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Factors that predict residual tumors in re-TUR patients

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Abstract
Introduction: The first and foremost rule in the treatment of superficial bladder cancer is correct and complete resection of the tumor. Histopathological analysis of the resected tumor will help to define the correct tumor stage, thus delaying or, ideally, avoiding tumor recurrence and progression.
Objectives: To examine the prognostic factors for residual tumors in the tumor base or in another area of the bladder in patients subjected to repeat transurethral resection (re-TUR).
Patients and methods: Between September 2009 and August 2014, 188/221 patients advised to undergo re-TUR for stage T1 tumors were subjected to the procedure. The following data were collected for this retrospective study: patients' age and sex, information on whether initial TUR was carried out for a primary tumor/primary tumors, tumor number, tumor size and tumor grade, as well as information on whether muscularis propria was found in the resected specimens of initial TUR, whether there was carcinoma in situ and whether single-dose intracavitary chemotherapy was administered following initial TUR.
Results: On re-TUR, new tumors outside of the previous resection area were found in 34 (18%) and residual tumors in the initial resection area in 48 (25.5%) patients. 61.7% of the patients diagnosed with new tumors outside of the previous tumor area and 62.5% of those with residual tumors in the initial resection area had initially undergone TUR for multifocal tumors. Both univariate and multivariate analysis revealed a significant relationship between male sex, multifocal primary tumors and the detection of residual tumors in the previous resection area during re-TUR.

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Conclusion: For the reasons mentioned above, we believe that re-TUR will influence the treatment strategies and have an impact on T1-tumor progression, especially with regard to multifocal tumors.

Introduction

The gold standard in the diagnosis and treatment of bladder cancer is transurethral resection (TUR). The first and the foremost rule in the treatment of superficial bladder cancer is the correct and complete resection of the tumor [1,2]. Histopathological analysis of the resected tumor will help to correctly define the tumor stage, and therefore delay and even avoid tumor recurrence and progression. Guidelines published by the European Association of Urology (EAU 2014) suggest repeat TUR (re-TUR) in all high-grade T1 and selected high-grade Ta tumors [3–5]. During re-TUR, microscopic and/or macroscopic residual tumors can be identified in the initial resection area or new areas. For the detection of residual tumors, the grade, stage, size and number of the initial tumor(s) is important [4–7]. It is known that residual tumors diagnosed during re-TUR may be due to technical insufficiency or to the fact that they have been overlooked during initial TUR [5,8–12]. Another important factor is the grade of tumor invasion [5,8–12]. In this study, we aimed to examine the prognostic factors for residual tumor detection in the tumor base or in another area in patients subjected to re-TUR.

Patients and methods

In this retrospective study, we reviewed the data of 1021 patients who underwent TUR for superficial bladder tumors between 2009 and 2014. As a routine practice in our clinic we perform a second TUR in patients with T1 tumors, regardless of the pathological grade, multiplicity or recurrence factor. 221 patients were advised to have re-TUR for T1 tumors. Of these, 18 refused re-TUR, 8 were subjected to radical cystectomy due to widespread tumors, 3 had a high anesthesia risk and 4 were lost to follow-up after initial TUR. Thus, 33 patients were excluded from the study, leaving a total of 188 patients subjected to re-TUR.

Initial TUR was done using standard 30° and 70° optic lenses for cystoscopy. Using a hot loop, all the visible tumors were excised with either en-bloc or graded resection, depending on the tumor size. The resected tumors as well as the tumor bases were sent for histopathological assessment. Patients with T1 pathology results were scheduled for re-TUR within a 4–6 week period from initial TUR. 96 patients scheduled for re-TUR received single-dose intracavitary chemotherapy following the initial operation. 92 patients with postoperative hematuria were not eligible for single-dose intracavitary chemotherapy. The patients were called 2 weeks after initial TUR to review their histopathological results and to discuss further treatment which was planned according to the pathology results.

During re-TUR, all visible tumors were resected. Afterwards, the areas of initial TUR were also resected and sent in different containers for histopathological analysis.

For statistical analysis, the following data were collected: patients' age and sex, information on whether initial TUR was carried out for a primary tumor/primary tumors, tumor number, tumor size and tumor grade, as well as information on whether muscularis propria was found in the resected specimens of initial TUR, whether there was carcinoma in situ (CIS) and whether single-dose intracavitary chemotherapy was administered following initial TUR.

SPSS 20.0 for Windows was used for statistical analysis. The logistic regression analysis and chi-square analysis were used for the data review.

Results

168 male and 20 female patients aged between 31 and 78 (mean 67.3) years received re-TUR. 157 (83.5%) patients had primary and 31 (16.5%) had recurrent tumors. Initial TUR was performed on 106 (56.3%) patients with a single tumor and 82 (43.7%) patients with multifocal tumors. 106 (56.3%) patients had high-grade and 82 (43.7%) low-grade T1 tumors. In 20 (10.6%) patients, additional CIS was detected. 96 (51%) patients received single-dose intracavitary chemotherapy, while 92 (49%) patients were not eligible for single-dose intracavitary chemotherapy due to hematuria.

On re-TUR, 34 (18%) patients were diagnosed with new tumors outside of the resection area, while 48 (25.5%) had residual tumors within the initial resection area. In 61.7% of the patients diagnosed with residual tumors outside of the initial resection area, initial TUR had been performed for multifocal tumors (Table 1). The tumor stage and grade were found to be increased in 5 (2%) and 6 (3%) patients, respectively. Radical cystectomy was performed on the patients with increased tumor stage. The other patients were treated with BCG immunotherapy.

Both univariate and multivariate analysis revealed a significant relationship between male sex, multifocal primary tumors and the detection of residual tumors in the previous resection area during re-TUR. (Table 2) ($p < 0.05$). A new tumor in a new area detected during re-TUR was found to be significantly related to multifocal primary tumors only (Table 3) ($p < 0.0001$). No morbidity or mortality was seen in the patients subjected to re-TUR in connection with this procedure.

Discussion

70–75% of newly diagnosed bladder tumors are non-muscle invasive bladder tumors (NMIBC). About 1–10% of those tumors are CIS, 70–80% of them are Ta and 20% of them are T1 tumors [13–15]. NMIBC type tumors are a heterogeneous disease group and cover a wide range in terms of recurrence, progression and survival rates. Stage pT1 tumors are usually high-grade tumors with a high risk for progression [16,17]. Those tumors tend to progress in 29–74% of the patients over a 5-year period [18]. The shift of superficial

Table 1 Patient characteristics.

		N (%)
Sex	Male	168 (89.3%)
	Female	20 (10.7%)
Primary tumor	+	157 (83.5%)
	−	31 (16.5%)
Grade	Low	82 (43.7%)
	High	106 (56.3%)
Tumor size	<3 cm	111 (59%)
	>3 cm	77 (41%)
Tumor number	Solitary	106 (56.3%)
	Multifocal	82 (43.7%)
Concomitant CIS	+	20 (10.6%)
	−	168 (89.3%)
Tumor stage (re-TUR)	T0	140 (74.4%)
	Ta	9 (4.7%)
	T1	33 (17.5%)
	T2	5 (2.6%)
	CIS	1 (0.5%)
	High grade	6 (3.1%)
Histopathological stage/grade (re-TUR)	T2	5 (2.6%)
	CIS	1 (0.5%)
	Total	12 (6.3%)

CIS: carcinoma in situ.

Table 2 Residual tumors detected on re-TUR.

Variant	Univariate (*p* score)	Multivariate (*p* score)
Sex (M/F)	**0.003**	**0.004**
Primary/recurrent Tumor	0.933	
Solitary/multifocal Tumor	**0.005**	**0.006**
Tumor size (<3 cm/ > 3 cm)	0.498	
Tumor grade (low/high)	0.886	
Presence of muscularis propria (+/−)	0.188	
Presence of CIS (+/−)	0.064	
Single-dose chemotherapy (+/−)	0.585	

CIS: carcinoma in situ.
Bold values indicate that *P* values <0.05 were considered to be statistically significant.

Table 3 Newly diagnosed tumors detected on re-TUR.

Variant	Univariate (*p* score)	Multivariate (*p* score)
Sex (M/F)	0.098	
Primary/recurrent Tumor	0.856	
Solitary/multifocal Tumor	**0.001**	
Tumor size (<3 cm/ > 3 cm)	0.652	
Tumor grade (low/high)	0.521	
Presence of muscularis propria (+/−)	0.213	
Presence of CIS (+/−)	0.078	
Single-dose chemotherapy(+/−)	0.645	

CIS: carcinoma in situ.
Bold values indicate that *P* values <0.05 were considered to be statistically significant.

tumors to muscle invasive tumors with time is reported to show a worse prognosis in comparison with initial muscle invasive tumor diagnosis [19]. This shows the importance of primary treatment in non-muscle invasive tumors [20].

Recurrence is detected during the first control cystoscopy in 20–81.5% of patients with superficial bladder tumors [21]. Whether this is due to insufficient resection or new tumor growth is still questionable. Tumor detection during the first control cystoscopy gives important clues about the prognosis of the disease and is accepted as a negative prognostic factor [22,23]. Especially in multiple and invasive tumors, single TUR is thought to be insufficient to completely remove the diseased tissue and may cause early recurrences and stage progression against the additional intravesical treatments [5,24].

Residual tumors in the initial resection area or in a new area can be seen microscopically or macroscopically during re-TUR. Stage, grade, number and size of the initial tumor(s) affect the detection of residual tumors [4–7,25–29]. One of the first studies in this subject was carried out by Klan et al. on 46 patients with stage pT1 disease. Even though the surgeon's reports showed complete tumor resection on TUR, 20 of 40 patients subjected to re-TUR were diagnosed with residual tumors [30]. Another important study performed by Herr et al. stresses the importance of re-TUR, as their results showed residual tumors in 76% and stage progression in 28% of their patients [11]. The first prospective study on this subject was done by Grimm et al. in 2003 [4]. In their study, they report on the long-term follow-up results of 83 patients (63 with stage Ta and 20 with stage T1 cancer) who underwent re-TUR. Residual tumors were seen in 33%, while low staging was seen in 8% of their patients. Residual tumors were found in the area of initial tumor resection in 46% and in a new area in 19% of the patients. Univariate analysis revealed a significant relationship between residual tumor detection and stage and grade of the initial tumor [4].

Another study reviewing the efficacy of re-TUR and residual tumor predictive factors was done by Schwaibold et al. [7]. In this study, 136 patients with stage pT1 tumors who had initially been subjected to standard TUR and underwent re-TUR were reviewed. 71(23%) of them were diagnosed with residual tumors during re-TUR. Stage or grade progression was seen in 28 (21%) patients. Residual tumors in the initial resection area were seen in 86% and in another area in 14% of the patients. The presence of residual tumors was found to be significantly related to multiple initial tumors, yet it was not related to tumor size or grade.

In the present study, we found a similar incidence of residual tumors detected on re-TUR. In accordance with other studies published in the literature, we found that multifocal tumors were an important factor leading to the risk of residual tumors after initial TUR. We believe that the reason for the increased occurrence of residual tumors in patients with multifocal tumors may be due to factors that obstruct the view during the intervention, such as bleeding, which increases the operation time and renders resection in all tumor areas more difficult.

The presence of residual tumors in patients with concomitant CIS was not found to be statistically significant in our study, but a close value. This can be explained with the low number of patients. Thus, concomitant CIS may also be a factor predictive of residual tumors.

The results of our study and the other studies found in the literature show a higher occurrence of residual tumors in stage-T1 tumor disease which highlights the importance of re-TUR as well as the need for more careful resection of multifocal tumors.

The observation in our study that more residual tumors were found in male compared to female patients may be attributed to the low number of female patients in our study.

The limited number of patients and the retrospective study type are the limitations of our study. We believe, however, that studies on a larger number of patients will support our results.

Conclusion

The fact that stage-T1 tumors have a larger tumor load than previously assumed has been supported by the results of our study and other studies in the literature. This can be seen more clearly in patients with multifocal tumors. For the reasons mentioned above, we believe that re-TUR will influence the treatment strategies and have an impact on T1-tumor progression, especially with regard to multifocal tumors.

Conflict of interest

No conflict of interest.

Ethical committee approval

Ethics committee approval was not obtained because of retrospective study.

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