

# The role of repeat transurethral resection in the management of high-risk superficial transitional cell bladder cancer

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## KEYWORDS

transitional cell bladder cancer, superficial bladder cancer, high-risk bladder cancer, transurethral resection, re-resection

## INTRODUCTION

High-risk superficial transitional cell bladder cancers are not muscle-invasive tumours but have a high predilection for the developing muscle invasion, metastasis and eventual mortality. The European Association of Urology guideline defines these cancers as bladder cancers with G3, T1, carcinoma *in situ*, multifocal or high recurrence characteristics [1]. However, primary carcinoma *in situ* is a distinct entity in terms of its biological behaviour and risk potential. Therefore, for the purpose of this review we have excluded the latter group.

Low-risk cancer is treated with transurethral resection (TUR) and intravesical chemotherapy administered if indicated. Patients with pT2 cancer, if fit enough, may be considered for radical therapies including cystectomy and radiotherapy, but the treatment for high-risk superficial bladder cancers has been fraught with controversy. The overriding issue is when should high-risk superficial cancers be treated conservatively with TUR with or with no intravesical chemotherapy, and at which point does a cystectomy become necessary to prevent progression to muscle-invasive disease. The problem is that the groups needing conservative or aggressive management are not clearly defined, meaning that there may be considerable over- and under-treatment of these cancers.

The crucial step in the diagnosis and treatment of any bladder cancer is the initial TUR. There is reported evidence that this TUR is often not performed to adequate standards

[2]. This has led some to suggest a repeat TUR (re-TUR) aimed at eradicating residual cancers and improving the staging of bladder cancers. This review examines the rationale and evidence for a re-TUR to optimize the management of high-risk superficial bladder cancers.

## TUR

Tumour may recur because of the persistence of tumour after an incomplete TUR, a lesion that has been overlooked, a new lesion developed from circulating tumour cells during the TUR, or a true new occurrence caused by the growth of a microscopic lesion to a macroscopic one. An incomplete TUR will compromise the patient's outcome, and therefore the recurrence rate at the first follow-up cystoscopy (RR-FFC). The early RR-FFC between institutions is of major interest; Brausi *et al.* [2] analysed the variability among institutions in the RR-FFC in 2410 patients from seven phase III trials of the European Organisation for the Research and Treatment of Cancer (EORTC). The RR-FFC varied widely among institutions and could not be explained by tumour characteristics, number of tumours at TUR or the use of adjuvant intravesical instillations (Table 1) [2]. The authors suggested that these variations can only be attributed to the differing quality of the TUR performed by the various centres.

At present, in addition to removing the exophytic growth, a separate loop resection of the tumour base is recommended [3]. This is favoured over the cold-cup forceps biopsy because in broad-based lesions the point of deeper invasion into the muscle can be difficult to determine macroscopically, and hence be missed with a forceps biopsy. The TUR should also include the margins of the resection area. A series by Flamm and Steiner [4] showed cancer present in 21% of patients who had margin resection during TUR. However, there is no mention of the concept

of a 'safe margin' in published reports, as is apparent in the surgical practise for other cancers of epithelial origin, e.g. squamous cell and basal cell carcinomas, and melanoma of the skin. Perhaps studies on histopathological specimens from cystectomies can determine if such a 'safe margin' exists and whether or not it should be incorporated in all routine TURs.

The TUR has limitations, as not all cancers are visible at the time of resection, and it can be difficult to judge the depth of resection to ensure that the muscularis propria has been sampled for histopathological staging. The presence of this layer is crucial if non-muscle invasive and muscle-invasive cancer are to be accurately differentiated. The absence of this layer may not necessarily be due to a lack of quality control during the TUR. Factors such as multiplicity of the cancer growth, awkward anatomical location of cancers (within a diverticulum, dome or anterior wall of bladder), trabeculated or thin bladder wall, incidental perforation and over-enthusiastic use of the diathermy loop are only some reasons which result in a suboptimal specimen collection at TUR.

A TUR technique incorporating 5-aminolaevulinic acid (ALA) photodynamic diagnosis has been examined as a solution to minimize the amount of cancer left behind [5,6], but this technique does not address the issue of errors from under-staging cancers caused by inadequate sampling of the muscularis propria. This technique, although promising, has yet to be incorporated widely in clinical practice. The cost of the ALA, blue-light source and technical problems such as quick 'photobleaching' are only part of the reasons for this delay.

## HISTOPATHOLOGY

The accurate staging of superficial bladder cancer is crucial, as all superficial cancers

carry a risk of progression (pTa, 4%; pT1, 30%) [7]. Any further treatment will be influenced by the accuracy of this staging. As previously stated, despite the best efforts to obtain samples, the quality of tissue obtained from TUR may be lacking. A series by Wijkstrom *et al.* [8] showed that 37% of TURs in their series lacked the muscularis propria in the histopathological specimen. To maintain the quality standard of the TUR, local histopathologists should be encouraged to report on the status of the muscularis propria in all TUR specimens analysed.

There is also a lack of conformity in the actual reporting of the final TUR histology [9,10]. Factors contributing include poor tissue orientation on prepared slides, and thermal or crush artefacts. Thus the true rates of high-risk cancers, including pT1G3, that have been reported in published reports is debatable. Van der Meijden [10] evaluated the impact of interobserver variability on the stage and grade assessment of Ta and T1 bladder cancers in 1175 tumour specimens obtained from five EORTC trials. The review pathologist agreed with the original observer in only 61% of 160 grade 3 tumours, and in only 47% of 88 T1G3 specimens. Similar inter- and intra-observer variability has been confirmed by other authors, but the routine involvement of a review histopathologist has not gained widespread acceptance thus far. The cancer outcome guidelines in the UK now make it compulsory for every case of high-risk bladder cancer which is considered for aggressive radical treatment to undergo a review histopathological assessment by a dedicated regional uropathologist.

### WHY REPEAT THE TUR?

Re-TUR could play a key role in managing high-risk superficial bladder cancers, by reducing the residual cancer rates and improving the staging accuracy. Early recurrence within 3 months after a TUR has been shown to be a poor prognosticator [11], but it is often difficult to distinguish between true early recurrences and residual disease after initial TUR. Other methods to detect residual cancers after initial TUR, such as early flexible cystoscopy or urine cytology, lack the sensitivity to be of any significant clinical use.

There is published information suggesting that a re-TUR at 2–8 weeks after the initial procedure is effective in detecting residual cancer and/or overlooked cancer, and in

Tumour features and treatment	RR-FFC, % (median)
Single, TUR only	3.5–20.6 (7.4)
Single, TUR + intravesical instillation	0–5.4 (5)
Multifocal, TUR + intravesical instillation	7.4–45.8 (18.9)

**TABLE 1**  
Results of RR-FFC of Ta and T1 bladder TCC from seven combined EORTC studies

**TABLE 2** Residual cancer and cancer upstaging rates in the re-TUR series

Reference	Number of patients	Re-TUR at, weeks	Residual cancer, %	Upstaging (muscle-invasive cancer), %
Klän <i>et al.</i> [12]	46	1–2	44	2
Herr <i>et al.</i> [13]	150	2–6	76	29
Brauers <i>et al.</i> [14]	42	4–6	64	5
Schwaibold <i>et al.</i> [15]	60	4–6	55	10
Schips <i>et al.</i> [16]	110	4–6	36	5
Grimm <i>et al.</i> [17]	83	mean 7	33	4

reducing under-staging of the cancer. Initially there was much scepticism of the high residual cancer rates (44%) reported by Klän *et al.* [12]. Additional reported evidence suggests that Klän *et al.* may not be alone in suggesting this (Table 2) [12–17]. These studies also suggested that re-TUR is a safe procedure, as no significant morbidity or mortality was reported.

Some would argue that because most TURs are performed by trainee urologists, the presence of residual cancer after initial TUR could result from the lack of experience. This is only an assumption, as in most re-TUR studies no comment is made on the level of experience of the surgeon doing the initial resection. There was a successful rebuttal of this assumption recently in a study which assessed the residual cancer rates after TURs by both experienced urologists and trainees; this showed no statistically significant difference between the groups [18].

Among patients in whom the re-TUR was clear (T0), none showed progression during a mean of 5 years of follow-up interval [14]. These patients also had favourable recurrence and progression rates when compared with patients who had cancer growths in the re-TUR specimen [14,17]. This provides indirect evidence that part of the disease relapse during follow-up may be caused by residual disease rather than *de novo* growths.

The next key issue is what should be done at the re-TUR procedure. The scar from the previous resection site must be resected; this

is again based on studies which showed that if residual cancer is found, it will be at the initial resection site in ≈80% of patients [15,17,19]. A further resection of the margin of the scar or tumour recurrence is also advisable. During this sitting there must be a systematic re-examination of the bladder and biopsies of any suspicious areas taken. A routine random biopsy of normal-appearing mucosa was also described but the published evidence remains equivocal as to whether it should be incorporated into routine clinical practice.

There is no agreed consensus on the interval between initial TUR and re-TUR. Periods suggested vary from 7 days to 3 months. An interval of 3 months may perhaps be too long as it could interfere with any adjuvant intravesical therapy that may need to be offered to the patients. Too short a resection interval again may not be acceptable to the patients and might pose logistical difficulties. A resection too early also defeats the purpose of the re-examination of the bladder, as inflammatory changes within the mucosa from the initial resection can make it difficult to distinguish truly suspicious lesions from normal postoperative inflammatory changes. We suggest that a 4–6 week interval is probably the best compromise on this.

### THE CASE AGAINST RE-TUR

Proponents of the cell-implantation theory suggest that re-TUR could induce seeding of the cancer within the denuded bladder mucosa. A study by El-Abbady *et al.* [20]

concluded that patients undergoing re-TUR are more likely to develop muscle-invasive disease than those who have not had a re-TUR. The former group had a higher incidence of blood and lymphatic spread, with an unusual pattern of invasion resulting in clusters of malignant tumour cells being found within the muscle fibres, the serosa and the perivesical fascia. Multiplicity was also another feature noted in this group. The authors suggested that a combination of the pumping action from bladder filling and emptying during re-TUR and that there are areas of denuded epithelium within the bladder facilitates the deep implantation of cancer cells [20]. These findings have not been reproduced by other studies incorporating re-TUR. On a more obvious point, if this was truly the case then the histological findings would be similar in all patients who had undergone the initial TUR, as technically the TUR and re-TUR procedures are identical. It is difficult to accept that one additional TUR can significantly alter the biological behaviour of the tumour so dramatically.

## CONCLUSION

A review of published evidence supports the rationale for incorporating re-TUR in the management of high-risk superficial transitional bladder cancer, for the following reasons:

- residual cancers are found in 33–76% of patients after their first TUR for Ta and T1 bladder cancer.
- errors in staging of bladder cancers are common and occur as a result of deficiencies in sampling and analysing after a TUR.
- a T0 status of superficial bladder cancers at re-TUR seems to confer a favourable effect on cancer recurrence and progression in the short to medium term.

The re-TUR could be used to distinguish between patients for whom watchful waiting and bladder conservation is appropriate from those who need an early cystectomy for disease control. There are no published data to support this claim, but this needs exploring. A multicentre randomized control trial to assess the impact of re-TURs on the natural history of high-risk superficial bladder cancer is long overdue.

Tumour grading and staging only complete part of the 'jigsaw' of the behaviour and natural history of high-risk superficial

transitional cell bladder cancer. Further advances in cancer genomics and proteomics will complete some of the missing pieces, thus improving patient selection for treatment in the future.

## CONFLICT OF INTEREST

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**Abbreviations:** (re-)TUR, (repeat) transurethral resection; EORTC, European

Organisation for the Research and Treatment of Cancer; RR-FFC, recurrence rate at first the follow-up cystoscopy; ALA, 5-aminolaevulinic acid.