Repeat Transurethral Resection in Non–muscle-invasive Bladder Cancer: A Systematic Review

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Article info

Article history:
Accepted February 13, 2018

Associate Editor:
James Catto

Keywords:
Bladder Cancer Recurrence Progression Detrusor Muscle Re-resection Upstaging

Abstract

Context: Initial treatment for most bladder cancers (BCs) involves transurethral resection (TUR) or tumours. Often more cancer is found after the initial treatment in around half of patients, requiring a second resection. Repeat transurethral resection (reTUR) is recommended for high-risk, non-muscle-invasive bladder cancer (NMIBC) to remove any residual disease and improve cancer outcomes.

Objective: To systematically review the practice and therapeutic benefit of an early reTUR for high-risk NMIBC.

Evidence acquisition: A systematic review of original articles was performed using PubMed/ Medline and Web of Science databases in December 2016 (initial) and October 2017 (final). We searched the references of included papers.

Evidence synthesis: We screened 15 209 manuscripts and selected 31 detailing 8409 persons with high-grade Ta and T1BC for inclusion. Detrusor muscle was found at initial TUR histology in 30–100% of cases. Residual tumour at reTUR was found in 17–67% of patients following Ta and in 20–71% following T1 cancer. Most residual tumours (36–86%) were found at the original resection site. Upstaging occurred in 0–8% (Ta to ≥T1) and 0–32% (T1 to ≥T2) of cases. Conflicting data report the impact of reTUR on subsequent recurrence and cancer-specific mortality. Recurrence for Ta was 16% in the reTUR group versus 58% in the non-reTUR group. For T1, recurrence ranged from 18% to 56%, but no clear trend was identified between reTUR and control. No clear relationship between reTUR and progression was found for Ta, although for T1 rates were higher in the non-reTUR group in series with control populations (5/6 studies). Overall mortality was slightly reduced in the reTUR group in two studies with controls (22–30% vs 26–36% [no reTUR]).

Conclusions: Residual tumour is common after TUR for high-risk NMIBC. The reTUR helps in the diagnosis of this residual cancer and may improve outcomes for cancers initially staged as T1. Patient summary: Some bladder cancers (BCs) are aggressive but confined to the bladder surface. Initial treatment includes endoscopic resection. More cancer is found after the initial treatment in approximately half of patients. In the aggressive but confined group of BC, a second resection, a few weeks after the first, may help find this residual cancer and improve outcomes, although the evidence quality for this is weak.

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https://doi.org/10.1016/j.eururo.2018.02.014
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1. Introduction

Bladder cancer (BC) is the fourth commonest male malignancy worldwide [1] and one of the most expensive cancers to manage [2]. Initial treatment for most BCs involves transurethral resection (TUR) of tumours to remove all possible tumours and obtain material for histological examination. Following resection, patients are started on treatment pathways that reflect the nature and potential of their disease (typically determined by histological grade and tumour-node-metastasis stage). Treatment for primary high-risk non–muscle-invasive BCs (NMIBC), such as high-grade (HG) or grade 3, Ta, or T1 cancers, often commences with a repeat TUR (reTUR) of bladder tumours within 2–6 wk of initial resection [3]. A reTUR is recommended by the European Association of Urology (EAU) guidelines if the first resection was incomplete, if detrusor muscle was not present in the initial specimen, if the clinical suspicion is of worse disease than reported by the pathologist, or to ensure the absence of muscle invasion [4]. These scenarios are in consensus across the major international guideline panels (Table 1). The reTUR should remove any residual disease and resample the initial resection area. Residual tumour at reTUR has been described in up to 75% of Ta and T1 patients [5,6]. Even more profound is the rate of upstaging from Ta to >T1 or T1 to >T2 at reTUR, which has been observed in up to 28% of initial T1 [5,7] and 9.5% of initial Ta-HG tumours [8], respectively. This is even more striking in cases where muscularis propria is missing in the first transurethral resection of bladder tumour (TURBT) specimens; here, upstaging to muscle-invasive disease has been reported in up to 45% of T1 patients undergoing a reTUR [9]. The reTUR may also have a therapeutic role. It may increase recurrence-free (RFS) [10,11], progression-free (PFS) [10], cancer-specific (CSS), and overall (OS) survival [10] after intravesical Bacillus Calmette-Guérin (BCG) immunotherapy and provide valuable prognostic information [8].

However, recent studies have questioned the benefit of reTUR. These reports, including patients with T1BC treated with/without BCG (according to study), did not show any improvement in PFS and CSS of patients undergoing a reTUR when detrusor muscle was included in the primary TURBT [12,13]. These authors suggest that reTUR may not be necessary for this group of patients, if muscle was present in the primary TURBT. The aim of this systematic review (SR) was two-fold. Patient Intervention Comparator Outcome (PICO) 1 was to evaluate the surgical practice of reTUR (including the presence of detrusor muscle in the primary resection), percentage of residual tumours found at reTUR (same site, different site, any site), and upstaging of disease pathology at reTUR. PICO 2 was to assess the therapeutic benefit of reTUR regarding disease recurrence, progression, OS, and CSS.

2. Evidence acquisition

2.1. Systematic review

We searched PubMed/Medline and Web of Science in December 2016 and again in October 2017, for all original articles, with no language or time limits applied. We used string terms “re”, “second”, “restaging”, “repeat”, “early” AND “transurethral resection”, “TUR”, “TURB”, “reTUR” AND “bladder” AND “cancer”, “tumor”, “tumour”, “neoplasm”, and “carcinoma” (Fig. 1). Manuscripts included were original articles investigating the role of reTUR and disease

Table 1 – Figure 1 ReTUR recommendations across guideline panels

<table>
<thead>
<tr>
<th>Guideline body</th>
<th>Recommendation on suitable reTUR candidates</th>
<th>Level of evidence given</th>
<th>Major differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAU (European Association of Urology)</td>
<td>1. Incomplete initial TUR</td>
<td>All Grade A (Strong)</td>
<td>Used as the reference standard</td>
</tr>
<tr>
<td></td>
<td>2. No muscle in specimen with the exception of LG-Ta/Gl and primary CIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. T1 tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUA (American Urological Association)</td>
<td>1. Incomplete initial TUR</td>
<td>1. Grade B (strong)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. HG-Ta tumours</td>
<td>2. Grade C (moderate)</td>
<td>No comment is made that HG-Ta tumours do not need reTUR if muscle is present in the initial TUR</td>
</tr>
<tr>
<td></td>
<td>3. T1 tumours</td>
<td>3. Grade B (strong)</td>
<td></td>
</tr>
<tr>
<td>NCCN (National Comprehensive Cancer Network)</td>
<td>1. Incomplete initial TUR</td>
<td>All Strong</td>
<td>Include large or multi-focal lesions as a reason to re-resect. Doesn't specifically mention CIS</td>
</tr>
<tr>
<td></td>
<td>2. No muscle in initial TUR for HG disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Large or multi-focal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. T1 tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Select HG-Ta especially if no muscle in initial TUR</td>
<td>All Strong</td>
<td></td>
</tr>
<tr>
<td>CUA (Canadian Urology Association)</td>
<td>1. Incomplete initial TUR</td>
<td>1. Grade A</td>
<td>Recommend reTUR in T1 or HG-Ta where muscle is present and not malignant.</td>
</tr>
<tr>
<td></td>
<td>2. T1 tumour in absence of muscle</td>
<td>2. Grade A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Any HG or T1 tumour with benign muscle</td>
<td>3. Grade C</td>
<td></td>
</tr>
<tr>
<td>NICE (National Institute for Clinical Excellence)</td>
<td>1. All high-risk non-muscle invasive bladder cancer</td>
<td>1. Low</td>
<td>Does not specify whether presence of muscle changes the approach.</td>
</tr>
<tr>
<td>ICUD (International Consultation on Bladder Cancer) 2012</td>
<td>1. T1 tumours (regardless of the presence of muscle)</td>
<td>1 Strong</td>
<td>Does not specify whether presence of muscle changes the approach.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Does not discuss HG-Ta tumours.</td>
</tr>
</tbody>
</table>

For PICO 1 on the practice of reTUR, data were collected on the presence of detrusor muscle status on the first TUR (when available), time interval to reTUR, delivery of intravesical chemotherapy, and residual tumour location (see the Supplementary material, eligibility criteria). For PICO 2 on the therapeutic benefit of reTUR, we collected information on both reTUR and control patients; cases with residual tumours; cases with residual tumours of lower and same stage, or those upstaged to invasive disease; and therapeutic outcome data. Adjusted risk effect data were used where provided to reduce the risk of unmeasured or predicted bias. We included only those papers where the initial TUR was thought to be complete, and only patients with HG Ta or T1 tumours were included.

An MA was attempted, but only one randomised controlled trial (RCT) was found on our search [10], which has received criticism [10,14].

2.3. Analysis

Predefined primary outcomes were rate of residual tumour (and location) at first cystoscopy and upstaging after reTUR (PICO 1). Coprimary outcomes were disease recurrence, progression, and overall (OM) and cancer-specific (CSM) mortality (PICO 2). Twenty-one papers addressed only PICO 1, one paper addressed only PICO 2, and nine addressed both PICOs.

2.4. Risk of bias

A pragmatic “risk-of-bias” (RoB) assessment was conducted and tabulated (Supplementary Fig. 1–7) using the Cochrane Handbook for Systematic Reviews of Interventions. We stratified the tables by study design. In nonrandomised comparative studies (NRCSs), RoB was assessed using additional domains to assess the risk of confounders, which were developed a priori. This approach was informed by methodological literature pertaining to assessing RoB in NRCSs [15,16]. The main confounding factors identified included baseline age, gender, tumour multifocality, tumour size, concomitant carcinoma in situ (CIS), and use of intravesical chemo-/immunotherapy. We did not consider tumour stage a confounding factor, but it was accounted for in our exclusion criteria (see above). RoB tables were constructed using the Cochrane RevMan (Review Manager, a computer program, Version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software. Confounders were agreed by consensus among M.G.C. and B.F. Conflicts were resolved by senior coauthors.

3. Evidence synthesis

Abstracts from 15 209 reports (Fig. 1) were reviewed by two researchers (M.G.C. and B.F.) independently. Five articles were excluded as they were in languages that none of the authors could translate (Japanese, Chinese, Russian, and Hungarian), and 99 full-text manuscripts were obtained. Of these, 68 were excluded because they either did not report
Table 2 – Practice of reTUR—residual tumour and upstaging for Ta NMIBC following reTUR

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study design</th>
<th>No. associated with CIS (%)</th>
<th>No. of detrusor in first (%)</th>
<th>Total no. in study</th>
<th>Cases of reTUR</th>
<th>Duration between first and reTUR in weeks (range)</th>
<th>Total no. of residual tumours (%)</th>
<th>No. of residual Ta (%)</th>
<th>No. of residual Tis (%)</th>
<th>No. of residual upstaged ≥T1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon (in press) [28]</td>
<td>NRCS</td>
<td>16/25 † ‡ [(64)]</td>
<td>26 (62)</td>
<td>932</td>
<td>42</td>
<td>(&lt;6–12)</td>
<td>24 (57)</td>
<td>NA</td>
<td>NA</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Fujikawa (2012) [29]</td>
<td>NRCS</td>
<td>13 (12)</td>
<td>NA (100)</td>
<td>117</td>
<td>9</td>
<td>4 (2–8)</td>
<td>6 (67)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Han (2008) [30]</td>
<td>NRCS</td>
<td>4 (7)</td>
<td>17 (30)</td>
<td>56</td>
<td>25</td>
<td>2 (2–8)</td>
<td>16 (64)</td>
<td>14 (56)</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Engelhardt (2003) [31]</td>
<td>NRCS</td>
<td>0 (0.0)</td>
<td>NA</td>
<td>75</td>
<td>6</td>
<td>8</td>
<td>3 (50)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

CIS = carcinoma in situ; NA = not available; NMIBC = non–muscle-invasive bladder cancer; NRCS = nonrandomised comparative study; reTUR = repeat transurethral resection.

Median follow-up.
† Incomplete data.

3.1. Results for PICO 1

3.1.1. Residual tumour at reTUR for Ta tumours

Five studies reported on 1294 patients. There were 88 reTURs across the five datasets. The total number of residual tumours was 50 (55%). The number of residual tumours ranged from 1 (17%) to 24 (67%). The median was 3 (mean 7) residual tumours (Table 2).

3.1.2. Residual tumour at reTUR for T1 tumours

Thirty studies reported on 8070 patients. Of these, 3601 patients underwent a reTUR. There were 1818 residual tumours at reTUR, which represents 51%. The range was from 20% to 71% (Table 3).

3.1.3. Upstaging at reTUR for Ta tumours

Four studies reported data on tumour upstaging for Ta tumours to ≥T1. Studies reported on 1294 patients. Five patients had upstaged disease at reTUR (0.4%). Upstaging occurred in 0–8% of cases within studies (Table 2).

3.1.4. Upstaging at reTUR for T1 tumours

Twenty-four studies reported on 4678 patients, which evaluated upstaging to ≥T2 at reTUR for T1 tumours at initial TUR. Within these studies, 2417 patients underwent a reTUR, of which 182 (8%) patients had their disease upstaged to ≥T2. The range was 0–34% of cases (0–32% within studies). The median number of patients with upstaged disease was 5 (4% of patients; Table 3).

3.1.5. Residual tumour location

Six studies clearly reported the location of residual tumours and compared same site as initial tumour with other loci. Of these six studies, four found that residual tumours are more frequently located at the original resection site (Supplementary Table 9). The greatest difference was reported by Schwaibold et al [17], where 86% of residual tumours where found at the initial resection site (Supplementary Table 9).

3.1.6. Practice of ReTUR

Mean time to reTUR was 5 wk (range 0–12 wk) after initial resection. The presence of CIS in the first TUR ranged from 0% to 64% across studies, and presence of detrusor muscle was reported in the first TUR between 30% and 100% of cases (Tables 2 and 3).

3.2. Results for PICO 2

3.2.1. Recurrence for Ta tumours

Only one paper described this item [18]. Of 347 patients in the study, 148 underwent a reTUR. There were 24 reTUR recurrences (16%) at 12-mo follow-up. Fifty-nine patients (58%) in the control (no reTUR) group had a recurrence in the same time period (Supplementary Table 3).

3.2.2. Recurrence for T1 tumours

Overall, recurrence occurred in 45% for patients with initial T1 tumours (747 out of 1651 patients) who underwent a reTUR (range 18–56%), which represents 17% of all patients within the study series on T1 tumours (747 out of 4209). In studies on T1 tumours, 30–71% of controls (non-reTUR) had recurrence. This represents 937/1910 across studies, which equates to 49% (compared with 45% in the reTUR group).

Follow-up durations ranged from 12 to 66 mo. BCG use ranged from 57% to 100% (Supplementary Table 4).

The greatest difference (%) in recurrence was shown by Herr [18], who reported on 67 reTUR cases. Of the control patients, 70% had recurrent disease within 1 yr compared with 18% of reTUR patients. The largest study in our series was by Gontero et al [13] who reported on 900 reTUR patients, wherein 55% of reTUR patients had recurrence within a median follow-up of 62 mo versus 49% for controls. The only RCT within this cohort was by Divrik et al [10]. They reported on 93 reTUR cases with a mean follow-up of 66 mo. The results reported that 40% of reTUR patients suffered recurrence compared with 71% of controls [10].

3.2.3. Progression for Ta tumours (Ta ≥T1)

Progression was defined as per the International Bladder Cancer Group. This describes progression as any increase in stage. For Ta tumours at first resection, two papers reported on 1277 patients. A total of 250 patients underwent a reTUR, with a mean follow-up of 48 mo. Eleven patients progressed in each study (7–13%). Herr’s study [18] had a control arm in data as stratified into different histological subtypes or contained <50 study participants, or the papers were not available. In total, we identified 31 manuscripts reporting 8409 persons for inclusion in this analysis (Fig. 1). The literature was richer for T1 than for Ta tumours.
Table 3 – Practice of reTUR—residual tumour and upstaging for T1 NMIBC following reTUR

| Publication | Study design | No. associated with CIS (%) | No. of detrusor in first (%) | Total no. in study | Cases of reTUR | Duration between first and reTUR in weeks (range) | Total no. of residuals (%) | No. of residual Ta (%) | No. of residual Tis (%) | No. of residual T1 (%) | No. of residual ≥T2 (%) | Upstaged (%)
|-------------|--------------|-----------------------------|------------------------------|-------------------|--------------|---------------------------------------------|--------------------------|----------------------|----------------------|----------------------|----------------------|---------------------|
| Divrik (2010) [10] | RCT | 0 (0) | 105 (100) | 210 | 105 | (2-6) | 35 (33) | 14 (13) | 4 (4) | 9 (9) | 8 (8) | 0.00%
| Audenet (2017) [32] | NRCS | NA | 107 (54) | 198 | 198 | 6 | 125 (63) | 27 (14) | 44 (22) | 50 (25) | 4 (2) | 0.00%
| Gordon (in press) [28] | NRCS | 32/75 * (43) | 115 (71) | 932 | 163 | (-6-12) | 97 (60) | NA | NA | NA | 34 (21) | 0.00%
| Hashine (2016) [33] | NRCS | 23 (14) | NA | 171 | 79 | (4-6) | 46 (58) | 15 (19) | 18 (23) | 12 (15) | 1 (1) | 0.00%
| Kamiya (2017) [34] | NRCS | 36 (18) | NA | 198 | 172 | (2-10) | NA | NA | NA | NA | 5 (3) | 0.00%
| Iida (2016) [35] | NRCS | 5 (8) | 65 (100) | 207 | 65 | (6-11) | 34 (52) | NA | NA | NA | 0 (0) | 0.00%
| Sanseverino (2016) [36] | NRCS | 6 (3) | 177 (90) | 196 | 196 | 5 (4-6) | 92 (47) | 8 (4) | 8 (4) | 48 (25) | 28 (14) | 0.00%
| Un (2016) [37] | NRCS | NA | NA (100) | 156 | 51 | 5 (4-6) | 19 (37) | NA | NA | NA | 0 (0) | 0.00%
| Cao (2015) [38] | NRCS | NA | NA (100) | 134 | 56 | 4 (2-6) | 30 (54) | NA | NA | NA | 0 (0) | 0.00%
| Turk (2016) [39] | NRCS | 20 (11) | NA | 221 | 188 | 5 | 82 (44) | NA | NA | NA | 5 (3) | 0.00%
| Angulo (2014) [12] | NRCS | 0 (0) | NA (100) | 425 | 162 | 5 (4-6) | 45 (28) | NA | NA | NA | 14 (9) | 12 (7) | 0.00%
| Gill (2014) [40] | NRCS | 8 (15) | 36 (69) | 52 | 25 | 1.2 | 15 (60) | NA | NA | NA | 8 (32) | 0.00%
| Takaoka (2013) [41] | NRCS | 15 (21) | 47 (64) | 73 | 73 | 6 | 37 (51) | NA | NA | 13 (18) | 3 (4) | 0.00%
| Geavlete (2012) [42] | NRCS | NA | NA | 220 | 69 | 4 | 14 (20) | NA | NA | NA | 1 (1) | 0.00%
| Fujikawa (2012) [29] | NRCS | 13 (12) | NA (100) | 117 | 53 | 4 (2-8) | 34 (64) | NA | NA | 8 (15) | 1 (2) | 0.00%
| Huang (2012) [43] | NRCS | 110 (51) | 216 | 47 | 4 (2-6) | 26 (55) | NA | NA | NA | NA | 0.00%
| Richterstetter (2012) [44] | NRCS | NA | NA | 221 | 76 | NA | 27 (36) | NA | NA | NA | NA | 0.00%
| Vaidei (2012) [45] | NRCS | 47 (10) | 345 (71) | 486 | 172 | 6 | 94 (55) | 21 (12) | 20 (12) | 41 (24) | 12 (3) | 0.00%
| Katumalla (2011) [46] | NRCS | NA | 50 (100) | 68 | 50 | 5 (4-6) | 18 (36) | NA | NA | NA | 2 (4) | 0.00%
| Ali (2010) [7] | NRCS | 3 (3) | NA (100) | 91 | 61 | 4 (2-6) | 41 (67) | 9 (15) | 0 (0) | 16 (26) | 16 (26) | 0.00%
| Parkin (2011) [47] | NRCS | 44 (43) | 90 (88) | 102 | 100 | NA | 24 (24) | NA | NA | NA | 3 (3) | 0.00%
| Gokcel (2010) [48] | NRCS | NA | NA (100) | 70 | 62 | 5 (3-6) | 22 (35) | 8 (13) | 1 (2) | 6 (10) | 7 (11) | 0.00%
| Dwivedi (2009) [49] | NRCS | 11 (21) | NA (100) | 50 | 42 | 5 | 12 (29) | NA | NA | NA | 4 (10) | 0.00%
| Gontero (2016) [13] | NRCS | 599 (24) | 1768 (72) | 2451 | 935 | 5 (4-6) | 668 (71) | 378 (40) | NA | 289 (31) | NA | 0.00%
| Han (2008) [30] | NRCS | 4 (7) | 17 (30) | 56 | 30 | NA | 20 (67) | 5 (17) | 1 (3) | 7 (23) | 7 (23) | 0.00%
| Schwaibold (2006) [17] | NRCS | 21 (15) | NA | 136 | 136 | 5 (4-6) | 71 (52) | 11 (8) | 15 (11) | 32 (24) | 13 (10) | 0.00%
| Engelhardt (2001) [31] | NRCS | 0 (0) | NA | 75 | 25 | 8 | 13 (52) | NA | NA | NA | 0 (0) | 0.00%
| Zurkirchen (2004) [50] | NRCS | NA | NA | 214 | 115 | 5 (4-6) | 42 (37) | 14 (12) | 5 (4) | 21 (18) | 2 (2) | 0.00%
| Grimm (2003) [11] | NRCS | 9 (4) | 208 (97) | 214 | 19 | 7 | 10 (53) | NA | NA | NA | NA | 0.00%
| Schups (2002) [51] | NRCS | NA | NA | 110 | 76 | 5 (4-6) | 25 (33) | NA | NA | 11 (15) | 8 (8) | 0.00%

CIS = carcinoma in situ; NA = not available; NMIBC = non-muscle-invasive bladder cancer; NRCS = nonrandomised comparative study; RCT = randomised controlled trial; reTUR = repeat transurethral resection; TUR = transurethral resection.

Median follow-up.

* Incomplete data.

which 32 patients progressed (31%), which represents four times that of the reTUR group. BCG was received by 100% of participants (Supplementary Table 5).

3.2.4. Progression for T1 tumours (T1 ≥T2)
Eight studies reported progression from initial T1 tumours at reTUR. These reported on 4902 persons, 1954 of whom had a reTUR. A total of 410 cases progressed (by stage), which represents 21%. Out of 2117 controls (non-reTUR), 350 progressed by stage (17%). Average follow-up ranged from 26 to 66 mo. Six of the eight studies reported on a control population. Of these six studies, progression was higher in the non-reTUR groups in five studies. Only one RCT [10] reported a difference between groups of 6% in the reTUR group versus 24% in the control arm (Supplementary Table 6).
3.2.5. T1 CSM
We found three studies reporting on 3593 persons of whom 1315 received a reTUR. Divrik et al [10] reported a survival benefit from reTUR (17% CSM in the reTUR arm vs 31% in the control arm), but the largest study [13] reported no survival benefit (10% CSM in the reTUR arm vs 9% in the control arm; Supplementary Table 7).

3.2.6. T1 OM
All-cause mortality was reported in three studies, reporting on 2661 persons, 993 of whom had a reTUR. Two studies had a control group [10,13]; both studies showed a modest reduction in OM within the reTUR group (30% vs 36%, and 22% vs 26%, respectively; Supplementary Table 8).

3.3. Discussion
Fritsche et al [19] showed that there is a large risk of upstaging after index TUR in T1 disease, with 50% of cystectomies for this histological subtype being MIBC at cystectomy [13]. Furthermore, Herr et al [20] suggested that at reTUR, up to 43% of patients might experience upstaging to ≥T2, with a significantly high proportion (85%) experiencing some form of recurrence. Clearly, this confers morbidity and cost implication. It is therefore not surprising that an RFS benefit has been shown in patients who undergo a reTUR [21]. However, this is not uniformly accepted, and some authors suggest that long-term RFS and PFS benefits remain unclear [12,22].

Many factors influence RFS and PFS, including the presence of detrusor muscle (significantly impacted by the seniority of surgeon [6]) in the index TUR, presence of CIS, and size and multifocality of tumour. Herr [5,18] has shown that a lack of muscle in the initial TUR (and subsequently the increased risk of recurrent tumour at reTUR) negatively impacts BCG response rates, and such patients with large and multiple tumours, incomplete resections, and high-risk NMIBC present in the resection undergo re-resection with 6 wk [3]. The importance of muscle in the initial resection is further strengthened by Gontero et al’s [13] findings that reTUR does not infer an RFS, PFS, CSS, or OS advantage in patients with pT1 disease, if muscle was present in the original sample.

We sought to provide the largest SR to date on this topic. We set out to pool study outcome data for the reTUR and control groups and ascertain their possible associations between Ta and T1 NMIBC and recurrence and progression (ideally long-term data). Unfortunately, a lack of randomised studies with like-for-like data capture precluded any formal summary risk estimates or comparisons. Without individual patient data, it was not possible to take into account prognostic subgroups. Instead, more global associations were made (see results sections), but this feels unsatisfactory to the authors. Nonetheless, our data suggest a trend that receiving reTUR may reduce the risk of progression (for Ta and T1) and OM (T1), but this is far from a universal finding. The evidence was even less clear for recurrence rates and CSM. This inconclusiveness is due to the lack of high-quality RCTs comparing reTUR with no reTUR. Our RoB tables show clearly that most studies included in this review are at a high RoB (Supplementary Fig. 1–7).

A recent MA by Naselli et al [23] looked at 29 manuscripts across three decades (1980–2016). They concluded that 50% of T1 tumours are residual at reTUR and that 10% upstage to invasive disease. They did not find that the presence of detrusor muscle affected this outcome. However, their MA included a number of non-RCT studies, which incurs the potential for a high RoB. Within our dataset, the two potentially most impactful studies were by Divrik et al [10] and Gontero et al [13]. The Divrik et al’s [10] study is the only RCT in our dataset. This paper reports a reduction in recurrence and progression rates in T1 tumours at initial TUR in reTUR versus non-reTUR groups. They did not comment on the significance of muscle in the specimen at initial TUR. The Gontero et al’s [13] study was a retrospective analysis of 2451 patients (largest study in this series) with T1 tumours at initial TUR. It reported only a difference in outcomes if muscle was absent from the first resection. These two studies share key differences, which are the nature of patient enrolment (prospective [Divrik]/retrospective [Gontero]) and that the Divrik et al’s study excluded those who underwent BCG treatments due to the presence of concurrent Tis.

Across the whole of our study, residual tumours found at second TUR ranged from 17% to 67% across studies for initial Ta disease. For T1 BC, it ranged from 20% to 71%. This is in keeping with current literature. Upstaging in initial Ta disease ranged from 0% to 23%, whereas for T1 BC from 0% to 32%. Studies included within this analysis with a greater mean length of follow-up did not seem to show a difference in PFS, RFS, OM, and CSM. The residual disease was found most often at the original resection site.

In conclusion, it is important to perform an oncologically sound initial resection. This involves ensuring that muscle is captured in the specimen and that all visual tumour is removed. We do not find enough evidence through this review to make strong recommendations or change current-day practice. The current EAU guidelines suggest that a reTUR is warranted in cases where the initial TURBT is incomplete; muscle is not present in the initial resection (except for TaG1 and primary CIS) and all T1 and HG/G3 tumours (except for CIS).

What is clear is that there is an unmet need for a large, multicentred, prospective, intention-to-treat RCT on re-resection for Ta and T1 tumours.

3.4. Limitations
As mentioned above, the literature contains a number of papers examining the impact of reTUR. Stage and grade at initial TUR, in addition to the presence of CIS or tumour multifocality, and presence of lymphovascular invasion (LVI) are seemingly the most important predictors of recurrence and progression.

Unfortunately, studies on this topic are varied in approach and becoming dated. The histological subtypes
examined are often not concordant. The paucity of RCTs makes inferring patterns and assigning strengths of association through meta-analysing data impossible to do. The only RCT (by Divrik et al. [10]) in our dataset has received criticism [14]. This is in part due to the exclusion of patients receiving BCG and early cystectomy in the reTUR group. Interestingly, another RCT (not included in this SR as it did not separate HG from low-grade Ta/T1) by Kim et al. [24] evaluated 126 patients, 63 of whom underwent a reTUR. Of these, 19% upstaged to T2 disease.

In nonrandomised studies, the RoB assessment revealed a moderate to high level of bias across studies due to potential patient selection bias and confounding, missing outcome data, and heterogeneous treatment and follow-up. This, along with small sample sizes, makes it difficult to provide a meaningful summary of patient outcome estimates. Eight of the 31 studies involved fewer than 100 patients.

Finally, some prognostic histological features are not uniformly reported. For example, LVI, which has been linked to increased disease progression [25] and residual disease [26] for T1 tumours, was scarcely accounted for in our series. There is also some evidence that the operator experience level can affect outcomes [27], and this was not controlled for/or obviously documented in all studies. Lastly, some histological variants of BC have a poor prognosis (eg, micropapillary, nested, and sarcomatoid) [3], and there remains some uncertainty about how to stratify these patients after TUR as studies have been historically small. The studies within our dataset did not comment on such histological features.

To rectify the limitations of this study, we propose a multicentre, prospective, randomised study assessing all putative prognostic subgroupings with stratification by grade, stage, and quality of the initial resection. Such studies should assess when patients move from Ta to T2 disease (rather than only to T1), as progression from Ta to T1 may not affect clinician decision making (patients may still be offered BCG rather than cystectomy).

4. Conclusions

Residual tumour is common after TUR for high risk NMIBC. The reTUR helps in the diagnosis of this residual cancer and may improve outcomes for cancers initially staged as T1.

Author contributions: Marcus G.K. Cumberbatch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cumberbatch, Foerster, Catto, Gontero.
Acquisition of data: Cumberbatch, Foerster, Jubber.
Analysis and interpretation of data: None.
Drafting of the manuscript: Cumberbatch, Foerster, Catto, Kassouf, Jubber, Shariat, Sylvester, Gontero.
Critical revision of the manuscript for important intellectual content: Catto, Kassouf, Shariat, Sylvester, Gontero.
Statistical analysis: None.
Obtaining funding: None.

Administrative, technical, or material support: None.
Supervision: Catto, Kamat, Kassouf, Shariat, Sylvester, Gontero.
Other: None.

Financial disclosures: Marcus G.K. Cumberbatch certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.02.014.

References


