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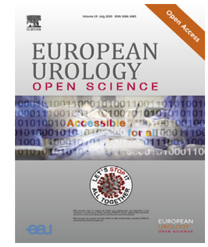

European Association of Urology

Brief Correspondence

Decreasing Non–bladder-cancer Mortality After Radical Cystectomy

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Abstract

Life expectancy is increasing in many parts of the world. Using proportional hazard models for competing risks, we investigated whether this increase has changed outcomes after radical cystectomy in a sample of 1419 consecutive patients treated between 1993 and 2018. During the observation period, the mean age and the proportion of patients with American Society of Anesthesiologists physical status class 3 or 4 increased, whereas the proportion of patients with heart disease decreased. Competing mortality (causes other than bladder cancer) decreased in all subgroups (hazard ratios [HRs] per year ranged from 0.931 to 0.963) and after controlling for increasing age (HRs ranged from 1.018 to 1.081). In an optimal model resulting from an analysis including age (HR per year 1.048, 95% confidence interval [CI] 1.027–1.070; $p < 0.0001$), comorbidity, tumor-related variables, body mass index, (neoadjuvant and adjuvant) chemotherapy and smoking status, the HR per increment for year of surgery was 0.928 (95% CI 0.886–0.973; $p = 0.0019$). The effect of year of surgery was greater than the decrease in competing mortality that may be expected with increasing life expectancy (4 yr for females, 6 yr for males).

Patient summary: In a review of data for 1993–2018, we found that death from other causes after removal of the bladder (radical cystectomy) for bladder cancer decreased over time. This decreasing trend might increase the age limit at which bladder cancer patients can benefit from radical cystectomy in the future.

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Although radical cystectomy (RC) is associated with considerable perioperative mortality and approximately one-third of patients die from disease recurrence within 5 yr [1,2], with the increasing life expectancy in many parts of the world, RC may increasingly be taken into consideration for vulnerable candidates with a short remaining life span in the future [3]. Concern has been expressed that RC may be underused in this population [4,5].

We reviewed data for 1419 consecutive patients undergoing RC for high-risk superficial or muscle-invasive urothelial or dedifferentiated bladder cancer between 1993 and 2018 at a single university center to determine the degree to which competing mortality (causes other than bladder cancer) as a surrogate for life expectancy has changed in recent decades. The median follow-up was 5.3 yr (censored patients) and the median age was 70 yr. Further

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demographic data are listed in Supplementary Table 1. Demographic trends (change in the percentage of patients in certain categories) were analyzed using linear regression analyses. During the observation period, the mean age and the proportion of patients with American Society of Anesthesiologists physical status class 3–4 increased, whereas the proportion of patients with heart disease decreased (Supplementary Table 2). Proportional hazard models for competing risks were used to analyze the combined effects of parameters. The analyses were performed by a senior biostatistician (R.K.) using the SAS v9.4 statistical package; the *p* values reported are not adjusted for multiple testing.

In models containing multiple covariables, later year of surgery was an independent predictor of lower mortality from competing causes (Table 1). In models containing only age as the covariable, competing mortality decreased in all subgroups investigated (Table 2). On controlling for comorbidity (ie, when all the variables analyzed in Table 1 were included in the analysis), year of surgery was also a significant predictor of competing mortality in all subgroups (hazard ratios [HRs] ranging between 0.917 and 0.956, *p* values ranging between 0.0209 and <0.0001). Most of the decrease in competing mortality was attributable to lower non-cancer mortality, but we also found a slight trend for lower second cancer mortality (Supplementary Table 3). This trend was stronger among younger patients and current smokers (Supplementary Table 4).

Decreasing other-cause mortality after RC has been observed in a population-based study of US patients treated between 1988 and 2011, particularly for elderly, unmarried, and male patients [6]. In our study, competing mortality decreased over time in all subgroups (Table 2). With a HR of 1.061 per year of age and 0.952 per increment for year of surgery (Supplementary Table 3), a 10-yr increment for year of surgery corresponded to an approximately 8.5-yr increment in age ($0.951^{10} \times 1.061^{8.5} = 1.001$). This decrease in competing mortality was higher than it may be expected considering the increase of life expectancy during the 26-year observation time period in Germany (4 yr for females and 6 yr for males [7]). The life expectancy increase in Germany particularly affects individuals aged ≥65 yr and is mostly attributable to decreases in cardiovascular mortality and, to a lesser degrees, cancer mortality [8]. It is likely that this development was reflected in our study. The contribution of second cancer mortality (Supplementary Tables 3 and 4) to the decrease in competing mortality was lower than that of noncancer mortality (Supplementary Tables 3 and 5). In Germany, tobacco use decreased during the observation period [9]. Although the proportion of current smokers did not decrease in our sample (Supplementary Table 2), less excessive tobacco use might explain some of the findings (decreasing second-cancer mortality for younger patients, males, and current smokers; Supplementary Table 4). Improvements in the prevention, diagnosis, and treatment of cardiovascular disease have contributed to the recent decrease in cardiovascular mortality in Germany [8]. These achievements are considered the main contributors to the increase in life expectancy observed in Eastern Germany [8]. In our study population, the prevalence of heart disease decreased after adjustment for the mean age in each year (Supplementary Table 2). At the same time, the age-adjusted prevalence of hypertension increased (Supplementary Table 2). Better diagnostics and awareness of risk factors and concomitant improvements in cardiac health could explain these observations.

The benefit of immediate RC for patients aged ≥70 yr with high-risk T1G3 bladder cancer (for whom reasonable alternatives to RC are available) has been questioned [10]. Decreasing competing mortality might shift this limit to older ages in the future. It has been hypothesized that decreasing other-cause mortality after RC may reflect better patient selection and might represent a positive quality indicator [6]. The results of our study do not support this hypothesis. After controlling for increasing mean age, changes in the comorbidity risk profile fit better to the

Table 1 – Full and optimal multivariate proportional-hazard models for competing risks predicting competing mortality (causes other than bladder cancer) after radical cystectomy, analyzing age and year of surgery together with tumor-related, comorbidity-related, and other demographic variables. The optimal model resulted from stepwise elimination of nonsignificant variables from the full model in monotonic backward steps

Hazard	Full model		Optimal model	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (CVE, per year)	1.045 (1.023–1.068)	<0.0001	1.048 (1.027–1.070)	<0.0001
Year of surgery (CVE, per year)	0.932 (0.889–0.978)	0.0042	0.928 (0.886–0.973)	0.0019
Body mass index (CVE, per kg/m^2)	0.999 (0.961–1.039)	0.9638		
Charlson comorbidity index (CVE, per point)	1.179 (1.098–1.266)	<0.0001	1.177 (1.099–1.261)	<0.0001
ASA class 3-4 (vs 1–2)	1.826 (1.263–2.641)	0.0014	1.742 (1.216–2.495)	0.0025
Female gender (vs male)	0.976 (0.666–1.432)	0.9030		
Extravesical disease (vs organ confined [a])	1.068 (0.747–1.527)	0.7173		
Positive lymph nodes (vs no or unknown)	0.695 (0.424–1.138)	0.1477		
Adjuvant cisplatin-based CTx (vs no/unknown)	0.411 (0.199–0.849)	0.0163		
Any neoadjuvant CTx (vs no)	0.291 (0.068–1.251)	0.0972	0.352 (0.188–0.659)	0.0011
Current smokers (vs others [b])	1.460 (0.992–2.149)	0.0549	1.458 (1.004–2.116)	0.0476

ASA = American Society of Anesthesiologists; CI = confidence interval; CTx = chemotherapy; CVE = continuous variable; HR = hazard ratio.
[a] Irrespective of lymph node status.
[b] Patients with unknown smoking status, nonsmokers. and former smokers.

Table 2 – Bivariate proportional-hazard models for competing risks showing the relationship between year of surgery and competing mortality (causes other than bladder cancer) in different subgroups after controlling for patient age

Hazard	HR (95% CI)	*p* value
Age <65 yr		
Age (continuous variable, per year)	1.073 (1.029–1.119)	0.0009
Year of surgery (continuous variable, per year)	0.955 (0.926–0.986)	0.0041
Age <70 yr		
Age (continuous variable, per year)	1.053 (1.025–1.082)	0.0002
Year of surgery (continuous variable, per year)	0.955 (0.931–0.979)	0.0004
Age ≥70 yr		
Age (continuous variable, per year)	1.049 (1.020–1.079)	0.0010
Year of surgery (continuous variable, per year)	0.953 (0.934–0.973)	<0.0001
Age ≥75 yr		
Age (continuous variable, per year)	1.018 (0.968–1.079)	0.4934
Year of surgery (continuous variable, per year)	0.953 (0.934–0.973)	<0.0001
Age ≥80 yr		
Age (continuous variable, per year)	1.049 (0.942–1.169)	0.3839
Year of surgery (continuous variable, per year)	0.931 (0.930–0.982)	0.0011
American Society of Anesthesiologists class 3-4		
Age (continuous variable, per year)	1.038 (1.019–1.058)	0.0001
Year of surgery (continuous variable, per year)	0.947 (0.928–0.968)	<0.0001
American Society of Anesthesiologists class 1–2		
Age (continuous variable, per year)	1.069 (1.047–1.090)	<0.0001
Year of surgery (continuous variable, per year)	0.939 (0.915–0.963)	<0.0001
Surgery in 1993–2005		
Age (continuous variable, per year)	1.055 (1.036–1.075)	<0.0001
Year of surgery (continuous variable, per year)	0.939 (0.904–0.976)	0.0015
Surgery in 2006–2018		
Age (continuous variable, per year)	1.065 (1.044–1.110)	<0.0001
Year of surgery (continuous variable, per year)	0.945 (0.905–0.988)	0.0386
Female		
Age (continuous variable, per year)	1.077 (1.044–1.110)	<0.0001
Year of surgery (continuous variable, per year)	0.963 (0.929–0.998)	0.0386
Male		
Age (continuous variable, per year)	1.059 (1.044–1.076)	<0.0001
Year of surgery (continuous variable, per year)	0.950 (0.934–0.967)	<0.0001
Married		
Age (continuous variable, per year)	1.070 (1.052–1.088)	<0.0001
Year of surgery (continuous variable, per year)	0.949 (0.931–0.967)	<0.0001
Single, widowed, divorced, unknown marital status (*n* = 1)		
Age (continuous variable, per year)	1.042 (1.020–1.065)	0.0002
Year of surgery (continuous variable, per year)	0.953 (0.926–0.981)	0.0009
University degree/master craftsperson		
Age (continuous variable, per year)	1.061 (1.025–1.099)	0.0009
Year of surgery (continuous variable, per year)	0.956 (0.921–0.992)	0.0169
No university degree/master craftsperson		
Age (continuous variable, per year)	1.065 (1.048–1.082)	<0.0001
Year of surgery (continuous variable, per year)	0.952 (0.931–0.973)	<0.0001
Current smoker		
Age (continuous variable, per year)	1.054 (1.032–1.077)	<0.0001
Year of surgery (continuous variable, per year)	0.947 (0.922–0.972)	<0.0001
Nonsmoker		
Age (continuous variable, per year)	1.081 (1.056–1.107)	<0.0001
Year of surgery (continuous variable, per year)	0.954 (0.930–0.978)	0.0002
Whole sample, only events occurring >90 d after RC		
Age (continuous variable, per year)	1.062 (1.047–1.077)	<0.0001
Year of surgery (continuous variable, per year)	0.947 (0.931–0.964)	<0.0001

CI = confidence interval; HR = hazard ratio; RC = radical cystectomy.

effects of improving cardiac health associated with increasing life expectancy (Supplementary Table 2). Acceptance of greater (tumor- and comorbidity-related) risks as experience with RC increases might even have the opposite effect. The trend towards increasing bladder cancer mortality fits this hypothesis (Supplementary Table 3). Although adverse tumor-related parameters remained stable over the observation period, the parameters evaluated do not necessarily take palliative RC, which has a particularly poor survival rate, into account, and palliative RC might have been performed more frequently in recent times. Overall, the decrease in noncancer mortality was outweighed by an increase in bladder cancer mortality, resulting in a trend towards increasing overall mortality (Supplementary Table 3).

This study has several limitations. Multiple testing should be taken into consideration when interpreting the *p* values. The decrease in competing mortality during the observation period outweighed the effect that would be expected with increasing life expectancy. By contrast, in our radical prostatectomy series treated between 1992 and 2016 (in which prostate cancer mortality accounted for only 22% of all deaths recorded), the size of this effect corresponded well with what was expected with the increase in life expectancy over time [11]. The elimination of the huge proportion of patients experiencing bladder cancer mortality, accounting for 56% of all deaths recorded in the study and occurring (in contrast to other-cause mortality) relatively early after surgery and virtually independent of age (Supplementary Table 6), might explain this observation.

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Study concept and design: Froehner.
Acquisition of data: Froehner, Heberling, Novotny, Hübler.
Analysis and interpretation of data: Froehner, Koch.
Drafting of the manuscript: Froehner, Koch, Hübler, Heberling, Borkowetz, Novotny, Wirth, Thomas.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2021.04.007.

References

[1] Nuhn P, May M, Sun M, et al. External validation of postoperative nomograms for prediction of all-cause mortality, cancer-specific mortality, and recurrence in patients with urothelial carcinoma of the bladder. Eur Urol 2012;61:58–64.
[2] Fonteyne V, Ost P, Bellmunt J, et al. Curative treatment for muscle invasive bladder cancer in elderly patients: a systematic review. Eur Urol 2018;73:40–50.
[3] Erlich A, Zlotta AR. Treatment of bladder cancer in the elderly. Investig Clin Urol 2016;57(Suppl 1):S26–35.
[4] Williams SB, Hudgins HK, Ray-Zack MD, et al. Systematic review of factors associated with the utilization of radical cystectomy for bladder cancer. Eur Urol Oncol 2019;2:119–25.
[5] Donat SM, Siegrist T, Cronin A, Savage C, Milowsky MI, Herr HW. Radical cystectomy in octogenarians—does morbidity outweigh the potential survival benefits? J Urol 2010;183:2171–7.
[6] Rosiello G, Knipper S, Palumbo C, et al. Rates of other-cause mortality after radical cystectomy are decreasing over time—a population-based analysis over two decades. J Surg Oncol 2020;121:1329–36.
[7] United Nations Department of Economic and Social Affairs World population prospects 2019. Mortality data. Life expectation at birth. https://population.un.org/wpp/Download/Standard/Mortality/.
[8] Klenk J, Rapp K, Büchele G, Keil U, Weiland SK. Increasing life expectancy in Germany: quantitative contributions from changes in age- and disease-specific mortality. Eur J Public Health 2007;17:587–92.
[9] Seitz NN, Lochbühler K, Atzendorf J, Rauschert C, Pfeiffer-Gerschel T, Kraus L. Trends in substance use and related disorders—analysis of the Epidemiological Survey of Substance Abuse 1995 to 2018. Dtsch Arztebl Int 2019;116:585–91.
[10] Kulkarni GS, Finelli A, Fleshner NE, Jewett MA, Lopushinsky SR, Alibhai SM. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. PLoS Med 2007;4:e284.
[11] Froehner M, Koch R, Hübler M, Lindner M, Wirth MP, Thomas C. Quantifying the relationship between increasing life expectancy and non-prostate cancer mortality after radical prostatectomy. Urology 2020;142:174–8.

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