A second transurethral resection could be not necessary in all high grade non-muscle-invasive bladder tumors

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Abstract

Objectives: To evaluate the rate of residual tumor, understaging and perioperative complications in patients with high grade non-muscle-invasive bladder cancer who underwent second transurethral resection (re-TUR).

Materials and methods: A retrospective review of 47 patients with high grade non-muscleinvasive bladder cancer who underwent second TUR from January 2007 to December 2009 at our institution. We evaluated the rate of residual tumor and understaging detected by re-TUR, complications, and the cost of the surgery.

Results: Twenty-two patients underwent second TUR because of the absence of muscle in the initial resection specimen (cTx). We observed residual disease in 8/47 patients (17%) and understaging in 2 cases (4.2%); in only 2 patients understaged, muscularis propria was not present in the sample of initial TUR. The other 20 cTx (90%) were cT0 in the re-TUR. We did not identify any case of cT1 understaged in the re-TUR (≥cT2). Six patients (12.6%) reported complications related with the second TUR (one urethral stricture, two patients required reintervention because of bleeding, one febrile urinary infection and two bladder perforations).

Conclusions: Our findings show that the absence of muscle in the initial resection specimen is the only risk factor for understaging. Therefore, we consider re-TUR is mandatory in these cases. On the other hand, when complete TUR has been performed and the muscularis propria is present and tumor free (cTa-T1), we consider that systematic re-TUR is not necessary and only indicated in selected patients, even more if we consider that re-TUR is not exempt from complications.

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Introducción

In 75–85% of the patients with bladder tumor, the disease is confined to the mucosa (Ta, Tis) or submucosa (T1); this is what we call non-muscle-invasive disease.¹ In this large group, high-grade non-muscle invasive bladder tumors (HG-NMIBT) have a special interest, as it has been observed that they have a high risk of recurrence and, what is more worrisome, of progression to muscle-invasive tumor (MIT).²

The initial TUR is the first step for a proper treatment of these tumors; on it depends a good specimen collection for its histologic study and clinical staging, while from it additional information of the tumor is obtained that can influence the initial treatment and prognosis: the size, location, multiplicity, grade, and the presence of associated carcinoma in situ (CIS).³ Although this is a procedure familiar to all urologists, it is not always performed correctly, and we do not often get the expected results, a fact that negatively affects the patient’s prognosis.⁴

The main drawback for the proper management of these tumors is the understaging and persistent disease after the transurethral resection (TUR),⁵ the absence of muscle in the TUR specimen being the most important understaging risk factor.⁶,⁷ The understaging in the bladder tumor involves being unaware of the presence of muscle-invasive disease and, therefore, an inadequate treatment. This situation entails often making radical surgery when the disease is not organ-confined and decreased survival.⁸

The high risk of progression together with the possibility of HG-NMIBT understaging is the argument that some authors argue to indicate immediate radical cystectomy in these patients, obtaining excellent survival rates in understaged patients (80–90%), but at the expense of a high rate of overtreatment.⁹,¹⁰ By contrast, the good response that these tumors have shown to intravesical BCG and the ability of maintenance therapies to reduce the risk of progression has made making a conservative treatment followed by a close follow-up the current mainstream trend.¹¹ Therefore, a good clinical staging of these patients is essential to avoid unnecessary risks. In order to improve the clinical staging and recurrence-free time,¹²,¹³ for some years, most international guidelines recommend performing a re-TUR before 4–6 weeks in all high-grade non-muscle invasive bladder tumors.¹⁴

Objetivo

The main objective of our study was to review the rate of understaging and residual tumor (persistence) in the patients with HG-NMIBT who underwent re-TUR, to see where this second TUR is really necessary. In turn, we also analyzed the costs and the immediate and short-term complications of this restaging TUR.

Materiales y métodos

Once the study was approved by the Clinical Research Ethics Committee of our center, we retrospectively reviewed the medical records of the patients undergoing a re-TUR between January 2007 and December 2009 in our oncological urology unit. In each patient, we assessed the anthropometric characteristics, the time between the initial TUR and the re-TUR, and the pathological anatomy of both surgeries. In the case of the re-TUR, we also analyzed the surgical time, the cystoscopic findings, the technique used, the
hospital stay, the approximate cost, and the perioperative complications.

In this period, the re-TUR was not systematically performed in our center. It was only indicated in HG-NMIBT with absence of muscularis propria (cT) and in very specific cases in which, despite an apparently complete TUR and presence of muscle, due to its size-extension, location, multiplicity, solid appearance, or understaging was considered the high-risk tumor for residual disease.

Initial TUR was defined as the surgery that reported the pathological anatomy that caused the re-TUR, regardless of whether it was a primary or recurrent tumor. In all cases, the re-TUR was performed before the 8 weeks after the initial TUR and before carrying out any intravesical treatment, in all cases using the same technique. After placing the patient in lithotomy position and under general or locoregional anesthesia, we performed exploratory cystoscopy with 70° optic carefully reviewing all the bladder walls in search of residual lesions and paying particular attention to resected areas. We described in all cases the previously resected areas, using 3 categories (suspected macroscopic tumor, slough, or scar). Once the cystoscopy was performed, using a resector with single (24 Fr) or double sheath (26 Fr), the previously resected areas were resected as well as any residual or suspicious lesion. In the cases of multiple initial tumors in which the information of the surgical blade did not let us identify the location of the HG-NMIBT which had justified the re-TUR, we resected all the scars that seemed recent. In all cases, the resection was with monopolar current and a broad and deep resection was performed to ensure margins and get muscularis propria. In 17 cases (36%), we took a sample after the resection of the tumor with cold forceps. After the procedure, Dufour 22 Fr (3-way) catheter was left with continuous bladder irrigation. We considered perioperative complication that directly related to the re-TUR and that occurred from the date of admission until 3 months later.

To analyze the data, we used the SPSS version 17.0 statistical programme. We performed a descriptive analysis of the qualitative variables of the study and calculated the mean, median, and standard deviation for the quantitative variables.

Results

Epidemiology-clinico-pathological

Between January 2007 and December 2009, 47 patients underwent re-TUR, representing 26.4% of the total of 178 patients who in the same period showed HG-NMIBT in the initial TUR. Higher incidence of men than of women (83 vs. 17%) and with a median age of 62 years (44–81). 43% of the patients were recurrent and 26% had received prior intravesical treatment, none of them between the initial TUR and the re-TUR. In all cases, the re-TUR was performed before the 8 weeks after the initial TUR, with a median of 43 days (18–55). In 22/47 cases (46%), we went for the re-TUR because of absence of muscularis propria (cT) in the initial TUR, the remaining cases due to HG-NMIBT (3 TTa, 8 T1, 2 T1a, 5 T1b, 7 T1c). In 63.6% of the AGT1s, the anatomicopathologist had achieved understaging according to the involvement of the muscularis mucosae.

Table 1  Correlation between the findings in the explorer cystoscopy during the re-TUR and the final pathological anatomy.

<table>
<thead>
<tr>
<th>Macroscopic finding in the re-TUR appearance/n/total (percentage)</th>
<th>Re-TUR pathological anatomy (percentage of residual disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slough = 15/47 (31.9%)</td>
<td>13 T0/2 T1 (13.3%)</td>
</tr>
<tr>
<td>Scar = 29/47 (61.7%)</td>
<td>22 T0/1 Ta/5 T1/1 T2 (24.3%)</td>
</tr>
<tr>
<td>Gross tumor = 3/47 (6.4%)</td>
<td>2 T0/1 T2 (33.3%)</td>
</tr>
</tbody>
</table>

The most common cystoscopy finding in the re-TUR was a scar area (61.7%), followed by slough (31.9%), and only in 3/47 cases (6.4%) suspected gross tumor. There was no correlation between the macroscopic findings and the pathology report (Table 1).

In 21.2% of the patients (10/47), the re-TUR showed residual disease in the bladder. In 8 cases (17.1%), it was persistence (<cT2), and in 2 (4.2%) understaging (≥cT2). In 8/25 patients (32%) with muscularis propria in the sample of the initial TUR, we found residual disease in the re-TUR, but never muscle-invasive disease. In the only 2 patients understaged, the indication for re-TUR had been due to the absence of muscularis propria in the sample of the initial TUR (cT) (Table 2).

In all the re-TUR samples, we obtained muscularis propria, and fat in some cases, the incidence of the latter being higher in the cases in which biopsy was taken with cold clamp (23.3 vs. 64.7%; p < 0.05 (Table 3).

Costs and complications of the transurethral re-resection

The average time of the patient in the operating room (anesthesia + surgery) for the re-TUR was 74 min (48–115). Most patients were discharged within 48 h after the surgery without urinary catheter, the median hospital stay, after the re-TUR, being 2.3 days with a range 2–9. Taking into account that the hospital stay, surgical material used, the processing, the study sample, and the postoperative management are similar to a first TUR, we can say that the economic cost of a re-TUR in our center is the same as that of a conventional TUR due to bladder tumor.

Six patients (12.6%) had secondary complications or related to the re-TUR. Two of them had to be reoperated endoscopically for bleeding. In another 2 cases, there was bladder perforation (one extraperitoneal, one intraperitoneal) that were managed conservatively. One patient had a febrile urinary tract infection requiring intravenous antibiotic treatment and prolonged his hospital stay. We observed a case of stenosis at the level of the bulbar urethra in the cystoscopic control at 3 months after the re-TUR, which was treated by internal urethrotomy. Only the 2 patients who had bladder perforation were discharged with a urinary catheter. In one of them it was removed after 7 days without complications and in the other case it had to be replaced after removing it, due to persistent perforation, finally removing it at 2 weeks under radiological control (Table 4).
Table 2  Anatomopathological correlation between the initial TUR and the re-TUR.

<table>
<thead>
<tr>
<th>cT initial TUR</th>
<th>cT0 n (%)</th>
<th>cT ≤ 2 n (%)</th>
<th>cT ≥ 2 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 T1 (46.8)</td>
<td>20 (91)</td>
<td>0 (0)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>3 Ta (6.3)</td>
<td>2 (66.6)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>8 T1 (17.1)</td>
<td>2 (25)</td>
<td>6 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2 T1a (4.3)</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5 T1b (10.6)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7 T1c (14.9)</td>
<td>6 (85.8)</td>
<td>1 (14.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total: 47 cases</td>
<td>37 cT0 (78.7)</td>
<td>8 persistence-recurrence (17.1)</td>
<td>2 understaging (4.2)</td>
</tr>
</tbody>
</table>

Table 3  Obtaining muscularis propria and fat depending on the technique for sample collection of the surgical site in the re-TUR.

<table>
<thead>
<tr>
<th>Re-TUR technique n (%)</th>
<th>Muscularis propria n (%)</th>
<th>Fat n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only TUR: 30 (63.8)</td>
<td>30 (100)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>TUR + cold clamps: 17 (21.2)</td>
<td>17 (100)</td>
<td>11 (64.7)</td>
</tr>
</tbody>
</table>

Table 4  Complications secondary to the re-TUR according to the revised Clavien-Dindo classification, 2004.

1. Bleeding-hematuria  
2. Bleeding-hematuria  
3. Bladder perforation  
4. Bladder perforation  
5. Urethral stenosis  
6. Febrile UTI  

<table>
<thead>
<tr>
<th>Grade</th>
<th>A</th>
</tr>
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UTI: urinary tract infection.

Discussion

The HG-NMIBTs have a high risk of recurrence and a moderate risk of progression to muscle-invasive disease. The TUR + intravesical BCG with maintenance therapy has proven to be an effective conservative treatment. The most widespread attitude, and the one that is currently recommended, is a correct clinical staging, through a good TUR and a close follow-up with cystoscopic controls and cytology every 3 months, especially, in the first 2 years for the early diagnosis of recurrence and, especially, of the progression, recommending the initiation radical surgery only in selected cases of HG-NMIBT presenting associated risk factors.

The initial TUR plays a major role in preventing recurrence-persistence and understaging. Brausi et al. in their analysis of 2410 patients from 7 different EORTC studies observed substantial differences between the early recurrence rates, ranging from 0 to 46%. In the multivariate analysis, they showed that these differences were not due to the variations in the nature of the tumor, but to the quality of the TUR performed by the different surgeons included in the study, the absence of muscularis propria in the specimen of the TUR being the main risk factor of understaging, a fact already shown in other studies. The same author recently demonstrated, in another study, that by improving the initial TUR with the routine use of a camera, the presence of an associate in the operating room, and sessions to teach how to resect, the early recurrence rate can be reduced from 28 to 16% and the presence of muscularis propria can be increased in the samples from 50 to 80%, in the patients operated on by residents. Although the TUR for bladder tumor is a routine procedure, and that has not changed over the past decades, the quality criteria have never been clearly defined. Validated criteria will have to be implemented to be able to establish the minimum requirements and have a quality control: sample rate without evidence of muscularis propria according to tumor grade, residual tumor rate, and understaging, recurrence, and progression at 3 months.

The published series, of re-TUR and early radical cystectomy in patients after the resection of a HG-NMIBT, have shown a high rate of persistence between 33 and 53% and of understaging between 4 and 25%, in some cases reaching 40%. To this we must add the fact that Grimm et al. found that in 81% of the cases, the residual disease was at the site of the initial TUR. In these high percentages of residual disease are based the guidelines and the international experts to recommend making a re-TUR in all the HG-NMIBT cases being: AG or T1 or Tx in absence of muscularis (excluding low-grade tumors).

In our series, the rate of persistence was 17.1% and the understaging one 4.2%. Only in 2 cases where there was no muscularis propria in the initial TUR, the re-TUR revealed muscle-invasive disease, which means that none of the 22 T1s was understaged. 17.1% of persistence may seem a high figure, but we must remember that it is not all the resected HG-NMIBTs, but a highly selected group that, because of their characteristics of location, size, appearance, or understaging, we considered at high-risk of residual disease. This previous selection makes the excellent result which represents only 4.2% of understaging have even more value. It should be noted that none of the 7 T1cs or 5 T1bss presented understaging. This low rate is validated internally, as it coincides with our rate of early progression in T1 bladder tumors published a few years ago.

We attribute this low incidence of understaging, comparable to the best results published so far, to a thorough initial TUR where wide margins and depth samples are obtained separately. Conducting a re-TUR to 22 cases for lack of muscle is only 12% of the total HG-NMIBTs resected during the same period in our center.

In the current literature, between 30 and 50% of the samples that are submitted for study do not have muscularis propria, and they are the cases that once the re-TUR is
performed show the highest percentage of understaging. That is why the absence of muscularis is the major risk factor of understaging, and there is no doubt that in its absence in patients with high-grade tumor it must always go to a re-TUR.

But there is greater controversy over what to do with the AGTas and the AGTIs where the muscularis is present and free of tumor. Regarding the AGTas, some authors have reported a low capacity of understaging and a progression of the AGTas lower than 10%, which would advise against a re-TUR when the initial TUR was complete; others indicate a low incidence of AGT tumors, suggesting that all the AG tumors should be considered as minimum T1 for their aggressive potential. To all this we must add the lack of consensus and variability among pathologists, as some studies have shown, when labeling the tumors as cTa or cT1. This difficulty can be increased by excessive cauterizing the tumor in the tumor bed at the time of the TUR.

When analyzing the AGT1 tumors, the overall progression rate is between 7 and 40%, which shows a great heterogeneity of behavior in this group. Since in 1990 Yones et al. described a subclassification of the TIs, using the muscularis mucosa as a reference, other groups have published their results with AGT1 tumors, confirming a trend toward greater progression and decreased survival at 5 years the deeper the infiltration of the lamina propria, being able to establish a prognosis in risk groups. The understaging requires learning, but, in some cases, because of the nature of the sample (no muscularis mucosa or artifact in some areas), it is not possible. However, when achieved, we have observed that it influences the prognosis and also the possibility of understaging. Orsola et al. noted that the possibility of residual disease in the cT1as was very low and in the cT1b it depended on other risk factors such as the size and the association with CIS, concluding that in all these cases it is probably not necessary to perform a re-TUR. In our series, none of the 7 cT1Cs or 5 cT1bs presented understaging, confirming the importance of a proper initial TUR.

The re-TUR implies a new surgery that requires general or locoregional anesthesia and like any surgical procedure is not free from complications. Furthermore, it is not an easy technique because we must resect a bladder wall of lower thickness due to the recent TUR and the macroscopic findings are not usually correlated with the anatomopathological ones. Articles on the complications of the TUR for bladder tumor have been published, but very few have analyzed, as in our case, the secondary complications to the re-TUR. The incidence of complications in a TUR for bladder tumor varies between 5.7 and 9.9%, bleeding, bladder perforation, and urinary tract infections being the most frequent. Our complication rate, in the patients undergoing re-TUR, was 12.6%. The fact of a patient undergoing a new surgery in a short period of time, lower bladder wall thickness at higher risk of perforation, and being a recent carrier of bladder catheter are factors that we believe influence this increase of complications. To this we must add the economic cost; the restaging is a cost for the health system and/or the patient. In a universal healthcare system like ours, different from the one in many other countries, with limited resources, oversaturating the system performing re-TUR to all the HG-NMIBTs means increasing waiting lists.

One of the advantages of the re-TUR is that the bladder is checked at 4–6 weeks, being able to find residual tumor, which could be misinterpreted at cystoscopy at 3 months as an early relapse, and if this is high-grade, indicate a radical treatment, when, in fact, it must be seen as a persistence of the disease. One limitation of our study is the fact that the strict criteria of re-TUR listed in the European guidelines have not been followed in all the patients; we have been more selective, choosing mostly Tx patients and those at high risk of residual disease. Nevertheless, these are the cases in which the worst understaging results are published.

Another limitation of our study is the lack of follow-up of the patients undergoing re-TUR in order to know the rates of early recurrence and progression. So is the fact that few AGTA patients have been included, which does not make it possible to assess the actual need to perform re-TUR in these cases. However, according to the results obtained in the T1 cases in our series, with no case of understaging it enables to estimate that in Ta it would also be minimal. The purpose of our study was to know our rate of persistence and understaging and also, a fact rarely mentioned in other articles, to review the complications of a second TUR in these patients.

Conclusions
The main requirement for good results (low persistence and low understaging) is a meticulous and systematic first TUR that must include muscularis propria. In our experience, the lack of muscularis in the specimen of the TUR is the only risk factor of understaging. In these cases, the re-TUR is mandatory and it must be carried out in a systematic way, with wide resection of the scar area to obtain muscularis propria; and in the case of high risk of perforation cold clamps can be used after a first cut with loop to obtain the biopsy of the surgical bed base.

In the cases where the initial TUR was complete and the muscularis propria is free of tumor (cTa, cT1), we believe that the systematic re-TUR is more arguable, and more, as it is not free from complications, economic cost, and socio-health implications. Therefore, we would only recommend it in very specific cases where because of the tumor characteristics (size, multiplicity, location), the risk of residual disease is high.

Conflict of interest
The authors declare that they have no conflict of interest.

References


