CANCER UROLOGY 3'2016 VOL. 12

Effectiveness of transurethral resection under the control of photodynamic diagnosis and intravesical instillation of bacillus Calmette–Guérin in case of poorly differentiated non-muscle-invasive bladder cancer

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Background. *High-grade non-muscle-invasive bladder cancer (NMIBC) is characterized by a high rate of recurrence, progression, and mortality associated with this disease. Organ-preserving treatment by transurethral resection and immunotherapy with bacillus Calmette-Guerin (BCG) is an initial approach to therapy in these patients. However, the efficacy of such therapy is limited. This justifies the use of other methods of treatment, such as TUR under the control of photodynamic diagnosis (PDD). Aim of this study was to evaluate the effectiveness of therapeutic interventions in patients with high-grade NMIBC.*

Materials and methods. *We have retrospectively analyzed results of follow-up of patients with primary or recurrent high-grade transitional cell NMIBC, treatment by TUR in conjunction with BCG or without it N.N. Alexandrov National Cancer Centre in the period from 2004 to 2013. In total, the study included 113 patients (27 women and 86 men), in the median age of 72 years. We have evaluated 5-year recurrence- and progression-free survival, analyzed an influence of prognostic factors and methods of treatment on the risk of recurrence and progression with Cox model and Kaplan–Meier method.*

Results. *With a median of follow up of 59 (12–116) months the rates of 5-year recurrence- and progression-free survival were respectively 42.5 and 71.6 %.*

Statistically significant association with the risk of recurrence was observed in multivariate Cox regression analysis for recurrent tumors (hazard ratio (HR) 2.73; 95 % confidence interval (CI) 1.61–4.62) and immunotherapy with BCG (HR 0.56; 95 % CI 0.31–0.99). BCG significantly increased recurrence-free survival in patients with both primary tumors, and with recurrent ones. Significant factors in the multivariate analysis with regard to the risk of progression were suspicion for muscle-invasive tumors according to the cystoscopic picture (HR 3.36; 95 % CI 1.09–10.4), abnormal tumor-free bladder mucosa, suspicious for carcinoma in situ (HR 7.23; 95 % CI 2.64–19.8), localization of tumor in the bladder neck, orifice zone, prostatic urethra (HR 2.91; 95 % CI 1.17–7.25) and PDD-assisted TUR (HR 0.10; 95 % CI 0.01–0.78). TUR under the control of photodynamic diagnosis significantly increased the survival to progression, regardless of the risk of progression, while BCG did not significantly affect the progression-free survival.

Conclusions. *6-week course of BCG therapy in patients with high-grade NMIBC significantly reduces the risk of recurrence and has no effect on the risk of tumor progression. PDD-assisted TUR provides a significant reduction in the risk of progression, but not recurrence. The findings justify the inclusion of both modalities in the treatment of high-grade NMIBC.*

Key words: *non-muscle-invasive bladder cancer, poorly differentiated, bladder-sparing therapy, bacillus Calmette-Guerin, photodynamic diagnostics, recurrence-free survival, progression-free survival*

DOI: 10.17650/1726-9776-2016-12-3-58-67

Introduction

Poorly differentiated bladder cancer (BC) is a small but important group of non-muscle invasive BCs (NMIBC). Thus, while in most cases of well-differentiated tumor the probability of progression into muscle invasive cancer, metastasis, or death from BC is very low, and the main task is prevention of local recurrences [1], in poorly differentiated tumors progression rate is rather significant: from 20 to 40 % [2]; tumor progression is associated with high mortality up to 10–15 % [3].

Treatment of this type of NMIBC is a subject of discussion, and it includes transurethral resection (TUR) with subsequent immunotherapy using bacillus Calmette-Guerin (BCG) or early radical cystectomy [4]. Considering relatively rare occurrence of poorly differentiated NMIBC, treatment guidelines for this pathology are based on non-randomized retrospective studies [5] or large protocols involving a mixed group of patients with NMIBC and poor or intermediate prognosis [6, 7]. In such conditions, even retrospective studies evaluating effectiveness of different types of therapy are pertinent. Moreover, the role of some relatively new treatment and diagnostic methods in this pathology, for example TUR under control of photodynamic diagnosis (PDD), is not yet clearly determined.

The study objective was to evaluate effectiveness of therapeutic interventions in patients with poorly differentiated NMIBC.

Materials and methods

N.N. Aleksandrov National Cancer Centre database was searched for cases satisfying the following criteria: visually radical TUR of the bladder performed in 2004–2013;

verification of transitional cell BC or its variants and absence of invasion into the muscle layer of the bladder according to postoperative histological examination of the removed material; low differentiation grade according to the 1973 WHO (grade 3) and/or 2004 WHO (high grade) classifications; organ preservation treatment with or without restaging TUR (re-TUR), and various types of intravesical therapy. Exclusion criteria were lack of follow-up data, stage advancement to T2 or higher after re-TUR, experimental therapy (photodynamic therapy), lack of monitoring data, and repeated cases of treatment of the same patient. The study included 113 patients: 27 women and 86 men aged 39–93 years (median 72 years).

From medical records patients' demographic characteristics (sex, age, place of residence), standard NMIBC prognostic factors (recurrence rate, multifocality, tumor size, T category, concomitant carcinoma *in situ* (CIS)), additional characteristics (detailed cytoscopic description of the tumor and bladder mucosa beyond the tumor, tumor location), and treatment characteristics (surgeon's experience, TUR combined with PDD, re-TUR, intravesical therapy) were extracted.

Surgical treatment under control of PDD was performed with 5-aminolevulinic acid (5-ALA) as a photosensibilizator (alamine, KhimFarmSintez, Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus) and commercial endoscopic equipment (Richard Wolf GmbH) using a previously described standard technique [8]. In aseptic conditions 90–120 minutes before TUR a fresh solution of 1.5 g 5-ALA in 3 % sodium bicarbonate was injected into the patient's bladder. The recommended time for solution retention was 2 hours. Then the patient was transferred into the operating room where cystoscopy in white and blue light and standard TUR/electrocoagulation of all visible in white and blue light tumors were performed.

As an adjuvant therapy, 41 (36.3 %) patients received a 6-week BCG induction course (imuron, N.F. Gamaleya Federal Research Center for Epidemiology & Microbiology) without maintenance therapy. Other patients didn't receive adjuvant intravesical therapy.

Correlations between BCG immunotherapy and PDD and various patient and tumor characteristics were analyzed. Statistical significance was evaluated using the χ^2-test or Fisher's exact test. The Kaplan-Meier estimator was used for evaluation of 5-year relapse-free survival and progression-free survival and their 95 % confidence intervals (CI).

Using the Cox model, a univariate regression analysis of prognostic factors in relation to relapse-free survival and progression-free survival was performed. Factors with a high level of risk ratio (RR) statistical significance ($p < 0.1$) were used in a multivariate regression analysis with stepwise exclusion of variables. Effectiveness of therapeutic interventions in various prognostic strata was evaluated using the Kaplan-Meier estimator; statistical significance of the differences was evaluated using the log-rank test; all p values were two-sided.

Results

In the studied patient cohort, women received BCG immunotherapy more frequently than men. PDD significantly correlated with an increased rate of CIS diagnosis (Table 1).

Median follow up duration for all 113 patients was 59 months (ranging from 12 to 116 months). In this time period, 59 (52.2 %) recurrences and 27 (23.9 %) cases of progression were observed. Five-year relapse-free survival was 42.5 % (95 % CI 32.1–52.9), 5-year progression-free survival was 71.6 % (95 % CI 62.2–81.0).

The Cox univariate regression analysis has shown a statistically significant correlation of the following factors with the recurrence risk: recurrent tumor in comparison with a primary tumor; absence of intravesical BCG immunotherapy; tumor location in the prostatic urethra, openings area, and neck (tendency towards statistical significance) (Table 2). In the multivariate analysis only recurrent tumor and BCG immunotherapy were statistically significant (Table 3). BCG immunotherapy significantly increased relapse-free survival in patients with both primary and recurrent tumors (Fig. 1). On the other hand, TUR combined with PDD didn't significantly affect relapse-free survival in any of the patient prognostic groups with poorly differentiated NMIBC (Fig. 2).

In the univariate analysis, a statistically significant correlation with the progression risk was observed for the following factors: suspicion of muscle invasive tumor after cystoscopy examination; changes in the tumor-free bladder mucosa; suspicion of CIS; tumor localization in the neck, openings area, prostatic urethra; TUR combined with PDD; recurrent tumor, and grade 3 compared to high grade (see Table 2). It should be noted, that there wasn't a statistically significant decrease in the progression risk for presence of a muscle layer in the sample compared to its absence (RR 0.62; 95 % CI 0.21–1.87). However, this can be a result of low statistical power associated with lack of pathomorphological data on this parameter in 34 (30.1 %) patients. Nonetheless, in 79 patients with pathomorphological evaluation of a muscle layer in the sample, progression was observed in 5 of 18 (27.8 %) patients without a muscle layer compared to 9 of 61 (14.8 %) patients with a muscle layer.

In the multivariate analysis, only the first 4 factors were statistically significant (Table 4). TUR combined with PDD significantly increased progression-free survival both in the low progression risk group (without non-modifiable progression risk factors) and the high progression risk group (cystoscopic suspicion of CIS, and/or tumor localization in the neck, openings area, prostatic urethra, and/or cystoscopic T2 stage) (Fig. 3). On the other hand, BCG immunotherapy didn't significantly affect progression-free survival in the 3 risk groups (Fig. 4).

Table 1. *Characteristics of patients included in the study and comparison of their distribution in respect to bacillus Calmette-Guerin therapy and photodynamic diagnosis. n (%)*

Characteristic	Total	BCG/without BCG	PDD/without PDD
Sex:			
female	27 (23.9)	16/11 (39.0/15.3)***	6/21 (26.1/23.3)
male	86 (76.1)	25/61 (61.0/84.7)***	17/69 (73.9/76.7)
Age:			
< 65	35 (31.0)	16/19 (39.0/26.4)	8/27 (34.8/30.0)
65–74	38 (33.6)	16/22 (39.0/30.6)	5/33 (21.7/36.7)
≥ 75	40 (35.4)	9/31 (22.0/43.1)	10/30 (43.5/33.3)
Recurrence rate:			
primary tumor	81 (71.7)	29/52 (70.7/72.2)	17/64 (73.9/71.1)
> 1 recurrence a year	18 (15.9)	8/10 (19.5/13.9)	3/15 (13.0/16.7)
< 1 recurrence a year	14 (12.4)	4/10 (9.8/13.9)	3/11 (13.0/12.2)
Clinical stage (cystoscopy):			
cT1	90 (79.6)	32/58 (78.0/80.6)	20/70 (87.0/77.8)
cT2	8 (7.1)	4/4 (9.8/5.6)	1/7 (4.3/7.8)
n/a	15 (13.3)	5/10 (12.2/13.9)	2/13 (8.7/14.4)
Multifocality:			
solitary	38 (33.6)	11/27 (26.8/37.5)	6/32 (26.1/35.6)
2–7	58 (51.3)	21/37 (51.2/51.4)	13/45 (56.5/50.0)
8 and more	17 (15.0)	9/8 (22.0/11.1)	4/13 (17.4/14.4)
Macroscopic tumor type:			
papillary	91 (80.5)	32/59 (78.0/81.9)	20/71 (87.0/78.9)
solid	21 (18.6)	9/12 (22.0/16.7)	3/18 (13.0/20.0)
n/a	1 (0.9)	0/1 (0/1.4)	0/1 (0/1.1)
Size in the largest dimension:			
< 3 cm	62 (54.9)	21/41 (51.2/56.9)	16/46 (69.6/51.1)
≥ 3 cm	50 (44.2)	20/30 (48.8/41.7)	6/44 (26.1/48.9)
n/a	1 (0.9)	0/1 (0/1.4)	1/0 (4.3/0)
Bladder mucosa pathology:			
hyperemia	18 (15.9)	8/10 (19.5/13.9)	7/11 (30.4/12.2)
suspicion of carcinoma in situ	10 (8.8)	6/4 (14.6/5.6)	3/7 (13.0/7.8)
bullous	4 (3.5)	1/3 (2.4/4.2)	9/4 (39.1/4.4)
total bladder mucosa pathologies	24 (21.2)	10/14 (24.4/19.4)	7/17 (30.4/18.9)
pT category:			
Ta	7 (6.2)	1/6 (2.4/8.3)	1/6 (4.3/6.7)
T1	106 (93.8)	40/66 (97.6/91.7)	22/84 (95.7/93.3)
Muscle layer in the sample:			
no	18 (15.9)	7/11 (17.1/15.3)	1/17 (4.3/18.9)
yes	61 (54.0)	23/38 (56.1/52.8)	18/43 (78.3/47.8)
n/a	34 (30.1)	11/23 (26.8/31.9)	4/30 (17.4/33.3)
Presence of concomitant carcinoma *in situ*	8 (7.1)	5/3 (12.2/4.2)	6/2 (26.1/2.2) *
Malignancy grade:			
high grade	65 (57.5)	21/44 (51.2/61.1)	16/49 (69.6/54.4)
grade 3	48 (42.5)	20/28 (48.8/38.9)	7/41 (30.4/45.6)
Tumor location:			
neck	28 (24.8)	11/17 (26.8/23.6)	5/23 (21.7/25.6)
right opening	6 (5.3)	3/3 (7.3/4.2)	1/5 (4.3/5.6)
left opening	6 (5.3)	2/4 (4.9/5.6)	1/5 (4.3/5.6)
trigone	28 (24.8)	12/16 (29.3/22.2)	7/21 (30.4/23.3)
right wall	56 (49.6)	20/36 (48.8/50.0)	12/44 (52.2/48.9)
left wall	46 (40.7)	16/30 (39.0/41.7)	11/35 (47.8/38.9)
posterior wall	67 (59.3)	30/37 (73.2/51.4) ****	16/51 (69.6/56.7)
prostatic urethra	8 (7.1)	3/5 (7.3/6.9)	0/8 (0/8.9)
fundus	32 (28.3)	12/20 (29.3/27.8)	3/29 (13.0/32.2)
anterior wall	21 (18.6)	6/15 (14.6/20.8)	2/19 (8.7/21.1)
Therapy:			
PDD	23 (20.4)	9/14 (22.0/19.4)	23/0 (100/0)
early single instillation	16 (14.2)	6/10 (14.6/13.9)	8/8 (34.8/8.9) **
BCG	41 (36.3)	41/0 (100/0)	9/32 (39.1/35.6)
repeat transurethral resection	21 (18.6)	11/10 (26.8/13.9)	4/17 (17.4/18.9)

Note: *BCG – bacillus Calmette-Guerin; PDD – photodynamic diagnosis; n/a – data not available. *p = 0.001; **p = 0.004; ***p = 0.009; ****p = 0.047; in other cases p > 0.05.*

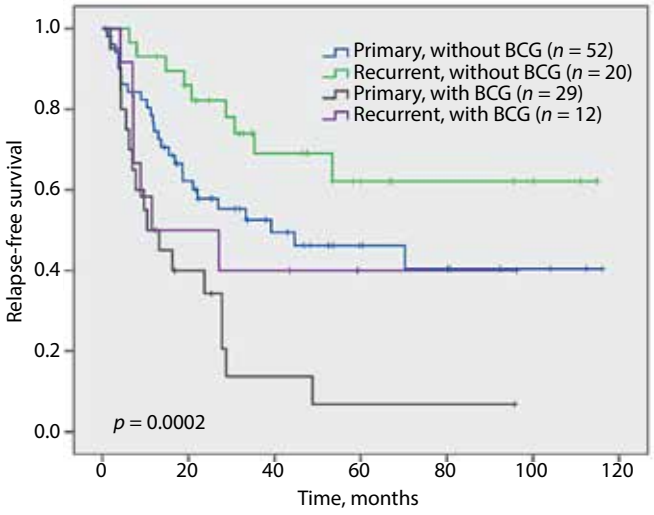

Fig. 1. *Relapse-free survival depending on the use of bacillus Calmette-Guerin therapy and recurrence status*

Discussion

Despite obvious successes in endoscopic eradication of tumors, more accurate prognosis evaluation, increased effectiveness of intravesical therapy, and improved methods of monitoring patients, treatment results in patients with poorly differentiated NMIBC remain unsatisfactory. This can be explained by the aggressive character of the disease and high rate of progression into muscle invasive tumors (reaching 20–40 %) despite long-term BCG immunotherapy which is considered the most effective treatment [9]. Although it's common in the literature to distinguish $T1G_3$ tumors among poorly differentiated NMIBCs, we didn't divide tumors by stage because prognosis in the studied cohort was approximately the same irrespective of the T category.

The European Association of Urology separates cases of poorly differentiated NMIBC into a subgroup with high and the highest risk, and recommends full-dose intravesical BCG immunotherapy combined with maintenance therapy for 1–3 years or radical cystectomy in cases with such additional unfavorable prognostic factors as concomitant CIS; multiple, large, or recurrent $T1G_3$ tumors; and atypical histological tumor variants [4]. However, in case of poorly differentiated tumors these guidelines are based on indirect data and were, for the most part, transferred from a heterogenous group of tumors with high and intermediate risk.

To critically assess proof of BCG effectiveness in $T1G_3$ tumors, it's necessary to separate studies comparing BCG effectiveness (usually, 6-week induction course) and monitoring [10–13]; studies comparing BCG effectiveness and intravesical chemotherapy [14–18]; and studies evaluating effectiveness of maintenance therapy [6, 7, 19] (Table 5). Studies including only $T1G_3$ tumors are usually retrospective [12, 13], while in prospective randomized studies the percentage of poorly differentiated tumors varied from 12.5 [18] to 65.0 % [19], so these studies aren't fully applicable to this type of NMIBCs.

It should be noted, that study results for all of the above-mentioned therapies are rather contradictory. Thus, in an early prospective randomized study including a large percentage of $T1G_3$ tumors [10], as well as its subanalysis including only these tumors [11], significant benefits of BCG therapy for progression prevention, overall and cancer-specific mortality were shown [12], while in another retrospective study, BCG immunotherapy somewhat

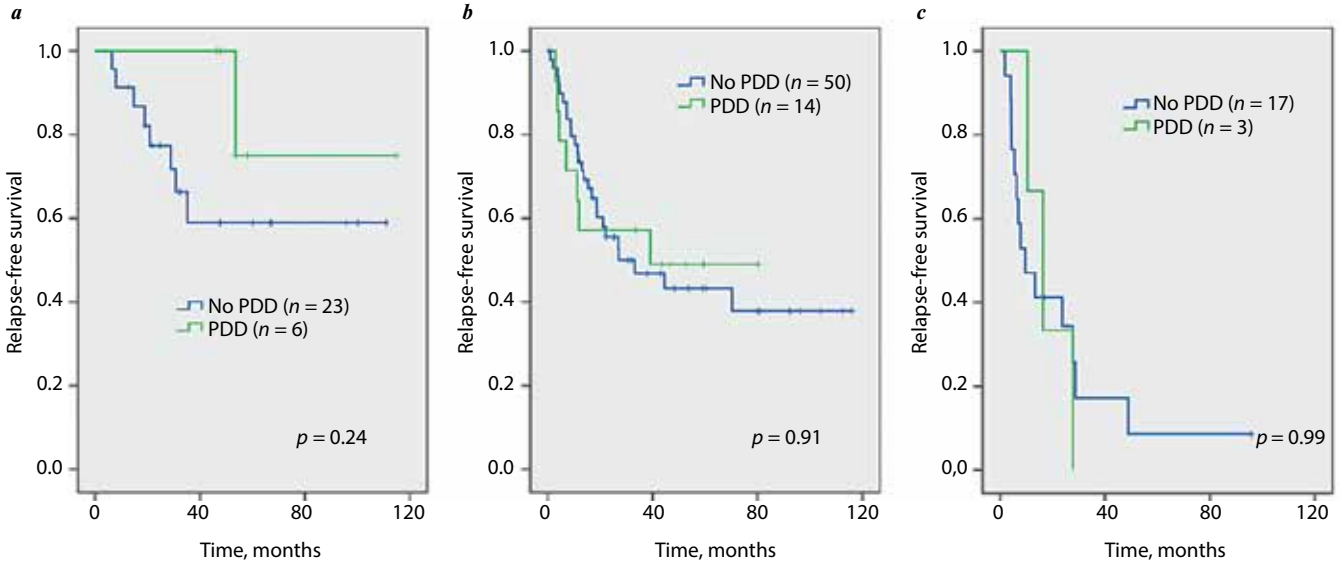

Fig. 2. *Relapse-free survival in patients depending on the use of photodynamic diagnosis during transurethral resection in the patient subgroups with primary tumors and intravesical bacillus Calmette-Guerin therapy (a), with recurrent tumors with bacillus Calmette-Guerin therapy or primary without immunotherapy (b), and with recurrent tumors without intravesical bacillus Calmette-Guerin therapy (c)*

Table 2. *Results of multivariant analysis*

Prognostic factor	Recurrence risk		Progression risk	
	Risk ratio (95 % confidence interval)	*p*	Risk ratio (95 % confidence interval)	*p*
Sex: male/female	1.49 (0.80–2.76)	0.21	0.70 (0.32–1.57)	0.39
Years, 1 year	1.01 (0.99–1.04)	0.26	1.03 (0.99–1.07)	0.15
Tumor: recurrent/primary	2.56 (1.51–4.32)	< 0.001	2.31 (1.08–4.93)	0.031
Multifocality: 1/2–7/≥ 8	1.00/1.00 (0.57–1.76)/ 1.00 (0.46–2.20)	1.00	1.0/1.20 (0.50–2.87)/1.62 (0.53–4.96)	0.70
Size: ≥ 3 cm/< 3 cm	0.74 (0.44–1.24)	0.25	0.86 (0.40–1.86)	0.70
Macroscopic tumor type: solid/papillary	0.77 (0.39–1.52)	0.44	1.88 (0.82–4.30)	0.14
Cystoscopic stage: cT2/cT1	1.65 (0.70–3.89)	0.25	4.13 (1.52–11.21)	0.005
Suspicion of carcinoma in situ (cystoscopy): yes/no	1.29 (0.55–3.00)	0.56	3.39 (1.36–8.41)	0.009
Tumor location:				
neck/no	1.71 (1.00–2.95)	0.052	2.44 (1.12–5.31)	0.025
right ureteral opening/no	2.73 (1.17–6.37)	0.020	4.10 (1.41–11.91)	0.01
left ureteral opening /no	0.63 (0.15–2.56)	0.51	1.87 (0.44–7.90)	0.40
trigon/no	1.07 (0.6–1.9)	0.83	1.92 (0.87–4.24)	0.11
right lateral wall/no	1.03 (0.61–1.72)	0.92	0.97 (0.45–2.10)	0.94
left lateral wall /no	1.07 (0.64–1.8)	0.80	1.06 (0.49–2.31)	0.88
posterior wall/no	0.96 (0.56–1.62)	0.86	1.08 (0.49–2.37)	0.86
prostatic urethra/no	2.84 (1.27–6.35)	0.011	4.48 (1.67–12.07)	0.003
fundus/no	1.19 (0.68–2.07)	0.55	1.16 (0.50–2.67)	0.73
anterior wall/no	1.12 (0.59–2.11)	0.73	1.01 (0.38–2.69)	0.98
Tumor location in the neck, openings area, prostatic urethra: yes/no	1.73 (1.03–2.91)	0.038	2.94 (1.38–6.30)	0.005
T category: T1/Ta	1.09 (0.40–3.02)	0.86	0.92 (0.22–3.91)	0.92
Muscle layer in the sample: yes/no	1.11 (0.53–2.37)	0.78	0.62 (0.21–1.87)	0.40
G grade: grade 3/high grade	1.16 (0.70–1.94)	0.57	2.35 (1.07–5.13)	0.032
Carcinoma in situ: yes/no	0.29 (0.07–1.18)	0.084	0.77 (0.18–3.25)	0.72
Surgeon: more experienced/less experienced	1.5 (0.86–2.64)	0.16	1.40 (0.62–3.14)	0.42
Photodynamic diagnosis: yes/no	0.76 (0.39–1.47)	0.42	0.11 (0.02–0.80)	0.029
Early single instillation of doxorubicin: yes/no	0.63 (0.29–1.40)	0.26	0.35 (0.08–1.50)	0.16
Re-staging transurethral resection: yes/no	0.68 (0.34–1.39)	0.29	0.70 (0.24–2.03)	0.51
Intravesical bacillus Calmette-Guerin therapy: yes/no	0.51 (0.29–0.91)	0.023	0.99 (0.45–2.16)	0.98

slowed down development of a recurrence, but didn't affect progression or mortality [13].

In the majority of prospective randomized studies comparing effectiveness of adjuvant BCG immunotherapy with maintenance therapy and intravesical chemotherapy, the former was superior in respect to relapse-free survival but not progression-free survival or mortality [14–17]. Only in the large EORTC protocol benefits of long-term BCG were clearly determined in respect to metastasis-free, overall, and cancer-specific survival. However, these effects were more pronounced in the intermediate risk patient group which didn't include poorly differentiated tumors [18]. In meta analyses considering patients with high risk of progression [16] or individual patient data [17], there was no decrease in the risk of progression in patients receiving BCG therapy. The last meta-analysis conclusively demonstrated that only maintenance therapy determines the benefit of BCG compared to intravesical chemotherapy with mitomycin C for recurrence prevention; otherwise, all immunotherapy advantages are lost. Nonetheless, these conclusions can't be transferred to poorly differentiated tumors, because in the article by P.U. Malmström et al. only 16.4 % of patients had this type of tumor [17].

Table 3. *Results of multivariate analysis in respect to recurrence risk*

Prognostic factor	Risk ratio (95 % confidence interval)	*p*
Recurrent tumor/ primary tumor	2.73 (1.61–4.62)	< 0,001
Bacillus Calmette-Guerin immunotherapy: yes/no	0.56 (0.31–0.99)	0,048
Presence of carcinoma *in situ* / absence of carcinoma *in situ*	0.29 (0.07–1.18)	0,084

Table 4. *Results of multivariate analysis in respect to progression risk*

Prognostic factor	Risk ratio (95 % confidence interval)	*p*
Suspicion of carcinoma *in situ* (cystoscopy): yes/no	7.23 (2.64–19.80)	< 0.001
Tumor location in the neck, openings area, prostatic urethra: yes/no	2.91 (1.17–7.25)	0.022
Photodynamic diagnosis: yes/no	0.10 (0.01–0.78)	0.028
Cystoscopic stage: cT2/cT1	3.36 (1.09–10.40)	0.035

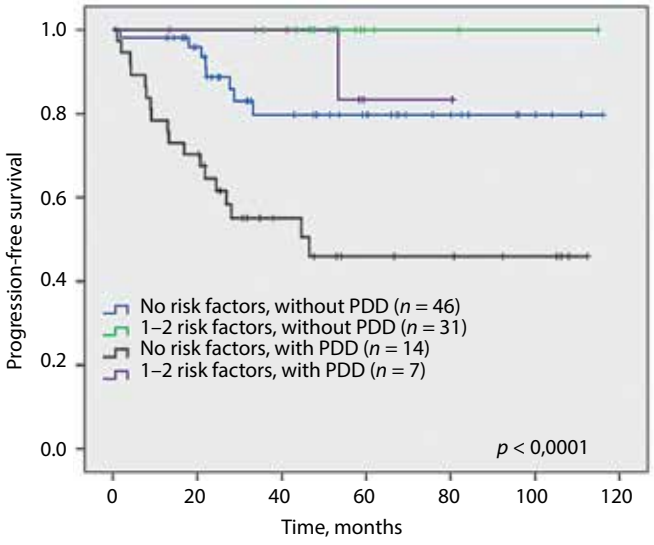

Fig. 3. *Progression-free survival depending on the use of photodynamic diagnosis and number of progression risk factors*

Finally, considering the necessity of maintenance therapy, it should be noted that there aren't any studies where it leads to an increase in survival before tumor progression into muscle invasive cancer for this type of tumor, and only D.L. Lamm et al. noted a decrease in disease propagation [6]. In their study, the authors considered the following factors: progression; necessity of cystectomy, beam or systemic chemotherapy; this approach elicited different responses from experts. Considering relapse-free survival, in a small Spanish randomized study including a small group of $T1G_3$ tumors, there weren't any differences in this characteristic [19], while in the large EORTC protocol including 26.6 % of poorly differentiated tumors, relapse-free survival improved for a long-term (3 years) full-dose BCG therapy compared to a shorter (1 year) course with a decreased dose [7].

Therefore, summarizing extremely diverse data from retrospective and randomized studies, it can be concluded that BCG immunotherapy significantly decreases recur-

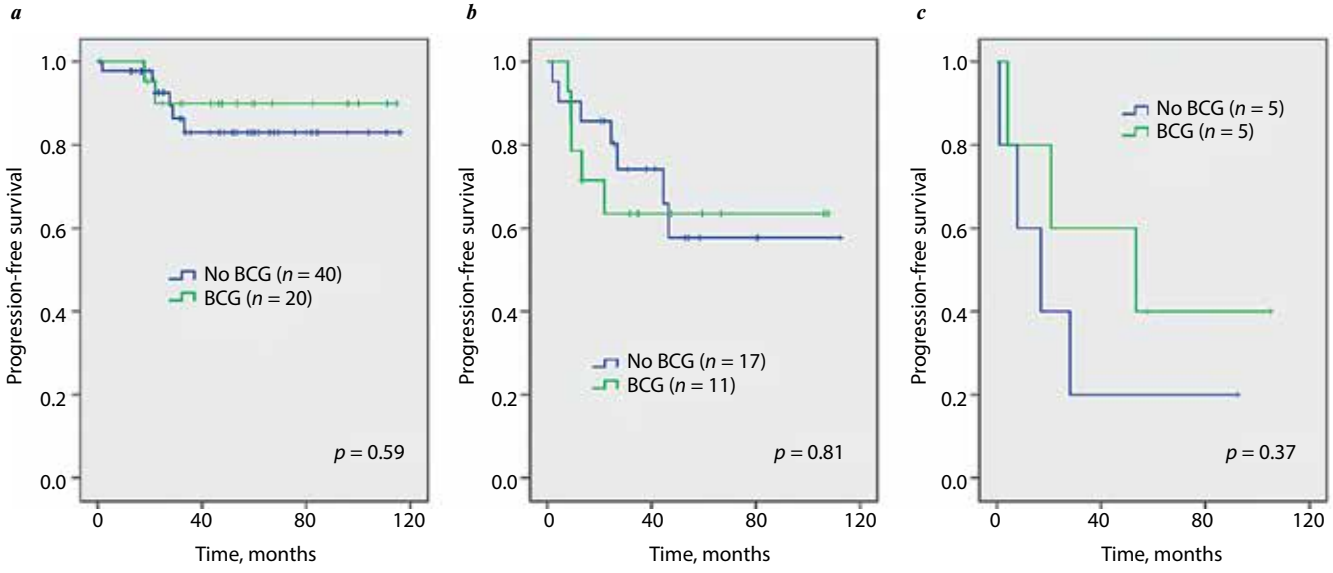

Fig. 4. *Progression-free survival in patients depending on the use of bacillus Calmette-Guerin adjuvant immunotherapy in patient subgroups without non-modifiable progression risk factors (a), with 1 risk factor (b), and 2 risk factors (c)*

Table 5. *Results of studies of bacillus Calmette-Guerin therapy effectiveness in patients with poorly differentiated non-muscle invasive bladder cancer*

Author	Number, category of patients, study type	Studied group	Control group	Follow up duration, years	Result
BCG immunotherapy vs. Monitoring					
H.W. Herr et al. [10]	86, high risk (56 % $T1G_3$), RCS	BCG × 6	Monitoring	10–14	PFS, CSS: BCG better
H.W. Herr [11]	48, $T1G_3$, RCS subgroup			10–15	PFS: BCG better
J.J. Patard et al. [12]	80, $T1G_3$, retrospective	BCG × 6 (+ MT in 26 %)	Monitoring	5.1–5.4	RFS, MFS, OS, CSS: BCG better
O. Shanin et al. [13]	153, $T1G_3$, retrospective	BCG × 6	Monitoring	5.3	RFS, MFS, OS, CSS: no differences
BCG immunotherapy vs. Chemotherapy					
P.U. Malmström et al. [14]	261, high risk (35 % G_3), RCS	BCG × 6 + MT 2 years	MMC × 6 + MT 2 years	5.0	RFS: BCG better, PFS, OS, CSS: no differences
T. Gårdmark et al. [15]				10.3	PFS, OS, CSS: no differences
M.D. Shelley et al. [16]	1901, high risk, meta-analysis	BCG × 6 ± MT	MMC 6–24 months	–	RFS: BCG better, PFS: no differences
P.U. Malmström et al. [17]	2820, 16 % G_3, meta-analysis	BCG 6 ± MT	MMC ± MT	–	RFS: without MT – MMC better, with MT – BCG better, PFS, OS, CSS: no differences
R.J. Sylvester et al. [18]	957, intermediate and high risk (13 % G_3), RCS	BCG × 6 + MT 3 years	EPI × 6 + MT 3 years	9.2	RFS, MFS, OS, CSS: BCG better (primarily for intermediate risk), PFS: no differences
Maintainance BCG therapy					
D.L. Lamm et al. [6]	386, high risk (G_3 wasn't noted), RCS	BCG × 6 + MT 3 years	BCG × 6	10.0–9.9	RFS, DFS: MT better, OS, CSS: no significant differences
J.R.Oddens et al. [7]	1355, intermediate and high risk (27 % G_3), RCS	BCG × 6 + MT 3 years	BCG × 6 + MT 1 year	7.1	RFS: intermediate risk – full dose, 1 year better; high risk – full dose, 3 years better, PFS: no differences
		Full dose BCG	1/3 full dose BCG		
J. Palou et al. [19]	131, carcinoma *in situ* or G_3 (65 % G_3), RCS	BCG × 6 + MT 2 years	BCG × 6	6.6	RFS, PFS: no significant differences

Note: *RFS – relapse-free survival; BCG – bacillus Calmette-Guerin; MFS – metastasis-free survival; PFS – progression-free survival; DFS – deterioration-free survival; OS – overall survival; MT – maintenance therapy; RCS – randomized control study; CSS – cancer-specific survival; MMC – mitomycin C; EPI – epirubicin.*

rence risk for poorly differentiated tumors, and supposedly this effect is more pronounced for prolonged therapy. There's no conclusive proof that this therapy affects progression-free survival or BC mortality, and this problem requires further investigation.

This study, though retrospective and thus containing all the faults of this type of research, adds some proof to the above-mentioned conclusions. Thus, 6-week immunotherapy course significantly decreases recurrence risk – in the multivariate analysis, recurrence RR for BCG use was 0.56 (95 % CI 0.31–0.99) – and didn't affect progression risk. It is noteworthy, that only a little more than a third part of our patients received adjuvant BCG immunotherapy, though it was available for the whole studied period. Despite the fact that the possible reasons for low rate of immunotherapy use were logistic problems, patients' old age, and comorbidity, a recent study has shown that BCG effectiveness justifies its use even in older patients [20]. Considering high effectiveness of immunotherapy among patients with poorly differentiated BC, the rate of its application can be used as a criterion of treatment quality for patients with NMIBC. An important part of this study is a demonstration of a correlation between the use of TUR combined with PDD in patients with poorly differentiated NMIBC and low probability of tumor progression without an effect upon recurrence risk. Though the first publica-

tions considering long-term results of TUR combined with PDD appeared in the early 2000s, this result was obtained for the first time here. Thus, meta-analysis of 12 prospective randomized studies, in 9 (1983 patients) of which progression-free survival was evaluated, TUR combined with PDD didn't affect progression rate compared to TUR in white light (odds ratio 0.85; $p = 0.39$) [21]. Unfortunately, significance of these results is limited by the fact that the meta-analysis included only 2 studies with sufficiently long follow up period [22, 23], though in one of them a small decrease in progression rate was observed in the PDD group [22].

Is it possible that a treatment method decreases progression risk but doesn't affect recurrence risk, or are these results an artefact? There are a number of studies showing that recurrence and progression of NMIBC are relatively independent processes with different pathogenesis, and they are influenced by different factors. The main markers for recurrence are multifocality and a history of frequent tumor recurrence, while progression is associated with poor differentiation and concomitant CIS [9, 24]. Therefore, a possible mechanism of TUR with PDD effectiveness may be elimination of dysplasia and CIS lesions, as well as a more thorough removal of poorly differentiated tumors. Although in this study the rate of CIS was only 7 %, which in many cases is a result of clear misinterpretation of morphological examinations due to local traditions, in the PDD patient group the rate of CIS was 26 % compared to 2 % in the group without PDD ($p = 0.001$).

Also noteworthy is the absence of objective factors (including morphological) affecting tumor progression. In literature, the most important factors considered during selection of the treatment course are presence of CIS and depth of tumor invasion determined morphologically [25]. However, in this study these data weren't replicated, which, on one hand, proves the necessity of improvement of morphological examinations, and on the other supports the search for new biomarkers which can give doctors objective information on disease progression.

Conclusions

In patients with poorly differentiated NMIBC, BCG induction course significantly decreases recurrence risk and doesn't affect progression risk. Application of TUR with PDD significantly decreases progression risk, but doesn't affect recurrence risk. Results of this study prove the necessity of using both interventions in the scheme of organ preservation treatment of poorly differentiated NMIBC.

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