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ORIGINAL ARTICLE

Results of a prospective randomized study assessing the efficacy of fluorescent cystoscopy-assisted transurethral resection and single instillation of doxorubicin in patients with non-muscle-invasive bladder cancer

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Abstract
Objectives To assess the efficacy of two treatment options for non-muscle-invasive bladder cancer (NMIBC): (1) transurethral resection (TUR) guided by fluorescence cystoscopy (FC) with the use of 5-aminolevulinic acid (5-ALA) and (2) single early instillation of doxorubicin in a single-center open-label prospective randomized study with a 2×2 factorial design.
Patients and methods Patients with clinical suspicion of primary or recurrent NMIBC were randomized into four study arms: FC-assisted TUR with 5-ALA and single instillation of doxorubicin, FC-assisted TUR without instillation, TUR in white light (WL) with single instillation of doxorubicin, and WL-TUR only. The study was designed to assess recurrence-free survival in arms with and without any of two interventions.
Results Of 525 patients included, 377 (72 %) were eligible for primary outcome assessment. The median follow-up was 54.8 months. FC statistically significantly decreased the risk of disease recurrence and progression with hazard ratio (HR) 0.56 (95 % CI 0.39–0.80, $p = 0.001$) and 0.33 (95 % CI 0.12–0.91, $p = 0.031$), respectively. The HRs for recurrence and progression for single instillation of doxorubicin were 0.76 (95 % CI 0.54–1.07, $p = 0.11$) and 0.65 (95 % CI 0.28–1.52, $p = 0.32$), respectively. The overall and cancer-specific survival rates did not differ significantly based on the therapeutic interventions.
Conclusions In patients with NMIBC, FC-assisted TUR with 5-ALA results in a substantial recurrence and progression risk reduction as compared to WL-TUR. The single early postoperative instillation of doxorubicin did not have a statistically significant impact on recurrence and progression risks.

Keywords Non-muscle-invasive bladder cancer · Fluorescence cystoscopy · 5-Aminolevulinic acid · Single early instillation of chemotherapeutic drug

Introduction

Bladder cancer is the second most common urological malignancy after prostate cancer. From 50 to 80 % of all primary bladder tumors are referred to non-muscle-invasive bladder cancer (NMIBC), for which, despite relatively favorable prognosis for survival, the local recurrence rate accounts for 50 % and the rate of progression to muscle-invasive disease is up to 10 % [1]. A number of studies have documented the causes of recurrence, among which incomplete transurethral resection (TUR) [2] and early tumor cell re-implantation after TUR [3] are the most important and potentially preventable. Several interventions were proposed to counteract these events, including TUR guided by fluorescence cystoscopy (FC) to improve the visualization of subclinical tumor foci and single early postoperative instillation of a chemotherapeutic agent. Despite numerous clinical studies showing the efficacy of those approaches [4–6], there are still a number of important questions to be answered. For example, what is the relative efficacy of these procedures, is there any interaction between them,

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and is it worth giving both treatments together. Besides, some studies questioned the clinical significance of single early instillation [7] and FC-assisted TUR [8, 9].

The purpose of this study is to assess the efficacy of two treatment options for NMIBC within a single-center prospective randomized study with a factorial design: FC-guided TUR guided with the use of 5-aminolevulinic acid (5-ALA) as a photosensitizer and single early instillation of doxorubicin.

Patients and methods

Patients

From March 2008 to September 2012, all the patients hospitalized at our institution with a suspicion of primary or recurrent NMIBC were offered to take part in a prospective open-label randomized study. Other inclusion criteria were: age at least 18 years; adequate physiologic bladder capacity; estimated life expectancy of at least 3 years, and informed patient consent to participate in the protocol. The exclusion criteria were ureterohydronephrosis and treatment of NMIBC in the previous 6 months.

The study protocol was approved by the institutional scientific board according to the national legislation. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Treatment

The patients that met the study inclusion criteria were randomized into four study arms. Patients in the first arm (FC + D) underwent FC-assisted TUR with 5-ALA ('Alamin', NPC KhimPharmSintez). Subsequently, those patients with macroscopically complete TUR and without signs of bladder perforation within 6 h after TUR received an intravesical instillation of 50 mg of doxorubicin diluted in 40 ml of normal saline for 60 min. The second arm (WL + D) underwent white light TUR plus single doxorubicin instillation (as described above). The third arm (FC + 0) received FC-assisted TUR without instillation and the fourth arm underwent standard TUR without doxorubicin.

The patients were considered ineligible if they underwent incomplete TUR or histological analysis of removed specimen showed tumor invasion of the muscle tissue.

Randomization

Randomization was performed by the computer software generating random numbers with equal allocation ratio. The procedure was done in the central randomization office via telephone or local network interface, which allowed concealment of generated random sequence. From June 2008 to June 2009, through a temporary lack of photosensitizer (5-ALA), patients were allocated only to the arms WL + D and WL + 0. Then, to compensate for the imbalance in the number of patients in a study arm, over the period from October, 2009 to October, 2010, patients were randomized only into the arms FC + D and FC + 0. All the changes were approved by the institutional scientific board; however, to exclude possible bias we undertook a subgroup analysis for FC-assisted TUR efficacy stratified by study period (four-arm vs. two-arm randomization) and multivariate Cox regression with the inclusion of interventions under the study and important prognostic variables (for recurrence) or EORTC risk group (for progression).

Instillation of 5-ALA and subsequent TUR

In the aseptic settings 120–90 min before TUR, patients were intravesically administered fresh solution of 1.5 g 5-ALA diluted in 3 % sodium bicarbonate solution. After the instillation patients were requested not to urinate until TUR procedure, which was performed under the WL first. Then the bladder was inspected in blue light ($\lambda = 400$ nm) with the use of commercially available equipment (Richard Wolf GmbH), and all suspicious lesions were removed or electrocoagulated.

Additional treatment

Removed tissue samples were examined by staff pathologists blinded to the patients' participation in the trial and their treatment arm. The decision on additional treatment administration after evaluation of prognostic factors was left to the patient's attending physician discretion within the local guidelines. The indication for re-TUR, which was performed without FC, was generally poorly differentiated tumors or suspicion of incomplete initial TUR. Adjuvant immunotherapy with Bacillus of Calmette–Guerin, which was, in most cases, limited to a 6-week induction course, was administered at high risk of recurrence/progression.

Patient follow-up

In the post-treatment period, patients were advised to undergo regular follow-up with WL cystoscopy and pelvic ultrasound. The follow-up was arranged mostly by a local healthcare provider outside the study center, which resulted in blinding to the patients' treatment arm allocation. For recurrence-free (RFS) and progression-free survival (PFS) analyses, patients with a follow-up period of minimum 12 months after TUR were eligible.

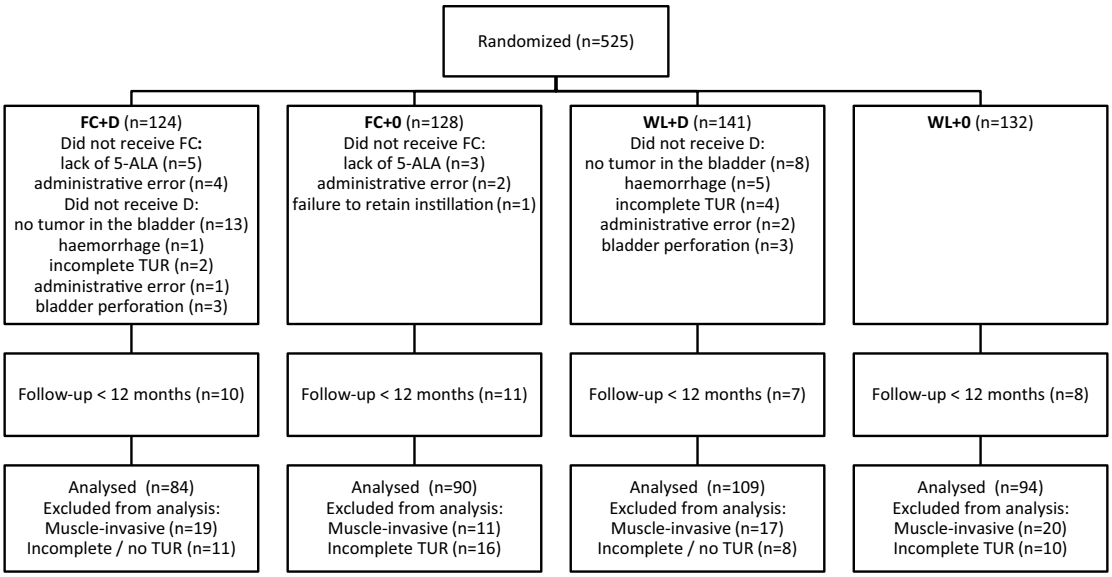

Fig. 1 Consort diagram. *TUR* transurethral resection, *FC* fluorescent cystoscopy-assisted transurethral resection, *D* doxorubicin; *0* no doxorubicin, *WL* transurethral resection in white light, *5-ALA* 5-aminolevulinic acid

Study endpoints

The study primary endpoint was to compare RFS in the arms with and without either of the two interventions. Recurrence was defined as the detection of a histologically proven tumor in the bladder of any stage. Progression-free, overall, and cancer-specific survival were additionally compared. Progression was defined as the detection of muscle-invasive or metastatic bladder cancer. The data on patients' deaths and their causes were obtained from the Belarusian Cancer Registry.

As the safety of single intravesical instillation of 5-ALA and doxorubicin had been well established in a number of studies [6, 10], we assessed only severe complications (Grade III and higher by the Clavien classification).

Statistical analysis

The number of patients in the study was planned on the assumption of the probability of 80 % detection of a 15 % statistically significant increase in 5-year RFS (from 40 to 55 %) with any treatment modality (FC or single instillation) compared to the control arms without this treatment with a two-sided alpha level 0.05. The number of ineligible patients was estimated as 20, and 10 % dropout rate was planned.

To compare categorical variables, Chi-square or Fisher's exact test were used. Patients were categorized by common prognostic factors and the European Organisation for Research and Treatment of Cancer (EORTC) risk groups [11]. Survival was calculated using Kaplan–Meier method according to the intention-to-treat principle. The therapy efficacy comparison in the study arms was done with Cox regression analysis stratified by interventions, and hazard ratios (HRs) and their 95 % confidence intervals (CI) were calculated. All the p values were two sided. The p value <0.05 was considered to be statistically significant. The software packages Statistica version 7.0. (StatSoft, Inc., Tulsa, OK) and IBM SPSS version 21.0. (Armonk, NY) were used for the statistical analysis.

Results

Patients

A total of 525 bladder cancer patients entered the study, of these, 377 patients (72 %) were eligible for efficacy analysis (Fig. 1). The characteristics of the eligible patients included in the study are shown in Table 1. The arms were generally comparable with respect to basic prognostic factors except for notable differences in the rate of benign histology and stage distribution. This led to some difference in the risk group distribution especially for progression. Most (97 %) operations were performed by five surgeons with a relative contribution from 7 to 34 % of all surgeries.

Efficacy assessment

The median follow-up for the arms FC + D, FC + 0, WL + D, and WL + 0 was 54 (95 % CI 48–60), 54 (95 % CI 51–57), 47 (95 % CI 32–63), and 66 (95 % CI 62–71)

Table 1 Patient characteristics in the study

Characteristic	Study arm				Total
	FC + D	FC + 0	WL + D	WL + 0	
Gender, *n* (%)					
Female	20 (24)	20 (22)	32 (29)	15 (16)	87 (23)
Male	64 (76)	70 (78)	77 (71)	79 (84)	290 (77)
Median age (range), years	65 (32–87)	69 (31–85)	66 (36–87)	67 (18–87)	66 (18–87)
Recurrent state, *n* (%)					
Primary	54 (64)	63 (70)	75 (69)	63 (67)	255 (68)
Recurrent	30 (36)	27 (30)	34 (31)	31 (33)	122 (32)
Number of tumors, *n* (%)					
0–1	43 (51)	39 (43)	47 (43)	42 (45)	171 (45)
2–7	34 (40)	40 (44)	49 (45)	38 (40)	161 (43)
≥8	7 (8)	11 (12)	13 (12)	14 (15)	45 (12)
Size, *n* (%)					
<3 cm*	69 (82)	69 (77)	86 (79)	65 (69)	289 (77)
≥3 cm	14 (17)	21 (23)	23 (21)	29 (31)	87 (23)
MD	1 (1)	0 (0)	0 (0)	0 (0)	1 (0.3)
Stage, *n* (%)					
No cancer	16 (19)	11 (12)	7 (6)	6 (6)	40 (11)
Ta[†]	29 (35)	24 (27)	55 (50)	37 (39)	145 (38)
T1	36 (43)	55 (61)	47 (43)	50 (53)	188 (50)
CIS	3 (4)	0 (0)	0 (0)	1 (1)	4 (1)
Grade (WHO, 1973)[‡], *n* (%)					
Papilloma	1 (1)	0 (0)	4 (4)	2 (2)	7 (2)
G1	40 (48)	49 (54)	60 (55)	52 (55)	201 (53)
G2	21 (25)	24 (27)	35 (32)	27 (29)	107 (28)
G3	4 (5)	6 (7)	3 (3)	4 (4)	17 (5)
MD	2 (2)	0 (0)	0 (0)	3 (3)	5 (1)
Recurrence risk[‡], *n* (%)					
Low	14 (17)	9 (10)	16 (15)	15 (16)	54 (14)
Intermediate	45 (54)	63 (70)	80 (73)	64 (68)	252 (67)
High	9 (11)	7 (8)	6 (6)	9 (10)	31 (8)
Progression risk[‡], *n* (%)					
Low	14 (17)	9 (10)	21 (19)	17 (18)	61 (16)
Intermediate	22 (26)	25 (28)	43 (39)	29 (31)	119 (32)
High	32 (38)	45 (50)	38 (35)	42 (45)	157 (42)
Subsequent management, *n* (%)					
reTUR	7 (8)	11 (12)	15 (14)	17 (18)	50 (13)
BCG	8 (10)	20 (22)	15 (14)	19 (20)	62 (16)

MD missed data, *CIS* carcinoma in situ; *WHO* Word Health Organisation, *reTUR* repeat transurethral resection, *BCG* bacillus Calmette–Guérin, *FC* fluorescent cystoscopy-assisted TUR, *D* doxorubicin, *0* no doxorubicin, *WL*-TUR in white light

* Including no visible tumor

[†] Including papilloma

[‡] Patients without tumor are not shown

months, respectively. The median follow-up in the arms with and without FC was 54 (95 % CI 50–57) and 65 (95 % CI 55–75) months, respectively. The number of events by the study arms is summed up in Supplementary Table 1.

When comparing RFS in the arms with FC with or without single instillation (FC + D and FC + 0) versus the arms without FC with or without single instillation (WL + D and WL + 0), the statistically significant

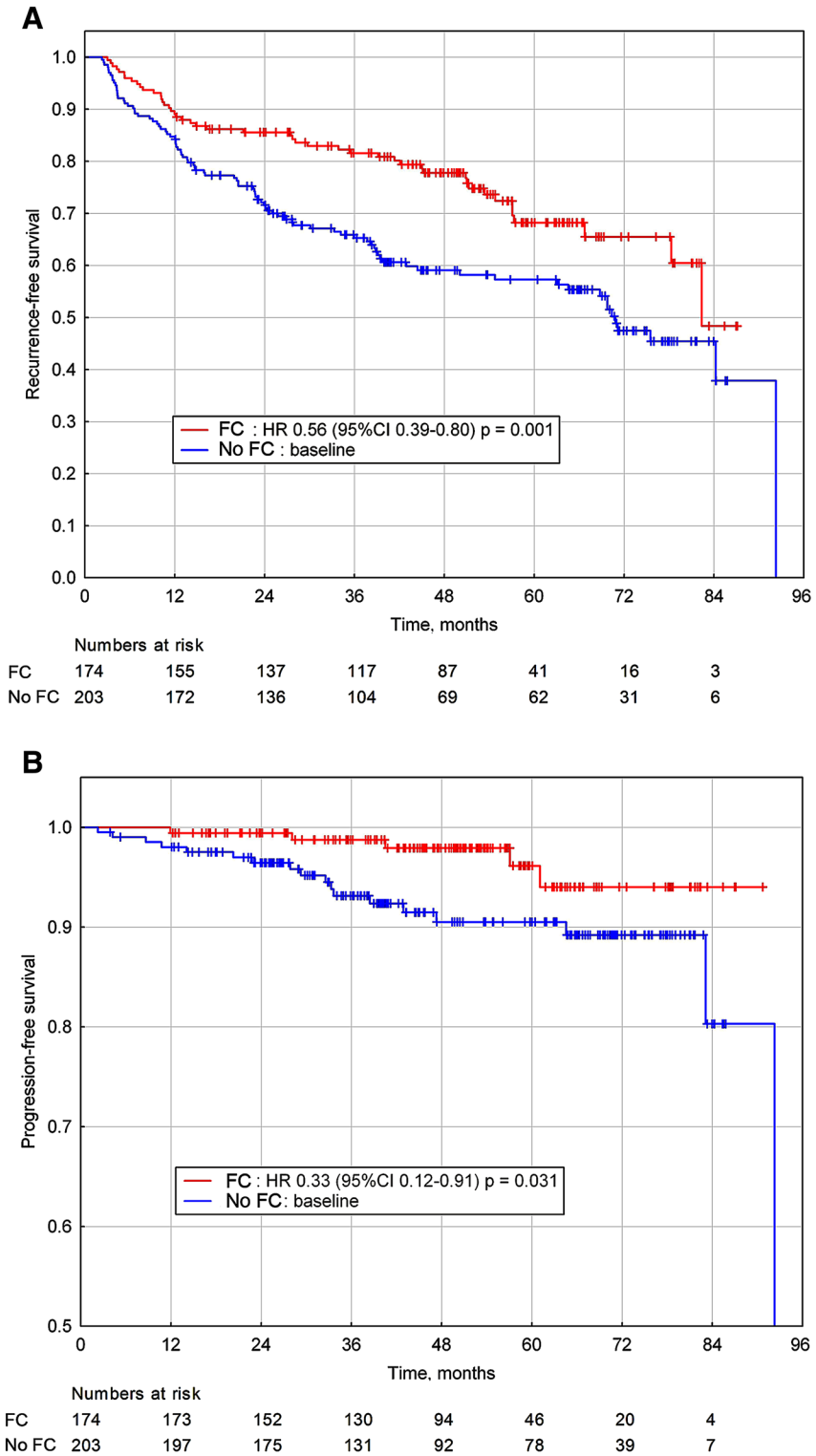

Fig. 2 Recurrence-free survival (**a**) and progression-free survival (**b**) in arms with fluorescence cystoscopy (FC) versus no FC

difference was observed with the 5-year estimates 68.2 % (95 % CI 59.8–76.6 %) and 57.3 % (95 % CI 49.9–64.7 %), respectively (Fig. 2a). PFS was also higher in the arms with FC—96.1 % (95 % CI 92.0–100 %) versus 90.5 % (95 % CI 85.8–95.2 %), respectively (Fig. 2b). This effect was consistent across the study periods: limiting the analysis to 200 patients randomized within a four-arm period resulted in HR of 0.51 (95 % CI 0.31–0.82) and 0.31 (95 % CI 0.08–1.12) for recurrence and progression, respectively. The post hoc multivariate analyses (Supplementary

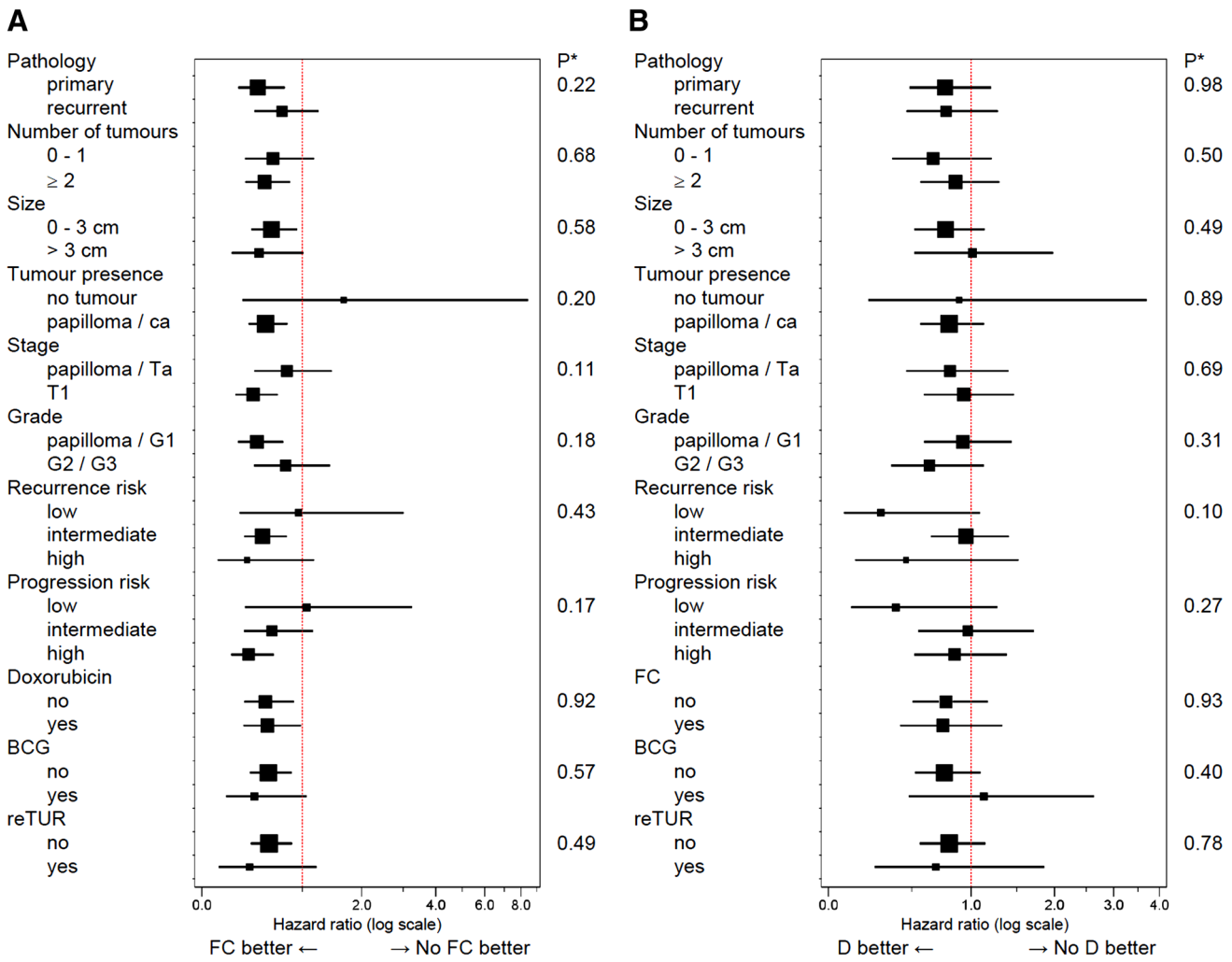

Fig. 3 Subgroup analysis of recurrence hazard ratios for fluorescence cystoscopy (FC)-assisted transurethral resection versus no FC (**a**) and single installation of doxorunicin (D) versus no instillation (**b**); *p-value for interaction

Tables 2–3) did not significantly affect HR values for recurrence and progression.

There were no statistically significant differences in RFS (HR 0.76, 95 % CI 0.54–1.07, $p = 0.11$) and PFS (HR 0.65, 95 % CI 0.28–1.52, $p = 0.32$) in the arms with and without single instillation of doxorubicin (Supplementary Figures 1–2). The comparison of overall and cancer-specific survival by two treatment options showed no significant difference (Supplementary Figures 3–6).The subgroup analysis of recurrence risk by interventions is shown in Fig. 3.

Safety assessment

Out of 525 patients included in the study 9 (1.7 %) patients underwent surgery for complications, including 8 endoscopic bladder revisions for clot evacuation and hemostasis and one open repair of bladder rupture. Those complications were observed in 3/252 (1.2 %) cases after FC-guided TUR compared to 6/273 (2.2 %) after WL-TUR ($p = 0.51$), and in 2/154 (1.3 %) cases after single instillation of doxorubicin compared to 3/260 (1.3 %) in patients randomized to no instillation.

Discussion

Despite a long history of research of FC in NMIBC and clear concept of its efficacy, dissemination of this technology into urologist's everyday practice remains relatively small. Among the main obstacles preventing its wider use may be high cost and skeptical view of a long-term benefit of this technology.

At present there are two photosensitizers for FC in NMIBC—5-ALA and hexylaminolevulinate. Despite the fact that the latter agent is the only registered compound,

there is no valid evidence of clinical superiority of either [12]. Besides, 5-ALA can have a substantial cost-effectiveness advantage over hexylaminolevulinate.

While it is agreed that FC has higher sensitivity to diagnose flat and papillary tumors in the bladder [13], the efficacy FC-guided TUR to prevent recurrence was not shown consistently in all studies, which is especially true for the trials with 5-ALA as a photosensitizer. So, the small studies by Daniltchenko et al. [14] and Babjuk et al. [15] and a larger one by Denzinger et al. [16] demonstrated a substantial advantage of FC with 5-ALA over WL-TUR. However, more recent multicenter studies by Schumacher et al. [17] and Stenzl et al. [8] did not find any advantages of this technology.

Despite the fact that our study was not designed to evaluate PFS, it is the first and only demonstrating the significant benefits of FC in decreasing NMIBC progression even if the new, more liberal definition is applied [18]. Since the new definition of progression was introduced while study was in progress [19], we used the predefined criterion which included the development of muscle-invasive disease and/or metastases, which appears to be a much more solid endpoint. It should be mentioned that the reported studies with a long-term follow-up period showed a decrease in progression rates with FC [14]; however, studies evaluating the progression rates with comparable power and follow-up period have not been conducted. Although NMIBC recurrence and progression are generally thought to be relatively independent processes with different pathogenesis and conditioned by different factors, the source of progression might be subclinical dysplastic lesions, carcinoma in situ (CIS) and recurrences of tumors with 'high progression risk'—the tumor subgroup in which FC efficacy may be the highest (Fig. 3). Though the detection rate of CIS was only 2.4 % (9/377) in our study, it resulted from obvious underdiagnosis of this pathology in many cases due to the local traditions of interpretation of morphological examination.

The efficacy of single instillation of a chemotherapeutic agent was confirmed by several meta-analyses and is beyond any doubt, on the whole [5, 6]. In our study single instillation provided a statistically insignificant reduction in recurrence risk of 24 %, which could be explained by inadequate statistical power of the study to detect such a difference. We emphasize that the most important finding in our study is that single instillation of doxorubicin is a significantly less effective intervention than FC-assisted TUR.

The question that still needs to be answered is value of single instillation in patients treated with FC-assisted TUR, i.e., possible interaction between FC and single instillation of a chemotherapeutic agent. Although this study is the first and only comparing these interventions with a factorial design, the analysis of their interaction was not planned and the power of the study was insufficient to assess this hypothesis. However, the subgroup analysis (Fig. 3) may give some clues suggesting very little, if any, interaction between them.

Among drawbacks and limitations of this study are a significant proportion of unevaluable patients with incomplete TUR or muscle-invasive disease and temporary violation of randomization due to 5-ALA shortages, which led to differences in the median follow-up in the study arms. The former reflects our clinical practice not to perform cystoscopy prior to TUR to limit invasive examination and do examination under anesthesia including biopsy and TUR in patients with any suspicion of tumor based on assessment by local urologists to reduce a risk of false-negative results. As to the latter, we suppose this fact did not harm the validity of the study conclusions as we did not observe fluctuations in patient characteristics during the study period, the median follow-up in the arms with and without FC did not differ significantly, and therapy efficacy was consistent across the periods with and without 5-ALA shortages.

In conclusion, FC-assisted TUR results in a substantial reduction in recurrence risk and statistically significant decrease in progression compared to WL-TUR in patients with NMIBC. Single early postoperative instillation of doxorubicin did not show a statistically significant impact on cancer recurrence and progression.

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Authors' contribution AI Rolevich contributed to protocol development, data collection, data analysis, and manuscript writing; AG Zhegalik, AA Mokhort, AA Minich, and VYu Vasilevich collected the data; SL Polyakov contributed to data collection, data analysis, and manuscript writing; SA Krasny and OG Sukonko developed the protocol and edited the manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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