

ORIGINAL PAPER

REPEATED TRANSURETHRAL RESECTION IN NON-MUSCLE INVASIVE BLADDER CANCER

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ABSTRACT

Introduction. The treatment requirements for non-muscle invasive bladder cancer (NMIBC) (Ta, T1) and muscular invasive bladder disease (T2) differ considerably, therefore a correct staging of the disease is most important. The staging of the disease is frequently underestimated during the primary tumour resection.

The objective of the study. To evaluate the results of repeated transurethral resections of the bladder tumours, to assess the treatment outcomes.

Material and methods. 160 patients diagnosed with NMIBC underwent transurethral resection of the bladder tumours (TUR) and repeated TUR (reTUR). A data analysis was carried out following the interventions, with histopathological examination, disease staging, and dynamic assessment after 1-year follow up.

Results. The average age of the patients was 65.7 years (range 28–86 years) and most of the patients were male, 139 (87%). In most of the cases, the tumours were single, less than 3 cm, and of low-grade in 52%. At reTUR, the residual disease was found in 33% (25/76) of cases. Of these patients, 12 were Ta and 7 were T1, while 2 were carcinoma in situ (Tis) with residual T1 and 4 were upstaged to T2 disease. 62% of

RÉSUMÉ

Résection endoscopique répétée du cancer de la vessie non-infiltrant le muscle

Introduction. Les exigences de traitement pour le cancer de la vessie non-infiltrant le muscle (Ta, T1) et la maladie de la vessie avec l'invasion de la paroi musculaire (T2) diffèrent considérablement, par conséquent, une stadification correcte de la maladie est très importante. Le stade de la maladie est souvent sous-estimé au cours de la résection primaire de la tumeur.

L'objectif de l'étude: évaluer les résultats des résections transurétrales répétées des tumeurs de la vessie afin d'évaluer les résultats du traitement.

Méthodes. 160 de patients diagnostiqués avec le cancer de la vessie non-infiltrant le muscle ont subi une résection endoscopique de tumeur de vessie (RTUTV) et une résection endoscopique de tumeur de vessie répétée (reRTUTV). On a effectué l'analyse des données des interventions du patient, l'examen histopathologique, la stadification de la maladie et l'évaluation dynamique pendant le temps d'un suivi d'un an.

Résultats. L'âge moyen des patients était de 65,7 ans (intervalle de 28 à 86 ans) et la majorité des patients étaient de sexe masculin 139 (87%). Dans la majorité

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residual tumours were detected within the initial resection area. The recurrence rate after 1-year follow-up in the group of reTUR vs. TUR group was lower (29% vs. 56%), as well as disease progression (5% vs. 13%), respectively, after the 1-year follow up.

Conclusions. Residual tumours commonly occur following a transurethral resection of high-risk non-muscle invasive bladder cancers. The repeated resection procedure helps in diagnosing residual tumours which have been initially assessed as the T1 stage and may improve the treatment outcomes.

Keywords: bladder cancer, staging, progression, repeated resection.

Abbreviations:

TUR – transurethral resection of the bladder tumours, reTUR – repeated transurethral resection of the bladder tumours,

NMIBC – non-muscle invasive bladder cancer,

MIBC – muscle-invasive bladder cancer.

INTRODUCTION

Stages Ta and T1 are known as non-muscle invasive bladder cancer (NMIBC) and make up the major part (about 60–80%) of bladder cancer cases^{1,2}. In general, these tumours are present in low-progression rates and high-recurrence rates. In other words, NMIBC in most cases are curable, but are often predisposed to recurrence and patients with the multifocal stage of Ta–T1 high-grade urinary bladder carcinoma have a high-risk of progression (5% in one year) and recurrence (40% in one year). Repeated transurethral resection of bladder tumour (reTUR) has been standing out as a substantial step to receive full tumour clearance and corresponding staging in T1 stage disease. A few standardized international and national guidelines recommend the procedure of reTUR, particularly in patients with T1 and/or high-grade bladder cancer¹.

In 2016, the global standardized incidence rate of patients with bladder cancer was 6.69 per 100000 persons⁴. The first and foremost rule in NMIBC is complete transurethral resection (TUR)^{5,7}. However, reTUR is essential in the diagnosis, treatment, and prognosis of patients with pT1 urinary bladder tumours and has the possibility of detecting from 1% to 32% of the patients with muscle-invasive disease⁸. Therefore, the benefits of a reTUR are evident as the necessity of applying consequent changes in the management of tumours which are often incompletely resected or under-staged¹.

des cas, les tumeurs étaient uniques, inférieures à 3 cm et de bas grade dans 52%. Lors d'une reRTUTV, la maladie résiduelle a été retrouvée dans 33% (25/76) des cas. Parmi ces patients, 12 étaient Ta et 7 étaient T1, tandis que 2 étaient Tis (carcinome in situ) avec T1 résiduel et 4 étaient passés à la maladie T2. 62% des tumeurs résiduelles ont été détectées dans la zone de résection initiale. Le taux de récurrence au cours du suivi à 1 an dans le groupe reRTUTV vs RTUTV a des taux inférieurs, 29% vs 56%, ainsi que la progression de la maladie 5% vs 13% respectivement au moment du suivi d'un an.

Conclusions. Les tumeurs résiduelles surviennent fréquemment après une résection transurétrale de cancers de la vessie sans invasion de la paroi musculaire à haut risque. La procédure de résection répétée aide à diagnostiquer les tumeurs résiduelles et peut améliorer les résultats du traitement, qui ont été initialement évalués comme stade T1.

Mots-clés: cancer de la vessie, stadification, progression, résection répétée.

The treatment requirements for NMIBC (Ta, T1) and muscular invasive bladder disease (T2) differ considerably. Hence, a correct staging of disease is extremely important. Within the primary tumour resection, the staging of the disease is frequently underestimated⁹⁻¹¹. At the histological evaluation of T1 bladder cancer, the possibility of detecting a muscle-invasive bladder cancer after repeated resection ranges between 4% to 25% and it can increase up to 45% if detrusor muscle fragments are absent at first morpho-pathological examination¹¹.

THE OBJECTIVE OF THE STUDY was to evaluate the results of reTUR in order to assess treatment outcomes.

MATERIAL AND METHODS

The study was conducted between January 2016 and February 2019, in the Department of Urology, “Timofei Mosneaga” Republican Clinical Hospital, Chair of Urology and Surgical Nephrology, “Nicolae Testemitanu” State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. A retrospective study of the data regarding patients' interventions, histopathological examination, disease staging, following by an assessment of a 1-year follow up was carried out. The patient's inclusion criteria were the diagnosis of NMIBC, repeated transurethral resection performed within 2 – 6 weeks after the initial resection, age over 18-year-old, and

the Eastern Cooperative Oncology Group (ECOG) score 0-2. The exclusion criteria were identified as follows: other non-urothelial tumours, severe comorbidities, ECOG score ≥ 3 , and pregnancy. The study protocol was approved by the University Ethics committee (N^o 11 on 5 November 2019). Statistic description and non-parametric comparison by Fisher exact test were used. The study was conducted according to the ethical standards in the Helsinki declaration of 1975, as revised in 2008(5).

RESULTS

The study included 160 patients diagnosed with NMIBC. All these patients underwent TUR and reTUR interventions. According to all standard procedures, all the patients were consequently investigated retrospectively. Depending on the performed intervention (TUR or reTUR), all patients were divided in two groups: the reTUR group and the TUR group. In the first group, 76 cases were included, and 84 cases in the second one (Table 1). To ensure a descriptive statistic of the patients included in the study, demographic data were analyzed and presented using mean values. In order to ensure relevant comparison between the cohorts, while working with test statistic, according to the STARD and STROBE guidelines, the following data were analyzed: characteristics of residual tumours,

recurrence rate and disease progression after one year (Table 2).

The patients included in the study were characterized as per descriptive statistic. The average age of the patients was 65.7 years overall (range 28–86 years). The gender distribution of the patients included in the study was overwhelmingly male (139 men, 87%). In the major of cases, tumours were single, had less than 3 cm in size, and they were of low-grade in 52% of the cases. Concluding the results of descriptive statistic data of the patients and the clinical features of cancer in these patients, it is important to point out that there was no significant difference in the demographic and baseline tumour characteristics between the cases of both cohorts.

Data analysis showed that after reTUR the residual disease was found in 33% (25 out of 76) of cases. 12 patients were Ta and 7 were T1, while 2 were Tis (carcinoma in situ) with residual T1 and 4 were upstaged to T2 disease. In 62% of cases, residual tumours were detected within the initial resection area. The comparative analysis of recurrence rate after 1-year follow-up showed that in the group of reTUR it makes up 29 % versus 56% in the group treated by TUR. So, the recurrence rate in the group of reTUR is significantly lower ($p < 0,05$). In the group treated by reTUR, the disease progression was 5% vs. 13% in the group treated by TUR. The disease progression was appreciated in the time frame of 1-year follow-up.

Table 1. Patients' demographics and tumour characteristics.

Parameters	Categories	Total (n=160)	reTUR (n=76)	TUR (n=84)
Gender	Men, n (%)	139 (87%)	67 (88%)	72 (86%)
	Women, n (%)	21 (13%)	9 (12%)	12 (14%)
Age, years	Mean age (CI 95%)	65,7 (28-86)	66,2 (33-86)	65,1 (28-82)
Tumour size	< 3 cm, n (%)	115 (72%)	56 (73,5%)	59 (70%)
	≥ 3 cm, n (%)	45 (28%)	20 (26,5%)	25 (30%)
Number of tumours:	Single tumours, n (%)	102 (64%)	50 (66%)	54 (63%)
	≥ 2 tumours, n (%)	58 (36%)	26 (34%)	32 (37%)

Note: TUR – Transurethral resection of bladder tumour, reTUR – Repeat transurethral resection of bladder tumour.

Table 2. Histological and oncological outcomes

Parameters	Categories	Total (n=160)	reTUR (n=76)	TUR (n=84)
Histopathology grade	Low-grade, n (%)	83 (52%)	36 (47%)	47 (56%)
	High-grade, n (%)	77 (48%)	40 (53%)	37 (44%)
Tumour recurrence	Recurrence, n (%) *	69 (43%)	22 (29%)	47 (56%)
Disease progression	Progression, n (%)	15 (9,5%)	4 (5%)	11 (13%)

Note: TUR – Transurethral resection of bladder tumour, reTUR – Repeat transurethral resection of bladder tumour, Low-grade – Low-grade papillary urothelial carcinoma, High-grade – High-grade papillary urothelial carcinoma, * – $p < 0,05$ statistically significant difference.

DISCUSSION

An efficient TUR is the first and most significant step in the treatment and diagnosis of NMIBC, while a reTUR is estimated to be of diagnostic, therapeutic, predictive, and prognostic value^{5,12}.

Correct staging is crucial to choose an adequate treatment for bladder cancer, because NMIBC and muscle-invasive bladder cancer (MIBC) have significantly different treatments and outcomes. Although considerable reports of tumour under-staging have been described, TUR remains the golden standard of treatment for this category of patients. A systematic review of 24 studies, which include the data of 2417 patients, upstaging of stage T1 disease at initial transurethral resection to T2 disease at reTUR ranged from 0% to 32% in individual studies, with a combined prevalence rate of 8%¹³. One of the recent meta-analyses shows that the combined prevalence rate of upstaging to stage T2 disease after reTUR was 11%, and for the subgroup which has detrusor muscle at first TUR, the combined prevalence rate of upstaging to T2 stage after reTUR was 10%¹⁴. According to another data analysis, the pooled prevalence rates of residual tumour at repeated TUR for stage Ta tumours range from 17% to 67% (55%) and T1 tumours range from 20% to 71% (51%)¹⁰. In the relevant literature, such a view on this problem is not entirely the same. Some authors suggest that reTUR may not be useful when an adequate first TUR has been performed^{15,16}.

A big multi-institutional cohort of 2451 patients with NMIBC (BCG-treated T1G3/HG), was evaluated retrospectively. Repeated TUR was performed in 935 cases and improved progression-free survival (PFS), recurrence-free survival (RFS), and overall survival (OS) only for patients without detrusor muscle layer in the specimen of the initial transurethral resection¹⁷.

In this study, the disease progression from stage T1 to stage T2 in 5% cases after reTUR and for 13% after TUR, after a one-year follow-up, was reported. Detrusor muscle layer was found in 74% of cases of the histopathological result after a primary TUR.

In a multicentre research, which included more than 2000 patients, the absence of detrusor in the histological report at first TUR is evident for a higher rate of residual disease in case of reTUR than in cases when detrusor muscle was primarily present (85.9% vs. 65.2%)¹⁰. Other studies have shown that reTUR led to reduced disease recurrence rates vs. TUR after 3 months (9.6% vs. 43.3%) and after 12 months (28.3% vs. 58.2%)¹⁸.

During reTUR, the residual disease was found in 25 patients (33% of cases). Out of 25 patients, 12 were Ta and 7 were T1, while 2 were Tis (carcinoma in situ) with residual T1 and 4 were upstaged to T2 disease. The majority of residual tumours were detected within the initial resection area, which makes up 62%. The recurrence rate in the time of one year follow-up in the reTUR group was 29%, and for TUR group it was 56% (Table 2).

Another example, residual tumour after reTUR has been reported in up to 74% of the patients with up-staging in up to 64% of those cases^{5,13,14}. If primary TUR is considered complete, the rate of residual disease ranged from 3.7% to 17.6% of the cases. Moreover, for the subgroups of patients with the high-risk disease data on progression and recurrence rates showed an obvious benefit for cases treated with reTUR¹⁹.

Not all the tumoural lesions are visible during the procedure of TUR, which is partly blind. Thereby, reTUR is the correct option, which allows to cover the constraints of TUR, even if the first TUR includes the muscle specimen and the procedure is considered "complete" by the surgeon^{20,21}. The results of the reTUR (under-staging and residual tumours) mirror the quality of the first TUR^{22,23}.

Another study reveals residual disease in 33.3% (35/105) of patients in the reTUR group, 8 patients were upstaged to pT2 disease. The reTUR group was associated with substantially lower rates of disease progression (9.7% vs. 31.6%), recurrence (43.0% vs. 75.5%) and disease-specific mortality (24.0% vs. 57.7%). Compared with the TUR group, reTUR should be performed as a routine manipulation for all NMIBC patients, stage pT1, with a life expectancy of at least 10 years, and proof its positive contribution to all oncological outcomes²⁴.

Therefore, theoretical risk factors, such as multiplicity and the absence of detrusor muscle in the specimen, do not seem to significantly act on the upstaging to invasive disease rate or residual cancer post reTUR⁸. In conclusion, reTUR must remain an important practice due to a high rate of residual disease and a low risk of tumour under-staging. The macroscopic clearance and presence of the detrusor muscle layer should not be utilized as surrogates for the adequacy of resection or approval of avoiding a reTUR, even for TaHG disease²⁵.

CONCLUSIONS

Residual tumours and tumour under-staging usually occur following a TUR of high-risk NMIBC. The repeated TUR procedure is useful for the

diagnosis of residual tumours and may improve the treatment outcomes, which have been initially assessed as the T1 stage.

Author Contributions:

Conceptualization, I.V., P.B., V.G.; methodology, I.V. and V.G.; software, I.V. and P.B.; validation, P.B. and V.G.; formal analysis, I.V. and P.B.; investigation, I.V. and P.B.; resources, I.V. and P.B.; data curation, I.V. and P.B.; writing—original draft preparation, I.V.; writing—review and editing, I.V., P.B. and V.G.; visualization, V.G.; supervision, V.G.; project administration, V.G. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

“The authors declare no conflict of interest regarding this article”

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study”

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