Efficacy of fluorescent cystoscopy-assisted transurethral resection in patients with non-muscle invasive bladder cancer and quality of surgery: post-hoc analysis of a prospective randomized study

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Introduction This paper aims to evaluate the influence of quality of transurethral resection in patients with non-muscle invasive bladder cancer on the benefit of fluorescent cystoscopy-assisted transurethral resection in the post hoc analysis of the single-center randomized controlled trial.

Material and methods We retrospectively analyzed the results of the prospective randomized study assessing the efficacy of fluorescent cystoscopy-assisted transurethral resection. The quality of transurethral resection was defined on the basis of a separate retrospective study estimating the variability in recurrence risk for the individual surgeon. The subgroup analysis of fluorescent cystoscopy-assisted transurethral resection efficacy depending on surgical experience was performed.

Results Of 377 eligible patients, transurethral resection was performed in 365 (97%) by surgeons with available grading information. Two 'experienced' surgeons performed 238 (63%) of all transurethral resections and three 'less experienced' surgeons completed 127 (34%) surgeries. The two surgical groups were comparable with respect to basic prognostic factors and subsequent therapy. The median follow-up was 56 months.

In the total cohort of patients, fluorescent cystoscopy significantly decreased the risk of recurrence with hazard ratio 0.58 (p = 0.004). In the 'experienced surgeons' subgroup the benefit of fluorescent cystoscopy was not significant (hazard ratio 0.81, p = 0.34), whereas the 'less experienced' subgroup showed a marked difference in favor of fluorescent cystoscopy-assisted transurethral resection (hazard ratio 0.31, p = 0.001), with a P-value for interaction of 0.021.

Conclusions Baseline quality of surgery may be a significant interacting factor affecting the magnitude of the benefit of fluorescent cystoscopy-assisted transurethral resection in patients with non-muscle invasive bladder cancer.

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INTRODUCTION

Despite numerous recent advances in diagnosis and therapy of non-muscle invasive bladder cancer (NMIBC) there is still a high local recurrence rate after curative treatment and a considerable risk of progression to muscle invasive disease that is associated with high mortality [1]. There is a strong consensus among urologists that one of the major causes of local disease relapse is persistence

of disease after therapy due to incomplete surgical excision.

The standard method of NMIBC surgical excision is transurethral resection of bladder tumor (TURBT) under endoscopic guidance in conventional white light (WL) [2]. However, there is a body of evidence that many tumor foci are invisible under the WL cystoscopy and cannot be completely removed, but may be identified with some advanced optical imaging technologies including fluorescent cystoscopy (FC) [3].

A number of clinical studies have documented an advantage of FC over WL cystoscopy in NMIBC diagnosis [4] and the efficacy of FC and TURBT combination in lowering the recurrence rate of NMIBC [5]. Still, there is a controversy regarding the long-term therapeutic benefit of FC-assisted TURBT, which, together with cost issues, leads to low acceptance of this technology among practicing urologists. Despite a number of positive studies [6, 7], there were also high-quality negative ones [8, 9, 10]. The source of heterogeneity between those studies demonstrating positive or negative results has not been completely explained. Baseline quality of TURBT, nonetheless, may have significant interaction with the efficacy of FC-assisted TURBT. The aim of this study was to evaluate the influence of quality of surgery on the benefit of FC-assisted TURBT in the post hoc analysis of the single-center randomized controlled trial.

MATERIAL AND METHODS

We retrospectively analyzed the results of the prospective randomized study assessing the efficacy of FC-assisted TURBT and single instillation of doxorubicin with 2×2 factorial design. The study methodology and results has been described in full previously [11]. In brief, between 2008 and 2012 all patients hospitalized at our institution with a suspicion of primary or recurrent NMIBC were randomized into four study arms. Patients in the first arm (FC+D) underwent FC-assisted TURBT with 5-aminolevulinic acid and single instillation of 50 mg of doxorubicin within 6 hours after surgery. The second arm (WL+D) underwent WL TURBT plus single doxorubicin instillation. The third arm (FC+0) received FC-assisted TURBT without instillation and the fourth arm (WL+0) underwent standard TURBT without doxorubicin. Patients were considered ineligible if they had no resectable bladder tumor, underwent incomplete TURBT, or had muscle invasive disease. The subsequent treatment, which included repeat TURBT and/or 6-week course of intravesical bacillus Calmette-Guérin (BCG) immuno-

therapy, was left to the treating physician's discretion and local guidelines. The patients were followed until recurrence and/or progression, which were defined as a detection of a histologically proven bladder tumor and diagnosis of muscle invasive or metastatic bladder cancer, respectively. The primary endpoint of the prospective randomized study was to compare recurrence risk in the arms with and without either of the two interventions (FC and single instillation of doxorubicin).

The quality of TURBT was defined on the basis of a separate retrospective study published elsewhere [12]. In this study the variability in the recurrence risk after complete TURBT was assessed in the multivariate analysis across different surgeons with adjustment to all potential prognostic factors and adjuvant therapy. We defined 'experienced' and 'less experienced' surgeons by multivariate hazard ratio (HR) for recurrence ≤1.4 or >1.4, respectively, compared to the surgeon with the lowest recurrence risk in the retrospective study [12]. Patients operated on by surgeons without available grading were excluded.

Subgroups of patients operated on by 'experienced' or 'less experienced' surgeons were assessed for the differences in continuous prognostic factors by Mann-Whitney U-test and for the differences in categorical ones by Fisher exact test with Freeman-Halton extension for >2×2 tables. The subgroup analysis of FC-assisted TURBT efficacy depending on the surgical 'experience' was performed. Recurrence-free survival with 95% confidence intervals (CI) was estimated with the Kaplan-Meier product limit method, we truncated Kaplan-Meier curves when there were fewer than 10 patients at risk. Also, HRs, 95% CIs, and p values for FC versus no FC use were obtained with the stratified Cox regression model. All the statistical tests were 2-tailed. The p-value <0.05 was considered to be statistically significant. All the statistical analyses were performed using IBM SPSS version 24.0. (Armonk, NY) software.

RESULTS

Of 377 eligible patients in the study TURBT was performed in 365 (97%) by surgeons with available grading information. Two 'experienced' surgeons performed 238 (63%) of all TURBTs and three 'less experienced' surgeons completed 127 (34%) procedures, out of which 109 (30%) and 60 (16%) were FC-assisted TURBTs, respectively. The two surgical groups were comparable with respect to basic prognostic factors and subsequent therapy (Table 1). The median follow-up was 56 months (range 12–83 months), during which recurrences were diag-

nosed in 139 (36%) patients, among whom 85 (36%) patients were operated on by 'experienced' surgeons and 45 (35%) by their 'less experienced' counterparts.

In a total cohort of patients, FC significantly decreased the risk of disease recurrence with HR 0.58 (95% CI 0.41–0.84, p = 0.004). There were no statistically significant differences in recurrence risk between 'experienced' and 'less experienced' surgeons regardless of the treatment arm (HR 0.94, 95% CI 0.66–1.36, p = 0.76). In the 'experienced' surgeons`

subgroup the benefit of FC was not significant, with 5-year recurrence-free survival 63% (95% CI 52-74%) in the FC arm and 63% (95% CI 53–72%) in the WL arm (HR 0.81, 95% CI 0.52–1.25, p = 0.34) (Figure 1). On the contrary, there were marked differences in recurrence-free survival in favor of FC-assisted TURBT with 5-year estimates 79% (95% CI 67–91%) vs 63% (95% CI 52–74%) for control (HR 0.31, 95% CI 0.16–0.61, p = 0.001) (Figure 2), P-value for interaction 0.021. The stratified analyses with the inclusion of adjuvant BCG immunotherapy or tumor

Table 1. *Patient characteristics in the subgroup analysis*

Characteristic	Baseline quality of transurethral resection						p value[†]
	'Experienced' surgeons (HR ≤1.4)			'Less experienced' surgeons (HR >1.4)			
	FC ±D	WL ±D	Total	FC ±D	WL ±D	Total	
Gender, n (%)							0.38
Female	24 (22)	36 (28)	60 (25)	16 (27)	10 (15)	26 (20)	
Male	85 (78)	93 (72)	178 (75)	44 (73)	57 (85)	101 (80)	
Median age (range), years	68 (31–87)	69 (18–87)	68 (18–87)	65 (39–85)	63 (40–87)	64 (39–87)	0.44
Recurrent state, n (%)							0.92
Primary	76 (70)	86 (67)	162 (68)	37 (62)	48 (72)	85 (67)	
Recurrent	33 (30)	43 (33)	76 (32)	23 (38)	19 (28)	42 (33)	
Number of tumors, n (%)							0.077
0–1	53 (49)	54 (42)	107 (45)	26 (43)	31 (46)	57 (45)	
2–7	41 (38)	55 (43)	96 (40)	31 (52)	30 (45)	61 (48)	
≥8	15 (14)	20 (16)	35 (15)	3 (5)	6 (9)	9 (7)	
Size, n (%)							0.69
<3 cm[‡]	85 (78)	100 (78)	185 (78)	49 (82)	47 (70)	96 (76)	
≥3 cm	23 (21)	29 (22)	52 (22)	11 (18)	20 (30)	31 (24)	
MD	1 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	
Stage, n (%)							0.63
No cancer	18 (17)	8 (6)	26 (11)	7 (12)	5 (8)	12 (9)	
Ta[§]	30 (28)	61 (47)	91 (38)	22 (37)	28 (42)	50 (39)	
T1	58 (53)	59 (46)	117 (49)	31 (52)	34 (51)	65 (51)	
CIS	3 (3)	1 (1)	4 (2)	0 (0)	0 (0)	0 (0)	
Grade (WHO, 1973)[¶], n (%)							0.78
Papilloma	0 (0)	5 (4)	5 (2)	1 (2)	1 (2)	2 (2)	
G1	52 (57)	75 (62)	127 (60)	36 (68)	34 (55)	70 (61)	
G2	32 (35)	34 (28)	66 (31)	11 (21)	24 (39)	35 (30)	
G3	7 (8)	6 (5)	13 (6)	3 (6)	1 (2)	4 (3)	
MD	0 (0)	1 (1)	1 (1)	2 (4)	2 (3)	4 (3)	
EORTC recurrence risk[¶], n (%)							0.48
Low	12 (13)	24 (20)	36 (17)	11 (21)	6 (10)	17 (15)	
Intermediate	66 (73)	88 (73)	154 (73)	39 (74)	51 (82)	90 (78)	
High	13 (14)	9 (7)	22 (10)	3 (6)	5 (8)	8 (7)	
EORTC progression risk[¶], n (%)							0.88
Low	12 (13)	26 (22)	38 (18)	11 (21)	11 (18)	22 (19)	
Intermediate	32 (35)	44 (36)	76 (36)	13 (25)	25 (40)	38 (33)	
High	47 (52)	51 (42)	98 (46)	29 (55)	26 (42)	55 (48)	
Subsequent management, n (%)							
D	46 (42)	71 (55)	117 (49)	35 (58)	35 (52)	70 (55)	0.33
reTURBT	13 (12)	25 (19)	38 (16)	5 (8)	7 (10)	12 (9)	0.12
BCG	23 (21)	24 (19)	47 (20)	5 (8)	10 (15)	15 (12)	0.076

[†]Comparison of 'experienced' and 'less experienced' surgeons for pooled FC±D and WL±D arms; [‡]including no visible tumor; [§]including papilloma; [¶]patients without tumor are not shown

BCG – bacillus Calmette-Guérin; CIS – carcinoma in situ; D – doxorubicin; EORTC – European Organization for Research and Treatment of Cancer; FC – fluorescent cystoscopy-assisted transurethral resection of bladder tumor; HR – hazard ratio; MD – missed data; reTURBT – repeat transurethral resection of bladder tumor; WHO – Word Health Organization; WL – transurethral resection of bladder tumor in white light
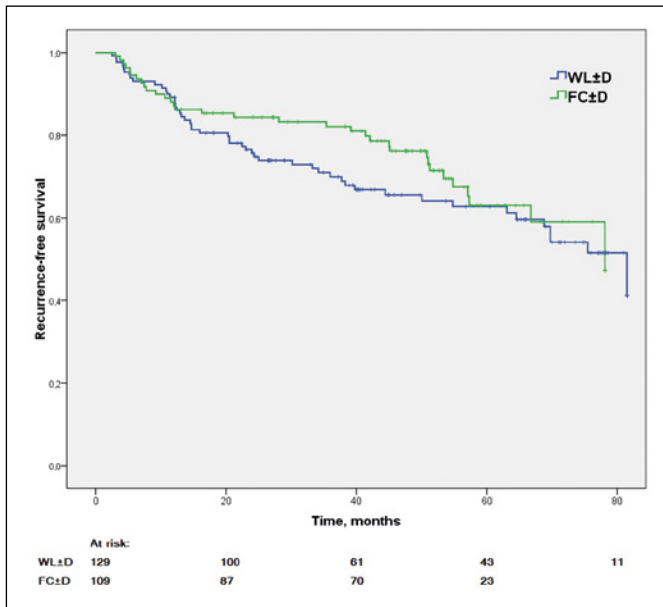
Figure 1. *Recurrence-free survival according to fluorescent cystoscopy use in patients operated on by 'experienced' surgeons.*

WL – transurethral resection of bladder tumor in white light; FC – fluorescent cystoscopy-assisted transurethral resection of bladder tumor; D – doxorubicin

Figure 2. *Recurrence-free survival according to fluorescent cystoscopy use in patients operated on by 'less experienced' surgeons.*

WL – transurethral resection of bladder tumor in white light; FC – fluorescent cystoscopy-assisted transurethral resection of bladder tumor; D – doxorubicin
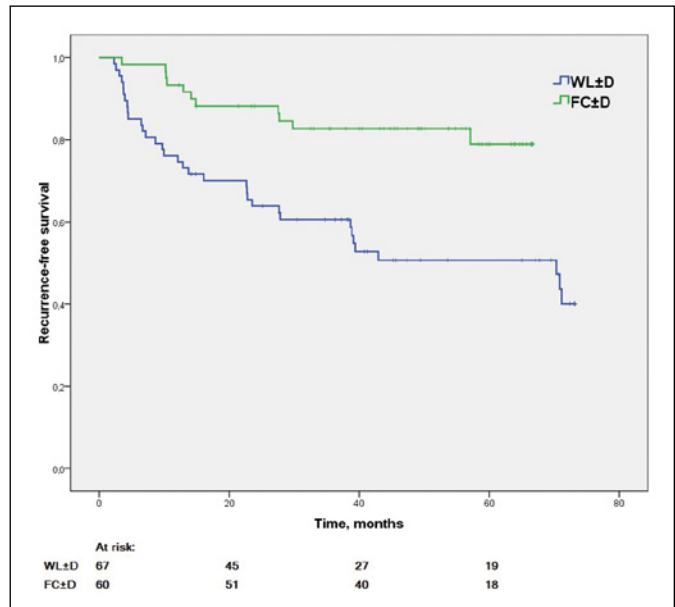
number came with similar results (Table 2). There were no significant differences in the FC-assisted TURBT efficacy in other subgroups of patients based on standard prognostic factors including the European Organization for Research and Treatment of Cancer risk groups.

DISCUSSION

The major obstacle to the widespread adoption of FC in combination with TURBT is a lack of convincing evidence of its clinical efficacy in preventing of NMIBC recurrences. Previous prospective randomized studies have been rather contradictory in evaluating the benefit of this intervention [6–11]. A recent meta-analysis has assessed the comparative effectiveness of TURBT under FC vs. WL cystoscopy on bladder cancer clinical outcomes. Although this

technology was associated with a decreased risk of bladder cancer recurrence at short-term, intermediate-term and long-term follow-up, the findings were inconsistent and potentially susceptible to performance and publication bias (low strength of evidence) [5]. The degree of heterogeneity in the effect was high and the I^2 statistics mostly exceeded 50%. This high heterogeneity in trials' results has never been adequately explained, though operators' experience or surgical skills may have crucial importance. When we discuss the experience, we mean the quality of TURBT performance including the ability to remove tumor foci in the most complete way possible. There is compelling evidence of high variability in the quality of TURBT in routine clinical practice [12, 13], nevertheless, the adequate measurement of TURBT quality (or completeness of tumor removal) is a challenging task. The presence of detrusor

Table 2. *The results of the stratified Cox proportional hazard model with the inclusion of adjuvant BCG immunotherapy or tumor number*

	'Experienced' subgroup		'Less experienced' subgroup		p value for interaction
	HR (95% CI)	p value	HR (95% CI)	p value	
Analysis with stratification by BCG use (yes vs. no)	0.79 (0.51–1.23)	0.30	0.33 (0.17–0.65)	0.001	0.034
Analysis with stratification by tumor number (0–1 vs. 2–7 vs. ≥8)	0.85 (0.54–1.32)	0.47	0.26 (0.13–0.53)	<0.001	0.005

BCG – bacillus Calmette-Guérin; CI – confidence interval; HR – hazard ratio

muscle in the resection specimen has been advocated as a quality indicator [14]. However, this variable may lack the association with long-term results [15] and have never been validated in a prospective study. The most direct way of measuring the quality of TURBT is the assessment of recurrence rate after complete TURBT in individual surgeons. Despite being more complex and time-consuming, this analysis produces a more reliable assessment of completeness of surgery compared to measurement of such surrogate indicators as length of surgical practice or surgical volume [16]. It can be assumed that some highly experienced and technically skilled surgeons may miss small tumors trying to do quick surgery. It is difficult to do a statistically sound analysis of results from several surgeons within one single center. However, we were able to accomplish this task within the study producing the direct evidence of association between individual surgeon and recurrence-free survival [12].

In the present study, we found a negative association between the quality or completeness of surgery and the benefit of FC-assisted TURBT in the prevention of NMIBC recurrences. This observation appears to be quite reasonable and logical. As is well known, FC enables visualization of subclinical tumor foci omitted by the standard endoscopic revision after completion of TURBT and therefore, by removing them, could potentially decrease the recurrence rate [17]. So, after high quality TURBTs with maximally complete tumor removal FC does not provide a significant decrease in recurrences since the baseline recurrence rate is low and there are no many subclinical tumor foci left. By contrast, after 'quick' and incomplete TURBTs this technology draws surgeons` attention to the extent of surgery forcing them to double check the bladder mucosa.

Adjuvant therapy may be an additional interaction variable for the efficacy of FC-assisted TURBT. For example, in the O'Brien et al. trial there was a hypothesis explaining a lack of the benefit of FC-assisted TURBT by providing single early postoperative instillation of mitomycin C to the patients' cohort [16]. Intravesical BCG may also serve as such a variable, mitigating potential differences in the recurrence-free survival [18, 19]. Nevertheless, the subgroup analysis of the trial that included both kinds of adjuvant therapy did not show any difference in the benefit of FC-assisted TURBT whether these therapies were provided or not [11]. Secondly, due to randomization there was an equal chance of doxorubicin instillation irrespective of FC or surgical group. Thirdly, despite more frequent use of BCG in the 'experienced' group, sensitivity analysis with stratification by the BCG use produced very little differences in the HR values.

The practical implication of our study is in placing emphasis on the increasing use of FC-assisted TURBT by residents and young surgeons. By doing that they not only will gain more skills in recognition of small subclinical tumor foci but also may improve their results by mitigating an adverse impact of incomplete tumor removal on their patients' health.

This study is not without its limitations, among which are its retrospective design and secondary data analysis. The strengths of our study include the use of directly measured quality of surgery indicator and random allocation of patients to FC and single instillation arms.

CONCLUSIONS

Baseline quality of TURBT may be a significant interacting factor affecting the magnitude of the benefit of FC-assisted TURBT in patients with NMIBC. Increasing use of FC-assisted TURBT by residents and young surgeons should be advocated.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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