An evaluation to define the role of repeat transurethral resection in a treatment algorithm for non-muscle-invasive bladder cancer

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ABSTRACT

Objective: Repeat transurethral resection (ReTUR) is an effective treatment for non-muscle-invasive bladder cancer (NMIBC) to prevent disease recurrence or progression. It also has an important role in stratifying patients according to histopathological results. Therefore, the end point of ReTUR should be considered in a treatment algorithm. We evaluated positive ReTUR to define its role in a treatment algorithm for NMIBC.

Materials and Methods: A second TUR was performed in 111 patients between July 2006 and February 2010. A third TUR was performed in 31 patients with T1/a/is tumors at the second TUR. The incidence of residual disease was calculated according to the NMIBC risk levels proposed by the International Bladder Cancer Group. We used ReTUR as a general term to indicate second and third TURs.

Results: Residual disease at the second TUR was detected in 51% of the patients; it was observed in 17%, 45%, and 65% patients in the low-, intermediate-, and high-risk disease groups, respectively (P = 0.01). Residual disease at the third TUR was detected in 48% patients; it was observed in 18% and 65% patients in the intermediate- and high-risk disease groups, respectively (P = 0.06).

Conclusion: The incidence of residual disease correlated with the risk levels for NMIBC. In the intermediate-risk disease group, nearly complete resection was accomplished after the third TUR. However, in the high-risk disease group, a high incidence of residual disease was identified even after the third TUR. Our results provide important data that may be useful in establishing an end point in a treatment algorithm for NMIBC.

Key words: Non-muscle-invasive bladder cancer, repeat transurethral resection, treatment algorithm

INTRODUCTION

To improve treatment results, repeat transurethral resection (ReTUR) has been recommended for non-muscle-invasive bladder cancer (NMIBC), especially in high-grade/T1 disease.¹ ReTUR provides more accurate staging information and potentially clears residual disease. Several reports have documented occult T2 disease in up to 10% of second TURs.²³ Meanwhile, high-grade, T1 or multifocal disease is included as the risk of disease remaining.³⁻⁵ Indeed, ReTUR is considered to improve recurrence-free survival (RFS) and progression-free survival (PFS) as compared to a single TUR¹⁻⁴,⁵. Moreover, at the second TUR, absence of residual disease (T0) showed a better correlation with a low recurrence or progression rate at follow-up as compared to pTa, Tis, or T1 residual disease.⁶⁻⁷ In some cases, residual disease was found even after the third TUR.⁵⁻⁸ A T0-ReTUR is desirable. However, the number of times ReTUR should be performed in order to reach T0 is unclear, and the predicting factor for the same is also unidentified. ReTUR is not only a treatment for NMIBC; it also has an important role in providing stratification of patients based on its results. The stratification is directly related to the selection for subsequent treatment such as intravesical prophylaxis or cystectomy. Based on the
stratification, treatment algorithms for NMIBC have been designed and proposed.\(^1\)\(^9\) Therefore, the end point of ReTUR should be considered in a treatment algorithm. In this study, we determined predicting factors that provide the number of ReTURs to reach T0. Moreover, we evaluated the significance of ReTUR in a treatment algorithm for NMIBC.

**MATERIALS AND METHODS**

A total of 117 patients underwent a second TUR between July 2006 and February 2010 at Yokohama Minato Red Cross Hospital and Yokohama Citizens Municipal Hospital. Of the 117 patients, 111 were included in this study. Six patients were excluded from this evaluation: 2 had macroscopically incomplete resections and 4 had inadequate muscular samples for a diagnosis at the first TUR. All of the resections were performed by experienced urologists in our departments. TUR of all visible tumors was extended to the lamina propria, and several deep muscular samples were also taken from the tumor base. The location, number, and size of bladder tumors were recorded on a cystoscopy diagram. A third TUR was recommended when T1/a/ is residual disease was observed during the second TUR. Here, we used ReTUR as a general term indicating the second and third TURs. If stage migration to muscle-invasive disease was observed at ReTUR, radical cystectomy was recommended instead of ReTUR. ReTUR was performed 2-8 weeks after the last TUR (a mean of 3.9 weeks). ReTUR consisted of wide resection of the margins and depth of each tumor site as well as complete resection and fulguration of all suspected residual tumors. Deep muscle specimens were taken, especially from the previous tumor areas and the margins. Tumors were classified according to the TNM system of the Union Internationale Contre le Cancer and were graded according to the World Health Organization classification.\(^9\)\(^10\) The definitions of NMIBC risk levels were proposed by the International Bladder Cancer Group.\(^9\)\(^10\) The definitions classify NMIBC into 3 different levels: Low- (solitary, primary low-grade Ta), intermediate- (multiple or recurrent low-grade), and high- (any T1, high-grade, or CIS) risk disease. Table 1 shows the number of patients according to risk level. Multivariate logistic regression analysis was used to determine independent variables of residual disease. Chi-square or Fisher’s exact test was used to determine whether the incidence of residual disease significantly correlates with the risk levels. A \(P\)-value of \(<0.05\) was considered significant. All tests were 2-sided. Informed consent for the treatment strategy was obtained from each patient, and approval from a local ethics committee was obtained.

**RESULTS**

The clinicopathological characteristics of the 111 patients at initial TUR are shown in Table 2. Of the 111 patients who underwent a second TUR, 57 (51%) had residual disease, as determined by histopathological analysis. Multivariate logistic regression analysis identified tumor grade (\(P = 0.006\) ) and multifocality (\(P = 0.02\) ) as the predicting factors of residual tumor [Table 3]. Residual tumor was observed in 33% (17/52) and 68% (40/59) of low- and high-grade tumors, respectively. Residual tumor was observed in 40% (21/53) and 62% (36/58) of single and multifocal tumors, respectively. Table 2 shows the number of patients and the incidence of residual disease at the second TUR at each of the risk levels. A statistically significant difference was observed by comparison of the 3 groups (\(P = 0.01\), \(\chi^2\) test). Of the 57 patients who had residual disease at the second TUR, 31 underwent a third TUR but 26 did not. Of these 26 patients, 25 were recommended a third TUR, which they declined. Of the 26 patients, 1 with stage migration to muscle-invasive disease at the second TUR underwent cystectomy. Of the 31 patients who

**Table 1: Risk levels and residual disease at the second TUR (n)**

| Level of risk | Number % (n) | Residual disease % (n) |
|--------------|--------------|------------------------|
| Low          | 16 (18)      | 17 (3/18)              |
| Intermediate | 30 (31)      | 45 (14/31)             |
| High         | 54 (62)      | 65 (40/62)             |

\(P\)-\(P\) value = 0.001 (\(\chi^2\)chi-square)

**Table 2: Patient characteristics**

| Mean age (y) (range) | 71 (56–86) |
|----------------------|------------|
| Sex distribution % (n) | Male 83 (92) |
|                       | Female 17 (19) |
| Number of tumors % (n) | Single 48 (53) |
|                       | Multifocal 52 (58) |
| Tumor diameter % (n) <3 cm | 70 (78) |
|                       | \(\leq 3\) cm 30 (33) |
| Prior recurrence rate % (n) | Primary 66 (73) |
|                       | Recurrent 34 (38) |
| T category % (n) Ta | 52 (58) |
|                       | T1 48 (53) |
| Tumor grade % (n) Low | 47 (52) |
|                       | High 53 (59) |
| CIS % (n) Negative | 88 (98) |
|                       | Positive 12 (13) |
| Level of risk Low | 16 (18) |
| Intermediate 30 (31) |
| High 54 (62) |
underwent a third TUR, 15 (48%) had residual disease, as determined by histopathological analysis. Multivariate logistic regression analysis did not identify any predicting factors for the incidence of residual tumor at the third TUR (data not shown). Table 4 shows the number of patients and the incidence of residual disease at the third TUR at each risk level. In the high-risk disease group, there was a tendency for a higher incidence of residual disease at the third TUR ($P = 0.06$, Fischer’s exact test). Of all 111 patients, 42 (38%) did not reach T0. The incidences of not reaching T0 were 17% (3/18), 23% (7/31), and 52% (32/62) in the low-, intermediate-, and high-risk groups, respectively. A statistically significant difference was observed by comparison of the 3 groups ($P = 0.01$, $\chi^2$ test).

Next, we evaluated the change in the T category by ReTUR [Figure 1]. Of the 50 patients with high-grade/T1 at the first TUR, 1 (2%), 8 (16%), 25 (50%), and 16 (32%) showed changes in the T category to T2, T1, Ta/is, and T0 at the second TUR, respectively. At the third TUR, T1 or worse disease was not found. In the 9 patients with high-grade/Ta at the first TUR, neither T2 nor T1 were found at the ReTUR. Three patients had low-grade/T1 at the first TUR, neither T2 nor T1 were found at the ReTUR. Three patients had low-grade/T1 tumors at the first TUR. All the patients reached T0 at the second TUR. Of the 49 patients with low-grade/Ta at the first TUR, 17 (35%) had residual tumors at the second TUR, and all were Ta/is. Two patients had residual tumors at the third TUR, and both were Ta/is.

No patient had major complications, such as bladder wall perforation or massive bleeding.

**DISCUSSION**

Divrik et al. showed incidences of residual tumor at the second TUR of 39% and 63% in grade 2 and 3 tumors, respectively; the risk of residual tumor directly correlated with the grade of the initial tumor.[11] Our results were essentially identical to theirs. The incidence of understaging at the first TUR was only 1%, which was relatively lower than that reported in other studies.[3,9]

We showed that the incidence of residual tumor correlates with the risk levels for NMIBC. Our results are as follows: (i) In the high-risk disease group, a high incidence of residual disease was identified even after the third TUR. (ii) In the intermediate-risk disease group, nearly complete resection was reached after the third TUR. (iii) In the low-risk disease group, nearly complete resection was reached after the second TUR.

In the high-risk disease group, ReTUR has been recommended to improve treatment results.[1] Actually, ReTUR provides more accurate staging information and potentially clears residual disease. Indeed, ReTUR is considered to improve recurrence-free survival (RFS) and progression-free survival (PFS) as compared to a single TUR.[1,4,5] Moreover, at the second TUR, absence of residual disease (T0) showed a better correlation with a low recurrence or progression rate at follow-up as compared to pTa, Tis, or T1 residual disease.[6,7] An algorithm for the treatment of high-grade/T1 bladder cancer has been proposed.[1] In the algorithm, bladder-sparing treatment by BCG induction is recommended in the case of Ta/is/0 at the second TUR. Our data showed that Ta/is residual tumor was found even after the third TUR, especially in cases of the high-risk disease. Therefore, doubt regarding whether
the presence of Ta/is residual disease after the third TUR can cause disease recurrence or progression could not be clarified completely. Actually, a higher progression rate was observed in Ta/is residual disease than in T0 residual disease at the second TUR. Hereafter, the necessity of constructing a new treatment algorithm in which a third TUR is included might arise for high-risk disease.

Intermediate-risk disease has a low potential to progress to muscle-invasive disease or distant metastasis. Therefore, a cystectomy as a result of muscle-invasive progression would be relatively rare. Instead, two or more repetitive recurrences of non-muscle-invasive disease must be prevented. An algorithm for the treatment of intermediate-risk disease has also been proposed; however, ReTUR has not been included in this algorithm. On the other hand, our data showed that residual disease was found in about 40% of patients with intermediate-risk disease after the second TUR. Therefore, the doubt that the presence of residual disease after the second TUR may cause disease recurrence or progression could not be clarified fully. Hereafter, if the incidence of repetitive recurrence is considerably high, the necessity for construction of a new treatment algorithm in which a second TUR is included might arise for intermediate-risk disease.

In low-risk disease, second TUR can be omitted because the incidence of residual tumor after the second TUR was relatively low in our study.

CONCLUSIONS

ReTUR is considered to improve RFS and PFS as compared to single TUR. However, ReTUR is not only a treatment for NMIBC, but it also plays a crucial role in providing stratification of NMIBC patients based on the results. Therefore, the end point of ReTUR should be considered in treatment algorithms. Our data will provide the essential guidance required to establish a treatment algorithm that functions as a “system” in toto.

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