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Surgeon has a major impact on long-term recurrence risk in patients with non-muscle invasive bladder cancer

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Introduction One of the factors responsible for the risk of recurrence after complete transurethral resection of the bladder tumor (TURBT) in patients with non-muscle invasive bladder cancer (NMIBC) is the quality of surgery that may vary between individual surgeons. The aim of the study was to evaluate the impact of the surgeon on recurrence-free survival in patients with NMIBC.

Material and methods The long-term results of a series of consecutive TURBTs performed by five staff urologists at a single institution were retrospectively analyzed. A total of 949 cases of organ-preserving treatment in 784 patients with NMIBC were included in the analysis.

Results With the median follow-up of 64.3 months (3–124 months), the 5-year recurrence-free survival rates according to the surgeon were 62.9% (95% CI 56.2–69.7%), 53.6% (95% CI 47.4–59.9%), 51.0% (95% CI 39.6–62.4%), 46.2% (95% CI 36.4–56.0%), and 44.2% (95% CI 36.8–51.7%), respectively (p <0.0001). In the multivariate analysis including all potential risk factors, the individual surgeon was associated with a risk of recurrence with a high degree of statistical significance (p = 0.0013). The between-surgeon differences in the recurrence risk were not that pronounced in less extensive tumors.

Conclusions A surgeon has a significant impact on the risk of recurrence after curative treatment of patients with NMIBC. This effect was observed despite the relatively extensive experience in bladder endoscopic surgery of all of the surgeons and practicing in a setting of one specialized center. These findings should be taken into account while performing and evaluating the results of comparative studies.

Key Words: non-muscle invasive bladder cancer ‹› transurethral resection ‹› quality of surgery

INTRODUCTION

Bladder cancer is the fifth most common malignancy in Europe with more than 151,000 new cases diagnosed annually, accounting for 4.4% of all cancers excluding non-melanoma skin cancer [1]. 70 to 80% of bladder tumors are classified as non-muscle invasive bladder cancer (NMIBC). It was repeatedly demonstrated that, despite relatively high survival rates, up to 70% of these tumors recur and 20-30% progress into muscle-invasive cancer after local curative therapy [2]. The standard treatment of NMIBC is a complete transurethral resection of the bladder tumor (TURBT), followed by intravesical instillation therapy in the presence of risk factors for recurrence or progression [3]. While there has been a large number of studies demonstrating the ability to reduce the risk of recurrence of NMIBC with different types of the intravesical therapy, less attention was paid to the quality of TURBT in improving long-term treatment results. However, besides the standard risk factors for recurrence and progression of NMIBC including clinical (frequency of recurrence, multifocality) and pathological (category pT, tumor grade) characteristics of the disease, the quality of TURBT, which may vary depending on the experience and

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style of surgery, can also significantly influence the risk of tumor recurrence. A number of studies have shown that limited surgical experience, which is generally defined as being a resident, is associated with an increased risk of disease recurrence as compared to the staff members [4, 5]. However, even amongst experienced surgeons, there might be a considerable variability in the quality of TURBT that could affect long-term outcomes, and this variability has not been sufficiently studied to date. The aim of this study was to evaluate the influence of the individual surgeon on the recurrence-free survival rate after the curative treatment of patients with NMIBC.

MATERIAL AND METHODS

A retrospective analysis of the data was done by searching the institutional database for patients with histologically confirmed primary or recurrent NMIBC, treated with visually complete TURBT with or without intravesical therapy between 2004 and 2013. A total of 1,550 consecutive cases were identified. Cases without follow-up data (n = 471) and operated by surgeons with fewer than 70 operations performed (n = 130) were excluded from the analysis. A total of 949 cases of organ preservation therapy in 784 patients (174 women and 610 men), with the age range from 23 to 93 years (median – 67 years) remained in the study. In recurrent tumors, the inclusion of several cases per patient was allowed if the treatment fell within the period of the study and the case did not meet the exclusion criteria. In total, there were 284 such cases in 119 patients with the number of TURBTs ranging from 2 to 5 (median – 2) per patient.

TURBTs were performed by five surgeons with comparable experience in endoscopic bladder surgery. The surgeons were coded from 1 to 5 according to an increase in the hazard ratio (HR) of recurrence. As a result, five surgical groups were created that included 225 (23.7%), 324 (34.1%), 78 (8.2%), 115 (12.1%) and 207 (21.8%) cases, respectively. Homogeneity of the groups by the main prognostic factors was assessed with the χ^2 test for categorical variables and one-way ANOVA for continuous ones.

Recurrence-free survival was defined as the time from the TURBT until the histologically confirmed recurrence or the last follow-up date. The data on follow-up were obtained from outpatient medical records and the National Cancer Registry. The rates of the recurrence-free survival by surgical group were calculated using the Kaplan-Meier method, a stratified analysis by recurrence risk group was also done. The log-rank test was used to assess the differences.

To mitigate the imbalance in prognostic variables or adjuvant therapy use between surgical groups, the uni- and multivariate Cox regression analyses were performed with adjustment to all potential prognostic factors. An explanatory analysis of the benefit of performing the surgical intervention by the two most successful surgeons as compared to the two least successful ones in various subgroups of patients was also conducted. The statistical calculations were done with the IBM SPSS V21.0. (Armonk, NY) software package.

RESULTS

The surgical groups were comparable with respect to age, gender, recurrence rate, T-stage, carcinoma *in situ* (CIS) rate, EORTC risk groups, and frequency of restaging TURBTs (Table 1). However, there were statistically significant differences between the surgical groups in the period of therapy ($p < 0.0001$), the number of tumors ($p < 0.0001$), the tumor grade ($p = 0.043$), and a trend for the differences in the tumor size ($p = 0.065$), and the use of the adjuvant intravesical BCG immunotherapy ($p = 0.068$).

The median follow-up time for the entire cohort was 64.3 months (range from 3 to 124 months), and for surgical groups 1–5: 64.3, 54.1, 72.4, 68.6, and 70.9, respectively. During this period, 433 (45.6%) recurrences were detected: 83 (36.9%), 136 (42.0%), 41 (52.6%), 59 (51.3%), and 114 (55.1%) in groups 1–5, respectively. The 5-year recurrence-free survival rates were 52.8% (95% CI 49.4–56.3%) for the entire cohort, and 62.9% (95% CI 56.2–69.7%), 53.6%

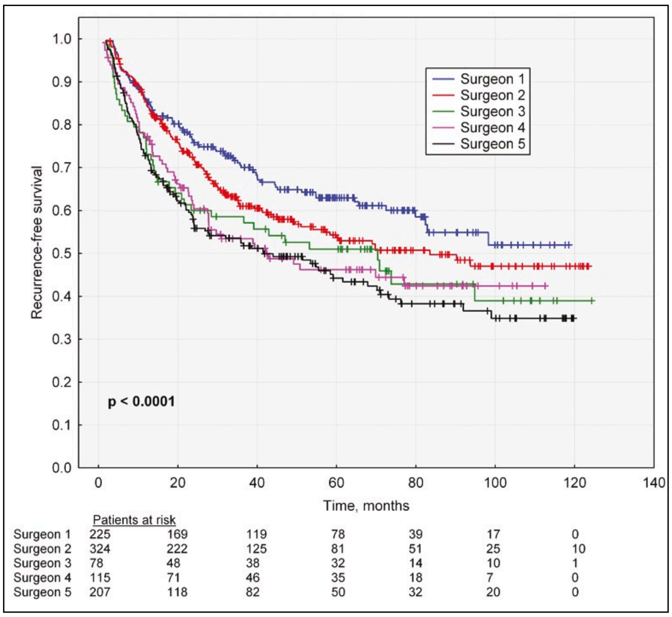

Figure 1. *Recurrence-free survival by individual surgeon.*

(95% CI 47.4–59.9%), 51.0% (95% CI 39.6–62.4%), 46.2% (95% CI 36.4–56.0%), and 44.2% (95% CI 36.8–51.7%) for groups 1–5, respectively (p <0.0001, Figure 1). In the subgroup with low or intermediate risk of recurrence the differences in the recurrence-free survival did not reach statistical significance (p = 0.36), however, in high-risk cases there were highly significant differences among the surgical groups (p <0.0001, Figure 2).

In the univariate Cox regression analysis, the statistically significant association of risk of recurrence was observed for recurrent, multifocal tumors, high tumor grade, duration of the TURBT and the individual surgeon (Table 2). In the multivariate analysis including all potential risk factors, the association of the individual surgeon with the recurrence risk remained significantly high (p = 0.0013). Amongst other factors significantly associated with recurrence were recurrent tumor state, multifocality, and adjuvant intravesical therapy.

The assessment of recurrence risk for the two most successful surgeons compared to the two least

Table 1. *Characteristics of the cases included*

Characteristic	Total	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4	Surgeon 5	p
Number of cases, n (%)	949 (100)	225 (100)	324 (100)	78 (100)	115 (100)	207 (100)	–
Gender, n (%)							
female	210 (22.1)	43 (19.1)	76 (23.5)	17 (21.8)	25 (21.7)	49 (23.7)	0.77
male	739 (77.9)	182 (80.9)	248 (76.5)	61 (78.2)	90 (78.3)	158 (76.3)	
Age, median (range)	67 (23-93)	69 (32-88)	66 (23-93)	65 (30-93)	66 (35-87)	65 (29-87)	0.075
Year of surgery, n (%)							
2004 – 07	378 (39.8)	80 (35.6)	112 (34.6)	38 (48.7)	55 (47.8)	93 (44.9)	<0.0001
2008 – 10	317 (33.4)	113 (50.2)	82 (25.3)	32 (41.0)	39 (33.9)	51 (24.6)	
2011 – 13	254 (26.8)	32 (14.2)	130 (40.1)	8 (10.3)	21 (18.3)	63 (30.4)	
Prior recurrence, n (%)							
primary	605 (63.8)	149 (66.2)	206 (63.6)	47 (60.3)	77 (67.0)	126 (60.9)	0.29
recurrent	343 (36.1)	76 (33.8)	118 (36.4)	31 (39.7)	37 (32.2)	81 (39.1)	
Number of tumors, n (%)							
1	385 (40.6)	106 (47.1)	121 (37.3)	35 (44.9)	51 (44.3)	72 (34.8)	<0.0001
2-7	438 (46.2)	72 (32.0)	166 (51.2)	35 (44.9)	54 (47.0)	111 (53.6)	
≥8	126 (13.3)	47 (20.9)	37 (11.4)	8 (10.3)	10 (8.7)	24 (11.6)	
Tumor size, n (%)							
<3 cm	645 (68.0)	157 (69.8)	205 (63.3)	50 (64.1)	74 (64.3)	159 (76.8)	0.065
≥3 cm	297 (31.3)	66 (29.3)	117 (36.1)	28 (35.9)	39 (33.9)	47 (22.7)	
NA	7 (0.7)	2 (0.9)	2 (0.6)	–	2 (1.7)	1 (0.5)	
T category, n (%)							
Ta	386 (40.7)	82 (36.4)	138 (42.6)	31 (39.7)	50 (43.5)	85 (41.1)	0.63
T1	563 (59.3)	143 (63.6)	186 (57.4)	47 (60.3)	65 (56.5)	122 (58.9)	
Tumor grade, n (%)							
G1	604 (63.6)	155 (68.9)	187 (57.7)	45 (57.7)	81 (70.4)	136 (65.7)	0.043
G2	266 (28.0)	50 (22.2)	104 (32.1)	30 (38.5)	25 (21.7)	57 (27.5)	
G3	57 (6.0)	14 (6.2)	27 (8.3)	1 (1.3)	5 (4.3)	10 (4.8)	
Gx	22 (2.3)	6 (2.7)	6 (1.9)	2 (2.6)	4 (3.5)	4 (1.9)	
CIS, n (%)	16 (1.7)	7 (3.1)	6 (1.9)	–	1 (0.9)	2 (1.0)	0.26
EORTC risk group, n (%)							
low	89 (9.4)	28 (12.4)	23 (7.1)	7 (9.0)	13 (11.3)	18 (8.7)	0.28
intermediate	304 (32.0)	79 (35.1)	98 (30.2)	23 (29.5)	38 (33.0)	66 (31.9)	
high	520 (54.8)	109 (48.4)	194 (59.9)	36 (56.5)	56 (48.7)	117 (56.5)	
NA	36 (3.8)	9 (4.0)	9 (2.8)	4 (5.1)	8 (7.0)	6 (2.9)	
Modified risk group *, n (%)							
low	281 (29.6)	73 (32.4)	89 (27.5)	24 (30.8)	45 (39.1)	50 (24.2)	0.052
intermediate	429 (45.2)	109 (48.4)	149 (46.0)	34 (43.6)	39 (33.9)	98 (47.3)	
high	239 (25.2)	43 (19.1)	86 (26.5)	20 (25.6)	31 (27.0)	59 (28.5)	
reTUR, n (%)	41 (4.3)	13 (5.8)	16 (4.9)	4 (5.1)	5 (4.3)	3 (1.4)	0.22
Intravesical therapy, n (%)							
BCG	200 (21.1)	47 (20.9)	79 (24.4)	14 (17.9)	21 (18.3)	39 (18.8)	0.068
chemotherapy	10 (1.1)	6 (2.7)	1 (0.3)	2 (2.6)	–	1 (0.5)	

n – number of cases; NA – data not available; CIS – carcinoma in situ; EORTC – European Organisation for Research and Treatment of Cancer; BCG – bacillus Calmette–Guérin; reTUR – restaging transurethral resection; * low risk – primary solitary tumor, intermediate risk – recurrent or miltifocal, high risk – recurrent and miltifocal tumor

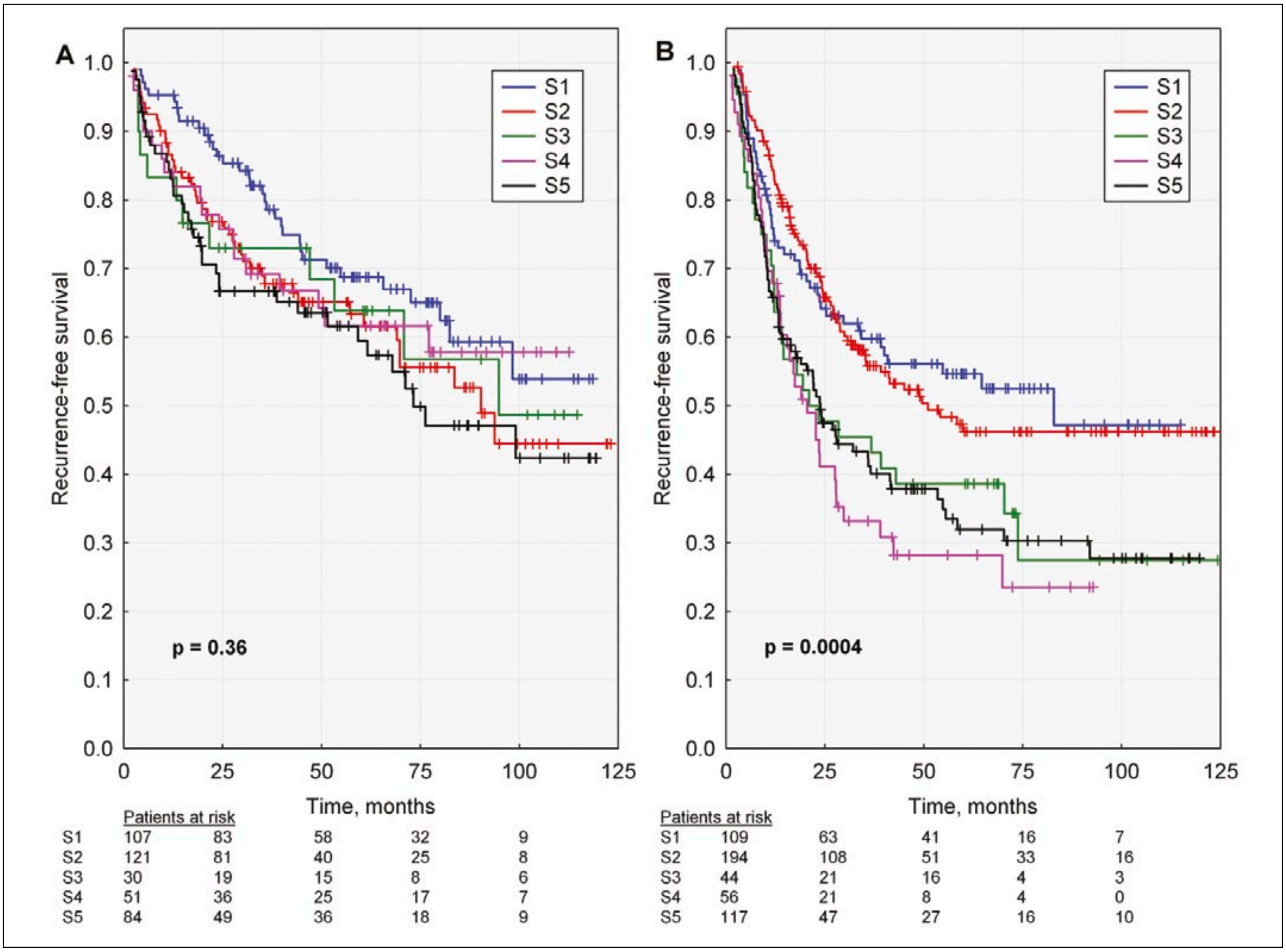

Figure 2. *Recurrence-free survival by individual surgeons in subgroups with low and intermediate risk of recurrence (a) and high risk of recurrence (b) by EORTC; S – surgeon.*

successful ones in different patient subgroups is shown in Figure 3. The maximum benefit from the surgical intervention performed by surgeons 1–2 was observed in more extensive cases (≥8 tumors, >3 cm, solid, T1, with high-risk of recurrence and without subsequent use of intravesical therapy). The results did not differ significantly in low-risk tumors. The distribution of early recurrence frequencies by the most and least successful surgeons stratified by the modified recurrence risk group (Table 3) showed that the most divergent figures without overlapping CIs were at 12 months after TURBT.

DISCUSSION

For many years, the cornerstone of recurrence prevention strategy in NMIBC patients was the use of intravesical instillation therapy. The quality of the surgical part of the treatment has come to the attention of the urological community after the publication by Brausi et al. [6], who assessed the variability in the early recurrence rate (i.e. identified at the first follow-up cystoscopy 3 months after the TURBT) between different urological clinics in the seven EORTC phase III trials including 2,410 patients with NMIBC. As a result, a significant variability was detected in the early recurrence rate which ranged from 3% to 21% for patients with a single tumor and from 7% to 46% for multiple tumors. It was stated that those differences could only be explained by the variability in the quality of the TURBT performed by individual surgeons, and a high rate of residual tumor after poor quality TURBT is responsible for high early recurrence rates.

Subsequent studies were focused on establishing the causes of this variability, identifying the criteria for the quality of TURBT, and finding ways to improve the thoroughness of the surgery. Later

Table 2. *Results of uni- and multivariate Cox regression analyses*

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Surgeon		<0.0001		0.0013
surgeon 1	1.0	—	1.0	—
surgeon 2	1.25 (0.95-1.64)	0.11	1.15 (0.85-1.56)	0.36
surgeon 3	1.59 (1.09-2.31)	0.016	1.42 (0.97-2.10)	0.075
surgeon 4	1.63 (1.17-2.28)	0.004	1.70 (1.19-2.41)	0.0033
surgeon 5	1.80 (1.35-2.39)	<0.0001	1.71 (1.26-2.32)	0.0005
Gender				
female	1.0	—	1.0	—
male	1.06 (0.84-1.33)	0.63	1.03 (0.82-1.30)	0.80
Age				
≤65 years	1.0	—	1.0	—
>65 years	1.06 (0.88-1.28)	0.55	1.03 (0.84-1.25)	0.79
Year of surgery		0.54		0.53
2004 – 07	1.0	—	1.0	—
2008 – 10	1.01 (0.81-1.26)	0.94	0.94 (0.74-1.20)	0.63
2011 – 13	1.14 (0.89-1.47)	0.30	1.11 (0.85-1.45)	0.45
Prior recurrence				
primary	1.0	—	1.0	—
recurrent	1.76 (1.46-2.13)	<0.0001	1.90 (1.54-2.34)	<0.0001
Number of tumors		<0.0001		0.0001
1	1.0	—	1.0	—
2–7	1.66 (1.34-2.05)	<0.0001	1.57 (1.25-1.97)	0.0001
≥8	1.95 (1.46-2.60)	<0.0001	1.87 (1.33-2.61)	0.0003
Tumor size				
<3 cm	1.0	—	1.0	—
≥3 cm	1.09 (0.89-1.33)	0.43	1.09 (0.85-1.39)	0.52
Macroscopic tumor type				
papillary	1.0	—	1.0	—
solid	1.22 (0.82-1.82)	0.32	1.29 (0.84-2.00)	0.25
T category				
Ta	1.0	—	1.0	—
T1	1.18 (0.97-1.44)	0.09	0.99 (0.8-1.22)	0.92
Tumor grade		0.041		0.28
G1	1.0	—	1.0	—
G2	1.26 (1.02-1.56)	0.029	1.13 (0.90-1.43)	0.29
G3	1.37 (0.94-2.00)	0.10	1.35 (0.90-2.02)	0.15
CIS				
no	1.0	—	1.0	—
yes	0.51 (0.21-1.22)	0.13	0.66 (0.24-1.78)	0.41
Length of surgery		0.045		0.41
≤20 min	1.0	—	1.0	—
21-30 min	1.27 (1.01-1.60)	0.045	1.11 (0.85-1.43)	0.45
31-40 min	1.21 (0.87-1.68)	0.26	1.06 (0.72-1.54)	0.78
>40 min	1.42 (1.10-1.83)	0.008	1.32 (0.94-1.87)	0.11
reTUR				
no	1.0	—	1.0	—
yes	1.39 (0.91-2.12)	0.13	1.26 (0.80-2.00)	0.32
Intravesical therapy				
no	1.0	—	1.0	—
yes	0.84 (0.67-1.06)	0.15	0.64 (0.50-0.82)	0.0005

HR – hazard ratio; CI – confidence interval; CIS – carcinoma in situ; reTUR – restaging transurethral resection

in the EORTC quality control study on TURBT, Brausi et al. showed that after adjustment for prognostic factors the reduction in the recurrence rate was associated with the use of a bladder diagram and being a staff urologist rather than a resident or a chief [6, 7]. In a retrospective study, Jacke et al. evaluated the impact of surgical experience on the recurrence and progression rates in 768 patients with primary NMIBC. They found a substantial decrease in the risk of recurrence after TURBTs performed by specialized urologists as compared to residents (OP = 0.68, 95% CI 0.53–0.87), but the risk of progression was basically the same (OP = 0.76, 95% CI 0.37–1.56). Surgical volume had no significant impact on the recurrence or progression rates [5].

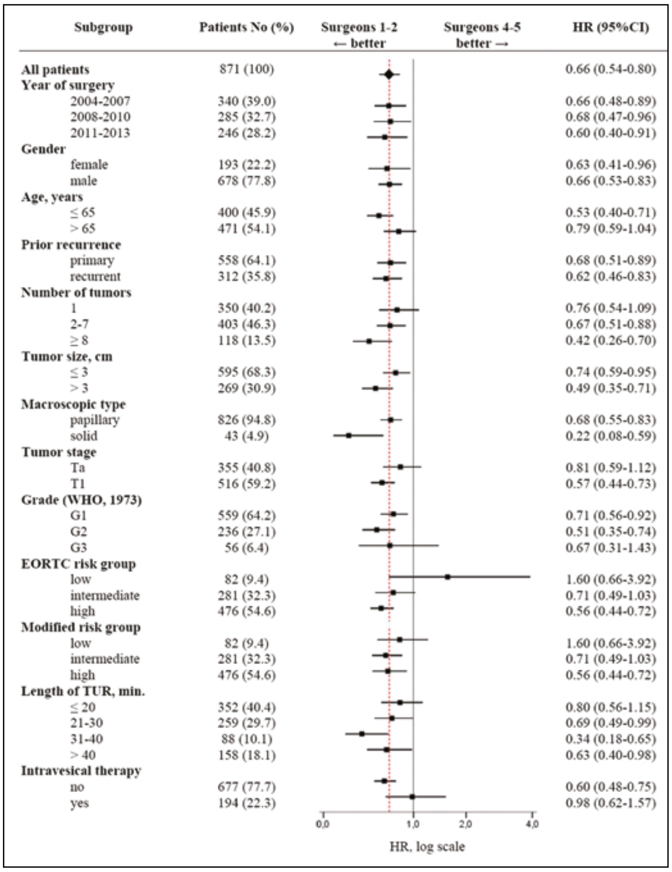

Figure 3. *Subgroup analysis of recurrence hazard ratio (HR) after transurethral resection (TUR) performed by the two most successful (1–2) surgeons as compared to the two least successful (4–5). CI – confidence interval; EORTC – European Organisation for Research and Treatment of Cancer; WHO – World Health Organisation.*

In a similar study by Di Zingaro et al., which included 209 patients with intermediate and high risk NMIBC, found high surgical volume (defined as experience in more than 100 TURBTs) to be predictive for recurrence and progression [8].

In contrast to these studies, in our series, all the surgeons had a status of specialist and their experience in performing TURBT significantly exceeded 100 surgical interventions. Therefore, the differences in the long-term outcomes in our study cannot entirely be explained by the poor basic technique associated with the initial training period. In addition, we could not detect the presence of a significant learning curve. For example, the risk of recurrence did not differ significantly based on the year of a surgery in the multivariate analysis. Furthermore, the analysis of the recurrence-free survival by experience in TURBTs, categorized as <10 and ≥10 years, showed worse results with increased experience both among the most and least successful surgeons (Figure 4), which might reflect a relative increase in more advanced cases over time.

There are several possible explanations for these observations: despite the fact that the TURBT is considered a simple surgical intervention, the learning curve for providing the best results with this operation may significantly exceed 100 cases or 4–5 years of residency. Another explanation could be that some of the surgeons' successes in achieving better results may be associated with certain inborn professional qualities (e.g. alertness, scrupulousness, etc.) and does not change substantially over time.

Meanwhile, these findings raise an important question on defining the quality of TURBT. In this regard, the mainstream idea was to consider the presence of muscle tissue in the specimen after TURBT as a key quality indicator of surgical completeness. As early as in 1999, Herr showed that this parameter predicted the rate of muscle-invasive disease after restaging TURBT in patients

Table 3. *Recurrence rate in the first 3, 6, and 12 months after TURB performed by the two most and two least successful surgeons within different prognostic groups*

Subgroup		Recurrence rate in 3 months		Recurrence rate in 6 months		Recurrence rate in 12 months	
		n / N (%)	95%CI	n / N (%)	95%CI	n / N (%)	95%CI
Primary solitary tumors	Surgeons 1-2	2/162 (1.2)	0-3	6/162 (3.7)	0.8-6.6	10/160 (6.3)	2.5-10.0
	Surgeons 4-5	4/95 (4.2)	0.1-8.3	6/93 (6.5)	1.4-11.5	10/92 (10.9)	4.4-17.4
Recurrent or multifocal tumors	Surgeons 1-2	2/258 (0.8)	0-1.9	23/255 (9.0)	5.5-12.6	36/252 (14.3)	9.9-18.6
	Surgeons 4-5	5/137 (3.6)	0.5-6.8	20/137 (14.6)	8.6-20.6	35/136 (25.7)	18.3-33.2
Recurrent and multifocal tumors	Surgeons 1-2	0/129 (0)	–	11/129 (8.5)	3.6-13.4	31/126 (24.6)	17.0-32.2
	Surgeons 4-5	4/90 (4.4)	0.1-8.8	11/90 (12.2)	5.3-19.1	37/90 (41.1)	30.7-51.5

CI – confidence interval, n – number of patients with recurrences, N – number of patients in the subgroup

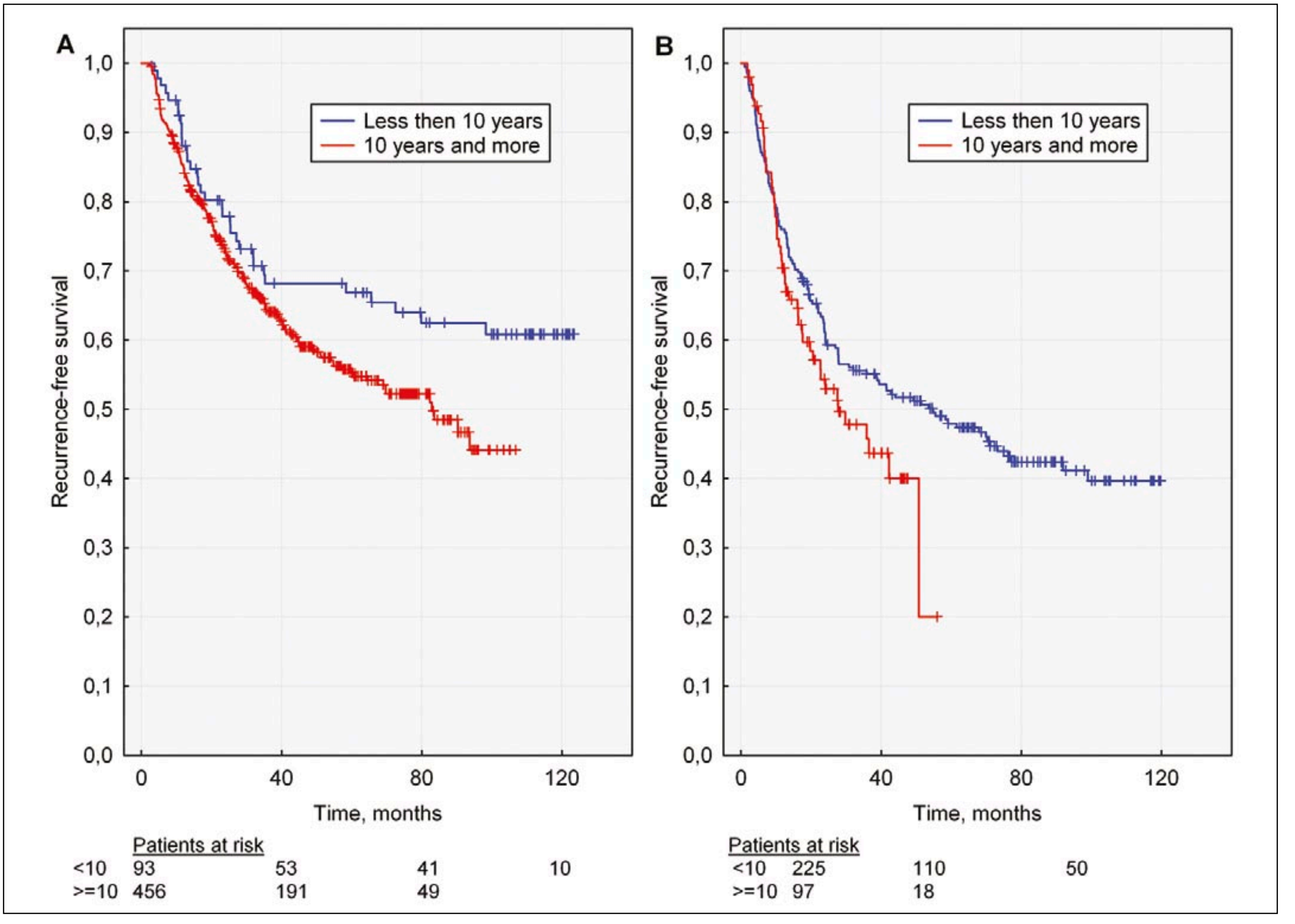

Figure 4. *Recurrence-free survival by length of TURBT experience (<10 vs. ≥10 years) among the most (A) and least successful (B) surgeons.*

initially staged as T1 [9]. However, there is some controversy in the current literature on the true significance of this criterion.

Mariappan et al. assessed the prognostic value of the presence of muscle tissue in the specimen after TURBT as a surrogate marker for the quality of the TURBT in a prospective database including 356 patients with NMIBC [4]. In the multivariate analysis, this parameter was associated with the resection of large, low-differentiated tumors and a senior surgeon that was defined as having 5 or more years of training. The early recurrence rate correlated with the absence of muscle in the specimen and a junior surgeon (odds ratio 2.9; 95% CI 1.6–5.4; p = 0.0002). In a similar study, Huang et al. found that the absence of muscle in the specimen after TURBT was more often observed with large tumors, tumors with difficult location and "young" surgeons (≤10 years of training) [10]. These factors, together with the absence of muscle in the specimen and T1 staging, were associated with the presence of residual tumor on repeat TURBT.

Rouprêt et al. evaluated the results of 340 TURBTs for pT1 NMIBC and found significant differences in the rate of muscle tissue detection in the specimen between junior and senior surgeons (61.3% *vs.* 73.8%; p = 0.02) [11]. However, in the multivariate analysis, only a junior surgeon as an operator, regardless of the presence or absence of the muscle tissue in the specimen, was predictive of recurrence (HR 2.33; 95% CI 1.45-3.74; p = 0.01). And finally, Shoshani et al., in the analysis of the data from 332 patients with NMIBC, found the association between the presence of muscle tissue in the specimen and high tumor grade, large size, multifocality and nonpapillary morphology, but not with the surgical experience [12]. Moreover, the lack of muscle tissue in the specimen had no effect on the long-term recurrence and progression rate in the overall patients' cohort. Therefore, the authors concluded that the presence of muscle in the specimen was determined more by the tumor extent than by the surgeon's experience, and the presence of muscle in the specimen can be a criterion of TURBT quality only in the T1 tumor subgroup.

Unfortunately, we were unable to evaluate the presence of the muscle tissue in the TURBT specimen in our cohort as this criterion has not been systematically assessed in a significant number of patients. However, we would like to focus the attention on a more relevant and direct measurement of the TURBT quality by evaluating the 12-month recurrence rate, which we found to be the most discriminative between more and less successful surgeons. A single institution study and a low number of surgeons could not allow us to provide firm recommendations on optimal cut-off values of these parameters. We suggest conducting a multi-institution prospective study for assessing the early recurrence rate as a surrogate marker for the quality of TURBT in patients with NMIBC.

Finally, we have to underscore a wide variation of recurrence risk between different surgeons in our study reaching up to 1.71, which is more than HR for multiple or large tumors in a pivotal EORTC prognostic study [13]. Whereas any comparative trial exploring new therapies in NMIBC used to be balanced for basic prognostic factors of the tumor, it is unusual to ensure balance of the study arms by the operating surgeon. However, this may introduce a significant bias in the results of the comparative trials in which one group may be operated on by better surgeons than the other with fewer recurrences mimicking an effect of additional interventions.

CONCLUSIONS

A surgeon has a significant impact on the risk of recurrence after curative treatment of patients with NMIBC, which should be taken into account while performing and evaluating the results of comparative studies in this field. In our study, a significant difference between the surgeons was observed despite relatively similar and extensive experience in bladder endoscopic surgery and practicing in a setting of one specialized center. These differences were less prominent in less extensive tumors. Early recurrence rate may be used as a criterion of the quality of the TURBT.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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