VILNIUS UNIVERSITY

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VALUE OF CLINICAL AND MOLECULAR PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH INVASIVE UROTHELIAL BLADDER CANCER

Summary of doctoral dissertation

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The doctoral dissertation has been prepared in the Clinic of Conservative Treatment in the Institute of Oncology of Vilnius University over the period of 2004 – 2008.

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VILNIAUS UNIVERSITETAS

Jolita Asadauskienė

KLINIKINIŲ IR MOLEKULINIŲ PROGNOZINIŲ VEIKSNIŲ REIKŠMĖ SERGANČIŲJŲ INVAZINIU UROTELINIU ŠLAPIMO PŪSLĖS VĖŽIU IŠGYVENAMUMUI

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TABLE OF CONTENTS

LIST OF ABREVIATIONS

ALT – alanine transaminase

AST – asparagine transaminase

CRT – chemoradiotherapy

CHT – chemotherapy

CTCAE – Common Terminology Criteria for Adverse Events

EORTC - European Organization for Research and Treatment of Cancer

ECOG - Eastern Cooperative Oncology Group

Gy – gray (unit of absorbed radiation dose)

HR – hazard risk

CT – computed tomography

CI – confidence interval

CTV– clinical target volume

MTp53 – mutated p53

PTV – planning target volume

RC – radical cystectomy

RTOG - Radiation Therapy Oncology Group

RT – radiotherapy

TURBT – transurethral resection of bladder tumor

1. INTRODUCTION

1.1. Actuality of the work

Approximately 100 000 new cases of invasive bladder cancer occur annually worldwide [Advanced Bladder Cancer Meta-analysis Collaboration, 2005]. The incidence of invasive bladder cancer in the European Union is 19.5 per 100 000 citizens and the mortality is 7.9 per 100 000 [ESMO Minimum Clinical Recommendations, 2009]. In Lithuania more than 400 new bladder cancer cases occurred annually and approximately 100 of them are the cases of invasive cancer. [Kurtinaitis et al, 2006]. The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of noninvasive tumors, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses invasive lesions, and the goal of therapy is to decide jointly by the doctor and the patient if the bladder should be removed or preserved without compromising survival. The critical concern of therapy for the third group, consisting of metastatic lesions, is how to prolong life without compromising the quality of life [NCCN Clinical Practice Guidelines in Oncology, 2009]. More than half of the patients diagnosed with invasive urothelial bladder cancer subsequently die. All cases of invasive bladder cancer ultimately metastasize and median overall survival for metastatic disease is about 11 months [Von der Masse et al, 2000]. In cases of invasive bladder cancer the doctor and patient must take the decision jointly to proceed to cystectomy or to preserve the bladder without compromising survival. Radical cystectomy (RC) with regional lymph node dissection is current standard of care for invasive bladder cancer in the European Union and the United States. This surgery is large and traumatic. RC in men usually involves removing the bladder, prostate, and seminal vesicles. In women, uterus and adnexa are removed along with the bladder. A urinary diversion surgery (a surgical procedure to create an urinary reservoir for urine storage usually from the bowels) is usually done with RC. Despite the large extent of the operation, five-year survival after RC with regional lymph nodes dissection remained somewhat higher than 50 percent [Ghoonheim MA, et al,

2000]. Over the last decade the surgery technique has developed and many new ways for construction of urinary reservoirs has been proposed. However artificial urinary bladder cannot substitute for the patient's own bladder. Patients with artificial bladder report decreased quality of life and sexual function. During the last decades many attempts have been made to create the new treatment methods that may allow the patients with invasive bladder cancer to avoid disabling cystectomy. Many clinical trials investigated the combination of transurethral resection of the bladder tumor (TURBT), systemic chemotherapy and radiotherapy. Some of these trials showed that combined modality treatment may be as effective as RC and may allow the bladder to be preserved without deferring the survival probability. Up-to-date analysis of clinical trials shows that integration of new agents into chemoradiation regimens is associated with significantly better outcomes in conservatively treated patients with invasive urothelial bladder cancer. Currently clinical and molecular prognostic factors that may help to tailor treatment to the individual are being investigated. However until now it remains unclear which chemotherapy agent in combination with radiotherapy is the most effective in managing patients with invasive urothelial cancer and there are no clear molecular markers in clinical practice which could help to predict the response to treatment. At the same time identification of prognostic markers that may be useful for selecting patients who might benefit from conservative or surgical treatment are run.

At the Institute of Oncology of Vilnius University patients with invasive urothelial bladder cancer are treated by surgery (radical cystectomy), radiotherapy and chemotherapy. This doctoral dissertation presents the analysis of the treatment outcome in patients with invasive urothelial bladder cancer treated at the Institute of Oncology of Vilnius University over the period of 2000 – 2008. Prospective analysis was done to investigate the value of the clinical and molecular prognostic factors on survival in patients treated by chemoradiotherapy. Retrospective analysis investigated the value of clinical prognostic factors on survival in patients treated by radical cystectomy and radiotherapy.

1.2. The aim

The aim of the study was to assess the influence of the clinical and molecular prognostic factors on the survival in patients with invasive urothelial bladder cancer that were treated by radical cystectomy, radiotherapy and combination of radiotherapy with gemcitabine therapy.

1.3. Objectives

1. Analysis of survival data in patients with invasive urothelial bladder cancer treated by radical cystectomy or by conservative therapy (chemoradiotherapy or radiotherapy) over the period of 2000 – 2008 at the Institute of Oncology of Vilnius University.

2. Evaluation of the value of clinical prognostic factors on survival in subgroups of patients with invasive urothelial bladder cancer that were treated by radical cystectomy and by conservative therapy (chemoradiotherapy or radiotherapy).

3. Identification of treatment related adverse events and comparison between radiotherapy-related and chemoradiotherapy-related adverse events.

4. Evaluation of the value of the expression of molecular markers on survival in patients treated by chemoradiotherapy.

1.4. Defended statements

1. Three-year survival rate for patients treated by radical cystectomy is the highest and opposite the lowest survival rate is for patients treated by radiotherapy alone.

2. The significant impact of radical TURBT on survival of patients treated by radical cystectomy, chemoradiotherapy and radiotherapy. The significant impact of dose of radiation and chemotherapy on survival of patients treated by chemoradiotherapy and radiotherapy.

3. Independent prognostic factor for survival in the patient subgroup treated by chemoradiotherapy is comorbidity. Independent prognostic factors in the patient

subgroup treated by radiotherapy alone are radicality of TURBT, hydronephrosis and T stage of the disease.

4. The most common adverse event in the group of patients treated by chemoradiotherapy is gastrointestinal toxicity (transitional elevation of liver enzymes).

5. Increased expression of MTp53 is a negative prognostic marker in the group of patients treated by chemoradiotherapy.

1.5. Scientific novelty

This research includes the evaluation of effectiveness of chemoradiotherapy in conservative treatment of invasive urothelial bladder cancer. For the first time the patients with invasive urothelial bladder cancer were given the combined treatment modality of gemcitabine (dose 300 mg/m^2 weekly) with radiotherapy. Assessment of the value of molecular markers as prognostic factors in patients treated by chemoradiotherapy was performed.

2. MATERIAL AND METHODS OF THE STUDY

The data of patients with invasive urothelial bladder cancer that were treated at Institute of Oncology of Vilnius University during the years 2000 - 2008 were analyzed. Data had been collected from medical records of 115 patients. The clinical research consisted of two parts – prospective and retrospective. Medical records of 23 patients were analyzed in prospective part of the study, and of 92 in retrospective. Molecular markers of tumor specimens obtained by TURBT were studied in prospective analysis.

2.1. Prospective part of the study

A protocol for prospective analysis was initiated and created at the Clinic of Conservative Treatment in the Institute of Oncology of Vilnius University. All patients included in the study had signed the informed consent form.

Study design

1. Initial TURBT was done and tissue for histological diagnosis was obtained. Then computed tomography (CT) of abdomen and pelvis was performed and TNM stage assessed.

2. Included patients with signed informed consent were treated by chemoradiotherapy (CRT) initiated 2-3 weeks after initial TURBT.

3. 1.5 months after CRT repeated TURBT was performed.

4. During follow-up period the patients were assessed every 3 months (cystoscopy, TURBT, ultrasound or CT of abdomen and pelvis if indicated). Alternative treatment methods were applied after disease progression was confirmed. The scheme of bladder sparing treatment is presented in Figure 1.

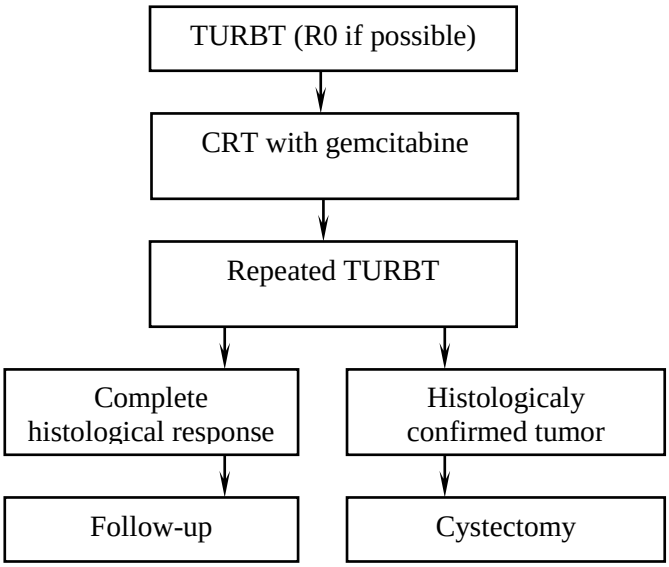

Figure 1. **The scheme of bladder sparing treatment in patients with invasive urothelial bladder cancer (Institute of Oncology Vilnius University)**

Study material

Prospective analysis included the data of the disease and treatment of 23 patients. 12 patients were dead by the end of this study. The most of the patients were men. The median age of the patients was 65 years. There were two patients with ECOG (Eastern Cooperative Oncology Group) performance status of 2, thirteen with ECOG performance status of 1 and eight patients with ECOG performance status of 0. 22 patients treated by CRT had stage T2 tumor, and 1 patient – stage T4. 21 of those patients had high-grade

(G3) tumor except for two with moderate grade (G2) tumor. There were no patients with regional lymph nodes metastases (N0). TURBT was radical (R0) in only 6 of study patients. More than half of patients (56,5 percents) treated by CRT had comorbidities. The treatment according protocol was not completed in 6 patients (26,1 percents). The analysis of homogeneity of clinical data in all patient groups mentioned above was done. All three groups were concordant for age and comorbidities and discordant for sex, depth of tumor infiltration (T), hydronephrosis, radicality of TUR and fulfilling the study treatment protocol. Characteristics of disease history, course of the disease and treatment are presented in Table 1.

Table 1. **Characteristics of patients before treatment**

		Cystectomy	Chemoradio-therapy	Radio-therapy	At all	p value
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	0,19
	Females	3 (6,5)	5 (21,2)	6 (13,1)	14	
Age	< 60 years	19 (41,3)	7 (30,4)	4 (8,7)	30	0,00
	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	
Primary tumor, T	T2	40 (87,0)	22 (95,7)	44 (95,6)	106	0,34
	T3	4 (8,7)	0	2 (4,4)	6	
	T4	2 (4,3)	1 (4,3)	0	33	
Hydro-nephrosis	No	21 (45,7)	14 (60,9)	26 (56,5)	61	0,56
	Yes	24 (52,2)	9 (39,1)	20 (43,5)	53	
	Not assessed	1 (2,1)	0	0	1	
Radicality of TURBT	R0	4 (8,7)	6 (26,1)	9 (19,6)	19	0,10
	R1	7 (15,2)	7 (30,4)	10 (21,7)	24	
	R2	35 (76,1)	10 (43,5)	27 (58,7)	72	
Comorbidi-ties	No	33 (71,7)	13 (56,5)	22 (47,8)	68	0,01
	Yes	13 (28,3)	10 (43,5)	24 (52,2)	47	
Dose of RT and CRT	Not fully completed	-	6 (26,1)	13 (28,3)	19	0,85
	Completed as planned	46 (100)	17 (73,9)	33 (71,7)	50	

CI – confidence interval,
TURBT – transurethral resection of bladder tumor,
R0 –radical, R1- microscopic residual disease, R2- macroscopic residual disease,
RT – radiotherapy, CRT - chemoradiotherapy

Methods of treatment

Radiotherapy

Facility **–** 8–15 MeV linear accelerator

Dose: daily dose of 1,8–2,0 Gy, total dose of 54-60 Gy in 30 fractions given 5 days per week over 6 weeks. Patients were treated in the supine position with legs held shoulder-widths apart, hands under the head and empty bladder.

*Radiation fields***:** 4-field box technique.

Radiation volume: 3-D CT scan planning was used. Clinical target volume (CTV) and planning target volume (PTV) was defined (PTV = CTV plus 1,5 cm) and critical organs (rectum, femoral heads) were outlined. For tumors with regional lymph nodes involvement small pelvis radiation therapy was given with a daily dose of 1,8–2 Gy to total dose of 44–45 Gy in 22 –25 fractions 5 days per week. Planned radiation volumes should took into account the whole bladder and regional (parailiac, presacral) lymph nodes. Then *boost* to bladder with a daily dose of 1,8–2,0 Gy in 5 fractions to a total dose of 54–55 Gy was used. The radiation dose delivered to rectum and femoral heads was less than 45-50 Gy. For tumors without regional lymph nodes metastases the whole bladder radiation was given with daily dose of 1,8–2,0 Gy to a total dose of 54–60 Gy delivered in 27–30 fractions.

Chemotherapy

Chemotherapy (CHT) was initiated on the same day as the initiation of radiotherapy (RT). 21 patients received gemcitabine, 300 mg/m² IV once weekly concomitantly with radiation. 2 patients received gemcitabine, 150 mg/m^2 IV once weekly concomitantly with radiation. Gemcitabine diluted in 500 ml of normal saline was given intravenously over 30 minutes. Once weekly before CHT hematology and biochemistry (hepatic and renal) analyses were taken. The scheme of CRT is presented in Figure 2.

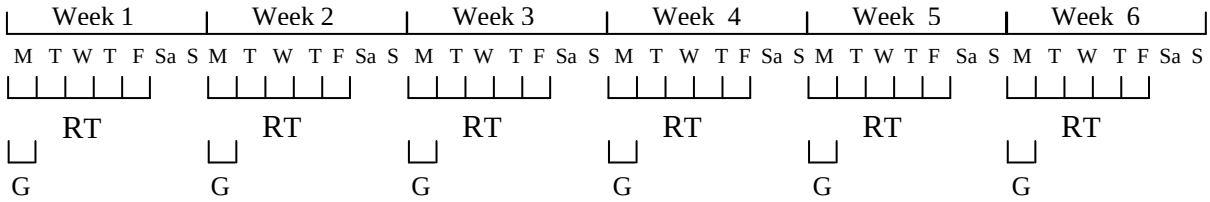

Figure 2. **The scheme of chemoradiotherapy in patients with invasive urothelial bladder cancer (Institute of Oncology Vilnius University)**

G – gemcitabine, 150 - 300 mg/m^2 on days 1, 8, 15, 22, 29, 36; RT – radiotherapy of 1,8 – 2 Gy per day 5 days in a week over 6 weeks; M, T, W, T, F, Sa, S – days of the week.

2.2. Retrospective part of the study

The data of disease and treatment of patients with invasive urothelial bladder cancer that were treated at Institute of Oncology Vilnius University during the years 2000 - 2008 were analyzed. The primary treatment in this patient group consisted of RC or external RT. All inclusion and exclusion criteria for retrospective study remained the same as it were in prospective part of the study. Data from inpatient and outpatient medical records of 500 patients with urothelial bladder cancer had been reviewed. Data of 92 patients who met all inclusion and exclusion criteria were included into analysis. The survival data and reasons of the death were obtained from the Residents' Register Service at the Ministry of the Interior of Republic of Lithuania.

Study material

Retrospective analysis included the data of the disease and treatment collected from outpatient and inpatient medical records of 92 patients with invasive urothelial bladder cancer. 46 patients were treated with RT and RC was performed for other 46 patients. Before the treatment all patients underwent TUR of bladder tumor to obtain the histology samples and confirm the diagnosis. All patients had abdominal and pelvic CT to assess the spread of disease. Most of the patients in RT and RC groups were men (respectively 86,9 and 93,5 percents). The median age of the patients in RT group was

70,5 years and in RC group - 60,5 years. Most of the patients included in retrospective analysis had stage T2N0 tumor before the treatment (in RC and RT groups 87 and 95,6 percents, respectively). TURBT was radical (R0) in only some of study patients (in RC and RT groups 19,6 and 8,7 percents, respectively). Patients treated by RT had more comorbidities than patients treated by RC (52,2 and 28,3 percents, respectively). RT was not completed in 28,3 percents of patients. Characteristics of patients are presented in Table 1.

Methods of treatment

Radiotherapy

Linear accelerator was used for RT. Dose fractionation was given in classical schedule: daily dose of 2 Gy to a total dose of 54–64 Gy in 27-32 fractions.

Surgery

RC in women involved removal of the bladder, uterus and adnexa along with anterior vaginal wall. RC in men involved removal of the bladder, prostate, and seminal vesicles. In all cases pelvic lymph node dissection was done. After RC the surgery for urinary diversion was performed: the surgical anastomosis of the ureters and segment of ileum (*ileum conduit*). This system had a stoma on anterior abdominal wall.

2.3. Examination of molecular markers

Immunohistochemical staining for expression of molecular markers p21, p53, mutated p53 (MTp53) and Bcl-2 of tumor specimens obtained by TURBT was done in prospective analysis. Molecular markers investigated and their role is presented in Table 2.

Table 2. **Molecular markers investigated and their role in cell cycle regulation**

Molecular marker	The role of marker
p53	Tumor suppressor
MT p53	Indirect stimulator of tumor growth
p21	Negative regulator of cell cycle progression
Bcl-2	Inhibitor of apoptosis

Patients investigated and their tumor samples

Molecular markers of tumor specimens obtained by TURBT were studied in prospective analysis. Patients included in prospective analysis, were given bladder-sparing CRT with gemcitabine. Molecular markers were examined by immunohistochemistry in 18 of 23 patients treated by CRT. Histology samples of 5 patients were not found as TURBT was performed in other hospitals in Lithuania.

2.4. Criteria for effectiveness of surgery and conservative treatment

Treatment response – histological examination of specimens obtained from primary tumor site after treatment was performed.

Treatment safety – details of treatment-related adverse events during the treatment and follow-up periods were recorded.

a) Evaluation of treatment safety

Treatment safety was evaluated in patients groups treated with CRT and RT. Details (grade of severity and frequency) of all treatment-related adverse events were recorded. Each treatment regimen-related adverse events were graded according to the scale of National Cancer Institute Common Toxicity Criteria (NCI CTC). Small pelvis toxicity was graded according Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/EORTC) radiation toxicity scale. Adverse events/toxicities were graded using a numerical scale from 0 to 4 (the

grade number gets higher as the severity of the adverse event increases). Treatment-related adverse events were evaluated on the last day of RT and CRT (for early toxicity).

In addition, postponement of chemotherapy, discontinuation of CRT in relation to the grade of adverse event was recorded.

b) Evaluation of treatment response

Treatment response was evaluated in patient groups treated with CRT and RT. Repeated TURBT from the primary tumor site was performed at 1 – 1,5 months later. Samples obtained were examined histologically for malignant features.

c) Survival analysis according to clinical and molecular factors

Progressive disease was defined as a local recurrence and/or development of distant metastases detected by TURBT and/or radiology tests (ultrasound of abdomen, chest X-ray, CT).

The patient has been observed in follow-up phase for as long as the patient remains alive. The dates of the death were verified with the Residents' Register Service at the Ministry of the Interior of Republic of Lithuania.

2.5. Statistical analysis

Statistical analysis of the clinical data of patients and expression of molecular markers detected by immunohistochemistry was performed.

Correlations of clinical characteristics between the patients' groups were tested using chi-square test. p values of 0,05 or less were considered significant.

The survival of the patients was analyzed using Kaplan-Meier method. Survival was calculated as the time from beginning of therapy until death (if patient died) or the last follow-up. 3-year survival was reported. Median follow-up was 18 months. Statistical analysis was performed using STATA programme. The differences between the survival curves were evaluated by log-rank test. p values of 0,05 or less were considered significant.

Analysis of treatment-related toxicity included patient's complaints, results of physical examination and laboratory tests. Toxicity related to CRT and RT was

compared. The chi-square test was used to determine whether there is a significant difference between the treatment groups. p values of 0,05 or less were considered significant.

The impact of clinical prognostic variables (and molecular variables in CRT group) on the survival was assessed by means of *Cox* model. A *Cox* univariate regression model provides an estimate of distinct prognostic variable on survival after adjustment for every clinical and molecular explanatory variable.

A *Cox* multivariate regression analysis was used to assess the impact and significance of the sum of clinical (and molecular in CRT group) variables on survival.

3. RESULTS

3.1. Survival in patients' groups treated by various methods

The survival of the patients was analyzed using Kaplan-Meier method. 3-year survival of all three treatment groups was estimated. Median follow-up was 18 months. Survival curves for treatment groups are presented in Figure 3.

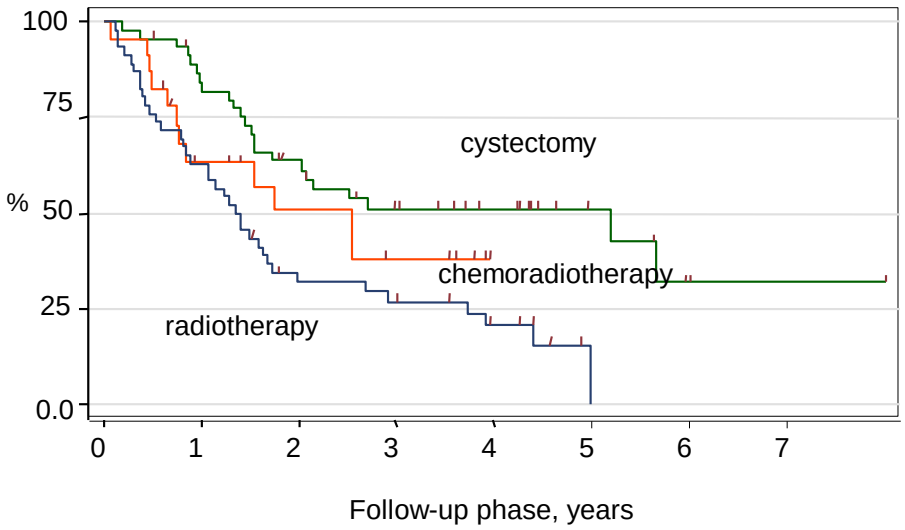

Figure 3. **Survival for treatment groups**

The 3-year survival was the best in RC group and reached 51,1%. The survival was a slightly worse in CRT group and reached 38,0%. The worst survival of 26,9% was

observed in RT group. The survival between different treatment groups was significantly different (p=0,001).

3.1.1. Clinical factors influencing survival

Prognostic factors for survival investigated in patients' groups treated by various regimens:

- age,
- sex,
- radicality of TUR,
- T stage,
- hydronephrosis,
- concomitant diseases,
- total doses of RT and CHT.

The age and sex, T stage, hydronephrosis, concomitant diseases did not have significant impact on survival in patients treated by various regimens.

3.1.1.1. Impact of radicality of TURBT on survival in patients treated by different regimens

The impact of radicality of TURBT on survival was assessed in patients' groups treated by different regimens. The radicality of TURBT before the initiation of treatment was divided in three categories: R0 (no microscopic disease), R1 (microscopic disease), R2 (macroscopic disease). The impact of radicality of TURBT on survival of patients treated with RC is shown on Figure 4.

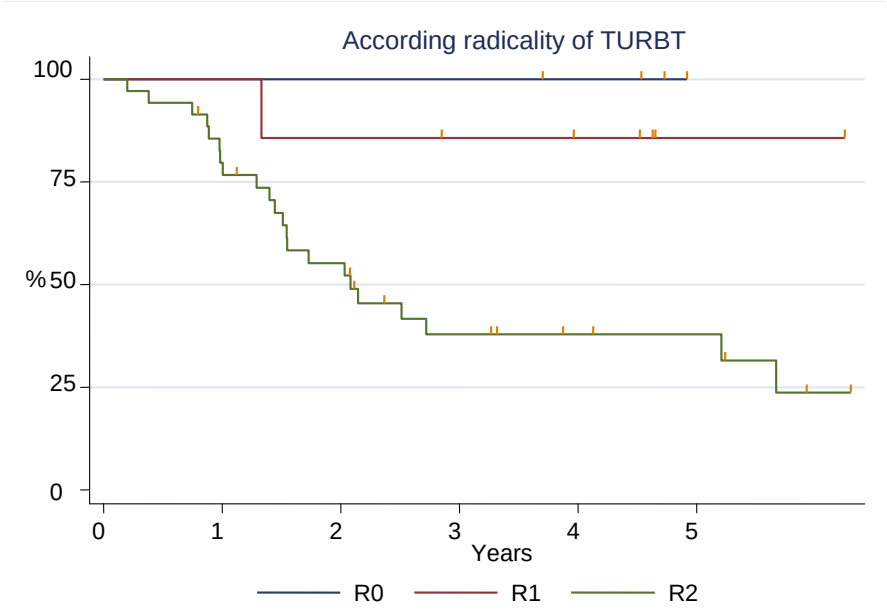

Figure 4. **Survival according to radicality of TURBT in patients treated by radical cystectomy**

3-year survival in patients treated by RC reached 100% if TURBT was microscopically radical (R0), 85,7% if there was microscopical disease left (R1) and 37,8% in cases of macroscopic tumor (R2). There was a significant difference (p=0,02) between survivals (Figure 4).

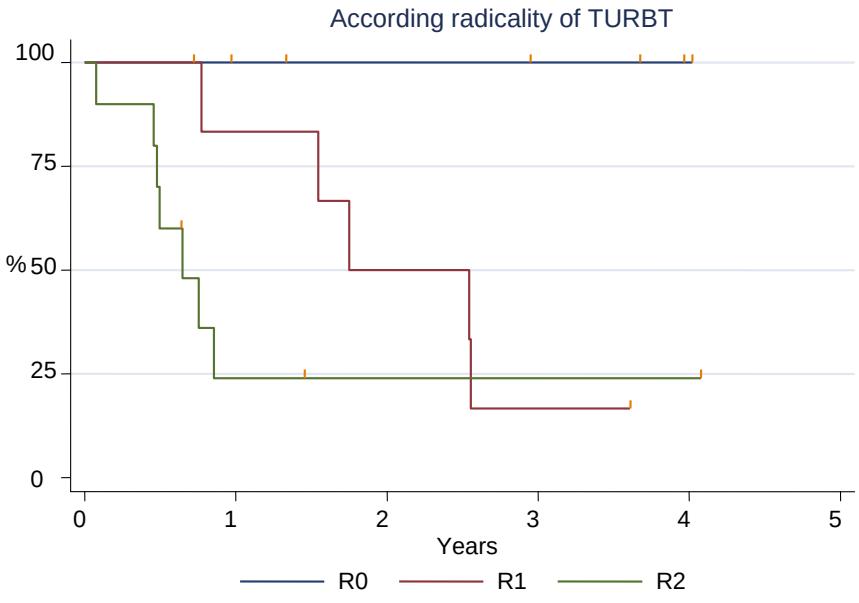

Figure 5. **Survival according to radicality of TURBT in patients treated with chemoradiotherapy**

Figure 5 presents the survival rate according to radicality of TURBT in patients treated with CRT. 3-year survival in patients treated by RC reached 100% if TURBT was microscopically radical (R0), 16,7 % if there was microscopical disease left (R1) and 24% in cases of macroscopic tumor (R2). There was a significant difference (p=0,005) between survivals.

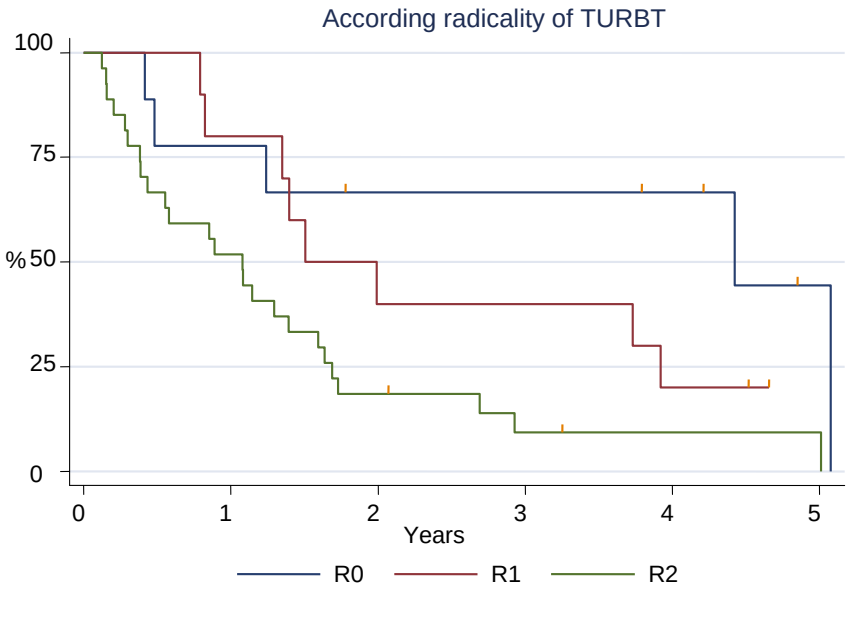

Figure 6. **Survival according to radicality of TURBT in patients treated with external RT**

Figure 6 presents the survival rate according to radicality of TURBT in patients treated with external RT. 3-year survival in patients treated by RC reached 66,7 % if TURBT was microscopically radical (R0), 40% if there was microscopical disease left (R1) and only 9,3 % in cases of macroscopic tumor (R2). There was a significant difference (p=0,008) between survivals.

3.1.1.2. Impact of a total dose of radiation and chemotherapy on survival in patients treated by chemoradiotherapy and radiotherapy

This study examined the impact of full planned RT and CHT dose or the dose given with deviations on survival in patients treated with RT and CRT. If the dose of RT or CHT delivered to a patient was 85% of planned dose or higher then it was accepted as a full dose. Figure 7 presents the impact of radiation or chemotherapy dose delivered to the patient on survival in patients treated with CRT.

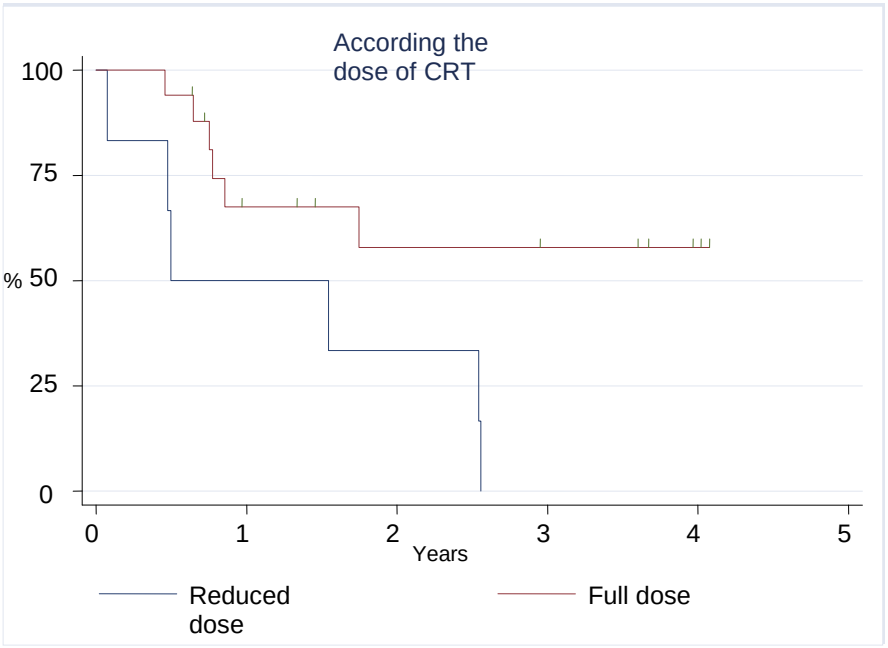

Figure 7. **Survival according radiation or chemotherapy dose delivered in patients treated with chemoradiotherapy**

The survival rate at 3-years was higher in patients treated by CRT with gemcitabine when the dose of RT and CRT delivered to the patient was not reduced. 3-year survival in this group of patients reached 57,9%. No patients were alive at 3-years in the group with reduced dose of CRT. The difference between groups was significant (p=0,02).

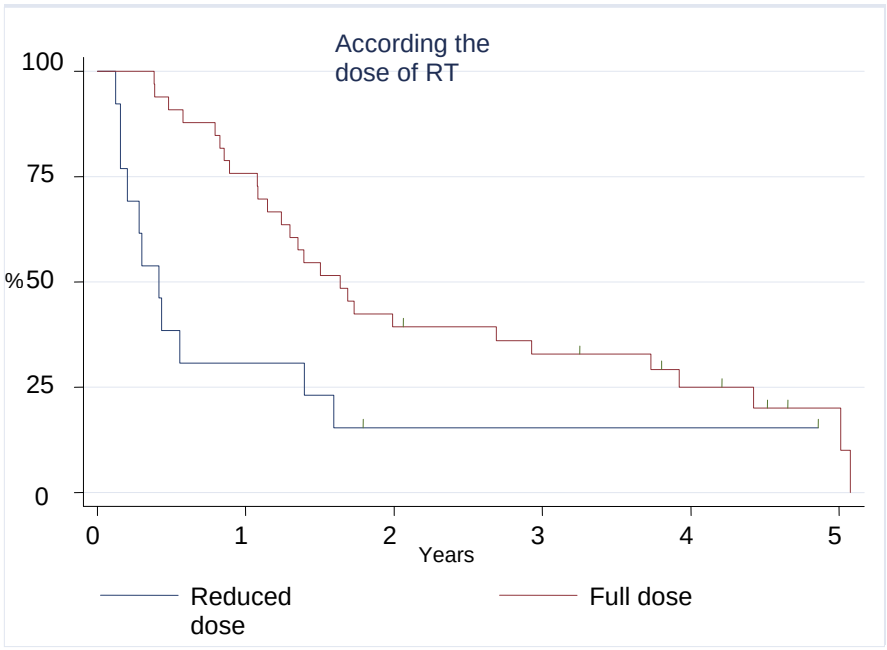

Figure 8. **Survival according radiation dose delivered in patients treated with radiotherapy**

Figure 8 presents the impact of delivered radiation dose on 3-year survival. The survival rate was higher in patients treated with a full dose of radiation. 3-year survival in this group of patients reached 32,8 %. Survival rate in patients treated with reduced dose of radiation was less and reached only 15,4%. The difference between groups was significant (p=0,01).

3.1.2. Impact of a molecular markers on survival in patients treated by chemoradiotherapy

This study assessed the impact of four molecular markers on survival in patients treated with CRT. p53, MTp53, p21 and Bcl-2 markers were examined.

The prognostic impact of Bcl-2 expression on survival in patients treated with CRT was examined. Negative Bcl-2 was associated with 25,5% of survival rate at 3 years. In cases with positive Bcl-2 the survival reached 100%. The difference between groups was not significant (p=0.19). Prognostic value of p53 expression on survival was assessed in patients treated with CRT. Negative p53 was associated with a negative outcome - no patients were alive at 3-years in the group treated with chemoradiotherapy. Positive p53 was associated with survival of 32,3%. The difference between groups was

not significant (p=0.55). The impact of p21 expression on survival in the group of patients treated with CRT was examined as well. 3-year survival rate was higher in patients with negative p21 and reached 55,6%. Survival rate in patients with positive p21 was less and reached 20,1 %. The difference between groups was not significant (p=0,13).

Multivariate and univariate *Cox* proportional hazards model was used to test all the mentioned molecular markers and their impact on survival.

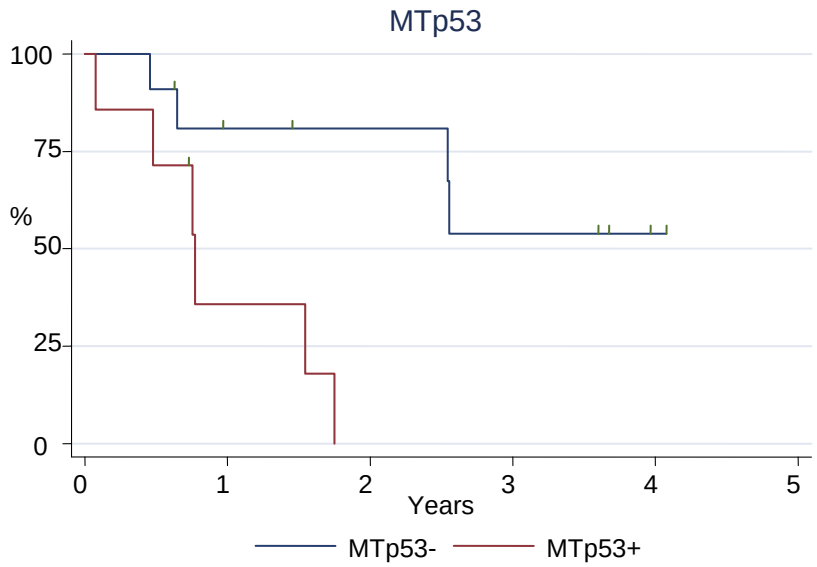

Figure 9. **Survival according to the expression of MTp53**

Figure 9 presents the prognostic value of mutated p53 oncogene (MTp53) expression on survival in patients treated with CRT. The patients with negative MTp53 lived longer. 3-year survival in this group was 53,9%. The difference between groups was significant (p=0.01).

Cox proportional hazards risk model using multivariate and univariate analysis showed that every marker separately and all variables combined had a prognostic value for survival. Univariate analysis showed that increased expression of MTp53 was a significant negative prognostic marker for survival in patients treated with CRT (HR=7,23, 95% CI=1,41 – 37,10, p-value=0,02). Increased MTp53 expression remained a significant negative prognostic factor for survival after multivariate analysis was done

(HR=5,76, 95% CI=0,95 – 35,65, p-value=0,01). The results of multivariate and univariate analysis on molecular prognostic markers in patients with invasive urothelial bladder cancer treated with CRT are presented in Table 3.

Table 3. **Univariate and multivariate analysis using *Cox* proportional hazards risk models**

Marker	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Bcl-2	-	-	-	-
p53	1.87 (0.23-15.06)	0,55	0.21 (0.01- 4.35)	0,65
MTp53	7.23 (1.41 – 37.10)	0,02	5.76 (0.93 – 35.65)	0,01
p21	3,16 (0,67 – 14,96)	0,15	4.22 (0.51 – 34.75)	0,28

HR – hazard risk,
CI – confidence interval,
p –value

3.2. Univariate analysis using *Cox* model of clinical prognostic factors in patients with invasive urothelial bladder cancer treated with various regimens

Univariate *Cox* proportional hazards risk model was used to assess the prognostic value on survival for each clinical factor separately in patients treated with RC, CRT and RT. Analysis showed the negative prognostic value of planned dose reduction on overall survival of patients treated with CRT. The planned schedule administered with dose reductions increased the risk of death by 3,66 times (CI=1,17 – 11,44, p-value=0,03). Concomitant diseases in patients treated with CRT had a tendency to increase the risk of death by 3,12 times (CI=0,83 – 11,76, p-value=0,09).

Patients of the elder age groups treated with RT have tendency 1,6 times increased the risk of death (CI=0,94 – 2,71, p-value=0,08). There is 3,46 time higher tendency to increase the risk of death in patients with T3 tumor (CI=0,78 – 15,32, p-

value=0,1). Full planned dose of radiation and radicality of TURBT were significant factors predicting survival in patients treated with RT. Reduction of planned dose of radiation increased the risk of death by 2,46 times (CI=1,20 – 5,05, p-value=0,01). Macroscopically incomplete (R2) TUR in patients treated with RT increased the risk of death by 4,39 times (CI=1,49 – 12,97, p-value=0,007).

Univariate analysis of clinical prognostic factors is presented in Table 4.

Table 4. **Univariate analysis using *Cox* model of clinical prognostic factors in patients with invasive urothelial 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
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 of primary tumor	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	-	-	-	-
Dose of RT and CHT		-	-	3,66(1,17-11,44)	0,03	2,46(1,20-5,05)	0,01

HR – hazard risk,
CI – confidence interval,
p –value, RT – radiotherapy, CHT - chemotherapy

3.3. Multivariate analysis using *Cox* model of clinical prognostic factors in patients with invasive urothelial bladder cancer treated with various regimens

Multivariate analysis of *Cox* proportional hazards risk model was used to assess the prognostic value on survival for all clinical variables combined in patients treated with RC, CRT and RT. Macroscopically incomplete (R2) TURBT was independent significant factor predicting survival in patients treated with RC. R2 TURBT increased the risk of death by 10,88 times in this group of patients (CI=1,44 – 82,41, p-value=0,02).

Concomitant diseases was independent prognostic factor and increased the risk of death by 14,34 times in patients treated by CRT (CI=1,44 – 142,66, p-value=0,02).

Multivariate analysis using *Cox* model showed that reduced dose of radiation was a significant prognostic factor for decreased survival in patients treated with RT. Reduced dose of radiation increased the risk of death by 5,19 times in this group of patients (CI=2,16 – 12,43, p-value=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 RT. R2 TURBT increased the risk of death by 2,98 times (CI=1,38 – 6,44, p-value=0,005). Hydronephrosis increased the risk of death by 2,32 times (CI=1,07 – 5,04, p-value=0,03). Stage T3 tumor increased the risk of death by 5,03 times (CI=1,06 – 24,02, p-value=0,04). The results of multivariate analysis of clinical prognostic factors are presented in Table 5.

Table 5. **Multivariate analysis using *Cox* model of clinical prognostic factors in patients with invasive urothelial 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
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 of primary tumor	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	-	-	-	-
Dose of RT and CHT		-	-	2,77(0,52-14,72)	0,23	5,19(2,16-12,43)	0,001

HR – hazard risk,
CI – confidence interval,
p –value, RT – radiotherapy, CHT - chemotherapy

All three treatment groups – radical cystectomy, chemoradiotherapy and radiotherapy - were compared. The results showed that RT to compare with RC was a significant prognostic factor predicting shorter survival (HR 2,67, 95% CI 1,56 – 4,57, p-value=0,00).

3.4. Assessment of chemoradiotherapy and radiotherapy-related adverse events

Chemoradiotherapy- and radiotherapy-related adverse events were evaluated. The most common toxicities were haematological, gastrointestinal and urinary bladder toxicities. Six patients (26,1%) in CRT group did not accomplish treatment per protocol. Two of them were removed from planned treatment due grade 3 liver enzyme elevation,

other two – due to prolonged grade 3 diarrhea and one patient due to thrombocytopenia. One patient refused to continue CRT because of grade 3 dysuria and afterwards underwent cystectomy.

Hematological toxicity (changes in neutrophil, haemoglobin and platelets numbers) and alteration of liver enzymes (alanine and asparagine transaminases) was assessed by CTCAE grading scale. Toxicity to small pelvis (dysuria and diarrhea) was evaluated according RTOG/EORTC criteria. No death due to toxicity was reported in any of two treatment groups. The most common toxicities were of grade 1 or 2. Observed early toxicities are presented in Table 6.

Table 6. **Early toxicities**

Event	Chemoradiotherapy, % N=23	Radiotherapy, % N=46	p-value
Anaemia (grade 1 and 2)	44/13	17/7	>0,05
Neutropenia (grade 1, 2 and 3)	9/35/4	0/2/0	-
Thrombocytopenia (grade 1 and 2)	26/4	4/0	> 0,05
Diarrhea (grade 1, 2 and 3)	22/26/9	0/7/0	-
Dysuria (grade 1, 2, 3 and 4)	26/44/4/0	15/54/17/2	-
Elevated ALT, AST levels (grade 1, 2 and 3)	13/4/4	Any	<0,05

ALT – alanine transaminase
AST – asparagine transaminase

Haematological toxicity such as grade 1 and 2 anaemia and thrombocytopenia was reported in both treatment groups. Anaemia was more common in patients treated with CRT. Anaemia was found in 13 patients (57 %) treated with CRT and in 12 patients (24 %) treated with RT. The difference between the groups was not statistically significant (p>0,05).

Thrombocytopenia was mild and more common in patients treated with CRT. Anaemia was observed in 7 patients (30 %) treated with CRT and in only 2 patients (4

%) treated with RT. The difference between the groups was not statistically significant (p>0,05).

Neutropenia was more common in patients treated with CRT and was observed in nearly half of patients (48%). One patient experienced grade 3 neutropenia and needed to postpone planned infusion of gemcitabine. Only one patient treated with RT experienced grade 2 neutropenia.

Diarrhea was more common in patients treated with CRT. In this group of patients diarrhea was diagnosed in 13 patients (57%) and two of them experienced grade 3 diarrhea. One patient with grade 3 diarrhea prematurely discontinued treatment. Another patient with grade 3 diarrhea was given symptomatic treatment that was successful. This patient in CRT group underwent treatment interruption. Diarrhea was much less common and milder in RT group and was observed in 3 patients (7 %).

The most common adverse event observed in both treatment groups was dysuria. Dysuria was diagnosed in 17 patients (74%) treated with CRT and one of them had grade 3 dysuria. The patient with grade 3 dysuria refused to continue CRT and discontinued treatment per protocol. Afterwards this patient underwent cystectomy. Dysuria was even more frequent finding in patients treated with RT. In this group of patients dysuria was observed in 41 patients (88%). 8 patients (17 %) had grade 3 dysuria and one – grade 4. Two patients with grade 3 dysuria and one patient with grade 4 dysuria could not complete the treatment per protocol.

Five patients (21%) in CRT group experienced transient elevation of liver enzymes ALT and AST that returned to normal range after completion of therapy. Grade 3 elevation of liver enzymes was noticed in only one patient. This patient did not complete the treatment according protocol due to combined toxicity of grade 3 elevation of liver enzymes together with grade 2 dysuria and diarrhea. There was no hepatic toxicity in RT group detected. In this case the difference between the groups was statistically significant (p<0,05).

At the time of the CRT group analysis 12 patients (52%) treated with gemcitabine were dead and 11 patients (48%) alive in follow-up phase. The cause of death found was urinary bladder cancer in all cases. 21 patients preserved bladder after bladder-sparing CRT except of two. One of these two patients had residual tumor after completed CRT, another one refused to continue CRT and insisted on radical cystectomy. All 11 patients

alive had preserved bladder. 3 patients (13%) in follow-up phase after CRT had a local recurrent disease, 6 patients (26%) were diagnosed with metastatic disease and 4 patients (17%) were lost in follow-up phase.

At the time of data analysis in RT group 8 patients (83%) were dead and 8 patients (17%) were still alive. The cause of death was bladder cancer in 35 cases, sepsis in 1 and cardiovascular diseases in 2. All patients in RT group preserved their bladders after bladder-sparing treatment. The detailed analysis of causes of death revealed the recurrent disease in 14 patients, distant metastases in 10 patients and recurrent disease together with distant metastases in remained 14 patients.

4. CONCLUSIONS

1. The best 3-year overall survival rate was demonstrated in patients treated with radical cystectomy (51,1%). Patients treated with chemoradiotherapy had worse survival rate (38%) and the worst survival was observed in patients treated with radiotherapy (26,9 %).
2. The radicality of TURBT was shown as significant independent prognostic factor for survival in all patients treatment groups – radical cystectomy, chemoradiotherapy and radiotherapy. Patients who underwent R0 TUR had the highest survival rate. The significant impact of dose of radiation and chemotherapy on survival of patients treated by chemoradiotherapy and radiotherapy.
3. The negative prognostic factor for survival in chemoradiotherapy treatment group was concomitant diseases. Independent prognostic factors in patients treated with radiotherapy were radicality of TUR, hydronephrosis and depth of tumor infiltration (T) and dose of radiation and chemotherapy.
4. Gastrointestinal toxicity (elevation of liver enzymes) was more common in patients treated with chemoradiotherapy.
5. Increased MTp53 expression had a negative impact on survival in patients treated with chemoradiotherapy.

5. PRACTICAL RECOMMENDATIONS

1. In invasive urothelial urinary bladder cancer radical cystectomy as a first priority treatment is recommended for patients in good general condition.
2. Chemoradiotherapy may be an option for patients that refused radical cystectomy. Better treatment results are expected in cases of radical TUR (R0) and in patients with any concomitant illness.
3. Increased expression of MTp53 may be a leading factor that may help to choose the conservative treatment versus surgery in patients with invasive urothelial bladder cancer.

6. LIST OF PUBLICATIONS

1. F. Jankevičius, J. Asadauskienė, E. Aleknavičius, A. Žilevičienė. Trimodality bladder-sparing treatment of muscle-invasive bladder cancer. Abstract on European Association of Urology 4th Baltic States Meeting, 3 – 4 June 2005, Riga, Latvia (tezės).
2. J. Asadauskienė, E. Aleknavičius, T. Pipirienė Želvienė, F. Jankevičius. Sergančiųjų invaziniu uroteliniu vėžiu šlapimo pūslę išsaugančio gydymo efektyvumas. Medicina (Kaunas). 2006: 42(10); 781-787.
3. J. Asadauskienė, E. Aleknavičius, T. Pipirienė Želvienė, A. Žilevičienė, F. Jankevičius. Efficacy and toxicity of concurrent radiochemotherapy with gemcitabine after transurethral resection of invasive bladder cancer. Acta medica Lituanica. 2007: 14(3); 178-183.
4. J. Asadauskienė, E. Aleknavičius, A. Žilevičienė, T. Pipirienė Želvienė, F. Jankevičius. Efficacy of radiochemotherapy with gemcitabine in organ-sparing treatment of bladder cancer. Abstract in EAU 2nd North Eastern European Meeting, 12-13 September 2008, Vilnius, Lithuania (tezės).
5. J. Asadauskienė, E. Aleknavičius, T. Pipirienė Želvienė, F. Jankevičius. Klinikinių prognozinių veiksnių reikšmė invaziniu uroteliniu šlapimo pūslės vėžiu sergančiųjų išgyvenamumui (Medicina, 2009, in press).

SUMMARY IN LITHUANIAN

Klinikinių ir molekulinių prognozinių veiksnių reikšmė sergančiųjų invaziniu uroteliniu šlapimo pūslės vėžiu išgyvenamumui

Europos Sąjungoje sergamumas invaziniu šlapimo pūslės vėžiu yra 19,5/100000 gyventojų, o mirtingumas nuo šios ligos – 7,9/100000 gyventojų [ESMO Minimum Clinical Recommendations, 2009]. Lietuvoje šlapimo pūslės vėžiu kasmet suserga daugiau negu 400 pacientų, ketvirtadaliui iš jų diagnozuojamas invazinis vėžys [Kurtinaitis et al, 2006]. Daugiau negu pusę pacientų, susirgusių ir mirusių dėl šlapimo pūslės vėžio, sudaro pacientai, susirgę invaziniu vėžiu. Invazinis šlapimo pūslės vėžys neišvengiamai metastazuoja, o vėžiui metastazavus, paciento vidutinė gyvenimo trukmė yra apie 11 mėnesių [Von der Masse et al, 2000]. Invazinio šlapimo pūslės vėžio atveju gydytojui kartu su pacientu reikia spręsti – pašalinti ar išsaugoti šlapimo pūslę nesumažinant paciento išgyvenimo trukmės. Radikali cistektomija kartu pašalinant ir sritinius limfmazgius šiuo metu yra invazinio šlapimo pūslės vėžio gydymo standartas Europos Sąjungoje ir Jungtinėse Amerikos Valstijose. Tai didelės apimties traumuojanti operacija. Nepaisant didelės operacijos apimties 5 metus išgyvena tik kiek daugiau negu 50 proc. taip gydytų pacientų [Ghoonheim MA, et al, 2000]. Per paskutinį dešimtmetį buvo tobulinama chirurginė technika ir pasiūlyta daug įvairių metodikų, kaip suformuoti šlapimo surinkimo rezervuarus. Tačiau dirbtinai suformuotas organas pacientui negali atstoti savos šlapimo pūslės. Nukenčia paciento gyvenimo kokybė ir lytinė funkcija. Pastaraisiais dešimtmečiais dedamos pastangos sukurti tokias gydymo metodikas, kurios leistų išvengti negalią sąlygojančios operacijos šios grupės pacientams. Buvo atlikta nemažai klinikinių tyrimų skiriant kombinuotą gydymą, kurį sudaro transuretrinė šlapimo pūslės naviko rezekcija, sisteminė chemoterapija ir spindulinis gydymas. Kai kurie iš tų tyrimų parodė, kad galima išsaugoti funkcionuojančią šlapimo pūslę ir užtikrinti tokius pat išgyvenamumo rodiklius, kaip ir po radikalios cistektomijos. Naujausių klinikinių tyrimų analizė rodo, kad, įtraukus į chemospindulinio gydymo protokolus naujesnius chemopreparatus, ženkliai pagerėja vietiškai išplitusio šlapimo

pūslės vėžio konservatyvaus gydymo veiksmingumas. Pastaruoju metu tiriami klinikiniai ir molekuliniai prognoziniai veiksniai, kurie galėtų padėti individualizuoti gydymą. Nepaisant įdėtų pastangų, iki šiol nėra aišku, koks chemopreparatas, naudojamas derinant su spinduline terapija yra veiksmingiausias invazinio urotelio vėžio atveju, nėra nustatyti ir įdiegti į klinikinę praktiką molekuliniai žymenys, kurie galėtų padėti prognozuoti atsaką į gydymą. Taip pat tęsiami tyrimai ieškant prognozinių veiksnių, kurie padėtų identifikuoti grupes pacientų, kuriems būtų galima siūlyti konservatyvųjį arba chirurginį gydymą, tikintis optimalaus rezultato.

Vilniaus universiteto Onkologijos institute invaziniu uroteliniu šlapimo pūslės vėžiu sergantiems pacientams taikomas operacinis gydymas (radikali cistektomija), spindulinis gydymas ir chemoterapija. Šiame darbe išanalizuoti Vilniaus universiteto Onkologijos institute 2000 – 2008 metais atlikto invazinio urotelinio šlapimo pūslės vėžio gydymo rezultatai. Perspektyvinėje tyrimo dalyje išanalizuota klinikinių ir molekulinių prognozinių veiksnių įtaka chemospinduliniu gydymo metodu gydytų pacientų išgyvenamumui. Retrospektyvinėje tyrimo dalyje išanalizuota klinikinių prognozinių veiksnių reikšmė radikalia cistektomija ir spinduliniu gydymo metodu gydytų pacientų išgyvenamumui.

Darbo tikslas

Įvertinti klinikinius ir molekulinius prognozinius veiksnius, darančius įtaką pacientų, sergančių invaziniu uroteliniu šlapimo pūslės vėžiu, išgyvenimo rodikliams, kai jie gydomi šiais metodais: radikalia cistektomija, spinduline terapija bei spinduline terapija, derinama su gydymu gemcitabinu.

Tyrimo uždaviniai

1. Įvertinti 2000 – 2008 m. Vilniaus universiteto Onkologijos institute gydytų pacientų, sergančių invaziniu uroteliniu šlapimo pūslės vėžiu, kuriems buvo atlikta

radikali cistektomija arba taikytas konservatyvusis gydymas (chemospindulinis arba spindulinis) išgyvenamumą.

2. Nustatyti klinikinių veiksnių svarbą pacientų, sergančių invaziniu uroteliniu šlapimo pūslės vėžiu, kuriems buvo atlikta radikali cistektomija, bei tų, kuriems buvo taikytas konservatyvusis gydymas (chemospindulinis arba spindulinis) išgyvenamumo prognozei.

3. Nustatyti ir palyginti spindulinio ir chemospindulinio gydymo metodų sukeltus nepageidaujamus poveikius organizmui.

4. Ištirti molekulinių žymenų raiškos svarbą pacientų, kuriems buvo taikytas chemospindulinis gydymas, išgyvenamumo prognozei.

Ginamieji teiginiai

1. Geriausias trejų metų išgyvenamumas buvo radikalia cistektomija gydytų pacientų grupėje, blogiausiai išgyveno spindulinės terapijos metodu gydyti pacientai.

2. Radikalios cistektomijos, chemospinduliniu ir išorinės spindulinės terapijos metodu gydytų pacientų išgyvenamumą reikšmingai sąlygojo transuretrinės rezekcijos radikalumas. Gydant pacientus konservatyviai (chemospinduliniu ir spinduliniu gydymo metodais), išgyvenamumui reikšmingas realizuotos dozės dydis.

3. Taikant chemospindulinį gydymo metodą, nepriklausomas prognozinis veiksnys yra gretutinės ligos. Spindulinio gydymo grupėje nepriklausomi prognoziniai veiksniai yra transuretrinės rezekcijos radikalumas, hidronefrozė, naviko (T) infiltracijos dydis.

4. Dažniausiai pasireiškiantis nepageidaujamas poveikis chemospindulinio gydymo grupėje pacientams yra toksinis poveikis virškinamajam traktui (kepenų fermentų padidėjimas).

5. Padidėjusi MTp53 raiška yra blogos prognozės rodiklis chemospinduliniu gydymo metodu gydytiems pacientams.

Darbo mokslinis naujumas ir reikšmė

Tirtas chemospindulinio gydymo veiksmingumas konservatyviai gydant invazinį urotelinį šlapimo pūslės vėžį. Pirmą kartą klinikinėje praktikoje urotelinis šlapimo pūslės vėžys gydytas gemcitabinu (dozė 300 mg/m^2) derinant šį metodą su spinduliniu gydymu. Buvo tirta molekulinių žymenų, kaip prognozinių veiksnių, reikšmė chemospinduliniu metodu gydytų pacientų išgyvenamumui.

Tyrimo medžiaga ir metodai

Klinikinis tyrimas atliktas, siekiant įvertinti, kokią įtaką alternatyvių (radikaliosios cistektomijos, chemospindulinio ir spindulinio gydymo metodų) invazinio urotelinio šlapimo pūslės vėžio gydymo taktikų pasirinkimas daro gydymo rezultatams.

Šiame darbe analizuojami ligos duomenys pacientų, kurie sirgo invaziniu uroteliniu šlapimo pūslės vėžiu 2000 - 2008 metais ir gydėsi Vilniaus universiteto Onkologijos institute. Iš viso išanalizuota 115 pacientų ligos duomenys. Klinikinis tyrimas susideda iš dvejų dalių – pacientai, kurie buvo gydyti pagal perspektyviojo klinikinio tyrimo protokolą ir retrospektyviai pagal įtraukimo kriterijų atitikimą atrinkti pacientai. Atliekant perspektyvinę tyrimo dalį išanalizuota 23 pacientų ligos duomenys, o retrospektyvinėje tyrimo dalyje – 92 pacientų ligos duomenys.

Perspektyvinės klinikinio tyrimo dalies pacientams po transuretrinės rezekcijos buvo taikomas konservatyvusis šlapimo pūslę išsaugantis chemospindulinis gydymas kaip chemopreparatą naudojant gemcitabiną. Iš navikinės medžiagos, kuri buvo gauta atlikus šlapimo pūslės naviko transuretrinę rezekciją perspektyvinės klinikinio tyrimo dalies tiriamiesiems imunohistocheminiu būdu buvo nustatyta p21, normalaus gamtinio tipo p53 (WTp53), mutantinio p53 (MTp53) ir Bcl-2 baltymų raiška. Retrospektyvinėje klinikinio tyrimo dalyje analizuoti ligos ir gydymo duomenys pacientų, kurie 2000–2008 metais Vilniaus universiteto Onkologijos institute buvo gydyti dėl invazinio urotelinio šlapimo pūslės vėžio. Pacientams kaip pirminis invazinio šlapimo pūslės vėžio gydymo būdas buvo atlikta radikali cistektomija arba išorinė spindulinė terapija. Atrenkant pacientus retrospektyviai, buvo laikomasi tokių pat įtraukimo ir neįtraukimo kriterijų kaip ir perspektyviniame tyrime. Atrinkti 92 pacientai, kurių ligos ir gydymo duomenys

atitiko klinikinio tyrimo įtraukimo ir neįtraukimo kriterijus. Pacientų mirties datos ir priežastys patikslintos Gyventojų registro tarnyboje prie Lietuvos Respublikos vidaus reikalų ministerijos.

Išvados

1. Įrodyta, kad didžiausias bendrasis trejų metų išgyvenamumas buvo radikaliosios cistektomijos metodu gydytų pacientų grupėje (51,1 proc.), mažesnis išgyvenamumas buvo chemospindulinio gydymo grupėje (38,0 proc.). Mažiausias išgyvenamumas buvo spinduline terapija gydytų pacientų (26,9 proc.).
2. Radikaliosios cistektomijos, chemospinduliniu ir spinduliniu metodu gydytų pacientų išgyvenamumą reikšmingai sąlygojo transuretrinės rezekcijos radikalumas; didžiausias išgyvenamumas buvo pacientų, kuriems buvo atlikta R0 transuretrinė rezekcija. Gydant pacientus konservatyviai (chemospinduliniu ir spinduliniu gydymo metodais), išgyvenamumui reikšmingas realizuotos dozės dydis.
3. Taikant chemospindulinį gydymo metodą, išryškėjo, kad gretutinės ligos daro neigiamą įtaką pacientų išgyvenamumui. Spindulinio gydymo grupėje kaip nepriklausomi prognoziniai veiksniai išryškėjo TUR radikalumas, hidronefrozė, naviko (T) infiltracijos gylis.
4. Toksinis poveikis virškinamajam traktui (kepenų fermentų padidėjimas) dažniau pasireiškė chemospinduliniu gydymo metodu gydytiems pacientams.
5. Pacientų, gydytų chemospinduliniu metodu, išgyvenamumas buvo trumpesnis, jeigu jiems buvo nustatyta padidėjusi MTp53 raiška.

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