Prognostic factors for survival after radical cystectomy for muscle-invasive urothelial bladder cancer

¹Andrei Boc, ²Ştefan C. Vesa, ³Alexandra A. Poienar, ⁴Bianca A. Azamfirei, ¹Cristian Porumbel, ¹Nicolae Crişan, ¹Ioan Coman

¹ Department of Urology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ² Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ³ Department of Ginecology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁴ "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. Objective: to observe the mortality rate at two years after radical cystectomy for muscle-invasive urothelial bladder cancer and to establish the value of several parameters as prognostic factors for survival. Material and methods: the study included 121 patients (63.9±7.8 years; 109 (90.1%) men and 12 (9.9%) women) that underwent radical cystectomy for muscle-invasive urothelial bladder cancer. Demographic, diseases and surgery related data were recorded. Patients were followed for 2 years after the surgery and the date of death was recorded.Results: During the follow-up of 23.6 (14.3; 40.5) months we recorded 53 (43.8%) deaths. The survival analysis identified the parameters independently associated with the mortality. The stages III-IVa were associated with the highest HR (3.3). Patients that underwent open cystectomy or presented low preoperative hemoglobin were also more likely to die during the two years follow-up period after the surgery (HR 2.3, HR 2.1 respectively). Conclusions: Almost half of the patients died in two years after radical cystectomy for muscle-invasive urothelial bladder cancer. Advanced disease, open cystectomy and preoperative anemia were independent prognostic factors for mortality.

Key Words: muscle-invasive urothelial bladder cancer, prognostic, mortality, radical cystectomy.

Corresponding author: N. Crişan, email: drnicolaecrisan@gmail.com

Introduction

Urothelial bladder cancer is the most frequent type of bladder cancer. It is the seventh most common cancer in men and three times more frequent than in women. In Romania, bladder cancer is the forth most common cancer in men, after lung, colon and prostate (Ferlay et al 2015).

Muscle-invasive urothelial bladder cancer is the most common bladder cancer. It is a heterogenous pathology with relative high recurrence rate. The prognosis of the disease is very difficult exactly because of the multiple factors that can interact with the recurrence and the survival. However, the prognosis is very important due to the fact that the management of the disease depends on the prognosis. Most frequent parameters studied for their value as prognostic factors include: age, gender, genetic markers, TNM stadialization, tumor grading, radiotherapy and chemotherapy, lymphatic nodes status, hemoglobin levels, C reactive protein (Karakiewicz et al 2006; Ishioka et al 2012; Riester et al 2012).

The aim of the study was to observe the mortality rate at two years after radical cystectomy for muscle-invasive urothelial bladder cancer and to establish the value of several parameters as prognostic factors.

Material and method

The study was prospective, longitudinal, analytic, observational and cohort. Consecutive patients, aged over 18 years, that underwent radical cystectomy (open or laparoscopic) for muscle-invasive urothelial bladder cancer or non-muscle invasive urothelial bladder cancer with high risk of progression, in the Department of Urology from Municipal Clinical Hospital of Cluj-Napoca, between July 2011 - April 2015, were included in the study. All patients signed an informed consent. The study protocol was examined and approved by the Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy

The exclusion criteria were: patient did not sign the informed consent form, patients diagnosed with nonurothelial carcinoma, patients with another active cancer, patients that died in the first month after the surgery.

We recorded several general data: age, gender, body mass index (BMI), history of cardiac diseases or diabetes mellitus, preoperative hemoglobin (values 12-16 g/dl for women, 13-16.5 g/dl for men). Cancer related data included: tumor stage and grading, neoadjuvant chemotherapy or radiotherapy, postoperative chemotherapy or radiotherapy. Surgery related data were noted: type of surgery, type of diversion, the need for reintervention, postoperative creatinine (normal values 0.8-1.2 mg/

Table 1. Comparison between deceased and survivors

Variables		Deceased	Survivors	p
Age		66 (58.5; 70)	62 (59; 69)	0.1
Age > 62 years		39 (73.6%)	33 (38.5%)	0.009
Gender	Female	7 (13.2%)	5 (7.1%)	0.4
	Male	46 (86.8%)	63 (92.6%)	
BMI (kg/m²)		23 (22; 27)	26 (24; 28)	0.3
Preoperative cardiac diseases		44 (83%)	52 (76.5%)	0.5
Preoperative diabetes mellitus		11 (20.8%)	14 (20.6%)	1
Preoperative hemoglobin (g/dl)		11.3±1.7	12.4±1.7	0.001
Preoperative hemoglobin < 11.6 g/dl		30 (56.6%)	19 (27.9%)	0.003
Postoperative creatinine (mg/dl)		1.04 (0.89; 1.29)	1 (0.85; 1.16)	0.2
Diversion type	Ileal neobladder	4 (7.5%)	7 (10.3%)	0.7
	Noncontinent	49 (92.5%)	61 (89.7%)	
Type of surgery	Open cystectomy	44 (83%)	36 (52.9%)	0.001
	Laparoscopic	9 (17%)	32 (47.1%)	
Stage	0	3 (5.7%)	8 (11.8%)	<0.001
	I	6 (11.3%)	17 (25%)	
	II	9 (17%)	27 (39.7%)	
	IIIa	15 (28.3%)	10 (14.7%)	
	IIIb	17 (32.1%)	6 (8.8%)	
	IVa	3 (5.7%)	-	
Stage	0-II	18 (34%)	52 (76.5%)	<0.001
	III-IVa	35 (66%)	16 (23.5%)	
Neoadjuvant chemotherapy		15 (28.3%)	12 (17.6%)	0.2
Neoadjuvant radiotherapy		3 (5.7%)	2 (2.9%)	0.6
Postoperative chemotherapy		31 (58.5%)	10 (14.7%)	<0.001
Postoperative radiotherapy		3 (5.7%)	3 (4.4%)	1
Tumor grading	G1	1 (1.9%)	9 (13.2%)	0.07
	G2	19 (35.8%)	23 (33.8%)	
	G3	33 (62.3%)	36 (52.9%)	
Return to OR within 30 days		4 (7.5%)	6 (8.8%)	1
Postoperative anemia at 30 days		30 (56.6%)	23 (33.8%)	0.02
Postoperative cardiovascular complications		3 (5.7%)	7 (10.3%)	0.5
Postoperative gastrointestinal complications		7 (13.2%)	6 (8.8%)	0.6

dl), and the following complications: anemia, cardiovascular and gastrointestinal.

Patients were followed for 2 years after the surgery and the date of death was recorded.

Statistical analysis was performed using the MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Continuous variables were tested for normality of distribution with the Kolmogorov Smirnov test and were characterized by median and 25-75 percentiles. Nominal variables were described by frequency and percentage. When comparing two groups we used the Mann-Whitney, Student t or chi-square test, depending of the situation. The area under the curve receiving operator was calculated and a cut-off value was chosen for age, where sensibility and sensitivity were maximum. Survival analysis was carried out with the Cox regression. Variables that achieved statistical significance in univariate analysis were introduced in the regression. A p value <0.05 was considered statistically significant. distribution. The correlation between variables was assessed by Pearson correlation coefficient for variables with normal distribution and Spearman correlation coefficient for variables with abnormal distribution. The level of significance was set at 0.05.

Results

During the follow-up of 23.6 (14.3; 40.5) months we recorded 53 (43.8%) deaths. The variables associated with the deaths can be observed in table 1. The deceased were elderly, were more likely to undergo open cystectomy, to have a higher cancer stage

Table 2. Survival analysis for muscle-invasive urothelial bladder cancer

Variables	B	P	HR	95.0% CI for HR	
				Lower	Upper
Preoperative hemoglobin < 11.6 g/dl	0.77	0.007	2.168	1.23	3.81
Age > 62 years	0.49	0.1	1.635	0.87	3.05
Open cystectomy	0.85	0.02	2.344	1.13	4.84
Stage III-IVa	1.19	<0.001	3.306	1.85	5.9

and grading, to receive postoperative chemotherapy and to suffer from postoperative anemia. For age we calculated a cut-off value in order to determine the chance of death: 62 years (AUC 0.572 (CI95% 0.479 to 0.661); Se 73.5 (CI95% 59.7 - 84.7), Sp 51.4 (39% - 63.8%) p=0.1). For preoperative hemoglobin we calculated a cut-off value in order to determine the chance of death: 11.6 g/dl (AUC 0.678 (CI95% 0.587 to 0.760); Se 62.2 (CI95% 47.9 - 75.2), Sp 70.5 (58.3% - 81%) p<0.001).
The survival analysis was performed using the Cox regression, which identified the parameters independently associated with the mortality (table 2). The stages III-IVa were associated with the highest HR (3.3). Patients that underwent open cystectomy or presented low preoperative hemoglobin were also more likely to die during the two years follow-up period after the surgery (HR 2.3, HR 2.1 respectively). Postoperative chemotherapy and postoperative anemia were not included in the final model due to the close correlation with the stage of the disease, or with the preoperative hemoglobin, respectively.

Discussion

The study established several the association between several variables and the mortality in patients that underwent radical cystectomy for muscle-invasive urothelial bladder cancer. The mortality rate was greater in elderly patients, patients with pre or postoperative anemia, that suffered open surgery, with an advanced disease, with a high grading tumor, or that followed postoperative chemotherapy. As those data are likely to be highly correlated one with the other, we used a multivariate analysis that revealed that only preoperative anemia, open cystectomy and advanced cancer were independently link to two years mortality.
The mortality rate at two years in our study was quite high (43.8%). In USA the 5-year relative survival rate is about 77% for all cases. For stage III and IV, the 5-year survival is much lower, 46%, 15% respectively (Noone et al 2018). In our study, almost half of patients were in stage III or IV. That explains, partially, the high death rate. In Romania, the death rate is 4.27 per 100,000, lower than the other Eastern European countries, but higher than Western Europe.
In our study we calculated a cut-off value for preoperative hemoglobin, under which the risk of death increased. The value (11.6 g/dl) was close to the one used to define anemia. Patients with hemoglobin value under 11.6 g/dl had a chance of dying within two years of radical cystectomy two times higher than those with greater hemoglobin. Anemia is one the most frequent comorbidities encountered in patients with cancer, as it is diagnosed

in between 30% and 60% of cases (Ludwig et al 2004; Ludwig et al 2009). The determinants of preoperative anemia are many, with two major ones: decrease production of erythropoietin and deficiency of vitamin B12 or iron. In patients with bladder cancer, anemia has another important cause as hematuria is usually one of the main symptoms. Preoperative anemia has been described as a prognostic factor for several cancers, including bladder neoplasm (Gierth et al 2015; Moschini et al 2016; Wang et al 2018). Anemia determines hypoxia which can trigger changes in gene expression, cells modifications, that can produce a different, more difficult to treat phenotype (Vaupel & Mayer 2005).
Open cystectomy was associated with a greater chance of death during the two years after the surgery. Radical cystectomy remains the gold standard for treating muscle-invasive urothelial bladder cancer. Studies have shown that the survival rate at three years for patients with high grade, muscle-invasive cancer, is low as only approximately 50% were cured, and most patients died within the follow-up (Stein et al 2001). In a study by Albisinni et al (2015) laparoscopic radical cystectomy was correlated with better survival: 79% at two years. In our study the survival in the laparoscopic group was almost identical: 78%. In the open cystectomy group the survival was almost twice as low: 45%. A recent study did not find differences for survival rate between open cystectomy and laparoscopic cystectomy. They found that patients that underwent open cystectomy were more likely to develop metastases (Bochner et al 2018). The main difference between their and our study is the proportion of open cystectomy/laparoscopic cystectomy. In our study almost two thirds were with open cystectomy, as compared with their study open cystectomy was performed in half of the patients. That might explain the low survival rate in our study for patients with open cystectomy.
Patients with advanced disease (stage III and IVa) had the highest risk of dying during the follow-up, as the HR was 3.3. Advanced stages of the cancer are linked to a shorter survival due to the extension of the disease locally and at distance. The majority of the studies that evaluated the survival in bladder cancer showed the association between mortality and stages of the bladder cancer (Solsona et al 2005; Catto et al 2009; Gondo et al 2012; Xylinas et al 2012; Feng et al 2015).Several limitations of the study: the relative moderate number of patients; the study included patients from just one center; we could not follow the patients more than two years after the surgery; we could not recorded some anamnestic or surgical data relevant for survival.

Conclusions

Almost half of the patients died in two years after radical cystectomy for muscle-invasive urothelial bladder cancer. Advanced disease, open cystectomy and preoperative anemia were independent prognostic factors for mortality.

References

Albisinni S, Rassweiler J, Abbou CC, Cathelineau X, Chlosta P, Fossion L, et al. Long-term analysis of oncological outcomes after laparoscopic radical cystectomy in Europe:results from a multicentre study by the European Association of Urology (EAU) section of Uro-technology. BJU Int 2015;115(6):937-45.

Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality:A Global Overview and Recent Trends. Eur Urol 2017;71(1):96-108.

Bochner BH, Dalbagni G, Marzouk KH, Sjoberg DD, Lee J, Donat SM, et al. Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy:Oncologic Outcomes. Eur Urol 2018 pii:S0302-2838(18)30336-1. doi:10.1016/j.eururo.2018.04.030.

Catto JW, Abbod MF, Linkens DA, et al. Neurofuzzy modeling to determine recurrence risk following radical cystectomy for nonmetastatic urothelial carcinoma of the bladder. Clin Cancer Res 2009;15:3150–5.

Chen C, Hu L, Li X, Hou J. Preoperative Anemia as a Simple Prognostic Factor in Patients with Urinary Bladder Cancer. Med Sci Monit 2017;23:3528-3535.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide:sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.

Feng H, Zhang W, Li J, Lu X. Different patterns in the prognostic value of age for bladder cancer-specific survival depending on tumor stages. Am J Cancer Res 2015;5(6):2090-7.

Gierth M, Mayr R, Aziz A, et al. Preoperative anemia is associated with adverse outcome in patients with urothelial carcinoma of the bladder following radical cystectomy. J Cancer Res Clin Oncol 2015;141:1819–26.

Gondo T, Nakashima J, Ozu C, et al. Risk stratification of survival by lymphovascular invasion, pathological stage, and surgical margin in patients with bladder cancer treated with radical cystectomy. Int J Clin Oncol 2012;17:456–61.

Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 2006;176:1354–61.

Ishioka J, Saito K, Sakura M, et al. Development of a nomogram incorporating serum C-reactive protein level to predict overall survival of patients with advanced urothelial carcinoma and its evaluation by decision curve analysis. Br J Cancer 2012;107:1031–6.

Moschini M, Bianchi M, Gandaglia G, Cucchiara V, Luzzago S, Pellucchi F, et al. The Impact of Perioperative Blood Transfusion on Survival of Bladder Cancer Patients Submitted to Radical Cystectomy:Role of Anemia Status. Eur Urol Focus 2016;2(1):86-91.

Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS):A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 2004;40:2293–306.

Ludwig H, Aapro M, Bokemeyer C, Macdonald K, Soubeyran P, Turner M, et al. Treatment patterns and outcomes in the management of anaemia in cancer patients in Europe:findings from the Anaemia Cancer Treatment (ACT) study. Eur J Cancer 2009;45(9):1603-15.

Riester M, Taylor JM, Feifer A, et al. Combination of a novel gene expression signature with a clinical nomogram improves the prediction of survival in high-risk bladder cancer. Clin Cancer Res 2012;18:1323–33.

Solsona E, Iborra I, Dumont R, et al. Risk groups in patients with bladder cancer treated with radical cystectomy:statistical and clinical model improving homogeneity. J Urol 2005;174:1226–30.

Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer:long-term results in 1,054 patients. J Clin Oncol 2001;19:666–675.

Vaupel P, Mayer A. Hypoxia and anemia:effects on tumor biology and treatment resistance. Transfus Clin Biol 2005;12(1):5-10.

Wang L, Shao ZH. Relationship between anemia and clinical features and prognosis of advanced lung cancer patients. Zhonghua Zhong Liu Za Zhi 2018;40(7):512-516.

Xylinas E, Cha EK, Sun M, et al. Risk stratification of pT1-3N0 patients after radical cystectomy for adjuvant chemotherapy counselling. Br J Cancer 2012;107:1826–32.

Authors

•Andrei Boc, Department of Urology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, Cluj-Napoca, Cluj, Romania, EU, email: boc.andrei@gmail.com

•Ștefan Cristian Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, Cluj-Napoca, Cluj, Romania, EU, email: stefanvesa@gmail.com

•Alexandra Andreea Poienar, Department of Ginecology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania, EU, email: Alexandra.poienar@gmail.com

•Bianca A. Azamfirei, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babes Street, Cluj-Napoca, Cluj, Romania, EU, email: azamfirei.bianca@yahoo.com

•Cristian Porumbel, Department of Urology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, Cluj-Napoca, Cluj, Romania, EU, email: Cristiporumbel@yahoo.com

•Nicolae Crişan, Department of Urology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, Cluj-Napoca, Cluj, Romania, EU, email: drnicolaecrisan@gmail.com

•Ioan Coman, Department of Urology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, Cluj-Napoca, Cluj, Romania, EU, email: Coman.ioan@uro-cluj.ro