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The importance of second-look transurethral resection for superficial bladder cancer

Ehab El-Barky1, Ahmed Sebaey1, Magdy Eltabey1, Ahmed Aboutaleb1, Sundus Hussein2 and Elijah O Kehinde3

Abstract
Objectives: The objective of this article is to evaluate the importance of a second-look transurethral resection of bladder tumour (TURBT) in patients with newly diagnosed superficial bladder cancer and its impact on subsequent treatment plan.

Methods: We carried out a prospective study on 100 consecutive patients with newly diagnosed superficial bladder cancer in whom a second-look TURBT was performed two to six weeks after initial resection. We assessed the incidence of residual tumours, sufficiency of initial pathological staging and grading. We also assessed the need for re-staging and grading after the second-look TURBT.

Results: Forty-five out of 75 patients (60%) who underwent second-look TURBT had no tumours, 18 (24%) had visible residual tumours and 12 (16%) had microscopic residual tumours. Of the 30 (40%) patients with residual tumours, five had pTa, three had carcinoma in situ (CIS), 12 had pT1, and 10 had pT2 disease. Upstaging and change of treatment plan as a result of the second-look TURBT were necessary in 18/75 (24%) cases, of which 10 cases (13%) underwent radical cystectomy for muscle-invasive tumours.

Conclusions: A second cystoscopy with or without TURBT is recommended two to six weeks after initial resection of stage Ta and T1 bladder tumours in patients with high-grade transitional carcinoma of the bladder or in patients with multiple tumours. Second-look cystoscopy in this category of patients may reveal the need for early change of treatment plan in about 25% of patients.

Keywords
Bladder cancer, second look, transurethral resection, treatment

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Introduction
Transurethral resection of bladder tumour (TURBT) remains the gold standard for the diagnosis and treatment of superficial bladder cancer, urothelial carcinoma (UC) without invasion (pTa) and with lamina propria invasion (stage T1). However, there is a 50%–70% risk of tumour recurrence, particularly during the first year.1 This might be related to many factors or theories. Of these the most accepted theory is the recurrence likely due to the persistence or re-growth of residual tumour that has not been
adequately resected at initial TURBT. Other related factors that result in the occurrence of new tumours are the progression of a microscopic lesion to a macroscopic one, or the growth of circulating tumour cells at the time of initial TURBT, and/or the aggressive biology of the resected tumour. To be very effective, white light cystoscopy with TURBT should be combined with fluorescence cystoscopy and narrow-band imaging technology as it allows for a higher detection rate and high quality of resection.

Furthermore, under-staging due to incomplete resection of initial tumour has an impact on the progression rate of 15%–25% of superficial bladder cancers. Also the muscle layer may be missed during the initial resection so its presence in the second TURBT can change the line of treatment. Consequently, many urologists advocate a second-look check cystoscopy plus/minus TURBT two to six weeks after the initial resection of superficial bladder tumours with the aim of improving the treatment outcome. However, the frequency of residual tumour after initial TURBT and the ability of second-look TURBT to control for complete resection have been widely neglected by the urological community. The objective of this prospective study was to evaluate the potential benefits of second-look TURBT in patients with newly diagnosed superficial bladder cancer and its impact on subsequent treatment policy.

Methods

From September 2009 to December 2012 a total of 100 consecutive patients with newly diagnosed superficial bladder cancer were enrolled in this prospective study for second-look cystoscopy with or without TURBT. The total number of patients with residual tumours and adequacy of clinical and pathological staging for subsequent treatment strategy at our urology departments were evaluated. The criteria of selecting patients after first TURBT were superficial papillary urothelial carcinoma including pTa with multiple tumour growths and pT1 tumours, provided deep muscle was sampled in the initial biopsy. The first TURBT was performed in a standardised manner where all visible tumours, tumour base and margins were resected and labelled separately. All tumours were documented on a bladder map by the surgeon immediately after the operation. The same surgeon performed the second-look cystoscopy with or without TURBT two to six weeks following the initial resection on patients histologically proven to have superficial bladder cancer. All the surgeons involved were experienced urologists. That is, the resectionists all had postgraduate residency training and qualifications in urology and were either senior registrar (SR) or consultant grade. Each had more than 10 years’ experience at SR or consultant level and had major interest in uro-oncology. Tumours were graded and staged according to 2004 World Health Organization (WHO)/International Society of Urologic Pathology (ISUP) classification and TNM system of Union of International Cancer Control (UICC). Patients with multiple tumours at first cystoscopy received intravesical course of mitomycin C chemotherapy before the second-look cystoscopy and/or TURBT. Patients with solitary lesions were not given any intravesical chemotherapy before second-look cystoscopy. Patients with carcinoma in situ (CIS) received intravesical Bacillus Calmette-Guérin (BCG) therapy for about a year.

Informed written consent for the treatment strategy was obtained from each patient according to the result of first TURBT. Formal approval for the study was not obtained from the ethics committee as the study did not change the treatment plan of the patients based on inclusion in this study. However, in carrying out the study, the principles of the Helsinki Declaration were followed.

The results including the presence of residual tumour and its staging were analysed using the Statistical Package for Social Sciences (SPSS) software.

Results

Of the 100 patients studied, 25 patients were excluded, 14 of whom were excluded because of lack of deep muscle sampling in the first TURBT specimens while 11 were excluded because they had a single focus of small low-grade pTa papillary UC and were considered low-risk superficial bladder cancer. The demographic data along with tumour characteristic of the 75 patients enrolled in the study are described in Tables 1 and 2 and Figure 1. The pathological findings of the 75 patients who underwent second TURBT are described in Tables 3 and 4 and Figure 1. The second TURBT was performed without any major morbidity for all the 75 patients. Minor complications encountered included prolonged bleeding in 12 cases (16%) and epididymitis in six cases (8%). These minor complications were successfully managed conservatively. Upstaging occurred in 18 cases (24%), which represented about two-thirds of all residual tumours detected by second TURBT. No upgrading occurred in any of the patients. Consequently, the treatment strategy was changed from conservative management to intravesical chemotherapy in eight cases (11%) of pTa (Figure 2) to pT1 (Figure 3) and to radical cystectomy in 10 cases (13%) of pT1 to pT2 (Figure 4). This meant that the treatment of 18 (24%) of our patients who were subjected to second TURBT was changed based on the finding of the second TURBT. Overall, low-grade transitional cell carcinoma (TCC) (Figure 5(a)) was found in 35 cases (35%), whereas high-grade TCC (Figure 5(b)) was found in 65 cases (65%). As shown in Figure 1 and Tables 2 to 4, the number of patients with CIS was only three in this series of patients. They had small lesions and responded to intravesical BCG therapy. No recurrence has occurred in the three patients after a mean follow-up of about 39 months. The three patients had primary CIS; that is, no patients had concurrent CIS and pT1 tumours.
Comprehensive resection of superficial bladder cancer including tumour base and margins are highly recommended in order to prevent local recurrences and avoid histological underestimation of resected tumour. Hence it has been shown that the quality of TURBT has a major impact on tumour recurrence and progression. Furthermore, inadequate resection of tumour base and margins has an estimated recurrence rate of 70%. In order to ensure complete resection, the so-called ‘safety resection’ is recommended.

Several prospective studies have documented the presence of residual tumours after the second TURBT. In most studies, the percentage of recurrences varies from 33% to 43%, which is comparable to the recurrence rate of 40% that we found in this study. However, Süer et al. in their study found that residual tumour was demonstrated in 57 out of 132 patients (43.2%). They reported that the time elapsed between the first and second TURBT was significantly shorter in patients without residual tumours compared to patients with residual tumour at second TURBT, and this duration is the most important parameter for residual tumour detection. However, the retrospective studies reported by Herr 1999 and Brauers et al. showed residual tumours recurrence rates of 64% and 53%, respectively. These retrospective studies have been criticised because they did not distinguish between incomplete and complete initial TURBT, and the frequency of recurrences may not reflect the actual number of patients with recurrence.

The grade and stage of the tumour may influence the rate of detection of residual tumour in second TURBT. Consequently, 37% of residual tumours are in patients with pTa disease who have been followed two to four weeks after initial TURBT and this rose to 43% in patients with pT1 tumours. Similar observations have been made for multiple tumours with higher-grade morphology. In this study, the incidence of pTa and pT1 bladder cancer cases that had residual tumours during second-look TURBT was 27% and 40%, respectively.

The majority of residual tumours on second TURBT were located at the site of initial TURBT and that was noted in two-thirds of our patients. This finding was also observed by Grimm et al., who concluded that the tumour was left behind despite optimal initial resection. In contrast to our findings, Lazica et al. (2013) reported that of 87 patients who underwent a second-look TURBT, tumour was found in 36 (41.4%); tumour was detected at the primary site in 35.9%, at other locations in 22.3% and at both in 38.9%. However, histology revealed pTa low-grade tumour in 13 (14.9%), pTa high-grade tumour in 15 (17.3%) and it was concluded that high-grade tumours show a higher rate of persistent tumour at second resection, most of them located at the primary site, hence it was recommended that patients with a high-grade tumour should undergo a second-look TURBT. Furthermore, Klän et al. reported a 40% correlation of initial cystoscopic and histological findings with the second TURBT.

Under-sampling of deep muscle in initial TURBT specimen results in under-staging of the first specimen. Gaya et al., in their study, found that the absence of muscle in the initial resection is the only factor for under-staging and they considered re-TURBT as mandatory in these cases. On the other hand, when complete TURBT has been performed and the muscularis propria is present and tumour free, they considered that systematic re-TURBT is not mandatory. Herr (1999) demonstrated 40% muscle invasion (pT2) on second TURBT of patients.

### Table 1. Characteristics of patients with bladder tumours.

<table>
<thead>
<tr>
<th>Total number of patient</th>
<th>$n = 100$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>81 (81%)</td>
</tr>
<tr>
<td>• Female</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>• &lt;50</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>• 50–60</td>
<td>38 (38%)</td>
</tr>
<tr>
<td>• 60–70</td>
<td>46 (46%)</td>
</tr>
<tr>
<td>• &gt;70</td>
<td>11 (11%)</td>
</tr>
</tbody>
</table>

### Table 2. Tumor characteristics at first TURBT.

<table>
<thead>
<tr>
<th>Pathological findings</th>
<th>$n = 100$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumours</td>
<td></td>
</tr>
<tr>
<td>• Solitary</td>
<td>61 (61%)</td>
</tr>
<tr>
<td>• Multiple (&gt;1)</td>
<td>39 (39%)</td>
</tr>
<tr>
<td>Tumour stage:</td>
<td></td>
</tr>
<tr>
<td>- pTa</td>
<td>34 (34%)</td>
</tr>
<tr>
<td>- Tis</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>- pT1</td>
<td>63 (63%)</td>
</tr>
<tr>
<td>Tumour grade</td>
<td></td>
</tr>
<tr>
<td>- Low-grade TCC</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>- High-grade TCC</td>
<td>65 (65%)</td>
</tr>
</tbody>
</table>

TURBT: transurethral resection of bladder tumour; TCC: transitional cell carcinoma.

### Discussion

Comprehensive resection of superficial bladder cancer including tumour base and margins are highly recommended in order to prevent local recurrences and avoid histological underestimation of resected tumour. Hence it has been shown that the quality of TURBT has a major impact on tumour recurrence and progression. Furthermore, inadequate resection of tumour base and margins has an estimated recurrence rate of 70%. In order to ensure complete resection, the so-called ‘safety resection’ is recommended.

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The majority of residual tumours on second TURBT were located at the site of initial TURBT and that was noted in two-thirds of our patients. This finding was also observed by Grimm et al., who concluded that the tumour was left behind despite optimal initial resection. In contrast to our findings, Lazica et al. (2013) reported that of 87 patients who underwent a second-look TURBT, tumour was found in 36 (41.4%); tumour was detected at the primary site in 35.9%, at other locations in 22.3% and at both in 38.9%. However, histology revealed pTa low-grade tumour in 13 (14.9%), pTa high-grade tumour in 15 (17.3%) and it was concluded that high-grade tumours show a higher rate of persistent tumour at second resection, most of them located at the primary site, hence it was recommended that patients with a high-grade tumour should undergo a second-look TURBT. Furthermore, Klän et al. reported a 40% correlation of initial cystoscopic and histological findings with the second TURBT.

Under-sampling of deep muscle in initial TURBT specimen results in under-staging of the first specimen. Gaya et al., in their study, found that the absence of muscle in the initial resection is the only factor for under-staging and they considered re-TURBT as mandatory in these cases. On the other hand, when complete TURBT has been performed and the muscularis propria is present and tumour free, they considered that systematic re-TURBT is not mandatory. Herr (1999) demonstrated 40% muscle invasion (pT2) on second TURBT of patients.
with initial T1 tumours in which deep muscle is undersampled. On the other hand, only 14% of pT2 tumours are diagnosed on second TURBT when smooth muscle was present in an initial TURBT specimen. Similarly our data demonstrated 13% pT2 tumours on second TURBT. Furthermore, it has been reported that in the second TURBT, a shift in the T1 to T2 stage occurred in 24% of cases, while in our series, this stage shift occurred in only 13% of cases from pT1 to pT2 stage, and in 11% of cases from pTa to pT1 stage. These had further impact on changing the treatment strategy of these patients who represented 24% of our second TURBT series. A recent study included re-TURBT in 1312 patients with papillary tumours. The risk of tumour upstaging in muscle-invasive disease by re-TURBT was 0% in Ta low-grade tumours, 5% in Ta high-grade tumours and 30% in T1 tumours. These data indicate that the risk of progression is higher the higher the grade and stage of disease at initial resection.

The role of second TURBT two to six weeks after initial diagnosis of superficial bladder cancer has been a subject of controversy among urologists, who have been divided into two main groups. One group believe residual tumour is rare and found in only 7% to 11%, and when present it has only a 1.5% risk of progression over a period of three months until the time of first-check cystoscopy. In contrast, other investigators emphasised the significance of second TURBT in separating between true tumour recurrence and residual tumour, which has been incorrectly classified as tumour recurrence. Thus, the most important prognostic factor in superficial bladder tumour is tumour recurrence at three months after initial TURBT.24,25

Table 3. Tumour characteristics at second TURBT.

<table>
<thead>
<tr>
<th>Total number of second TURBT</th>
<th>n = 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent residual tumours</td>
<td>45 (60%)</td>
</tr>
<tr>
<td>Total residual tumours:</td>
<td>30 (40%)</td>
</tr>
<tr>
<td>- Macroscopic residual tumours</td>
<td>18 (24%)</td>
</tr>
<tr>
<td>- Microscopic residual tumours</td>
<td>12 (16%)</td>
</tr>
</tbody>
</table>

TURBT: transurethral resection of bladder tumour.

Table 4. Pathological features of residual tumours.

<table>
<thead>
<tr>
<th>Total number of residual tumours</th>
<th>n = 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour sites</td>
<td></td>
</tr>
<tr>
<td>- Primary tumour site</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>- Another tumour site</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>- Both sites</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Tumor stage:</td>
<td></td>
</tr>
<tr>
<td>- pTa</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>- Tis</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>- pT1</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>- pT2</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Tumour grade:</td>
<td></td>
</tr>
<tr>
<td>- Low-grade TCC</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>- High-grade TCC</td>
<td>18 (60%)</td>
</tr>
</tbody>
</table>

TURBT: transurethral resection of bladder tumour; TCC: transitional cell carcinoma.
In addition, the five-year tumour recurrence-free rate is significantly improved in patients with second-look TURBT (63%) in comparison to 40% in whom only TURBT was performed. Re-TURBT can affect tumour staging and hence improve recurrence-free survival. Re-TURBT two to six weeks after initial resection is recommended in any patient with a pT1 or high-grade tumour, when the specimen obtained on initial TURBT contains no deep muscle as reported by the pathologist and when the tumour is extensive and multiple and the urologist is uncertain that the initial resection was complete, particularly in extensive and multiple tumours. It is evident that the goals of the second TURBT are to detect residual tumours, to provide a tumour-free repeat recurrence, to reduce tumour burden before adjuvant treatment, and to provide appropriate management plans for individual patients in cases of upstaging or upgrading. Limitations of this study include the relatively small number of patients studied and the short period of follow-up.

In conclusion, our findings in this study support the notion that second-look cystoscopy with or without TURBT is a prerequisite in patients with superficial bladder cancers except for patients with solitary, small low-grade pTa tumours. It is particularly highly recommended for patients with extensive and multiple tumours at the first TURBT. This is because it identifies residual tumours and separates those from true recurrences which are often detected three months after the first cystoscopy and TURBT. In addition, the procedure enables an early change in treatment policy in a significant percentage of patients in whom tumours were under-graded or under-staged. However, further studies are required to confirm our results.
Conflicting interests
None declared.

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Ethical Approval
Not applicable.

Guarantor
EOK.

Contributorship
EE and EOK researched literature, conceived the study, were the operating surgeons and carried out data analysis. AS, ME and AA were involved in protocol development, patient recruitment and were also operating surgeons. SH carried out all histopathological examinations of specimens. EE wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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None.

References

Figure 5(b). Microscopic picture of high-grade bladder tumours.


**List of abbreviations used**