Brief Correspondence

Decreasing Non–bladder-cancer Mortality After Radical Cystectomy

Michael Froehner a, *, Rainer Koch h, i, Ulrike Heberling a, Angelika Borkowetz b, Matthias Hübler c, Vladimir Novotny d, Manfred P. Wirth b, Christian Thomas b

Article info

Article history:
Accepted April 22, 2021

Associate Editor:
Guillaume Ploussard

Keywords:
Life expectancy
Age
Comorbidity
Bladder cancer
Radical cystectomy
Mortality
Competing risk analysis
Selection

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, (neo)adjuvant 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.

© 2021 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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
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             |
|                                             |                    |                     |
| Age (CVE, per year)                         | 1.045 (1.023–1.068) | -0.0001             |
| Year of surgery (CVE, per year)             | 0.932 (0.889–0.978) | 0.0042              |
| Body mass index (CVE, per kg/m²)            | 0.999 (0.961–1.039) | 0.9638              |
| Charlson comorbidity index (CVE, per point) | 1.179 (1.098–1.266) | -0.0001             |
| ASA class 3–4 (vs 1–2)                      | 1.826 (1.263–2.641) | 0.0014              |
| Female gender (vs male)                     | 0.976 (0.666–1.432) | 0.9030              |
| Extravesical disease (vs organ confined *)  | 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 noadjuvant CTx (vs no)                  | 0.291 (0.068–1.251) | 0.0972              |
| Current smokers (vs others *)               | 1.460 (0.992–2.149) | 0.0549              |

ASA = American Society of Anesthesiologists; CI = confidence interval; CTx = chemotherapy; CVE = continuous variable; HR = hazard ratio.

* Irrespective of lymph node status.

* Patients with unknown smoking status, nonsmokers, and former smokers.

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 (0.95110 × 1.06110 = 1.001). This decrease in competing mortality was higher than it was 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 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 craftsman                                     |                  |         |
| 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 craftsman                                   |                  |         |
| 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.

The 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.

Author contributions: Michael Froehner 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.

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, Borkowitz, Novotny, Wirth, Thomas.

Critical revision of the manuscript for important intellectual content: Froehner, Koch, Hübler, Heberling, Borkowitz, Novotny, Wirth, Thomas.

Statistical analysis: Koch, Froehner.

Obtaining funding: None.

Administrative, technical, or material support: Wirth, Thomas.

Supervision: Wirth, Thomas.

Other: None.

Financial disclosures: Michael Froehner certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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.evuro.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] Rosselli 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, Flesher 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, Hübner 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.