The value of clinical prognostic factors for survival in patients with invasive urinary bladder cancer

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Key words: *bladder cancer; chemotherapy; radiotherapy; transurethral resection of bladder tumor; radical cystectomy.*

Summary. *The aim of the study was to evaluate the value of clinical prognostic factors for survival of patients with invasive urinary bladder cancer treated with radical cystectomy, chemotherapy, and radiotherapy.*

Material and methods. A total of 115 patients with invasive urinary bladder cancer were analyzed. Twenty-three patients with invasive urinary bladder cancer (pT2–T4) were treated according to the protocol of a prospective clinical study. In all the cases, transurethral resection was followed by radiation and chemotherapy. A total dose of 54–60 Gy of radiotherapy was delivered by daily fractions of 1.8–2.0 Gy each. Simultaneous chemotherapy was started on the same day as radiotherapy; gemcitabine at a dose of 175–300 mg/m^2 was delivered once a week intravenously for 6 weeks. Individual patient data was analyzed in a retrospective part of the study. Radical cystectomy was performed to 46 patients with invasive urinary bladder cancer, and radiotherapy was delivered to 46 patients. Inclusion criteria for patients into a prospective or retrospective trial were equal. We evaluated a prognostic value of various clinical factors for patients treated with radical cystectomy, chemoradiation with gemcitabine, and radiation alone.

Results. The 3-year overall survival in the cystectomy group was 51.1%, in the chemoradiation group 38.0%, and in the radiotherapy group 26.9% (P=0.001). In univariate analysis in the chemoradiation group, completion of treatment according to the protocol showed a significant influence on overall survival (P=0.03). In the radiation group, completion of treatment according to the protocol showed a significant influence on overall survival too (P=0.01). In the radical cystectomy group, an important factor was a complete or incomplete TUR (P=0.02). Multivariate analysis showed a significance of hydronephrosis (P=0.03) and T stage (P=0.04) in the radiation therapy group. Comorbidity was found to be an independent prognostic factors in the chemoradiation group (P=0.02).

Conclusions. The best 3-year overall survival was in the radical cystectomy group. Chemoradiation with gemcitabine could be offered as an alternative to patients refusing cystectomy. Better overall survival in the chemoradiation group was for patients without comorbidities and when treatment protocol was completed.

Introduction

Urinary bladder cancer is the second most common urological malignancy in males. A 5-year survival rate for patients with invasive urinary bladder cancer is 20–70%, because invasive urinary bladder cancer tends to metastasize.

Currently, the survival in patients with invasive urinary bladder cancer is poor. Radical cystectomy and radiotherapy are the oldest options for the treatment of invasive urinary bladder cancer. Radical cystectomy due to its large extent and removal of the bladder is associated with decreased quality of life. Radiation treatment gives much worse survival results. Conservative bladder-sparing treatment methods that may allow improving survival without compromising quality of life have been created. Treatment protocols based on transurethral resection of bladder tumor (TURBT), radiotherapy, and chemotherapy have been investigated and used in clinical practice for more than two decades. However, until now it remains unclear which conservative regimen is an optimal choice with little toxicity and good survival results. Currently, clinical factors that can have an impact on treatment response and overall survival have been identified. However, until now it is not clear which factors could help to choose between the treatment methods – surgery or conservative bladder-sparing treatment.

This study was designed to assess the influence of clinical prognostic factors on the survival of patients with invasive urinary bladder cancer.

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Materials and methods

The data of patients with invasive urinary bladder cancer, who were treated at the Institute of Oncology of Vilnius University during 2000–2008, were analyzed in the study. Data had been collected from medical records of 115 patients. This clinical study consisted of two parts. The prospective part included the patients who were given a prospective clinical study protocol, and the retrospective part included a retrospective analysis of the patients who fulfilled inclusion criteria.

The patients in the prospective clinical study arm were treated by bladder-sparing chemoradiation therapy. Conservative bladder-sparing treatment scheme for invasive urinary bladder carcinoma was created and consisted of chemoradiotherapy with gemcitabine administered after TURBT (1). TURBT was done trying to remove as much cancerous tissue as possible. Bladder tissue was taken from the central part of tumor, the tumor border adjacent to normal tissues, and if possible, from muscle tissue to evaluate the depth of tumor invasion into the bladder wall. The Lithuanian Bioethics Committee and the State Medicine Control Agency of Lithuania approved the clinical study protocol (protocol No. A2-7). Gemcitabine dosing recommendation was made based on the data from a few small phase I clinical trials of chemoradiotherapy in invasive urinary bladder cancer (2–5). All patients included had signed the informed consent form before study entry. Twenty-three patients received treatment according to the clinical study protocol. All patients met inclusion criteria. Seven patients (30.4%) who were included in the prospective study and treated by chemoradiotherapy with gemcitabine refused radical cystectomy. Sixteen patients (69.6%) did not undergo surgery because of comorbidities.

Study inclusion criteria: histologically confirmed invasive urinary bladder cancer, stage pT2–T4A, N0–N1, M0 (after TUR); TNM system was used for cancer staging; no history of malignancy and no previous treatment for any cancer other than basocellular carcinoma; age of ≥18 years; ECOG performance status of 0–2; hematology: white blood cells $\geqslant 3\times10^9$/L, neutrophils $\geqslant 1.5\times10^9$/L, platelets $\geqslant 100\times10^9$/L, hemoglobin ⩾80 g/L; liver function tests: total bilirubin ⩽1.5×upper normal limit (UNL), GPT⩽1.5×UNL, GOT⩽1.5×UNL, alkaline phosphatase ⩽2.5×UNL; creatinine clearance of ⩾60 mL/min; closed urinary bladder system; sterile urine (after urine culture); no concomitant diseases such as acute cardiovascular, gastrointestinal, respiratory diseases, active infection, and severe psychiatric disorders.

Study exclusion criteria: histologically unconfirmed urinary bladder cancer; histologically confirmed urinary bladder cancer of other types than urinary cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and others); superficial or metastatic urinary bladder cancer; any other cancer except basocellular carcinoma; age of <18 years; ECOG performance status of >2; hematology: white blood cells $<3\times10^9$/L, neutrophils $<1.5\times10^9$/L, platelets $<100\times10^9$/L, hemoglobin <80 g/L; liver function tests: total bilirubin >1.5×UNL, GPT>1.5×UNL, GOT>1.5×UNL, alkaline phosphatase >2.5×UNL; creatinine clearance <60 mL/min; cystostomy; pregnancy; severe concomitant cardiovascular, gastrointestinal, and respiratory disorders, severe infection, severe psychiatric disorders.

Treatment methods. Combination of radiotherapy and chemotherapy with gemcitabine, 175–300 mg/m^2 once weekly, was given concomitantly with radiation for six weeks from the first day of radiation. Two patients received gemcitabine at a dose of 175 mg/m^2 and 21 patients received gemcitabine at a dose of 300 mg/m^2 once weekly.

Radiotherapy. Linear accelerator facility was used. Dosage was as follows: daily dose of 1.8–2.0 Gy, total dose of 54–60 Gy in 27–30 fractions given 5 days per week over 6 weeks. To evaluate treatment effect, repeated TUR was performed 1.5 months after chemoradiotherapy.

All inclusion criteria for the retrospective study remained the same as in the prospective part of the study. Data from medical records of 500 patients with urinary bladder cancer were reviewed. Data of 92 patients who met all inclusion criteria were included into analysis. The date and reasons of the death were obtained from the Residents' Register Service at the Ministry of the Interior of Republic of Lithuania.

Forty-six patients were treated with radiotherapy, and radical cystectomy was performed to other 46 patients. Linear accelerator was used to treat the patients in the radiotherapy arm. A planned daily dose of radiation was 2 Gy to a total dose of 60–66 Gy. Most patients underwent radical cystectomy with urinary diversion by Bricker. Radical cystectomy in women involved removal of the bladder, uterus, and adnexa, and removal of the bladder, prostate, and seminal vesicles in men. Urinary diversion was constructed from the ileum (ileum conduit). Characteristics of all patients are presented in Table 1.

Analysis of clinical prognostic factors for survival of patients with invasive urinary bladder cancer treated by various methods did not include the value of grade of malignancy (G) and regional lymph node metastases (N). Patients' data analysis showed that most of the patients had grade G3 malignancy without clear evidence of metastases to regional lymph nodes (N0) before the start of treatment.

Table 1. Characteristics of patients before treatment

Characteristic		Cystectomy	Chemoradiotherapy	Radiotherapy	In total
Number of patients		N=46 (%)	N=23 (%)	N=46 (%)	115
Age, median (95% CI)		60.5 (57.8–64.1)	65.0 (59.3–72.7)	70.5 (68.0–74.0)	
Sex	Males	43 (93.5)	18 (78.3)	40 (86.9)	101
	Females	3 (6.5)	5 (21.2)	6 (13.1)	14
Age	<60 years	19 (41.3)	7 (30.4)	4 (8.7)	30
	60–69 years	21 (45.7)	7 (30.4)	17 (37.0)	45
	⩾70 years	6 (13.0)	9 (39.1)	25 (54.3)	40
T stage	T2	40 (87.0)	22 (95.7)	44 (95.6)	106
	T3	4 (8.7)	0	2 (4.4)	6
	T4	2 (4.3)	1 (4.3)	0	33
Hydronephrosis	No	21 (45.7)	14 (60.9)	26 (56.5)	61
	Yes	24 (52.2)	9 (39.1)	20 (43.5)	53
	Not assessed	1 (2.1)	0	0	1
Radicality of TUR	R0	4 (8.7)	6 (26.1)	9 (19.6)	19
	R1	7 (15.2)	7 (30.4)	10 (21.7)	24
	R2	35 (76.1)	10 (43.5)	27 (58.7)	72
Comorbidities	No	33 (71.7)	13 (56.5)	22 (47.8)	68
	Yes	13 (28.3)	10 (43.5)	24 (52.2)	47
Accomplished treatment protocol	Not fully completed	–	6 (26.1)	13 (28.3)	19
	Completed as planned	46 (100)	17 (73.9)	33 (71.7)	96

CI, confidence interval; TUR, transurethral resection; R0, radical; R1, nonradical microscopically; R2, nonradical macroscopically.

This was the reason why our analysis could not find statistically significant differences in survival rates between the patients groups according to their G and N characteristics.

Statistical analysis. Survival of the patients was analyzed using the Kaplan-Meier method. Survival was calculated as the time from beginning of therapy until death (if patient died) or the last follow-up. The 3-year survival was reported. The median follow-up was 18 months. Statistical analysis was performed using STATA program. Survival differences between the arms were evaluated by the log-rank test. *P* values of 0.05 or less were considered significant.

Univariate Cox proportional hazards models were run for each clinical factor separately. Univariate Cox proportional hazards risk model was used to assess the prognostic value and statistical significance of each clinical factor separately on survival. Multivariate analysis of Cox proportional hazards risk model was used to assess the prognostic value and statistical significance of the sum of clinical variables on survival.

Results

The survival of all evaluated groups of the patients are presented in Fig. 1. The 3-year survival was the best in the radical cystectomy group and reached 51.1%. The survival was slightly worse in the chemoradiotherapy group and reached 38.0%. The worst survival was observed in the radiotherapy group (26.9%). The survival among three treatment groups was significantly different (P=0.001).

Some clinical studies showed that disease-related clinical prognostic factors influencing treatment response in invasive urinary bladder cancer treated by surgery and conservative therapy are the stage of the disease (T stage of tumor), hydronephrosis, and number of lymph nodes involved in patients treated with radical cystectomy. Radicality of TURBT in bladder-sparing treatment was reported to be an independent prognostic factor for survival of patients with invasive urinary bladder cancer. Urothelial bladder cancer is more common in the elderly, and the influence of comorbidities on the outcome of the disease is important as well. Literature search showed that some clinical trials investigating a conservative approach of bladder-sparing treatment were discontinued due to the high toxicity. We analyzed the impact of full planned or reduced dose of therapy on the survival.

The impact of clinical prognostic factors on survival in three treatment groups (radical cystectomy, chemoradiotherapy, and radiotherapy) of patients with invasive urinary bladder cancer was assessed. We analyzed the impact of age, sex, radicality of

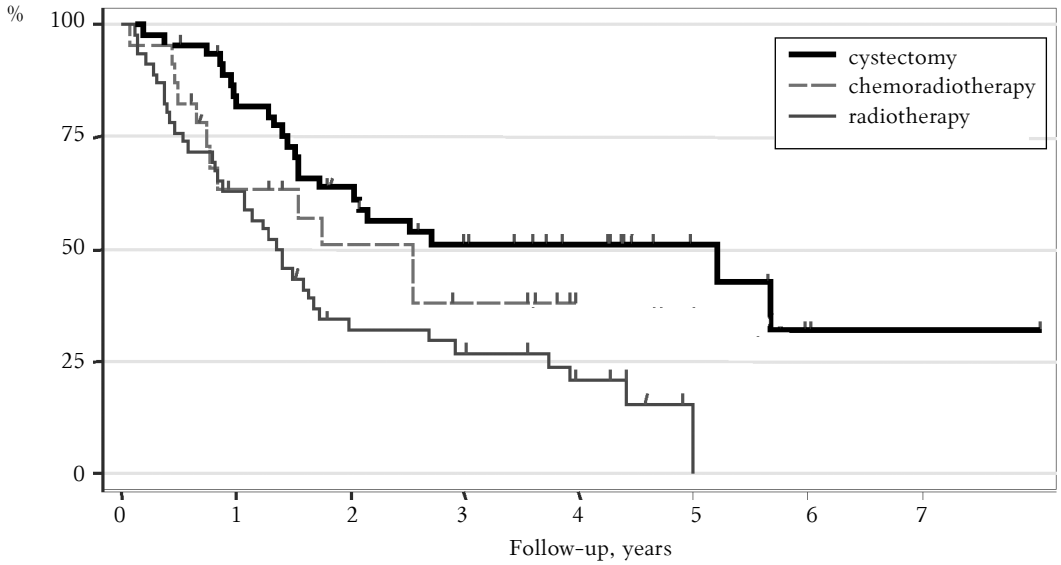

Fig. 1. Survival of patients by different treatment

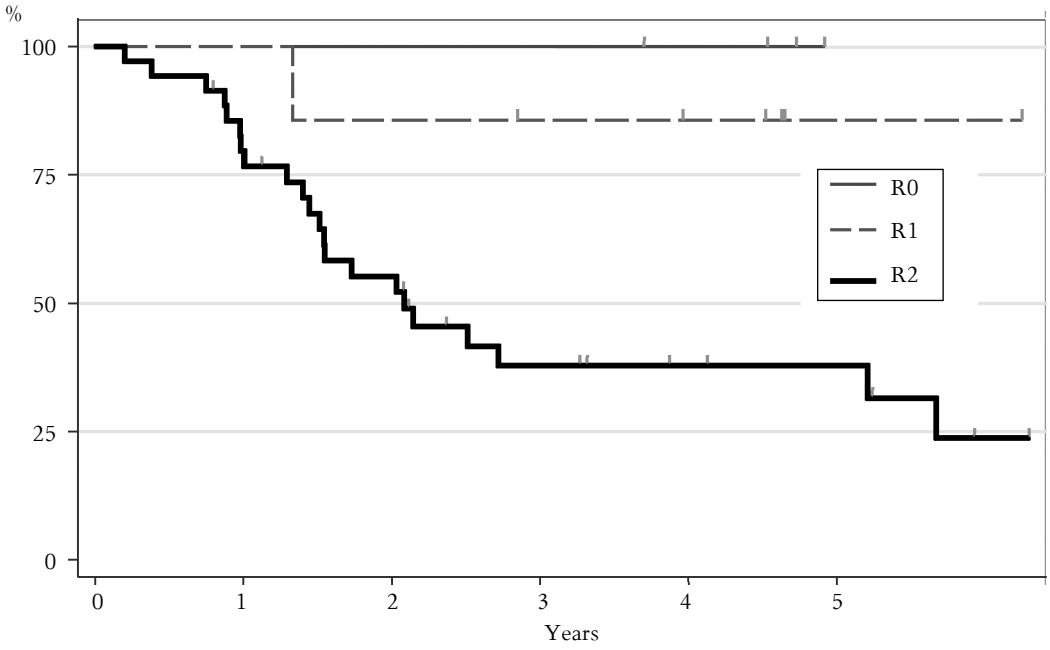

Fig. 2. Survival of patients treated with radical cystectomy by radicality of transurethral resection of bladder tumor

TURBT, hydronephrosis, T stage, and treatment protocol compliance on survival in the patients' groups treated by various regimens. The impact of comorbidities (chronic cardiovascular, respiratory, endocrine, and neurological diseases) on survival of patients with invasive bladder cancer treated by various regimens was analyzed as well.

Radicality of TURBT was a significant factor predicting survival in the group of patients treated with radical cystectomy. Radicality of TURBT was checked visually by cystoscopy and by histological examination of biopsy samples. The 3-year survival in patients treated by radical cystectomy reached 100% if TURBT was microscopically radical (R0), 85.7% if there was microscopical disease left (R1), and only 37.8% in cases of nonradical TURBT and macroscopic tumor (R2). There was a significant difference (P=0.02) comparing survival (Fig. 2).

A full planned dose of therapy had a significant prognostic value for survival of patients treated by chemoradiotherapy with gemcitabine (P=0.02). If the dose of therapy delivered to a patient was 85% of the planned dose or higher, then it was accepted as treatment according to the protocol without major deviations. The median radiation dose was 54 Gy (range, 32–66 Gy) in the radiotherapy group and 47.5 Gy (range, 28–60 Gy) in the chemoradiotherapy group. The median number of chemotherapies

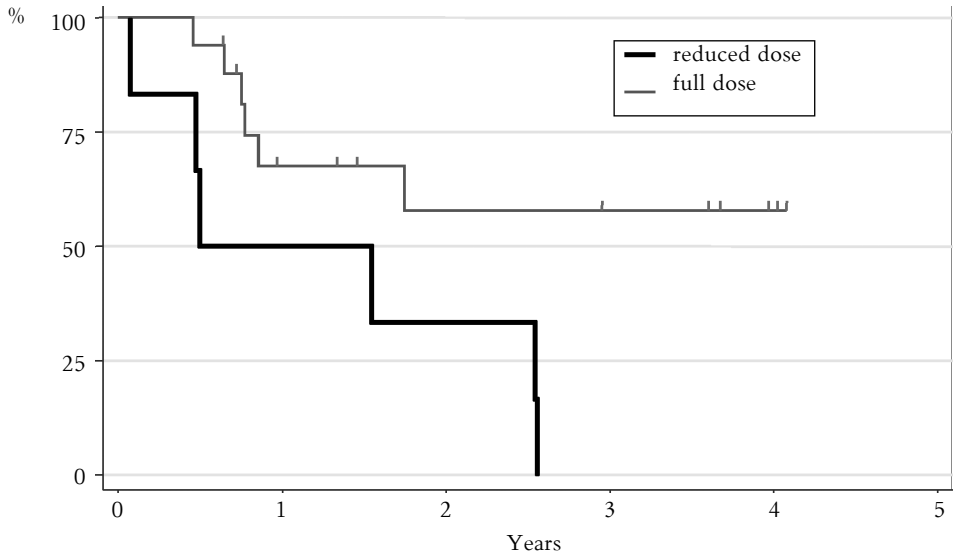

Fig. 3. Survival of patients treated with chemoradiotherapy by accomplishment of treatment protocol

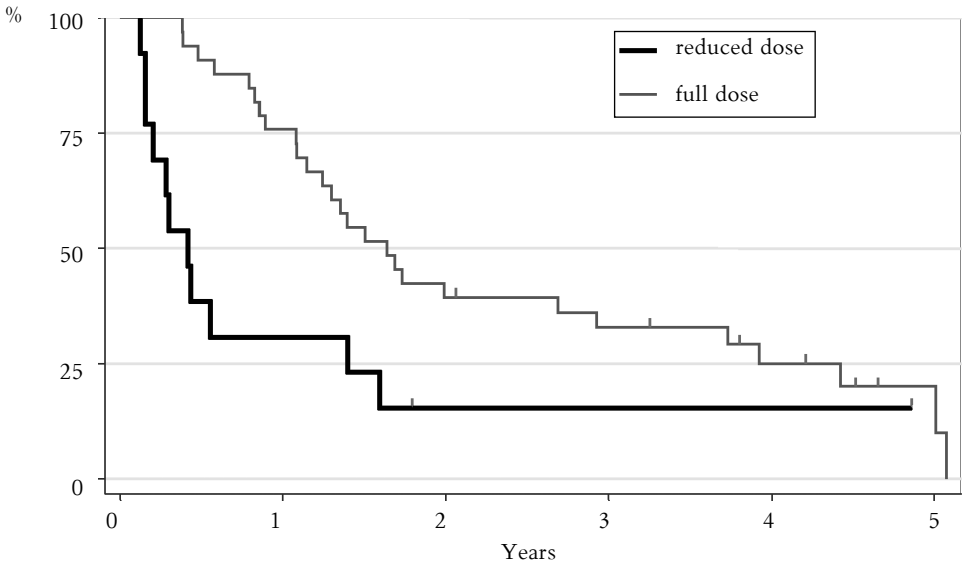

Fig. 4. Survival of patients treated with radiotherapy by accomplishment of treatment protocol

with gemcitabine infusions was 4.9 (range, 2–6). Six patients (26.1%) in the chemoradiotherapy group did not accomplish treatment per protocol. Two of them were removed from planned treatment due to grade 3 liver enzyme elevation, other two due to prolonged grade 3 diarrhea, and one patient due to thrombocytopenia. One patient refused to continue chemoradiotherapy because of grade 3 dysuria and afterward underwent cystectomy. The survival rate at 3 years was higher in patients treated by chemoradiotherapy when the dose of therapy delivered to a patient was not reduced and given per protocol. The 3-year survival in this group of patients reached 57.9%. No patients were alive at 3 years in the group that received a reduced dose of chemoradiotherapy. The difference was statistically significant comparing the groups with a full delivered dose and reduced dose (Fig. 3).

Survival analysis in patients treated by chemoradiotherapy showed a tendency to a worse survival in patients with hydronephrosis (P=0.1). A negative prognostic factor for survival in the chemoradiotherapy treatment group was concomitant diseases (P=0.08). The survival rate in patients treated by radiotherapy was significantly higher in patients that received a full planned dose per protocol (P=0.01). The 3-year survival in this group of patients reached 32.8%. The survival rate in patients treated with a reduced dose of radiation was lower and reached only 15.4%. The difference between groups was statistically significant (Fig. 4).

A tendency to a worse survival in the radiotherapy group was noticed in patients with hydronephrosis (P=0.08).

The univariate Cox model was used to assess the prognostic value of each clinical factor separately on survival in patients treated by radical cystectomy, chemoradiotherapy, and radiotherapy (Table 2).

The analysis showed a positive prognostic value of full planned dose given for overall survival of patients treated with chemoradiotherapy. The planned schedule administered without dose reductions reduced the risk of death by 3.66 times (95% CI, 1.17–11.44; P=0.03). Concomitant diseases in patients treated with chemoradiotherapy had a tendency to increase the risk of death by 3.12 times (95% CI, 0.83–11.76; P=0.09).

A trend toward a 1.6-fold increased risk of death was seen for older patients treated with radiotherapy (95% CI, 0.94–2.71; P=0.08). There was a trend toward a 3.46-fold increased risk of death in elderly patients with T3 tumor (95% CI, 0.78–15.32; P=0.1). Full planned dose per protocol and radicality of TURBT were significant factors predicting survival in patients treated with radiotherapy. Delivery of full planned dose reduced the risk of death by 2.46 times (95% CI, 1.20–5.05; P=0.01). Macroscopically incomplete (R2) TURBT in patients treated with radiotherapy increased the risk of death by 4.39 times (95% CI, 1.49–12.97; P=0.007).

Multivariate analysis of Cox proportional hazards risk model was used to assess the prognostic value of all clinical variables combined for survival of patients treated with radical cystectomy, chemoradiotherapy, and radiotherapy (Table 3).

Macroscopically incomplete (R2) TURBT be-

Table 2. Univariate analysis using Cox model of clinical prognostic factors in patients with bladder cancer treated by various regimens

Factor		Cystectomy HR (95% CI)	*P* value	Chemoradiotherapy HR (95% CI)	*P* value	Radiotherapy HR (95% CI)	*P* value
Age		0.86 (0.46–1.60)	0.63	1.48 (0.72–3.02)	0.23	1.60 (0.94–2.71)	0.08
Sex		0.55 (0.07–4.12)	0.56	1.99 (0.53–7.43)	0.30	1.47 (0.56–3.85)	0.43
Radicality of TURBT	R0/R1	–	–	–	–	2.09 (0.63–6.98)	0.23
	R0/R2	–	–	–	–	4.39 (1.49–12.97)	0.007
Hydronephrosis		1.27 (0.55–2.95)	0.58	2.53 (0.80–7.95)	0.11	1.78 (0.92–3.44)	0.09
Concomitant diseases		1.37 (0.58–3.24)	0.48	3.12 (0.83–11.76)	0.09	1.06 (0.54–2.09)	0.87
T stage	T2/T3	0.89 (0.20–4.03)	0.88	–	–	3.46 (0.78–15.32)	0.10
	T2/T4	0.88 (0.12–6.57)	0.90	–	–	–	–
Accomplishment of treatment protocol		–	–	3.66 (1.17–11.44)	0.03	2.46 (1.20–5.05)	0.01

HR, hazard risk; CI, confidence interval; TURBT, transurethral resection of bladder tumor; R0, radical; R1, nonradical microscopically; R2, nonradical macroscopically.

Table 3. Multivariate analysis using Cox model of clinical prognostic factors in patients with urinary bladder cancer treated by various regimens

Factor		Cystectomy HR (95% CI)	*P* value	Chemoradiotherapy HR (95% CI)	*P* value	Radiotherapy HR (95% CI)	*P* value
Age		1.03 (0.97–1.09)	0.31	0.98 (0.85–1.14)	0.82	1.03 (0.97–1.09)	0.29
Sex		0.40 (0.13–1.25)	0.11	0.03 (0.00–1.91)	0.1	0.77 (0.18–3.40)	0.73
Radicality of TURBT	R0/R1	–	–	–	–	2.00 (0.80–11.20)	0.10
	R0/R2	10.88 (1.44–82.41)	0.02	–	–	2.98 (1.38–6.44)	0.005
Hydronephrosis		1.75 (0.66–4.59)	0.26	1.69 (0.32–8.77)	0.54	2.32 (1.07–5.04)	0.03
Concomitant diseases		1.60 (0.34–7.55)	0.55	14.34 (1.44–142.66)	0.02	0.87 (0.30–2.56)	0.80
T stage	T2/T3	0.78 (0.33–1.85)	0.58	–	–	5.03 (1.06–24.02)	0.04
	T2/T4	0.94 (0.30–2.94)	0.92	–	–	–	–
Accomplishment of treatment protocol		–	–	2.77 (0.52–14.72)	0.23	5.19 (2.16–12.43)	0.001

HR, hazard risk; CI, confidence interval; TURBT, transurethral resection of bladder tumor; R0, radical; R1, nonradical microscopically; R2, nonradical macroscopically.

fore cystectomy was an independent significant factor predicting a statistically significantly worse survival in patients treated with radical cystectomy. R2 TURBT increased the risk of death by 10.88 times in this group of patients (95% CI, 1.44–82.41; P=0.02).

Concomitant diseases were found to be an independent prognostic factor and increased the risk of death by 14.34 times in patients treated by chemoradiotherapy (95% CI, 1.44–142.66; P=0.02).

Multivariate analysis using the Cox model showed that a reduced dose of radiation was a significant prognostic factor for decreased survival in patients treated with radiotherapy. Incomplete treatment increased the risk of death by 5.19 times in this group of patients (95% CI, 2.16–12.43; P=0.001). Other independent prognostic factors were macroscopically incomplete (R2) TURBT, hydronephrosis, and stage T3 tumor. All these clinical factors had a negative impact on survival in patients treated with radiotherapy. R2 TURBT increased the risk of death in the radiotherapy group by 2.98 times (95% CI, 1.38–6.44; P=0.005). Hydronephrosis increased the risk of death in this group of patients by 2.32 times (95% CI, 1.07–5.04; P=0.03). Stage T3 tumor increased the risk of death in the radiotherapy group by 5.03 times (95% CI,1.06–24.02; P=0.04).

Discussion

To date, all over the world, there are no randomized clinical trials comparing the effectiveness of radical cystectomy with bladder-sparing treatment methods in patients with invasive urinary bladder cancer. The impact of radical surgery and radiotherapy on survival and factors influencing survival were analyzed in retrospective clinical studies. Prospective chemoradiation protocols were developed and implemented attempting to improve the results of conservative treatment in patients with invasive urinary bladder cancer. Our clinical study in the prospective and retrospective parts presents the analysis of survival and the value of clinical prognostic factors for survival of patients with invasive urinary bladder cancer treated by surgery and conservative methods. Our chemoradiation treatment protocol included gemcitabine due to its radiosensitization phenomenon and activity in metastatic urinary bladder cancer (6).

Radical cystectomy. Early clinical series of radical cystectomy in the 1980s and early 1990s indicated a 5-year survival of 40% in patients with stage T2 tumor and only about 20% in patients with tumors of greater than stage T2. Later trials were conducted in the era of improved surgical technique and showed a better survival rate in patients treated by radical cystectomy. Stein et al. and Madersbacher et al. reported the largest clinical trials on effectiveness of radical cystectomy. These authors reported the effect of T and N stage on survival after radical cystectomy.

Stein and coauthors (7) has conducted a large trial and analyzed the treatment results of 1054 patients with invasive urinary bladder cancer treated by radical cystectomy. The 5-year overall survival reached 60%. The patients with stage pT2 tumor lived longer, and patients with stage T4 tumor lived shorter. The worst survival rate was reported for patients with lymph node metastases. The authors noticed that most deaths from bladder cancer occurred within the first 3 years after cystectomy, after which survival changed only slightly. The similar data were presented in a clinical trial by Madersbacher and coauthors (8).

Our data showed that in patients after radical cystectomy, an overall survival at 3 and 5 years did not differ and was 51.74%. Our results after radical cystectomy were comparable to the results reported from other treatment centers over the world. We could not prove a statistically significant effect of T stage on survival due to a small number of patients (P=0.39). Survival data of our patients with lymph node metastases found after surgery were consistent with those reported by Madersbacher and coauthors, and survival rate reached 25% but was not statistically significant (P=0.26). Other authors (Nishiyama et al., Stein et al.) have reported better 5-year survival rates of patients with lymph node metastases after radical surgery – 35% and 31%, respectively (9). Radical cystectomy with extended lymph node dissection (at least 8–14 sentinel lymph nodes should be retrieved) is the gold standard of treatment (10). In our study, 8 or more lymph nodes were dissected in only 8 patients (17.4%), and all other patients underwent dissection of less than 8 lymph nodes. This could be associated with a worse survival rate in our patients.

Our study showed significantly different results of survival according to radicality of TURBT before radical cystectomy. The patients who underwent radical TURBT (R0) lived significantly longer. At 3 years, all patients were alive. The 3-year survival reached only 37.8% in cases of macroscopically nonradical TURBT (R2). There was a significant difference among the groups (P=0.02). Multivariate Cox analysis showed that TURBT radicality was an independent significant factor predicting survival. These results can be explained by the fact that nonradical TURBT is associated with large bladder tumor and possible micrometastases that lead to worse survival in this group of patients.

Chemoradiotherapy. The 3-year survival rate of 38.0% was observed in patients treated by chemoradiotherapy with gemcitabine in our study. The survival rate in this group of patients was lower than that in patients treated by radical cystectomy.

It is not possible to compare our survival data with other data as chemoradiotherapy with gemcitabine is quite a new regimen in urinary bladder-sparing treatment protocols, and published survival rates at 3 and 5 years are not available yet. Comparing our data with survivals reported by experienced centers that work on chemoradiotherapy in invasive urinary bladder cancer over decades and after analysis of RTOG protocols, we can conclude that some investigators reached better survival results. Results from the Radiation Therapy Oncology Group (RTOG) 85-12 protocol reported by Tester et al. showed a 3-year survival of 64% (11). Results from the RTOG phase II trial 88-02 reported by the same authors revealed a 4-year survival of 44% in patients who received bladder-sparing treatment (12). Housset et al. demonstrated a 3-year survival of 59% (13). The 5-year survival reported by other authors ranged from 47 to 54% (14). Better survival results were achieved by Hagan and colleagues that worked on the RTOG 97-06 protocol. Their results showed a 3-year survival of 61% (15). Only 45% of patients completed this protocol without or with minor deviations. The treatment in the RTOG 88-02 trial was accomplished per protocol in 79% of patients (12). In our study, the full planned dose per protocol or treatment with minor deviations from protocol was given to 17 patients (73.9%). Our results showed that reduced treatment doses had a significant impact on survival. The survival rate at 3 years when the dose of radiation and chemotherapy delivered to a patient was not reduced reached 57.9%, and no patients were alive at 3 years in the group of patients who received a reduced dose of chemoradiotherapy (P=0.02). Univariate analysis confirmed a prognostic value of the full treatment dose but multivariate analysis did not. This means that a prognostic value of compliance with treatment protocol is affected by other factors, possibly comorbidity that was showed to be a statistically significant prognostic factor by multivariate analysis.

Other above-mentioned authors reported survival rates better than ours. The treatment schemes included different chemotherapy drugs and used various radiation regimens, thus direct comparison of results was impossible. The procedure schemes for treatment varied among the trials also. In our study, all patients that refused radical cystectomy or were not suitable for cystectomy due to their bad medical condition (age or comorbidity) were included in the bladder-sparing treatment group. The above-mentioned investigators in bladder-sparing treatment protocols included only patients with good performance status that were suitable for aggressive treatments. Chemotherapy regimens with a well-known radiosensibilizing agent, cisplatin, were used. After induction, the patients in these trials were divided into two parts. The part of patients with response to treatment continued chemoradiotherapy. The other part with residual cancer after induction therapy underwent radical cystectomy.

Good survival results in some clinical trials using urinary bladder-sparing treatment protocols were related to selection of patients. Kaufman and coauthors (16) pointed hydronephrosis as a negative prognostic factor in patients treated by chemoradiotherapy. The 5-year survival rate reported in this trial was 27% in patients with hydronephrosis and 63% in patients without hydronephrosis. For this reason, the RTOG 95-06 and RTOG 97-06 trials excluded patients with hydronephrosis. This exclusion significantly increased 3-year overall survival rates in the RTOG 95-06 and RTOG 97-06 trials to 83% and 61%, respectively. Chemoradiotherapy was given to 14 patients (60.9%) without hydronephrosis and 9 (39.1%) with hydronephrosis in our study. A tendency to different survival of these patients was noticed. The survival rates were 48.4% and 20%, respectively (P=0.1). Univariate and multivariate analyses showed that this factor was not significant for survival.

Analysis of patients treated by chemoradiotherapy in our study revealed a tendency to a shorter survival in patients with comorbidities. The group of patients with comorbidities lived much shorter than patients without comorbidities – 11.7% and 70.1%, respectively (P=0.08). Multivariate analysis showed that **c**oncomitant diseases were an independent prognostic factor and increased the risk of death by 14.34 times in patients treated by chemoradiotherapy. We should note that analysis of death reasons after chemoradiotherapy showed that all patients died because of urinary bladder cancer. Literature search failed to obtain data about the influence of comorbidities on survival of patients with invasive urinary bladder cancer treated by conservative methods.

One of the most important reasons for chemoradiotherapy in invasive urinary bladder cancer is a possibility to preserve urinary bladder function. Data analysis showed that 12 patients (52%) in the chemoradiotherapy group died and 11 patients (48%) were alive during follow-up phase. All 11 alive patients (100%) preserved urinary bladder function. These findings as compared with literature data are excellent. According to literature, from 45% to 62% of surviving patients have preserved urinary bladder function (17).

Radiotherapy. Literature data showed that 3- and 5-year survival of patients with invasive urinary bladder cancer treated by radiotherapy is similar and ranges from 20% to 41% (18–20). The trials have failed to show benefit from accelerated radiotherapy (21). Survival data of our patients treated by radiotherapy are comparable to data reported by other centers. Our data analysis showed that very signifi-

cant prognostic factor on survival was fully completed treatment per protocol. The 3-year survival rate was 32.8% if the treatment protocol was completed without or with minor deviations. In patients with reduced doses of therapy, the 3-year survival rate was twice lower and reached only 15.4%. The difference between groups was significant (P=0.01). Moonen et al. stressed on importance of fully completed treatment protocol (19). These authors reported much more relapses and worse survival in patients who received a total dose of radiation lower than 57.5 Gy.

Univariate and multivariate Cox analysis confirmed the prognostic value of TURBT radicality, hydronephrosis, and T stage on survival in patients treated by radiotherapy. Nonradical TURBT, hydronephrosis before the treatment, and stage T3 tumor significantly increased the risk of death in patients treated with radiotherapy. Data from our study were comparable to published data. Tanoli and coauthors demonstrated an impact of patient age, T stage, and dose of radiation on survival of patients treated by radiotherapy. This trial included more older patients with a poorer performance status and not suitable for radical surgery (22). Similarly, our study included older patients (median age, 70.5 years). More than half of them (52.2%) had concomitant diseases. By comparing all treatment groups in our study, we found that the oldest patients and patients with the most concomitant diseases were accumulated in the radiotherapy group. The most of patients from this group were not offered more radical therapy.

Our results confirm that conservative treatment with radiotherapy is not enough effective in invasive urinary bladder cancer. Radiotherapy should be reserved as palliative treatment for patients with poorer performance status and as a method to stop bladder bleeding when radical cystectomy and chemoradiotherapy are contraindicated.

Conclusions

The 3-year survival rate for patients treated by radical cystectomy reached 51.1% and was better than that observed in patients treated by chemoradiotherapy after transurethral resection of bladder tumor (38.0%) or radiotherapy only (26.9%). Chemoradiotherapy may be an option for patients who refused radical cystectomy. The negative prognostic factors for survival in the chemoradiotherapy treatment group was concomitant diseases and in radiotherapy group – radicality of transurethral resection of bladder tumor (R2), hydronephrosis, higher T stage, and uncompleted treatment protocol. A negative prognostic factor for survival of patients treated by radical cystectomy was nonradical transurethral resection of bladder tumor (R2) that is associated with more locally advanced disease.

Klinikinių prognozinių veiksnių reikšmė ligonių, sergančių invaziniu šlapimo pūslės vėžiu, išgyvenamumui

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Raktažodžiai: šlapimo pūslės vėžys, chemoterapija, radioterapija, transuretrinė šlapimo pūslės naviko rezekcija, radikali cistektomija.

Santrauka. *Tyrimo tikslas.* Įvertinti klinikinių prognozinių veiksnių reikšmę radikalia cistektomija, chemospinduliniu ir spinduliniu gydymo metodais gydytų pacientų išgyvenamumui.

Tyrimo medžiaga ir metodai. Išanalizuoti 115 pacientų, sergančių invaziniu šlapimo pūslės vėžiu, gydymo rezultatai. Pagal perspektyviojo klinikinio tyrimo protokolą buvo gydyti 23 pacientai, sergantys invaziniu urotelio vėžiu (pT2–pT4). Jiems buvo atlikta maksimaliai radikali transuretrinė šlapimo pūslės naviko rezekcija (TUR). Po jos taikytas chemospindulinis gydymas – radioterapijos suminė židininė dozė 54–60 Gy ir chemoterapija gemcitabinu 175–300 mg/m^2 vieną kartą per savaitę, šešių savaičių spindulinio gydymo metu. Retrospektyviai išanalizuoti duomenys 92 pacientų, sergančių invaziniu urotelio vėžiu: 46 pacientai gydyti radioterapija, 46 pacientai, kuriems buvo atlikta radikali cistektomija. Retrospektyvaus klinikinio tyrimo pacientų įtraukimo kriterijai atitiko prospektyviojo tyrimo įtraukimo kriterijus. Nustatėme įvairių klinikinių veiksnių reikšmę redikalia cistektomija, chemospinduliniu ir spinduliniu metodais gydytų pacientų išgyvenamumui.

Rezultatai. Trejus metus išgyveno 51,1 proc. radikalia cistektomija gydytų pacientų, 38,0 proc. chemospinduliniu metodu gydytų pacientų ir 26,9 proc. spinduliniu metodu gydytų pacientų (p=0,001). Pagal Cox'o vienaveiksnę analizę nustatėme, kad, taikant chemospindulinį gydymą, reikšmingas pacientų išgyvenamumo prognozinis veiksnys yra visiškai realizuotas klinikinio tyrimo protokolas (p=0,03). Šio veik-

snio reikšmingumas nustatytas ir taikant spindulinį gydymą (p=0,01). Svarbus veiksnys, turintis įtakos pacientų išgyvenamumui po radikalios cistektomijos, buvo TUR radikalumas (p=0,02). Kaip nepriklausomas prognozinis veiksnys išryškėjo TUR radikalumas ir spindulinio gydymo grupėje (p=0,01). Išryškėjo hidronefrozės (p=0,03), T stadijos (p=0,04), kaip nepriklausomų veiksnių reikšmė spinduliniu metodu gydytų pacientų išgyvenamumui. Kaip nepriklausomas prognozinis veiksnys chemospindulinio gydymo grupėje išryškėjo gretutinės ligos (p=0,02).

Išvados. Geriausias trejų metų išgyvenamumas pasiektas radikalia cistektomija gydytų pacientų grupėje. Chemospindulinis gydymo metodas gali būti rekomenduojamas pacientams, kurie atsisako nuo radikalios cistektomijos. Geresnių rezultatų, taikant chemospindulinį gydymo metodą, galima tikėtis užbaigus gydymą pagal protokolą ir tiems pacientams, kurie neserga gretutine patologija.

References

1. Asadauskienė J, Aleknavičius E, Pipirienė Želvienė T, Jankevičius F. Sergančiųjų invaziniu uroteliniu vėžiu šlapimo pūslę išsaugančio gydymo efektyvumas. (Bladder preservation possibilities in the treatment of muscle-invasive bladder cancer.) Medicina (Kaunas) 2006;42(10):781-7.
2. Throuvalas N, Antonadou D, Pantelakos P, Lisiaos G, Bakiras A. Early results of concurrent radiochemotherapy with gemcitabine in locally advanced bladder cancer. Proc Annu Meet Am Soc Clin Oncol 2002;21:A2412.
3. Sangar VK, Lyons J, Ramani VAC, Logue J, Wylie J, Clarke NW, et al. Chemo-radiation with once-weekly gemcitabine for invasive bladder cancer. European Urology Supplements 2003;127(1):A497.
4. Caffo O, Fellin G, Graffer U, Valduga F, Bolner A, Luciani L, et al. Phase I trial of gemcitabine (G) and cisplatin (C) with concurrent irradiation (XRT) for the conservative treatment of invasive transitional bladder cancer (ITBC). Proc Annu Meet Am Soc Clin Oncol 2002;21:A764.
5. Kent E, Sandler H, Montie J, Lee C, Herman J, Esper P, et al. Combined-modality therapy with gemcitabine and radiotherapy as a bladder preservation strategy: results of a phase I trial. J Clin Oncol 2004;22(13):2540-5.
6. Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter phase III study. J Clin Oncol 2000;17:3068-77.
7. Stein JP, Lieskovsky G, Cote RJ, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long term results in 1,054 patients. J Clin Oncol 2001;19:666-75.
8. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al. Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003:21(4):690-6.
9. Tsukamoto T, Kitamura H, Takahashi A, Masumori N. Treatment of invasive bladder cancer: lessons from the past and perspective for the future. Jpn J Ocol 2004;34(6):295-306.
10. Raj GV, Bochner BH. Radical cystectomy and lymphadenectomy for invasive bladder cancer: towards evolution of an optimal surgical standard. Semin Oncol 2007;34(2):110-21.
11. Tester W, Porter A, Asbell S, Coughlin C, Heaney J, Krall J, et al. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. Int J Radiat Oncol Biol Phys 1993;25:783-90.
12. Tester W, Caplan R, Heaney J, Venner P, Whiltington R, Byhardt R, et al. Neoadjuvant combined modality program with selective bladder preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. J Clin Oncol 1996;14:119-26.
13. Housset M, Moulard C, Chretien Y, Dufour B, Delanian S, Huart J, et al. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. J Clin Oncol 1993;11:2150-7.
14. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, et al. Selective bladder preservation by combined modality protocol treatment: long term outcomes of 190 patients with invasive bladder cancer. Urology 2002;60:62-8.
15. Hagan MP, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, et al. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys 2003;57(3):665-72.
16. Kaufman DS, Shipley WU, Griffin PP, Heney NM, Althausen AF, Efird JT. Selective bladder preservation by combination treatment of invasive bladder cancer. N Engl J Med 1993;329:1377-82.
17. Torres-Roca JF. Bladder preservation protocols in the treatment of muscle-invasive bladder cancer. Cancer Control 2004;11(6):358-63.
18. Greven KM, Solin LJ, Hanks GE. Prognostic factors in patients with bladder carcinoma treated definitive irradiation. Cancer 1990;65:908-12.
19. Moonen L, van der Voet H, de Nijs R, Horenblas S, Hart AAM, Bartelink H. Muscle-invasive bladder cancer treated with external beam radiation: influence of total dose, overall treatment time, and treatment interruption on local control. Int J Radiat Oncol Biol Phys 1998;42(3):525-30.
20. McBain CA, Logue JP. Radiation therapy for muscle-invasive bladder cancer: treatment planning and delivery in the 21st century. Sem Rad Oncol 2005;15:42-8.
21. Horwich A, Dearnaley D, Huddart R, Graham J, Bessell E, Mason M, et al. A randomised trial of accelerated radiotherapy for localised invasive bladder cancer. Radiother Oncol 2005;75(1):34-43.
22. Tanoli S, Bertoni F, De Stefani A, Vitali E, De Tomasi D, Caraffini B, et al. Radical radiotherapy for bladder cancer: retrospective analysis of a series of 459 patients treated in an Italian institution. Clin Oncol (R Coll Radiol) 2006;18(1):52-9.

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