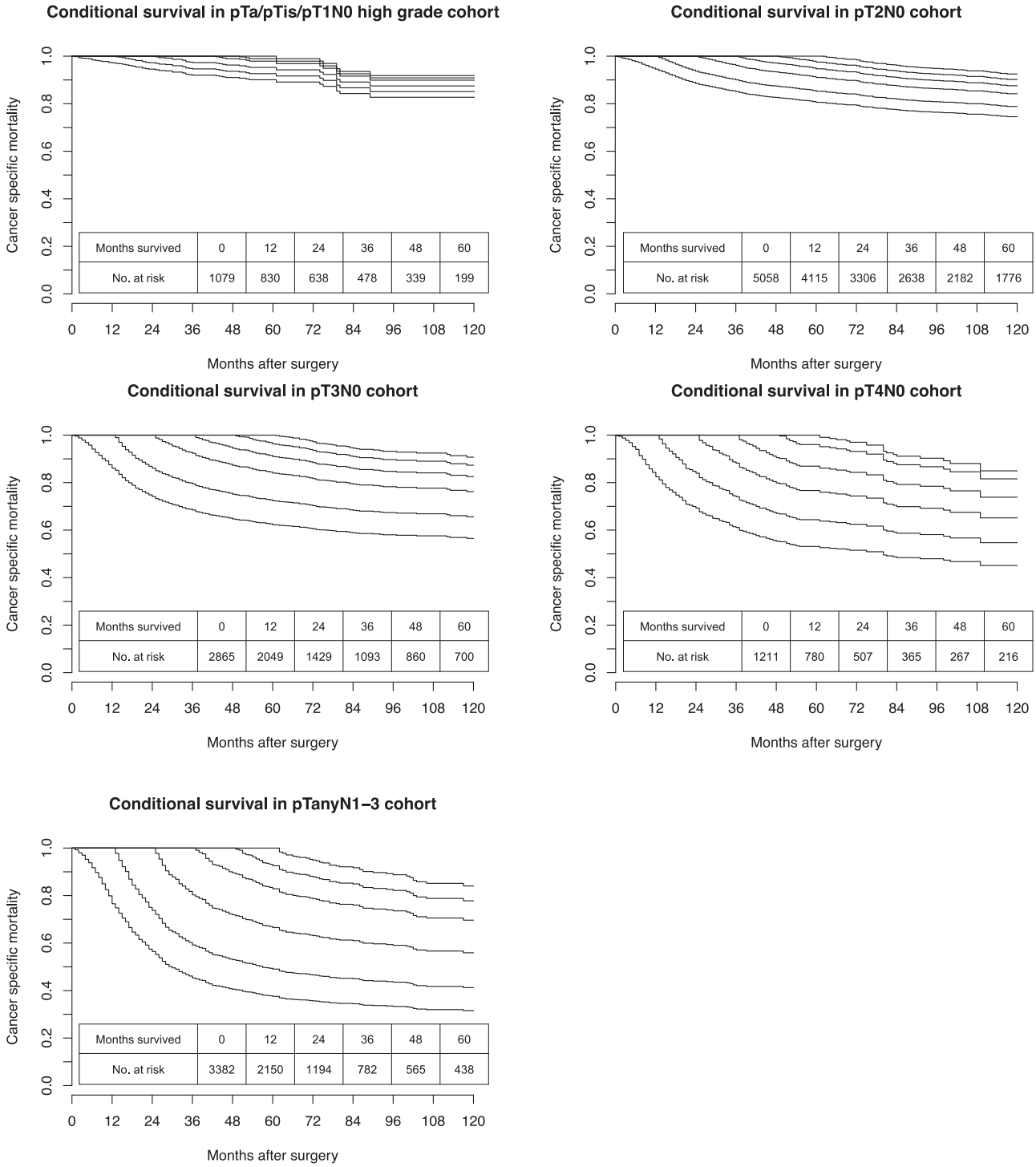


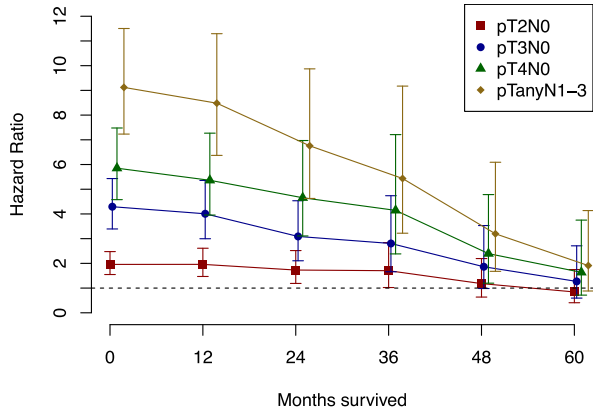
Fig. 1. Conditional cancer specific mortality-free estimates of 13,595 patients with nonmetastatic urothelial carcinoma of the urinary bladder, according to months survived after radical cystectomy. Data were stratified according to T and N stage groupings.

Conversely, attrition due to mortality was the highest in pTanyN1-3 patients (Table 2), as evidenced by conditional CSM-free estimates that ranged from 37.5% to 84.0% at respectively baseline and 5 years of event-free follow-up.

Finally, the 5-year other-cause mortality rates at baseline were 8.0, 9.6, 14.0, 15.4, and 13.3% for respectively pTa/pTis/pT1N0, pT2N0, pT3N0, pT4N0, and pTanyN1-3 patients.

3.3. Multivariable Cox regression models predicting CSM

In MCR models predicting CSM (Fig. 2), T and N stages were independent predictors of CSM risk. However, CSM hazard decreased over time and no more statistically significant difference was recorded at either 48 and 60 months after surgery, relative to referent pTa/pTis/pT1N0. Specifically,



Months survived after surgery	0	12	24	36	48	60
pTa/pTis/pT1N0	Ref	--	--	--	--	--
pT2N0	1.9 (1.5-2.5) p<0.001	1.9 (1.5-2.6) p<0.001	1.7 (1.2-2.5) p=0.004	1.7 (1.1-2.8) p=0.04	1.2 (0.6-2.2) p=0.59	0.8 (0.4-1.7) p=0.64
pT3N0	4.3 (3.4-5.4) p<0.001	4.0 (2.9-5.3) p<0.001	3.1 (2.1-4.5) p<0.001	2.8 (1.7-4.7) p<0.001	1.9 (0.9-3.5) p=0.056	1.3 (0.6-2.7) p=0.53
pT4N0	5.8 (4.6-7.5) p<0.001	5.4 (3.9-7.3) p<0.001	4.6 (3.1-6.9) p<0.001	4.1 (2.4-7.2) p<0.001	2.4 (1.2-4.8) p=0.047	1.6 (0.7-3.7) p=0.23
pTanyN1-3	9.1 (7.2-11.5) p<0.001	8.5 (6.4-11.3) p<0.001	6.7 (4.6-9.9) p<0.001	5.4 (3.2-9.2) p<0.001	3.2 (1.7-6.1) p<0.001	1.9 (0.8-4.1) p=0.10

Fig. 2. Graphical depiction of proportional multivariable Cox regression models derived hazard ratios, predicting cancer-specific mortality in non-metastatic urothelial carcinoma of the urinary bladder patients according to months survived after radical cystectomy. Variable of interest was T and N stage (reference pTa/pTis/pT1N0). Additional adjustment variables consisted of age, gender and ethnicity, histological subtype, grade (low vs. high grade) and chemotherapy status (chemotherapy not received vs. received).

the magnitude of CSM hazard decreases increased with higher stage and was the highest for pTanyN1-3 patients (Hazard ratio [HR] from 9.1 $P< 0.001$ at baseline to HR 1.9 $P= 0.10$ at 60 months after surgery). An intermediate CSM hazard decrease was recorded for stages pT2N0, pT3N0, and pT4N0. The CSM hazards were no more statistically significant at respectively 48 (HR from 1.9 $P< 0.001$ to 1.2 $P = 0.59$), 48 (HR from 4.3 $P< 0.001$ to 1.9 $P= 0.056$) and 60 (HR from 5.8 $P< 0.001$ to 1.6 $P= 0.23$) months after surgery.

In the developed nomogram with its conditional counterpart (Supplementary Fig. 1A and B), the concordance-index (c-index) was 0.69, showing a moderate discrimination capacity (Supplementary Fig. 2). Careful inspection of the actual nomogram showed that its prediction was predominantly based on T stage and to a lesser extent to N stage, with marginal contribution by other variables. Indeed, the c-index of T-stage derived predictions was 0.65 vs. 0.69 for T and N stages combined vs. 0.69 for all variables combined.

4. Discussion

The 2 most contemporary studies [2,3] addressing CS estimates in nmUCUB patients treated with RC are limited by their relatively historic patient composition. Moreover, they do not allow to ascertain conditional CSM-free estimates according to specific T and N stage groupings, that include all possible combinations of pTa–pT4 stages with pN0 vs. pN1–3 stages. Such omission is important since lymph node involvement in bladder cancer is common, occurring in almost 30% of pT2 and 60% of pT3 and pT4 patients [7]. It also has prognostic implications, as evidenced by lower survival rates in each T stage [8], when lymph node involvement is present. We addressed these 2 important limitations by evaluating conditional 5-year CSM-free estimates within a large contemporary population-based cohort of nmUCUB with specific emphasis on T and N stage groupings. Our analyses resulted in several interesting findings.

First, a direct relationship between event-free follow-up duration and CSM-free probability was recorded in all stage groupings: pTa/pTis/pT1N0, pT2N0, pT3N0, pT4N0, and pTanyN1-3. The magnitude of survival gains according to event-free follow-up was the highest in patients with the most aggressive stage groupings, namely those with lymph node involvement. In pTanyN1-3 patients, conditional 5-year CSM-free estimates increased from 37.5% after 1 year to 84.0% after 5 years of event-free follow-up, with a survival gain of 23.6%, relative to baseline. Conversely, patients with less aggressive stage groupings experienced survival gains of progressively lower magnitude, such as from 80.6% after 1 vs. 92.5% after 5 years of event-free follow-up in pT2N0 patients. Finally, patients with pTa/pTis/pT1N0 stage demonstrated CS estimates that were virtually unchanged during a 5-year event-free follow-up (from 90.1% after 1 vs. 91.8% after 5 years of event-free follow-up) with a survival gain of +1.7%. As hypothesized, for patients with stage groupings pT2N0 or higher the CS gains with event-free follow-up are higher than those from historical reports [2,3]. The differences in CS gains according to event-free follow-up validate the heterogeneity in CSM prognosis within nmUCUB patients and further validate the rationale of the current study.

Second, we also identified important differences in CSM during the intervals of observation that distinguish patients with specific T and N stage groupings. The highest rate of attrition due to CSM was recorded in pTanyN1–3 patients, as evidenced by 475 deaths, that accounted for 39.8% of patients at risk during the third year of observation. This interval of time-specific CSM rate are in sharp contrast with those of pTa/pTis/pT1aN0, as evidenced by 26 deaths, that accounted for 3.1% of patients at risk during the second year of observation. These observations validate again the extreme heterogeneity of nmUCUB patients' prognosis and the need for T and N stage specific CS stratification.

Third, graphical representation of HRs for specific event-free follow-up intervals showed a decrease from elevated levels to non-statistically significant levels at 48 months of event free follow-up for pT2N0 and pT3N0, as well as at 60 months for pT4N0 and pTanyN1-3, relative to pTa/pTis/pT1aN0. These changes in HR associated with event-free follow-up intervals validate the importance of

stage specific CS predictions. In clinical practice, these data suggest that few if any additional CSM events may be expected in pT2N0 and pT3N0 individuals with event-free follow-up of 36 months or more. Similarly, in pT4N0 and pTanyN1-3 patients few if any additional CSM events may be expected after event-free follow-up of 48 months or more. Our results are in general agreement with the two more historical reports [2,3]. However, the historical data provided less details due to the lack of combination analyses of T and N stage groupings. More historical data on different primaries showed distinct CS profile according to histology. For example, in kidney cancer [9] and lung cancer patients [10], higher stages showed a decrease in CSM-risk that however did not reach a plateau after 5 years of event-free follow-up. In breast cancer [11] and head and neck squamous carcinomas [12], the greatest gains in CS was also recorded for patients with the poorest initial survival. However, only a minimal improvement was recorded for lower stages, even after a long period of event-free follow-up. In consequence, in broad terms, a similar decreased of hazard over time is applicable across multiple primaries and to most significant extent this decrease is noted for higher disease stages. Nonetheless, primary-specific HRs with nuances between neighboring stages exists. These observations demonstrate that each primary has a distinct CS profile and further emphasize the need for primary-specific, stage-specific, as well as most probably population-specific CS estimates.

Fourth, despite the improved CSM with increasing event-free follow-up, we also recorded an important attrition, in part due to CSM. This attrition predominantly affected patients with more aggressive T and N stage groupings. Specifically, of pTanyN1−3 patients only 12.9% were still alive after 5 years of event-free follow-up. In consequence, CSM gains may be off-set by attrition due to mortality, especially in patients with more aggressive disease phenotype.

Finally, the developed nomogram with its conditional counterpart showed a moderate discrimination capacity, as suggested by the c-index on receiver operator characteristics analysis of 0.69. Additionally, the predictions of the developed nomogram were predominantly based on T stage and to a lesser extent to N stage, with marginal contribution by other variables. For these reasons, the nomogram cannot be endorsed for routine use in clinical practice. Nonetheless, it emphasizes the importance of T and N stages in prediction of CSM in the current patients' cohort. We do believe that the graphical representation of HRs for specific combinations of T and N stages at specific event-free follow-up intervals provides more valuable tools for CS predictions after specific event-free follow-up intervals.

Several take home messages can be generated from our observations. First, the most important conditional CSM-free survival gains will benefit higher T and N stage groupings after event-free follow-up of several years. Second, these gains are unfortunately offset by high attrition rates due to mortality in the same patients, namely those with higher T and N stage groupings. In consequence, when disease phenotype is aggressive, clinicians will may be faced with the dilemma of only few patients to whom the good news of CS gains me be communicated after and event-free follow-up of several years. Conversely, clinicians will be faced with marginal if any CS gains in individuals with most favorable disease characteristics, even after event-free follow-up of several years. Nonetheless, in this scenario marginal or no attrition will be operational. Third, conditional CSM-free estimates vary according to T and N stage groupings and therefore specific T and N stage groupings estimates are required. Last but not least, conditional CSM-free estimates are also sensitive to favorable stage migration that in general applies to more contemporary patients. In consequence periodic updates of TNM stage-specific CS prediction are required. From a clinical perspective, information derived from the current conditional model could be combined with standard pathological stage information obtained at RC to tailor the frequency of imaging and/or tailor the administration of adjuvant therapy.

Despite the strengths of this study, important limitations need to be acknowledged. Our data represents a retrospective analysis with high potential for selection biases. Additionally, recurrence and metastatic progression are not available. Finally, despite large patient population, the amount of details is limited relative to smaller institutional studies. These limitations apply to all population-based analyses that were based on SEER, National Cancer Database or other nation-based data repository.

5. Conclusions

CS showed a direct relationship between event-free follow-up duration and survival probability. Conditional CSM-free estimates increased in proportion with event-free follow-up but also resulted in equally proportional increase in attrition rates.

Conflict of interest

All the authors declare no potential conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.05.020.

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