

# Factors affecting one-year survival after radical cystectomy: A prospective study

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**Citation:** Kwiatkowska M, Dybowski B, Kuczkiewicz-Siemion O, et al. Factors affecting one-year survival after radical cystectomy: A prospective study. Cent European J Urol. 2017; 70: 238-244.

## Article history

Submitted: June 11, 2017

Accepted: Aug. 4, 2017

Published online: Aug. 8, 2017

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**Introduction** Survival after radical cystectomy (RC) is affected by various factors. Significance of preoperative health status and its influence on treatment outcome is uncertain. The aim of the study was to prospectively evaluate overall survival, cause of death and the role of comorbidities in mortality during the first 12 months following RC.

**Material and methods** All patients who underwent RC between January 2014 and May 2016 for T1–T4 bladder cancer in a single center were prospectively followed. Stage and comorbidities were explored as predictors of overall survival (OS). Patient status was assessed for at least 12 months.

**Results** Follow-up was available for 25 men and 19 women at the mean age 67. Median time of follow-up for survivors was 16 months. Six-month and 1-year OS was 84% and 77%. Out of 11 deaths, 8 were related to cancer progression and 3 patients died for other causes. All deaths apart from one occurred in the first year after surgery. One-year OS was affected mostly by tumor stage: 95% for pT1-2 vs. 62.5% for pT3-4;  $p = 0.01$ . Worse outcome was found in patients  $\geq 72$  years old, (44% vs. 86%;  $p = 0.02$ ) and among women (63% vs. 88%;  $p = 0.07$ ). When patients who died were compared to survivors the following distribution of comorbidities was found: diabetes mellitus – 30.0% vs. 11.8%,  $p = 0.3$ ; history of stroke – 30.0% vs. 2.9%,  $p = 0.1$ ; thyroid disease – 30.0% vs. 11.8%,  $p = 0.3$ .

**Conclusions** Majority of patients died because cystectomy was performed too late. History of stroke, diabetes mellitus, and thyroid diseases should be assessed as possible risk factors in larger studies.

**Key Words:** bladder cancer <> cystectomy <> diabetes mellitus <> stroke <> thyroid gland <> mortality

## INTRODUCTION

Bladder cancer (BC) is a significant global health concern, being the ninth most common cancer with more than 330 000 new cases per year and causing more than 30 000 deaths annually [1]. The incidence of BC is constantly rising and increasing with advancing age [2]. Radical cystectomy (RC) and a pelvic lymph node dissection (PLND), followed by urinary diversion is considered the gold-standard treatment for muscle-invasive and high risk non-muscle invasive BC [3]. According to the large analysis on outcomes after RC, the 5-year overall survival (OS) is estimated between 50% and 80%, but it varies when the oncological

staging of the disease is concerned [4]. Some of the most significant predictors of overall survival are well known: stage, grade, nodal status, neoadjuvant chemotherapy, smoking habits [5], age [6], general condition status [7], time delay from the first symptoms to surgery [8] and the American Society of Anesthesiologists Score [9]. Recently, searching for predictive models of survival incorporating effects of comorbidities on early survival and perioperative risk have become of broad and current interest [10]. Epidemiological indices for bladder cancer in Poland are disturbing when compared to other European countries and the country ranks second in Europe in terms of mortality [11].

Various factors affecting the early survival have not been investigated meticulously yet. Furthermore, there is no evidence of the prospective analysis concerning this matter performed in Poland.

Following the recent retrospective study on the effects of comorbidities on a 5-year overall survival [12], we decided to continue the investigation on factors affecting early survival after RC prospectively. The primary objective was to assess causes of death during the first 12 months after RC. The secondary objective was to evaluate effects of comorbidities on mortality during this period.

## MATERIAL AND METHODS

All patients who underwent RC for T1–T4 bladder cancer between January 2014 and May 2016 in a single academic center were prospectively included and followed. Diagnosis of other than invasive bladder cancer (of any histological type) and lack of relevant clinical information about the follow-up during 12 months following RC were exclusion criteria. Preoperative clinical staging of each patient included transurethral resection (TURBT), physical examination, chest and abdominal CT scans. Neoadjuvant chemotherapy was not used in the specified group as we did not regard existing evidence strong enough to delay surgery.

Cystectomy was accompanied by extended bilateral lymphadenectomy (external, internal and common iliac, obturator and presacral lymph nodes) in all cases. Patients with extravesical disease were referred to oncological centers, where adjuvant chemo- or radiotherapy was left to the decision of a physician. Ileal conduit was a predominant type of urinary diversion. Staging of all specimens obtained during the surgery was performed according to the 2009 TNM staging system of the American Joint Committee on Cancer [13]. Grading was established according to the 2004 WHO criteria. Cancer stage and major comorbidities were related to the surgery outcome. The primary endpoint was the 12-month overall survival. Patients status was assessed with abdominal and chest CT scans, blood tests and family reports concerning the progression of the disease and health condition, every 4 to 6 months for at least 12 months. Descriptive analyses were used to characterize the total cohort. The variables that were tested for significance in the analysis are as follow: stage and grade of the tumor, time from the first episode of hematuria to cystectomy, time from the staging resection (or the last resection in case of recurrent tumors) to cystectomy, age, sex, perioperative and postoperative complications, specific comorbidities such as hypertension, congestive heart disease and myocardial infarction,

cerebrovascular incidents, chronic obstructive pulmonary disease, diabetes mellitus (DM), moderate or severe renal disease and thyroid disease.

Follow-up was completed on April 30<sup>th</sup>, 2017 and defined as the time between the cystectomy and date of death or date of censoring, whichever came first.

Univariate analysis was performed to identify factors associated with survival. Overall survival (OS) was calculated from the date of cystectomy to the date of death.

Kaplan-Meier estimates of the survival function, Fischer's exact test and chi-square test were utilized for univariate statistical analysis, with  $P < 0.05$  considered statistically significant.

Distribution of values for analyzed variables was checked for normality using a Shapiro-Wilk test. When it was proved to be normal, mean and standard deviation values were implemented. If contrary, median values and quartiles in brackets were presented.

## RESULTS

In the specified period, 48 patients underwent RC. Four patients were excluded as clinically relevant information was lacking or cystectomy was performed for a reason other than invasive bladder cancer (BC). One patient did not agree for the follow-up CT scan and so the observation ended 6 months following the surgery. Follow-up was available for 25 men and 19 women of the mean age of 67 (46;85). Their clinical and pathological characteristics are summarized in Table 1. Type of urine diversion was not considered as a predicting factor as in 41 patients ileal conduit was performed, while ureterocutaneostomy was used twice and ileal bladder was created in one patient. Adjuvant chemotherapy was used for 10 fit patients with metastases to the nodes or invasion of the adjacent organs, prostate or vagina.

Median (min-max) of the follow-up for survivors was 16 (12–32) months. Six-month and 12-month overall survival (OS) was available for all patients and reached 84% and 77%, respectively.

For 17 patients, follow-up was longer than 18 months and in this group OS was 100%.

Out of 11 deaths, 8 were related to cancer progression confirmed in the imaging studies and 3 patients died of other causes. As a result, cancer – specific survival reached 82% after 12 months. All deaths apart from one occurred in the first year after surgery. Characteristics of patients who died are presented in Table 2. Significantly worse outcome was in patients  $\geq 72$  years old, and with stage pT3–4. Also a trend was found for a higher mortality rate among women. Median time from hematuria to the surgery (5 months for the whole group), as well as, median

time from the last TURBT (2 months for the whole group) was not significantly related with the survival ( $P = 0.95$  and  $P = 0.5$  respectively).

When patients who died were compared with survivors the following distribution of comorbidities was found: diabetes mellitus – 30.0% vs. 11.8%,  $P = 0.3$ ; history of stroke – 30.0% vs. 2.9%,  $P = 0.1$ ; thyroid disease – 30.0% vs. 11.8%,  $P = 0.3$ ; ischemic heart disease – 14.7% vs. 10.0%,  $P = 0.96$ ; chronic obstructive pulmonary disease – 20.0% vs. 17.6%,  $P = 0.84$ . One-year OS for patients with/without specific comorbidities is shown in Table 3, while Kaplan-Meier curves for chosen variables are presented in Figures 1 and 2. Intra- and postoperative complications Grade 3–5 in Clavien-Dindo classification occurred in 17 patients (39%), including 6 of 10 patients who died and 11 of 34 survivors (32%). Two patients died as a consequence of sequence of postoperative complications. In both cases, venous thromboembolism was diagnosed either before or after surgery (Table 2). There was only one death related neither to cancer progression nor to postoperative complications. Mean length of postoperative hospital stay was insignificantly longer for patients who died (25 days) than for survivors (19 days).

## DISCUSSION

It is suggested that health status considerably affects survival after oncological therapy. However, impact of comorbidities on the outcome of patients

**Table 1.** Patients' clinical and pathological characteristics with 1-year overall survival calculated for subgroups

Variable	No of patients	1-year OS (%)	p-value
<b>Gender</b>			
Female	19	12 (63%)	0.07
Male	25	22 (88%)	
<b>Age</b>			
≤72 yrs	35	30 (86%)	0.02
>72 yrs	9	4 (44%)	
<b>Pathological stage</b>			
pT1	8	7 (87%)	0.01 for T1-2 vs. T3-4
pT2	12	12 (100%)	
pT3	15	9 (60%)	
pT4	9	6 (67%)	
<b>Lymphnode status</b>			
N0	29	24 (83%)	0.3 for N0 vs. N+
N1	4	2 (50%)	
N2	11	8 (72%)	
<b>Grade</b>			
LG	4	4 (100%)	0.6
HG	40	28 (70%)	
CIS			
<b>Present</b>			
Present	6	5 (83%)	0.7
Absent	38	29 (76%)	

OS – overall survival

**Table 2.** Patients who died after radical cystectomy, their cancer characteristics, comorbidities and postoperative complications divided by the cause of death

Sex/Age	T	N	Grade/Type	OS	Comorbidities	Postoperative complications
<b>Cancer – related deaths</b>						
M73	3A	2	HGUC	4	COPD, CVA	–
K80	3B	1	HGSSC	8	–	–
K67	4A	2	HGUC	6	DM	Wound infection
K85	3B	2	HGUC	10	–	–
M63	4A	2	HGUC	3		
M62	4A	2	HGUC	13	CVA, DM IHD	Evisceration
K61	3A	0	HGCU	10	–	–
K65	4A	1	HGSSC	6	Thyr	Ileal anastomosis dehiscence, wound infection
<b>Other – cause deaths</b>						
M78	3A	0	HGUC	3	COPD	Ileus, Atrial fibrillation, ureteroileal anastomosis leakage, VTE, intra abdominal infection, septic shock
K73	3A	0	HGUC	1	CVE, DM, Thyr, VTE	Hypovolemic shock, ureteroileal anastomosis leakage, MDR sepsis
K64	1	0	HGUC	6	IHD, Thyr, dialysis	–

COPD – chronic obstructive pulmonary disease; CVA – cerebro vascular accident; DM – diabetes mellitus; HG – high grade; IHD – ischemic heart disease; MDR – multi drug resistance; SSC – squamous cell carcinoma; Thyr – thyroid disease; UC – urothelial carcinoma; VTE – venous thromboembolism

**Table 3.** One-year overall survival depending on specific comorbidities and complications. Complication severity was graded according to Clavien-Dindo classification

Variable	N (%)	1 year overall survival (present vs. absent)	p-value
Arterial hypertension	31	81% vs. 71%	0.5
Ischemic heart disease	7	83% vs. 76%	1.0
Thyroid disease	7	57% vs. 82%	0.3
Chronic obstructive pulmonary disease	8	75% vs. 78%	0.8
Chronic renal disease	9	78% vs. 78%	1.0
Diabetes mellitus	8	63% vs. 81%	0.5
Cerebrovascular event	5	40% vs. 83%	0.1
Postoperative complications grade 3–5	17	71% vs. 81%	0.5

after RC is still uncertain. Current literature does not answer whether any comorbidity/performance indices can be used in decisions on management of invasive bladder cancer. Several groups still underline the need of external, prospective validation of such tools [14]. As local factors such as population health status or access to specialized medical centers may influence treatment outcome, we decided to carry out this first prospective analysis of early survival after radical cystectomy in Poland to understand effects of disease stage and comorbidities on poor survival after cystectomy reported in previous Polish studies. Surprisingly, one-year survival reported in this series is significantly higher than in the previous study from our center (77% vs. 58.7%) [12]. More restrictive patient selection according to the disease stage and comorbidities as well as implementation of extended lymphadenectomy in all patients may be responsible for that significant improvement.

In the current study special attention was paid to the effect of comorbidities, although disease stage was also investigated. Remarkably, the direct effect of comorbidities was not significant in the first 12 months after surgery as the majority of deaths occurred as a result of BC progression. Small size of the group precluded obtaining significant differences, but it must be stressed that prevalence of three diseases among patients who died was clearly higher than in survivors, that is stroke, DM, and thyroid disease.

In the previous study from the same center [12], a strong trend toward significance for association of OS and DM in patients after RC was found with 10% 5-year OS for diabetics. This association was confirmed here with very low, 62% 1-year OS in this group. Recent paper [15] states that the influence of diabetes as a risk factor for BC may be elucidated

by detection bias, due to increased urinary screening of patients with albuminuria, but this argument is contrary to our findings. Our unpublished results show no difference in stage, grade, and recurrence rate of primary tumors between diabetics and non-diabetics. Different mechanism must explain worse outcomes after RC with possible immunologic, angiogenic or genetic effects.

Difference in frequency of stroke history was even more striking with 30% of affected patients who died and only one case among those who survived. Patients with aggressive cancer frequently have strokes, both from traditional risk factors and from mechanisms unique to malignancy like: hypercoagulability, non-bacterial thrombotic endocarditis, direct tumor compression of blood vessels, or treatment-related effects [16]. In our study it was stroke which was first. There are very few studies which discuss the impact of this comorbidity on survival after RC. Recently, in the study presented by Dell'Oglio et al., cerebrovascular disease was proven to be one of the most accurate variables used in the Deyo adaptation of the Charlson Comorbidity Index [17].

Thromboembolism is a settled severe and life-threatening complication of major surgeries, especially in the pelvis [18]. This is not surprising that this condition was mentioned either as a comorbidity or a complication in two out of three non-cancer-related deaths despite heparin-based prophylaxis started the day before surgery and continued for at least four weeks after surgery.

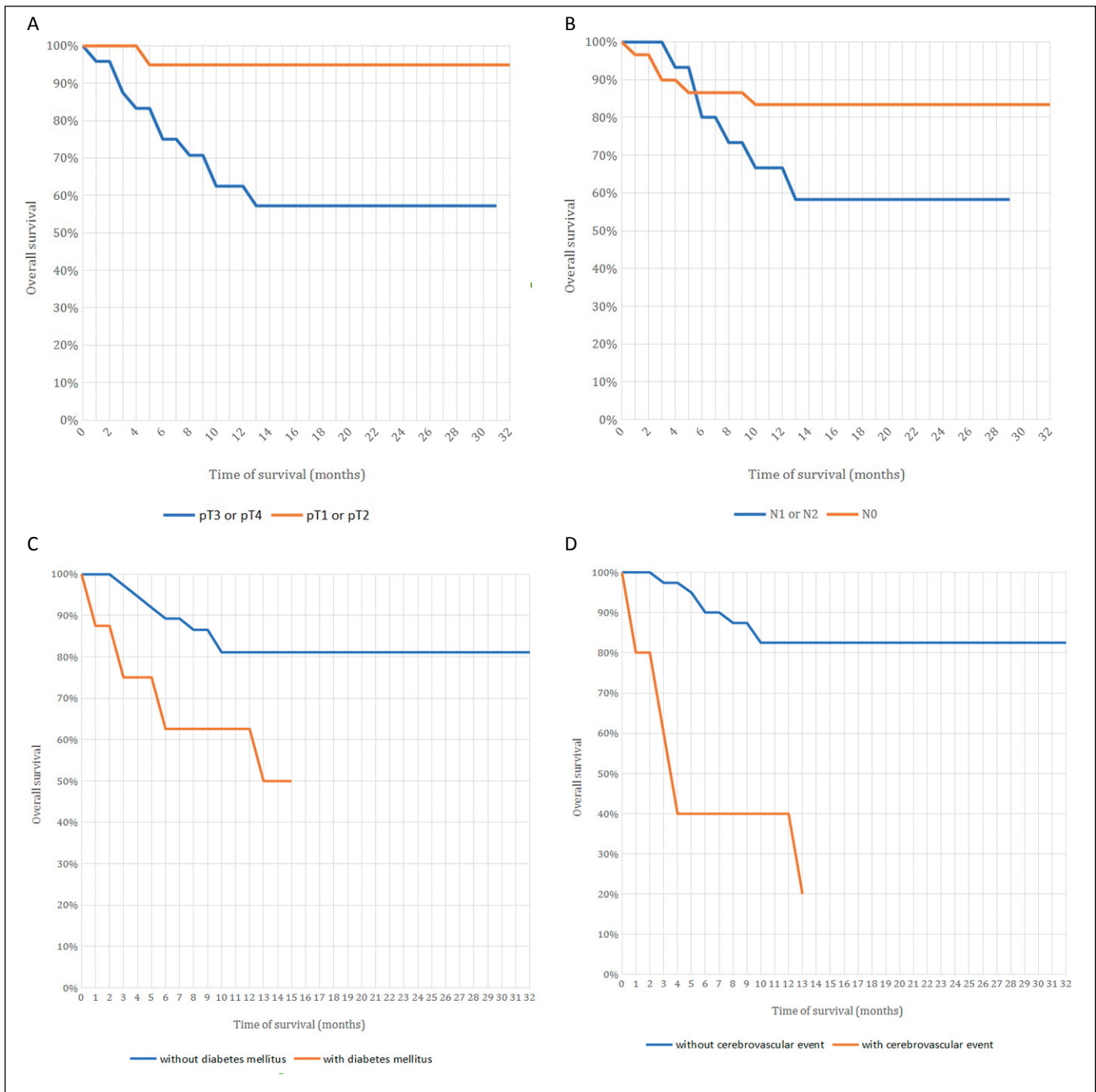
Age is not a contraindication nor a comorbidity. There is a number of studies showing comparable RC outcomes in the octogenarian [19]. Despite those studies, in our group age above 72, there was a significant relation to the risk of death. The comparable analysis conveys the similar information, concerning the age of either 75 or 80 as associated with worse survival [14, 20].

Gender is another demographic variable important for postcystectomy outcome prediction. Dramatic difference to the disadvantage of female patients was found in this study, which is consistent with findings from other groups [21, 22]. However, Mitra et al. proved that this was tumor stage at the time of surgery, which was responsible for that difference. When a large cohort of female patients was well-matched with a cohort of male patients, the difference of survival disappeared [23]. Higher stages among women can be explained by some independent variables like age or delayed diagnosis and surgery. Differential diagnosis of hematuria in women may be more troublesome [24]. That is why some authors underline the need to improve the standardization of hematuria evaluation [25].

Tumor stage and node status are always the best predictors of survival. However, in both our studies, node status was not related to survival. Although in all but one cancer death case, metastases to nodes were confirmed, still a large proportion of patients with positive lymph nodes was found among survivors. On the contrary, extension of the tumor beyond the bladder wall brings very

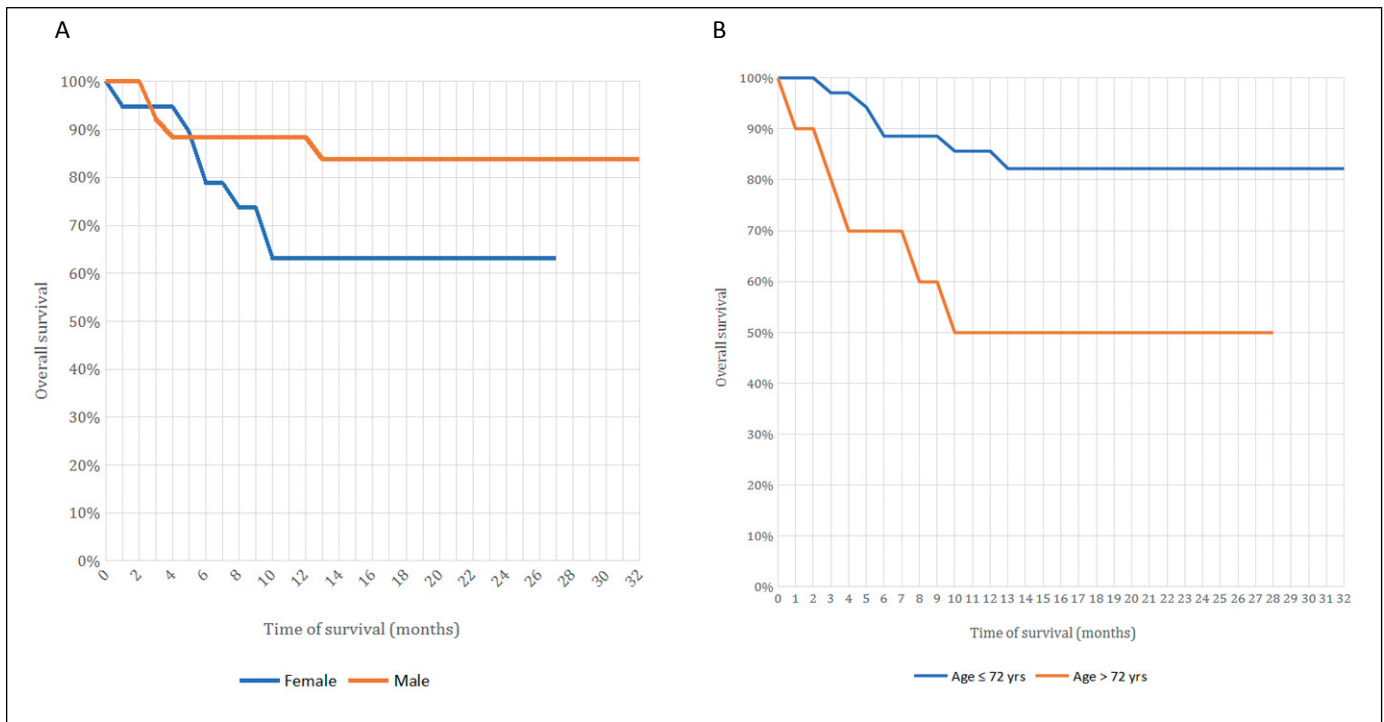
high risk of progression and death. It seems that either lymphadenectomy has its positive effect on survival or local growth of the tumor makes the risk of dissemination higher than in case of the lymphatic route.

Due to its single – center construction and small number of patients enrolled prospectively, we were not able to reliably confirm the effects of comorbid-



**Figure 1.** The Kaplan–Meier estimates of overall survival related to specific variables: **A)** tumor stage, **B)** nodal status, **C)** diabetes mellitus, **D)** cerebrovascular event before cystectomy.





**Figure 2.** The Kaplan–Meier estimates of overall survival related to specific variables: **A)** gender, **B)** age.

ties on survival after cystectomy. Nevertheless, the main aim which was to evaluate the reasons of a high death rate after cystectomy was achieved.

## CONCLUSIONS

Advanced tumor stage found in more than half of the group was responsible for the progression and was the leading cause of death after RC in our cen-

ter. The consequence of DM, CVEs and thyroid disease for survival need larger cohorts to be explained. Careful preoperative evaluation, close follow-up implementation, and adjuvant therapy should be considered in elderly patients with advanced disease and those comorbidities.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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